FILE HISTORY

US 11,406,598

PATENT:	11,406,598
INVENTORS:	CHODAVARAPU BALA TRIPURA SUNDARI
	MANGALI THIRUPATHI
	SHUKLA JAY
	SHUKLA ANAND
	LAKKARAJU DASARADHI
TITLE:	Lyophilized compositions of phenobarbital sodium salt
APPLICATION NO:	US17025881A
FILED:	18 SEP 2020
ISSUED:	09 AUG 2022
COMPILED:	13 FEB 2025

Lyophilized compositions of phenobarbital sodium salt

Transaction History

Date	Transaction Description
09-18-2020	Patent Term Adjustment - Ready for Examination
09-18-2020	Applicants have given acceptable permission for participating foreign
09-18-2020	PTO-SB-69-Authorize EPO Access to Search Results
09-18-2020	Track 1 Request
09-18-2020	Petition Entered
09-18-2020	Entity Status Set To Undiscounted (Initial Default Setting or Status Change)
09-18-2020	Initial Exam Team nn
09-28-2020	Sent to Classification Contractor
09-28-2020	FITF set to YES - revise initial setting
09-28-2020	Applicant Has Filed a Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27
09-29-2020	Email Notification
09-29-2020	Application ready for PDX access by participating foreign offices
09-29-2020	Application Is Now Complete
09-29-2020	Filing Receipt
10-20-2020	Pet Dec Track 1 Grant
10-21-2020	Mail Pet Dec Track 1 Grant
10-21-2020	Record Petition Decision of Granted to Make Special
10-22-2020	Email Notification
10-22-2020	Track 1 Request Granted
10-22-2020	Mail-Record Petition Decision of Granted to Make Special
10-28-2020	Application Dispatched from OIPE
10-29-2020	Track 1 Request Granted
11-03-2020	Case Docketed to Examiner in GAU
11-23-2020	Non-Final Rejection
11-30-2020	Electronic Review
11-30-2020	Email Notification
11-30-2020	Mail Non-Final Rejection
12-01-2020	Electronic Information Disclosure Statement
12-01-2020	Information Disclosure Statement (IDS) Filed
02-12-2021	Response after Non-Final Action
02-16-2021	track 1 ON
02-16-2021	Date Forwarded to Examiner
02-17-2021	Information Disclosure Statement considered
02-23-2021	Final Rejection
02-26-2021	Electronic Review
02-26-2021	Email Notification
02-26-2021	Mail Final Rejection (PTOL - 326)
03-25-2021	PG-Pub Issue Notification
03-26-2021	Email Notification
05-13-2021	Affidavit(s) (Rule 131 or 132) or Exhibit(s) Received
05-13-2021	Request for Continued Examination (RCE)
05-13-2021	Workflow - Request for RCE - Begin
05-14-2021	Date Forwarded to Examiner
05-14-2021	Disposal for a RCE - CPA - R129
05-25-2021	Non-Final Rejection
06-01-2021	Electronic Review
06-01-2021	Email Notification
06-01-2021	Mail Non-Final Rejection
08-17-2021	Electronic request for Examiner Interview
08-24-2021	Miscellaneous Incoming Letter
08-24-2021	Response after Non-Final Action
08-24-2021	Miscellaneous Incoming Letter
08-24-2021	Interview Summary - Applicant Initiated - Telephonic

08-24-2021	Interview Summary Record
08-26-2021	Date Forwarded to Examiner
08-27-2021	Email Notification
08-27-2021	Mail Examiner Interview Summary (PTOL - 413)
09-01-2021	Third Party IDS communication
09-02-2021	Mail Third Party IDS communication
09-03-2021	Email Notification
09-20-2021	Final Rejection
09-23-2021	Electronic Review
09-23-2021	Email Notification
09-23-2021	Mail Final Rejection (PTOL - 326)
12-22-2021	Request for Continued Examination (RCE)
12-22-2021	Workflow - Request for RCE - Begin
01-07-2022	Date Forwarded to Examiner
01-07-2022	Disposal for a RCE - CPA - R129
01-31-2022	Case Docketed to Examiner in GAU
02-03-2022	Restriction-Election Requirement
02-08-2022	Electronic Review
02-08-2022	Email Notification
02-08-2022	Mail Restriction Requirement
03-09-2022	Response to Election - Restriction Filed
03-10-2022	Date Forwarded to Examiner
03-15-2022	Interview Summary - Examiner Initiated - Telephonic
03-28-2022	Notice of Allowance Data Verification Completed
03-30-2022	Electronic Review
03-30-2022	Email Notification
03-30-2022	Mail Notice of Allowance
06-30-2022	Issue Fee Payment Verified
06-30-2022	Issue Fee Payment Received
07-06-2022	Dispatch to FDC
07-06-2022	Application Is Considered Ready for Issue
07-20-2022	Issue Notification Mailed
07-21-2022	Email Notification
08-09-2022	Recordation of Patent Grant Mailed
08-09-2022	Patent Issue Date Used in PTA Calculation

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

CPC								
Symbol							Type	Version
A61K	/	9	/	19			F	2013-01-01
A61K	/	31	/	515			I	2013-01-01
A61K	/	9	/	0019			I	2013-01-01

CPC Combination Sets								
Symbol					Type	Set	Ranking	Version
	/		/					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	15 March 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20220315

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	9	/	19

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	15 March 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

U.S. Patent and Trademark Office — Part of Paper No.: 20220315

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	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	28	10	37												
2	29	11	38												
3	30	12	39												
4	31	13	40												
5	32	14	41												
6	33	15	42												
7	34														
8	35														
9	36														

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/CARLOS A AZPURU/ Primary Examiner, Art Unit 1617	15 March 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1A

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	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

CPC - Searched*		
Symbol	Date	Examiner
A61K9/19 or A61K9/0019	11/23/2020	Y. Zhang
A61K31/515	11/23/2020	Y. Zhang
A61K 9/19	03/15/2022	CA
A61K 31/515	03/15/2022	CA

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	CARLOS A AZPURU	1617

Search Notes		
Search Notes	**Date**	**Examiner**
EAST search including cpc and key words: see attached	11/23/2020	Y. Zhang
PALM inventor search	11/23/2020	Y. Zhang
EAST search including ipc: see attached	02/18/2021	Y. Zhang
Updated EAST search: see attached	05/25/2021	Y. Zhang
pH and key words search via Google: see attached	05/25/2021	Y. Zhang
IDS-3P considered	09/07/2021	Y. Zhang
Google search water and lyophilized product	09/07/2021	Y. Zhang
EAST key word search: see attached	09/08/2021	Y. Zhang
inventor and assignee name search	03/15/2022	CA
Google Chrome search	03/15/2022	CA
East search	03/15/2022	CA

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
A61K 9/19	East search	03/15/2022	CA

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	YANZHI ZHANG	1617

CPC - Searched*		
Symbol	Date	Examiner
A61K9/19 or A61K9/0019	11/23/2020	Y. Zhang
A61K31/515	11/23/2020	Y. Zhang

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST search including cpc and key words: see attached	11/23/2020	Y. Zhang
	11/23/2020	Y. Zhang

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/YANZHI ZHANG/ Primary Examiner, Art Unit 1617	11/23/2020

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	YANZHI ZHANG	1617

CPC - Searched*		
Symbol	Date	Examiner
A61K9/19 or A61K9/0019	11/23/2020	Y. Zhang
A61K31/515	11/23/2020	Y. Zhang

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST search including cpc and key words: see attached	11/23/2020	Y. Zhang
	11/23/2020	Y. Zhang

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/YANZHI ZHANG/ Primary Examiner, Art Unit 1617	11/23/2020

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	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
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A61K9/19 or A61K9/0019	11/23/2020	Y. Zhang
A61K31/515	11/23/2020	Y. Zhang

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
EAST search including cpc and key words: see attached	11/23/2020	Y. Zhang
PALM inventor search	11/23/2020	Y. Zhang
EAST search including ipc: see attached	02/18/2021	Y. Zhang
Updated EAST search: see attached	05/25/2021	Y. Zhang
pH and key words search via Google: see attached	05/25/2021	Y. Zhang

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/YANZHI ZHANG/ Primary Examiner, Art Unit 1617	05/25/2021

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	YANZHI ZHANG	1617

CPC - Searched*		
Symbol	Date	Examiner
A61K9/19 or A61K9/0019	11/23/2020	Y. Zhang
A61K31/515	11/23/2020	Y. Zhang

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

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Search Notes	Date	Examiner
EAST search including cpc and key words: see attached	11/23/2020	Y. Zhang
PALM inventor search	11/23/2020	Y. Zhang
EAST search including ipc: see attached	02/18/2021	Y. Zhang
Updated EAST search: see attached	05/25/2021	Y. Zhang
pH and key words search via Google: see attached	05/25/2021	Y. Zhang
IDS-3P considered	09/07/2021	Y. Zhang
Google search water and lyophilized product	09/07/2021	Y. Zhang
EAST key word search: see attached	09/08/2021	Y. Zhang

/YANZHI ZHANG/ Primary Examiner, Art Unit 1617	09/08/2021

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	17/025,881	Chodavarapu et al.
	Examiner	Art Unit
	YANZHI ZHANG	1617

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/YANZHI ZHANG/ Primary Examiner, Art Unit 1617	09/08/2021

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	322	(Phenobarbital adj Sodium) and lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/08 08:32
L2	6	1 and amorphous same powder	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/08 08:33
L3	6	2 and Phenobarbital	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/08 08:34
S1	2	amorphous same (Phenobarbital adj Sodium)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:03
S2	145,382	(A61K9/19 or A61K9/0019 or A61K31/515).cpc.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:20
S3	856	S2 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:22
S4	514	S3 and water same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:22
S5	3	S4 and water same (sparged near4 nitrogen)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:23
S6	145,382	(A61K9/19 or A61K9/0019 or A61K31/515).cpc.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
S7	856	S6 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
S8	514	S7 and water same injection	US-PGPUB; USPAT; FPRS;	OR	OFF	2020/11/18 14:56

			EPO; JPO; DERWENT			
S9	210	S8 and (ssaline or dextrose) same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
S10	303	S8 and (saline or dextrose) same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:57
S11	0	S10 and (Phenobarbital adj Sodium)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:58
S12	9	S10 and Phenobarbital	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:58
S13	9	S12 and (lyophilized or lyophilizing or lyophilize)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:59
S14	7	S13 and (reconstitute or dissolve)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 15:00
S15	0	Nivagen adj pharmaceuticals.AS.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 11:58
S16	1	NIVAGEN adj pharmaceuticals	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 11:59
S17	25	(Chodavarapu adj Bala or Mangali adj Thirupathi or Shukla adj Jay or Shukla adj Anand or Lakkaraju adj Dasaradhi).IN.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 12:02
S18	0	S17 and (Phenobarbital adj Sodium)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 12:03
S19	0	S17 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 12:03

S20	271,244	(A61K9/19 or A61K9/00 or A61K31/515).ipc.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:44
S21	540	S20 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:44
S22	67	S21 and (adding same water) same lyophiliz$3	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:46
S23	46	S22 and water same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:47
S24	22	S23 and (reconstitute or dissolve) same water	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:48
S25	8	S24 and (saline or dextrose) same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:49
S26	1	S25 and Phenobarbital	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:50
S27	2	wo-2017085687-$.did.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 13:07
S28	2	us-20170143719-$.did.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 13:08
S29	12	(Phenobarbital adj Sodium) and amorphous same (lyophilized or powder)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/05/25 12:14
S30	9	S29 and solution same (pH)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/05/25 12:16
S31	2	S30 and water same (sparged near4 nitrogen)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/05/25 12:17

S32	0	us-20170143719-$.did.	USPAT	OR	OFF	2021/09/07 08:52
S33	2	us-20170143719-$.did.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/07 08:53
S34	2	us-20170143719-$.did.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/07 10:09
S35	2	(Phenobarbital adj Sodium) and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/07 11:44
S36	25	(Phenobarbital adj Sodium) same powder	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/07 11:46
S37	0	(Phenobarbital adj Sodium) same powder.clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/07 11:48
S38	4	S36 and lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/09/07 11:49

9/8/2021 8:34:52 AM
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After the drying process, the final residual water content in the product is very low with around **1% to 4%**. Nevertheless, higher amounts of water in the lyophilized drug formulation can reduce the stability of some drugs.

https://www.mt.com › ... › Titration

Water Content of Lyophilized vaccines - Titration - Mettler Toledo

About featured snippets · Feedback

https://www.pharmtech.com › view › residual-moisture-...

Residual Moisture Testing Methods for Lyophilized Drug ...

Apr 22, 2018 — Because water can be present in a lyophilized product in a number of ways, measurement of the residual moisture and the method used to ...

https://www.researchgate.net › post › How_does_the_mov...

How does the movement of water / moisture in lyophilized ...

The water from the atmosphere then hydrates the powder homogeneously and establishes an equilibrium with the entire product. You can check the amount of ...

2 answers · 0 votes: I have got some experience preparing hydrated protein powders. The pro...

https://www.americanpharmaceuticalreview.com › 8886 ...

Considering Residual Moisture Measurement in Lyophilized ...

Dec 23, 2019 — The transfer of stopper moisture to the product is critical for products with a low fill volume as the transfer of water from the stopper ...

https://pubmed.ncbi.nlm.nih.gov › ...

Determining the optimum residual moisture in lyophilized ...

by CC Hsu · 1992 · Cited by 135 — The amount of water adsorbed on each protein can be determined and approximated as a monolayer by the Brunauer-Emmett-Teller method. The ...

https://www.fda.gov › inspection-guides › lyophilizatio...

Lyophilization of Parenteral (7/93) | FDA - US Food and Drug ...

Nov 17, 2014 — Lyophilization or freeze drying is a process in which water is removed from a product after it is ... Enhanced stability of a dry powder ...

Google amount of water in lyophilized powder

by A Duralliu · 2020 · Cited by 5 — Case Study 1: Freeze Drying of a High Concentration IgG ... mL volume screw capped vials (41.5 × 18 mm i.d. Schott VC005, Adelphi Tubes, ...

https://www.pharmaceuticalonline.com › doc › moistur...

Moisture Determination of Dry Product - Pharmaceutical Online

... stability and shelf life of lyophilized pharmaceutical product, sterile powders, ... Studies have demonstrated that the amount of headspace water vapor ...

https://www.drugdiscoverytrends.com › lyophilization-t...

Lyophilization: The Basics - Drug Discovery and Development

Mar 7, 2017 — Lyophilization, defined as a freeze-drying process that removes water ... Enhancing the stability of a dry powder as well as the product ...

https://core.ac.uk › download › pdf · PDF

Determination of moisture content in lyophilized mannitol ...

by CR Muzzio · Cited by 17 — total amount of water in lyophilized mannitol through intact glass vials with a reflectance ... particle size and powder packing, several authors (Shenk ...

10 pages

Related searches

usp <921 method 1c

how does freeze drying work

lyophilization

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	12	(Phenobarbital adj Sodium) and amorphous same (lyophilized or powder)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/05/25 12:14
L2	9	1 and solution same (pH)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/05/25 12:16
L3	2	2 and water same (sparged near4 nitrogen)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/05/25 12:17

5/25/2021 12:18:14 PM
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pH of sodium phenobarbital injection solution

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The **pH** range is 9.2-10.2. The **sodium** salt of **phenobarbital** occurs as a white, slightly bitter powder, crystalline granules or flaky crystals; it is soluble in alcohol and practically insoluble in ether or chloroform.

dailymed.nlm.nih.gov › dailymed › fda › fdaDrugX...

Phenobarbital Sodium Injection, USP CIV FOR IM OR SLOW ...

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People also ask

Is phenobarbital an acid or base?

How do you dilute phenobarbital?

Is phenobarbital water soluble?

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Feedback

pubmed.ncbi.nlm.nih.gov › ...

Stability of phenobarbital sodium diluted in 0.9% sodium ...

by MC Nahata · 1986 · Cited by 8 · Related articles

The stability of phenobarbital sodium diluted to 10 mg/mL in 0.9% sodium chloride injection was studied at an unadjusted pH (9.5) and an adjusted pH (10.0) at ...

www.medicines.org.uk › emc › product › smpc

Phenobarbital Sodium 60mg/ml Injection - Summary of ... - eMC

Each ml of solution contains 60mg of Phenobarbital Sodium ... pH = 10.0 - 11.0. 4. ... 5mg per kg body weight as a single dose by intramuscular injection.

www.sandoz.ca › Phenobarbital Product Monograph

Phenobarbital sodium injection USP - Sandoz Canada

Feb 26, 2015 — acid (to adjust pH), water for injection. Phenobarbital Sodium Injection USP contains in the following dosage forms: Solution for injection, 30 mg ...

ufdc.ufl.edu › ...

The stability of solutions of phenobarbital sodium

A 10% solution of phenobarbital sodium saturated with the free acid has a pH of ... solution of phenobarbital suitable for intramuscular injection can be made by ...

patents.google.com › patent

WO2017085687A1 - Stable formulation of phenobarbital ...

Stable phenobarbital sodium solutions for injection that do not generate ... mg/mL and have a pH of between 9 and 12 which is adjusted to that range by adding ...

www.rxlist.com › nembutal-drug

Nembutal (Pentobarbital): Uses, Dosage, Side Effects ... - RxList

2 days ago — NEMBUTAL Sodium Solution (pentobarbital sodium injection) is a ... The pH is adjusted to approximately 9.5 with hydrochloric acid and/or ...

publications.iarc.fr › ...publications › media › download

Phenobarbital and its Sodium Salt - IARC Publications

by DCASR Nos · Related articles
solution of an equivalent quantity of sodium hydroxide and evaporating at low temper- ... It is given by slow intravenous injection for control of acute convulsive ... NOEA, 40 or 50 mg/kg bw, ip (18 h after PN); 1 week, PB 0.05% with choline-

www.fshealth.gov.za › Statistics › DWoods › Minutes

PHENOBARBITONE/PHENOBARBITONE SODIUM

Phenobarbitone sodium is very soluble in water (1 in 3) and soluble in alcohol (1 in 25) ... precipitated from solutions of phenobarbitone sodium depending on the pH ... Phenobarbitone sodium injection is usually formulated with ethanol and ...

patents.justia.com › patent

US Patent for Stable formulation of phenobarbital sodium ...

Feb 27, 2018 — Stable phenobarbital sodium solutions for injection that do not ... and antioxidants in order to form stable solutions at pH values of 5 to 8.

Searches related to pH of sodium phenobarbital injection solution

phenobarbital sodium injection	phenobarbital **dilution in normal saline**
phenobarbital **intramuscular** injection	**phenobarbitone** injection **1mg**
phenobarbital **iv dilution**	phenobarbital injection **200mg 2ml**
phenobarbital solution	phenobarbital **iv push dilution**

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Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	271,244	(A61K9/19 or A61K9/00 or A61K31/515).ipc.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:44
L2	540	1 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:44
L3	67	2 and (adding same water) same lyophiliz$3	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:46
L4	46	3 and water same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:47
L5	22	4 and (reconstitute or dissolve) same water	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:48
L6	8	5 and (saline or dextrose) same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:49
L7	1	6 and Phenobarbital	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2021/02/18 12:50

2/18/2021 12:58:56 PM
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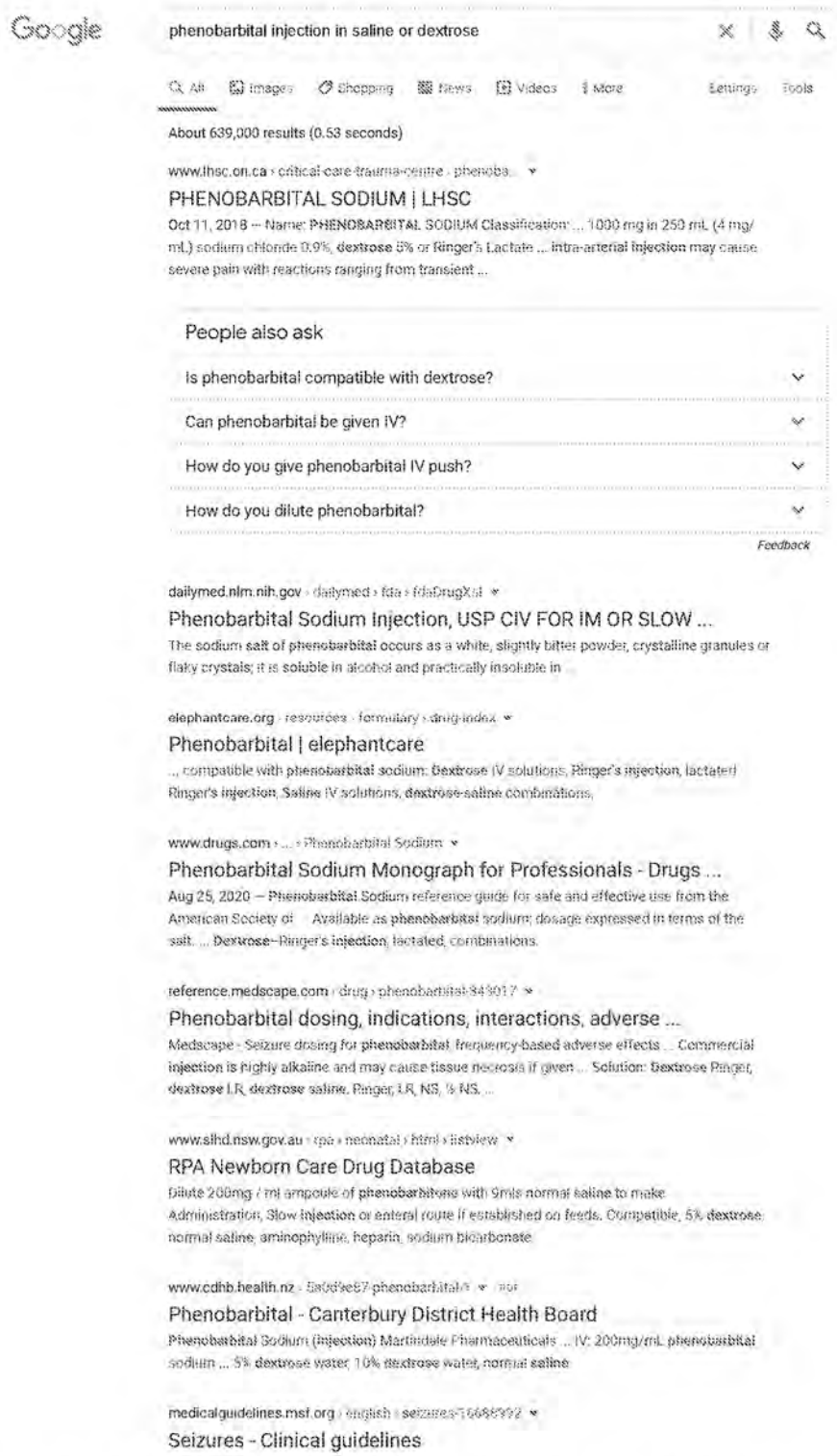
EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	145,382	(A61K9/19 or A61K9/0019 or A61K31/515).cpc.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
L6	856	L5 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
L7	514	L6 and water same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
L8	210	L7 and (ssaline or dextrose) same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
L9	303	L7 and (saline or dextrose) same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:57
L10	0	9 and (Phenobarbital adj Sodium)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:58
L11	9	9 and Phenobarbital	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:58
L12	9	11 and (lyophilized or lyophilizing or lyophilize)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:59
L13	7	12 and (reconstitute or dissolve)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 15:00
S1	2	amorphous same (Phenobarbital adj Sodium)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:03
S2	145,382	(A61K9/19 or A61K9/0019 or A61K31/515).cpc.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:20
S3	856	S2 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:22
S4	514	S3 and water same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:22

S5	3	S4 and water same (sparged near4 nitrogen)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:23

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www.lhsc.on.ca › critical-care-trauma-centre › phenoba...
PHENOBARBITAL SODIUM | LHSC
Oct 11, 2018 — Name: PHENOBARBITAL SODIUM Classification: ... 1000 mg in 250 mL (4 mg/mL) sodium chloride 0.9%, dextrose 5% or Ringer's Lactate ... Intra-arterial injection may cause severe pain with reactions ranging from transient ...
People also ask
Is phenobarbital compatible with dextrose?
Can phenobarbital be given IV?
How do you give phenobarbital IV push?
How do you dilute phenobarbital?
Feedback
dailymed.nlm.nih.gov › dailymed › fda › fdaDrugXsl
Phenobarbital Sodium Injection, USP CIV FOR IM OR SLOW ...
The sodium salt of phenobarbital occurs as a white, slightly bitter powder, crystalline granules or flaky crystals; it is soluble in alcohol and practically insoluble in ...
elephantcare.org › resources › formulary › drug-index
Phenobarbital | elephantcare
... compatible with phenobarbital sodium: Dextrose IV solutions, Ringer's injection, lactated Ringer's injection, Saline IV solutions, dextrose-saline combinations.
www.drugs.com › ... › Phenobarbital Sodium
Phenobarbital Sodium Monograph for Professionals - Drugs ...
Aug 25, 2020 — Phenobarbital Sodium reference guide for safe and effective use from the American Society of ... Available as phenobarbital sodium; dosage expressed in terms of the salt. ... Dextrose-Ringer's injection, lactated, combinations.
reference.medscape.com › drug › phenobarbital-343017
Phenobarbital dosing, indications, interactions, adverse ...
Medscape - Seizure dosing for phenobarbital, frequency-based adverse effects ... Commercial injection is highly alkaline and may cause tissue necrosis if given ... Solution: Dextrose Ringer, dextrose LR, dextrose saline, Ringer, LR, NS, ½ NS, ...
www.slhd.nsw.gov.au › rpa › neonatal › html › listview
RPA Newborn Care Drug Database
Dilute 200mg / ml ampoule of phenobarbitone with 9mls normal saline to make ... Administration, Slow injection or enteral route if established on feeds. Compatible, 5% dextrose, normal saline, aminophylline, heparin, sodium bicarbonate
www.cdhb.health.nz › 5a0d9e87-phenobarbital-i... › pdf
Phenobarbital - Canterbury District Health Board
Phenobarbital Sodium (Injection) Martindale Pharmaceuticals ... IV: 200mg/mL phenobarbital sodium ... 5% dextrose water, 10% dextrose water, normal saline
medicalguidelines.msf.org › english › seizures-16688992
Seizures - Clinical guidelines

Child weighing 8 kg: 120 mg (15 mg x 8 kg), i.e. 0.6 ml of phenobarbital in 20 ml
Hypoglycaemia: administer glucose by slow IV injection to all patients who do ...

publications.iarc.fr › publications › media › download PDF

Phenobarbital and its Sodium Salt - IARC Publications

Synonyms: 5-Ethyl-5-phenylbarbituric acid sodium; phenobarbital sodium; pheno- barbitone sodium ... G6PDH, glucose 6-phosphate dehydrogenase ... barbital (38 newborn mice) or a single intraperitoneal injection of saline alone (24
by DCASR Nos - Related articles

gh.bmj.com › embed › inline-supplementary-material-2

Neonatal Drug Formulary

D5, 5 % dextrose - NS, 0.9% saline ... Intravenous (IV): Slow IV injection over 3-5 minutes ... Vial, 1000mg (1g) powder for injection. Dose: ... 10% or 5% Dextrose (D5 or D10) ... Neonatal seizures NOT responding to phenobarbitone alone.

Searches related to phenobarbital injection in saline or dextrose

phenobarbital **dilution** in **normal** saline	**how to dilute** phenobarbital
phenobarbital **iv push dilution**	phenobarbital **sodium** injection
phenobarbital **intramuscular** injection	phenobarbital **iv push alcohol withdrawal**
phenobarbital **iv push administration**	phenobarbital injection **dose**

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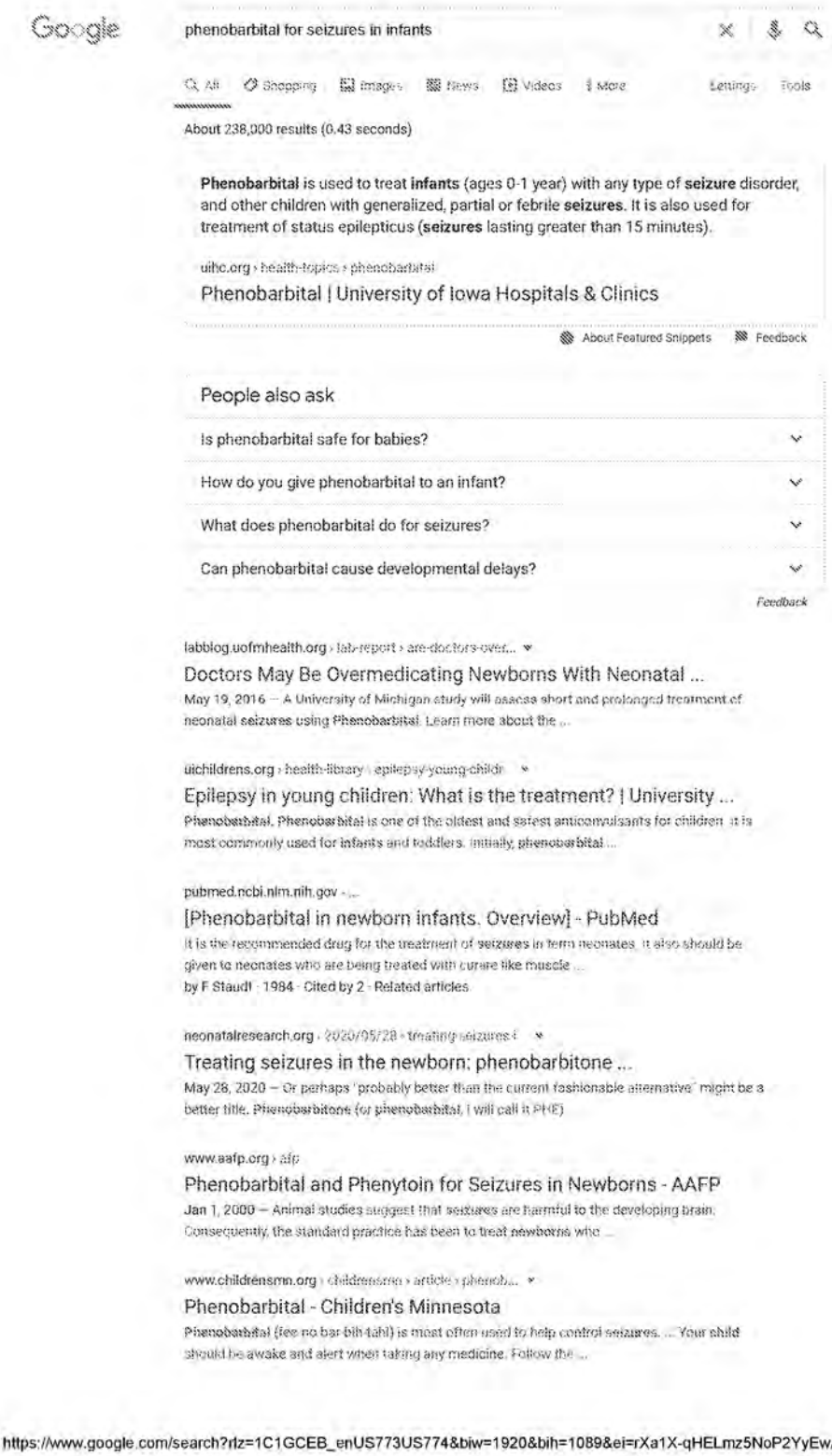
EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L6	0	Nivagen adj pharmaceuticals.AS.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 11:58
L7	1	NIVAGEN adj pharmaceuticals	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 11:59
L8	25	(Chodavarapu adj Bala or Mangali adj Thirupathi or Shukla adj Jay or Shukla adj Anand or Lakkaraju adj Dasaradhi).IN.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 12:02
L9	0	8 and (Phenobarbital adj Sodium)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 12:03
L10	0	8 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/23 12:03
S1	2	amorphous same (Phenobarbital adj Sodium)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:03
S2	145,382	(A61K9/19 or A61K9/0019 or A61K31/515).cpc.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:20
S3	856	S2 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:22
S4	514	S3 and water same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:22
S5	3	S4 and water same (sparged near4 nitrogen)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 13:23
S6	145,382	(A61K9/19 or A61K9/0019 or A61K31/515).cpc.	US-PGPUB; USPAT; FPRS;	OR	OFF	2020/11/18 14:56

			EPO; JPO; DERWENT			
S7	856	S6 and amorphous same lyophilized	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
S8	514	S7 and water same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
S9	210	S8 and (ssaline or dextrose) same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:56
S10	303	S8 and (saline or dextrose) same injection	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:57
S11	0	S10 and (Phenobarbital adj Sodium)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:58
S12	9	S10 and Phenobarbital	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:58
S13	9	S12 and (lyophilized or lyophilizing or lyophilize)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 14:59
S14	7	S13 and (reconstitute or dissolve)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT	OR	OFF	2020/11/18 15:00

11/23/2020 12:04:00 PM
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phenobarbital for seizures in infants
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Phenobarbital is used to treat infants (ages 0-1 year) with any type of seizure disorder, and other children with generalized, partial or febrile seizures. It is also used for treatment of status epilepticus (seizures lasting greater than 15 minutes).
uihc.org › health-topics › phenobarbital
Phenobarbital | University of Iowa Hospitals & Clinics
About Featured Snippets
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People also ask
Is phenobarbital safe for babies?
How do you give phenobarbital to an infant?
What does phenobarbital do for seizures?
Can phenobarbital cause developmental delays?
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labblog.uofmhealth.org › lab-report › are-doctors-over...
Doctors May Be Overmedicating Newborns With Neonatal ...
May 19, 2016 — A University of Michigan study will assess short and prolonged treatment of neonatal seizures using Phenobarbital. Learn more about the ...
uichildrens.org › health-library › epilepsy-young-childr...
Epilepsy in young children: What is the treatment? | University ...
Phenobarbital. Phenobarbital is one of the oldest and safest anticonvulsants for children. It is most commonly used for infants and toddlers. Initially, phenobarbital ...
pubmed.ncbi.nlm.nih.gov › ...
[Phenobarbital in newborn infants. Overview] - PubMed
It is the recommended drug for the treatment of seizures in term neonates. It also should be given to neonates who are being treated with curare like muscle ...
by F Staudt · 1984 · Cited by 2 · Related articles
neonatalresearch.org › 2020/05/28 › treating-seizures-t...
Treating seizures in the newborn: phenobarbitone ...
May 28, 2020 — Or perhaps "probably better than the current fashionable alternative" might be a better title. Phenobarbitone (or phenobarbital, I will call it PHE)
www.aafp.org › afp
Phenobarbital and Phenytoin for Seizures in Newborns - AAFP
Jan 1, 2000 — Animal studies suggest that seizures are harmful to the developing brain. Consequently, the standard practice has been to treat newborns who ...
www.childrensmn.org › childrensmn › article › pheno...
Phenobarbital - Children's Minnesota
Phenobarbital (fee no bar bih tahl) is most often used to help control seizures. ... Your child should be awake and alert when taking any medicine. Follow the ...

www.medicinesforchildren.org.uk › phenobarbital-prev... ▾

Phenobarbital for preventing seizures | Medicines for Children

Dec 9, 2011 — How should I give it? Tablets should be swallowed whole with a glass of water, milk or juice. Your child should not chew the tablet. You can ...

www.epilepsy.com › phenobarbital › advanced ▾

Phenobarbital | Epilepsy Foundation

It has traditionally been considered the first choice to treat neonatal seizures (seizures in newborn infants). Most studies have found that phenobarbital controls ...

www.aboutkidshealth.ca › Article ▾

Phenobarbital - AboutKidsHealth

Mar 13, 2010 — Your child needs to take the medicine called phenobarbital. ... It's a medication used to control or prevent certain types of seizures. You may ...

Searches related to phenobarbital for seizures in infants

phenobarbital **infant dosage**	phenobarbital for **infant jaundice**
long-term effects of phenobarbital in infants	phenobarbital **side effects**
phenobarbital **infant development**	**newborn** seizures **treatment**
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Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	84,538	lyophilized and (phenobarbital sodium)	USPAT	OR	OFF	2022/03/15 12:10
S2	78,236	S1 and pH	USPAT	OR	OFF	2022/03/15 12:10
S3	11,050	S2 not (organic solvent)	USPAT	OR	OFF	2022/03/15 12:11
S4	11,046	S3 and (sodium chloride)	USPAT	OR	OFF	2022/03/15 12:11
S5	3,053	S4 and freez?	USPAT	OR	OFF	2022/03/15 12:11
S6	0	S5 and dry?	USPAT	OR	OFF	2022/03/15 12:12
S7	1,255	S5 and drying	USPAT	OR	OFF	2022/03/15 12:12
S8	103	S7 and amorphous	USPAT	OR	OFF	2022/03/15 12:12
S9	47	S8 and vacuum	USPAT	OR	OFF	2022/03/15 12:12
S10	47	S9 and temperature	USPAT	OR	OFF	2022/03/15 12:13
S11	41	S10 and (moisture content)	USPAT	OR	OFF	2022/03/15 12:13
S12	35	S11 and storage	USPAT	OR	OFF	2022/03/15 12:14
S13	15	S12 and A61K 9/19.ccls.	USPAT	OR	OFF	2022/03/15 12:14
S14	15	S13 and A61K 31/515.CCLS.	USPAT	OR	OFF	2022/03/15 12:15

3/15/2022 6:37:59 PM
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Web Search History

date, time	web site	search string
3/15/2022 12:08:08 PM	Google	lyophilized phenobarbital sodium water pH freezing drying vacuum pressure

Application ID:	17025881
Application Reached PTAB	No
Effective Filing Date	06/28/19
Rush Requested	No
Description	A pharmaceutical composition comprising a storage-stable powder form of lyophilized amorphous Phenobarbital Sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, wherein the storage-stable powder form of lyophilized amorphous Phenobarbital Sodium is produced by: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution with a pH at or between 9.3 to 9.6; and lyophilizing the Phenobarbital Sodium solution to produce the storage-stable powder form of lyophilized amorphous Phenobarbital Sodium with water content at or below 1.1%, wherein the lyophilizing comprises freezing, evacuating, and primary drying at a temperature below 0 °C, followed by evacuating and secondary drying at a stable or declining temperature above 0°C.
Additional Comments:	Novelty: 1. Low impurity: no more than 0.2% phenylethylacetylurea (PEAU); 2. Low water content: at or below 1.1%; 3. Narrow pH: at or between 9.3 to 9.6 Thanks.

1

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L1            1 SEA ABB=ON  PLU=ON  "PHENOBARBITAL SODIUM"/CN
                SEL L1 CHEM
L2              QUE ABB=ON  PLU=ON  ("GARDENAL SODIUM"/BI OR LINASEN/BI OR
                "LUMINAL SODIUM"/BI OR PHENEMALUM/BI OR "PHENOBAL SODIUM"/B
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                "SODIUM LUMINAL"/BI OR "SODIUM PHENOBARBITAL"/BI OR
                "SODIUM PHENOBARBITONE"/BI OR "SODIUM PHENYLETHYLBARBITURAT
                E"/BI OR "SODIUM PHENYLETHYLMALONYLUREA"/BI OR "SODIUM
                5-ETHYL-5-PHENYLBARBITURATE"/BI OR "SOL PHENOBARBITAL"/BI
                OR "SOL PHENOBARBITONE"/BI OR "SOLUBLE PHENOBARBITAL"/BI
                OR "SOLUBLE PHENOBARBITONE"/BI OR 125-36-0/BI OR "5-ETHYL-5
                -PHENYLBARBITURIC ACID SODIUM"/BI OR 57-30-7/BI OR
                8050-96-2/BI)


                E PHENYLETHYLACETYLUREA/CN
L4            1 SEA ABB=ON  PLU=ON  PHENYLETHYLACETYLUREA/CN
                SEL L4 CHEM
L5              QUE ABB=ON  PLU=ON  (.ALPHA.-PHENYL-.ALPHA.-ETHYLACETYLUREA
                /BI OR "(2-PHENYLBUTANOYL)UREA"/BI OR BENURIDE/BI OR
                DL-PHENETURIDE/BI OR EPA/BI OR ETHYLPHENACEMIDE/BI OR
                LIRCAPYL/BI OR "M 551"/BI OR "N-(.ALPHA.-PHENYLBUTYRYL)UREA
                "/BI OR "N-(AMINOCARBONYL)-.ALPHA.-ETHYLBENZENEACETAMIDE"/B
                I OR PBU/BI OR PHENETURIDE/BI OR PHENURIDE/BI OR PHENYLETHY
                LACETYLUREA/BI OR "S 46"/BI OR "1-((ETHYL)PHENYLACETYL)UREA
                "/BI OR 2-PHENYLBUTYRYLUREA/BI OR 6509-31-5/BI OR 90-49-3/BI)

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L1            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PHENOBARBITAL SODIUM"/CN
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                OR "LUMINAL SODIUM"/BI OR PHENEMALUM/BI OR "PHENOBAL SODI
                UM"/BI OR PHENOBAL/BI OR "PHENOBARBITAL SODIUM"/BI OR "PH
                ENOBARBITONE SODIUM"/BI OR "SODIUM ETHYLPHENYLBARBITURATE
                "/BI OR "SODIUM LUMINAL"/BI OR "SODIUM PHENOBARBITAL"/BI
                OR "SODIUM PHENOBARBITONE"/BI OR "SODIUM PHENYLETHYLBARBI
                TURATE"/BI OR "SODIUM PHENYLETHYLMALONYLUREA"/BI OR "SODI
                UM 5-ETHYL-5-PHENYLBARBITURATE"/BI OR "SOL PHENOBARBITAL"
                /BI OR "SOL PHENOBARBITONE"/BI OR "SOLUBLE PHENOBARBITAL"
                /BI OR "SOLUBLE PHENOBARBITONE"/BI OR 125-36-0/BI OR "5-E
                THYL-5-PHENYLBARBITURIC ACID SODIUM"/BI OR 57-30-7/BI OR
                8050-96-2/BI)
L3        36479 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR L2 OR PHENOBARBITAL(
                1W)(?SODIUM? OR NA) OR GARDENAL OR HYSTEP## OR LUMINAL OR
                PHENEMAL OR PHENOBARTITONE OR PHENYLBARBITAL OR PHENYLETHYL
                BARBITURIC OR (PHENYL OR PH)(W)(BARBITAL OR ETHYLBARBITURIC
                 OR (ETHYL OR ET)(W)BARBITURIC)
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENYLETHYLACETYLUREA/CN
L5              QUE  ABB=ON  PLU=ON  (.ALPHA.-PHENYL-.ALPHA.-ETHYLACETYLU
                REA/BI OR "(2-PHENYLBUTANOYL)UREA"/BI OR BENURIDE/BI OR D
                L-PHENETURIDE/BI OR EPA/BI OR ETHYLPHENACEMIDE/BI OR LIRC
                APYL/BI OR "M 551"/BI OR "N-(.ALPHA.-PHENYLBUTYRYL)UREA"/
                BI OR "N-(AMINOCARBONYL)-.ALPHA.-ETHYLBENZENEACETAMIDE"/B
                I OR PBU/BI OR PHENETURIDE/BI OR PHENURIDE/BI OR PHENYLET
                HYLACETYLUREA/BI OR "S 46"/BI OR "1-((ETHYL)PHENYLACETYL)
                UREA"/BI OR 2-PHENYLBUTYRYLUREA/BI OR 6509-31-5/BI OR 90-
                49-3/BI)
L6          115 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PEAU OR PHENYLETHYLACETYLU
                REA OR (PHENYL OR PH)(W)(ETHYLACETYLUREA OR (ETHYL OR
                ET)(W)(ACETYLUREA OR (AC OR ACETYL)(W)UREA) OR PHENYLETHYL(
                W)(ACETYLUREA OR (AC OR ACETYL)(W)UREA)) OR PHENYLETHYLACET
                YL UREA OR BENURIDE
L7           80 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (ETHYL OR ET)(W)(PHENACEMI
                DE OR PHENYLACETYLUREA OR (PHENYL OR PH)(W)(ACETYLUREA OR
                (ACETYL OR AC)(W)UREA)) OR ETHYLPHENYLACETYLUREA OR
                PHENETURIDE
L8           44 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND (L6 OR L7 OR L4 OR
                L5)
L9            7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND (POWDER? OR
                GRANUL?)
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L1            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "PHENOBARBITAL SODIUM"/CN
L2              QUE  ABB=ON  PLU=ON  ("GARDENAL SODIUM"/BI OR LINASEN/BI
                OR "LUMINAL SODIUM"/BI OR PHENEMALUM/BI OR "PHENOBAL SODI
                UM"/BI OR PHENOBAL/BI OR "PHENOBARBITAL SODIUM"/BI OR "PH
                ENOBARBITONE SODIUM"/BI OR "SODIUM ETHYLPHENYLBARBITURATE
                "/BI OR "SODIUM LUMINAL"/BI OR "SODIUM PHENOBARBITAL"/BI
                OR "SODIUM PHENOBARBITONE"/BI OR "SODIUM PHENYLETHYLBARBI
                TURATE"/BI OR "SODIUM PHENYLETHYLMALONYLUREA"/BI OR "SODI
                UM 5-ETHYL-5-PHENYLBARBITURATE"/BI OR "SOL PHENOBARBITAL"
                /BI OR "SOL PHENOBARBITONE"/BI OR "SOLUBLE PHENOBARBITAL"
                /BI OR "SOLUBLE PHENOBARBITONE"/BI OR 125-36-0/BI OR "5-E
                THYL-5-PHENYLBARBITURIC ACID SODIUM"/BI OR 57-30-7/BI OR
                8050-96-2/BI)
L3        36479 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 OR L2 OR PHENOBARBITAL(
                1W)(?SODIUM? OR NA) OR GARDENAL OR HYSTEP## OR LUMINAL OR
                PHENEMAL OR PHENOBARTITONE OR PHENYLBARBITAL OR PHENYLETHYL
                BARBITURIC OR (PHENYL OR PH)(W)(BARBITAL OR ETHYLBARBITURIC
                 OR (ETHYL OR ET)(W)BARBITURIC)
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENYLETHYLACETYLUREA/CN
L5              QUE  ABB=ON  PLU=ON  (.ALPHA.-PHENYL-.ALPHA.-ETHYLACETYLU
                REA/BI OR "(2-PHENYLBUTANOYL)UREA"/BI OR BENURIDE/BI OR D
                L-PHENETURIDE/BI OR EPA/BI OR ETHYLPHENACEMIDE/BI OR LIRC
                APYL/BI OR "M 551"/BI OR "N-(.ALPHA.-PHENYLBUTYRYL)UREA"/
                BI OR "N-(AMINOCARBONYL)-.ALPHA.-ETHYLBENZENEACETAMIDE"/B
                I OR PBU/BI OR PHENETURIDE/BI OR PHENURIDE/BI OR PHENYLET
                HYLACETYLUREA/BI OR "S 46"/BI OR "1-((ETHYL)PHENYLACETYL)
                UREA"/BI OR 2-PHENYLBUTYRYLUREA/BI OR 6509-31-5/BI OR 90-
                49-3/BI)
L6          115 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PEAU OR PHENYLETHYLACETYLU
                REA OR (PHENYL OR PH)(W)(ETHYLACETYLUREA OR (ETHYL OR
```

		ET)(W)(ACETYLUREA OR (AC OR ACETYL)(W)UREA) OR PHENYLETHYL(W)(ACETYLUREA OR (AC OR ACETYL)(W)UREA)) OR PHENYLETHYLACET YL UREA OR BENURIDE
L7	80	SEA FILE=HCAPLUS ABB=ON PLU=ON (ETHYL OR ET)(W)(PHENACEMI DE OR PHENYLACETYLUREA OR (PHENYL OR PH)(W)(ACETYLUREA OR (ACETYL OR AC)(W)UREA)) OR ETHYLPHENYLACETYLUREA OR PHENETURIDE
L8	44	SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (L6 OR L7 OR L4 OR L5)
L10	8	SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND (PH OR (H OR HYDROGEN)(5W)(CONCENTRATION OR CONC##))

L1	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PHENOBARBITAL SODIUM"/CN
L2		QUE ABB=ON PLU=ON ("GARDENAL SODIUM"/BI OR LINASEN/BI OR "LUMINAL SODIUM"/BI OR PHENEMALUM/BI OR "PHENOBAL SODI UM"/BI OR PHENOBAL/BI OR "PHENOBARBITAL SODIUM"/BI OR "PH ENOBARBITONE SODIUM"/BI OR "SODIUM ETHYLPHENYLBARBITURATE "/BI OR "SODIUM LUMINAL"/BI OR "SODIUM PHENOBARBITAL"/BI OR "SODIUM PHENOBARBITONE"/BI OR "SODIUM PHENYLETHYLBARBI TURATE"/BI OR "SODIUM PHENYLETHYLMALONYLUREA"/BI OR "SODI UM 5-ETHYL-5-PHENYLBARBITURATE"/BI OR "SOL PHENOBARBITAL" /BI OR "SOL PHENOBARBITONE"/BI OR "SOLUBLE PHENOBARBITAL" /BI OR "SOLUBLE PHENOBARBITONE"/BI OR 125-36-0/BI OR "5-E THYL-5-PHENYLBARBITURIC ACID SODIUM"/BI OR 57-30-7/BI OR 8050-96-2/BI)
L3	36479	SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR L2 OR PHENOBARBITAL(1W)(?SODIUM? OR NA) OR GARDENAL OR HYSTEP## OR LUMINAL OR PHENEMAL OR PHENOBARTITONE OR PHENYLBARBITAL OR PHENYLETHYL BARBITURIC OR (PHENYL OR PH)(W)(BARBITAL OR ETHYLBARBITURIC OR (ETHYL OR ET)(W)BARBITURIC)
L4	1	SEA FILE=REGISTRY ABB=ON PLU=ON PHENYLETHYLACETYLUREA/CN
L5		QUE ABB=ON PLU=ON (.ALPHA.-PHENYL-.ALPHA.-ETHYLACETYLU REA/BI OR "(2-PHENYLBUTANOYL)UREA"/BI OR BENURIDE/BI OR D L-PHENETURIDE/BI OR EPA/BI OR ETHYLPHENACEMIDE/BI OR LIRC APYL/BI OR "M 551"/BI OR "N-(.ALPHA.-PHENYLBUTYRYL)UREA"/ BI OR "N-(AMINOCARBONYL)-.ALPHA.-ETHYLBENZENEACETAMIDE"/B I OR PBU/BI OR PHENETURIDE/BI OR PHENURIDE/BI OR PHENYLET HYLACETYLUREA/BI OR "S 46"/BI OR "1-((ETHYL)PHENYLACETYL) UREA"/BI OR 2-PHENYLBUTYRYLUREA/BI OR 6509-31-5/BI OR 90-49-3/BI)
L6	115	SEA FILE=HCAPLUS ABB=ON PLU=ON PEAU OR PHENYLETHYLACETYLU REA OR (PHENYL OR PH)(W)(ETHYLACETYLUREA OR (ETHYL OR ET)(W)(ACETYLUREA OR (AC OR ACETYL)(W)UREA) OR PHENYLETHYL(W)(ACETYLUREA OR (AC OR ACETYL)(W)UREA)) OR PHENYLETHYLACET YL UREA OR BENURIDE
L7	80	SEA FILE=HCAPLUS ABB=ON PLU=ON (ETHYL OR ET)(W)(PHENACEMI DE OR PHENYLACETYLUREA OR (PHENYL OR PH)(W)(ACETYLUREA OR (ACETYL OR AC)(W)UREA)) OR ETHYLPHENYLACETYLUREA OR PHENETURIDE
L8	44	SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (L6 OR L7 OR L4 OR L5)
L11	30	SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND (COMPOSITION OR COMP## OR PREP? OR FORMULATION OR SOLUTION OR SOLN OR MIXTURE)

L1	1	SEA FILE=REGISTRY ABB=ON PLU=ON "PHENOBARBITAL SODIUM"/CN
L2		QUE ABB=ON PLU=ON ("GARDENAL SODIUM"/BI OR LINASEN/BI OR "LUMINAL SODIUM"/BI OR PHENEMALUM/BI OR "PHENOBAL SODI UM"/BI OR PHENOBAL/BI OR "PHENOBARBITAL SODIUM"/BI OR "PH ENOBARBITONE SODIUM"/BI OR "SODIUM ETHYLPHENYLBARBITURATE "/BI OR "SODIUM LUMINAL"/BI OR "SODIUM PHENOBARBITAL"/BI OR "SODIUM PHENOBARBITONE"/BI OR "SODIUM PHENYLETHYLBARBI TURATE"/BI OR "SODIUM PHENYLETHYLMALONYLUREA"/BI OR "SODI UM 5-ETHYL-5-PHENYLBARBITURATE"/BI OR "SOL PHENOBARBITAL" /BI OR "SOL PHENOBARBITONE"/BI OR "SOLUBLE PHENOBARBITAL" /BI OR "SOLUBLE PHENOBARBITONE"/BI OR 125-36-0/BI OR "5-E THYL-5-PHENYLBARBITURIC ACID SODIUM"/BI OR 57-30-7/BI OR 8050-96-2/BI)
L3	36479	SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR L2 OR PHENOBARBITAL(1W)(?SODIUM? OR NA) OR GARDENAL OR HYSTEP## OR LUMINAL OR PHENEMAL OR PHENOBARTITONE OR PHENYLBARBITAL OR PHENYLETHYL

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                BARBITURIC OR (PHENYL OR PH)(W)(BARBITAL OR ETHYLBARBITURIC
                 OR (ETHYL OR ET)(W)BARBITURIC)
L4            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  PHENYLETHYLACETYLUREA/CN
L5              QUE  ABB=ON  PLU=ON  (.ALPHA.-PHENYL-.ALPHA.-ETHYLACETYLU
                REA/BI OR "(2-PHENYLBUTANOYL)UREA"/BI OR BENURIDE/BI OR D
                L-PHENETURIDE/BI OR EPA/BI OR ETHYLPHENACEMIDE/BI OR LIRC
                APYL/BI OR "M 551"/BI OR "N-(.ALPHA.-PHENYLBUTYRYL)UREA"/
                BI OR "N-(AMINOCARBONYL)-.ALPHA.-ETHYLBENZENEACETAMIDE"/B
                I OR PBU/BI OR PHENETURIDE/BI OR PHENURIDE/BI OR PHENYLET
                HYLACETYLUREA/BI OR "S 46"/BI OR "1-((ETHYL)PHENYLACETYL)
                UREA"/BI OR 2-PHENYLBUTYRYLUREA/BI OR 6509-31-5/BI OR 90-
                49-3/BI)
L6          115 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PEAU OR PHENYLETHYLACETYLU
                REA OR (PHENYL OR PH)(W)(ETHYLACETYLUREA OR (ETHYL OR
                ET)(W)(ACETYLUREA OR (AC OR ACETYL)(W)UREA) OR PHENYLETHYL(
                W)(ACETYLUREA OR (AC OR ACETYL)(W)UREA)) OR PHENYLETHYLACET
                YL UREA OR BENURIDE
L7           80 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (ETHYL OR ET)(W)(PHENACEMI
                DE OR PHENYLACETYLUREA OR (PHENYL OR PH)(W)(ACETYLUREA OR
                (ACETYL OR AC)(W)UREA)) OR ETHYLPHENYLACETYLUREA OR
                PHENETURIDE
L8           44 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 AND (L6 OR L7 OR L4 OR
                L5)
L12           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L8 AND (LYOPHILIS? OR
                LYOPHILIZ? OR FREEZ?)



L13        2137 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "PHENOBARBITAL SODIUM"+PFT
                /CT
L14         191 SEA FILE=HCAPLUS ABB=ON  PLU=ON  PHENETURIDE+PFT/CT
L15          11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 AND L14



L16          33 SEA ABB=ON  PLU=ON  (L9 OR L10 OR L11 OR L12) OR L15
L17          31 SEA ABB=ON  PLU=ON  L16 AND (PY<2019 OR AY<2019 OR
                PRY<2019)
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Ans. set limited to patent/non-patent citations dated prior to 2019

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L17  ANSWER 1 OF 31  HCAPLUS  COPYRIGHT 2021 ACS on STN
ED   Entered STN:  12 Feb 2021
ACCESSION NUMBER:         2021:365999  HCAPLUS Full-text
DOCUMENT NUMBER:          174:490232
TITLE:                    Preparation of substituted
                          pyrrolo[2,3-b]pyridines for suppressing toxic
                          endoplasmic reticulum stress
INVENTOR(S):              Stockwell, Brent R.; Wichterle, Hynek; Bos,
                          Pieter; Zask, Arie; Thams, Sebastian; Lowry, Emily
                          Rohdes
PATENT ASSIGNEE(S):       The Trustees of Columbia University in the City of
                          New York, USA
SOURCE:                   U.S. Pat. Appl. Publ., 281pp., Cont.-in-part of
                          Appl. No. PCT/US2019/020362.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:
     PATENT NO.          KIND  DATE        APPLICATION NO.          DATE
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     US 20210040091       A1   20210211    US 2020-17009450         20200901

     WO 2019169306        A1   20190906    WO 2019-US20362          20190301

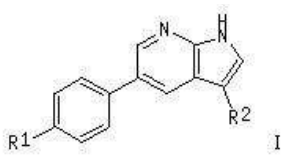
PRIORITY APPLN. INFO.:                     US 2018-62637242      P  20180301

                                           WO 2019-US20362       A2 20190301

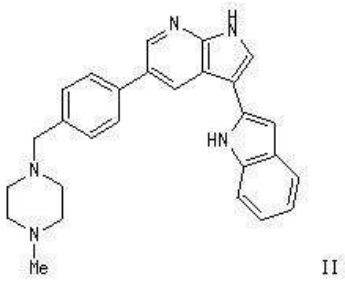
PATENT STATUS PATENT INFORMATION:
     PATENT NO.          KIND  STATUS          STATUS DATE
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     US 20210040091       A1   Alive           20210218
     WO 2019169306        A1   Alive           20201220
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
```

5

OTHER SOURCE(S): CASREACT 174:490232; MARPAT 174:490232
GI



I



II

AB The present invention provides, inter alia, a **compd**. I [R1 = (un)substituted alkyl-heterocycloalkyl or alkyl-heterobicycloalkyl; R2 = (un)substituted **Ph**, indolyl, pyridyl, etc.; with the proviso] or an N-oxide, cryst. form, hydrate, or a pharmaceutically acceptable salt thereof. E.g., a multi-step synthesis of II, starting from 5-bromo-1H-pyrrolo[2,3-b]pyridine and 4-formylphenylboronic acid, was described. Exemplified **compds**. I were tested for their ability to inhibit MAP4K4 (data given). Also provided are **compns**. contg. a pharmaceutically acceptable carrier and one or more **compds**. I. Further provided are methods for treating or ameliorating the effects of a disorder in a subject, methods of suppressing the toxicity of endoplasmic reticulum (ER) stress in a subject, methods of treating or ameliorating the effects of a disease involving axon degeneration in a subject, and methods for treating or ameliorating the effects of a neurodegenerative disease.

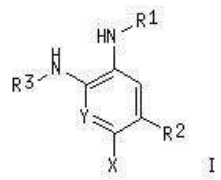
L17 ANSWER 2 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 04 Jun 2020
ACCESSION NUMBER: 2020:1067837 HCAPLUS Full-text
DOCUMENT NUMBER: 173:97280
TITLE: Compounds, **compositions**, and methods for modulating ferroptosis and treating excitotoxic disorders
INVENTOR(S): Stockwell, Brent R.; Zask, Arie; Tan, Hui; Daniels, Jacob
PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, USA
SOURCE: PCT Int. Appl., 179pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2020113028	A1	20200604	WO 2019-US63640		20191127
AU 2019390478	A1	20210708	AU 2019-390478		20191127
CN 113286777	A	20210820	CN 2019-80087314		20191127
PRIORITY APPLN. INFO.:			US 2018-62771841	P	20181127
			WO 2019-US63640	W	20191127

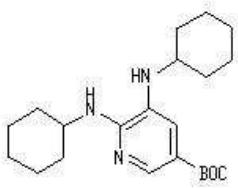
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2020113028	A1	Alive	20201203

AU 2019390478 A1 Alive 20210715
OTHER SOURCE(S): CASREACT 173:97280; MARPAT 173:97280
GI



I



II

AB The disclosure provides **compds**. of formula I, wherein R1 is H, (un)substituted alkyl, (un)substituted aryl, etc.; R2 is (un)substituted oxazolyl, (un)substituted oxadiazolyl, (un)substituted amido, etc.; R3 is (un)substituted C3-12 carbocyclyl, (un)substituted polyynyl; X is H, (un)substituted alkyl, halo; Y is CH and N; with the proviso that when R1 and X are both H, Y is CH and R3 is cyclohexyl, R2 cannot be COOEt; and N-oxides, cryst. forms, hydrates, or pharmaceutically acceptable salts thereof, are claimed. Also provided are **compns**. contg. a pharmaceutically acceptable carrier and one or more **compds**. according to the present disclosure. Further provided are methods for treating or ameliorating the effects of an excitotoxic disorder in a subject, methods of modulating ferroptosis in a subject, methods of reducing reactive oxygen species (ROS) in a cell, methods for treating or ameliorating the effects of a neurodegenerative disease, methods for alleviating side effects in a subject undergoing radiotherapy and/or immunotherapy, and methods for treating or ameliorating the effects of an infection assocd. with ferroptosis in a subject. Example **compd**. II was **prepd**. by a general procedure (procedure given). Biol. activities of ferrostatin-1 analogs were evaluated (some data given).
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 04 Jun 2020
ACCESSION NUMBER: 2020:1066820 HCAPLUS Full-text
DOCUMENT NUMBER: 173:83486
TITLE: **Preparation** of neuroprotective PDI modulating small molecules and methods of use thereof
INVENTOR(S): Stockwell, Brent R.; Zask, Arie; Kaplan, Anna
PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, USA
SOURCE: PCT Int. Appl., 235pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

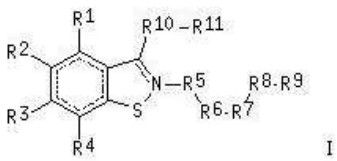
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2020113222	A1	20200604	WO 2019-US64024	20191202

PRIORITY APPLN. INFO.: US 2018-62773266 P 20181130
US 2018-62773278 P 20181130
US 2018-62773288 P 20181130
US 2019-62842038 P 20190502

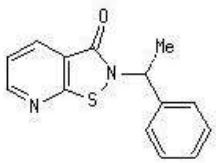
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2020113222	A1	Alive	20201203

OTHER SOURCE(S): CASREACT 173:83486; MARPAT 173:83486
GI



I



II

AB The invention relates to **compds**. of formula I, wherein dashed line is an optional double bond; X, Y, and Z are independently C, N, S and O; R1-R4 are independently H, D, O, halo, etc.; R5-R8 and R10 are independently O, CO, S, SO, etc.; R9 are R11 are independently H, O, S, SO, SO2, etc.; and N-oxides, cryst. forms, hydrates thereof, and pharmaceutically acceptable salt thereof. The present invention also provides a method for treating or ameliorating the effects of a condition assocd. with increased protein disulfide isomerase (PDI) activity and a method of modulating PDI activity in a cell. The present invention also provides **compds**., salts, **compns**. and kits useful for the provided methods. Example **compd**. II was **prepd**. by cyclization of 2-mercaptonicotinic acid with (R)-1-phenylethan-1-amine.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 30 Nov 2018
ACCESSION NUMBER: 2018:2351537 HCAPLUS Full-text
DOCUMENT NUMBER: 174:268334
TITLE: Glyphosate-based herbicide enhances the uterine sensitivity to estradiol in rats
AUTHOR(S): Schimpf, Marlise Guerrero; Milesi, Maria M.; Luque, Enrique H.; Varayoud, Jorgelina
CORPORATE SOURCE: Instituto de Salud y Ambiente del Litoral (ISAL, UNL-CONICET), Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Santa Fe, Argent.
SOURCE: Journal of Endocrinology (**2018**), 239(2), 197-213
CODEN: JOENAK; ISSN: 1479-6805
URL: https://joe.bioscientifica.com
DIGITAL OBJECT ID: 10.1530/joe-18-0207
PUBLISHER: Bioscientifica Ltd.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB In a previous work, we detected that postnatal exposure to a glyphosate-based herbicide (GBH) alters uterine development in **prepubertal** rats causing endometrial hyperplasia and increasing cell proliferation. Our goal was to det. whether exposure to low dose of a GBH during postnatal development might enhance the sensitivity of the uterus to an estrogenic treatment. Female Wistar pups were s.c. injected with saline **soln**. (control) or GBH using the ref. dose (2 mg/kg/day, **EPA**) on postnatal days (PND) 1, 3, 5 and 7. At weaning (PND21), female rats were bilaterally ovariectomized and treated with silastic capsules contg. 17β-estradiol (E2, 1 mg/mL) until they were 2 mo of age. On PND60, uterine samples were removed and processed for histol., immunohistochem. and mRNA extn. to evaluate: (i) uterine morphol., (ii) uterine cell proliferation by the detection of Ki67, (iii) the expression of the estrogen receptors alpha (ESR1) and beta (ESR2) and (iv) the expression of WNT7A and CTNNB1. GBH-exposed animals showed increased **luminal** epithelial height and stromal nuclei d. The **luminal** and glandular epithelium were markedly hyperplastic in 43% of GBH-exposed animals. GBH exposure caused an increase in E2-induced cell proliferation in assocn. with an induction of both ESR1 and ESR2. GBH treatment decreased membranous and cytoplasmic expression of CTNNB1 in **luminal** and glandular epithelial cells and increased WNT7A expression in the **luminal** epithelium. These results suggest that early postnatal exposure to a GBH enhances the sensitivity of the rat uterus to estradiol and induces histomorphol. and mol. changes assocd. with uterine hyperplasia.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE

RE FORMAT

L17 ANSWER 5 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 06 Apr 2018
ACCESSION NUMBER: 2018:701463 HCAPLUS Full-text
DOCUMENT NUMBER: 168:404869
TITLE: Small molecule oxidizers of protein disulfide isomerase (PDI) and their use for treating neurodegenerative disorder
INVENTOR(S): Stockwell, Brent R.; Kaplan, Anna
PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, USA
SOURCE: U.S. Pat. Appl. Publ., 136 pp., Cont.-in-part of Appl. No. PCT/US2016/014149.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

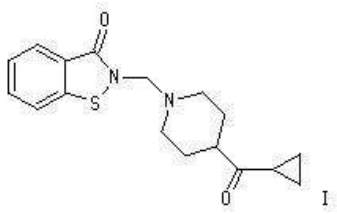
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20180092908	A1	20180405	US 2017-15655712	20170720
WO 2016118639	A1	20160728	WO 2016-US14149	20160120

PRIORITY APPLN. INFO.: US 2015-62105656 P 20150120
WO 2016-US14149 A2 20160120

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20180092908	A1	Alive	20210401
WO 2016118639	A1	Dead	20201201

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 168:404869; MARPAT 168:404869; CASFORMULTNS 2018:701463
GI



I

AB The present invention provides a method for treating or ameliorating the effects of a neurodegenerative disorder in a subject in need thereof. The method includes, for example, administering to the subject an effective amt. of a **compd** . such as I, combinations thereof, or an N-oxide, cryst. form, hydrate thereof, or a pharmaceutically acceptable salt thereof. The present invention also provides a method for treating or ameliorating the effects of a condition assocd. with increased protein disulfide isomerase (PDI) activity and a method of modulating PDI activity in a cell. The present invention also provides **compds** ., salts, **compns** . and kits useful for the provided methods.

L17 ANSWER 6 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 25 May 2017
ACCESSION NUMBER: 2017:827077 HCAPLUS Full-text
DOCUMENT NUMBER: 167:13268
TITLE: Stable **formulation** of **phenobarbital** **sodium** injection
INVENTOR(S): Parker, Michael G.; Wilson, Scott S.; Chahal, Yasmeen; Hovius, Kelly W.; McAnany, David E.
PATENT ASSIGNEE(S): Eurohealth International Sarl, Switz.; West-Ward Pharmaceuticals International Limited
SOURCE: U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English

9

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20170143719	A1	20170525	US 2016-15355868	20161118
US 9901576	B2	20180227		
WO 2017085687	A1	20170526	WO 2016-IB56973	20161118

PRIORITY APPLN. INFO.: US 2015-62258000 P 20151120

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20170143719	A1	Alive	20201121
US 9901576	B2	Alive	20201121
WO 2017085687	A1	Dead	20201202

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASFORMULTNS 2017:827077
AB Stable **phenobarbital sodium solns** . for injection that do not generate impurities during extended storage. These **solns** . include **phenobarbital sodium** in an amt. of 15 to 200 mg/mL; a C1-C4 alc. such as ethanol in an amt. of 105 to 160 mg/mL; and a glycol such as propylene glycol in an amt. of between 620 and 830 mg/mL and have a **pH** of between 9 and 12 which is adjusted to that range by adding acid or base, as required. No more than 50 mg/mL water is present including any water introduced by the acid or base. The **solns** . contain no more than 0.8% of **Ph Et acetyl urea** impurity as well as no detectable amt. of **Ph** butyric acid after two years storage at room temp.
IT **90-49-3**, **Phenyl ethyl acetyl urea**
RL: OCU (Occurrence, unclassified); OCCU (Occurrence)
(stable **formulation** of **phenobarbital sodium** injection)
IT **57-30-7**, **Phenobarbital sodium**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable **formulation** of **phenobarbital sodium** injection)

L17 ANSWER 7 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 24 Feb 2017
ACCESSION NUMBER: 2017:326952 HCAPLUS Full-text
DOCUMENT NUMBER: 172:549918
TITLE: Uptake of benzo[a]pyrene, but not of phenanthrene, is inhibited by fatty acids in intestinal brush border membrane vesicles of rainbow trout (Oncorhynchus mykiss)
AUTHOR(S): de Gelder, Stefan; van Och, Liselot; Zethof, Jan; Pelgrim, Thamar N. M.; Rasinger, Josef D.; Flik, Gert; Berntssen, Marc H. G.; Klaren, Peter H. M.
CORPORATE SOURCE: Institute for Water and Wetland Research, Department of Animal Ecology and Physiology, Radboud University, Nijmegen, 6500 GL, Neth.
SOURCE: Comparative Biochemistry and Physiology, Part C: Toxicology & Pharmacology (**2017**), 195, 1-8
CODEN: CBPPFK; ISSN: 1532-0456
DIGITAL OBJECT ID: 10.1016/j.cbpc.2017.02.003
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB Partial replacement of fish ingredients with vegetable ingredients has elevated levels of polycyclic arom. hydrocarbons (PAHs) in Atlantic salmon reared on these feeds. PAH uptake in the intestinal tract is postulated to occur in assocn. with lipid absorption and could well be affected by fatty acid **compn**. We therefore investigated the effects of a fish oil and vegetable oil fatty acid, eicosapentaenoic acid (**EPA**; 20:5n - 3) and oleic acid (18:1n - 9) resp., on the uptake of benzo[a]pyrene (BaP) and phenanthrene (PHE) across the intestinal brush border membrane in the salmonid species rainbow trout (Oncorhynchus mykiss). BaP and PHE were solubilized in mixed micelles composed of either **EPA** or oleic acid and administrated to isolated brush border membrane vesicles (BBMV) derived from the pyloric caeca, proximal intestine and distal intestine. In the absence of free fatty acids (FFA) trans-membrane uptake of BaP and PHE was 2-7 times lower

than the fraction assocd. to or in the membrane. In the presence of FFA, trans-membrane BaP uptake had decreased by 80 and 40% at the highest **EPA** and oleic acid concn., resp., whereas PHE uptake was virtually unaffected. In the presence of BaP, but not PHE, trans-membrane **EPA** uptake in BBMV had decreased. This study obtained evidence for PAH-dependent interactions with FFA uptake. We conclude that intestinal BaP uptake is reduced by **luminal** FFA contents whereas PHE uptake is not. A large fraction of the administrated BaP and PHE remains assocd. with the cellular membrane of enterocytes and may interfere with uptake of nutrients.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN

ED Entered STN: 28 Jul 2016

ACCESSION NUMBER: 2016:1239499 HCAPLUS Full-text

DOCUMENT NUMBER: 165:232948

TITLE: Small molecule oxidizers of PDI and their use

INVENTOR(S): Stockwell, Brent R.; Kaplan, Anna

PATENT ASSIGNEE(S): The Trustees of Columbia University in the City of New York, USA

SOURCE: PCT Int. Appl., 221pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2016118639	A1	20160728	WO 2016-US14149	20160120
US 20180092908	A1	20180405	US 2017-15655712	20170720

PRIORITY APPLN. INFO.:

US 2015-62105656	P	20150120
WO 2016-US14149	A2	20160120

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2016118639	A1	Dead	20201201
US 20180092908	A1	Alive	20210401

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): CASREACT 165:232948; MARPAT 165:232948; CASFORMULTNS 2016:1239499

AB The present invention provides a method for treating or ameliorating the effects of a neurodegenerative disorder in a subject in need thereof comprising administering to the subject an effective amt. of a **compd** . selected from the group consisting of combinations thereof, or an N-oxide, cryst. form, hydrate, or pharmaceutically acceptable salt thereof. The present invention also provides a method for treating or ameliorating the effects of a condition assocd. with increased protein disulfide isomerase (PDI) activity and a method of modulating PDI activity in a cell. The present invention also provides **compds** ., salts, **compns** . and kits useful for the provided methods.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN

ED Entered STN: 12 Jun 2015

ACCESSION NUMBER: 2015:980822 HCAPLUS Full-text

DOCUMENT NUMBER: 163:92859

TITLE: **Preparation** of adamantylaminobenzoate derivatives for modulating ferroptosis and treatment of excitotoxic disorders

INVENTOR(S): Stockwell, Brent R.; Skouta, Rachid; Dixon, Scott

PATENT ASSIGNEE(S): Columbia University In the City of New York, USA

SOURCE: PCT Int. Appl., 341pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2015084749	A1	20150611	WO 2014-US67977	20141201
AU 2014357375	A1	20160707	AU 2014-357375	20141201
AU 2014357375	B2	20200430		
EP 3076962	A1	20161012	EP 2014-867950	20141201
EP 3384908	A1	20181010	EP 2018-168252	20141201
EP 3384908	B1	20200930		
EP 3791870	A1	20210317	EP 2020-196973	20141201
US 20160297748	A1	20161013	US 2016-15100967	20160601
US 10259775	B2	20190416		
US 20190292135	A1	20190926	US 2019-16297190	20190308

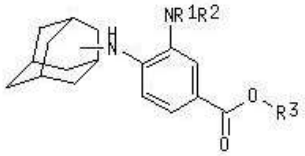
PRIORITY APPLN. INFO.:

US 2013-61910580	P	20131202
US 2014-61948242	P	20140305
EP 2014-867950	A3	20141201
EP 2018-168252	A3	20141201
WO 2014-US67977	W	20141201
US 2016-15100967	A1	20160601

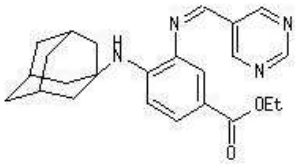
PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
WO 2015084749	A1	Dead	20201202
AU 2014357375	A1	Alive	20201121
AU 2014357375	B2	Alive	20201120
EP 3076962	A1	Dead	20201203
EP 3384908	A1	Indeterminate	20201107
EP 3384908	B1	Indeterminate	20201107
EP 3791870	A1	Alive	20210318
US 20160297748	A1	Alive	20201121
US 10259775	B2	Alive	20201121
US 20190292135	A1	Alive	20201121

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 163:92859; MARPAT 163:92859
GI



I



II

AB The invention relates to **prepn**. of adamantylaminobenzoate derivs. of 12

formula I wherein R1 and R2 are independently selected from H, D, O, halo, etc.; R3 is H, C1-6-alkyl-aryl, C1-6-alkyl-heteroaryl, etc., a pharmaceutically acceptable carrier. The example **compd**. II was **prepd**. in multistep synthesis (procedure disclosed) was tested in multiple bioassays and showed potent activity in modulating ferroptosis and potential for treatment of excitotoxic disorders (data shown). Further provided are methods for treating or ameliorating the effects of an excitotoxic disorder in a subject, methods of modulating ferroptosis in a subject, methods of reducing reactive oxygen species (ROS) in a cell, and methods for treating or ameliorating the effects of a neurodegenerative disease.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN

ED Entered STN: 24 Apr 2013

ACCESSION NUMBER: 2013:631295 HCAPLUS Full-text

DOCUMENT NUMBER: 159:2864

TITLE: Profiling 976 ToxCast Chemicals across 331 Enzymatic and Receptor Signaling Assays

AUTHOR(S): Sipes, Nisha S.; Martin, Matthew T.; Kothiya, Parth; Reif, David M.; Judson, Richard S.; Richard, Ann M.; Houck, Keith A.; Dix, David J.; Kavlock, Robert J.; Knudsen, Thomas B.

CORPORATE SOURCE: National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC, 27711, USA

SOURCE: Chemical Research in Toxicology (**2013**), 26(6), 878-895
CODEN: CRTOEC; ISSN: 0893-228X

DIGITAL OBJECT ID: 10.1021/tx400021f

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal; (online computer file)

LANGUAGE: English

AB Understanding potential health risks is a significant challenge due to the large nos. of diverse chems. with poorly characterized exposures and mechanisms of toxicities. The present study analyzes 976 chems. (including failed pharmaceuticals, alternative plasticizers, food additives, and pesticides) in Phases I and II of the U.S. **EPA**'s ToxCast project across 331 cell-free enzymic and ligand-binding high-throughput screening (HTS) assays. Half-maximal activity concns. (AC50) were identified for 729 chems. in 256 assays (7135 chem.-assay pairs). Some of the most commonly affected assays were CYPs (CYP2C9 and CYP2C19), transporters (mitochondrial TSPO, norepinephrine, and dopaminergic), and GPCRs (aminergic). Heavy metals, surfactants, and dithiocarbamate fungicides showed promiscuous but distinctly different patterns of activity, whereas many of the pharmaceutical **compds**. showed promiscuous activity across GPCRs. Literature anal. confirmed >50% of the activities for the most potent chem.-assay pairs (54) but also revealed 10 missed interactions. Twenty-two chems. with known estrogenic activity were correctly identified for the majority (77%), missing only the weaker interactions. In many cases, novel findings for previously unreported chem.-target combinations clustered with known chem.-target interactions. Results from this large inventory of chem.-biol. interactions can inform read-across methods as well as link potential targets to mol. initiating events in adverse outcome pathways for diverse toxicities.

IT **57-30-7**
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(Profiling 976 ToxCast Chems. across 331 Enzymic and Receptor Signaling Assays)

OS.CITING REF COUNT: 99 THERE ARE 99 CAPLUS RECORDS THAT CITE THIS RECORD (99 CITINGS)

REFERENCE COUNT: 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 11 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN

ED Entered STN: 16 Jan 2004

ACCESSION NUMBER: 2004:37989 HCAPLUS Full-text

DOCUMENT NUMBER: 140:422947
TITLE: Suppression of Calcium Sparks in Rat Ventricular Myocytes and Direct Inhibition of Sheep Cardiac RyR Channels by **EPA**, DHA and Oleic Acid
AUTHOR(S): Honen, B. N.; Saint, D. A.; Laver, D. R.
CORPORATE SOURCE: Department of Physiology, University of Adelaide, Adelaide, SA 5005, Australia
SOURCE: Journal of Membrane Biology (**2003**), 196(2), 95-103
CODEN: JMBBBO; ISSN: 0022-2631
DIGITAL OBJECT ID: 10.1007/s00232-003-0628-9
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The anti-arrhythmic effects of long-chain polyunsatd. fatty acids (PUFAs) may be related to their ability to alter calcium handling in cardiac myocytes. We investigated the effect of eicosapentanoic acid (**EPA**) and docosahexaenoic acid (DHA) on calcium sparks in rat cardiac myocytes and the effects of these PUFAs and the monounsatd. oleic acid on cardiac calcium release channels (RyRs). Visualization of subcellular calcium concns. in single rat ventricular myocytes showed that intensity of calcium sparks was reduced in the presence of **EPA** and DHA (15 μM). It was also found that calcium sparks decayed more quickly in the presence of **EPA** but not DHA. Sarcoplasmic vesicles contg. RyRs were **prepd**. from sheep hearts and RyR activity was detd. by either [3H]ryanodine binding or by single-channel recording. Bilayers were formed from phosphatidylethanolamine and phosphatidylcholine dissolved in either n-decane or n-tetradecane. **EPA** inhibited [3H]ryanodine binding to RyRs in SR vesicles with KI = 40 μM. Poly- and mono-unsatd. free fatty acids inhibited RyR activity in lipid bilayers. **EPA** (cytosolic or **luminal**) inhibited RyRs with KI =32 μM and Hill coeff., n1 = 3.8. Inhibition was independent of the n-alkane solvent and whether RyRs were activated by ATP or Ca2+. DHA and oleic acid also inhibited RyRs, suggesting that free fatty acids generally inhibit RyRs at micromolar concns.

OS.CITING REF COUNT: 39 THERE ARE 39 CAPLUS RECORDS THAT CITE THIS RECORD (39 CITINGS)
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 08 Jul 2002
ACCESSION NUMBER: 2002:508049 HCAPLUS Full-text
DOCUMENT NUMBER: 137:245248
TITLE: Lipids and nitric oxide in porcine retinal and choroidal blood vessels
AUTHOR(S): Kulkarni, Prasad; Cai, Jian; Hurst, Harrell E.
CORPORATE SOURCE: Department of Ophthalmology and Visual Science, Kentucky Lions Eye Research Center, University of Louisville School of Medicine, Louisville, KY, USA
SOURCE: Journal of Ocular Pharmacology and Therapeutics (**2002**), 18(3), 265-275
CODEN: JOPTFU; ISSN: 1080-7683
DIGITAL OBJECT ID: 10.1089/108076802760116188
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lipid profiles of porcine retina, and retinal and choroidal vessels were analyzed using the gas chromatog./mass spectrometry (GC/MS) technique. The retina and both isolated retinal and choroidal vessels contained satd. fatty acid stearic acid and polyunsatd. fatty acids, including arachidonic (C20:4, AA), a precursor for vasoactive prostaglandin (PG-2) series, and W-6 docosahexaenoic acids (C22:6, DHA). However, eicosapentaenoic acid (C20:5, **EPA**), a precursor for PG-3 series, was not detected in these vessels. When stearic acid was used for normalization of tissue sample, the retina contained relatively higher amts. of DHA than AA, retinal vessels had equal amts. of AA and DHA, while choroidal vessels contained higher amts. of AA than DHA. We also examd. the endogenous synthesis of vasoactive endothelial-derived factors like PGs and nitric oxide (NO). Since vasoactive angiotensin II (Ang II) releases these products from blood vessels, this polypeptide was used in a porcine retinal circulation model. The porcine retinal central artery was perfused with oxygenated/heparinized physiol. salt **soln**. at 37°C. Changes

in A1 and A2 arteriolar diams. induced by Ang II were detd. in the absence and presence of the nitric oxide synthase inhibitor, 1-NO Arginine (LNOA), and cyclooxygenase inhibitor, flurbiprofen (FB). The central retinal artery designated as the first order arteriole A1 and subsequent branch was defined as A2. **Luminal** diams. of A1 and A2 arterioles were 35 ± 2 µm and 10 ± 1 µm, resp. Topical Ang II (10-10 M-10-6 M) caused small vasoconstrictions in a dose-dependent manner. This response was enhanced after inhibition of PG synthesis by (10-6 M) FB. Ang II induced-constrictions were further enhanced in the presence of NO synthase inhibitor, LNOA (10-7 M). There was slightly more increase in Ang II-induced vasoconstrictions in the presence of both NO and PG inhibitors, suggesting that NO may cause release of PGs from these vessels. This study demonstrates that the porcine retinal arterioles have the ability to regulate vasoconstriction responses induced by Ang II by synthesis and release of endogenous vasodilating PGs and NO (esp. NO); and these substances may play a vital role in porcine retinal circulation.

OS.CITING REF COUNT: 10 THERE ARE 10 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

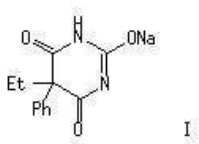
L17 ANSWER 13 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 27 Dec 1991
ACCESSION NUMBER: 1991:678740 HCAPLUS Full-text
DOCUMENT NUMBER: 115:278740
ORIGINAL REFERENCE NO.: 115:47349a,47352a
TITLE: Effect of fish oil supplementation on the prevention of angiographic restenosis after percutaneous transluminal coronary angioplasty
AUTHOR(S): Yamaguchi, Tetsu; Isshiki, Takaaki; Soumitsu, Yasunari; Ikari, Yuji; Nakamura, Masato; Saeki, Fumihiko
CORPORATE SOURCE: Div. Cardiol., Mitsui Mem. Hosp., Tokyo, 101, Japan
SOURCE: Domyaku Koka (**1991**), 19(6/7), 635-41
CODEN: DOMKDM; ISSN: 0386-2682
DIGITAL OBJECT ID: 10.5551/jat1973.19.6-7_635
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB To assess the effect of fish oil supplementation on the incidence of angiog. restenosis after successful percutaneous transluminal coronary angioplasty (PTCA), 36 male patients with stable angina received 5.4 g/day of fish oil (1.6 g eicosapentaenoic acid: **EPA**, 0.6 g docosahexaenoic acid: DHA), beginning 7 days before PTCA, in addn. to the treatment with antiplatelet drugs, nitrates, and Ca antagonists. All 34 successful patients were tolerant of the study medication. Of these, 2 patients with poor compliance and 2 asymptomatic patients without a follow-up (F/U) angiog. were excluded from the anal. Thirty patients (mean age 58 ± 8 yr, 41 lesions: fish oil group) were compared with 43 male patients (mean age 58 ± 8 yr, 66 lesions: control group) treated by conventional medical therapy. Despite of a greater percentage of left anterior descending artery lesions in the fish oil group, there was no difference in the baseline characteristics between the 2 groups. No significant changes in serum lipids after fish oil supplementation were obsd. in the fish oil group. The **compn**. of plasma fatty acids was measured in 15 patients of the fish oil group at baseline, 1 wk after (at PTCA), and at F/U angiog. (an av. of 3.8 mo after PTCA). **EPA** was increased after 1 wk and at F/U angiog., resp. DHA was also increased significantly. Arachidonic acid (AA) remained unchanged, and the **EPA**/AA ratio increased. Angiog. restenosis was defined as a loss of >50% of the gain at PTCA in **luminal** diam. Restenosis occurred in 20% of patients in the fish oil group and in 37% of patients in the control group. Restenosis occurred in 15% of lesions in the fish oil group, which was significantly lower than in the control group. Multiple logistic regression anal. using both fish oil and control groups also demonstrated that no use of the fish oil was the highest independent risk factor for restenosis. Thus, a dietary supplement of fish oil, administered from 1 wk before PTCA, reduces the rate of restenosis after successful PTCA in male patients and that **EPA** plays a major role in the prevention of restenosis.

L17 ANSWER 14 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 15 Nov 1991
ACCESSION NUMBER: 1991:606806 HCAPLUS Full-text
DOCUMENT NUMBER: 115:206806
ORIGINAL REFERENCE NO.: 115:35281a,35284a
TITLE: Effects of n-3 fatty acids on fluid and electrolyte transport in rat intestine in vivo and in vitro
AUTHOR(S): Loeschke, K.; Schreiner, J.; Oberst, G.
CORPORATE SOURCE: Med. Klin. Innenstadt, Univ. Munich, Munich, W-8000/2, Germany
SOURCE: Zeitschrift fuer Gastroenterologie (1991), 29(5), 227-30
CODEN: ZGASAX; ISSN: 0044-2771
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of docosahexaenoic acid (DHA) and eicosapentaenoic acid (**EPA**) on fluid and electrolyte transport were tested in the rat colon and jejunum. In ligated colon loops in vivo, DHA (10-5-10-3M luminally) diminished net Na an fluid absorption, an stimulated net K secretion. Similar but smaller effects were produced by **EPA**. In the jejunum, transport parameters were not influenced by either DHA or **EPA**. In isolated distal colonic mucosa in vitro, DHA (10-4-10-3M on the mucosal side) reduced the elec. resistance, p.d., short-circuit current, and the net absorption of Na and Cl due to increased unidirectional serosal to mucosal fluxes. These changes were prevented when Ca was replaced by Sr in the bathing **soln.**, suggesting that n-3 fatty acids increase colonic conductance indirectly by binding **luminal** Ca.

L17 ANSWER 15 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1983:581352 HCAPLUS Full-text
DOCUMENT NUMBER: 99:181352
ORIGINAL REFERENCE NO.: 99:27759a,27762a
TITLE: Degradation product of sodium phenobarbital injection
AUTHOR(S): Wen, Yulin; Wang, Zhili; Liu, Renkuan; Pang, Hui
CORPORATE SOURCE: Renmin Pharm. Fact., Tianjin, Peop. Rep. China
SOURCE: Yaoxue Xuebao (**1983**), 18(5), 392-3
CODEN: YHHPAL; ISSN: 0513-4870
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB dl-Pheneturide (I) [**90-49-3**], having anticonvulsant properties, was the major degrdn. product of Na phenobarbital (II) [**57-30-7**] injections stored at room temp. or heated at 100°.
IT **57-30-7**
RL: PRP (Properties)
(degrdn. of, in injections, pheneturide from)
IT **90-49-3**
RL: BIOL (Biological study)
(sodium phenobarbital degrdn. product, in injections)

L17 ANSWER 16 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1981:503397 HCAPLUS Full-text
DOCUMENT NUMBER: 95:103397
ORIGINAL REFERENCE NO.: 95:17275a,17278a
TITLE: Rapid determination by HPLC of both **sodium phenobarbital** and a degradation product in a syrup
AUTHOR(S): Bennati, E.; Piergiovanni, L.
CORPORATE SOURCE: Milan, Italy
SOURCE: Bollettino Chimico Farmaceutico (**1981**), 120(3), 172-8
CODEN: BCFAAI; ISSN: 0006-6648
DOCUMENT TYPE: Journal
LANGUAGE: Italian
GI



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16

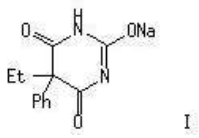
AB Na phenobarbital (I) [57-30-7] and its principal degrdn. product, phenylethylacetylurea [90-49-3], were detd. directly in pharmaceutical syrups (merely after 1:1 diln. with H2O) by high-pressure liq. chromatog. (HPLC) of 1-4 µL of the dild. syrups on Partisil 10 ODS; the mobile phase was 0.01 m KH2PO4 contg. 35% MeOH and brought to pH 3.5 with 5% H3PO4. Phenacetin was used as internal std., and detection was by UV light at 205 nm. The retention times of I, phenacetin, and degrdn. product were 2.6, 3.8, and 10.4 min, resp. The threshold of detection of phenylethylacetylurea was ~1% of the I present. The detection response was linear over the range 1-12 µg I.

IT 90-49-3
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in phenobarbital syrup, by high-pressure liq. chromatog.)

IT 57-30-7
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in syrups, by high-pressure liq. chromatog.)

L17 ANSWER 17 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1980:635787 HCAPLUS Full-text
DOCUMENT NUMBER: 93:235787
ORIGINAL REFERENCE NO.: 93:37723a,37726a
TITLE: Biochemical homology between rat dorsal prostate and coagulating gland. Purification of a major androgen-induced protein
AUTHOR(S): Wilson, Elizabeth M.; French, Frank S.
CORPORATE SOURCE: Dep. Pediatrics Biochem., Univ. North Carolina, Chapel Hill, NC, 27514, USA
SOURCE: Journal of Biological Chemistry (1980), 255(22), 10946-53
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The rat dorsal prostate and coagulating gland display remarkable homol. in protein compn., including 2 major androgen-dependent secretory proteins, referred to as dorsal proteins (DP) I and II. DPI was purified and is a dimer composed of 2 identical subunits with sedimentation coeff. 4.6 S, Stokes radius 32 Å, and mol. wt. 71,000 (62,000 by SDS-polyacrylamide gel electrophoresis). The dimer (6.8 S, 46 Å, mol. wt. 150,000) dissocs. at high ionic strength and can be partially reconstituted by removal of salt. DP I is a basic carbohydrate-contg. protein (pI 9) with high lysine content and binds to phosphocellulose but not to DEAE-Sepharose. DP I is produced only in dorsal prostate and coagulating gland; it constitutes ~25% of total cytosol protein in both organs, yet makes up only 5% of coagulating gland luminal fluid and ejaculated seminal fluid. It is not found in the rat dorsal prostate tumor (Dunning R3327H). DP II is a larger protein (mol. wt. 80,000 by SDS gel electrophoresis) with higher carbohydrate content. Under nondenaturing conditions, it has a Stokes radius of >200 Å, corresponding to mol. wt. of >300,000. DP II represents a smaller proportion of total cytosol protein than does DP I, yet is the predominant protein of coagulating gland fluid. These proteins will be useful probes for studies on androgen regulation of specific gene expression and prostatic secretory mechanisms.
OS.CITING REF COUNT: 21 THERE ARE 21 CAPLUS RECORDS THAT CITE THIS RECORD (21 CITINGS)

L17 ANSWER 18 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1979:174587 HCAPLUS Full-text
DOCUMENT NUMBER: 90:174587
ORIGINAL REFERENCE NO.: 90:27619a,27622a
TITLE: Stability of phenobarbital sodium in solutions
AUTHOR(S): Guven, Kasim Cemal; Akbuga, Julide
CORPORATE SOURCE: Eczacilik Fak., Istanbul Univ., Istanbul, Turk.
SOURCE: Eczacilik Bulteni (1977), 19(4), 59-64
CODEN: ECBUAN; ISSN: 0367-0236
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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AB Chloral hydrate [302-17-0] and low temp. storage increased the degrdn. of **phenobarbital Na** (I) [**57-30-7**]. **Phenylethylacetylurea** [**90-49-3**] and PhCHEtCO2H [90-27-7] were identified as degrdn. products of I.

IT **90-49-3**
RL: BIOL (Biological study)
(**phenobarbital sodium** degrdn. product)

IT **57-30-7**
RL: PRP (Properties)
(stability of, in **soln**.)

L17 ANSWER 19 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1977:150368 HCAPLUS Full-text
DOCUMENT NUMBER: 86:150368
ORIGINAL REFERENCE NO.: 86:23543a,23546a
TITLE: Binding of anticonvulsant drugs to cytochrome P-450: correlation with evidence of induction of hepatic microsomal enzymes
AUTHOR(S): Latham, A. N.; Sweeney, G. D.
CORPORATE SOURCE: Med. Cent., McMaster Univ., Hamilton, ON, Can.
SOURCE: Canadian Journal of Physiology and Pharmacology (**1976**), 54(6), 844-9
CODEN: CJPPA3; ISSN: 0008-4212
DIGITAL OBJECT ID: 10.1139/y76-118
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Mephenytoin [50-12-4], diphenylhydantoin [630-93-3], **pheneturide** [**90-49-3**], and **phenobarbital Na** [**57-30-7**] produced a concn.-dependent inhibition in the binding of hexobarbital to cytochrome P-450 [9035-51-2] at the type 1 site, while sulthiame [61-56-3] slightly potentiated, and ethosuximide [77-67-8] did not affect the binding characteristics of hexobarbital. Diphenylhydantoin, phenobarbital, and **pheneturide** have previously been shown to enhance the urinary excretion of D-glucaric acid (DGA), while sulthiame inhibited the potentiation of DGA excretion caused by these drugs, and ethosuximide produced no change. The results suggest a close relationship between the ability of these drugs to induce hepatic microsomal drug-metabolizing enzyme systems (as indicated by enhancement of DGA excretion) and binding behavior at the type 1 site.

IT **57-30-7** **90-49-3**
RL: BIOL (Biological study)
(cytochrome P-450 binding of, drug-metabolizing enzyme induction in relation to)

L17 ANSWER 20 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1976:456631 HCAPLUS Full-text
DOCUMENT NUMBER: 85:56631
ORIGINAL REFERENCE NO.: 85:9083a,9086a
TITLE: Effects of anticonvulsant drugs on bone resorption induced by parathyroid extract in vitro
AUTHOR(S): Rowe, David J. F.; Harris, Malcolm
CORPORATE SOURCE: King's Coll. Hosp. Dent. Sch., London, UK
SOURCE: Study Group of the Institute for Research into Mental and Multiple Handicap (**1976**), 9(Anticonvulsant Drugs Enzyme Induction), 113-21
CODEN: SGIHDY; ISSN: 0165-0955
DOCUMENT TYPE: Journal
LANGUAGE: English

AB There was dose-related inhibition of the parathyroid hormone [9002-64-6] stimulated resorption of mouse calvaria in tissue culture when micromolar concns. of phenytoin Na [630-93-3], pheneturide [**90-49-3**] and diazepam [439-14-5] were added to the culture medium. Diazepam, and to a lesser extent phenytoin, also inhibited unstimulated bone turnnover. Phenobarbitone Na [**57-30-7**] and carbamazepine [298-46-4] in similar concns. did not appear to be inhibitory. These results and the in vivo findings of hypocalcemia

and tooth root abnormalities in many epileptics suggest that anticonvulsant drugs may interfere with the action of parathyroid hormone on bone and cause the appearance of hypoparathyroid-like symptoms in some epileptic subjects.

IT **57-30-7** **90-49-3**
RL: BIOL (Biological study)
(bone resorption induced by parathyroid hormone response to)

L17 ANSWER 21 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1973:418660 HCAPLUS Full-text
DOCUMENT NUMBER: 79:18660
ORIGINAL REFERENCE NO.: 79:2999a,3002a
TITLE: Ureide ring scission of **phenobarbital** by **sodium** borohydride
AUTHOR(S): Chafetz, Lester; Chen, Tsun-Ming; Greenough, R. Clive
CORPORATE SOURCE: Dep. Anal. Phys. Chem., Warner-Lambert Res. Inst., Morris Plains, NJ, USA
SOURCE: Journal of Pharmaceutical Sciences (**1973**), 62(3), 512
CODEN: JPMSAE; ISSN: 0022-3549
DIGITAL OBJECT ID: 10.1002/jps.2600620341
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA through Vol 151.
AB During reaction of phenobarbital (I) in aq. alkali, MeOH, or MeOH-ether **mixts**. with excess NaBH4, the ureide ring is cleaved with formation of 2-phenyl-1-butanol. This was found by thin layer chromatog. methods and by NMR. The mechanism of reaction route was not investigated, but it is assumed that at first the ring of I is hydrolyzed, despite the fact that the first product of hydrolysis of I, **phenylethylacetylurea** was not found on the thin layer chromatograms. It was also obsd. that I was stable in **mixts**. in which the borohydride had been allowed to decomp. to borate.

L17 ANSWER 22 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 12 May 1984
ACCESSION NUMBER: 1972:556320 HCAPLUS Full-text
DOCUMENT NUMBER: 77:156320
ORIGINAL REFERENCE NO.: 77:25661a,25664a
TITLE: Alkaline hydrolysis of phenobarbital
AUTHOR(S): Plessas, Ch. T.
CORPORATE SOURCE: Lab. Metab. Med., Univ. Geneve, Geneva, Switz.
SOURCE: Chimika Chronika (**1972**), 1(2), 109-14
CODEN: CMCRCZ; ISSN: 0366-693X
DOCUMENT TYPE: Journal
LANGUAGE: French
AB Complete hydrolysis of a 6% **soln**. of phenobarbital-2-14C Na by heating for 24 hr at 80° yielded NaHCO3, urea, and **1**-[(**ethyl**)**phenylacetyl**]**urea** (I). The same treatment of phenobarbital-5-14C yielded bicarbonate, I, and ethyl(phenyl)acetic acid (II). Simple dissolution of phenobarbital-5-14C in 0.45N NaOH yielded bicarbonate, phenobarbital, II and I. The rate of hydrolysis was 4% within 3 min, and 5.5% within the first hour.

IT **57-30-7**
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrolysis of)
IT **90-49-3**
RL: BIOL (Biological study)
(phenobarbital hydrolysis product)
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L17 ANSWER 23 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 22 Apr 2001
ACCESSION NUMBER: 1959:102036 HCAPLUS Full-text
DOCUMENT NUMBER: 53:102036
ORIGINAL REFERENCE NO.: 53:18390b-c
TITLE: Separation of decomposed products of **phenobarbital sodium** by paper chromatographic technique
AUTHOR(S): Kapadia, A. J.; Goyan, J. E.; Autian, J.
CORPORATE SOURCE: Univ. of Michigan, Ann Arbor
SOURCE: Journal of the American Pharmaceutical Association

(1912-1977) (1959), 48, 407-9
CODEN: JPHAA3; ISSN: 0003-0465
DIGITAL OBJECT ID: 10.1002/jps.3030480712
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Two solvent systems, one with AmOH satd. with borate buffer and the other a 1-phase system composed of iso-PrOH, hexyl alc., MeOH, and NH4OH, were suitable for the sepn., by paper chromatography, of **phenylethylacetylurea**, 2-phenylbutyric acid, and urea from the degradation of aq. **solns**. of Na phenobarbital.
IT **57-30-7**, **Phenobarbital sodium**
(decompn. products of, chromatography of)
IT **90-49-3P**, Urea, (2-phenylbutyryl)-
RL: PREP (Preparation)
(formation from **phenobarbital sodium**, chromatography of)
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L17 ANSWER 24 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 22 Apr 2001
ACCESSION NUMBER: 1958:47095 HCAPLUS Full-text
DOCUMENT NUMBER: 52:47095
ORIGINAL REFERENCE NO.: 52:8461g-i,8462a
TITLE: Counter-current distribution of barbituric acid derivatives
AUTHOR(S): Brauniger, H.; Stens, B.
CORPORATE SOURCE: Univ. Rostock, Germany
SOURCE: Pharmazie (**1957**), 12, 794-7
CODEN: PHARAT; ISSN: 0031-7144
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Sepn. of barbital, phenobarbital (I), 5-(2-butenyl)-5-ethylbarbituric acid (Kalypnon), phanodorn (II), dial, and sandoptal was effected with a 25-stage app. and CHCl3/aq. HCONH2 **soln**. Identification was better made by m.ps. than by chromatography of the sepd. fractions. For detn. of barbituric acid derivs., the method of Heiz (C.A. 46, 6551f) (modified) was used, a **mixt**. of pyridine bases being used to dissolve the derivs. which were titrated with 0.1N Li methylate **soln**. (III) with 2 ml. pyridine added to the CHCl3 **soln**. of the unknown, and 1% **soln**. of thymol blue in MeOH as indicator. (Bromothymol blue for II). III was standardized against freshly sublimed BzOH in Me2NOCH **soln**. Inactin (5-ethyl-5-isobutyl-2-thiobarbituric acid), after conversion to the free acid, could be shaken out only by increasing the concn. of the HCONH2 **soln**. to 50%. Sepn. of mixed barbiturates was demonstrated, also the sepn. of I Na and **phenylethylacetylurea** formed from it by boiling its aq. **soln**. I Na sepd. in tube 4, its deriv in tube 16. Titration of these **compds**. was accomplished by using Azo Violet **soln**. as indicator and titrating to the same color shade as was obtained with an exactly neutralized control **soln**.
IT **57-30-7P**, **Phenobarbital sodium**
RL: PREP (Preparation)
(sepn. and identification of)
IT **90-49-3P**, Urea, (2-phenylbutyryl)-
RL: PREP (Preparation)
(sepn. from **phenobarbital sodium** and identification of)

L17 ANSWER 25 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 22 Apr 2001
ACCESSION NUMBER: 1956:60321 HCAPLUS Full-text
DOCUMENT NUMBER: 50:60321
ORIGINAL REFERENCE NO.: 50:11352b-i,11353a
TITLE: Stability in **solution** of the sodium salts of a few sedatives of the barbituric acid series. V
AUTHOR(S): Aspelund, Helge; Stolt, Sven
SOURCE: Acta Acad. Aboensis, Math. et Phys. (**1955**), 20(No. 4), 26 pp.
DOCUMENT TYPE: Journal
LANGUAGE: German
AB The work was extended to long reaction times at room temp. with 2-3 equivs. alkali, and to include 1,5,5-trisubstituted barbituric acids. The resistance to alkalies under these conditions conformed with that obsd. previously at lower alkalinities. The trisubstituted barbituric

acids had very poor stability and were decompd. by 2 equivs. NaOH in 15 min. at the b.p. or by 3 equivs. 12 h. at room temp. The substituted malonamides were generally of good stability and could be isolated, but in the case of barbituric acids in which both alkyl substituents in the 5-position were primary, only traces of diamides could be isolated. The actual amt. of diamide increased with increasing size of the alkyl groups. In many cases, malonamic acids were isolated. They were undoubtedly formed from N-carbamoylmalonamic precursors. The stability of the latter was best for derivs. from barbituric acids contg. secondary alkyl groups in the 5-position. In many cases the N-carbamoylmalonamic acids were hydrolyzed directly to malonic acids and urea, in which case little or no malonamic acids were isolated. The monoamides that were isolated probably resulted from decarboxylation of malonamic acids or decompn. of N-acyl ureas. The complete scheme for alk. decompn. of barbituric acids is given. The following **compds**. were isolated, in addn. to those obsd. in previous work at milder alky., from various A (5-substituents, R and R' shown): from Veronal (XIV) (Et, Et), RR'C(CO2H)CONHCONH2, m. 143-6° (decompn.), RR'C(CO2H)CONH2, m. 144-5°, RR'CHCONHCONH2, RR'C(CO2H)2, and traces of RR'C(CONH2)2; from A (Et, Pr) (XV), RR'C(CO2H)CONH2, m. 140° (decompn. to RR'CHCONHCONH2, m. 101-3°), RR'C(CO2H)2, m. 117-18°, and traces of RR'C(CONH2)2; from A (Et, allyl) (XVI), RR'CHCONHNH2, RR'C(CO2H)CONHCONH2, and RR'C(CO2H)2; from Dial (XVII) (allyl, allyl), RR'C(CO2H)2, RR'CHCONHCONH2, m. 157-8°, and traces of RR'C(CONH2)2; from Neonal (XVIII) (Et, Bu), RR'C(CONH2)2, m. 184-5°, RR'C(CO2H)CONH2, and RR'C(CO2H)2, m. 113-14°; from Amytal (XIX) (Et, iso-Am), RR'C(CONH)2, m. 190°, RR'C(CO2H)CONH2, and RR'C(CO2H)2, m. 122-3°; from A (iso-Am, iso-Am) (XX), RR'CHCONHCONH2, m. 137-8° (from EtOH), RR'C(CO2H)CONHCONH2, RR'C(CO2H)2, m. 153-5°, and a very small amt. of RR'C(CONH2)2, m. 225-30°; from A (Et, iso-Bu) (XXI), RR'C(CONH2)2, m. 208-9°, RR'C(CO2H)CONH2, and RR'C(CO2H)2; from **Luminal** (XXII) (Et, **Ph**), RR'C(CONH2)2, m. 121°, EtCHPhCONHCONH2, m. 149-50°, EtCHPhCONH2, m. 84-5°, EtCHPhCO2H, m. 44-5°, and EtCHPhC(CO2H)2, m. 155-7°; from Numal (XXIII) (allyl, iso-Pr), RR'C(CO2H)CONHCONH2 and RR'C(CONH2)2, m. 176°; from Ipral (XXIV) (Et, iso-Pr), RR'C(CONH2)2, m. 179-80°; from Butisol (XXV) (2-Bu, Et), RR'C(CONH2)2, m. 163-4°; from Delvinal (XXVI) (Et, EtCH:CMe), RR'C(CONH2)2, m. 130°, and RR'C(CO2H)CONH2. From 1,5,5-trisubstituted barbituric acids (B) (5,5,1 substituents = R,R', and R'', resp., shown) were obtained: from B (allyl, allyl, Me), RR'CHCONHCONHR'', m. 64°, RR'C(CONH2)CONHMe, m. 147°, RR'C(CO2H)2, m. 130-2°, and "diallyl-N-methylmalonuric acid" [RR'C(CO2H), CONHCONHCONHMe]; from B (allyl, allyl, **Ph**), phenylurea, m. 145-6°, RR'CHCONHCONHR'', m. 80° (from aq. alc.), N-RR'C(CO2H)CONHCONHR'', m. 124-5° (with decompn. to the urea), and RR'C(CO2H)2; from Prominal (Et, **Ph**, Me), EtCHPhCONHCONHR'', m. 138-9°, RR'C(CONH2)CONHR'', m. 141-2°, RR'C(CO2H)CONHCONHMe, m. 131-2° (decompn.), RR'CHCO2H, and RR'C(CO2H)2, m. 145-7°; from Evipan (Me, 1-cyclohexen-1-yl,Me), RR'CHCONHCONHMe, m. 114-15°, RR'C(CO2H)CONHCONHR'', and RR'C(CO2H)2, m. 139-40°. From III was obtained 2-(1-cyclohexen-1-yl)-2-ethylmalonamic acid, m. 121-3° (decompn.), and from V, (PhCH2)2C(CO2H)2, m. 173-4° (decompn.). The stability of the various barbituric acids on standing in aq. **soln**. 30 days at room temp. with 3 equivs. of NaOH fell in the following order (listing **compd**. and % undecompd. in test). II, 91; I, 90; XXV, 90; XXIV, 82; III, 78; IV, 73; XXVI, 70; XXI, 63; V, 48; XIX, 16; XV, 10; XVIII, 10; XIV, 5; XXII, 0; XX is probably comparable to XIX, and XVI to XXII, while XVII and the trisubstituted barbituric acids are much poorer than any of the others.

IT **90-49-3P**, Urea, (2-phenylbutyryl)-
RL: PREP (Preparation)
(**prepn**. of)

L17 ANSWER 26 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 22 Apr 2001
ACCESSION NUMBER: 1954:37196 HCAPLUS Full-text
DOCUMENT NUMBER: 48:37196
ORIGINAL REFERENCE NO.: 48:6653f-h
TITLE: Keeping properties of **sodium phenobarbital solution**
AUTHOR(S): O'Reilly, W. J.; Wright, S. E.

CORPORATE SOURCE: Univ. Sydney
SOURCE: Australasian Journal of Pharmacy (**1954**), 37, 135
CODEN: AUPHAY; ISSN: 0004-8399
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Quant. data on the decompn. of Na phenobarbital in aq. **soln**. at 3 concns. (5, 10, and 20%) and at 3 different temp. levels (5-7°, 14-17°, and 30°) are presented. After 35 days the percentage losses were: 5% **solns**.-at 5°, 0; at 15°, 8.4; at 30° (25 days), 14; 10% **solns**.-at 5°, 8.4; at 15°, 9.4; at 30° (25 days), 17.8; 20% **solns**.-at 5°, 5.1; at 15°, 6.0; at 30° (25 days), 13.0. At 30° pptn. of phenobarbital occurred after 3-5 days and pptn. of **phenylethylacetylurea** after 15-25 days. Pptn. of **phenylethylacetylurea** occurred after about 35 days at other temps. The concn. of a 10% Na phenobarbital **soln**. in 50% alc. was reduced to 9.7% after 35 days. A 20% **soln**. in a 60:40 by vol. **mixt**. of propylene glycol and water showed no significant loss in strength after 35 days.
IT **57-30-7**, **Phenobarbital sodium**
(keeping properties of)

L17 ANSWER 27 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 22 Apr 2001
ACCESSION NUMBER: 1953:12189 HCAPLUS Full-text
DOCUMENT NUMBER: 47:12189
ORIGINAL REFERENCE NO.: 47:2180d-i,2181a-c
TITLE: Barbituric acid and its derivatives. XII. A new synthesis of open-chain N-arylureides
AUTHOR(S): Ridi, Mario; Venturini, Pietro; Zilletti, Lucilla
CORPORATE SOURCE: Univ. Florence, Italy
SOURCE: Annali di Chimica (Rome, Italy) (**1952**), 42, 25-31
CODEN: ANCRAI; ISSN: 0003-4592
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA through Vol 151.
AB cf. Gazz. chim. ital. 82, 23-30(1952); C.A. 45, 7021a. N-Aryl substituted pyrimidines are hydrolyzed at reflux temp. in good yields to open-chain ureides. Refluxing 10 g. POCl3, 3.33 g. CH2(CO2H)2, 4.27 g. PhNHCONH2 (I), and 33 g. CHCl3 8 h. gives PhN.CO.NH.CO.CH2.CO (II), white crystals from H2O. To 4.43 g. Na in 45 cc. EtOH are added successively 7.36 g. I and 5.65 g. NCCH2CO2Et, the **mixt**. is refluxed 30 h., cooled, acidified with HCl, and the resulting white ppt. repeatedly washed with boiling H2O and EtOH to give iminophenylbarbituric acid (III), m. 300°, which is quant. converted to II by refluxing with HCl. II (1 g.) in water refluxed 6 **h**. and the **mixt**. **concd**. to half its vol. and cooled deposits PhNHCONHAc, silky needles, m. 183-4°, also obtained by refluxing III and 1% aq. NH3 4 h. II (0.5 g.) refluxed 2 h. with 10 cc. 10% aq. KOH yields almost quant. PhNHCONH2. II (1 g.) and 8 g. Ac2O refluxed 2 h. give PhN.CO.NH.CO.CH-Ac.CO (IV), small white needles, m. 225° (from AcOH). To 1.2 g. Na in 40 cc. abs. EtOH are added 4.8 g. CH2-(CO2Et)2 and 4.56 g. PhNHCSNH2, the **mixt**. is refluxed 6 h., cooled, acidified with dil. HCl (1:1), the resulting white ppt. filtered off, washed with H2O, dissolved in 5% aq. KOH, and the **soln**. filtered and acidified with HCl to yield 8 g. PhN.CS.NH.CO.CH2.CO (V), white prisms, m. 220-1° (decompn.) (from EtOH). V refluxed with H2O gives PhNHCSNHAc, m. 169-70°. Similarly as above are **prepd**. from 5 g. dulcin and 2.8 g. NCCH2CO2Et imino-(p-ethoxyphenyl)barbituric acid, m. 315° (decompn.), hydrolyzed almost quant. to p-EtOC6H4N.CO.NH.CO.CH2.CO (VI) by boiling with dil. HCl. VI is hydrolyzed by H2O and dil. NH4OH at reflux temp. to p-EtOC6H4-NHCONHCH2Ac, small glistening needles, m. 225° (from EtOH), also obtained from dulcin and Ac2O. Refluxing 10 g. POCl3, 3.33 g. CH2(CO2H)2, 5.15 g. dulcin, and 33 g. CHCl3 6 h. gives p-EtOC6H4N.CO.NH.CO.CHAc.CO (VII), white crystals, m. 231° (from EtOH), also obtained by refluxing 1 g. VI with 6 g. Ac2O 3 h. II(1 g.) and 0.3 g. urea heated 1 h. at 160° and the **mixt**. taken up in EtOH and recrystd. from dioxane gives about 90% 1-phenyl-2, 6-dioxohexahydro-5-pyrimidinecarboxylic acid (VIII), small glistening needles, m. 280° (decompn.). Similarly from VI is **prepd**. the 1-(p-ethoxyphenyl) analog (IX) of VIII, m. 285° (decompn.). II (2 g.) and 0.69 g. NaNO2 in 100 cc. 15% aq. NaOH slowly acidified with dil. H2SO4 (1:10) at 0°, and the resulting ppt. dissolved in aq. Na2CO3 and repptd. with dil. H2SO4

gives 1-phenylvioluric acid (X), m. 211° (decompn.). Similarly from VI is obtained 1-(p-ethoxyphenyl)violuric acid (XI), m. 205° (decompn.); X and XI are sol. in aq. Na2CO3 with an intense red color, and sparingly sol. in cold org. solvents. PhNHCONH2 (3 g.) and 4.7 g. BuCH(CO2Et)2 in 30 g. MeOH contg. 2 g. Na refluxed 45 h. give as above PhN.CO.NH.CO.CHBu.CO (XII), white glistening prisms, m. 140° (from EtOH). XII refluxed 4 h. with 1% aq. NH3 gives PhNHCONHCOAm, small, white, glistening needles, m. 100° (from 50% aq. EtOH). PhN.CO.NH.CO.CEt2.CO refluxed 3 h. with 1% aq. NH3 yield PhNHCONHCOCHEt2 small white needles, m. 128-9° (from 50% aq. EtOH). **Luminal** gives similarly EtPhCHCONHCONH2, white prisms, m. 148° (from 50% aq. AcOH). VI (1 g.) and 3 g. BzH in EtOH refluxed 3 h. in the presence of 3 drops pyridine give p-EtOC6H4N.CO.NH.CO.C(:CHPh).CO, yellow solid, m. 240° (from EtOH). IV, VII, VIII, and IX are not attacked by refluxing 10 h. with H2O and give with 1% aq. NH3 the corresponding NH4 salts. X and XI refluxed 5 h. with dil. NH4OH (1:4) give PhNHCONH2 and dulcin, resp., together with other products not yet identified.

IT **90-49-3P**, Urea, (2-phenylbutyryl)-
RL: PREP (Preparation)
(**prepn**. of)

OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L17 ANSWER 28 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 22 Apr 2001
ACCESSION NUMBER: 1952:68469 HCAPLUS Full-text
DOCUMENT NUMBER: 46:68469
ORIGINAL REFERENCE NO.: 46:11456d-f
TITLE: The anticonvulsant activity of ureides
AUTHOR(S): Lubienska, Jolanta
CORPORATE SOURCE: Z. Zakladu Farm., Kracow, Pol.
SOURCE: Polska Akad. Umiejetnosci Rozprawy Wydzialu Lekarskiego (**1951**), 12(No. 6), 20 pp.
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB The anticonvulsant activities were studied of the ureide derivs. of phenylacetate (I), α-phenylpropionate (II), β-phenylpropionate, α-phenylbutyrate (III), γ-phenylbutyrate, phenylcyanate, α-chlorophenylacetate, and α-bromophenylacetate. These **compds**., practically insol. in H2O, were given as 10% suspensions in gum acacia. The most potent anticonvulsant was I. For comparison purposes **phenylethylbarbituric** acid (IV) and the Na salt of diphenylhydantoin (V) were used. By the elec. method on rabbits, IV and V were 4 times as potent as I in rats. I was 1.2 times stronger than II and III had min. activity; the rest of the derivs. were without activity. In shocks produced by cardiac glycosides and coramine, I was 1.3 times as potent as V; in coramine-induced shocks I was 1.9 times as potent as V. I was effective in abolishing convulsions produced by malononitrile in white mice and protected frogs against picrotoxin-induced convulsions.

IT **90-49-3**, Urea, [2-phenylbutyryl]-
(anticonvulsant activity of)

L17 ANSWER 29 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 22 Apr 2001
ACCESSION NUMBER: 1949:52431 HCAPLUS Full-text
DOCUMENT NUMBER: 43:52431
ORIGINAL REFERENCE NO.: 43:9375c-d
TITLE: The decomposition of **sodium phenobarbital** in **solutions** of aliphatic amines and alkanolamines
AUTHOR(S): Dunker, Melvin F. W.
SOURCE: Journal of the American Pharmaceutical Association (1912-1977) (**1949**), 38, 409-11
CODEN: JPHAA3; ISSN: 0003-0465
DIGITAL OBJECT ID: 10.1002/jps.3030380715
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB The decompn. of aq. **solns**. of Na phenobarbital resulting in the formation of PhEtAc urea was studied in the presence of 22 selected aliphatic amines (I) and alkanolamines (II). The decompn. proceeded more slowly in the **solns**. of II.

IT **57-30-7**, **Phenobarbital sodium**
(decompn. in **solns**. of aliphatic amines and

alkanolamines)
IT **90-49-3P**, Urea, (2-phenylbutyryl)-
RL: PREP (Preparation)
(formation from phenobarbital)

L17 ANSWER 30 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 16 Dec 2001
ACCESSION NUMBER: 1938:1874 HCAPLUS Full-text
DOCUMENT NUMBER: 32:1874
ORIGINAL REFERENCE NO.: 32:309d-f
TITLE: Sterilization of aqueous **solutions** of **sodium phenobarbital**
AUTHOR(S): Tomski, H. W.; Waller, L. J.
SOURCE: Pharmaceutical Journal (**1937**), 139, 421
CODEN: PHJOAV; ISSN: 0031-6873
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB As aq. **solns**. of this substance (A), now often used for injections, are unstable upon keeping, (cf. Nielsen, C. A. 27, 5146), the loss of A was detd. (cf. Hegland, C. A. 29, 2659.4) under different exptl. conditions. The loss by heat depends on the temp., time of exposure to heat, alky. and to a lesser degree on concn. of the **soln**. A 20% **soln**. of A loses 20% on autoclaving at 115° for 30 min., 10% on steaming at 100° for 1 hr., 6-7% on tyndallization and 1% when the **soln**. is sterilized by the Brit. Pharm. emergency method. When a 20% **soln**. is sterilized by heat, it forms, upon cooling, a white ppt. of **phenylethylacetyl urea**. **Solns**. of A for injection should have a **pH** as low as possible, should be sterilized by filtration only and be stored for short periods in a cool place.
IT **57-30-7**, **Phenobarbital sodium**
(sterilization of **solns**. of)

L17 ANSWER 31 OF 31 HCAPLUS COPYRIGHT 2021 ACS on STN
ED Entered STN: 16 Dec 2001
ACCESSION NUMBER: 1930:46631 HCAPLUS Full-text
DOCUMENT NUMBER: 24:46631
ORIGINAL REFERENCE NO.: 24:5048g-i
TITLE: The detection of **luminal** in urine
AUTHOR(S): Koenig, W.; Kluge, H.
SOURCE: Chemiker-Zeitung (**1930**), 54, 451
CODEN: CMKZAT; ISSN: 0009-2894
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The 24-hr. specimen of urine is acidified with tartaric acid and shaken with Et2O. After the ether ext. is washed with 30 cc. of H2O, it is filtered through a dry filter paper and reduced to a sirupy consistency on a water bath. The residue is dissolved in hot H2O, treated with animal charcoal and filtered. After cooling to room temp. the **soln**. is made alk. with dil. NaOH **soln**. and again shaken with Et2O(ether **soln**. A). The aq. layer which seps. is acidified with dil. H2SO4, mixed with solid NaHCO3 until alk. to litmus and again shaken with ether (B). The aq. fraction this time is acidified with dil. H2SO4 and extd. with ether (C). The ether **solns**. A, B and C are each washed with H2O, filtered dry and the ether layer is evapd. (A) leaves an oily residue, not easily identified because of the **phenylethylacetyl urea** usually present. The residue from **soln**. (B) is treated with hot H2O and animal charcoal. After evapg. to a small vol. (1.cc.) white crystals of **luminal** sep. The usual **luminal** detection tests may be used for its identification. The residue from **soln**.(C) treated as (B) yields hippuric acid crystals. Oral administration of **luminal** increases the output of hippuric acid.

FILE 'MEDLINE' ENTERED AT 08:33:12 ON 30 AUG 2021

FILE 'BIOSIS' ENTERED AT 08:33:12 ON 30 AUG 2021
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L18 297 SEA ABB=ON PLU=ON L8
L19 2 SEA ABB=ON PLU=ON L18 AND (POWDER? OR GRANUL?)
L20 1 SEA ABB=ON PLU=ON L18 AND (LYOPHILIS? OR LYOPHILIZ? OR FREEZ?)
L21 57 SEA ABB=ON PLU=ON L18 AND (COMPOSITION OR COMP## OR PREP? OR FORMULATION OR SOLUTION OR SOLN OR MIXTURE)
L22 10 SEA ABB=ON PLU=ON L18 AND (PH OR (H OR HYDROGEN)(5W)(CONCENTRATION OR CONC##))
L23 53 SEA ABB=ON PLU=ON ((L19 OR L20 OR L21 OR L22)) AND (PY<2019 OR AY<2019 OR PRY<2019)

FILE 'WPIX, PQSCITECH' ENTERED AT 08:25:42 ON 30 AUG 2021
L24 7 SEA ABB=ON PLU=ON L8
L25 2 SEA ABB=ON PLU=ON L24 AND TEMP/PHP
L26 4 SEA ABB=ON PLU=ON L24 AND PER/PHP
L27 0 SEA ABB=ON PLU=ON L24 AND PHV/PHP
L28 1 SEA ABB=ON PLU=ON L24 AND MASS/PHP
L29 2 SEA ABB=ON PLU=ON ((L25 OR L26 OR L27) OR L28) AND (PY<2019 OR AY<2019 OR PRY<2019)

L30 40 DUP REM L29 L23 (15 DUPLICATES REMOVED)

L30 ANSWER 1 OF 40 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
ACCESSION NUMBER: 2018:304495 BIOSIS Full-text
DOCUMENT NUMBER: PREV201800304495
TITLE: Stable **formulation** of **phenobarbital sodium** injection.
AUTHOR(S): Parker, Michael G. [Inventor]; Anonymous; Wilson, Scott S. [Inventor]; Chahal, Yasmeen [Inventor]; Hovius, Kelly W. [Inventor]; McAnany, David E. [Inventor]
CORPORATE SOURCE: Cherry Hill, NJ USA
ASSIGNEE: West Ward Pharmaceuticals International Limited
PATENT INFORMATION: US 09901576 20180227
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (**FEB 27 2018**)
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Mar 2018
Last Updated on STN: 22 Mar 2018
AB Stable **phenobarbital sodium solutions** for injection that do not generate impurities during extended storage. These **solutions** include **phenobarbital sodium** in an amount of 15 to 200 mg/mL; a C1-C4 alcohol such as ethanol in an amount of 105 to 160 mg/mL; and a glycol such as propylene glycol in an amount of between 620 and 830 mg/mL and have a **pH** of between 9 and 12 which is adjusted to that range by adding acid or base, as required. No more than 50 mg/mL water is present including any water introduced by the acid or base. The **solutions** contain no more than 0.8% of **phenyl ethyl acetyl urea** impurity as well as no detectable amount of phenyl butyric acid after two years storage at room temperature.

L30 ANSWER 2 OF 40 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
DUPLICATE 1
ACCESSION NUMBER: 2018:1064071 BIOSIS Full-text
DOCUMENT NUMBER: PREV201900092116
TITLE: Glyphosate-based herbicide enhances the uterine sensitivity to estradiol in rats.
AUTHOR(S): Guerrero Schimpf, Marlise [Reprint Author]; Milesi, Maria M.; Luque, Enrique H.; Varayoud, Jorgelina [Reprint Author]
CORPORATE SOURCE: Univ Nacl Litoral, Fac Bioquim and Ciencias Biol, ISAL, CONICET, Santa Fe, Argentina
varayoud@fbcb.unl.edu.ar
SOURCE: Journal of Endocrinology, (**NOV 2018**) Vol. 239, No. 2, pp. 197-213. http://joe.endocrinology-journals.org/.
CODEN: JOENAK. ISSN: 0022-0795. E-ISSN: 1479-6805.
DIGITAL OBJECT ID: 10.1530/JOE-18-0207
DOCUMENT TYPE: Article

LANGUAGE: English
ENTRY DATE: Entered STN: 19 Dec 2018
Last Updated on STN: 13 Nov 2019

AB In a previous work, we detected that postnatal exposure to a glyphosate-based herbicide (GBH) alters uterine development in **prepubertal** rats causing endometrial hyperplasia and increasing cell proliferation. Our goal was to determine whether exposure to low dose of a GBH during postnatal development might enhance the sensitivity of the uterus to an estrogenic treatment. Female Wistar pups were subcutaneously injected with saline **solution** (control) or GBH using the reference dose (2 mg/kg/day, **EPA**) on postnatal days (PND) 1, 3, 5 and 7. At weaning (PND21), female rats were bilaterally ovariectomized and treated with silastic capsules containing 17 beta-estradiol (E2, 1 mg/mL) until they were 2 months of age. On PND60, uterine samples were removed and processed for histology, immunohistochemistry and mRNA extraction to evaluate: (i) uterine morphology, (ii) uterine cell proliferation by the detection of Ki67, (iii) the expression of the estrogen receptors alpha (ESR1) and beta (ESR2) and (iv) the expression of WNT7A and CTNNB1. GBH-exposed animals showed increased **luminal** epithelial height and stromal nuclei density. The **luminal** and glandular epithelium were markedly hyperplastic in 43% of GBH-exposed animals. GBH exposure caused an increase in E2-induced cell proliferation in association with an induction of both ESR1 and ESR2. GBH treatment decreased membranous and cytoplasmic expression of CTNNB1 in **luminal** and glandular epithelial cells and increased WNT7A expression in the **luminal** epithelium. These results suggest that early postnatal exposure to a GBH enhances the sensitivity of the rat uterus to estradiol and induces histomorphological and molecular changes associated with uterine hyperplasia.

L30 ANSWER 3 OF 40 MEDLINE ® on STN
ACCESSION NUMBER: 2020194838 MEDLINE (EPUB AHEAD OF PRINT) Full-text
DOCUMENT NUMBER: PubMed ID: 30121576
TITLE: Glyphosate-based herbicide enhances the uterine sensitivity to estradiol in rats.
AUTHOR: Guerrero Schimpf Marlise
CORPORATE SOURCE: M Guerrero Schimpf, Catedra de Fisiologia Humana, Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Instituto de Salud y Ambiente del Litoral (ISAL, UNL-CONICET), Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Santa Fe, Argentina.
AUTHOR: Milesi Maria M
CORPORATE SOURCE: M Milesi, Catedra de Fisiologia Humana, Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Instituto de Salud y Ambiente del Litoral (ISAL, UNL-CONICET), Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Santa Fe, Argentina.
AUTHOR: Luque Enrique H
CORPORATE SOURCE: E Luque, Catedra de Fisiologia Humana, Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Instituto de Salud y Ambiente del Litoral (ISAL, UNL-CONICET), Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Santa Fe, Argentina.
AUTHOR: Varayoud Jorgelina
CORPORATE SOURCE: J Varayoud, Catedra de Fisiologia Humana, Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Instituto de Salud y Ambiente del Litoral (ISAL, UNL-CONICET), Facultad de Bioquimica y Ciencias Biologicas, Universidad Nacional del Litoral, Santa Fe, Argentina. varayoud@fbcb.unl.edu.ar
SOURCE: The Journal of endocrinology, **(2018 Aug 18)** .
Electronic Publication Date: 18 Aug 2018
Journal code: 0375363. E-ISSN: 1479-6805. L-ISSN: 0022-0795.
DIGITAL OBJECT ID: http://dx.doi.org/10.1530/JOE-18-0207
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: EPUB AHEAD OF PRINT; NONMEDLINE; NONINDEXED
FILE SEGMENT: Print; Electronic
ENTRY DATE: Entered STN: 20 Aug 2018

Last Updated on STN: 20 Aug 2018
OS.CITING REF COUNT: 5 There are 5 MEDLINE records that cite this record
AB In a previous work, we detected that postnatal exposure to a glyphosate-based herbicide (GBH) alters uterine development in **prepubertal** rats causing endometrial hyperplasia and increasing cell proliferation. Our goal was to determine whether exposure to low-dose of a GBH during postnatal development might enhance the sensitivity of the uterus to an estrogenic treatment. Female Wistar pups were subcutaneously injected with saline **solution** (control) or GBH using the reference dose (2 mg/kg/day, **EPA**) on postnatal days (PND) 1, 3, 5, and 7. At weaning (PND21), female rats were bilaterally ovariectomized and treated with silastic capsules containing 17β-estradiol (E2, 1mg/ml) until they were two months of age. On PND60, uterine samples were removed and processed for histology, immunohistochemistry and mRNA extraction to evaluate: i) uterine morphology, ii) uterine cell proliferation by the detection of Ki67, iii) the expression of the estrogen receptors alpha (ESR1) and beta (ESR2), and iv) the expression of WNT7A and β-catenin. GBH-exposed animals showed increased **luminal** epithelial height and stromal nuclei density. The **luminal** and glandular epithelium were markedly hyperplastic in 43% of GBH-exposed animals. GBH exposure caused an increase in E2-induced cell proliferation in association with an induction of both ESR1 and ESR2. GBH treatment decreased membranous and cytoplasmic expression of β-catenin in **luminal** and glandular epithelial cells and increased WNT7A expression in the **luminal** epithelium. These results suggest that early postnatal exposure to a GBH enhances the sensitivity of the rat uterus to estradiol, and induces histomorphological and molecular changes associated with uterine hyperplasia.

L30 ANSWER 4 OF 40 WPIX COPYRIGHT 2021 CLARIVATE ANALYTICS on STN
DUPLICATE 2
ACCESSION NUMBER: 2017-340631 [201738] WPIX Full-text
TITLE: **Phenobarbital sodium** solution used for treating partial and generalized tonic-clonic seizures and neonatal seizures, comprises **phenobarbital sodium**, alcohol, and propylene glycol
DERWENT CLASS: A96; B03; B07; P33; Q31; Q34
INVENTOR: CHAHAL Y; HOVIUS K W; MCANANY D E; PARKER M G; WILSON S S
PATENT ASSIGNEE: (EURO-N) EUROHEALTH INT SARL; (WWAR-N) WEST WARD PHARM INT LTD
COUNTRY COUNT: 132

PATENT INFO ABBR.:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
US 20170143719	A1	20170525	(201738)*	EN	9[0]	
WO 2017085687	A1	20170526	(201738)	EN		
US 9901576	B2	20180227	(201816)	EN		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 20170143719	A1	**US 2016-15355868**	**20161118**
US 20170143719	A1 Provisional	**US 2015-258000P**	**20151120**
WO 2017085687	A1	**WO 2016-IB56973**	**20161118**
US 9901576	B2 Provisional	**US 2015-258000P**	**20151120**
US 9901576	B2	**US 2016-15355868**	**20161118**

FILING DETAILS:

PATENT NO	KIND	PATENT NO
US 9901576	B2 Previous Publ	US 2017143719 A

PRIORITY APPLN. INFO: **US 2016-15355868** **20161118**
US 2015-258000P **20151120**
AN 2017-340631 [201738] WPIX Full-text
AB US 20170143719 A1 UPAB: 20170612

NOVELTY - **Phenobarbital sodium** solution comprises 15-200 mg/ml **phenobarbital sodium**, 105-160 mg/ml 1-**4C** alcohol, and 620-830 mg/ml propylene glycol. The solution has a pH of 9-12 which is adjusted to that range by adding a sufficient amount of acid or base, the solution comprises not greater than 50 mg/ml water including water introduced by acid or base that is added to provide the desired pH, and the solution comprises not greater than 0.**8**% of **phenyl ethyl acetyl urea** (**PEAU**) impurity after 2 years storage at room temperature.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) sealed container comprising 0.5-20 ml **phenobarbital sodium** solution; and

(2) method for making the **phenobarbital sodium** solution, which involves mixing the **phenobarbital sodium** with alcohol and glycol and adjusting the pH to desired range as necessary by adding acid or base.

ACTIVITY - Anticonvulsant. No biological data given.

MECHANISM OF ACTION - None given.

USE - The **phenobarbital sodium** solution is useful for treating partial and generalized tonic-clonic seizures and neonatal seizures.

ADVANTAGE - The **phenobarbital sodium** solution is free of preservatives, antioxidants, wetting agents, emulsifying agents, surfactants or dispersing agents, does not contain a detectable amount of phenyl butyric acid after 2 years storage at room temperature, and other drug active, exhibits 0.**8**% or less hydrolysis impurities and is an impurity-free formulation, and has enhanced stability under various stress conditions, and faster dissolution rate.

Member(0001)

ABEQ US 20170143719 A1 UPAB 20170612

NOVELTY - **Phenobarbital sodium** solution comprises 15-200 mg/ml **phenobarbital sodium**, 105-160 mg/ml 1-**4C** alcohol, and 620-830 mg/ml propylene glycol. The solution has a pH of 9-12 which is adjusted to that range by adding a sufficient amount of acid or base, the solution comprises not greater than 50 mg/ml water including water introduced by acid or base that is added to provide the desired pH, and the solution comprises not greater than 0.**8**% of **phenyl ethyl acetyl urea** (**PEAU**) impurity after 2 years storage at room temperature.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) sealed container comprising 0.5-20 ml **phenobarbital sodium** solution; and

(2) method for making the **phenobarbital sodium** solution, which involves mixing the **phenobarbital sodium** with alcohol and glycol and adjusting the pH to desired range as necessary by adding acid or base.

ACTIVITY - Anticonvulsant. No biological data given.

MECHANISM OF ACTION - None given.

USE - The **phenobarbital sodium** solution is useful for treating partial and generalized tonic-clonic seizures and neonatal seizures.

ADVANTAGE - The **phenobarbital sodium** solution is free of preservatives, antioxidants, wetting agents, emulsifying agents, surfactants or dispersing agents, does not contain a detectable amount of phenyl butyric acid after 2 years storage at room temperature, and other drug active, exhibits 0.**8**% or less hydrolysis impurities and is an impurity-free formulation, and has enhanced stability under various stress conditions, and faster dissolution rate.

L30 ANSWER 5 OF 40 MEDLINE ® on STN DUPLICATE 3

ACCESSION NUMBER: 2018284634 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 28216010

TITLE: Uptake of benzo[a]pyrene, but not of phenanthrene, is inhibited by fatty acids in intestinal brush border membrane vesicles of rainbow trout (Oncorhynchus mykiss).

AUTHOR: de Gelder Stefan

CORPORATE SOURCE: Radboud University, Institute for Water and Wetland Research, Department of Animal Ecology and Physiology, P.O. Box 9010, 6500 GL Nijmegen, The Netherlands, National Institute of Nutrition and Seafood Research, P.O. Box 2029, Nordnes, 5817 Bergen, Norway. s.degelder@science.ru.nl

AUTHOR: van Och Liselot; Zethof Jan; Pelgrim Thamar N M; Flik

Gert; Klaren Peter H M
CORPORATE SOURCE: Radboud University, Institute for Water and Wetland Research, Department of Animal Ecology and Physiology, P.O. Box 9010, 6500 GL Nijmegen, The Netherlands.
AUTHOR: Rasinger Josef D; Berntssen Marc H G
CORPORATE SOURCE: National Institute of Nutrition and Seafood Research, P.O. Box 2029, Nordnes, 5817 Bergen, Norway.
SOURCE: Comparative biochemistry and physiology. Toxicology & pharmacology : CBP, **(2017 May)** Vol. 195, pp. 1-8. Electronic Publication Date: 12 Feb 2017
Journal code: 100959500. ISSN: 1532-0456. L-ISSN: 1532-0456.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/j.cbpc.2017.02.003
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print; Electronic
ENTRY MONTH: 201703
ENTRY DATE: Entered STN: 21 Feb 2017
Last Updated on STN: 31 Mar 2017
Indexing Added: 31 Mar 2017
Entered Medline: 30 Mar 2017

AB Partial replacement of fish ingredients with vegetable ingredients has elevated levels of polycyclic aromatic hydrocarbons (PAHs) in Atlantic salmon reared on these feeds. PAH uptake in the intestinal tract is postulated to occur in association with lipid absorption and could well be affected by fatty acid **composition**. We therefore investigated the effects of a fish oil and vegetable oil fatty acid, eicosapentaenoic acid (**EPA**; 20:5n-3) and oleic acid (18:1n-9) respectively, on the uptake of benzo[a]pyrene (BaP) and phenanthrene (PHE) across the intestinal brush border membrane in the salmonid species rainbow trout (Oncorhynchus mykiss). BaP and PHE were solubilized in mixed micelles composed of either **EPA** or oleic acid and administrated to isolated brush border membrane vesicles (BBMV) derived from the pyloric caeca, proximal intestine and distal intestine. In the absence of free fatty acids (FFA) trans-membrane uptake of BaP and PHE was 2-7 times lower than the fraction associated to or in the membrane. In the presence of FFA, trans-membrane BaP uptake had decreased by 80 and 40% at the highest **EPA** and oleic acid concentration, respectively, whereas PHE uptake was virtually unaffected. In the presence of BaP, but not PHE, trans-membrane **EPA** uptake in BBMV had decreased. This study obtained evidence for PAH-dependent interactions with FFA uptake. We conclude that intestinal BaP uptake is reduced by **luminal** FFA contents whereas PHE uptake is not. A large fraction of the administrated BaP and PHE remains associated with the cellular membrane of enterocytes and may interfere with uptake of nutrients.
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L30 ANSWER 6 OF 40 MEDLINE ® on STN DUPLICATE 4
ACCESSION NUMBER: 2017034675 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 27222841
TITLE: Vascular **composition** data supporting the role of N-3 polyunsaturated fatty acids in the prevention of cardiovascular disease events.
AUTHOR: Ohwada Takayuki; Hotsuki Yu; Sakamoto Takayuki; Watanabe Kenichi
CORPORATE SOURCE: Fukushima Red Cross Hospital, Department of Cardiology, Fukushima, Japan.
AUTHOR: Yokokawa Tetsuro; Kanno Yuki; Nakazato Kazuhiko; Takeishi Yasuchika
CORPORATE SOURCE: Fukushima Medical University, Department of Cardiology and Hematology, Fukushima, Japan.
SOURCE: Data in brief, **(2016 Jun)** Vol. 7, pp. 1237-47. Electronic Publication Date: 7 Apr 2016
Journal code: 101654995. ISSN: 2352-3409. L-ISSN: 2352-3409.
Report No.: PMC-PMC4867859.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/j.dib.2016.03.101
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; PUBMED-NOT-MEDLINE
FILE SEGMENT: Electronic; eCollection

ENTRY MONTH: 201605
ENTRY DATE: Entered STN: 26 May 2016
Last Updated on STN: 26 May 2016
Indexing Added: 26 May 2016
Entered Medline: 25 May 2016
OS.CITING REF COUNT: 2 There are 2 MEDLINE records that cite this record
MEDLINE REFERENCE COUNT: 7 There are 7 cited references available in MEDLINE for this document.

AB N-3 polyunsaturated fatty acids (PUFAs) are thought to have protective effects against cardiovascular disease. Here, we report the relationship between serum PUFA concentrations and plaque **composition**, as evaluated by virtual histology-intravascular ultrasound (VH-IVUS). Consecutive patients (n=61) who underwent percutaneous coronary intervention (PCI) were pre-operatively examined using VH-IVUS to assess the **composition** of culprit plaques. Gray-scale IVUS and VH-IVUS data of fibrous, fibro-fatty, necrotic core, and dense calcium regions of plaques were estimated at the minimal **luminal** area sites of culprit lesions. Serum levels of high-sensitivity C-reactive protein (hsCRP) and PUFAs, including eicosapentaenoic acid (**EPA**), docosahexaenoic acid (DHA), and arachidonic acid (AA), were compared between patients with (ACS, n=27) and without acute coronary syndrome (non-ACS, n=34) before PCI. Multiple logistic regression analysis of the data showed that **EPA**/AA under the median was more highly associated with ACS than hsCRP over the median. In addition, **EPA**/AA was negatively correlated with the percentage of fibrous plaque regions and **EPA**/AA and DHA/AA were positively correlated with the percentage of dense calcium regions in plaques. Furthermore, the correlation index of **EPA**/AA was the most highly (R=0.513) correlated with the percentage of dense calcium regions in plaques.

L30 ANSWER 7 OF 40 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN
ACCESSION NUMBER: 2017:779737 BIOSIS Full-text
DOCUMENT NUMBER: PREV201700779737
TITLE: Characterization of the Human EA.hy926 Endothelial Cell Response to Dietary Polyunsaturated Fatty Acids as a Function of Growth Conditions.
AUTHOR(S): Du, Youjia [Reprint Author]; Taylor, Carla; Aukema, Harold; Zahradka, Peter
CORPORATE SOURCE: Univ Manitoba, Winnipeg, MB, Canada
SOURCE: FASEB Journal, (**APR 2016**) Vol. 30, No. Suppl. 1, pp. 684.10. http://www.fasebj.org/.
Meeting Info.: Experimental Biology Meeting. San Diego, CA, USA. April 02 -06, 2016. Amer Assoc Anatomists; Amer Physiol Soc; Amer Soc Biochem & Mol Biol; Amer Soc Investigat Pathol; Amer Soc Nutr; Amer Soc Pharmacol & Expt Therapeut.
CODEN: FAJOEC. ISSN: 0892-6638. E-ISSN: 1530-6860.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 11 Oct 2017
Last Updated on STN: 14 Mar 2018

AB Background Endothelial cells line the **luminal** surface of blood vessels and play an important role in maintaining vascular homeostasis. Inappropriate elevated levels of non-esterified fatty acids in the blood may negatively affect endothelial cell function. The development of endothelial dysfunction is believed to be the initial step leading to atherosclerosis.Objective This study compared the effects of different polyunsaturated fatty acids (PUFAs) on the viability and proliferation of subconfluent and confluent human EA. hy926 cells grown with and without Matrigel (a **mixture** of extracellular matrix proteins that provide a surface for cellular attachment).Methods EA. hy926 were seeded (9000 cells/cm(2)) on plastic dishes with and without Matrigel coating and cultured in Dulbecco's Modified Eagle Medium and 10% fetal bovine serum for up to 12 days without changing the media. Dietary PUFAs (linoleic acid, arachidonic acid - AA, alpha-linolenic acid, eicosapentaenoic acid - **EPA**, docosahexaenoic acid - DHA) were **prepared** in phosphate-buffered saline containing 5% fatty acid-free bovine serum albumin and then added at final concentrations of 1 to 150 mu M to subconfluent (4 d after seeding) and confluent cells (8 d after seeding) for 24 h. Viability was assessed using the Cell Counting Kit-8 (CCK) while proliferation was assessed with a BrdU cell proliferation assay.Results Cells reached a maximum number 8 days

after seeding on both plain and Matrigel coated dishes. However, BrdU incorporation peaked on day 7 when cells were grown on Matrigel and then started decreasing, whereas BrdU incorporation by cells grown on uncoated dishes continued for up to 10 days. On uncoated dishes, AA and DHA decreased the viability of subconfluent cells in a dose-dependent manner, while **EPA** only had a slight effect. PUFA treatment had no effect on confluent cells. No decrease in viability was observed upon PUFA treatment of subconfluent and confluent cells when grown on Matrigel coated plates. On the other hand, the BrdU assay indicated that AA and DHA decrease the proliferation of both subconfluent and confluent cells in a dose-dependent manner on Matrigel coated dishes.Conclusions EA. hy926 cells reach confluence 8 day after seeding on Matrigel coated and uncoated plates, but became quiescent only on Matrigel coated plates after becoming confluent suggesting extracellular matrix is important for normal function. AA and DHA showed an adverse effect on viability of endothelial cells, and their effects were greatest in subconfluent cells and in the absence of extracellular matrix. Survival of subconfluent cells exposed to high concentrations of PUFAs was greatest on Matrigel. The proliferative potential of both subconfluent and confluent cells was decreased by exposure to high concentration of AA and DHA on Matrigel.Significance Subconfluent and confluent endothelial cells have different responses to different concentration of different dietary PUFAs in relation to viability and proliferation. However, growth on Matrigel, which resembles the complex extracellular environment of blood vessels, promotes cell survival under high concentration of PUFAs, particularly AA and DHA, compared to the low survival rate of cells grown on uncoated dishes. This implies that Matrigel, by providing a more physiological relevant physical and chemical substrate, may also affect the response of endothelial cells to dietary PUFAs on other aspects, thus warranting further investigation.

L30 ANSWER 8 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 0052282393 EMBASE Full-text
DOCUMENT NUMBER: 72320471
TITLE: Characterization of the human EA.hy926 endothelial cell response to dietary polyunsaturated fatty acids as a function of growth conditions.
AUTHOR: Du, Youjia (correspondence); Taylor, Carla; Aukema, Harold; Zahradka, Peter
CORPORATE SOURCE: University of Manitoba, Winnipeg, MB, Canada.
AUTHOR: Du, Youjia (correspondence); Taylor, Carla; Aukema, Harold; Zahradka, Peter
CORPORATE SOURCE: Canadian Centre for Agri-Food Research in Health and Medicine, Winnipeg, MB, Canada.
SOURCE: FASEB Journal, (**April 2016**) Vol. 30, Supp. Meeting Abstracts.
Meeting Info: Experimental Biology 2016, EB. San Diego, CA, United States. 02 Apr 2016-06 Apr 2016
ISSN: 1530-6860
PUBLISHER: FASEB.
DOCUMENT TYPE: Journal; Conference; (Conference Abstract)
FILE SEGMENT: CONF
FILE SEGMENT: Intellectual Indexing
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 29 Jun 2016
Last Updated on Embase: 29 Jun 2016

AB Background Endothelial cells line the **luminal** surface of blood vessels and play an important role in maintaining vascular homeostasis. Inappropriate elevated levels of non-esterified fatty acids in the blood may negatively affect endothelial cell function. The development of endothelial dysfunction is believed to be the initial step leading to atherosclerosis. Objective This study compared the effects of different polyunsaturated fatty acids (PUFAs) on the viability and proliferation of subconfluent and confluent human EA.hy926 cells grown with and without Matrigel (a **mixture** of extracellular matrix proteins that provide a surface for cellular attachment). Methods EA.hy926 were seeded (9000 cells/cm2) on plastic dishes with and without Matrigel coating and cultured in Dulbecco's Modified Eagle Medium and 10% fetal bovine serum for up to 12 days without changing the media. Dietary PUFAs (linoleic acid, arachidonic acid - AA, α-linolenic acid, eicosapentaenoic acid - **EPA**,

docosahexaenoic acid - DHA) were **prepared** in phosphate-buffered saline containing 5% fatty acid-free bovine serum albumin and then added at final concentrations of 1 to 150 µM to subconfluent (4 d after seeding) and confluent cells (8 d after seeding) for 24 h. Viability was assessed using the Cell Counting Kit-8 (CCK) while proliferation was assessed with a BrdU cell proliferation assay. Results Cells reached a maximum number 8 days after seeding on both plain and Matrigel coated dishes. However, BrdU incorporation peaked on day 7 when cells were grown on Matrigel and then started decreasing, whereas BrdU incorporation by cells grown on uncoated dishes continued for up to 10 days. On uncoated dishes, AA and DHA decreased the viability of subconfluent cells in a dose-dependent manner, while **EPA** only had a slight effect. PUFA treatment had no effect on confluent cells. No decrease in viability was observed upon PUFA treatment of subconfluent and confluent cells when grown on Matrigel coated plates. On the other hand, the BrdU assay indicated that AA and DHA decrease the proliferation of both subconfluent and confluent cells in a dose-dependent manner on Matrigel coated dishes. Conclusions EA.hy926 cells reach confluence 8 day after seeding on Matrigel coated and uncoated plates, but became quiescent only on Matrigel coated plates after becoming confluent suggesting extracellular matrix is important for normal function. AA and DHA showed an adverse effect on viability of endothelial cells, and their effects were greatest in subconfluent cells and in the absence of extracellular matrix. Survival of subconfluent cells exposed to high concentrations of PUFAs was greatest on Matrigel. The proliferative potential of both subconfluent and confluent cells was decreased by exposure to high concentration of AA and DHA on Matrigel. Significance Subconfluent and confluent endothelial cells have different responses to different concentration of different dietary PUFAs in relation to viability and proliferation. However, growth on Matrigel, which resembles the complex extracellular environment of blood vessels, promotes cell survival under high concentration of PUFAs, particularly AA and DHA, compared to the low survival rate of cells grown on uncoated dishes. This implies that Matrigel, by providing a more physiological relevant physical and chemical substrate, may also affect the response of endothelial cells to dietary PUFAs on other aspects, thus warranting further investigation.

L30 ANSWER 9 OF 40 PQSCITECH COPYRIGHT 2021 ProQuest LCC on STN.
ACCESSION NUMBER: 2014:215088 PQSCITECH Full-text
DOCUMENT NUMBER: 18961008
TITLE: Relationship between coronary flow reserve evaluated by phase-contrast cine cardiovascular magnetic resonance and serum eicosapentaenoic acid
AUTHOR(S): Kato, Shingo; Fukui, Kazuki; Kawaguchi, Junko; Ishii, Nao; Koga, Masashi; Kusakawa, Yuka; Kusama, Ikuyoshi; Nakachi, Tatsuya; Nakagawa, Takeshi; Terauchi, Yasuo; Uchino, Kazuaki; Kimura, Kazuo; Umemura, Satoshi
CORPORATE SOURCE: Department of Cardiology, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomiokahigashi, Kanazawa-ku, Yokohama, Kanagawa 236-0051, Japan
SOURCE: Journal of Cardiovascular Magnetic Resonance [J. Cardiovasc. Magn. Reson.]. Vol. 15, no. 1, 106 p. 2013., 32 refs.
ISSN: 1532-429X
DOI: 10.1186/1532-429X-15-106
Published by: BioMed Central Ltd., Floor 6 London WC1X 8HL United Kingdom
URL (Document): http://jcmr-online.com/content/15/1/106
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Computer and Information Systems Abstracts (CI)
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Mar 2014
Last updated on STN: 14 Mar 2014
AN 2014:215088 PQSCITECH Full-text
AB Background: Long-term intake of long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs), especially eicosapentaenoic acid (**EPA**) is associated with a low risk for cardiovascular disease. Phase-contrast cine cardiovascular magnetic resonance (PC cine CMR) can assess coronary flow reserve (CFR). The present study investigates the relationship between CFR evaluated by PC cine CMR

and the serum **EPA**. Methods: We studied 127 patients (male, 116 (**91**%); mean age, 72.2 plus or minus 7.4 years) with known or suspected coronary artery disease (CAD). X-ray coronary angiography revealed no significant coronary arterial stenoses (defined as **luminal** diameter reduction > or =50% on quantitative coronary angiogram (QCA) analysis) in all study participants. Breath-hold PC cine CMR images of the coronary sinus (CS) were acquired to assess blood flow of the CS both at rest and during adenosine triphosphate (ATP) infusion. We calculated CFR as CS blood flow during ATP infusion divided by that at rest. Patients were allocated to groups according to whether they had high (n = 64, **EPA** greater than or equal to 75.8 mu g/mL) or low (n = 63, **EPA** < 75.8 mu g/mL) median serum **EPA**. Results: CFR was significantly lower in the low, than in the high **EPA** group (2.54 plus or minus 1.00 vs. 2.91 plus or minus 0.98, p = 0.038). Serum **EPA** positively correlated with CFR (R = 0.35, p < 0.001). We defined preserved CFR as > 2.5, which is the previously reported lower limit of normal flow reserve without obstructive CAD. Multivariate analysis revealed that **EPA** is an independent predictor of CFR > 2.5 (odds ratio, 1.01; **95**% confidence interval, 1.00 - 1.02, p = 0.008). Conclusions: The serum **EPA** is significantly correlated with CFR in CAD patients without significant coronary artery stenosis.

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ACCESSION NUMBER: 2012393865 EMBASE Full-text
DOCUMENT NUMBER: 365194044 PMID: 22544726
TITLE: Recommendations for the treatment of epilepsy in adult patients in general practice in Belgium: An update.
AUTHOR: Boon, Paul (correspondence)
CORPORATE SOURCE: Department of Neurology, Ghent University Hospital, 185 De Pintelaan, 9000 Ghent, Belgium. Paul.Boon@Ugent.be
AUTHOR: Engelborghs, Sebastiaan
CORPORATE SOURCE: Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium.
AUTHOR: Hauman, Henri
CORPORATE SOURCE: Department of Neurology, Sint-Maarten Hospital, Duffel, Belgium.
AUTHOR: Jansen, An
CORPORATE SOURCE: Department of Paediatric Neurology, University Hospital Brussels, Free University Brussels, Brussels, Belgium.
AUTHOR: Lagae, Lieven
CORPORATE SOURCE: Department of Paediatric Neurology, University Hospital, Leuven, Belgium.
AUTHOR: Legros, Benjamin
CORPORATE SOURCE: Department of Neurology, Hopital Erasme, Universite Libre de Bruxelles, Brussels, Belgium.
AUTHOR: Ossemann, Michel
CORPORATE SOURCE: Department of Neurology, University Hospital Mont-Godinne, Universite Catholique de Louvain, Yvoir, Belgium.
AUTHOR: Sadzot, Bernard
CORPORATE SOURCE: Department of Neurology, University Hospital Centre Sart-Tilman, Li`ege, Belgium.
AUTHOR: Smets, Katrien
CORPORATE SOURCE: Department of Neurology, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium.
AUTHOR: Urbain, Etienne
CORPORATE SOURCE: Department of Neurology, Grand Hopital de Charleroi, Charleroi, Belgium.
AUTHOR: van Rijckevorsel, Kenou
CORPORATE SOURCE: Department of Paediatric Neurology, Saint Luc University Hospital, Universite Catholique de Louvain, Brussels, Belgium.
SOURCE: Acta Neurologica Belgica, (**June 2012**) Vol. 112, No. 2, pp. 119-131.
Refs: 51
ISSN: 0300-9009; E-ISSN: 2240-2993 CODEN: ANUBBR
DIGITAL OBJECT ID: 10.1007/s13760-012-0070-9
PUBLISHER: Springer-Verlag Italia s.r.l..
COUNTRY: Belgium
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: Intellectual Indexing

037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
050 Epilepsy Abstracts
008 Neurology and Neurosurgery
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 23 Jul 2012
Last Updated on Embase: 8 Dec 2014

AB In 2008, a group of Belgian epilepsy experts published recommendations for antiepileptic drug (AED) treatment of epilepsies in adults and children. Selection of compounds was based on the registration and reimbursement status in Belgium, the level of evidence for efficacy, common daily practice and the personal views and experiences of the authors. In November 2011 the validity of these recommendations was reviewed by the same group of Belgian epilepsy experts who contributed to the **preparation** of the original paper. The recommendations made in 2008 for initial monotherapy in paediatric patients were still considered to be valid, except for the first choice treatment for childhood absence epilepsy. This update therefore focuses on the treatment recommendations for initial monotherapy and add-on treatment in adult patients. Several other relevant aspects of treatment with AEDs are addressed, including considerations for optimal combination of AEDs (rational polytherapy), pharmacokinetic properties, pharmacodynamic and pharmacokinetic interaction profile, adverse effects, comorbidity, treatment of elderly patients, AED treatment during pregnancy, and generic substitution of AEDs. © 2012 The Author(s).

L30 ANSWER 11 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2007604124 EMBASE Full-text
DOCUMENT NUMBER: 350246372 PMID: 18086463
TITLE: A randomized trial of polyunsaturated fatty acids for refractory epilepsy.
AUTHOR: Bromfield, Edward (correspondence); Dworetzky, Barbara; Eluri, Zina; Lane, Lara; Replansky, Sonia
CORPORATE SOURCE: Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States. ebromfield@partners.org
AUTHOR: Hurwitz, Shelley
CORPORATE SOURCE: Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States.
AUTHOR: Mostofsky, David
CORPORATE SOURCE: Department of Psychology, Boston University, Boston, MA, United States.
SOURCE: Epilepsy and Behavior, (**January 2008**) Vol. 12, No. 1, pp. 187-190.
Refs: 30
ISSN: 1525-5050; E-ISSN: 1525-5069 CODEN: EBPEA4
DIGITAL OBJECT ID: 10.1016/j.yebeh.2007.09.011
PUBLISHER: Academic Press Inc., 6277 Sea Harbor Drive, Orlando, FL 32887-4900, United States.
PUBLISHER IDENT.: S 1525-5050(07)00317-4
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
050 Epilepsy Abstracts
FILE SEGMENT:ClinicalTrials.gov
CLINICAL TRIAL NO.: NCT00299533
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 3 Jan 2008
Last Updated on Embase: 3 Jan 2008

AB Objective: Though polyunsaturated fatty acids (PUFA) reduce seizures in several animal models, results have been inconsistent in humans. The goal of the present study was to assess the effectiveness of a PUFA supplement as adjunctive treatment for intractable focal or generalized epilepsy in humans. Methods: Adults with uncontrolled epilepsy were randomized to either mineral oil placebo or a PUFA supplement (eicosapentanoic acid (**EPA**) plus docosahexanoic acid (DHA), 2.2 mg/day in a 3:2 ratio). Following a 4-week prospective

baseline and 1-week titration, subjects entered a 12-week treatment period, followed by an optional 4-week open-label phase. Results: Of 21 subjects (12 PUFA and 9 placebo), 0 on PUFA versus 2 on placebo had at least a 50% decrease in seizure frequency from baseline (P = 0.17). Overall, seizure frequency increased 6% on PUFA and decreased 12% on placebo (P = 0.21). During optional open-label administration, however, 15 of 19 subjects had fewer seizures than during baseline (P = 0.02). Conclusions: Based on the randomized, blinded portion of this study, the PUFA **preparation** used was not superior to placebo as adjunctive treatment for intractable epilepsy. It is not known whether different doses or different **EPA**:DHA ratios would be effective. © 2007 Elsevier Inc. All rights reserved.

L30 ANSWER 12 OF 40 BIOSIS COPYRIGHT (c) 2021 Clarivate Analytics on STN

ACCESSION NUMBER: 2004:123696 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400126954
TITLE: The effects of fatty acids on SR calcium release channels from cardiac muscle.
AUTHOR(S): Honen, Bonny N. [Reprint Author]; Saint, David A.; Van Helden, Dirk F. [Reprint Author]; Laver, Derek R. [Reprint Author]
CORPORATE SOURCE: Biomedical Sciences, University of Newcastle, Callaghan, NSW, Australia
SOURCE: Biophysical Journal, (**January 2004**) Vol. 86, No. 1, pp. 239a-240a. print.
Meeting Info.: 48th Annual Meeting of the Biophysical Society. Baltimore, MD, USA. February 14-18, 2004. Biophysical Society.
ISSN: 0006-3495 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Mar 2004
Last Updated on STN: 3 Mar 2004

AB The anti-arrhythmic effects of long chain polyunsaturated fatty acids (PUFAs) may be related to their ability to alter calcium handling in cardiac myocytes. Therefore we investigated the effects of the PUFAs, docosahexaenoic acid (DHA) and eicosapentaenoic acid (**EPA**) as well as monounsaturated oleic acid on the kinetics of the cardiac calcium release channels (i.e. the ryanodine receptor (RyR) and the inositol triphosphate receptor (IP3R)). Sarcoplasmic vesicles containing calcium release channels were **prepared** from sheep hearts and activity was determined by (3H)ryanodine binding (for RyRs) and single channel recording in lipid bilayers. IP3Rs were identified by their activation by 1 muM IP3 and inhibition by 10 muM heparin, a reversible IP3R blocker. IP3R activity fell upon the application of 50 muM **EPA**. Poly- and mono-unsaturated free fatty acids inhibited RyRs activity in lipid bilayers. **EPA** (cytosolic and **luminal**) inhibited RyRs with KI=32 muM and Hill coefficient, nI=3.8. Inhibition was independent of whether RyRs were activated by ATP or Ca2+. DHA and oleic acid also inhibited RyRs, suggesting that free fatty acids generally, inhibit RyRs at micro molar concentrations. **EPA** inhibited (3H)ryanodine binding to RyRs in SR vesicles with KI=40 muM. The results suggest that both **EPA** and DHA affect calcium handling by directly inhibiting calcium release channels at micro molar concentrations. The actions of both **EPA** and DHA may be mediated via the membrane or by binding to a hydrophobic site on the channel itself. Both mono and polyunsaturated free fatty acids inhibit the RyR, however monounsaturated fatty acids don't exhibit antiarrhythmic actions. This is consistent with the specific release of PUFAs from phospholipid membranes that occurs during ischemia.

L30 ANSWER 13 OF 40 MEDLINE ® on STN DUPLICATE 5

ACCESSION NUMBER: 2004025265 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14724746
TITLE: Suppression of calcium sparks in rat ventricular myocytes and direct inhibition of sheep cardiac RyR channels by **EPA**, DHA and oleic acid.
AUTHOR: Honen B N
CORPORATE SOURCE: Department of Physiology, University of Adelaide, Adelaide, SA 5005, Australia.
AUTHOR: Saint D A; Laver D R
SOURCE: The Journal of membrane biology, **(2003 Nov 15)** Vol. 196, No. 2, pp. 95-103.

Journal code: 0211301. ISSN: 0022-2631. L-ISSN: 0022-2631.
DIGITAL OBJECT ID: http://dx.doi.org/10.1007/s00232-003-0628-9
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 16 Jan 2004
Last Updated on STN: 28 Jul 2004
Entered Medline: 27 Jul 2004
OS.CITING REF COUNT: 15 There are 15 MEDLINE records that cite this record
MEDLINE REFERENCE COUNT: 43 There are 43 cited references available in MEDLINE for this document.

AB The anti-arrhythmic effects of long-chain polyunsaturated fatty acids (PUFAs) may be related to their ability to alter calcium handling in cardiac myocytes. We investigated the effect of eicosapentanoic acid (**EPA**) and docosahexaenoic acid (DHA) on calcium sparks in rat cardiac myocytes and the effects of these PUFAs and the monounsaturated oleic acid on cardiac calcium release channels (RyRs). Visualization of subcellular calcium concentrations in single rat ventricular myocytes showed that intensity of calcium sparks was reduced in the presence of **EPA** and DHA (15 micro M). It was also found that calcium sparks decayed more quickly in the presence of **EPA** but not DHA. Sarcoplasmic vesicles containing RyRs were **prepared** from sheep hearts and RyR activity was determined by either [(3)H]ryanodine binding or by single-channel recording. Bilayers were formed from phosphatidylethanolamine and phosphatidylcholine dissolved in either n-decane or n-tetradecane. **EPA** inhibited [(3)H]ryanodine binding to RyRs in SR vesicles with K(I) = 40 micro M. Poly- and mono-unsaturated free fatty acids inhibited RyR activity in lipid bilayers. **EPA** (cytosolic or **luminal**) inhibited RyRs with K(I) =32 micro M and Hill coefficient, n(1) = 3.8. Inhibition was independent of the n-alkane solvent and whether RyRs were activated by ATP or Ca(2+). DHA and oleic acid also inhibited RyRs, suggesting that free fatty acids generally inhibit RyRs at micromolar concentrations.

L30 ANSWER 14 OF 40 MEDLINE ® on STN
ACCESSION NUMBER: 2002224701 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11960778
TITLE: Regulation of triacylglycerol and phospholipid trafficking by fatty acids in newborn swine enterocytes.
AUTHOR: Yao Ying
CORPORATE SOURCE: Children's Foundation Research Center at Le Bonheur Children's Medical Center, University of Tennessee Health Science Center, Memphis, Tennessee 38103, USA.
AUTHOR: Eshun John K; Lu Song; Berschneider Helen M; Black Dennis D
SOURCE: American journal of physiology. Gastrointestinal and liver physiology, **(2002 May)** Vol. 282, No. 5, pp. G817-24.
Journal code: 100901227. ISSN: 0193-1857. L-ISSN: 0193-1857.
DIGITAL OBJECT ID: http://dx.doi.org/10.1152/ajpgi.00397.2001
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 19 Apr 2002
Last Updated on STN: 17 May 2002
Entered Medline: 16 May 2002
GRANT FUNDING ORG.: United States NICHD NIH HHS
GRANT FUNDING NUM.: R01 HD022551-17; R01 HD022551-14A1; R01 HD022551-15; HD-22551; R01 HD022551-18; R01 HD022551-13; R01 HD022551-11; R01 HD022551-09A1; R01 HD022551-08; R01 HD022551-16; R01 HD022551-12; R01 HD022551
GRANT FUNDING ORG.: United States NIDDK NIH HHS

GRANT FUNDING NUM.: DK-42100
OS.CITING REF COUNT: 3 There are 3 MEDLINE records that cite this record
AB We (Wang H, Berschneider HM, Du J, and Black DD. Am J Physiol Gastrointest Liver Physiol 272: G935-G942, 1997; Wang H, Lu S, Du J, Yao Y, Berschneider HM, and Black DD. Am J Physiol Gastrointest Liver Physiol 280: G1137-G1144, 2001) previously showed that different fatty acids influence synthesis and secretion of triacylglycerol (TG) and phospholipid (PL) in a newborn swine enterocyte cell line (IPEC-1). The most striking effects were produced by stearic acid (SA; 18:0), which modestly affected TG and PL synthesis but reduced TG and PL secretion, and by eicosapentaenoic acid (**EPA**; 20:5), which reduced TG and PL synthesis and TG secretion relative to oleic acid (OA; 18:1). To define the mechanism of these effects, differentiated IPEC-1 cells were incubated for 24 h with OA, SA, or **EPA** and [(3)H]glycerol. Endoplasmic reticulum (ER) and Golgi (G) content of labeled lipids and apolipoprotein (apo) B and apoAI protein were measured. Relative to OA, SA did not impair ER TG synthesis, but reduced movement of labeled TG from ER to G. **EPA** impaired both ER TG synthesis and movement of labeled TG from ER to G. PL followed the same pattern, except ER synthesis of PL was relatively unaffected by **EPA**. Carbonate treatment demonstrated decreased partitioning of labeled lipid from ER membrane to lumen in **EPA**-treated cells. Organelle apoB and apoAI content demonstrated opposite patterns after SA and **EPA** incubation. We conclude that SA and **EPA** adversely influence immature enterocyte ER to G lipid trafficking, compared with OA. Furthermore, **EPA** inhibits ER lipid synthesis and transfer of membrane lipid to **luminal** particles. Regulation of apoAI ER to G trafficking is independent of that of apoB.

L30 ANSWER 15 OF 40 MEDLINE ® on STN DUPLICATE 6
ACCESSION NUMBER: 2002356317 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12099547
TITLE: Lipids and nitric oxide in porcine retinal and choroidal blood vessels.
AUTHOR: Kulkarni Prasad
CORPORATE SOURCE: Department of Ophthalmology and Visual Science, University of Louisville School of Medicine, Kentucky Lions Eye Research Center, 40292, USA. pskulk01@louisville.edu
AUTHOR: Cai Jian; Hurst Harrell E
SOURCE: Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics, **(2002 Jun)** Vol. 18, No. 3, pp. 265-75.
Journal code: 9511091. ISSN: 1080-7683. L-ISSN: 1080-7683.
DIGITAL OBJECT ID: http://dx.doi.org/10.1089/108076802760116188
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 9 Jul 2002
Last Updated on STN: 8 Jan 2003
Entered Medline: 7 Jan 2003
OS.CITING REF COUNT: 3 There are 3 MEDLINE records that cite this record
AB Lipid profiles of porcine retina, and retinal and choroidal vessels were analyzed using the gas chromatography/mass spectrometry (GC/MS) technique. The retina and both isolated retinal and choroidal vessels contained saturated fatty acid stearic acid and polyunsaturated fatty acids, including arachidonic (C20:4, AA), a precursor for vasoactive prostaglandin (PG-2) series, and W-6 docosahexaenoic acids (C22:6, DHA). However, eicosapentaenoic acid (C20:5, **EPA**), a precursor for PG-3 series, was not detected in these vessels. When stearic acid was used for normalization of tissue sample, the retina contained relatively higher amounts of DHA than AA, retinal vessels had equal amounts of AA and DHA, while choroidal vessels contained higher amounts of AA than DHA. We also examined the endogenous synthesis of vasoactive endothelial-derived factors like PGs and nitric oxide (NO). Since vasoactive angiotensin II (Ang II) releases these products from blood vessels, this polypeptide was used in a porcine retinal circulation model. The porcine retinal central artery was perfused with oxygenated/heparinized physiological salt **solution** at 37

degrees C. Changes in A1 and A2 arteriolar diameters induced by Ang II were determined in the absence and presence of the nitric oxide synthase inhibitor, l-NO Arginine (LNOA), and cyclooxygenase inhibitor, flurbiprofen (FB). The central retinal artery designated as the first order arteriole A1 and subsequent branch was defined as A2. **Luminal** diameters of Al and A2 arterioles were 35 +/- 2 am and 10 +/- 1 microm, respectively. Topical Ang II (10(-10) M-10(-6) M) caused small vasoconstrictions in a dose-dependent manner. This response was enhanced after inhibition of PG synthesis by (10-6 M) FB. Ang II induced-constrictions were further enhanced in the presence of NO synthase inhibitor, LNOA (10(-7) M). There was slightly more increase in Ang II-induced vasoconstrictions in the presence of both NO and PG inhibitors, suggesting that NO may cause release of PGs from these vessels. This study demonstrates that the porcine retinal arterioles have the ability to regulate vasoconstriction responses induced by Ang II by synthesis and release of endogenous vasodilating PGs and NO (especially NO); and these substances may play a vital role in porcine retinal circulation.

L30 ANSWER 16 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1995011808 EMBASE Full-text
DOCUMENT NUMBER: 25010539 PMID: 7702359
TITLE: Effect of dietary alpha-linolenic, eicosapentaenoic and docosahexaenoic acids on liver microsomal mixed-function oxidases in rats.
AUTHOR: Saito, M., Dr. (correspondence)
CORPORATE SOURCE: Division of Food Science, National Inst. Health and Nutrition, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162, Japan .
SOURCE: Annals of Nutrition and Metabolism, (**1994**) Vol. 38, No. 6, pp. 313-321.
ISSN: 0250-6807 CODEN: ANUMDS
DIGITAL OBJECT ID: 10.1159/000177828
PUBLISHER: S. Karger AG.
COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
002 Physiology
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 25 Jan 1995
Last Updated on Embase: 3 Mar 2021

AB This study was undertaken to compare the effects of three major dietary n-3 fatty acids, i.e. α-linolenic acid (C18:3, n-3; LN), eicosapentaenoic acid (C20:5, n-3; **EPA**) and docosahexaenoic acid (C22:6, n-3; DHA), on liver microsomal mixed-function oxidase activities with and without phenobarbital (PB) induction. Male Sprague-Dawley rats were fed a 5% lipid diet containing either LN, **EPA** or DHA as major constituent fatty acid (about 40%) of dietary lipids for 15 days. The fatty acid **compositions** of liver microsomal lipids of each n-3 fatty acid group were characteristically different, particularly in the n-3 fatty acid **compositions**, but were nearly the same with and without PB treatment. Dietary LN, **EPA** and DHA did not affect the levels of PB-inducible cytochrome P-450 species nor the activities of aminopyrine N-demethylase and aniline hydroxylase. However, the PB-uninduced constitutive levels of cytochromes P-450 increased in the following order with a slight but significant difference between LN and DHA groups: LN group < **EPA** group < DHA group. Both the PB-uninduced activities of aminopyrine N-demethylase and aniline hydroxylase changed in a very similar manner to the constitutive levels of cytochromes P-450. These results suggest that the uninduced constitutive level of certain cytochrome P-450 species is modulated differentially by dietary LN, **EPA** and DHA, whereas dietary LN, **EPA** and DHA do not affect the PB-inducible levels of cytochrome P-450 species.

L30 ANSWER 17 OF 40 MEDLINE ® on STN DUPLICATE 7
ACCESSION NUMBER: 1992057027 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1950030
TITLE: Effects of n-3 fatty acids on fluid and electrolyte transport in rat intestine in vivo and in vitro.
AUTHOR: Loeschke K
CORPORATE SOURCE: Medizinische Klinik Innenstadt der Universitat Munchen.

AUTHOR: Schreiner J; Oberst G
SOURCE: Zeitschrift fur Gastroenterologie, **(1991 May)** Vol. 29, No. 5, pp. 227-30.
Journal code: 0033370. ISSN: 0044-2771. L-ISSN: 0044-2771.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 199112
ENTRY DATE: Entered STN: 24 Jan 1992
Last Updated on STN: 3 Feb 1997
Entered Medline: 17 Dec 1991

AB Potential therapeutic benefits of dietary n-3 fatty acids are presently evaluated in arteriosclerotic and chronic inflammatory diseases. Because some other long-chain fatty acids inhibit intestinal fluid absorption, the effects of docosahexaenoic acid (DHA) and eicosapentaenoic acid (**EPA**) on fluid and electrolyte transport were tested in rat colon and jejunum. In ligated colon loops in vivo, DHA (10(-5)-10(-3) M luminally) diminished net sodium and fluid absorption, and stimulated net potassium secretion. Similar but smaller effects were produced by **EPA**. In the jejunum, transport parameters were not influenced by DHA and **EPA**. In isolated distal colonic mucosa in vitro, DHA (10(-4)-10(-3) M on the mucosal side) reduced the electrical resistance, potential difference, short-circuit current and the net absorption of sodium and chloride due to increased unidirectional serosal to mucosal fluxes. These changes were prevented when calcium was replaced by strontium in the bathing **solution**. The data suggest that n-3 fatty acids increase colonic conductance indirectly by binding **luminal** calcium.

L30 ANSWER 18 OF 40 MEDLINE ® on STN DUPLICATE 8
ACCESSION NUMBER: 1989061201 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3196097
TITLE: Effects of aspirin, dipyridamole, and cod liver oil on accelerated myointimal proliferation in canine veno-arterial allografts.
AUTHOR: DeCampli W M
CORPORATE SOURCE: Department of Cardiovascular Surgery, Stanford University School of Medicine, California 94305-5247.
AUTHOR: Kosek J C; Mitchell R S; Handen C E; Miller D C
SOURCE: Annals of surgery, **(1988 Dec)** Vol. 208, No. 6, pp. 746-54.
Journal code: 0372354. ISSN: 0003-4932. L-ISSN: 0003-4932.
Report No.: PMC-PMC1493836.
DIGITAL OBJECT ID: http://dx.doi.org/10.1097/00000658-198812000-00013
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 198901
ENTRY DATE: Entered STN: 8 Mar 1990
Last Updated on STN: 3 Feb 1997
Entered Medline: 12 Jan 1989
GRANT FUNDING ORG.: United States NHLBI NIH HHS
GRANT FUNDING NUM.: R01 HL37499
OS.CITING REF COUNT: 2 There are 2 MEDLINE records that cite this record
MEDLINE REFERENCE COUNT: 44 There are 44 cited references available in MEDLINE for this document.

AB The effects of the administration of aspirin (ASA), dipyridamole (DPM), and cod liver oil (CLO) on graft patency rate and degree of intimal hyperplasia were investigated in a canine, hypercholesterolemic veno-arterial allograft model in an attempt to modify this immunologically mediated vascular injury. The drug regimens were ASA 1 mg/kg/day, DPM 10 mg/kg/day, combined ASA and DPM (ASA + DPM), and CLO (1.8 g/day eicosapentanoic acid [**EPA**] and 1.2 g/day docosahexanoic acid [DHA]), and control. The early angiographic

patency rate (1-3 weeks) was 81% +/- 10% (+/- 70% confidence limits); the 90-day overall patency rate was 60% +/- 4% (87/144), with no statistically significant differences among the groups (range 46 +/- 10-71 +/- 9%). Qualitatively, there was no difference in **luminal** thrombus, intimal hemorrhage, or lesion eccentricity. Considering the relatively short time of graft implantation, an extensive amount of microscopic disease was observed; quantitatively, the mean intimal thickness was 515 +/- 17 microgram overall but was not statistically different between the groups. The fraction of potential lumenal area occupied by intimal thickening was 0.37 +/- 0.01 but again did not differ significantly between the groups. These doses of ASA, DPM, ASA + DPM, and CLO did not alter graft occlusion or retard the marked degree of subintimal myointimal cell hyperplasia that was generated in this hypercholesterolemic canine veno-arterial allograft **preparation**. Possible explanations for these negative findings include inadequate dosage or form of omega-3 fatty acids and the antiplatelet drugs administered, excessive variability in graft response due to uncharacterized immunologic histocompatibility, and the possible influence of non-platelet-mediated mechanisms. Nevertheless, this **preparation** is attractive as a reproducible model of accelerated (immunologically mediated) experimental arteriosclerosis.

L30 ANSWER 19 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1984231353 EMBASE Full-text
DOCUMENT NUMBER: 14006509 PMID: 6435683
TITLE: Acylureas: A new class of barbiturate-like bacterial cytochrome P-450 inducers.
AUTHOR: Ruettinger, R.T.; Kim, B.H.; Fulco, A.J.
CORPORATE SOURCE: Department of Biological Chemistry, UCLA School of Medicine, University of California, Los Angeles, CA 90024, United States.
SOURCE: Biochimica et Biophysica Acta - General Subjects, (**1984**) Vol. 801, No. 3, pp. 372-380.
ISSN: 0304-4165 CODEN: BBGSB3
DIGITAL OBJECT ID: 10.1016/0304-4165(84)90141-7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered Embase: 10 Dec 1991
Last Updated on Embase: 10 Dec 1991

AB The soluble, cytochrome P-450-dependent fatty acid monooxygenase of Bacillus megaterium ATCC 14581 is induced by phenobarbital and at least twelve other barbiturates (Kim, B.-H. and Fulco, A.J. (1983) Biochem. Biophys. Res. Commun. 116, 843-850). We have since found that inducer potency of phenobarbital and of six other of these barbiturates was enhanced by adding them to the growth medium prior to sterilization by autoclaving. A similar 'activation' was effected simply by autoclaving these barbiturates in distilled water at **pH** 8.0. When the hydrolytic products resulting from such treatment of phenobarbital were identified and screened for inducer activity, the major product, **2-phenylbutyrylurea**, was found to be 3-5 times more potent than the phenobarbital itself. The racemic **mixture** (±)-**2-phenylbutyrylurea** was somewhat more active as an inducer than was either of the enantiomers ((±) or (-)) tested singly. Of the other hydrolytic products of phenobarbital, only 2-phenylbutyramide had significant inducer activity (about the same as phenobarbital). Among other ureides tested, two monosubstituted acetylureas (phenylacetylurea and dodecanoylurea) were inactive as inducers, but six of seven disubstituted acetylureas were better inducers than **2-phenylbutyrylurea**.

L30 ANSWER 20 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1984060602 EMBASE Full-text
DOCUMENT NUMBER: 14185654 PMID: 6707135
TITLE: Simultaneous determination of eleven antiepileptic compounds in serum by high-performance liquid chromatography.
AUTHOR: Wad, N.
CORPORATE SOURCE: Swiss Epilepsy Center, 8008 Zurich, Switzerland.
SOURCE: Journal of Chromatography - Biomedical Applications,

(1984) Vol. 305, No. 1, pp. 127-133.
CODEN: JCBADL
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
029 Clinical and Experimental Biochemistry
030 Clinical and Experimental Pharmacology
050 Epilepsy Abstracts
008 Neurology and Neurosurgery
LANGUAGE: English
ENTRY DATE: Entered Embase: 10 Dec 1991
Last Updated on Embase: 10 Dec 1991

AB A high-performance liquid chromatographic method for the simultaneous determination of carbamazepine, CGP 10000 (a common metabolite of carbamazepine and oxcarbazepine), desmethylmephenytoin, 10,11-epoxycarbamazepine, ethosuximide, GP 47 779 (the active metabolite from oxcarbazepine, a new drug made by Ciba-Geigy), mephenytoin, phenylethylmalonamide, primidone, **pheneturide**, phenobarbital and phenytoin is described. The serum is extracted with ethyl acetate at **pH** 3.9 and the dried extract is dissolved in 70% ethanol in water and an aliquot is injected into a Hewlett-Packard 1084 B liquid chromatograph. A reversed-phase (RP-8) column is used with acetonitrile and water as the mobile phase. The eluted drugs are detected at 207 nm. The recovery of the compounds varies from 76% to 95% with the day-to-day precision (C.V.) between 3.8% and 9.8%, the within-day precision between 1.8% and 5.8% and run-to-run precision between 1.0% and 2.6%.

L30 ANSWER 21 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1981240416 EMBASE Full-text
DOCUMENT NUMBER: 11016416
TITLE: Single drug or combination therapy for epilepsy?.
AUTHOR: Reynolds, E.H.; Shorvon, S.D.
CORPORATE SOURCE: Univ. Dept. Neurol., Inst. Psychiat., London, United Kingdom.
SOURCE: Current Therapeutics, (1981) Vol. 22, No. 5, pp. 135-153.
ISSN: 0311-905X CODEN: CUTHDB
COUNTRY: Australia
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
050 Epilepsy Abstracts
LANGUAGE: English
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 9 Dec 1991

L30 ANSWER 22 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1981094363 EMBASE Full-text
DOCUMENT NUMBER: 11190150 PMID: 6781884
TITLE: Monotherapy or polytherapy for epilepsy?.
AUTHOR: Reynolds, E.H.; Shorvon, S.D.
CORPORATE SOURCE: Univ. Dept. Neurol., Inst. Psychiat., London, United Kingdom.
SOURCE: Epilepsia, (1981) Vol. 22, No. 1, pp. 1-10.
ISSN: 0013-9580 CODEN: EPILAK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
008 Neurology and Neurosurgery
050 Epilepsy Abstracts
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: German
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 9 Dec 1991

AB Although anticonvulsant polytherapy has been widely and traditionally used in the treatment of epilepsy, there is little evidence of its advantages over monotherapy. It does, however, lead to problems of chronic toxicity, drug interactions, failure to evaluate individuals drugs, and sometimes exacerbation of seizures. There are many causes of polytherapy which could be avoided by more careful monitoring and

supervision of therapy. Studies in new, previously untreated referrals suggest there is considerable potential for monotherapy. In the event of failure of optimum monotherapy, the value of polytherapy is not yet clear. In chronic patients on polytherapy there may be scope for careful rationalization to two or sometimes one drug, with reduction in chronic toxicity and sometimes improved seizure control. Reduction of therapy, however, may be impossible or hazardous due to withdrawal seizures. Even after successful reduction, seizure control is much less satisfactory than in new referrals It is easier to avoid polytherapy than to reduce it. There is a need to define more carefully the limits of effective anticonvulsant therapy.

L30 ANSWER 23 OF 40 MEDLINE ® on STN DUPLICATE 9
ACCESSION NUMBER: 1981046960 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 7191854
TITLE: Biochemical homology between rat dorsal prostate and coagulating gland. Purification of a major androgen-induced protein.
AUTHOR: Wilson E M; French F S
SOURCE: The Journal of biological chemistry, **(1980 Nov 25)** Vol. 255, No. 22, pp. 10946-53.
Journal code: 2985121R. ISSN: 0021-9258. L-ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 198101
ENTRY DATE: Entered STN: 16 Mar 1990
Last Updated on STN: 3 Mar 2000
Entered Medline: 29 Jan 1981
GRANT FUNDING ORG.: United States NICHD NIH HHS
GRANT FUNDING NUM.: HD04466-09
OS.CITING REF COUNT: 6 There are 6 MEDLINE records that cite this record
AB The anatomically distinct organs, rat dorsal prostate and coagulating gland, were found to display remarkable homology in protein **composition**, including two major androgen-dependent secretory proteins, referred to as dorsal proteins I and II. Dorsal protein I has been purified and found to be a dimer composed of two identical subunits with sedimentation coefficient 4.6 S, Stokes radium 32 A, and Mr = 71,000 (62,000 by sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis). This dimer (6.8 **S**, **46** A, Mr = 150,000) dissociates at high ionic strength and can be partially reconstituted by removal of salt. Dorsal protein I is a basic protein (pI 9) with high lysine content and binds to phosphocellulose but not to DEAE-Sepharose. Schiff's staining shows that it contains carbohydrate. Quantitative rocket immunoelectrophoresis using a rabbit antiserum indicates dorsal protein I is produced only in dorsal prostate and coagulating gland. The protein constitutes approximately 25% of total cytosol protein in both organs, yet makes up on 5% of coagulating gland **luminal** fluid and ejaculated seminal fluid. It was not detected in the rat dorsal prostate tumor (Dunning R3327H). Dorsal protein II is a larger protein (Mr = 80,000 by SDS gel electrophoresis) with higher carbohydrate content. Under nondenaturing conditions, it has a Stokes radius of > 200 A, corresponding to Mr of > 300,000. Dorsal protein II represents a smaller proportion of total cytosol protein than does dorsal protein I, yet is the predominant protein of coagulating gland fluid. The proteins will be useful probes for studies on androgen regulation of specific gene expression and prostatic secretory mechanisms.

L30 ANSWER 24 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1981115567 EMBASE Full-text
DOCUMENT NUMBER: 11147354 PMID: 7439133
TITLE: Multi-institutional study on the teratogenicity and fetal toxicity of antiepileptic drugs: A report of a collaborative study group in Japan.
AUTHOR: Nakane, Y.; Okuma, T.; Takahashi, R.
CORPORATE SOURCE: Dept. Neuropsychiat., Nagasaki Univ. Sch. Med., Nagasaki, Japan.
AUTHOR: Sato, Y.; Wada, T.; Sato, T.; Fukushima, Y.; Kumashiro,

H.; Ono, T.; Takahashi, T.; Aoki, Y.; Kazamatsuri, H.; Inami, M.; Komai, S.; Seino, M.; Miyakoshi, M.; Tanimura, T.; Hazama, H.; Kawahara, R.; Otsuki, S.; Hosokawa, K.; Inanaga, K.; Nakazawa, Y.; Yamamoto, K.
SOURCE: Epilepsia, (1980) Vol. 21, No. 6, pp. 663-680.
ISSN: 0013-9580 CODEN: EPILAK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
038 Adverse Reactions Titles
037 Drug Literature Index
008 Neurology and Neurosurgery
022 Human Genetics
021 Developmental Biology and Teratology
050 Epilepsy Abstracts
LANGUAGE: English
SUMMARY LANGUAGE: German; French
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 9 Dec 1991

AB A multi-institutional collaborative study was conducted concerning the course of pregnancy and delivery and the incidence of abnormal infants delivered of epileptic women. Of 657 women receiving antiepileptic drugs, 73% delivered live infants, 14% had miscarriage or stillbirth, and 13% underwent induced abortion. In contrast to the above findings, 80% of 162 patients not receiving antiepileptic drugs delivered live infants and 4% had miscarriage or stillbirth. The latter outcome was significantly increased in the medicated patients. In this series, 63 (9.9%) of 638 live births were malformed, 55 (11.5%) being from medicated mothers and 3 (2.3%) from nonmedicated mothers. The incidence of fetal malformation in medicated mothers was thus five times as high as that in nonmedicated mothers. Cleft lip and/or palate and malformations involving the cardiovascular system were found frequently in the infants from medicated mothers. General background factors that might exert teratogenic effects on pregnant patients with epilepsy were studied, and the potential toxicity of antiepileptic drugs to the fetus was also analyzed. In this regard, consideration should be given to whether the patient has partial epileptic seizures, whether the patient herself exhibits any malformation,or whether her previous pregnancy resulted in an abnormal outcome. The incidence of fetal malformation was the highest (12.7%) in the medicated patients who had epileptic seizures during the pregnancy. It is resumed on the basis of the results of analysis of the data that a combination of more than three drugs and a daily dose greater than a certain minimal level is likely to produce malformed infants.

L30 ANSWER 25 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1980103284 EMBASE Full-text
DOCUMENT NUMBER: 10134042 PMID: 7363472
TITLE: Measurement of anticonvulsants in serum by reversed-phase ion-pair liquid chromatography.
AUTHOR: Christofides, J.A.; Fry, D.E.
CORPORATE SOURCE: Epsom Hosp. Lab., West Park Hosp., Epsom, United Kingdom.
SOURCE: Clinical Chemistry, (1980) Vol. 26, No. 3, pp. 499-501.
ISSN: 0009-9147 CODEN: CLCHAU
DIGITAL OBJECT ID: 10.1093/clinchem/26.3.0499
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
050 Epilepsy Abstracts
008 Neurology and Neurosurgery
LANGUAGE: English
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 19 Feb 2021

AB We describe a method for the simultaneous liquid-chromatographic determination of ethosuximide, **ethylphenacemide**, primidone, phenobarbital, carbamazepine, and phenytoin in serum. The drugs, together with an internal standard, are extracted into ethyl acetate at **pH** 7.0. The extract is analyzed isocratically at ambient temperature on a reversed-phase column of 'SAS Hypersil' with a mobile

phase of acetonitrile/tetrabutyl ammonium phosphate **solution** (2/8 by volume). The eluted drugs are detected by their absorption at 200 nm, and quantitated from their peak heights as compared with those of extracted standards. The day-to-day CV of the method varied between 5.1 and 9.6% for concentrations ranging from less than therapeutic to toxic. The results, when compared with those by gas chromatography, gave correlation coefficients of 0.936 for phenytoin, 0.977 for phenobarbital, and 0.939 for primidone. No drug interference was found except that amobarbital and **ethylphenacemide** co-chromatographed.

L30 ANSWER 26 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1981008272 EMBASE Full-text
DOCUMENT NUMBER: 11232053 PMID: 6968264
TITLE: Carbamazepine intoxication due to triacetyloleandomycin administration in epileptic patients.
AUTHOR: Mesdjian, E.; Dravet, C.; Cenraud, B.; Roger, J.
CORPORATE SOURCE: INSERM, Lab. Pharmacol. Med., Fac. Med., Marseille, France.
SOURCE: Epilepsia, (**1980**) Vol. 21, No. 5, pp. 489-496.
ISSN: 0013-9580 CODEN: EPILAK
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
038 Adverse Reactions Titles
037 Drug Literature Index
008 Neurology and Neurosurgery
050 Epilepsy Abstracts
LANGUAGE: English
SUMMARY LANGUAGE: French; German
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 9 Dec 1991
AB In 17 epileptics receiving carbamazepine (CBZ) alone or in combination with other anticonvulsant drugs, administration of triacetyloleandomycin (Tri A) led to an acute and unexpected intoxication (drowsiness, nausea, vomiting, and dizziness). Similar symptoms occurred again in 3 patients after Tri A was administered a second time. The same toxic manifestations were observed in two patients receiving CBZ and erythromycin. A rapid increase in plasma levels of CBZ occurred after institution of Tri A therapy in 6 patients, the CBZ levels quickly returning to normal after withdrawal of Tri A. Thus, it is suggested that the observed intoxication is due to the simultaneous administration of CBZ and Tri A (or erythromycin). The possible role of hepatic dysfunction in this syndrome of intoxication is discussed. Furthermore, the intoxication may be at least partially related to serum electrolyte disturbances, as suggested by one case in which obvious signs of water intoxication were detected. The severity and frequency of intoxication should lead to proscribing Tri A or other macrolide antibiotics in patients receiving CBZ.

L30 ANSWER 27 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1980094156 EMBASE Full-text
DOCUMENT NUMBER: 10187392 PMID: 7387759
TITLE: 3-Sulfamoylmethyl-1,2-benzisoxazole, a new type of anticonvulsant drug. Pharmacological profile.
AUTHOR: Masuda, Y.; Karasawa, T.; Shiraishi, Y.
CORPORATE SOURCE: Res. Lab., Dainippon Pharmaceut. Co. Ltd., Osaka, Japan.
AUTHOR: Hori, M.; Yoshida, K.; Shimizu, M.
SOURCE: Arzneimittel-Forschung/Drug Research, (**1980**) Vol. 30, No. 3, pp. 477-483.
ISSN: 0004-4172 CODEN: ARZNAD
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
030 Clinical and Experimental Pharmacology
LANGUAGE: English
SUMMARY LANGUAGE: German
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 9 Dec 1991
AB The anticonvulsant and neurotoxic properties of 3-sulfamoylmethyl-1,2-benzisoxazole (AD-810) have been demonstrated.

AD-810 suppressed electrically and chemically induced maximal seizures but did not prevent minimal seizures in experimental animals. In rats, rabbits and dogs, the anticonvulsant activity of AD-810 against maximal electroshock seizures was more potent than those of diphenylhydantoin and carbamazepine. In rats, AD-810 showed more rapid onset as well as longer duration of anticonvulsant activity than the above two drugs. The anticonvulsant effect of AD-810 was reduced but not abolished by reserpine. No tolerance developed to the anticonvulsant action of AD-810 by consecutive treatment. The compound showed much less neurotoxicity and lethal toxicity than the existing antiepileptic drugs for grand mal, and also showed the least hypnotic effect by itself or by combination with hexobarbital. Thus, AD-810 possesses a profile of anti-convulsant activity most similar to that of diphenylhydantoin or carbamazepine, providing a high protective index as well as other favorable properties.

L30 ANSWER 28 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1980155169 EMBASE Full-text
DOCUMENT NUMBER: 10122755
TITLE: [Prescription of carbamazepine in a center for pediatric neurology].
PRESCRIPTION DU TEGRETOL DANS UNE CONSULTATION DE NEUROLOGIE INFANTILE.
AUTHOR: Desurmont-Deveugle, M.
CORPORATE SOURCE: Serv. Professeur Gaudier, Hop. Calmette, 59000 Lille, France.
SOURCE: Journal des Sciences Medicales de Lille, (1980) Vol. 98, No. 2, pp. 43-45.
ISSN: 0021-8111 CODEN: JSMLAE
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
007 Pediatrics and Pediatric Surgery
008 Neurology and Neurosurgery
050 Epilepsy Abstracts
LANGUAGE: French
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 9 Dec 1991

L30 ANSWER 29 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1980076873 EMBASE Full-text
DOCUMENT NUMBER: 10170672
TITLE: [Monotherapy or polytherapy].
EPILEPSIES: MONOTHERAPIE OU POLYTHERAPIE?.
AUTHOR: Sallou, C.
CORPORATE SOURCE: Serv. Neurol., Hop. St Joseph, 75674 Paris Cedex 14, France.
SOURCE: Revue du Praticien, (1979) Vol. 29, No. 59, pp. 4479-4485.
ISSN: 0035-2640 CODEN: REPRA3
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
050 Epilepsy Abstracts
037 Drug Literature Index
008 Neurology and Neurosurgery
LANGUAGE: French
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 9 Dec 1991
AB Considerable changes have taken place in the treatment of epilepsy leading to a reinforcement of monotherapy at the expense of polytherapy. Monotherapy consists in using only one drug, considered a major antiepileptic agent. Polytherapy associates two or more antiepileptic medications. Monotherapy is used in priority: in the treatment of epilepsy at its beginning: in certain clinical forms, such as primary generalized epilepsy in the forms of absences, Rolandic paroxysmal forms and certain partial forms with elementary semiology. Polytherapy is indicated: in cases where monotherapy failed; in certain clinical forms such as generalised epilepsy associating Grand Mal and Petit Mal, partial epilepsy with complex semiology and especially epilepsy secondary to convulsion-producing

encephalopathies. Resorting to polytherapy implies checking dosage and useful level of each antiepileptic drug, and elimination of all those which are not convincingly effective. The occurrence of epileptic attacks in a patient who is correctly treated does not necessarily mean failure, but may be accounted for by extrinsic factors of the disease. It therefore does not demand systematic increase of dosage of antiepileptic substances. The major concern for the practitioner, whatever the method, is to avoid overdosage and its complications.

L30 ANSWER 30 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1980070674 EMBASE Full-text
DOCUMENT NUMBER: 10164501
TITLE: Diphenylhydantoin blood levels in childhood epilepsy: A comparison of two **preparation** with different particle sizes.
AUTHOR: Takahashi, K.; Honda, T.; Takahashi, H.; Ohtsuka, C.
CORPORATE SOURCE: Dept. Ped., Juntendo Univ. Sch. Med., Tokyo, Japan.
SOURCE: No To Hattatsu, (**1979**) Vol. 11, No. 6, pp. 18-22.
ISSN: 0029-0831 CODEN: NTHAA7
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
050 Epilepsy Abstracts
037 Drug Literature Index
007 Pediatrics and Pediatric Surgery
008 Neurology and Neurosurgery
LANGUAGE: Japanese
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: 9 Dec 1991
Last Updated on Embase: 9 Dec 1991
AB Two diphenylhydantoin (PHT) **preparations** with different particle sizes and shapes, of 'large' spherical crystals of 100-300 µm in diameter and of 'small' rod-like crystals of 10-50 µm in width and 50-150 µm in length, were compared with regard to blood levels and clinical effects on 20 epileptic children as a crossover experiment. The small particle PHT **preparation** caused 2-3 fold higher blood levels than the large particle **preparation**. Five patients on the small size **preparation** showed definite clinical improvement, with a decrease in frequency of seizures. It is concluded that the PHT blood levels should be monitored whenever the **preparations** of this anti-convulsant are to be changed.

L30 ANSWER 31 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1978130158 EMBASE Full-text
DOCUMENT NUMBER: 8129590 PMID: 893583
TITLE: Gas liquid chromatography of eight anticonvulsant drugs in plasma.
AUTHOR: Sengupta, A.; Peat, M.A.
CORPORATE SOURCE: Dept. Forens. Med., Charing Cross Hosp. Med. Sch., London, United Kingdom.
SOURCE: Journal of Chromatography, (**1977**) Vol. 137, No. 1, pp. 206-209.
CODEN: JOCRAM
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered Embase: 1978
Last Updated on Embase: 1978

L30 ANSWER 32 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1978012380 EMBASE Full-text
DOCUMENT NUMBER: 8012272
TITLE: Simultaneous determination of phenobarbitone, primidone and phenytoin in small samples of blood by gas liquid chromatography.
AUTHOR: Bruce, A.M.; Smith, H.
CORPORATE SOURCE: Dept. Forens. Med., Univ. Glasgow, United Kingdom.
SOURCE: Analyst, (**1977**) Vol. 102, No. 1210, pp. 35-41.
ISSN: 0003-2654 CODEN: ANALAO

DIGITAL OBJECT ID: 10.1039/an9770200035
DOCUMENT TYPE: Journal
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered Embase: 1978
Last Updated on Embase: 1978

L30 ANSWER 33 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1978000756 EMBASE Full-text
DOCUMENT NUMBER: 8000720
TITLE: Rapid thin layer chromatographic method for the simultaneous determination of carbamazepine, diphenylhydantoin, mephenytoin, phenobarbital and primidone in serum.
AUTHOR: Wad, N.; Hanifl, E.; Rosenmund, H.
CORPORATE SOURCE: Dept. Clin. Chem., Kantonsspit., Zurich, Switzerland.
SOURCE: Journal of Chromatography, (**1976**) Vol. 143, No. 1, pp. 89-93.
CODEN: JOCRAM
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered Embase: 1978
Last Updated on Embase: 1978

L30 ANSWER 34 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1977030440 EMBASE Full-text
DOCUMENT NUMBER: 7030428
TITLE: Clinico electroencephalographic observations in epileptic patients during long term treatment with benzonal (Polish).
AUTHOR: Bittner Manicka, M.; Wasilewski, R.
CORPORATE SOURCE: Klin. Neurol., AM, Warszawa, Poland.
SOURCE: Neurologia i Neurochirurgia Polska, (**1975**) Vol. 25, No. 6, pp. 727-733.
ISSN: 0028-3843 CODEN: NNPOBE
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
008 Neurology and Neurosurgery
050 Epilepsy Abstracts
030 Clinical and Experimental Pharmacology
LANGUAGE: Polish
ENTRY DATE: Entered Embase: 1977
Last Updated on Embase: 1977
AB Benzonal was given to 52 epileptics. In 50 cases the duration of treatment ranged from 3 mth to 7 yr (mean 18 mth) in doses of 100-500 mg daily; in 2 cases it had to be withdrawn after a short term treatment because of intolerance. In all cases the drug was given together with other anticonvulsants: hydantoin, derivatives, mysodin, Tegretol, pheneturid or Ospolot in place of previously administered phenobarbital. It was found that benzonal significantly reduced the frequency of partial simple seizures (in 16 out of 20 cases) and grand mal seizures (in 24 out of 34 cases), while its action on the partial complex seizures was much weaker (improvement in only 7 out of 20 cases). The drug was usually well tolerated, side effects of greater intensity developed in 2 cases only, transient somnolence was observed in another 6 cases. In EEG records a slight favorable effect was exerted on pathological background activity with absent effect in focal changes and increase of seizure activity. The authors believe that in view of its favorable clinical action and good tolerance the drug may be widely used in properly selected cases of epilepsy.

L30 ANSWER 35 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1977004452 EMBASE Full-text
DOCUMENT NUMBER: 7004445
TITLE: [Considerations on a case of florid rachitis during treatment with anticonvulsants].
CONSIDERAZIONI SU DI UN CASO DI RACHITISMO FLORIDO IN CORSO DI TRATTAMENTO CON **PREPARATI** ANTICOMIZIALI.

AUTHOR: Tordini, M.L.
CORPORATE SOURCE: Div. Ped., Osp. Magg. C.A. Pizzardi, Ente Osp. Reg., Bologna, Italy.
SOURCE: Clinica Pediatrica, (**1975**) Vol. 57, No. 9, pp. 401-412.
CODEN: CLPEAI
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
007 Pediatrics and Pediatric Surgery
LANGUAGE: Italian
ENTRY DATE: Entered Embase: 1977
Last Updated on Embase: 1977

L30 ANSWER 36 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1976190422 EMBASE Full-text
DOCUMENT NUMBER: 6190341
TITLE: [**Composition** of the most important antiepileptic drugs].
ZUSAMMENSTELLUNG DER WICHTIGSTEN ANTIEPILEPTIKA.
AUTHOR: Dreyer, R.
CORPORATE SOURCE: Klin. Anfallskrankh. Mara, Anst. Bethel/Bielefeld, Germany.
SOURCE: Chirurgische Praxis, (**1975**) Vol. 20, No. 1, pp. 165-169.
ISSN: 0009-4846 CODEN: CHPRBU
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
050 Epilepsy Abstracts
030 Clinical and Experimental Pharmacology
008 Neurology and Neurosurgery
LANGUAGE: German
ENTRY DATE: Entered Embase: 1976
Last Updated on Embase: 1976
AB This compendium of color photographs of the most commonly sold anti epileptic drugs is intended as an aid to the identification of the kind of drug a patient has been using when treated by another doctor. It can be shown to the patient or to his or her relatives, the illustrations of packages and tablets prompting memory of the dosage etc., making continued treatment more successful.

L30 ANSWER 37 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1976061268 EMBASE Full-text
DOCUMENT NUMBER: 6061263 PMID: 1132312
TITLE: Anti epileptic drugs: some factors influencing absorption and metabolism.
AUTHOR: ANONYMOUS
SOURCE: Drug and Therapeutics Bulletin, (**1975**) Vol. 13, No. 12, pp. 47-48.
ISSN: 0012-6543 CODEN: DRTBAE
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: Intellectual Indexing
037 Drug Literature Index
050 Epilepsy Abstracts
030 Clinical and Experimental Pharmacology
008 Neurology and Neurosurgery
LANGUAGE: English
ENTRY DATE: Entered Embase: 1976
Last Updated on Embase: 1976
AB The absorption of anti epileptic drugs may be influenced by the excipient and the physical ad chemical state of the drug. Anti epileptic drugs alter the absorption an metabolism of some drugs and vitamins, especially Vitamin D and folate.

L30 ANSWER 38 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 0047882008 EMBASE Full-text
DOCUMENT NUMBER: 287077041
TITLE: [Clinical and EEG observations with a **mixture** ('trinuride') of **ethylphenacemide**, phenytoin and phenobarbital in psychomotor epilepsy and intractable centrocephalic epilepsy].

Etude clinique et electroencephalographique du trinuride dans l'epilepsie de type psychomoteur et l'epilepsie centro-cephalique rebelle.
AUTHOR: Pluvinage, R.; Delarue, R.; Amstutz, C.
CORPORATE SOURCE: Serv. de Neurol., Hop. de Bicetre, Le Kremlin-Bicetre.
SOURCE: Therapie, (**1967**) Vol. 22, No. 3, pp. 695-704.
ISSN: 0040-5957
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: CLASSIC
FILE SEGMENT: Intellectual Indexing
LANGUAGE: French
SUMMARY LANGUAGE: English
ENTRY DATE: Entered Embase: Jun 2010
Last Updated on Embase: Jun 2010
AB The abovenamed drug **mixture** (of which **ethylphenacemide** is the chief component) has been used in 90 cases of epilepsy, including 32 cases of grand mal, 17 cases comprising grand mal and petit mal together, 18 cases of Jacksonian epilepsy, and 23 cases of psychomotor epilepsy. In general, the results were parallel to those of the classical associations of phenobarbial and hydantoin derivatives but are of interest because of the severity of the forms of epilepsy treated. Side effects were generally mild and responded to dose reduction; they occurred in 23 cases. It seems useful to supplement treatment with small extra doses of phenobarbital and possibly of hydantoin derivatives.

L30 ANSWER 39 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 0048460270 EMBASE Full-text
DOCUMENT NUMBER: 281496724
TITLE: [Anti-epileptic activity of a **mixture** of **ethylphenacemide**, phenobarbital and phenytoin ('trinuride')].
Activite anti-epileptique du trinuride.
AUTHOR: Loiseau, P.; Cohadon, S.
SOURCE: Presse Medicale, (**1964**) Vol. 72, No. 33, pp. 1969-1970.
ISSN: 0755-4982
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: CLASSIC
FILE SEGMENT: Intellectual Indexing
LANGUAGE: French
ENTRY DATE: Entered Embase: Jun 2010
Last Updated on Embase: Jun 2010

L30 ANSWER 40 OF 40 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 0014227793 EMBASE Full-text
DOCUMENT NUMBER: 81738174 PMID: 14227793
COPYRIGHT: MEDLINE® is the source for the citation and abstract of this record.
TITLE: [PHARMACOLOGIC DATA ON THE THERAPEUTIC COMBINATION: **PHENETURIDE**-BIURET-DIPHENYLHYDANTOIN-PHENOBARBITAL.].
DONN'EES PHARMACOLOGIQUES SUR L'ASSOCIATION TH'ERAPEUTIQUE:
PH'EN'ETURIDE-BIURET-DIPH'ENYLHYDANTOUINE-**PH**'ENOBARBITAL..
AUTHOR: VINCENT, D. (correspondence)
SOURCE: Therapie, (**1964 Sep-Oct**) Vol. 19, pp. 1297-1311.
ISSN: 0040-5957
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: MEDLINE
FILE SEGMENT: Intellectual Indexing
LANGUAGE: French
ENTRY DATE: Entered Embase: Nov 2016
Last Updated on Embase: Nov 2016
First Entered Embase or Embase Alert: Nov 2016

FILE 'MEDLINE' ENTERED AT 08:33:29 ON 30 AUG 2021

FILE COVERS 1946 TO DATE.
FILE LAST UPDATED: 29 Aug 2021 (20210829/UP).

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This file contains CAS Registry Numbers for easy and accurate substance identification.

See HELP RANGE before carrying out any RANGE search.

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L31       18659 SEA FILE=MEDLINE ABB=ON  PLU=ON  (PHENOBARBITAL/CT OR
                D3.383.742.698.253.650./CT)
L32      119110 SEA FILE=MEDLINE ABB=ON  PLU=ON  (UREA/CT OR D2.65.950./CT)
L33         245 SEA FILE=MEDLINE ABB=ON  PLU=ON  L32 AND L31
L34       13837 SEA FILE=MEDLINE ABB=ON  PLU=ON  ("FREEZE DRYING"/CT OR
                E1.370.225.500.620.760.160.260./CT OR E1.370.225.750.600.76
                0.160.260./CT OR E2.792.156.260./CT OR E5.200.500.620.760.1
                60.260./CT OR E5.200.750.600.760.160.260./CT OR E5.760.156.
                260./CT)
L35           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L33 AND L34



L31       18659 SEA FILE=MEDLINE ABB=ON  PLU=ON  (PHENOBARBITAL/CT OR
                D3.383.742.698.253.650./CT)
L32      119110 SEA FILE=MEDLINE ABB=ON  PLU=ON  (UREA/CT OR D2.65.950./CT)
L33         245 SEA FILE=MEDLINE ABB=ON  PLU=ON  L32 AND L31
L36     3963026 SEA FILE=MEDLINE ABB=ON  PLU=ON  ("HYDROGEN-ION CONCENTRATI
                ON"/CT OR G2.300./CT)
L37          22 SEA FILE=MEDLINE ABB=ON  PLU=ON  L33 AND L36



L38          21 SEA ABB=ON  PLU=ON  L37 AND PY<2019

L38  ANSWER 1 OF 21     MEDLINE ®  on STN
ACCESSION NUMBER:   2007180781     MEDLINE Full-text
DOCUMENT NUMBER:    PubMed ID: 17349620
TITLE:              Attenuated function and expression of P-glycoprotein at
                    blood-brain barrier and increased brain distribution of
                    phenobarbital in streptozotocin-induced diabetic mice.
AUTHOR:             Liu HaiYan
CORPORATE SOURCE:   Center of Drug Metabolism and Pharmacokinetics, China
                    Pharmaceutical University, Nanjing 210009, China.
AUTHOR:             Zhang DongMei; Xu Xiao; Liu XiaoDong; Wang GuangJi; Xie
                    Lin; Pang XiaoYan; Liu Li
SOURCE:             European journal of pharmacology, (2007 Apr 30) Vol.
                    561, No. 1-3, pp. 226-32.  Electronic Publication Date:
                    8 Feb 2007
                    Journal code: 1254354. ISSN: 0014-2999. L-ISSN:
                    0014-2999.
DIGITAL OBJECT ID:  http://dx.doi.org/10.1016/j.ejphar.2007.01.062
PUB. COUNTRY:       Netherlands
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
                    (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:           English
FILE SEGMENT:       MEDLINE; Priority Journals
FILE SEGMENT:       Print; Electronic
ENTRY MONTH:        200705
ENTRY DATE:         Entered STN: 27 Mar 2007
                    Last Updated on STN: 23 May 2007
                    Entered Medline: 22 May 2007
OS.CITING REF COUNT: 13   There are 13 MEDLINE records that cite this
                          record
ED   Entered STN: 27 Mar 2007
     Last Updated on STN: 23 May 2007
     Entered Medline: 22 May 2007
AB   The aim of the study was to investigate whether diabetes mellitus
     modulated the function and expression of P-glycoprotein and the
     distribution of phenobarbital in the brain of 3-week
     streptozotocin-induced diabetic mice.  P-glycoprotein function in
     blood-brain barrier was assessed by measuring the brain-to-plasma
     concentration ratios of rodamine123, a well-known P-glycoprotein
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substrate, in non-diabetic mice and diabetic mice. P-glycoprotein expression in the brain cortex was evaluated with western blot. Whether diabetes mellitus changed the distribution of phenobarbital (60 mg/kg, i.v.) in brain of mice was measured, and whether the changed distribution caused the difference of phenobarbital (80 and 100 mg/kg) -induced loss of the righting reflex in non-diabetic and diabetic mice were also investigated. The results showed that the brain-to-plasma concentration ratio value of rodamine123 in diabetic mice was significantly higher than that of non-diabetic mice, western blot suggested that the protein level of P-glycoprotein in the brain of 3-week diabetic mice was significantly lower than that of non-diabetic mice, and insulin treatment restored the impairment of P-glycoprotein. The exposure of phenobarbital in brain of diabetic mice was 1.30-fold of that of non-diabetic mice, while in plasma the fold was 1.09. The increased distribution of phenobarbital in the brain of diabetic mice significantly increased the duration of phenobarbital-induced loss of the righting reflex and reduced the latency time of loss of the righting reflex. All the results suggested that the function and expression of P-glycoprotein might be impaired and the brain distribution of phenobarbital was increased in brain of streptozotocin-induced diabetic mice.

L38 ANSWER 2 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 2003238017 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12760400
TITLE: Phenobarbital-induced alterations in the sexual differentiation of the female rat: reversal by hydroxyurea and cycloheximide.
AUTHOR: Gupta C
CORPORATE SOURCE: Department of Pediatrics, School of Medicine, University of Pennsylvania, USA.
AUTHOR: Yaffe S J
SOURCE: Pediatric pharmacology (New York, N.Y.), **(1982)** Vol. 2, No. 2, pp. 85-91.
Journal code: 8400778. ISSN: 0270-322X. L-ISSN: 0270-322X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 23 May 2003
Last Updated on STN: 11 Jun 2003
Entered Medline: 10 Jun 2003
ED Entered STN: 23 May 2003
Last Updated on STN: 11 Jun 2003
Entered Medline: 10 Jun 2003
AB The possible mechanism of action of phenobarbital in prenatal female rats has been studied using different inhibitors of protein/DNA/RNA synthesis. Administration of phenobarbital (40 mg/kg/day) subcutaneously from day 17 to day 20 of pregnancy resulted in a delay of the onset of puberty, disorders of estrous cycle, infertility, and high estrogen levels in the female offspring. Cycloheximide (60 microg/kg/day)--a protein synthesis inhibitor and hydroxyurea (160 mg/kg/day)--a DNA synthesis inhibitor when combined with phenobarbital, significantly reduced the incidence of reproductive dysfunctions listed above. Alpha-amanitin (15 microg/kg/day), an inhibitor of m-RNA synthesis, produced reproductive disorders in the female offspring when administered alone to pregnant rats and also failed to reverse the PB-induced reproductive alterations. Cycloheximide and hydroxyurea produced no effect upon reproductive function when administered alone. Cycloheximide administration resulted in low body weight at birth and delayed eye opening. These results suggest that prenatal administration of phenobarbital produces its effect via new protein synthesis and that cycloheximide and hydroxyurea protect the offspring from phenobarbital-induced toxic effects by inhibiting its biochemical action.

L38 ANSWER 3 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1997013718 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9213437
TITLE: Glucose inhibits phenobarbital-induced delta-aminolevulinate synthase expression in normal but not in diabetic rat hepatocytes.

AUTHOR: Varone C L
CORPORATE SOURCE: Departamento de Quimica Biologica, Universidad de Buenos Aires, Argentina.
AUTHOR: Canepa E T; Llambias E B; Grinstein M
SOURCE: Biochemistry and cell biology = Biochimie et biologie cellulaire, **(1996)** Vol. 74, No. 2, pp. 271-81. Journal code: 8606068. ISSN: 0829-8211. L-ISSN: 0829-8211.
DIGITAL OBJECT ID: http://dx.doi.org/10.1139/o96-029
PUB. COUNTRY: Canada
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 21 Jul 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 7 Jul 1997
ED Entered STN: 21 Jul 1997
Last Updated on STN: 6 Feb 1998
Entered Medline: 7 Jul 1997
AB In the present work, we demonstrate the presence of a glucose inhibitory effect on the phenobarbital-mediated induction of the delta-aminolevulinate synthase mRNA in normal rat hepatocytes, consistent with the results obtained with the delta-aminolevulinate synthase activity previously reported. This "glucose effect" can be prevented by adding cAMP, adenylate cyclase activators, or a phosphodiesterase inhibitor. Delta-Aminolevulinate synthase mRNA half-life is not modified in the presence of phenobarbital or glucose. When the same experiments are performed using diabetic cells, no glucose effect is observed, even when the endogenous cAMP content is lowered to normal levels. The results obtained in this study suggest that glucose decreases delta-aminolevulinate synthase biosynthesis by acting at a pretranslational step. Assuming that the glucose effect operates by a repression mechanism exerted by metabolites derived from or related to glucose, the present results may reflect a derangement in the formation of these metabolites as a result of the abnormal metabolism operating in the diabetic state.

L38 ANSWER 4 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1993284686 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8508500
TITLE: Measurement and characterization of the denitrosation of tauromustine and related nitrosoureas by glutathione transferases in liver cytosol from various species.
AUTHOR: Tuvesson H
CORPORATE SOURCE: Department of Pharmacokinetics, Kabi Pharmacia AB, Helsingborg, Sweden.
AUTHOR: Gunnarsson P O; Seidegard J
SOURCE: Carcinogenesis, **(1993 Jun)** Vol. 14, No. 6, pp. 1143-7. Journal code: 8008055. ISSN: 0143-3334. L-ISSN: 0143-3334.
DIGITAL OBJECT ID: http://dx.doi.org/10.1093/carcin/14.6.1143
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 23 Jul 1993
Last Updated on STN: 6 Feb 1998
Entered Medline: 12 Jul 1993
OS.CITING REF COUNT: 1 There are 1 MEDLINE records that cite this record
ED Entered STN: 23 Jul 1993
Last Updated on STN: 6 Feb 1998
Entered Medline: 12 Jul 1993
AB The denitrosation of a novel nitrosourea, 1-(2-chloroethyl)-3-[(2-dimethylaminosulfonyl)-ethyl]-1-nitrosoure a, tauromustine (TCNU), has been investigated in liver cytosol from various species and with a pool of cytosolic rat liver glutathione transferases (GSTs). In addition, the denitrosation of related nitrosoureas, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) have been

investigated. By using radioactive nitrosoureas as substrates and HPLC to detect the denitrosated products, a sensitive assay has been developed. The activities towards additional substrates, 1-chloro-2,4-dinitrobenzene (CDNB) and trans-stilbene oxide (tSBO) were also measured in the various cytosol fractions. The apparent Vmax and Km values for the denitrosation of TCNU in rat liver cytosol were calculated to be 830 pmol/min/mg protein and 8.4 mM respectively. The rate of denitrosation of TCNU was found to be highest in the mouse, followed by the rat and the dog. The induction of GSTs by phenobarbital in rats increased the denitrosation of TCNU similar to the activities found towards CDNB and tSBO as substrates. The highest denitrosation activity by GST was determined towards BCNU, followed by CCNU and TCNU. Our results suggest that the denitrosation of various nitrosoureas via GST may play an important role in the deactivating process occurring in vivo and for the efficacy of nitrosoureas used in chemotherapy.

L38 ANSWER 5 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1991178265 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2007767
TITLE: CCl4 cirrhosis in rats: irreversible histological changes and differentiated functional impairment.
AUTHOR: Fischer-Nielsen A
CORPORATE SOURCE: Department of Medicine A, Rigshospitalet, Copenhagen, Denmark.
AUTHOR: Poulsen H E; Hansen B A; Hage E; Keiding S
SOURCE: Journal of hepatology, **(1991 Jan)** Vol. 12, No. 1, pp. 110-7.
Journal code: 8503886. ISSN: 0168-8278. L-ISSN: 0168-8278.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/0168-8278(91)90919-3
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 199104
ENTRY DATE: Entered STN: 19 May 1991
Last Updated on STN: 19 May 1991
Entered Medline: 30 Apr 1991
OS.CITING REF COUNT: 3 There are 3 MEDLINE records that cite this record
ED Entered STN: 19 May 1991
Last Updated on STN: 19 May 1991
Entered Medline: 30 Apr 1991
AB Cirrhosis of the rat liver was induced by a 12 week individualized CCl4/phenobarbital treatment. After treatment, all surviving animals (81%) showed cirrhosis of the liver. The cirrhosis induced was irreversible when evaluated 24 weeks after cessation of treatment. Quantitative liver function measurements were reduced in a differentiated manner. Ranked according to the most pronounced changes they are: capacity of urea-N synthesis (CUNS), galactose elimination capacity (GEC) and antipyrine clearance (APC). Hepatic glutathione concentrations were only slightly decreased after the CCl4 treatment. It is possible to produce a high incidence of irreversible cirrhosis with differentiated functional impairment in the rat.

L38 ANSWER 6 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1990378220 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1697977
TITLE: Tumor promoting effect of goitrogens on the rat thyroid.
AUTHOR: Kanno J
CORPORATE SOURCE: Department of Pathology, Faculty of Medicine, Tokyo Medical and Dental University, Japan.
AUTHOR: Matsuoka C; Furuta K; Onodera H; Miyajima H; Maekawa A; Hayashi Y
SOURCE: Toxicologic pathology, **(1990)** Vol. 18, No. 2, pp. 239-46.
Journal code: 7905907. ISSN: 0192-6233. L-ISSN: 0192-6233.
DIGITAL OBJECT ID: http://dx.doi.org/10.1177/019262339001800202
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY) Journal; Article; (JOURNAL ARTICLE)

(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 22 Nov 1990
Last Updated on STN: 29 Jan 1996
Entered Medline: 18 Oct 1990
OS.CITING REF COUNT: 11 There are 11 MEDLINE records that cite this record
ED Entered STN: 22 Nov 1990
Last Updated on STN: 29 Jan 1996
Entered Medline: 18 Oct 1990
AB To evaluate the mechanism of the promoting effect of goitrogens on thyroid tumorigenesis, well-known goitrogens having different pharmacologic action, i.e., thiourea, phenobarbital sodium (PB), potassium thiocyanate (KSCN), and 3,4,5,6-tetrachloro-2',4',5',7'-tetraiodo-fluorescein sodium salt (Rose Bengal B, FD&C Red No. 105) (FR105) were administered to the DHPN-initiated and non-initiated F344 male rats in the drinking water for 25 weeks. Remington's iodine deficient diet (I-def) was fed as a positive control. These goitrogens showed significant tumor promoting effect or promoting tendency on the rat thyroids. According to the changes in thyroid morphology and thyroid-related hormone titers observed in the present study, we proposed to classify goitrogens at least into 2 groups, i.e., iodine deficiency-type promoters and the iodine excess-type promoters. The former contains goitrogens inducing TSH-stimulated diffuse goiter composed of uniform follicles with activated tall follicular epithelial cells, such as thiourea, KSCN and PB, and the latter contains goitrogens inducing colloid goiter composed of a mixture of colloid-rich follicles with flat follicular cells and normal-looking follicles with cuboidal follicular cells, such as FR105. This classification may be useful for the risk assessment of goitrogens.

L38 ANSWER 7 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1990268704 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2140731
TITLE: Differential effects of renal carcinogens and tumor promoters on growth promotion and inhibition of gap junctional communication in two rat renal epithelial cell lines.
AUTHOR: Konishi N
CORPORATE SOURCE: Tumor Pathology and Pathogenesis Section, National Cancer Institute, Frederick, MD 21701-1013.
AUTHOR: Donovan P J; Ward J M
SOURCE: Carcinogenesis, **(1990 Jun)** Vol. 11, No. 6, pp. 903-8. Journal code: 8008055. ISSN: 0143-3334. L-ISSN: 0143-3334.
DIGITAL OBJECT ID: http://dx.doi.org/10.1093/carcin/11.6.903
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 199007
ENTRY DATE: Entered STN: 10 Aug 1990
Last Updated on STN: 10 Aug 1990
Entered Medline: 12 Jul 1990
OS.CITING REF COUNT: 3 There are 3 MEDLINE records that cite this record
ED Entered STN: 10 Aug 1990
Last Updated on STN: 10 Aug 1990
Entered Medline: 12 Jul 1990
AB To evaluate the effects of renal carcinogens and tumor promoters on gap junctional intercellular communication (IC) and colony formation, two rat kidney epithelial cell lines were examined in vitro. The NRK-52E line was obtained from the American Type Culture Collection and the NK-4 line was established by us from male F344/NCr rats. The NRK-52E line was co-cultured on a confluent monolayer of lethally irradiated NRK-52E cells to determine colony-forming ability (cloning efficiency) and clonal expansion (average surface area of the colonies, SA) and the NK-4 line was cultured on collagen gel. Streptozotocin (STZ), a renal carcinogen, and trisodium nitrilotriacetate monohydrate (NTANa3), a renal carcinogen and tumor promoter, showed mild growth-enhancing effects on both cell lines, as

determined by significant increases in SA, but not in cloning efficiency (CE). Sodium barbital (BBNa), a renal tumor promoter, had similar effects, while phenobarbital sodium (PBNa), a non-renal tumor promoter, lacked such activity. The effects of these compounds on gap junctional function were investigated by the Lucifer Yellow dye transfer microinjection assay using monolayers of NRK-52E and NK-4 cells. We found that STZ, NTANa3 and BBNa inhibited IC in NRK-52E cells, in accordance with their reported tumorigenic and/or tumor-promoting activity in vivo, while PBNa did not. Thus, we could present these findings in NRK-52E cells as an in vitro model to examine the potential tissue-specific effects of renal carcinogens and tumor promoters in vitro. We found, however, that other growth control mechanisms beside IC may play a role, because although the NK-4 line did not possess normal IC, the tumor promoters studied had identical growth-promoting effects on colony formation and expansion in both this cell line and the NRK-52E line.

L38 ANSWER 8 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1990056554 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2818619
TITLE: Cytochrome P-450-dependent formation of alkylating metabolites of the 2-chloroethylnitrosoureas MeCCNU and CCNU.
AUTHOR: Kramer R A
CORPORATE SOURCE: Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD 20892.
SOURCE: Biochemical pharmacology, **(1989 Oct 01)** Vol. 38, No. 19, pp. 3185-92.
Journal code: 0101032. ISSN: 0006-2952. L-ISSN: 0006-2952.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/0006-2952(89)90612-6
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 198911
ENTRY DATE: Entered STN: 28 Mar 1990
Last Updated on STN: 28 Mar 1990
Entered Medline: 28 Nov 1989
ED Entered STN: 28 Mar 1990
Last Updated on STN: 28 Mar 1990
Entered Medline: 28 Nov 1989
AB Rat liver microsomes catalyzed the biotransformation of the clinically important nitrosourea anticancer agents 1-(2-chloroethyl)-3-(trans-4-methyl-cyclohexyl)-1-nitrosourea (MeCCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) to alkylating metabolites that bound covalently to microsomal protein and to DNA. The enzyme-mediated microsomal alkylation required NADPH and oxygen and was inhibited by carbon monoxide, indicating the participation of a cytochrome P-450-dependent monooxygenase. Additional studies with inhibitors such as piperonyl butoxide and with the inducers 3-methylcholanthrene and phenobarbital were consistent with this view. In contrast to these observations on the formation of alkylating metabolites, carbamylation reactions were not affected significantly by microsomal metabolism. Reduced glutathione, cysteine or N-acetylcysteine decreased the microsomal alkylation by MeCCNU and produced a corresponding increase in the formation of polar metabolites that was resolved by HPLC as three distinct N-acetylcysteine-MeCCNU adducts. The addition of semicarbazide to the reaction decreased microsomal alkylation by 30%, indicating that the formation of the alkylating species may proceed via an aldehyde intermediate. Renal microsomes were not found to catalyze the alkylation reaction. Moreover, MeCCNU inhibited the renal slice accumulation of p-aminohippuric acid only in the presence of liver microsomes and NADPH, suggesting that a liver metabolite may be responsible for the renal toxicity of the parent nitrosourea.

L38 ANSWER 9 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1986036747 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 3863922
TITLE: In vitro metabolism of ACNU, 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitroso urea hydrochloride, a water-soluble antitumor nitrosourea.

AUTHOR: Nishigaki T; Nakamura K; Tanaka M
SOURCE: Journal of pharmacobio-dynamics, **(1985 Jun)** Vol. 8, No. 6, pp. 409-16.
Journal code: 7901854. ISSN: 0386-846X. L-ISSN: 0386-846X.
DIGITAL OBJECT ID: http://dx.doi.org/10.1248/bpb1978.8.409
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 198511
ENTRY DATE: Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 25 Nov 1985
OS.CITING REF COUNT: 1 There are 1 MEDLINE records that cite this record
ED Entered STN: 21 Mar 1990
Last Updated on STN: 21 Mar 1990
Entered Medline: 25 Nov 1985
AB In vitro decomposition of ACNU, 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride, in various conditions was studied with the use of the 14C-labeled compound. Metabolite A, 3,4-dihydro-7-methylpyrimido[4,5-d]pyrimidin-2(1H)-one (an intramolecular cyclized product), was formed spontaneously in the phosphate buffer (pH 7.4) with simultaneous liberation of the alkylating moiety. With rat liver enzyme preparations, formation of three metabolites was observed. Those were metabolite B, 1-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-3-(2-chloroethyl)urea (a denitrosated product), metabolite C, 1-[(4-amino-2-methyl-5-pyrimidinyl) methyl]-5-hydroxy-3-nitroso-2-imidazolidinone (a product via oxidative dechlorination), and metabolite D, 1-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-hydroxy-2-imidazolidinone (a denitrosated product of metabolite C). Formation of metabolite B was catalyzed with both cytosolic and microsomal enzymes, not inhibited with SKF-525A, and partly dependent on nicotinamide adenine dinucleotide phosphate (NADPH). These results suggest that at least two enzymatic steps would be involved in the formation of this product. Metabolites C and D were produced by the microsomal preparation, being dependent on O2 and NADPH, inhibited by CO and SKF-525A, and enhanced by phenobarbital pretreatment. When metabolite C was incubated with cytosolic and microsomal preparations, more efficient formation of metabolite D with the former than the latter was observed. From these results, it was assumed that oxidative dechlorination of ACNU to metabolite C would be catalyzed with the microsomal mixed function oxidase, and metabolite D would be produced via denitrosation process of metabolite C.

L38 ANSWER 10 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1985033786 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 6492196
TITLE: Ethylenethiourea-induced hindpaw deformities in mice and effects of metabolic modifiers on their occurrence.
AUTHOR: Khera K S
SOURCE: Journal of toxicology and environmental health, **(1984)** Vol. 13, No. 4-6, pp. 747-56.
Journal code: 7513622. ISSN: 0098-4108. L-ISSN: 0098-4108.
DIGITAL OBJECT ID: http://dx.doi.org/10.1080/15287398409530536
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 198411
ENTRY DATE: Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 28 Nov 1984
OS.CITING REF COUNT: 4 There are 4 MEDLINE records that cite this record
ED Entered STN: 20 Mar 1990
Last Updated on STN: 20 Mar 1990
Entered Medline: 28 Nov 1984
AB Time-mated Swiss-Webster mice were pretreated in separate experiments with phenobarbital (60 mg/kg X d sc on d 7-10 of pregnancy), SKF-525A

(40 mg/kg ip on d 12 of pregnancy) or 3-methylcholanthrene (20 mg/kg X d on d 10-12 of pregnancy). On the d 12 of pregnancy (1 h after SKF-525A or 3-methylcholanthrene treatment), one group each of pretreated mice was given a single oral dose of 1600, 2000, or 2400 mg/kg of ethylenethiourea (ETU) as a 5% concentrate in a 1.5% aqueous gelatin solution, which as a vehicle was given to other pretreated groups. The respective volume doses were 3.2, 4.0, or 4.8 ml/100 g body weight with the controls given 4.8 ml/100 g body weight of vehicle alone. Maternal toxicity was observed in all groups given ETU, whether pretreated with metabolic modifiers or not. In the three experiments, treatment with ETU alone reduced fetal weight by 15% at 2400 mg/kg and 8% with the remaining 2 doses, and increased the incidence of resorptions (19-62% with the 2400 mg/kg dose, 8-59% at 2000 mg/kg, and 7-32% at the 1600 mg/kg dose). The significant defects with incidence ranges in three experiments were: hindpaw ectrodactyly, 2-6% at 1600 mg/kg, 4-20% at 2000, and 20-29% at 2400 mg/kg; and hindpaw syndactyle, 3% at 16 mg/kg, 6-14% at 2000, and 2-12% at 2400 mg/kg doses. Minor incidences of cleft palate and hindpaw polydactyly were also observed. Phenobarbital pretreatment did not change the ETU-induced maternal or fetal effects. SKF-525A enhanced the resorptions and reduced the litter-size but had no effect on fetal malformations. The 3-methylcholanthrene pretreatment reduced the ETU-induced incidences of hindpaw ectrodactyly, hindpaw syndactyly, and cleft palate at the 2000 and 2400 mg/kg doses. Previous studies with rats and hamsters revealed that SKF-525A enhanced the ETU-induced fetal malformations but phenobarbital and 3-methyl-cholanthrene had no effect in these two species.

L38 ANSWER 11 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1979023844 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 29738
TITLE: Drug concentration in saliva.
AUTHOR: Mucklow J C; Bending M R; Kahn G C; Dollery C T
SOURCE: Clinical pharmacology and therapeutics, **(1978 Nov)** Vol. 24, No. 5, pp. 563-70.
Journal code: 0372741. ISSN: 0009-9236. L-ISSN: 0009-9236.
DIGITAL OBJECT ID: http://dx.doi.org/10.1002/cpt1978245563
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 197812
ENTRY DATE: Entered STN: 14 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 29 Dec 1978
OS.CITING REF COUNT: 29 There are 29 MEDLINE records that cite this record
ED Entered STN: 14 Mar 1990
Last Updated on STN: 6 Feb 1998
Entered Medline: 29 Dec 1978
AB It is possible to predict plasma concentrations of drugs by measurement in saliva, obviating the need for venipuncture. Using a selection of weakly acidic and basic drugs, we have found this prediction reliable for drugs largely nonionized at normal plasma pH (phenytoin, phenobarbital, antipyrine) but unreliable for ionized drugs (chlorpropramide, tolbutamide, propranolol, meperidine). Deliberate alteration of saliva flow rate and pH using different stimuli have produced twofold changes in saliva drug concentrations. Wide interindividual variability of saliva pH is the likely explanation for the inconstancy of saliva to plasma concentration ratios for ionized drugs.

L38 ANSWER 12 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1977230907 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 328966
TITLE: Changes in sensitivity of mice to anticonvulsant drugs following bilateral olfactory bulb ablations.
AUTHOR: Ueki S; Araki Y; Watanabe S
SOURCE: Japanese journal of pharmacology, **(1977 Apr)** Vol. 27, No. 2, pp. 183-92.
Journal code: 2983305R. ISSN: 0021-5198. L-ISSN: 0021-5198.

DIGITAL OBJECT ID: http://dx.doi.org/10.1254/jjp.27.183
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 197709
ENTRY DATE: Entered STN: 14 Mar 1990
Last Updated on STN: 14 Mar 1990
Entered Medline: 22 Sep 1977
ED Entered STN: 14 Mar 1990
Last Updated on STN: 14 Mar 1990
Entered Medline: 22 Sep 1977
AB Changes in sensitivity to anticonvulsant drugs were investigated after bilateral olfactory bulb ablations in mice. The sensitivity to benzodiazepines and acetazolamide increased, whereas that to phenylacetylurea and dipropylacetic acid decreased, and sensitivity to phenobarbital, diphenylhydantoin and trimethadion was not significantly changes after olfactory bulb ablations. Increase in sensitivity to benzodiazepines was the most significant in both electroshock and pentetrazol convulsions. It was suggested that altered activities and denervation supersensitivity in the limbic system, hypothalamus and midbrain might account for these changes in sensitivity to anticonvulsant drugs after olfactory bulb ablations.

L38 ANSWER 13 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1975181959 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 237450
TITLE: Theophylline-induced seizures in adults. Correlation with serum concentrations.
AUTHOR: Zwillich C W; Sutton F D; Neff T A; Cohn W M; Matthay R A; Weinberger M M
SOURCE: Annals of internal medicine, **(1975 Jun)** Vol. 82, No. 6, pp. 784-7.
Journal code: 0372351. ISSN: 0003-4819. L-ISSN: 0003-4819.
DIGITAL OBJECT ID: http://dx.doi.org/10.7326/0003-4819-82-6-784
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 197509
ENTRY DATE: Entered STN: 10 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 9 Sep 1975
OS.CITING REF COUNT: 65 There are 65 MEDLINE records that cite this record
ED Entered STN: 10 Mar 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 9 Sep 1975
AB Eight patients developed grand mal seizures during intravenous theophylline therapy. None had a history of neurologic disorder, and all were acutely ill with severe pulmonary or cardiovascular disease, or both. Serum theophylline concentrations obtained within 1 hour of the seizure ranged from 25 mug/ml to 70mug/ml, with a mean value (53 plus or minus 4.8 mug/ml) more than twice the upper limit of the recommended therapeutic concentration. This serum theophylline concentration was greater than the concentration found in a group of patients with less severe drug-related symptoms (35 plus or minus 1.8 mug/ml, P less than 0.01). A third group of patients without drug-related symptoms had a mean theophylline serum concentration of 19 plus or minus 2.0 mug/ml, which was less than that found in either group with toxicity symptoms (P less than 0.05). Factors predisposing to the high serum concentrations in the patients with seizures were both higher drug dosage, compared with the other groups (P less than 0.01), and hepatic dysfunction, which was more common in both groups with drug-related symptoms.

L38 ANSWER 14 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1972011876 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 5538026
TITLE: Lipid-electrolyte ("lipo-lyte") dialysis--experimental and preliminary clinical observations.

AUTHOR: Whang R; Orndorff M; Papper S
SOURCE: Clinical toxicology, **(1970 Dec)** Vol. 3, No. 4, pp. 551-60.
Journal code: 0205535. ISSN: 0009-9309. L-ISSN: 0009-9309.
DIGITAL OBJECT ID: http://dx.doi.org/10.3109/15563657008990127
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 197112
ENTRY DATE: Entered STN: 10 Mar 1990
Last Updated on STN: 10 Mar 1990
Entered Medline: 12 Dec 1971
OS.CITING REF COUNT: 1 There are 1 MEDLINE records that cite this record
ED Entered STN: 10 Mar 1990
Last Updated on STN: 10 Mar 1990
Entered Medline: 12 Dec 1971

L38 ANSWER 15 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1971290674 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 5571215
TITLE: Mechanism of intraocular pressure response after optic nerve transection.
AUTHOR: Podos S M; Krupin T; Becker B
SOURCE: American journal of ophthalmology, **(1971 Jul 30)** Vol. 72, No. 1, pp. 79-87.
Journal code: 0370500. ISSN: 0002-9394. L-ISSN: 0002-9394.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/0002-9394(71)91594-7
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Abridged Index Medicus Journals; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 197111
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 16 Nov 1971
ED Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 16 Nov 1971

L38 ANSWER 16 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1971278162 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 4398023
TITLE: Interference of barbiturates with pyrimidine incorporation. II. Structural specificity of the inhibition of orotate uptake in Bacillus cereus.
AUTHOR: Mandel H G; Riis M
SOURCE: Biochemical pharmacology, **(1970 Jun)** Vol. 19, No. 6, pp. 1867-77.
Journal code: 0101032. ISSN: 0006-2952. L-ISSN: 0006-2952.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/0006-2952(70)90285-6
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 197110
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 28 Oct 1971
OS.CITING REF COUNT: 3 There are 3 MEDLINE records that cite this record
ED Entered STN: 1 Jan 1990
Last Updated on STN: 6 Feb 1995
Entered Medline: 28 Oct 1971

L38 ANSWER 17 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1969267943 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 5804759

TITLE: Studies on bilirubin production and excretion in mice and rats treated with phenobarbital, chlorpromazine, norethandrolone, acetohexamide or enovid.
AUTHOR: Roberts R J; Plaa G L
SOURCE: Toxicology and applied pharmacology, **(1969 Sep)** Vol. 15, No. 2, pp. 483-92.
Journal code: 0416575. ISSN: 0041-008X. L-ISSN: 0041-008X.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/0041-008x(69)90046-5
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 196910
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 7 Oct 1969
OS.CITING REF COUNT: 2 There are 2 MEDLINE records that cite this record
ED Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 7 Oct 1969

L38 ANSWER 18 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1968323925 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 6014912
TITLE: [On the resportion profile of drugs. 2. On studies with the resorption model].
Uber Resorptionsprofile von Arzneimitteln. 2. Uber Versuche mit dem Resorptionsmodell.
AUTHOR: Dibbern H W
SOURCE: Arzneimittel-Forschung, **(1966 Oct)** Vol. 16, No. 10, pp. 1304-6.
Journal code: 0372660. ISSN: 0004-4172. L-ISSN: 0004-4172.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: German
FILE SEGMENT: MEDLINE; Priority Journals
FILE SEGMENT: Print
ENTRY MONTH: 196809
ENTRY DATE: Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 5 Sep 1968
OS.CITING REF COUNT: 2 There are 2 MEDLINE records that cite this record
ED Entered STN: 1 Jan 1990
Last Updated on STN: 1 Jan 1990
Entered Medline: 5 Sep 1968

L38 ANSWER 19 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1965127648 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14322974
TITLE: ENHANCED SULFOBROMOPHTHALEIN DISAPPEARANCE IN MICE PRETREATED WITH VARIOUS DRUGS.
AUTHOR: FUJIMOTO J M; EICH W F; NICHOLS H R
SOURCE: Biochemical pharmacology, **(1965 Apr)** Vol. 14, pp. 515-24.
Journal code: 0101032. ISSN: 0006-2952. L-ISSN: 0006-2952.
DIGITAL OBJECT ID: http://dx.doi.org/10.1016/0006-2952(65)90224-8
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: OLDMEDLINE; NONMEDLINE
FILE SEGMENT: Print
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 16 Jul 1999
Last Updated on STN: 16 Jul 1999
Entered Medline: 1 Dec 1996
OS.CITING REF COUNT: 2 There are 2 MEDLINE records that cite this record
ED Entered STN: 16 Jul 1999
Last Updated on STN: 16 Jul 1999
Entered Medline: 1 Dec 1996

L38 ANSWER 20 OF 21 MEDLINE ® on STN

ACCESSION NUMBER: 1964095341 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 14137442
TITLE: [ACTION OF VARIOUS UREIDES ON K GRADIENTS OF MAMMALIAN CEREBRAL TISSUE ELECTRICALLY STIMULATED IN VITRO]. ACTION DE DIVERS UR'EIDES SUR LES GRADIENTS DE K DU TISSU C'ER'EBRAL DE MAMMIF'ERE STIMUL'E 'ELECTRIQUEMENT IN VITRO.
AUTHOR: CORRIOL J; JOANNY P; FONDARAI J
SOURCE: Comptes rendus des seances de la Societe de biologie et de ses filiales, **(1963)** Vol. 157, pp. 2224-7.
Journal code: 7505439. ISSN: 0037-9026. L-ISSN: 0037-9026.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: French
FILE SEGMENT: OLDMEDLINE; NONMEDLINE
FILE SEGMENT: Print
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 16 Jul 1999
Last Updated on STN: 16 Jul 1999
Entered Medline: 1 Dec 1996
ED Entered STN: 16 Jul 1999
Last Updated on STN: 16 Jul 1999
Entered Medline: 1 Dec 1996

L38 ANSWER 21 OF 21 MEDLINE ® on STN
ACCESSION NUMBER: 1954010335 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 13089576
TITLE: [Peripheral action of anticonvulsants: phenobarbital, phenylethylacetylurea and diphenylhydantoine]. De l'action peripherique des anticonvulsivants phenobarbital, phenylethylacetyluree ou S 46, diphenylhydantoine. II.
AUTHOR: FROMMEL E; RADOUCO C; GOLD P; BURGERMEISTER-GUEX G; DUCOMMUN M
SOURCE: Schweizerische medizinische Wochenschrift, **(1953 Jul 18)** Vol. 83, No. 29, pp. 681-3.
Journal code: 0404401. ISSN: 0036-7672. L-ISSN: 0036-7672.
Report No.: CLML-5425:10346:36:55:226:303.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: UNSPECIFIED
FILE SEGMENT: OLDMEDLINE; NONMEDLINE
FILE SEGMENT: Print
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: Feb 2004
Last Updated on STN: Feb 2004
Entered Medline: 1 May 2003
ED Entered STN: Feb 2004
Last Updated on STN: Feb 2004
Entered Medline: 1 May 2003

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     FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PQSCITECH'
     ENTERED AT 14:24:50 ON 30 AUG 2021
L1           22 SEA ABB=ON  PLU=ON  ("THIRUPATHI M"? OR "MANGALI T"?)/AU
L2        13104 SEA ABB=ON  PLU=ON  "SHUKLA A"?/AU
L3         2429 SEA ABB=ON  PLU=ON  "SHUKLA J"?/AU
L4          106 SEA ABB=ON  PLU=ON  ("DASARADHI L"? OR "LAKKARAJU D"?)/AU
L5       338281 SEA ABB=ON  PLU=ON  ("BALA"? OR "TRIPURA"? OR "SUNDARI"?
                OR "CHODAVARAPU"?)/AU
L6            2 SEA ABB=ON  PLU=ON  L1 AND L2 AND L3 AND L4 AND L5
L7            2 SEA ABB=ON  PLU=ON  L1 AND ((L2 OR L3 OR L4 OR L5))
L8          167 SEA ABB=ON  PLU=ON  L2 AND ((L3 OR L4 OR L5))
L9           14 SEA ABB=ON  PLU=ON  L3 AND (L4 OR L5)
L10           2 SEA ABB=ON  PLU=ON  L4 AND L5

     FILE 'REGISTRY' ENTERED AT 14:26:39 ON 30 AUG 2021
                E PHENOBARBITAL SODIUM/CN
L11           1 SEA ABB=ON  PLU=ON  "PHENOBARBITAL SODIUM"/CN
                SEL L11 CHEM
L12             QUE ABB=ON  PLU=ON  ("GARDENAL SODIUM"/BI OR LINASEN/BI OR
                "LUMINAL SODIUM"/BI OR PHENEMALUM/BI OR "PHENOBAL SODIUM"/B
                I OR PHENOBAL/BI OR "PHENOBARBITAL SODIUM"/BI OR "PHENOBARB
                ITONE SODIUM"/BI OR "SODIUM ETHYLPHENYLBARBITURATE"/BI OR
                "SODIUM LUMINAL"/BI OR "SODIUM PHENOBARBITAL"/BI OR
                "SODIUM PHENOBARBITONE"/BI OR "SODIUM PHENYLETHYLBARBITURAT
                E"/BI OR "SODIUM PHENYLETHYLMALONYLUREA"/BI OR "SODIUM
                5-ETHYL-5-PHENYLBARBITURATE"/BI OR "SOL PHENOBARBITAL"/BI
                OR "SOL PHENOBARBITONE"/BI OR "SOLUBLE PHENOBARBITAL"/BI
                OR "SOLUBLE PHENOBARBITONE"/BI OR 125-36-0/BI OR "5-ETHYL-5
                -PHENYLBARBITURIC ACID SODIUM"/BI OR 57-30-7/BI OR
                8050-96-2/BI)
                E PHENYLETHYLACETYLUREA/CN
L13           1 SEA ABB=ON  PLU=ON  PHENYLETHYLACETYLUREA/CN
                SEL L13 CHEM
L14             QUE ABB=ON  PLU=ON  (.ALPHA.-PHENYL-.ALPHA.-ETHYLACETYLUREA
                /BI OR "(2-PHENYLBUTANOYL)UREA"/BI OR BENURIDE/BI OR
                DL-PHENETURIDE/BI OR EPA/BI OR ETHYLPHENACEMIDE/BI OR
                LIRCAPYL/BI OR "M 551"/BI OR "N-(.ALPHA.-PHENYLBUTYRYL)UREA
                "/BI OR "N-(AMINOCARBONYL)-.ALPHA.-ETHYLBENZENEACETAMIDE"/B
                I OR PBU/BI OR PHENETURIDE/BI OR PHENURIDE/BI OR PHENYLETHY
                LACETYLUREA/BI OR "S 46"/BI OR "1-((ETHYL)PHENYLACETYL)UREA
                "/BI OR 2-PHENYLBUTYRYLUREA/BI OR 6509-31-5/BI OR 90-49-3/B
                I)

     FILE 'HCAPLUS' ENTERED AT 14:27:21 ON 30 AUG 2021
L15       36479 SEA ABB=ON  PLU=ON  L11 OR L12 OR PHENOBARBITAL(1W)(?SODIUM
                ? OR NA) OR GARDENAL OR HYSTEP## OR LUMINAL OR PHENEMAL OR
                PHENOBARTITONE OR PHENYLBARBITAL OR PHENYLETHYLBARBITURIC
                OR (PHENYL OR PH)(W)(BARBITAL OR ETHYLBARBITURIC OR (ETHYL
                OR ET)(W)BARBITURIC)
L16         115 SEA ABB=ON  PLU=ON  PEAU OR PHENYLETHYLACETYLUREA OR
                (PHENYL OR PH)(W)(ETHYLACETYLUREA OR (ETHYL OR ET)(W)(ACETY
                LUREA OR (AC OR ACETYL)(W)UREA) OR PHENYLETHYL(W)(ACETYLURE
                A OR (AC OR ACETYL)(W)UREA)) OR PHENYLETHYLACETYL UREA OR
                BENURIDE
L17          80 SEA ABB=ON  PLU=ON  (ETHYL OR ET)(W)(PHENACEMIDE OR
                PHENYLACETYLUREA OR (PHENYL OR PH)(W)(ACETYLUREA OR
                (ACETYL OR AC)(W)UREA)) OR ETHYLPHENYLACETYLUREA OR
                PHENETURIDE
L18          44 SEA ABB=ON  PLU=ON  L15 AND (L13 OR L14 OR L16 OR L17)
L19          30 SEA ABB=ON  PLU=ON  L18 AND (COMPOSITION OR COMP## OR
                PREP? OR FORMULATION OR SOLUTION OR SOLN OR MIXTURE)
L20          11 SEA ABB=ON  PLU=ON  ("PHENOBARBITAL SODIUM"+PFT AND
                PHENETURIDE+PFT)/CT

     FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PQSCITECH'
     ENTERED AT 14:31:41 ON 30 AUG 2021
L21           2 SEA ABB=ON  PLU=ON  ((L1 OR L2 OR L3 OR L4 OR L5) OR L8)
                AND L18
L22           1 SEA ABB=ON  PLU=ON  ((L1 OR L2 OR L3 OR L4 OR L5) OR L8)
                AND L20
L23          14 SEA ABB=ON  PLU=ON  L6 OR L7 OR L9 OR L10 OR L21 OR L22
L24           9 DUP REM L23 (5 DUPLICATES REMOVED)

L24  ANSWER 1 OF 9  HCAPLUS  COPYRIGHT 2021 ACS on STN DUPLICATE 1
ACCESSION NUMBER:        2021:709379  HCAPLUS Full-text
```

DOCUMENT NUMBER: 174:647882
TITLE: Lyophilized compositions of **phenobarbital sodium** salt
INVENTOR(S): **Chodavarapu, Bala Tripura Sundari**; **Mangali, Thirupathi**; **Shukla, Jay**; **Shukla, Anand**; **Lakkaraju, Dasaradhi**
PATENT ASSIGNEE(S): Nivagen Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 58pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 20210085608	A1	20210325	US 2020-17025881		20200918
PRIORITY APPLN. INFO.:			US 2019-62903511	P	20190920

PATENT STATUS PATENT INFORMATION:

PATENT NO.	KIND	STATUS	STATUS DATE
US 20210085608	A1	Alive	20210401

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB A compn. of, method for producing, and use of an amorphous lyophilized **Phenobarbital Sodium** having high purity are presented. The amorphous lyophilized **Phenobarbital Sodium** is storage-stable being essentially void of impurities (e.g., **phenylethylacetylurea** (**PEAU**), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water.

L24 ANSWER 2 OF 9 EMBASE COPYRIGHT (c) 2021 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 20200074447 EMBASE
DOCUMENT NUMBER: 2003542012 PMID: 31891112
TITLE: Global variation in anastomosis and end colostomy formation following left-sided colorectal resection.
AUTHOR: Ademuyiwa, Adesoji O.; Sale, Danjuma
CORPORATE SOURCE: Barau Dikko Teaching Hospital, Nigeria.
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CORPORATE SOURCE: Aminu KanoTeaching Hospital, Nigeria.
AUTHOR: Ali, Samuel Sani; Odeyemi, Babatunde; Olori, Samson; Mshelbwala, Philip; Samson, Garba; Timothy, Oyediran Kehinde; Samuel, Sani Ali; Osagie, Olabisi
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AUTHOR: Nigo, Samuel; Kabba, Juana; Ngwa, Tagang Ebogo; Brown, James
CORPORATE SOURCE: Mbingo Baptist Hospital, Cameroon.
AUTHOR: Hall, Nigel; King, Sebastian; Agarwal, Arnav; Zani, Augusto; Firdouse, Mohammed; Azzie, Georges; Kushwaha, Sameer; Jamal, Luai
CORPORATE SOURCE: The Hospital For Sick Children, Canada.
AUTHOR: Bailey, Karen; Cameron, Brian; Livingston, Michael
CORPORATE SOURCE: McMaster Children's Hospital, Canada.
AUTHOR: Horobjowsky, Alexandre; Deckelbaum, Dan L.; Razek, Tarek
CORPORATE SOURCE: Centre for Global Surgery, McGill University Health Centre, Canada.
AUTHOR: Marinkovic, Boris; Grasset, Eugenio; D'Aguzan, Nicole

CORPORATE SOURCE: Hospital Del Salvador, Chile.
AUTHOR: Grasset, Eugenio; Jimenez, Julio; Macchiavello, Roberto
CORPORATE SOURCE: Hospital Luis Tisne, Chile.
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AUTHOR: Correa, Juan Camilo; Montes, Irene; Sierra, Sebastian; Mendez, Manuela
CORPORATE SOURCE: Clinica Ces, Colombia.
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CORPORATE SOURCE: Clinica Las Vegas, Colombia.
AUTHOR: Aristizabal, Fred Alexander Naranjo; Botero, Jaime Andres Montoya; Riaza, Victor Manuel Quintero
CORPORATE SOURCE: Hospital Pablo Tobon Uribe, Colombia.
AUTHOR: Arango, Maria Clara Mendoza; Restrepo, Jakeline; Morales, Carlos
CORPORATE SOURCE: Hospital Universitario San Vicente Fundacion, Colombia.
AUTHOR: Arango, Maria Clara Mendoza; Cruz, Herman; Munera, Alejandro
CORPORATE SOURCE: Ips Universitaria Clinica Leon Xiii, Colombia.
AUTHOR: Karlo, Robert; Domini, Edgar; Mihanovic, Jakov; Dijan, Emilio
CORPORATE SOURCE: Zadar General Hospital, Croatia.
AUTHOR: Radic, Mihael; Zamarin, Kresimir; Pezelj, Nikica
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AUTHOR: Negida, Ahmed; Salem, Hosni Khairy; Khyrallh, Ahmed; Hassan, Ahamed; Shimy, Gamal; Fahmy, Mohamed A. Baky
CORPORATE SOURCE: Al-Azher Universty Hospital, Egypt.
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CORPORATE SOURCE: Alexandria Main University Hospital, Egypt.
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CORPORATE SOURCE: Belbes Central Hospital, Egypt.
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CORPORATE SOURCE: Mansoura University Hospitals, Egypt.
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L24 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2021 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2015:190032 HCAPLUS Full-text
DOCUMENT NUMBER: 163:190360
TITLE: Involvement of interleukin-18 in the pathogenesis of human eosinophilic esophagitis
AUTHOR(S): Niranjan, Rituraj; Rajavelu, Priya; Ventateshaiah, Sathisha Upparahalli; **Shukla, Jai Shankar**; Zaidi, Asifa; Mariswamy, Siddesha Jalahalli; Mattner, Jochen; Fortgang, Ilana; Kowalczyk, Monika; **Balart, Luis**; Shukla, Anshi; Mishra, Anil
CORPORATE SOURCE: Cincinnati Children's Hospital Medical Center, Cincinnati, OH, 45229, USA
SOURCE: Clinical Immunology (Amsterdam, Netherlands) (2015), 157(2), 103-113
CODEN: CLIIFY; ISSN: 1521-6616

DIGITAL OBJECT ID: 10.1016/j.clim.2015.01.007
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English
AB IL-18 is induced in food allergy and EoE is food allergen-induced disease. Therefore, we tested the hypothesis whether IL-18 is involved in food allergen-induced EoE pathogenesis. Accordingly, we examd. normal SPT + and SPT - EoE patient blood and biopsy samples for IL-18, IL-18Rα, ICAM and VCAM expression. Herein, we show increased IL-18 level is highly significant in food allergen SPT + compared to SPT - EoE patients. We also report that IL-18Rα + cells and mRNA levels are induced in the esophageal biopsies of EoE patients and blood IL-18 levels correlate with esophageal eosinophilia ($P < 0.01$). Addnl., we report that the levels of esophageal eosinophil and mast cells correlate with ICAM expression in human EoE. Mechanistically, we show that IL-18 in vitro stimulates iNKT cells and endothelial cells and induce eosinophil active cytokines IL-5 and IL-13. We provide the evidence that IL-18 is crit. cytokine involved in activation of iNKT cells and ICAM in promoting human EoE.
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L24 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2021 ACS on STN
ACCESSION NUMBER: 1999:340624 HCAPLUS Full-text
DOCUMENT NUMBER: 131:93303
TITLE: Measurement of mass and width of the W boson at LEP
AUTHOR(S): Acciarri, M.; Achard, P.; Adriani, O.; Aguilar-Benitez, M.; Alcaraz, J.; Alemanni, G.; Allaby, J.; Aloisio, A.; Alviggi, M. G.; Ambrosi, G.; Anderhub, H.; Andreev, V. P.; Angelescu, T.; Anselmo, F.; Arefiev, A.; Azemoon, T.; Aziz, T.; Bagnaia, P.; Baksay, L.; **Balandras, A.**; Ball, R. C.; Banerjee, S.; Banerjee, Sw.; Banicz, K.; Barczyk, A.; Barillere, R.; Barone, L.; Bartalini, P.; Basile, M.; Battiston, R.; Bay, A.; Becattini, F.; Becker, U.; Behner, F.; Berdugo, J.; Berges, P.; Bertucci, B.; Betev, B. L.; Bhattacharya, S.; Biasini, M.; Biland, A.; Blaising, J. J.; Blyth, S. C.; Bobbink, G. J.; Bohm, A.; Boldizsar, L.; Borgia, B.; Bourilkov, D.; Bourquin, M.; Braccini, S.; Branson, J. G.; Brigljevic, V.; Brochu, F.; Buffini, A.; Buijs, A.; Burger, J. D.; Burger, W. J.; Busenitz, J.; Button, A.; Cai, X. D.; Campanelli, M.; Capell, M.; Cara Romeo, G.; Carlino, G.; Cartacci, A. M.; Casaus, J.; Castellini, G.; Cavallari, F.; Cavallo, N.; Cecchi, C.; Cerrada, M.; Cesaroni, F.; Chamizo, M.; Chang, Y. H.; Chaturvedi, U. K.; Chemarin, M.; Chen, A.; Chen, G.; Chen, G. M.; Chen, H. F.; Chen, H. S.; Chereau, X.; Chiefari, G.; Cifarelli, L.; Cindolo, F.; Civinini, C.; **Clare, I.**; Clare, R.; Coignet, G.; Colijn, A. P.; Colino, N.; Costantini, S.; Cotorobai, F.; Cozzoni, B.; de la Cruz, B.; Csilling, A.; Dai, T. S.; van Dalen, J. A.; D'Alessandro, R.; de Asmundis, R.; Deglon, P.; Degre, A.; Deiters, K.; della Volpe, D.; Denes, P.; DeNotaristefani, F.; De Salvo, A.; Diemoz, M.; van Dierendonck, D.; Di Lodovico, F.; Dionisi, C.; Dittmar, M.; Dominguez, A.; Doria, A.; Dova, M. T.; Duchesneau, D.; Dufournand, D.; Duinker, P.; Duran, I.; El Mamouni, H.; Engler, A.; Eppling, F. J.; Erne, F. C.; Extermann, P.; Fabre, M.; Faccini, R.; Falagan, M. A.; Falciano, S.; Favara, A.; Fay, J.; Fedin, O.; Felcini, M.; Ferguson, T.; Ferroni, F.; Fesefeldt, H.; Fiandrini, E.; Field, J. H.; Filthaut, F.; Fisher, P. H.; Fisk, I.; Forconi, G.; Fredj, L.; Freudenreich, K.; Furetta, C.; Galaktionov, Yu.; Ganguli, S. N.; Garcia-Abia, P.; Gataullin, M.; Gau, S. S.; Gentile, S.; Gheordanescu, N.; Giagu, S.; Gong, Z. F.; Grenier, G.; Gruenewald, M. W.; van Gulik, R.; Gupta, V.

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72

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PUBLISHER: Elsevier Science B.V.
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AB We report on measurements of the mass and total decay width of the W boson with the L3 detector at LEP. W-pair events produced in e+e- interactions between 161 GeV and 183 GeV center-of-mass energy are selected in a data sample corresponding to a total luminosity of 76.7 pb-1. Combining all final states in W-pair prodn., the mass and total decay width of the W boson are detd. to be mW=80.61±0.15 GeV and ΓW=1.97±0.38 GeV, resp.
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ACCESSION NUMBER: 1999:209543 HCAPLUS Full-text
DOCUMENT NUMBER: 130:329713
TITLE: Study of neutral-current four-fermion and ZZ production in e+e- collisions at √s= 183 GeV
AUTHOR(S): Acciarri, M.; Achard, P.; Adriani, O.; Aguilar-Benitez, M.; Alcaraz, J.; Alemanni, G.; Allaby, J.; Aloisio, A.; Alviggi, M. G.; Ambrosi, G.; Anderhub, H.; Andreev, V. P.; Angelescu, T.; Anselmo, F.; Arefiev, A.; Azemoon, T.; Aziz, T.; Bagnaia, P.; Baksay, L.; **Balandras, A.**; Ball, R. C.; Banerjee, S.; Banerjee, Sw.; Banicz, K.; Barczyk, A.; Barillere, R.; Barone, L.; Bartalini, P.; Basile, M.; Battiston, R.; Bay, A.; Becattini, F.; Becker, U.; Behner, F.; Berdugo, J.; Berges, P.; Bertucci, B.; Betev, B. L.; Bhattacharya, S.; Biasini, M.; Biland, A.; Blaising, J. J.; Blyth, S. C.; Bobbink, G. J.; Bohm, A.; Boldizsar, L.; Borgia, B.; Bourilkov, D.; Bourquin, M.; Braccini, S.; Branson, J. G.; Brigljevic, V.; Brochu, F.; Buffini, A.; Buijs, A.; Burger, J. D.; Burger, W. J.; Busenitz, J.; Button, A.; Cai, X. D.; Campanelli, M.; Capell, M.; Cara Romeo, G.; Carlino, G.; Cartacci, A. M.; Casaus, J.; Castellini, G.; Cavallari, F.; Cavallo, N.; Cecchi, C.; Cerrada, M.; Cesaroni, F.; Chamizo, M.; Chang, Y. H.; Chaturvedi, U. K.; Chemarin, M.; Chen, A.; Chen, G.; Chen, G. M.; Chen, H. F.; Chen, H. S.; Chereau, X.; Chiefari, G.; Cifarelli, L.; Cindolo, F.; Civinini, C.; Clare, I.; Clare, R.; **Coignet, G.**; Colijn, A. P.; Colino, N.; Conventi, F.; Costantini, S.; Cotorobai, F.; de la Cruz, B.; Csilling, A.; Dai, T. S.; van Dalen, J. A.; D'Alessandro, R.; de Asmundis, R.; Deglon, P.; Degre, A.; Deiters, K.; Della Pietra, M.; della Volpe, D.; Denes, P.; DeNotaristefani, F.; De Salvo, A.; Diemoz, M.; van Dierendonck, D.; Di Lodovico, F.; Dionisi, C.; Dittmar, M.; Dominguez, A.; Doria, A.; Dova, M. T.; Duchesneau, D.; Dufournand, D.; Duinker, P.; Duran, I.; El Mamouni, H.; Engler, A.; Eppling, F. J.; Erne, F. C.; Extermann, P.; Fabre, M.; Faccini, R.; Falagan, M. A.; Falciano, S.; Favara, A.; Fay, J.; Fedin, O.; Felcini, M.; Ferguson, T.; Ferroni, F.; Fesefeldt, H.; Fiandrini, E.; Field, J. H.; Filthaut, F.; Fisher, P. H.; Fisk, I.; Forconi, G.; Fredj, L.; Freudenreich, K.; Furetta, C.; Galaktionov, Yu.; Ganguli, S. N.; Garcia-Abia, P.; Gataullin, M.; Gau, S. S.; Gentile, S.; Gheordanescu, N.; Giagu, S.; Goldfarb, S.; Gong, Z. F.; Gruenewald, M. W.; van Gulik, R.; Gupta, V. K.; Gurtu, A.; Gutay, L. J.; Haas, D.; Hasan, A.; Hatzifotiadou, D.; Hebbeker, T.; Herve, A.; Hidas, P.; Hirschfelder, J.; Hofer, H.; Holzner, G.; Hoorani, H.; Hou, S. R.; Iashvili, I.; Jin, B. N.; Jones, L. W.; de Jong, P.; Josa-Mutuberria, I.; Khan, R. A.; Kamrad, D.; Kapustinsky, J. S.; Kaur,

M.; Kienzle-Focacci, M. N.; Kim, D.; Kim, D. H.; Kim, J. K.; Kim, S. C.; Kinnison, W. W.; Kirkby, J.; Kiss, D.; Kittel, W.; Klimentov, A.; Konig, A. C.; Kopp, A.; Korolko, I.; Koutsenko, V.; Kraemer, R. W.; Krenz, W.; Kunin, A.; Lacentre, P.; Ladron de Guevara, P.; Laktineh, I.; Landi, G.; Lapoint, C.; Lassila-Perini, K.; Laurikainen, P.; Lavorato, A.; Lebeau, M.; Lebedev, A.; Lebrun, P.; Lecomte, P.; Lecoq, P.; Le Coultre, P.; Lee, H. J.; Le Goff, J. M.; Leiste, R.; Leonardi, E.; Levtchenko, P.; Li, C.; Lin, C. H.; Lin, W. T.; Linde, F. L.; Lista, L.; Liu, Z. A.; Lohmann, W.; Longo, E.; Lu, Y. S.; Lubelsmeyer, K.; Luci, C.; Luckey, D.; Luminari, L.; Lustermann, W.; Ma, W. G.; Maity, M.; Majumder, G.; Malgeri, L.; Malinin, A.; Mana, C.; Mangeol, D.; Marchesini, P.; Marian, G.; Martin, J. P.; Marzano, F.; Massaro, G. G. G.; Mazumdar, K.; McNeil, R. R.; Mele, S.; Merola, L.; Meschini, M.; Metzger, W. J.; von der Mey, M.; Migani, D.; Mihul, A.; Milcent, H.; Mirabelli, G.; Mnich, J.; Molnar, P.; Monteleoni, B.; Moulik, T.; Muanza, G. S.; Muheim, F.; Muijs, A. J. M.; Nahn, S.; Napolitano, M.; Nessi-Tedaldi, F.; Newman, H.; Niessen, T.; Nippe, A.; Nisati, A.; Nowak, H.; Oh, Y. D.; Organtini, G.; Ostonen, R.; Palomares, C.; Pandoulas, D.; Paoletti, S.; Paolucci, P.; Park, H. K.; Park, I. H.; Pascale, G.; Passaleva, G.; Patricelli, S.; Paul, T.; Pauluzzi, M.; Paus, C.; Pauss, F.; Peach, D.; Pedace, M.; Pei, Y. J.; Pensotti, S.; Perret-Gallix, D.; Petersen, B.; Petrak, S.; Piccolo, D.; Pieri, M.; Piroue, P. A.; Pistolesi, E.; Plyaskin, V.; Pohl, M.; Pojidaev, V.; Postema, H.; Pothier, J.; Produit, N.; Prokofiev, D.; Quartieri, J.; Rahl-Callot, G.; Raja, N.; Rancoita, P. G.; Raven, G.; Razis, P.; Ren, D.; Rescigno, M.; Reucroft, S.; van Rhee, T.; Riemann, S.; Riles, K.; Robohm, A.; Rodin, J.; Roe, B. P.; omero, L.; Rosier-Lees, S.; Rubio, J. A.; Ruschmieier, D.; Rykaczewski, H.; Sakar, S.; Salicio, J.; Sanchez, E.; Sanders, M. P.; Sarakinos, M. E.; Schafer, C.; Schegelsky, V.; Schmidt-Kaerst, S.; Schmitz, D.; Scholz, N.; Schopper, H.; Schotanus, D. J.; Schwenke, J.; Schwering, G.; Sciacca, C.; Sciarrino, D.; Servoli, L.; Shevchenko, S.; Shivarov, N.; Shoutko, V.; Shukla, J.; Shumilov, E.; Shvorob, A.; Siedenburg, T.; Son, D.; Smith, B.; Spillantini, P.; Steuer, M.; Stickland, D. P.; Stone, A.; Stone, H.; Stoyanov, B.; Straessner, A.; Sudhakar, K.; Sultanov, G.; Sun, L. Z.; Suter, H.; Swain, J. D.; Szillasi, Z.; Tang, X. W.; Tauscher, L.; Taylor, L.; Timmermans, C.; Ting, Samuel C. C.; Ting, S. M.; Tonwar, S. C.; Toth, J.; Tully, C.; Tung, K. L.; Uchida, Y.; Ulbricht, J.; Valente, E.; Vesztergombi, G.; Vetlitsky, I.; Viertel, G.; Villa, S.; Vivargent, M.; Vlachos, S.; Vogel, H.; Vogt, H.; Vorobiev, I.; Vorobyov, A. A.; Vorvolakos, A.; Wadhwa, M.; Wallraff, W.; Wang, J. C.; Wang, X. L.; Wang, Z. M.; Weber, A.; Weber, M.; Wienemann, P.; Wilkens, H.; Wu, S. X.; Wynhoff, S.; Xia, L.; Xu, Z. Z.; Yang, B. Z.; Yang, C. G.; Yang, H. J.; Yang, M.; Ye, J. B.; Yeh, S. C.; You, J. M.; Zalite, An.; Zalite, Yu.; Zemp, P.; Zhang, Z. P.; Zhu, G. Y.; Zhu, R. Y.; Zichichi, A.; Ziegler, F.; Zilizi, G.; Zoller, M.
CORPORATE SOURCE: Sez. Milano, INFN, Milan, I-20133, Italy
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AB A study of neutral-current four-fermion processes is performed using a data sample corresponding to 55.3 pb-1 of integrated luminosity collected by the L3 detector at LEP at an av. center-of-mass energy of

183 GeV. The neutral-current four-fermion cross sections for final states with a pair of charged leptons plus jets and with four charged leptons are measured to be consistent with the Std. Model predictions. Events with fermion pair masses close to the Z boson mass are selected in all observable final states and the ZZ prodn. cross section is measured to be σZZ=0.30+0.22 +0.07-0.16 -0.03 pb, in agreement with the Std. Model expectation. No evidence for the existence of anomalous triple gauge boson ZZZ and ZZγ couplings is found and limits on these couplings are set.

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L24 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2021 ACS on STN

ACCESSION NUMBER: 1999:341444 HCAPLUS Full-text

DOCUMENT NUMBER: 131:50504

TITLE: Heavy quarkonium production in Z decays

AUTHOR(S): Acciarri, M.; Achard, P.; Adriani, O.; Aguilar-Benitez, M.; Alcaraz, J.; Alemanni, G.; Allaby, J.; Aloisio, A.; Alviggi, M. G.; Ambrosi, G.; Anderhub, H.; Andreev, V. P.; Angelescu, T.; Anselmo, F.; Arefiev, A.; Azemoon, T.; Aziz, T.; Bagnaia, P.; Baksay, L.; **Balandras, A.**; Ball, R. C.; Banerjee, S.; Banerjee, Sw.; Banicz, K.; Barczyk, A.; Barillere, R.; Barone, L.; Bartalini, P.; Basile, M.; Battiston, R.; Bay, A.; Becattini, F.; Becker, U.; Behner, F.; Berdugo, J.; Berges, P.; Bertucci, B.; Betev, B. L.; Bhattacharya, S.; Biasini, M.; Biland, A.; Blaising, J. J.; Blyth, S. C.; Bobbink, G. J.; Bohm, A.; Boldizsar, L.; Borgia, B.; Bourilkov, D.; Bourquin, M.; Braccini, S.; Branson, J. G.; Brigljevic, V.; Brochu, F.; Buffini, A.; Buijs, A.; Burger, J. D.; Burger, W. J.; Busenitz, J.; Button, A.; Cai, X. D.; Campanelli, M.; Capell, M.; Cara Romeo, G.; Carlino, G.; Cartacci, A. M.; Casaus, J.; Castellini, G.; Cavallari, F.; Cavallo, N.; Cecchi, C.; Cerrada, M.; Cesaroni, F.; Chamizo, M.; Chang, Y. H.; Chaturvedi, U. K.; Chemarin, M.; Chen, A.; Chen, G.; Chen, G. M.; Chen, H. F.; Chen, H. S.; Chereau, X.; Chiefari, G.; Cifarelli, L.; Cindolo, F.; Civinini, C.; Clare, I.; Clare, R.; Coignet, G.; **Colijn, A. P.**; Colino, N.; Costantini, S.; Cotorobai, F.; De la Cruz, B.; Csilling, A.; Dai, T. S.; Van Dalen, J. A.; D'Alessandro, R.; De Asmundis, R.; Deglon, P.; Degre, A.; Deiters, K.; Della Volpe, D.; Denes, P.; DeNotaristefani, F.; De Salvo, A.; Diemoz, M.; Van Dierendonck, D.; Di Lodovico, F.; Dionisi, C.; Dittmar, M.; Dominguez, A.; Doria, A.; Dova, M. T.; Duchesneau, D.; Dufournand, D.; Duinker, P.; Duran, I.; El Mamouni, H.; Engler, A.; Eppling, F. J.; Erne, F. C.; Extermann, P.; Fabre, M.; Faccini, R.; Falagan, M. A.; Falciano, S.; Favara, A.; Fay, J.; Fedin, O.; Felcini, M.; Ferguson, T.; Ferroni, F.; Fesefeldt, H.; Fiandrini, E.; Field, J. H.; Filthaut, F.; Fisher, P. H.; Fisk, I.; Forconi, G.; Fredj, L.; Freudenreich, K.; Furetta, C.; Galaktionov, Yu.; Ganguli, S. N.; Garcia-Abia, P.; Gataullin, M.; Gau, S. S.; Gentile, S.; Gheordanescu, N.; Giagu, S.; Goldfarb, S.; Gong, Z. F.; Gruenewald, M. W.; Van Gulik, R.; Gupta, V. K.; Gurtu, A.; Gutay, L. J.; Haas, D.; Hasan, A.; Hatzifotiadou, D.; Hebbeker, T.; Herve, A.; Hidas, P.; Hirschfelder, J.; Hofer, H.; Holzner, G.; Hoorani, H.; Hou, S. R.; Iashvili, I.; Jin, B. N.; Jones, L. W.; De Jong, P.; Josa-Mutuberria, I.; Kasser, A.; Khan, R. A.; Kamrad, D.; Kapustinsky, J. S.; Kaur, M.; Kienzle-Focacci, M. N.; Kim, D.; Kim, D. H.; Kim, J. K.; Kim, S. C.; Kinnison, W. W.; Kirkby, J.; Kiss, D.; Kittel, W.; Klimentov, A.; Konig, A. C.; Kopp, A.; Korolko, I.; Koutsenko, V.; Kraemer, R. W.; Krenz, W.; Kunin,

A.; Lacentre, P.; Ladron de Guevara, P.; Laktineh, I.; Landi, G.; Lapoint, C.; Lassila-Perini, K.; Laurikainen, P.; Lavorato, A.; Lebeau, M.; Lebedev, A.; Lebrun, P.; Lecomte, P.; Lecoq, P.; Le Coultre, P.; Lee, H. J.; Le Goff, J. M.; Leiste, R.; Leonardi, E.; Levtchenko, P.; Li, C.; Lin, C. H.; Lin, W. T.; Linde, F. L.; Lista, L.; Liu, Z. A.; Lohmann, W.; Longo, E.; Lu, Y. S.; Lubelsmeyer, K.; Luci, C.; Luckey, D.; Luminari, L.; Lustermann, W.; Ma, W. G.; Maity, M.; Majumder, G.; Malgeri, L.; Malinin, A.; Mana, C.; Mangeol, D.; Marchesini, P.; Marian, G.; Martin, J. P.; Marzano, F.; Massaro, G. G. G.; Mazumdar, K.; McNeil, R. R.; Mele, S.; Merola, L.; Meschini, M.; Metzger, W. J.; Von der Mey, M.; Mi, Y.; Migani, D.; Mihul, A.; Milcent, H.; Mirabelli, G.; Mnich, J.; Molnar, P.; Monteleoni, B.; Moulik, T.; Muanza, G. S.; Muheim, F.; Muijs, A. J. M.; Nahn, S.; Napolitano, M.; Nessi-Tedaldi, F.; Newman, H.; Niessen, T.; Nippe, A.; Nisati, A.; Nowak, H.; Oh, Y. D.; Organtini, G.; Ostonen, R.; Palomares, C.; Pandoulas, D.; Paoletti, S.; Paolucci, P.; Park, H. K.; Park, I. H.; Pascale, G.; Passaleva, G.; Patricelli, S.; Paul, T.; Pauluzzi, M.; Paus, C.; Pauss, F.; Peach, D.; Pedace, M.; Pei, Y. J.; Pensotti, S.; Perret-Gallix, D.; Petersen, B.; Petrak, S.; Piccolo, D.; Pieri, M.; Piroue, P. A.; Pistolesi, E.; Plyaskin, V.; Pohl, M.; Pojidaev, V.; Postema, H.; Pothier, J.; Produit, N.; Prokofiev, D.; Quartieri, J.; Rahal-Callot, G.; Raja, N.; Rancoita, P. G.; Raven, G.; Razis, P.; Ren, D.; Rescigno, M.; Reucroft, S.; Van Rhee, T.; Riemann, S.; Riles, K.; Robohm, A.; Rodin, J.; Roe, B. P.; Romero, L.; Rosier-Lees, S.; Rosselet, Ph.; Rubio, J. A.; Ruschmeier, D.; Rykaczewski, H.; Sakar, S.; Salicio, J.; Sanchez, E.; Sanders, M. P.; Sarakinos, M. E.; Schafer, C.; Schegelsky, V.; Schmidt-Kaerst, S.; Schmitz, D.; Scholz, N.; Schopper, H.; Schotanus, D. J.; Schwenke, J.; Schwering, G.; Sciacca, C.; Sciarrino, D.; Servoli, L.; Shevchenko, S.; Shivarov, N.; Shoutko, V.; Shukla, J.; Shumilov, E.; Shvorob, A.; Siedenburg, T.; Son, D.; Smith, B.; Spillantini, P.; Steuer, M.; Stickland, D. P.; Stone, A.; Stone, H.; Stoyanov, B.; Straessner, A.; Sudhakar, K.; Sultanov, G.; Sun, L. Z.; Suter, H.; Swain, J. D.; Szillasi, Z.; Tang, X. W.; Tauscher, L.; Taylor, L.; Timmermans, C.; Ting, Samuel C. C.; Ting, S. M.; Tonwar, S. C.; Toth, J.; Tully, C.; Tung, K. L.; Uchida, Y.; Ulbricht, J.; Valente, E.; Vesztergombi, G.; Vetlitsky, I.; Viertel, G.; Villa, S.; Vivargent, M.; Vlachos, S.; Vogel, H.; Vogt, H.; Vorobiev, I.; Vorobyov, A. A.; Vorvolakos, A.; Wadhwa, M.; Wallraff, W.; Wang, J. C.; Wang, X. L.; Wang, Z. M.; Weber, A.; Weber, M.; Wienemann, P.; Wilkens, H.; Wu, S. X.; Wynhoff, S.; Xia, L.; Xu, Z. Z.; Yang, B. Z.; Yang, C. G.; Yang, H. J.; Yang, M.; Ye, J. B.; Yeh, S. C.; You, J. M.; Zalite, An.; Zalite, Yu.; Zemp, P.; Zhang, Z. P.; Zhu, G. Y.; Zhu, R. Y.; Zichichi, A.; Ziegler, F.; Zilizi, G.; Zoller, M.

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AB Measurements are reported of the inclusive prodn. of heavy quarkonium states in Z decays based on the anal. of 3.6 million hadronic events collected by the L3 detector at LEP. The measurement of inclusive J prodn. and an improved 95% confidence level upper limit on .UPSILON. prodn. are presented. In addn., two independent measurements of the ratio, fp, of prompt J mesons to those from B decay were made using

two different isolation cuts to sep. prompt J mesons from J mesons produced in the decays of b hadrons. The results are: Br(Z → J + X) = (3.21 ± 0.21 (stat.)-0.28+0.19 (sys.)) × 10-3, Br(Z → .UPSILON.(1S) + X) < 4.4 × 10-5, fp = (7.1 ± 2.1 (stat.) ± 1.2(sys.)-0.8+1.5(theor.)) × 10-2.

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L24 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2021 ACS on STN

ACCESSION NUMBER: 1999:341393 HCAPLUS Full-text

DOCUMENT NUMBER: 131:50488

TITLE: Inclusive charm production in two-photon collisions at LEP

AUTHOR(S): Acciarri, M.; Achard, P.; Adriani, O.; Aguilar-Benitez, M.; Alcaraz, J.; Alemanni, G.; Allaby, J.; Aloisio, A.; Alviggi, M. G.; Ambrosi, G.; Anderhub, H.; Andreev, V. P.; Angelescu, T.; Anselmo, F.; Arefiev, A.; Azemoon, T.; Aziz, T.; Bagnaia, P.; Baksay, L.; **Balandras, A.**; Ball, R. C.; Banerjee, S.; Banerjee, Sw.; Banicz, K.; Barczyk, A.; Barillere, R.; Barone, L.; Bartalini, P.; Basile, M.; Battiston, R.; Bay, A.; Becattini, F.; Becker, U.; Behner, F.; Berdugo, J.; Berges, P.; Bertucci, B.; Betev, B. L.; Bhattacharya, S.; Biasini, M.; Biland, A.; Blaising, J. J.; Blyth, S. C.; Bobbink, G. J.; Bock, R.; Bohm, A.; Boldizsar, L.; Borgia, B.; Bourilkov, D.; Bourquin, M.; Braccini, S.; Branson, J. G.; Brigljevic, V.; Brochu, F.; Buffini, A.; Buijs, A.; Burger, J. D.; Burger, W. J.; Busenitz, J.; Button, A.; Cai, X. D.; Campanelli, M.; Capell, M.; Cara Romeo, G.; Carlino, G.; Cartacci, A. M.; Casaus, J.; Castellini, G.; Cavallari, F.; Cavallo, N.; Cecchi, C.; Cerrada, M.; Cesaroni, F.; Chamizo, M.; Chang, Y. H.; Chaturvedi, U. K.; Chemarin, M.; Chen, A.; Chen, G.; Chen, G. M.; Chen, H. F.; Chen, H. S.; Chereau, X.; Chiefari, G.; Cifarelli, L.; Cindolo, F.; Civinini, C.; Clare, I.; Clare, R.; **Coignet, G.**; Colijn, A. P.; Colino, N.; Costantini, S.; Cotorobai, F.; De la Cruz, B.; Csilling, A.; Dai, T. S.; Van Dalen, J. A.; D'Alessandro, R.; De Asmundis, R.; Deglon, P.; Degre, A.; Deiters, K.; Della Volpe, D.; Denes, P.; DeNotaristefani, F.; De Salvo, A.; Diemoz, M.; Van Dierendonck, D.; Di Lodovico, F.; Dionisi, C.; Dittmar, M.; Dominguez, A.; Doria, A.; Dova, M. T.; Duchesneau, D.; Dufournand, D.; Duinker, P.; Duran, I.; El Mamouni, H.; Engler, A.; Eppling, F. J.; Erne, F. C.; Extermann, P.; Fabre, M.; Faccini, R.; Falagan, M. A.; Falciano, S.; Favara, A.; Fay, J.; Fedin, O.; Felcini, M.; Ferguson, T.; Ferroni, F.; Fesefeldt, H.; Fiandrini, E.; Field, J. H.; Filthaut, F.; Fisher, P. H.; Fisk, I.; Forconi, G.; Fredj, L.; Freudenreich, K.; Furetta, C.; Galaktionov, Yu.; Ganguli, S. N.; Garcia-Abia, P.; Gataullin, M.; Gau, S. S.; Gentile, S.; Gheordanescu, N.; Giagu, S.; Goldfarb, S.; Gong, Z. F.; Gruenewald, M. W.; Van Gulik, R.; Gupta, V. K.; Gurtu, A.; Gutay, L. J.; Haas, D.; Hartmann, B.; Hasan, A.; Hatzifotiadou, D.; Hebbeker, T.; Herve, A.; Hidas, P.; Hirschfelder, J.; Hofer, H.; Holzner, G.; Hoorani, H.; Hou, S. R.; Iashvili, I.; Jin, B. N.; Jones, L. W.; De Jong, P.; Josa-Mutuberria, I.; Khan, R. A.; Kamrad, D.; Kapustinsky, J. S.; Kaur, M.; Kienzle-Focacci, M. N.; Kim, D.; Kim, D. H.; Kim, J. K.; Kim, S. C.; Kinnison, W. W.; Kirkby, J.; Kiss, D.; Kittel, W.; Klimentov, A.; Konig, A. C.; Kopp, A.; Korolko, I.; Koutsenko, V.; Kraemer, R. W.; Krenz, W.; Kunin, A.; Lacentre, P.; Ladron de Guevara, P.; Laktineh, I.; Landi, G.; Lapoint, C.; Lassila-Perini, K.; Laurikainen, P.; Lavorato,

A.; Lebeau, M.; Lebedev, A.; Lebrun, P.; Lecomte, P.; Lecoq, P.; Le Coultre, P.; Lee, H. J.; Le Goff, J. M.; Leiste, R.; Leonardi, E.; Levtchenko, P.; Li, C.; Lin, C. H.; Lin, W. T.; Linde, F. L.; Lista, L.; Liu, Z. A.; Lohmann, W.; Longo, E.; Lu, Y. S.; Lubelsmeyer, K.; Luci, C.; Luckey, D.; Luminari, L.; Lustermann, W.; Ma, W. G.; Maity, M.; Majumder, G.; Malgeri, L.; Malinin, A.; Mana, C.; Mangeol, D.; Marchesini, P.; Marian, G.; Martin, J. P.; Marzano, F.; Massaro, G. G. G.; Mazumdar, K.; McNeil, R. R.; Mele, S.; Merola, L.; Meschini, M.; Metzger, W. J.; Von der Mey, M.; Migani, D.; Mihul, A.; Milcent, H.; Mirabelli, G.; Mnich, J.; Molnar, P.; Monteleoni, B.; Moulik, T.; Muanza, G. S.; Muheim, F.; Muijs, A. J. M.; Nahn, S.; Napolitano, M.; Nessi-Tedaldi, F.; Newman, H.; Niessen, T.; Nippe, A.; Nisati, A.; Nowak, H.; Oh, Y. D.; Organtini, G.; Ostonen, R.; Palomares, C.; Pandoulas, D.; Paoletti, S.; Paolucci, P.; Park, H. K.; Park, I. H.; Pascale, G.; Passaleva, G.; Patricelli, S.; Paul, T.; Pauluzzi, M.; Paus, C.; Pauss, F.; Peach, D.; Pedace, M.; Pei, Y. J.; Pensotti, S.; Perret-Gallix, D.; Petersen, B.; Petrak, S.; Piccolo, D.; Pieri, M.; Piroue, P. A.; Pistolesi, E.; Plyaskin, V.; Pohl, M.; Pojidaev, V.; Postema, H.; Pothier, J.; Produit, N.; Prokofiev, D.; Quartieri, J.; Rahal-Callot, G.; Raja, N.; Rancoita, P. G.; Raven, G.; Razis, P.; Ren, D.; Rescigno, M.; Reucroft, S.; Van Rhee, T.; Riemann, S.; Riles, K.; Robohm, A.; Rodin, J.; Roe, B. P.; Romero, L.; Rosier-Lees, S.; Roth, S.; Rubio, J. A.; Ruschmeier, D.; Rykaczewski, H.; Sakar, S.; Salicio, J.; Sanchez, E.; Sanders, M. P.; Sarakinos, M. E.; Schafer, C.; Schegelsky, V.; Schmidt-Kaerst, S.; Schmitz, D.; Scholz, N.; Schopper, H.; Schotanus, D. J.; Schwenke, J.; Schwering, G.; Sciacca, C.; Sciarrino, D.; Servoli, L.; Shevchenko, S.; Shivarov, N.; Shoutko, V.; Shukla, J.; Shumilov, E.; Shvorob, A.; Siedenburg, T.; Son, D.; Smith, B.; Spillantini, P.; Steuer, M.; Stickland, D. P.; Stone, A.; Stone, H.; Stoyanov, B.; Straessner, A.; Sudhakar, K.; Sultanov, G.; Sun, L. Z.; Suter, H.; Swain, J. D.; Szillasi, Z.; Tang, X. W.; Tauscher, L.; Taylor, L.; Timmermans, C.; Ting, Samuel C. C.; Ting, S. M.; Tonwar, S. C.; Toth, J.; Tully, C.; Tung, K. L.; Uchida, Y.; Ulbricht, J.; Valente, E.; Vesztergombi, G.; Vetlitsky, I.; Viertel, G.; Villa, S.; Vivargent, M.; Vlachos, S.; Vogel, H.; Vogt, H.; Vorobiev, I.; Vorobyov, A. A.; Vorvolakos, A.; Wadhwa, M.; Wallraff, W.; Wang, J. C.; Wang, X. L.; Wang, Z. M.; Weber, A.; Wilkens, H.; Wu, S. X.; Wynhoff, S.; Xia, L.; Xu, Z. Z.; Yang, B. Z.; Yang, C. G.; Yang, H. J.; Yang, M.; Ye, J. B.; Yeh, S. C.; You, J. M.; Zalite, An.; Zalite, Yu.; Zemp, P.; Zeng, Y.; Zhang, Z. P.; Zhu, G. Y.; Zhu, R. Y.; Zichichi, A.; Ziegler, F.; Zilizi, G.

CORPORATE SOURCE: L3 Collaboration, I. Physikalisches Institut, RWTH, Aachen, D-52056, Germany

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LANGUAGE: English

AB The cross section of charm prodn. in γγ collisions σ(e+e- → e+e-c¯c X) was measured at LEP with the L3 detector at center-of-mass energies from 91 to 183 GeV. The charmed hadrons were identified by electrons and muons from semileptonic decays. The direct process γγ → c¯c is insufficient to describe the data. The measured cross section values and event distributions require contributions from resolved processes, which are sensitive to the gluon d. in the photon.

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L24 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2021 ACS on STN
ACCESSION NUMBER: 1999:341351 HCAPLUS Full-text
DOCUMENT NUMBER: 131:50482
TITLE: Formation of χc2 in two-photon collisions at LEP
AUTHOR(S): Acciarri, M.; Achard, P.; Adriani, O.; Aguilar-Benitez, M.; Alcaraz, J.; Alemanni, G.; Allaby, J.; Aloisio, A.; Alviggi, M. G.; Ambrosi, G.; Anderhub, H.; Andreev, V. P.; Angelescu, T.; Anselmo, F.; Arefiev, A.; Azemoon, T.; Aziz, T.; Bagnaia, P.; Baksay, L.; **Balandras, A.**; Ball, R. C.; Banerjee, S.; Banerjee, Sw.; Banicz, K.; Barczyk, A.; Barillere, R.; Barone, L.; Bartalini, P.; Basile, M.; Battiston, R.; Bay, A.; Becattini, F.; Becker, U.; Behner, F.; Berdugo, J.; Berges, P.; Bertucci, B.; Betev, B. L.; Bhattacharya, S.; Biasini, M.; Biland, A.; Blaising, J. J.; Blyth, S. C.; Bobbink, G. J.; Bock, R.; Bohm, A.; Boldizsar, L.; Borgia, B.; Bourilkov, D.; Bourquin, M.; Braccini, S.; Branson, J. G.; Brigljevic, V.; Brochu, F.; Buffini, A.; Buijs, A.; Burger, J. D.; Burger, W. J.; Busenitz, J.; Button, A.; Cai, X. D.; Campanelli, M.; Capell, M.; Cara Romeo, G.; Carlino, G.; Cartacci, A. M.; Casaus, J.; Castellini, G.; Cavallari, F.; Cavallo, N.; Cecchi, C.; Cerrada, M.; Cesaroni, F.; Chamizo, M.; Chang, Y. H.; Chaturvedi, U. K.; Chemarin, M.; Chen, A.; Chen, G.; Chen, G. M.; Chen, H. F.; Chen, H. S.; Chereau, X.; Chiefari, G.; Cifarelli, L.; Cindolo, F.; Civinini, C.; Clare, I.; Clare, R.; **Coignet, G.**; Colijn, A. P.; Colino, N.; Costantini, S.; Cotorobai, F.; De la Cruz, B.; Csilling, A.; Dai, T. S.; Van Dalen, J. A.; D'Alessandro, R.; De Asmundis, R.; Deglon, P.; Degre, A.; Deiters, K.; Della Volpe, D.; Denes, P.; DeNotaristefani, F.; De Salvo, A.; Diemoz, M.; Van Dierendonck, D.; Di Lodovico, F.; Dionisi, C.; Dittmar, M.; Dominguez, A.; Doria, A.; Dova, M. T.; Duchesneau, D.; Dufournand, D.; Duinker, P.; Duran, I.; El Mamouni, H.; Engler, A.; Eppling, F. J.; Erne, F. C.; Extermann, P.; Fabre, M.; Faccini, R.; Falagan, M. A.; Falciano, S.; Favara, A.; Fay, J.; Fedin, O.; Felcini, M.; Ferguson, T.; Ferroni, F.; Fesefeldt, H.; Fiandrini, E.; Field, J. H.; Filthaut, F.; Fisher, P. H.; Fisk, I.; Forconi, G.; Fredj, L.; Freudenreich, K.; Furetta, C.; Galaktionov, Yu.; Ganguli, S. N.; Garcia-Abia, P.; Gataullin, M.; Gau, S. S.; Gentile, S.; Gheordanescu, N.; Giagu, S.; Goldfarb, S.; Gong, Z. F.; Gruenewald, M. W.; Van Gulik, R.; Gupta, V. K.; Gurtu, A.; Gutay, L. J.; Haas, D.; Hartmann, B.; Hasan, A.; Hatzifotiadou, D.; Hebbeker, T.; Herve, A.; Hidas, P.; Hirschfelder, J.; Hofer, H.; Holzner, G.; Hoorani, H.; Hou, S. R.; Iashvili, I.; Jin, B. N.; Jones, L. W.; De Jong, P.; Josa-Mutuberria, I.; Khan, R. A.; Kamrad, D.; Kapustinsky, J. S.; Kaur, M.; Kienzle-Focacci, M. N.; Kim, D.; Kim, D. H.; Kim, J. K.; Kim, S. C.; Kinnison, W. W.; Kirkby, J.; Kiss, D.; Kittel, W.; Klimentov, A.; Konig, A. C.; Kopp, A.; Korolko, I.; Koutsenko, V.; Kraemer, R. W.; Krenz, W.; Kunin, A.; Lacentre, P.; Ladron de Guevara, P.; Laktineh, I.; Landi, G.; Lapoint, C.; Lassila-Perini, K.; Laurikainen, P.; Lavorato, A.; Lebeau, M.; Lebedev, A.; Lebrun, P.; Lecomte, P.; Lecoq, P.; Le Coultre, P.; Lee, H. J.; Le Goff, J. M.; Leiste, R.; Leonardi, E.; Levtchenko, P.; Li, C.; Lin, C. H.; Lin, W. T.; Linde, F. L.; Lista, L.; Liu, Z. A.; Lohmann, W.; Longo, E.; Lu, Y. S.; Lubelsmeyer, K.; Luci, C.; Luckey, D.;

Luminari, L.; Lustermann, W.; Ma, W. G.; Maity, M.; Majumder, G.; Malgeri, L.; Malinin, A.; Mana, C.; Mangeol, D.; Marchesini, P.; Marian, G.; Martin, J. P.; Marzano, F.; Massaro, G. G. G.; Mazumdar, K.; McNeil, R. R.; Mele, S.; Merola, L.; Meschini, M.; Metzger, W. J.; Von der Mey, M.; Migani, D.; Mihul, A.; Milcent, H.; Mirabelli, G.; Mnich, J.; Molnar, P.; Monteleoni, B.; Moulik, T.; Muanza, G. S.; Muheim, F.; Muijs, A. J. M.; Nahn, S.; Napolitano, M.; Nessi-Tedaldi, F.; Newman, H.; Niessen, T.; Nippe, A.; Nisati, A.; Nowak, H.; Oh, Y. D.; Organtini, G.; Ostonen, R.; Palomares, C.; Pandoulas, D.; Paoletti, S.; Paolucci, P.; Park, H. K.; Park, I. H.; Pascale, G.; Passaleva, G.; Patricelli, S.; Paul, T.; Pauluzzi, M.; Paus, C.; Pauss, F.; Peach, D.; Pedace, M.; Pei, Y. J.; Pensotti, S.; Perret-Gallix, D.; Petersen, B.; Petrak, S.; Piccolo, D.; Pieri, M.; Pirou, P. A.; Pistolesi, E.; Plyaskin, V.; Pohl, M.; Pojidaev, V.; Postema, H.; Pothier, J.; Produit, N.; Prokofiev, D.; Quartieri, J.; Rahal-Callot, G.; Raja, N.; Rancoita, P. G.; Raven, G.; Razis, P.; Ren, D.; Rescigno, M.; Reucroft, S.; Van Rhee, T.; Riemann, S.; Riles, K.; Robohm, A.; Rodin, J.; Roe, B. P.; Romero, L.; Rosier-Lees, S.; Roth, S.; Rubio, J. A.; Ruschmeier, D.; Rykaczewski, H.; Sakar, S.; Salicio, J.; Sanchez, E.; Sanders, M. P.; Sarakinos, M. E.; Schafer, C.; Schegelsky, V.; Schmidt-Kaerst, S.; Schmitz, D.; Scholz, N.; Schopper, H.; Schotanus, D. J.; Schwenke, J.; Schwering, G.; Sciacca, C.; Sciarrino, D.; Servoli, L.; Shevchenko, S.; Shivarov, N.; Shoutko, V.; Shukla, J.; Shumilov, E.; Shvorob, A.; Siedenburg, T.; Son, D.; Smith, B.; Spillantini, P.; Steuer, M.; Stickland, D. P.; Stone, A.; Stone, H.; Stoyanov, B.; Straessner, A.; Sudhakar, K.; Sultanov, G.; Sun, L. Z.; Suter, H.; Swain, J. D.; Szillasi, Z.; Tang, X. W.; Tauscher, L.; Taylor, L.; Timmermans, C.; Ting, Samuel C. C.; Ting, S. M.; Tonwar, S. C.; Toth, J.; Tully, C.; Tung, K. L.; Uchida, Y.; Ulbricht, J.; Valente, E.; Vesztergombi, G.; Vetlitsky, I.; Viertel, G.; Villa, S.; Vivargent, M.; Vlachos, S.; Vogel, H.; Vogt, H.; Vorobiev, I.; Vorobyov, A. A.; Vorvolakos, A.; Wadhwa, M.; Wallraff, W.; Wang, J. C.; Wang, X. L.; Wang, Z. M.; Weber, A.; Wilkens, H.; Wu, S. X.; Wynhoff, S.; Xia, L.; Xu, Z. Z.; Yang, B. Z.; Yang, C. G.; Yang, H. J.; Yang, M.; Ye, J. B.; Yeh, S. C.; You, J. M.; Zalite, An.; Zalite, Yu.; Zemp, P.; Zeng, Y.; Zhang, Z. P.; Zhu, G. Y.; Zhu, R. Y.; Zichichi, A.; Ziegler, F.; Zilizi, G.

CORPORATE SOURCE: L3 Collaboration, I. Physikalisches Institut, RWTH, Aachen, D-52056, Germany

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DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two-photon formation of the charmonium resonance χc2 was studied with the L3 detector at LEP. The χc2 was identified through its decay χc2 → γJ/ψ → e+e- or J/ψ → μ+μ-. With an integrated luminosity of 140 pb-1 at √ ≃ 91 GeV and 52 pb-1 at √s ≃ 183 GeV, the two-photon width of the χc2 was measured to be Γγγ(χc2) = 1.02 ± 0.40(stat.) ± 0.15(sys.) ± 0.09(BR.)keV.

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L24 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2021 ACS on STN

ACCESSION NUMBER: 1996:257772 HCAPLUS Full-text
DOCUMENT NUMBER: 124:300698
ORIGINAL REFERENCE NO.: 124:55511a,55514a
TITLE: Radiation stability of inorganic [ion] exchangers. II
AUTHOR(S): Rao, K. L. N.; Varma, R. N.; **Balasubramanian, K. R.**; Murthy, T. S.; **Shukla, J. P.**
CORPORATE SOURCE: Isotope Div., Bhabha At. Res. Cent., Bombay, 400 085, India
SOURCE: Journal of the Indian Chemical Society (1996), 73(1), 85-7
CODEN: JICSAH; ISSN: 0019-4522
PUBLISHER: Indian Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methods were developed for the sepn. of kCi amts. of fission products using synthetic inorg. ion exchangers. The results of detailed studies on polyantimonic acid and Zr antimonate are described. These materials are to be used on a pilot-scale operation in the flow sheet for the sepn. of 90Sr and 144Ce from spent fuel waste soln.
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

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     FILE 'REGISTRY' ENTERED AT 08:09:53 ON 30 AUG 2021
                  E PHENOBARBITAL SODIUM/CN
L1             1 SEA ABB=ON  PLU=ON  "PHENOBARBITAL SODIUM"/CN
                  SEL L1 CHEM
L2                QUE ABB=ON  PLU=ON  ("GARDENAL SODIUM"/BI OR LINASEN/BI OR
                  "LUMINAL SODIUM"/BI OR PHENEMALUM/BI OR "PHENOBAL SODIUM"/B
                  I OR PHENOBAL/BI OR "PHENOBARBITAL SODIUM"/BI OR "PHENOBARB
                  ITONE SODIUM"/BI OR "SODIUM ETHYLPHENYLBARBITURATE"/BI OR
                  "SODIUM LUMINAL"/BI OR "SODIUM PHENOBARBITAL"/BI OR
                  "SODIUM PHENOBARBITONE"/BI OR "SODIUM PHENYLETHYLBARBITURAT
                  E"/BI OR "SODIUM PHENYLETHYLMALONYLUREA"/BI OR "SODIUM
                  5-ETHYL-5-PHENYLBARBITURATE"/BI OR "SOL PHENOBARBITAL"/BI
                  OR "SOL PHENOBARBITONE"/BI OR "SOLUBLE PHENOBARBITAL"/BI
                  OR "SOLUBLE PHENOBARBITONE"/BI OR 125-36-0/BI OR "5-ETHYL-5
                  -PHENYLBARBITURIC ACID SODIUM"/BI OR 57-30-7/BI OR
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     FILE 'HCAPLUS' ENTERED AT 08:10:25 ON 30 AUG 2021
L3         36479 SEA ABB=ON  PLU=ON  L1 OR L2 OR PHENOBARBITAL(1W)(?SODIUM?
                  OR NA) OR GARDENAL OR HYSTEP## OR LUMINAL OR PHENEMAL OR
                  PHENOBARTITONE OR PHENYLBARBITAL OR PHENYLETHYLBARBITURIC
                  OR (PHENYL OR PH)(W)(BARBITAL OR ETHYLBARBITURIC OR (ETHYL
                  OR ET)(W)BARBITURIC)

     FILE 'REGISTRY' ENTERED AT 08:10:42 ON 30 AUG 2021
                  E PHENYLETHYLACETYLUREA/CN
L4             1 SEA ABB=ON  PLU=ON  PHENYLETHYLACETYLUREA/CN
                  SEL L4 CHEM
L5                QUE ABB=ON  PLU=ON  (.ALPHA.-PHENYL-.ALPHA.-ETHYLACETYLUREA
                  /BI OR "(2-PHENYLBUTANOYL)UREA"/BI OR BENURIDE/BI OR
                  DL-PHENETURIDE/BI OR EPA/BI OR ETHYLPHENACEMIDE/BI OR
                  LIRCAPYL/BI OR "M 551"/BI OR "N-(.ALPHA.-PHENYLBUTYRYL)UREA
                  "/BI OR "N-(AMINOCARBONYL)-.ALPHA.-ETHYLBENZENEACETAMIDE"/B
                  I OR PBU/BI OR PHENETURIDE/BI OR PHENURIDE/BI OR PHENYLETHY
                  LACETYLUREA/BI OR "S 46"/BI OR "1-((ETHYL)PHENYLACETYL)UREA
                  "/BI OR 2-PHENYLBUTYRYLUREA/BI OR 6509-31-5/BI OR 90-49-3/B
                  I)

     FILE 'HCAPLUS' ENTERED AT 08:11:30 ON 30 AUG 2021
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                  (PHENYL OR PH)(W)(ETHYLACETYLUREA OR (ETHYL OR ET)(W)(ACETY
                  LUREA OR (AC OR ACETYL)(W)UREA) OR PHENYLETHYL(W)(ACETYLURE
                  A OR (AC OR ACETYL)(W)UREA)) OR PHENYLETHYLACETYL UREA OR
                  BENURIDE
L7            80 SEA ABB=ON  PLU=ON  (ETHYL OR ET)(W)(PHENACEMIDE OR
                  PHENYLACETYLUREA OR (PHENYL OR PH)(W)(ACETYLUREA OR
                  (ACETYL OR AC)(W)UREA)) OR ETHYLPHENYLACETYLUREA OR
                  PHENETURIDE
L8            44 SEA ABB=ON  PLU=ON  L3 AND (L6 OR L7 OR L4 OR L5)
L9             7 SEA ABB=ON  PLU=ON  L8 AND (POWDER? OR GRANUL?)
L10            8 SEA ABB=ON  PLU=ON  L8 AND (PH OR (H OR  HYDROGEN)(5W)(CONC
                  ENTRATION OR CONC##))
L11           30 SEA ABB=ON  PLU=ON  L8 AND (COMPOSITION OR COMP## OR PREP?
                  OR FORMULATION OR SOLUTION OR SOLN OR MIXTURE)
L12            1 SEA ABB=ON  PLU=ON  L8 AND (LYOPHILIS? OR LYOPHILIZ? OR
                  FREEZ?)
L13         2137 SEA ABB=ON  PLU=ON  "PHENOBARBITAL SODIUM"+PFT/CT
L14          191 SEA ABB=ON  PLU=ON  PHENETURIDE+PFT/CT
L15           11 SEA ABB=ON  PLU=ON  L13 AND L14
L16           33 SEA ABB=ON  PLU=ON  (L9 OR L10 OR L11 OR L12) OR L15
L17           31 SEA ABB=ON  PLU=ON  L16 AND (PY<2019 OR AY<2019 OR
                  PRY<2019)

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PQSCITECH' ENTERED AT
     08:20:04 ON 30 AUG 2021
L18          297 SEA ABB=ON  PLU=ON  L8
L19            2 SEA ABB=ON  PLU=ON  L18 AND (POWDER? OR GRANUL?)
L20            1 SEA ABB=ON  PLU=ON  L18 AND (LYOPHILIS? OR LYOPHILIZ? OR
                  FREEZ?)
L21           57 SEA ABB=ON  PLU=ON  L18 AND (COMPOSITION OR COMP## OR
                  PREP? OR FORMULATION OR SOLUTION OR SOLN OR MIXTURE)
L22           10 SEA ABB=ON  PLU=ON  L18 AND (PH OR (H OR HYDROGEN)(5W)(CONC
                  ENTRATION OR CONC##))
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L23          53 SEA ABB=ON  PLU=ON  ((L19 OR L20 OR L21 OR L22)) AND
                (PY<2019 OR AY<2019 OR PRY<2019)

     FILE 'WPIX, PQSCITECH' ENTERED AT 08:25:42 ON 30 AUG 2021
L24           7 SEA ABB=ON  PLU=ON  L8
L25           2 SEA ABB=ON  PLU=ON  L24 AND TEMP/PHP
L26           4 SEA ABB=ON  PLU=ON  L24 AND PER/PHP
L27           0 SEA ABB=ON  PLU=ON  L24 AND PHV/PHP
L28           1 SEA ABB=ON  PLU=ON  L24 AND MASS/PHP
L29           2 SEA ABB=ON  PLU=ON  ((L25 OR L26 OR L27) OR L28) AND
                (PY<2019 OR AY<2019 OR PRY<2019)

     FILE 'HCAPLUS' ENTERED AT 08:33:04 ON 30 AUG 2021
                D QUE L9
                D QUE L10
                D QUE L11
                D QUE L12
                D QUE L15
                D L17 1-31

     FILE 'MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PQSCITECH' ENTERED AT
     08:33:12 ON 30 AUG 2021
L30          40 DUP REM L29 L23 (15 DUPLICATES REMOVED)
                D L30 1-40

     FILE 'MEDLINE' ENTERED AT 08:33:29 ON 30 AUG 2021
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                .650./CT)
L32      119110 SEA ABB=ON  PLU=ON  (UREA/CT OR D2.65.950./CT)
L33         245 SEA ABB=ON  PLU=ON  L32 AND L31
L34       13837 SEA ABB=ON  PLU=ON  ("FREEZE DRYING"/CT OR E1.370.225.500.6
                20.760.160.260./CT OR E1.370.225.750.600.760.160.260./CT
                OR E2.792.156.260./CT OR E5.200.500.620.760.160.260./CT OR
                E5.200.750.600.760.160.260./CT OR E5.760.156.260./CT)
L35           0 SEA ABB=ON  PLU=ON  L33 AND L34
L36     3963026 SEA ABB=ON  PLU=ON  ("HYDROGEN-ION CONCENTRATION"/CT OR
                G2.300./CT)
L37          22 SEA ABB=ON  PLU=ON  L33 AND L36
L38          21 SEA ABB=ON  PLU=ON  L37 AND PY<2019
                D QUE L35
                D L38 1-21

     FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PQSCITECH'
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L1           22 SEA ABB=ON  PLU=ON  ("THIRUPATHI M"? OR "MANGALI T"?)/AU
L2        13104 SEA ABB=ON  PLU=ON  "SHUKLA A"?/AU
L3         2429 SEA ABB=ON  PLU=ON  "SHUKLA J"?/AU
L4          106 SEA ABB=ON  PLU=ON  ("DASARADHI L"? OR "LAKKARAJU D"?)/AU
L5        338281 SEA ABB=ON  PLU=ON  ("BALA"? OR "TRIPURA"? OR "SUNDARI"?
                OR "CHODAVARAPU"?)/AU
L6            2 SEA ABB=ON  PLU=ON  L1 AND L2 AND L3 AND L4 AND L5
L7            2 SEA ABB=ON  PLU=ON  L1 AND ((L2 OR L3 OR L4 OR L5))
L8          167 SEA ABB=ON  PLU=ON  L2 AND ((L3 OR L4 OR L5))
L9           14 SEA ABB=ON  PLU=ON  L3 AND (L4 OR L5)
L10           2 SEA ABB=ON  PLU=ON  L4 AND L5

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                SEL L11 CHEM
L12             QUE ABB=ON  PLU=ON  ("GARDENAL SODIUM"/BI OR LINASEN/BI OR
                "LUMINAL SODIUM"/BI OR PHENEMALUM/BI OR "PHENOBAL SODIUM"/B
                I OR PHENOBAL/BI OR "PHENOBARBITAL SODIUM"/BI OR "PHENOBARB
                ITONE SODIUM"/BI OR "SODIUM ETHYLPHENYLBARBITURATE"/BI OR
                "SODIUM LUMINAL"/BI OR "SODIUM PHENOBARBITAL"/BI OR
                "SODIUM PHENOBARBITONE"/BI OR "SODIUM PHENYLETHYLBARBITURAT
                E"/BI OR "SODIUM PHENYLETHYLMALONYLUREA"/BI OR "SODIUM
                5-ETHYL-5-PHENYLBARBITURATE"/BI OR "SOL PHENOBARBITAL"/BI
                OR "SOL PHENOBARBITONE"/BI OR "SOLUBLE PHENOBARBITAL"/BI
                OR "SOLUBLE PHENOBARBITONE"/BI OR 125-36-0/BI OR "5-ETHYL-5
                -PHENYLBARBITURIC ACID SODIUM"/BI OR 57-30-7/BI OR
                8050-96-2/BI)
                E PHENYLETHYLACETYLUREA/CN
L13           1 SEA ABB=ON  PLU=ON  PHENYLETHYLACETYLUREA/CN
                SEL L13 CHEM
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L14             QUE ABB=ON  PLU=ON  (.ALPHA.-PHENYL-.ALPHA.-ETHYLACETYLUREA
                /BI OR "(2-PHENYLBUTANOYL)UREA"/BI OR BENURIDE/BI OR
                DL-PHENETURIDE/BI OR EPA/BI OR ETHYLPHENACEMIDE/BI OR
                LIRCAPYL/BI OR "M 551"/BI OR "N-(.ALPHA.-PHENYLBUTYRYL)UREA
                "/BI OR "N-(AMINOCARBONYL)-.ALPHA.-ETHYLBENZENEACETAMIDE"/B
                I OR PBU/BI OR PHENETURIDE/BI OR PHENURIDE/BI OR PHENYLETHY
                LACETYLUREA/BI OR "S 46"/BI OR "1-((ETHYL)PHENYLACETYL)UREA
                "/BI OR 2-PHENYLBUTYRYLUREA/BI OR 6509-31-5/BI OR 90-49-3/B
                I)

     FILE 'HCAPLUS' ENTERED AT 14:27:21 ON 30 AUG 2021
L15        36479 SEA ABB=ON  PLU=ON  L11 OR L12 OR PHENOBARBITAL(1W)(?SODIUM
                ? OR NA) OR GARDENAL OR HYSTEP## OR LUMINAL OR PHENEMAL OR
                PHENOBARTITONE OR PHENYLBARBITAL OR PHENYLETHYLBARBITURIC
                OR (PHENYL OR PH)(W)(BARBITAL OR ETHYLBARBITURIC OR (ETHYL
                OR ET)(W)BARBITURIC)
L16           115 SEA ABB=ON  PLU=ON  PEAU OR PHENYLETHYLACETYLUREA OR
                (PHENYL OR PH)(W)(ETHYLACETYLUREA OR (ETHYL OR ET)(W)(ACETY
                LUREA OR (AC OR ACETYL)(W)UREA) OR PHENYLETHYL(W)(ACETYLURE
                A OR (AC OR ACETYL)(W)UREA)) OR PHENYLETHYLACETYL UREA OR
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L17            80 SEA ABB=ON  PLU=ON  (ETHYL OR ET)(W)(PHENACEMIDE OR
                PHENYLACETYLUREA OR (PHENYL OR PH)(W)(ACETYLUREA OR
                (ACETYL OR AC)(W)UREA)) OR ETHYLPHENYLACETYLUREA OR
                PHENETURIDE
L18            44 SEA ABB=ON  PLU=ON  L15 AND (L13 OR L14 OR L16 OR L17)
L19            30 SEA ABB=ON  PLU=ON  L18 AND (COMPOSITION OR COMP## OR
                PREP? OR FORMULATION OR SOLUTION OR SOLN OR MIXTURE)
L20            11 SEA ABB=ON  PLU=ON  ("PHENOBARBITAL SODIUM"+PFT AND
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     FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIX, JAPIO, PQSCITECH'
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                AND L18
L22             1 SEA ABB=ON  PLU=ON  ((L1 OR L2 OR L3 OR L4 OR L5) OR L8)
                AND L20
L23            14 SEA ABB=ON  PLU=ON  L6 OR L7 OR L9 OR L10 OR L21 OR L22
L24             9 DUP REM L23 (5 DUPLICATES REMOVED)
                D L24 1-9

     FILE 'HOME' ENTERED AT 14:47:12 ON 30 AUG 2021


     FILE HOME

     FILE REGISTRY
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FILE COVERS 1926 TO DATE.
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FILE COVERS: Embase-originated material 1947 to 27 Aug 2021 (20210827
Unique MEDLINE content 1948 to present

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>>> Limits for structure search have been increased - for details

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    see HELP SLIMITS <<<

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MOST RECENT PUBLICATION DATE: 25 OCT 2012       <20121025/PD>

>>> STATIC FILE - FOR CURRENT JAPANESE PATENTS GO TO FILE JPFULL <<<

FILE PQSCITECH
FILE LAST UPDATED: 24 AUG 2021       <20210824/UP>
FILE COVERS 1962 TO DATE

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION AVAILABLE IN THE
    BASIC INDEX (/BI), ABSTRACT (/AB), and TITLE (/TI) FIELDS <<<
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US011406598B2

(12) **United States Patent**
Chodavarapu et al.

(10) **Patent No.: US 11,406,598 B2**
(45) **Date of Patent: Aug. 9, 2022**

(54) **LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT**

(71) Applicant: **Nivagen Pharmaceuticals, Inc.**, Sacramento, CA (US)

(72) Inventors: **Bala Tripura Sundari Chodavarapu**, Davis, CA (US); **Thirupathi Mangali**, Sacramento, CA (US); **Jay Shukla**, Sacramento, CA (US); **Anand Shukla**, Denver, CO (US); **Dasaradhi Lakkaraju**, Sacramento, CA (US)

(73) Assignee: **NIVAGEN PHARMACEUTICALS, INC.**, Sacramento, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/025,881**

(22) Filed: **Sep. 18, 2020**

(65) **Prior Publication Data**

US 2021/0085608 A1 Mar. 25, 2021

Related U.S. Application Data

(60) Provisional application No. 62/903,511, filed on Sep. 20, 2019.

(51) **Int. Cl.**

A61K 9/19	(2006.01)
A61K 31/515	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 9/19*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 31/515*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 9/19; A61K 9/0019; A61K 31/515

See application file for complete search history.

(56) **References Cited**

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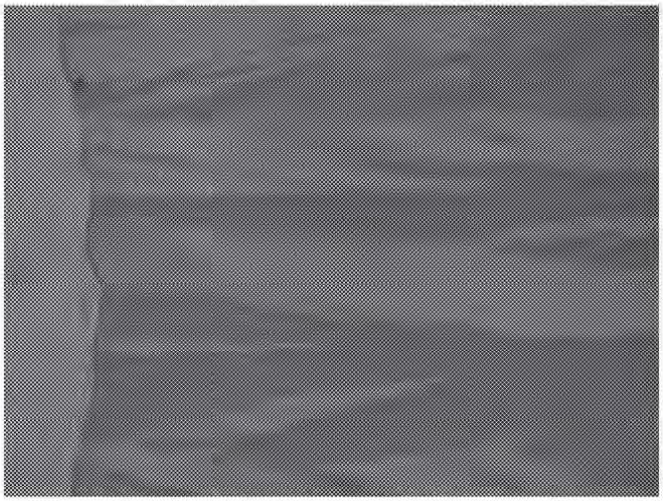
Primary Examiner — Carlos A Azpuru

(74) *Attorney, Agent, or Firm* — Umberg Zipser LLP

(57) **ABSTRACT**

A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (e.g., phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water.

15 Claims, 39 Drawing Sheets



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Fig. 1A

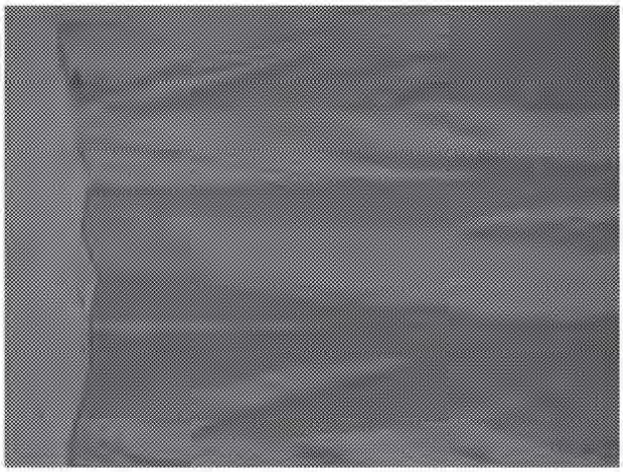


Fig. 1B



Fig. 1C

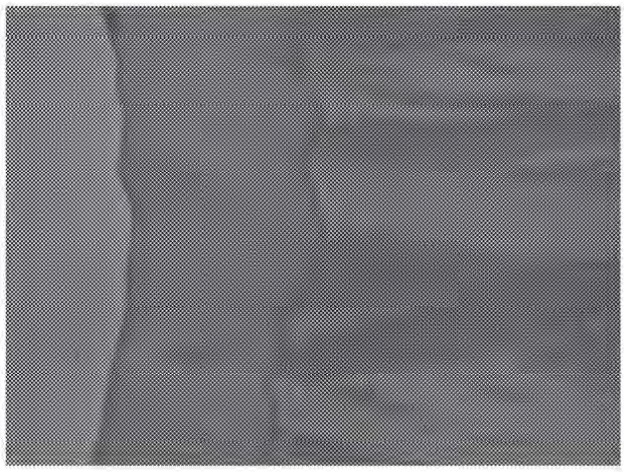


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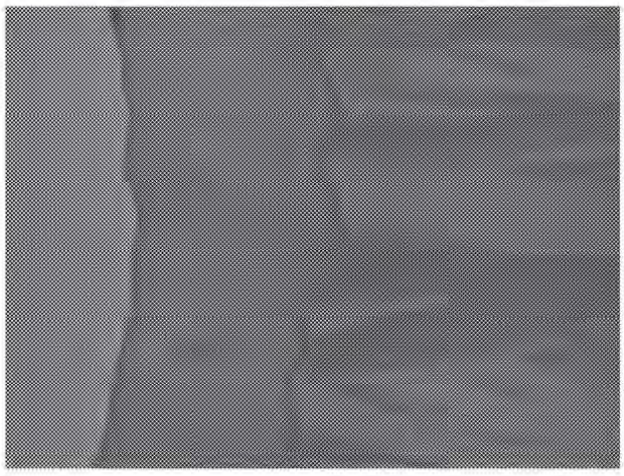


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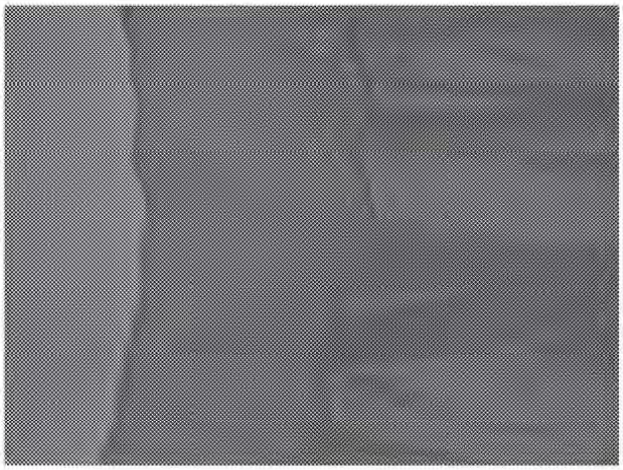


Fig. 1F

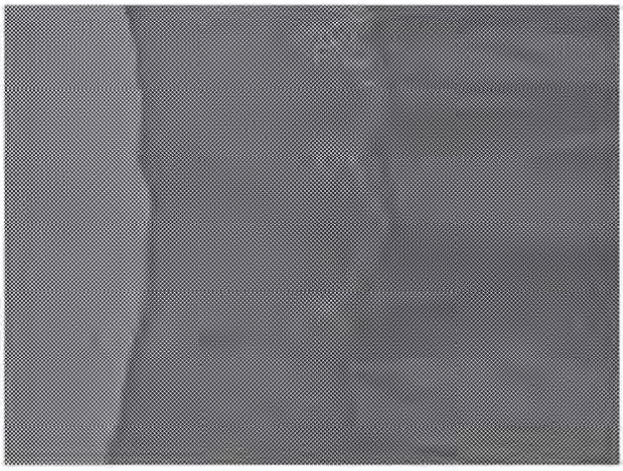


Fig. 2A

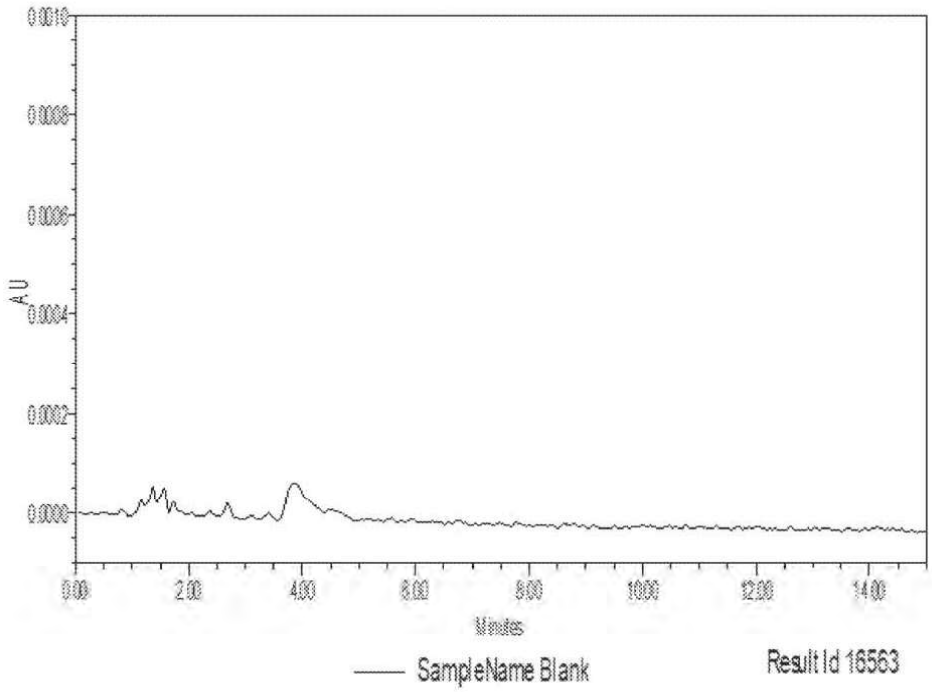
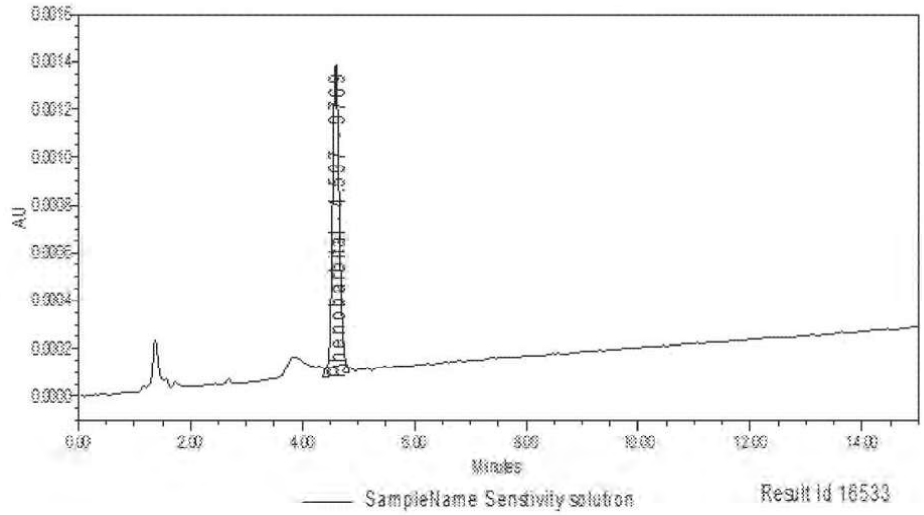
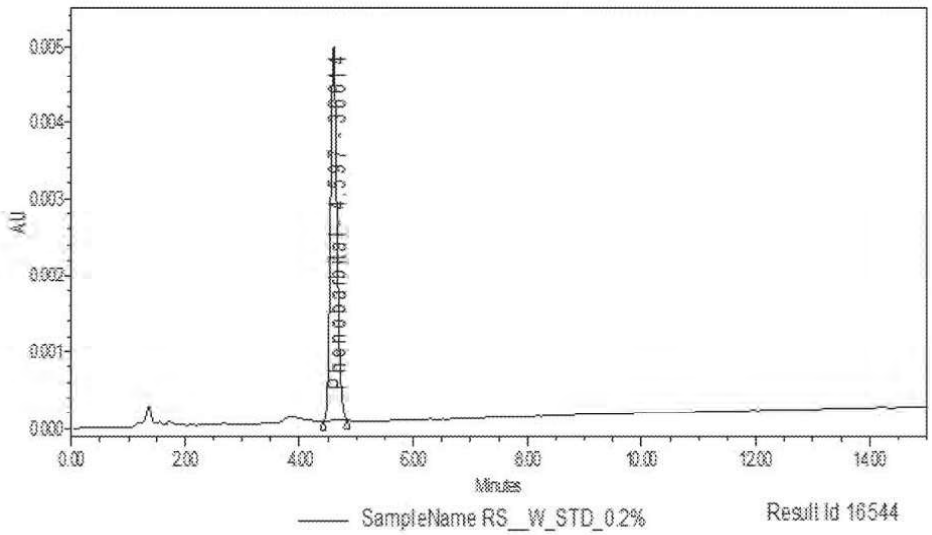

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0.0008
0.0006
0.0004
0.0002
0.0000
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2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes
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Fig. 2B



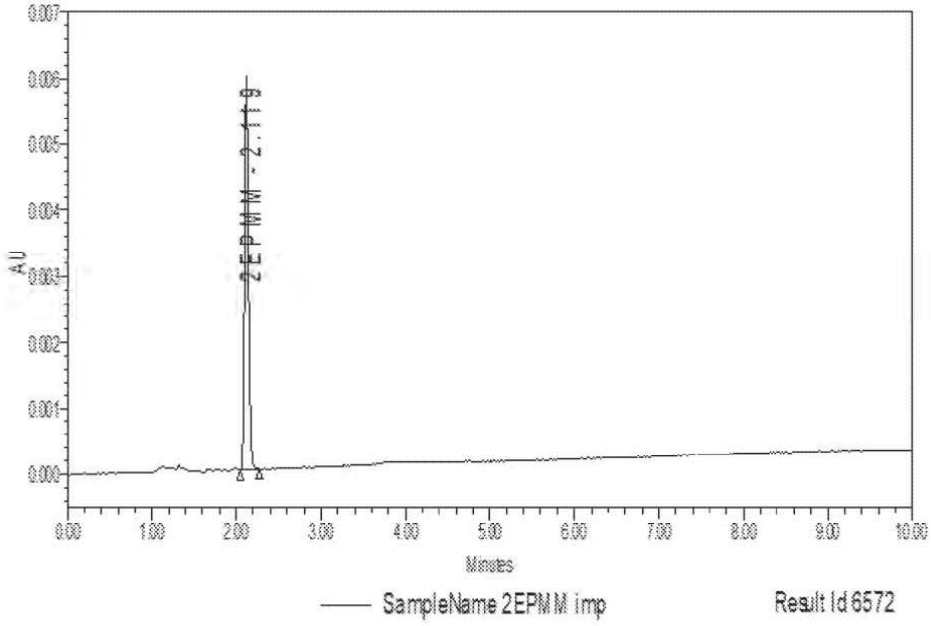
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Fig. 2C



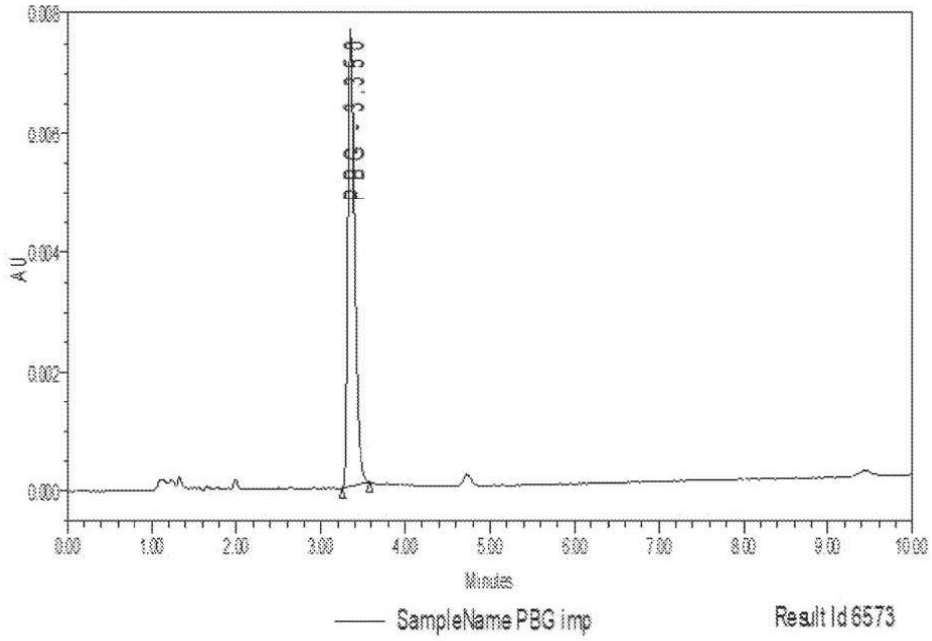
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Fig. 2D



	PeakName	RT	Area	% Area	s/n	USP Plate Count	USP Tailing	PurityM Angle	PurityM Threshold
1	2EPMM	2.119	19797	100.00	1472	9573.6	1.2	0.674	1.803

Fig. 2E



	PeakName	RT	Area	% Area	s/n	USP Plate Count	USP Tailing	Purity Angle	Purity Threshold
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Fig. 2F

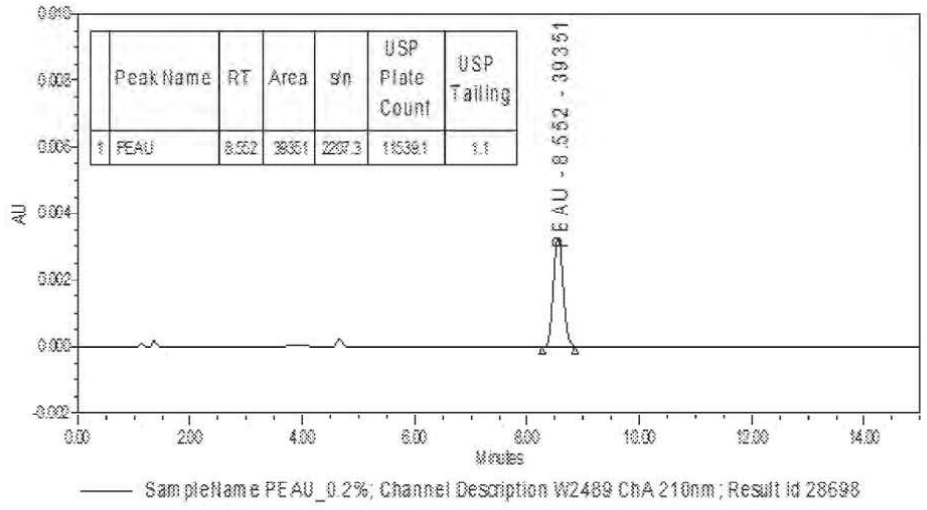

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Area
s/n
USP Plate Count
USP Tailing
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39351
2297.3
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Minutes
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Fig. 2G

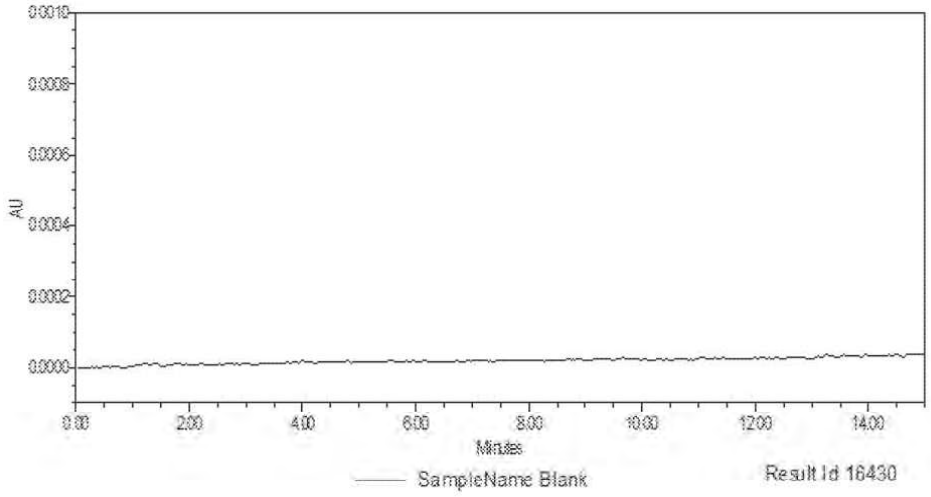
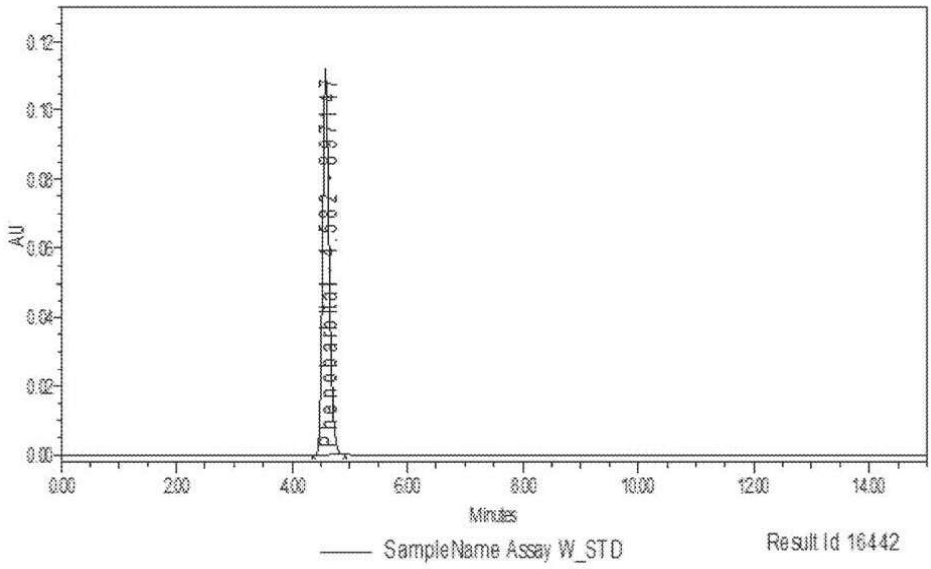
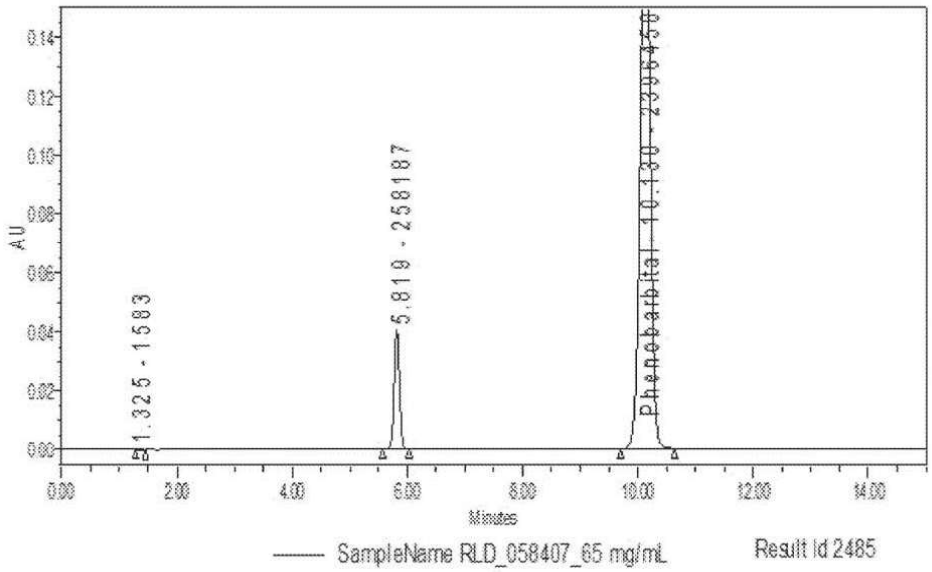

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0.0006
AU
0.0004
0.0002
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0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
Minutes
SampleName Blank
Result Id 16430

Fig. 2H



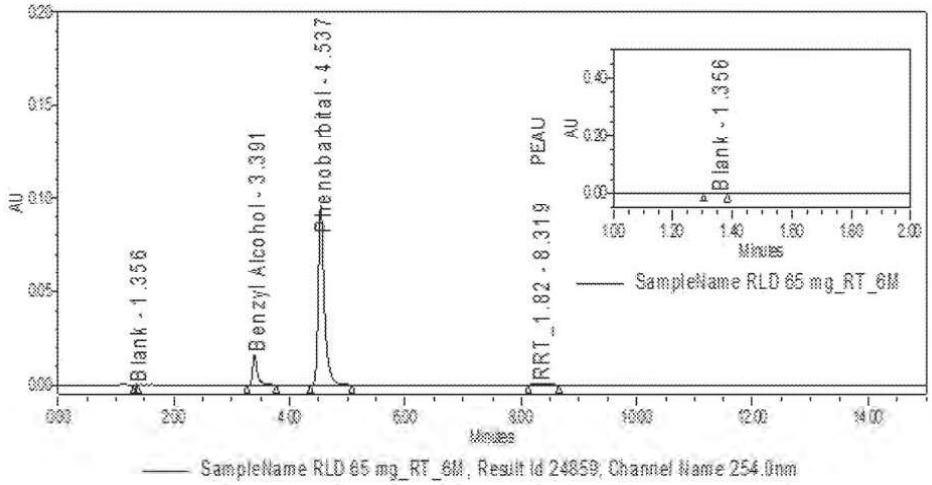
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.582	897147	0.476	50940.058185	7493.0	1.2

Fig. 3A



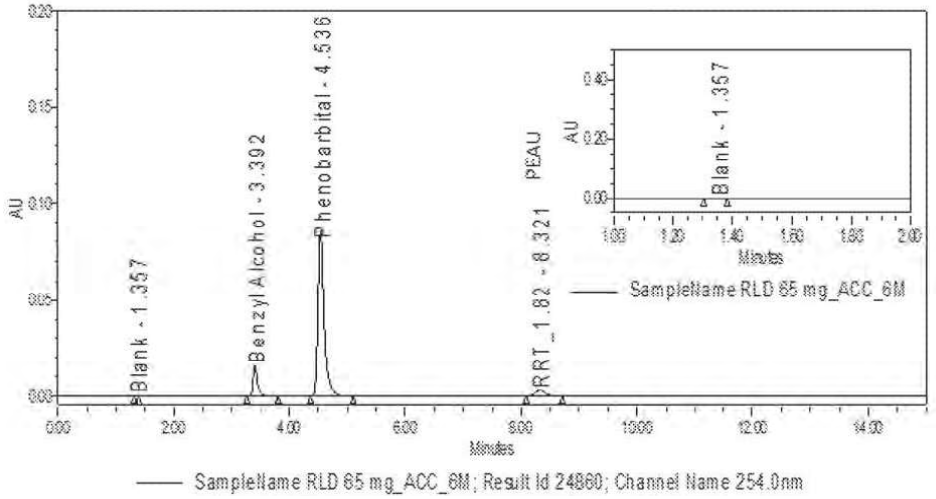
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.130	2396458	60.823	17.9	17534.1	1.0	112.1

Fig. 3B



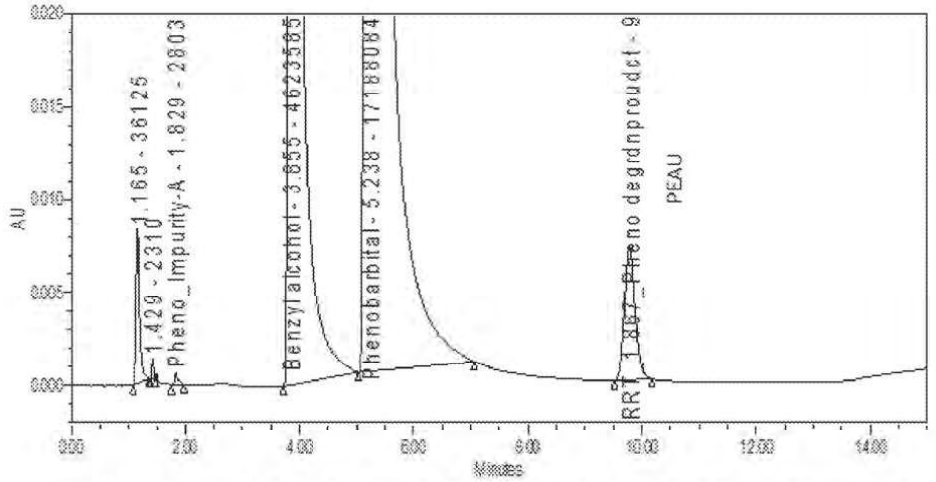
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	87091	10.96	14.994	mg/mL	105.2	23.7	1.7
2	Blank	1.356	828	0.10	0.068	mg/mL			1.0
3	Phenobarbital	4.537	697184	87.71	57.200	mg/mL	96.3	7.2	1.5
4	RRT_1.82	8.319	9745	1.23	0.800	mg/mL		15.0	1.3

Fig. 3C



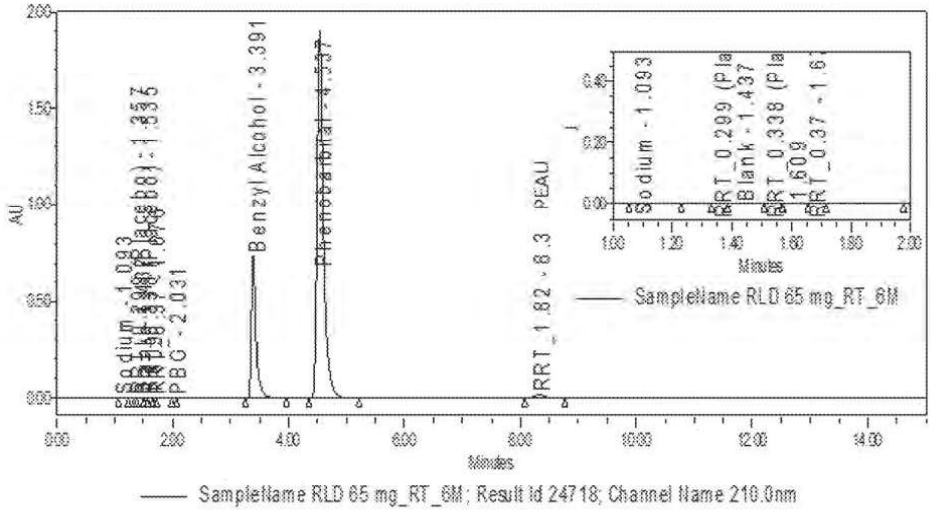
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	84435	11.25	14.537	mg/mL	102.0	23.7	1.7
2	Blank	1.357	798	0.11	0.065	mg/mL			1.1
3	Phenobarbital	4.536	627538	83.64	51.486	mg/mL	86.7	7.2	1.5
4	RRT_1.82	8.321	37484	5.00	3.075	mg/mL		14.6	1.2

Fig. 3D



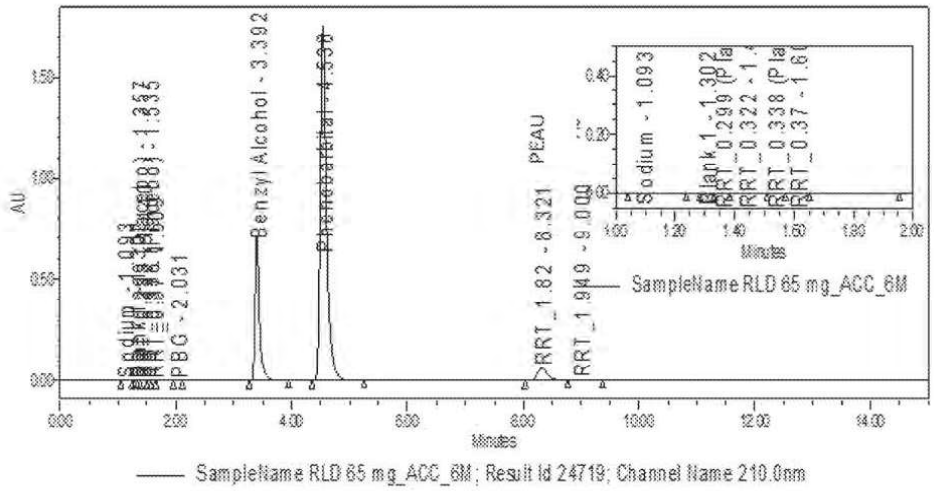
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzylalcohol	3.855	4623585	21.07	17.1	390.1	12312.8	1.5
2	Pheno_ImpurityA	1.829	2803	0.01	5.2	0.3	7606.2	1.6
3	Phenobarbital	5.238	17188084	78.32	8.0	1018.9	11239.0	1.4
4	RRT_1.867_Pheno degrdnproudct	9.781	92897	0.42	16.5	3.5	13191.8	1.2

Fig. 3E



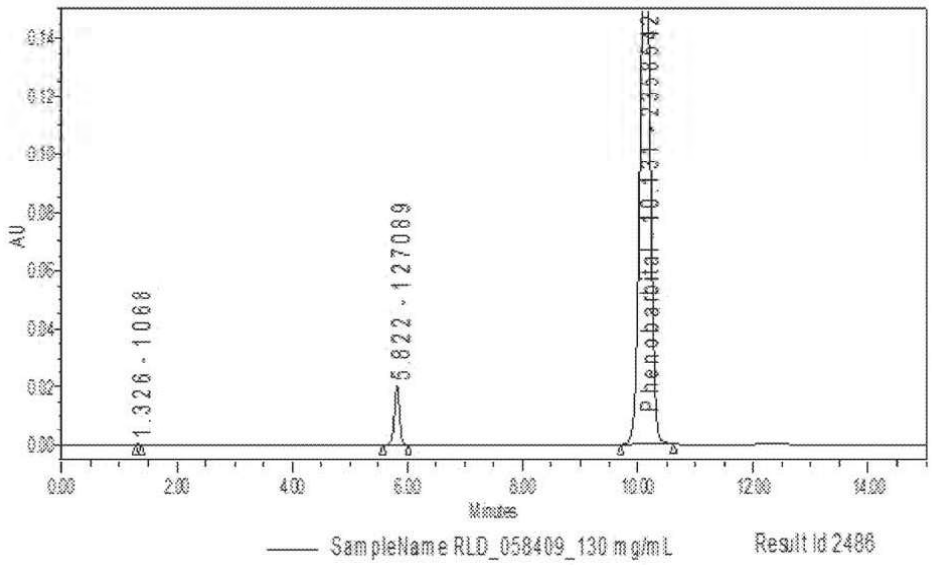
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	3972837	21.25	16.272	mg/mL	13.8	1.7
2	Phenobarbital	4.537	14515521	77.64	56.435	mg/mL	7.1	1.5
3	RRT_1.82	8.321	200110	1.07	0.778	mg/mL	14.6	1.3

Fig. 3F



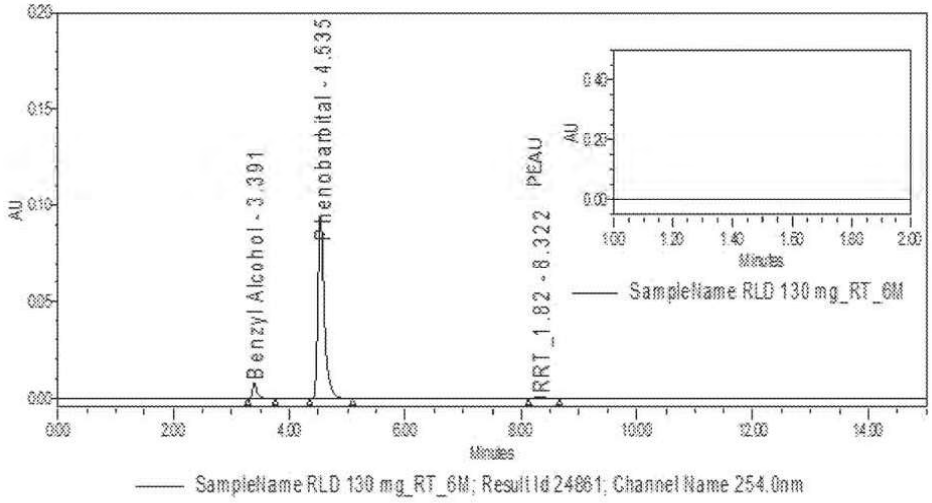
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	3833550	21.50	15.701	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13183528	73.94	51.257	mg/mL	7.1	1.5
3	RRT_1.82	8.321	762556	4.28	2.965	mg/mL	14.6	1.3
4	RRT_1.949	9.000	42716	0.24	0.166	mg/mL	1.9	1.3

Fig. 3G



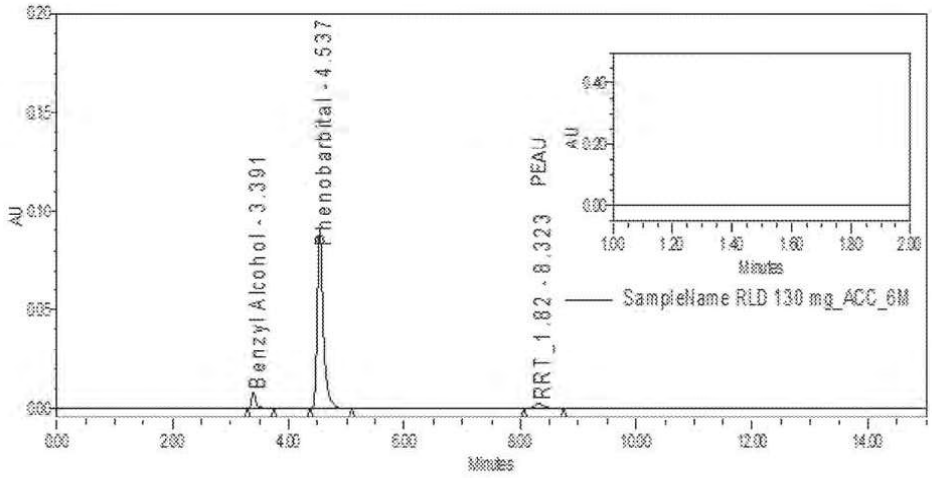
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.131	2358542	119.721	17.9	17563.1	1.0	110.3

Fig. 3H



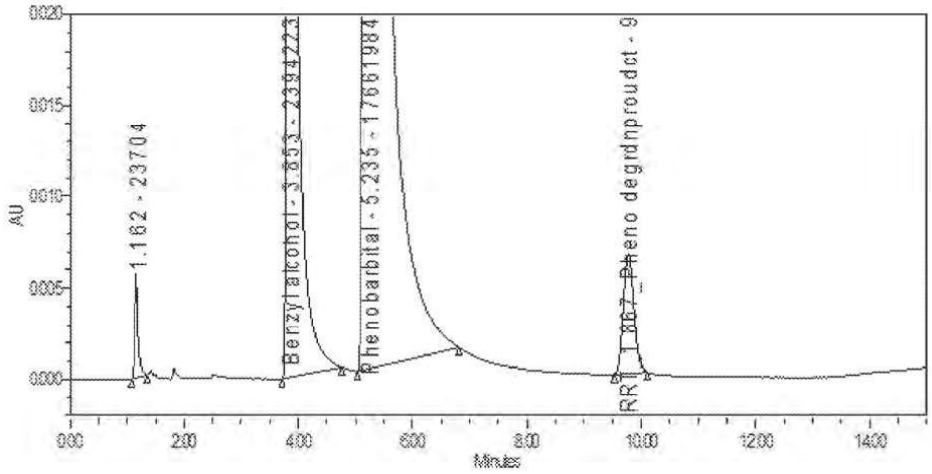
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43232	5.84	14.886	mg/mL	104.5		1.7
2	Phenobarbital	4.535	688747	93.10	113.015	mg/mL	95.2	7.2	1.5
3	RRT_1.82	8.322	7837	1.06	1.286	mg/mL		14.5	1.2

Fig. 3I



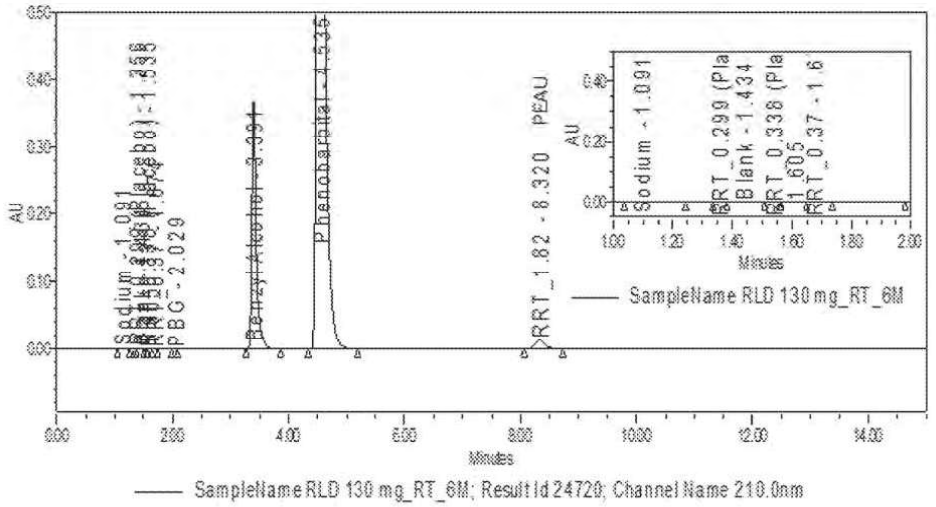
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43440	5.94	14.958	mg/mL	105.0		1.7
2	Phenobarbital	4.537	657548	89.99	107.895	mg/mL	90.9	7.2	1.5
3	RRT_1.82	8.323	29742	4.07	4.880	mg/mL		14.6	1.2

Fig. 3J



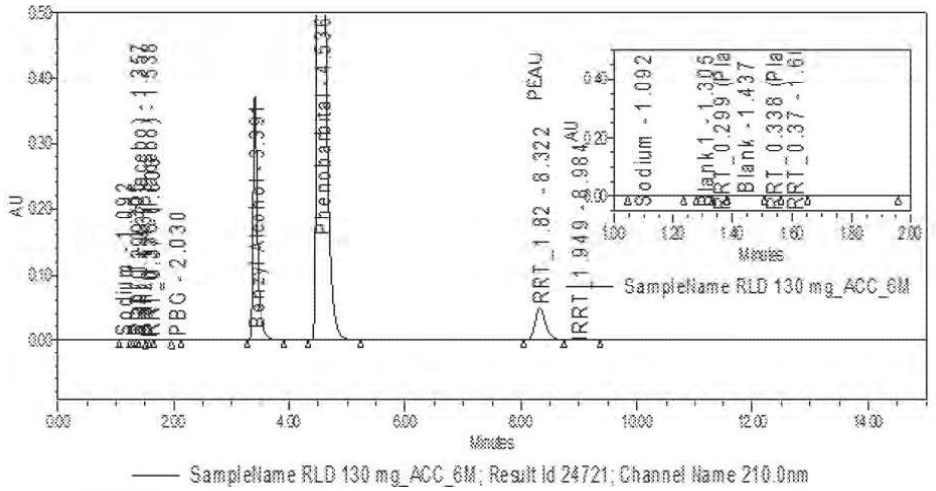
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzylalcohol	3653	2394223	11.87	20.8	223.9	12436.0	1.5
2	Phenobarbital	5235	17661984	87.59	8.0	1144.4	11214.3	1.4
3	RRT_1.867_Phenodegrdnproudct	9.776	83640	0.41	16.6	3.5	13612.7	1.1

Fig. 3K



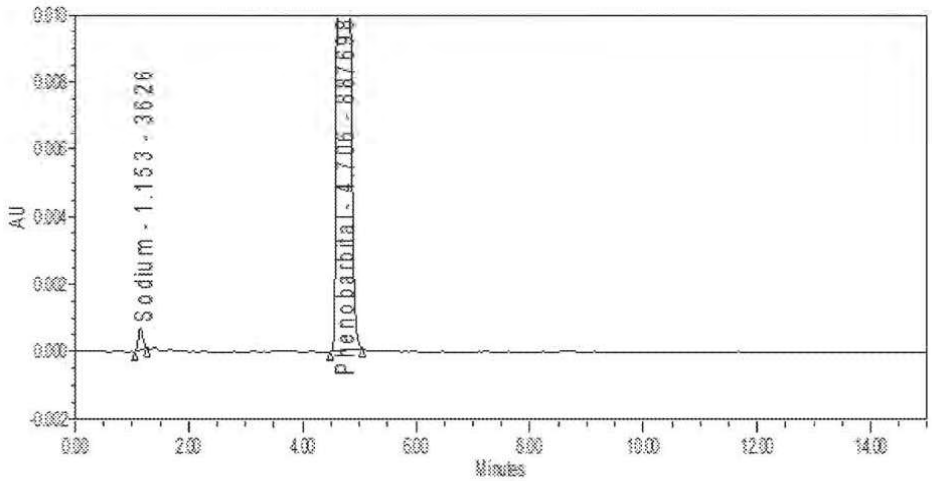
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1963213	11.91	16.081	mg/mL	13.4	1.7
2	Phenobarbital	4.535	14347574	87.06	111.565	mg/mL	7.1	1.5
3	RRT_1.82	8.320	162620	0.99	1.265	mg/mL	14.6	1.3

Fig. 3L



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1984788	12.10	16.258	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13768702	83.93	107.064	mg/mL	7.1	1.5
3	RRT_1.82	8.322	594916	3.63	4.628	mg/mL	14.6	1.2
4	RRT_1.949	8.984	48228	0.29	0.375	mg/mL	1.8	1.3

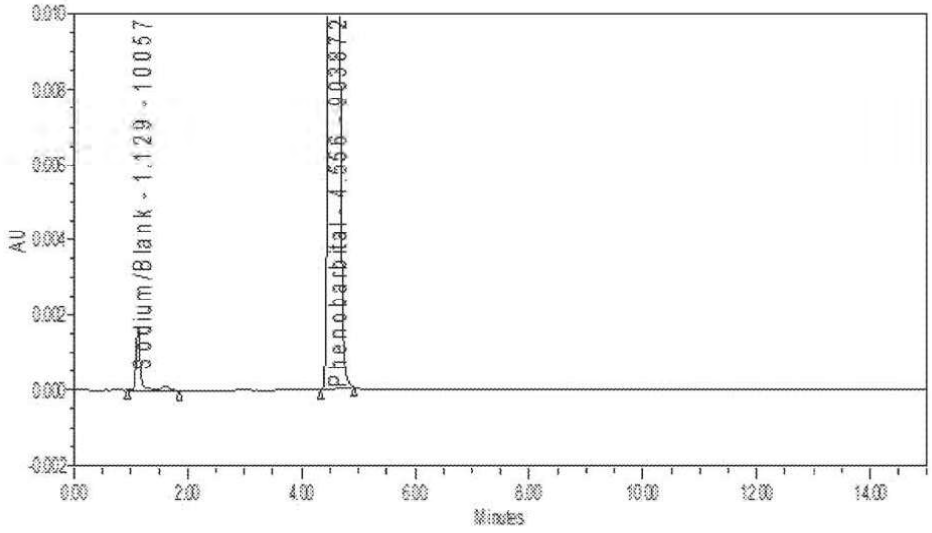
Fig. 4A



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13991

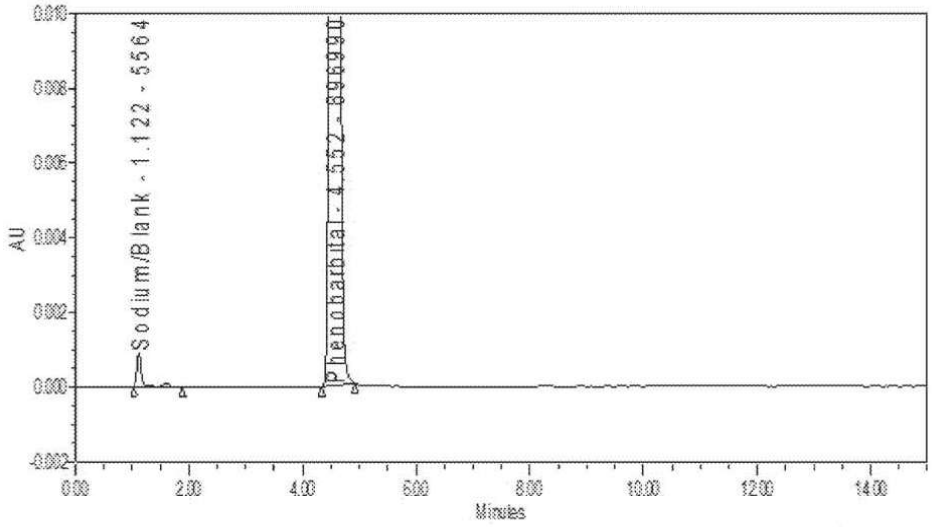
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.706	887698	58.858	mg/mL	99.1	193	52343.5	7952.5	1.2
2	Sodium	1.153	3626					318.4	943.9	1.1

Fig. 4B



	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.556	903872	59.388	mg/mL	100.0	20.8	44822.6	8704.0	1.1
2	Sodium/Blank	1.129	10057	0.661	mg/mL			646.7	1292.0	1.3

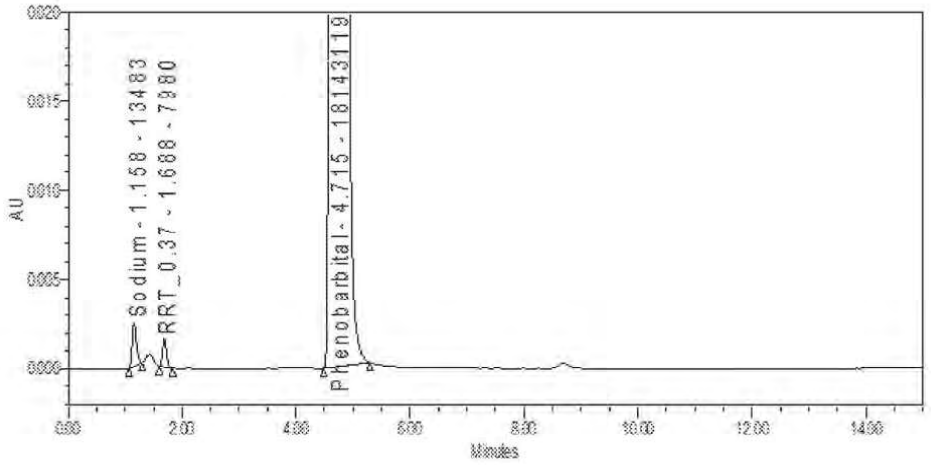
Fig. 4C



SampleName NPH1907_65mg_ACC_6M; Channel Description W2489 ChB 254nm; Result Id 31320

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.552	89690	58.936	mg/mL	99.3	21.1	48295.1	8573.3	1.1
2	Sodium/Blank	1.122	5564	0.366	mg/mL			364.9	1275.7	1.3

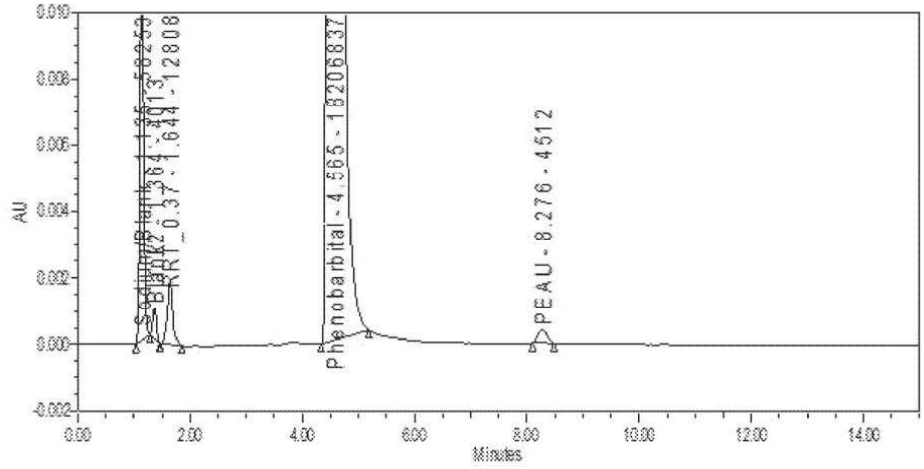
Fig. 4D



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14043

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.715	18143119	99.89	58.972	mg/mL	17.3	9573101.3	7804.1	1.2
2	RRT_0.37	1.688	7980	0.04	0.026	mg/mL	37	772.4	2602.6	1.2
3	Sodium	1.158	13483	0.07	0.044	mg/mL		1197.5	1039.2	1.2

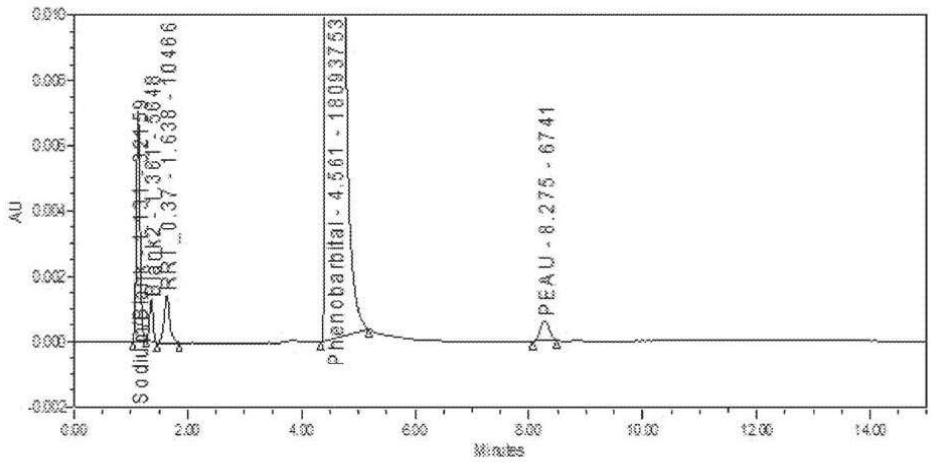
Fig. 4E



SampleName NPH1907_65mg_RT_6M ; Channel Description W2489 ChA 210nm; Result Id 31629

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.364	4013	0.02			1.9	626.1	2241.7	1.1
2	PEAU	8.276	4512	0.02	0.013	mg/mL	14.8	278.0	12299.1	1.1
3	Phenobarbital	4.565	18206837	99.56	53.971	mg/mL	15.2	16166675.4	8239.9	1.1
4	RRT_0.37	1.644	12808	0.07	0.038	mg/mL	1.9	1270.5	1640.7	1.1
5	SodiumBlank	1.135	58253	0.32	0.173	mg/mL		8406.1	1363.0	1.1

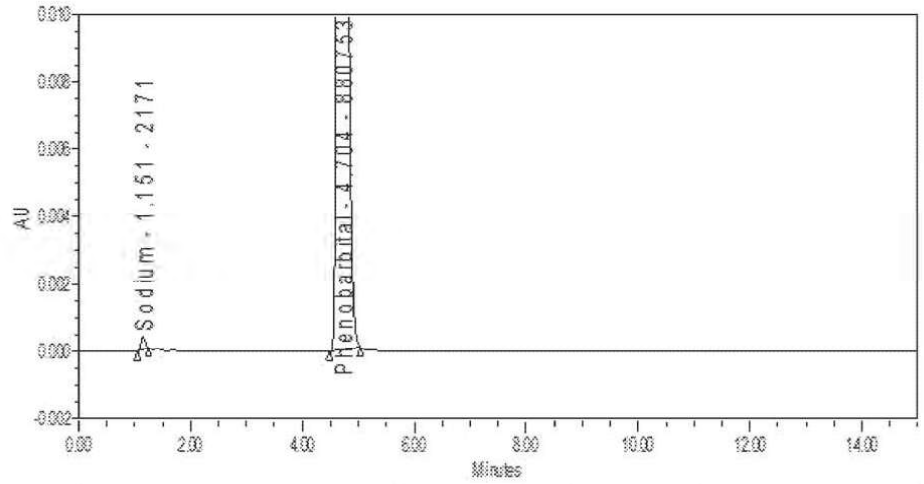
Fig. 4F



SampleName NPH1907_65mg_ACC_6M ; Channel Description W2489 ChA 210nm; Result Id 31632

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.361	9548	0.03			1.9	899.0	2143.9	1.0
2	PEAU	8.275	6741	0.04	0.020	mg/mL	14.6	427.7	11918.9	1.0
3	Phenobarbital	4.561	18093753	99.70	53.636	mg/mL	15.2	1699108.6	8445.9	1.1
4	RRT_0.37	1.638	10466	0.06	0.031	mg/mL	1.9	1084.2	1482.5	1.1
5	SodiumBlank	1.131	32159	0.18	0.095	mg/mL		4912.0	1362.2	1.1

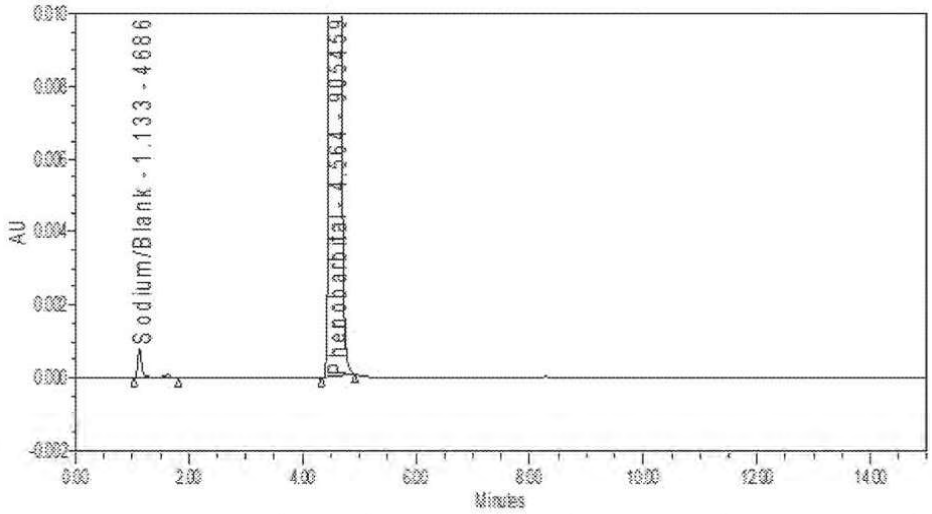
Fig. 4G



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13996

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.704	880753	116.795	mg/mL	98.3	19.3	401921	7866.8	1.2
2	Sodium	1.151	2171					148.3	959.0	1.0

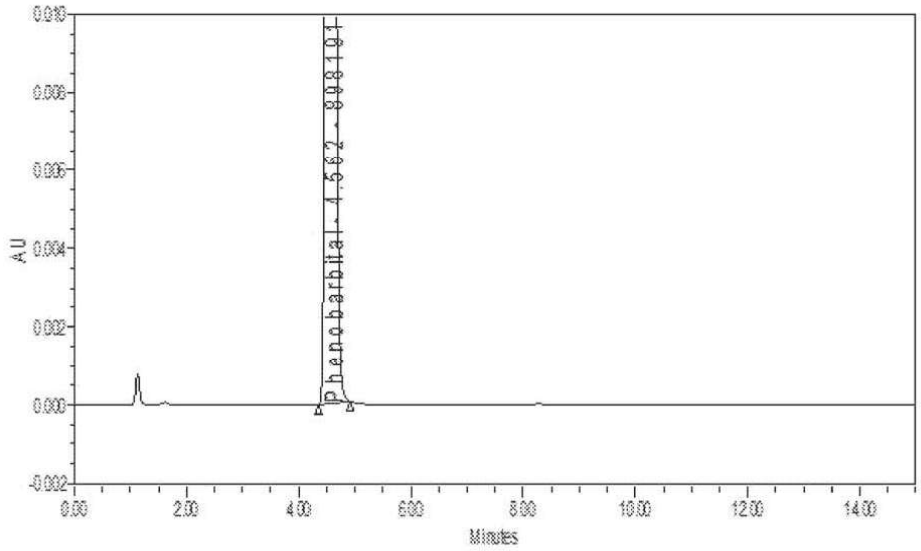
Fig. 4H



—— SampleName NPH1912_130mg_RT_6M ; Channel Description W2489 ChB 254nm; Result Id 31325

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.564	905459	118.985	mg/mL	100.2	20.7	59858.2	8639.9	1.1
2	Sodium/Blank	1.133	4686	0.616	mg/mL			358.4	1316.2	1.4

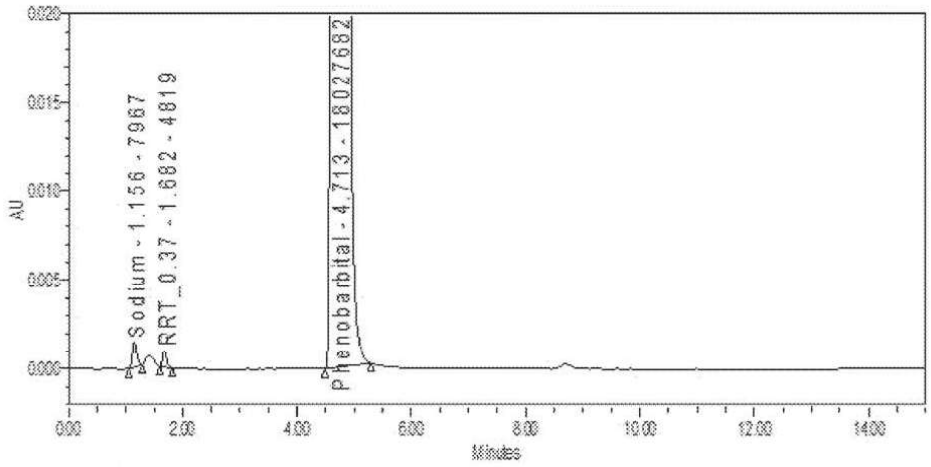
Fig. 4I



SampleName NPH1912_130mg_ACC_6M ; Channel Description W2489 ChB 254nm; Result Id 31328

	Peak Name	RT	Area	Amount	Units	Assay	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.562	898191	118.030	mg/mL	99.4	553756	8698.8	1.1

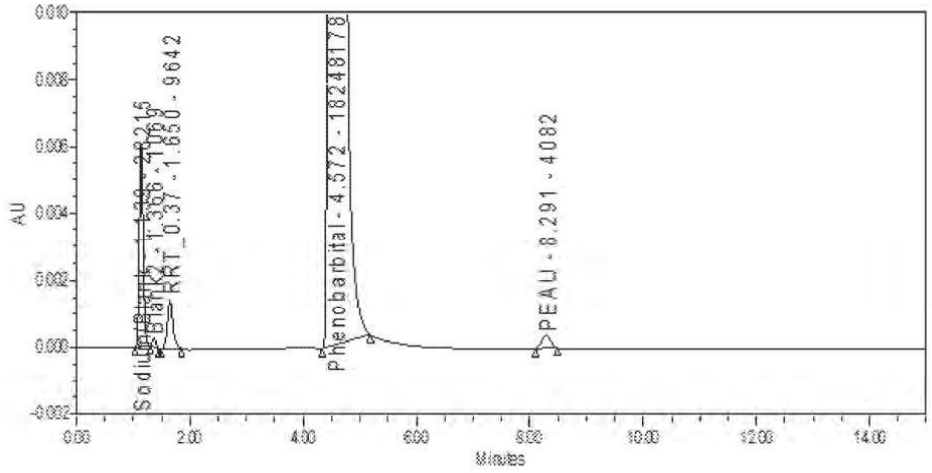
Fig. 4J



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14048

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.713	18027682	99.93	116.995	mg/mL	17.8	1001026.8	7649.3	1.2
2	RRT_0.37	1.682	4819	0.03	0.031	mg/mL	3.6	403.7	2401.3	1.2
3	Sodium	1.156	7967	0.04	0.052	mg/mL		649.1	941.5	1.1

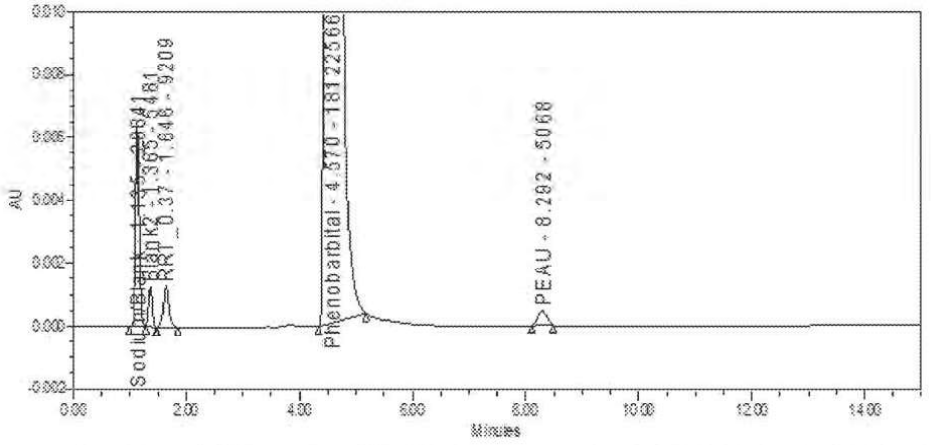
Fig. 4K



SampleName NPH1912_130mg_RT_6M; Channel Description W2489 ChA 210nm; Result Id 31637

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.366	1069	0.01			1.9	143.5	2247.2	1.1
2	PEAU	8.291	4082	0.02	0.024	mg/mL	14.8	213.9	12463.8	1.0
3	Phenobarbital	4.572	18248178	99.76	106.187	mg/mL	15.9	1373582.2	8426.5	1.1
4	RRT_0.37	1.850	9642	0.05	0.057	mg/mL	2.0	832.7	1616.4	1.1
5	Sodium/Blank	1.139	28215	0.15	0.167	mg/mL		3438.2	1382.8	1.1

Fig. 4L



SampleName NPH1912_130mg_ACC_6M; Channel Description W2489 ChA 210nm; Result Id 31640

	PeakName	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.385	5481	0.03			1.9	887.2	2149.1	1.1
2	PEAU	8.282	5068	0.03	0.030	mg/mL	14.8	256.8	12320.6	1.0
3	Phenobarbital	4.570	18122566	99.73	107.442	mg/mL	15.1	1328658.2	6330.4	1.1
4	RRT_0.37	1.846	9209	0.05	0.055	mg/mL	1.8	725.3	1461.0	1.1
5	SodiumBlank	1.135	28841	0.16	0.171	mg/mL		3440.5	1382.6	1.1

Fig. 5A

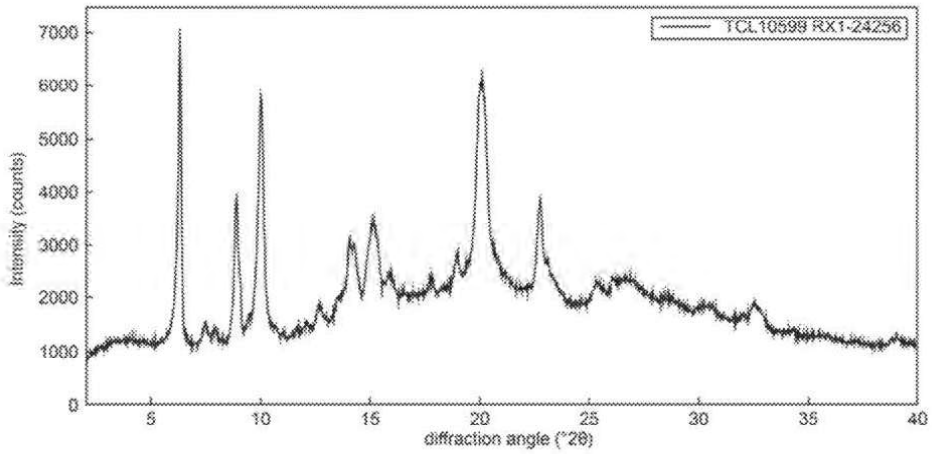

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1000
0
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 5B

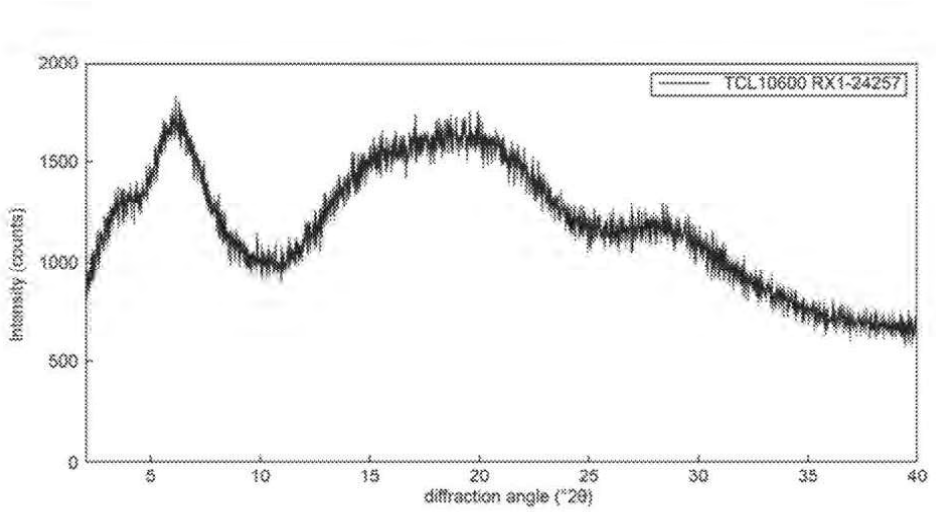

TCL10600 RX1-24257
Intensity (counts)
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1000
500
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5
10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 5C

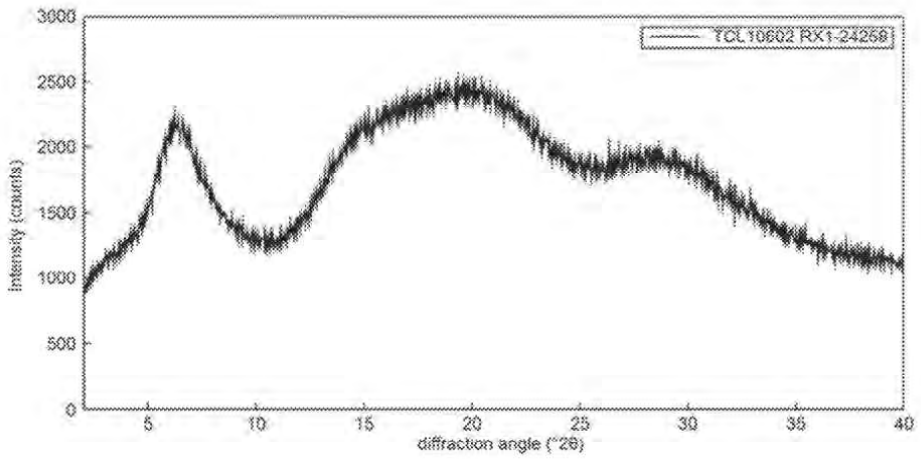
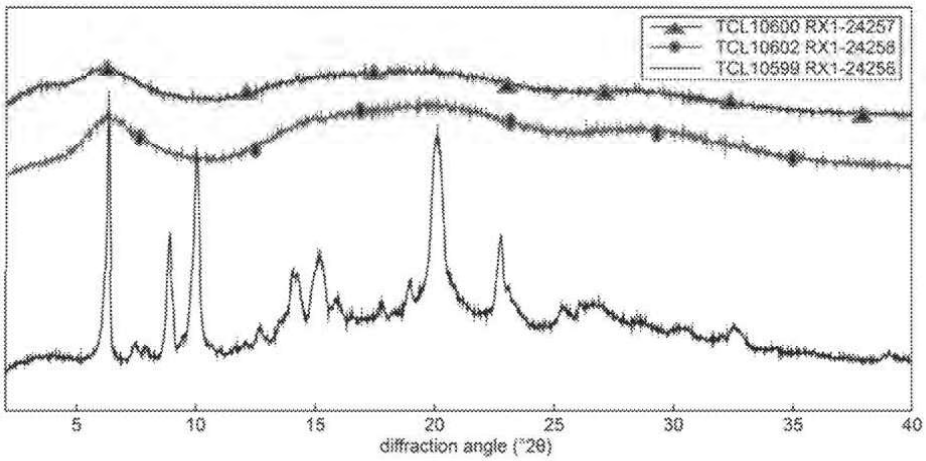

TCL10602 RX1-24258
Intensity (counts)
3000
2500
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 5D


TCL10600 RX1-24257
TCL10602 RX1-24256
TCL10599 RX1-24256
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No. 62/903,511, filed on Sep. 20, 2019, which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present disclosure relates to compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water.

BACKGROUND OF THE INVENTION

The background description includes information that may be useful in understanding the present disclosure. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

Phenobarbital Sodium is a well-known barbiturate that is most commonly administered as an anti-convulsant for the treatment of seizures and may also be administered as a sedative, a sleep aide, or a pre-anesthetic. Phenobarbital Sodium is typically a liquid formulation administered intramuscularly (IM) or intravenously (IV) with crystalline granules or crystals dissolved in an aqueous solvent. For example, WO 2017/085687 to Parker et al. discloses a liquid formulation of Phenobarbital Sodium dissolved in water along with a C1-C4 alcohol and a glycol.

The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, in water alone or in water with an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate.

Over the years of medical administration, efforts have been made to decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation. For example, Gupta, V. D., (*J. Pharm Sci.*, 1984, 73:1661-1662) describes the effects of ethanol, glycerol, and propylene glycol on the stability of Phenobarbital Sodium in aqueous solutions. Specifically, Gupta discloses that ethanol has the best effect followed by propylene glycol and glycerol relative to water alone. Years after Gupta, Parker et al., (WO 2017/085687) focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products. Parker addresses the hydrolysis issue by limiting the amount of water (e.g., to no more than 50 mg/mL) in the liquid formulation. Parker's minimized water formulations also include a C1-C4 alcohol such as ethanol and a glycol such as propylene glycol. However, while the amount of impurities in Parker's liquid formulation may have decreased compared to prior formulations, impurities such a PEAU are still present in undesirable amounts, particularly after extended storage.

In addition to the degradation impurities, the current marketed liquid formulation of Phenobarbital Sodium (e.g., Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL), includes organic solvents such as alcohol, which are not desirable in general and indeed not suitable for administration to newborns as described in the art, e.g., Williams et al., 1998, "Evaluating Toxic Alcohol Poisoning in the Emergency Setting," *Laboratory Medicine*, Vol. 29, No. 2; Wood et al., 2007, *J. of Perinatology*, 27:183-185; Kumar, 1985, "Adverse Drug Reactions in the Newborn," *Annals of Clin. And Lab. Sci*, Vol. 15, No. 3; and Cuzzolin, 2018, *J. Pediatric and Neonatal Individualized Med.*, doi: 10.7363/070112.

Accordingly, there is still a need for a stable Phenobarbital Sodium formulation in a formulation that is storage stable and void or essentially void of degradation impurities upon solubilization in water.

SUMMARY

Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium.

The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see e.g., C. Ahlneck and G. Zografi "The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State," Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations.

Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. Alternatively, the percentage of the lyophilized formulation that is amorphous can be 100%. In addition, the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (e.g., 20%-100%, 25%-95%. etc.).

Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU) is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40° C., 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, having a pH between 9.2 to 10.2, and lyophilizing the bulk solution. In some embodiments, the water is Water for Injection.

In preferred embodiments, the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium.

For adjusting the pH of the Phenobarbital Sodium solution, the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition may also include measuring the pH of the Phenobarbital Sodium solution, wherein if the pH is higher than 10.2, the adjusting includes adding hydrochloric acid (HCl).

Typically, the resulting lyophilized Phenobarbital Sodium forms no more than 0.1% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months both at RT and accelerated stability conditions. More typically, the resulting lyophilized Phenobarbital Sodium forms no more than 0.05% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and under accelerated stability conditions (40° C.). Additionally, or alternatively, the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at RT and accelerated stability conditions.

According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, the stability of the lyophilized Phenobarbital Sodium is determined by reconstituting the lyophilized Phenobarbital Sodium in an aqueous solution and measuring the amount of or the presence of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG).

Additional embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is filtered prior to lyophilization.

Further embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is aliquoted into a vial prior to lyophilization, and after lyophilization, a closure is applied to the vial under vacuum.

Aspects of the present disclosure also include a method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution, in which the method includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2, and lyophilizing the Phenobarbital Sodium solution to form stable white lyophilized powder of Phenobarbital Sodium.

In preferred embodiments, the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium.

For adjusting the pH of the Phenobarbital Sodium solution, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution may also include measuring the pH of the Phenobarbital Sodium solution, wherein if the pH is higher than 10.2, the adjusting includes adding Hydrochloric acid (HCl).

In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution.

In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no more than 0.2% PEAU, 2 EPMM, and/or PBG, and preferably has 0.05% or less PEAU and no detectable amount of 2 EPMM or PBG.

Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection.

Additional aspects of the present disclosure include a pharmaceutical product including a vial containing the white lyophilized powder of Phenobarbital Sodium for reconstitution prior to administration, in which the composition was lyophilized in the vial and the vial includes a closure positioned in order to seal the vial under vacuum after Lyophilization.

Therefore, the inventors also contemplate lyophilized Phenobarbital Sodium.

Various objects, features, aspects, and advantages will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawings.

BRIEF DESCRIPTION OF DRAWINGS

FIG. **1**A is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −50° C., as indicated.

FIG. **1**B is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −45.5° C. as indicated.

FIG. **1**C is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −40.0° C. as indicated.

FIG. **1**D is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −39.6° C. as indicated.

FIG. **1**E is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −39.2° C. as indicated.

FIG. **1**F is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at −38.8° C. as indicated.

FIG. **2**A is a chromatogram from an injection of a "blank solution" for assay by high performance liquid chromatography (HPLC) at a detection wavelength of 210 nanometers (nm), as described herein.

FIG. **2**B is a chromatogram from an injection of the "Sensitivity solution" of Phenobarbital for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**C is a chromatogram from an injection of a "related substance" (RS) working standard at 0.2% impurity level) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**D is a chromatogram from an injection of 2-ethyl-2-phenylmalonamide (2EPMM) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**E is a chromatogram from an injection of alpha-phenylbutyrylguanidine (PBG) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**F is a chromatogram from an injection of phenylethylacetylurea (PEAU) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **2**G is a chromatogram from an injection of a "blank solution" for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **211** is a chromatogram from an injection of an "assay working standard" for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**A is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**B is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**C is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**D is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**E is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**F is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**G is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**H is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**I is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

FIG. **3**J is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**K is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **3**L is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

FIG. **4**A is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. **4**B is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. **4**C is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. **4**D is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for related

substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. **4**E is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. **4**F is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. **4**G is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. **411** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. **4**I is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

FIG. **4**J is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. **4**K is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. **4**L is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

FIG. **5**A is an X-ray powder diffraction (XRPD) pattern of Phenobarbital Sodium Grade P

FIG. **5**B is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

FIG. **5**C is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

FIG. **5**D is a stack plot of the XRPD patterns of FIGS. **5**A, **5**B, and **5**C.

DETAILED DESCRIPTION

The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25° C., 65% RH and 40° C., 75% RH) for up to at least 6 months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution (e.g. solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

The Phenobarbital Sodium composition as described herein refers to Phenobarbital Sodium having an IUPAC (International Union of Pure and Applied Chemistry) name of sodium 5-ethyl-4,6-dioxo-5-phenyl-1H-pyrimidin-2-olate, a Chemical Abstract Service (CAS) No. 57-30-7, and a molecular formula of $C_{12}H_{11}N_2NaO_3$.

In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of FIGS. **1**A-**1**F and the XRPD analysis shown in FIG. **5**A-**5**D, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (e.g., not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG.

The contemplated method for producing a storage-stable lyophilized Phenobarbital Sodium composition includes adding purified Phenobarbital Sodium to water. Preferably the purified Phenobarbital Sodium solid is purchased from a chemical supplier (e.g., Siegfried, USA) that adheres to the United States Pharmacopeia (USP) manufacturing and synthesis guidelines. The USP grade of the Phenobarbital Sodium is preferably USP "purified" or "practical" (P) grade indicating that it is a good quality chemical. As understood in the art, the USP grade (P) active pharmaceutical ingredient (API) of Phenobarbital Sodium is not suitable for administration because it is not sterile, is hygroscopic, and as such, maintaining anhydrous conditions of this grade of API is not feasible. Structurally, the analyzed USP grade P API (Siegfried, USA) is polymorphous—containing both crystalline and non-crystalline material. With reference to FIG. **5**A, an X-ray powder diffraction (XRPD) pattern is shown of this compound.

Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to Water for Injection and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O_2) gas from the water (e.g., Water for Injection), it is also preferred that the water is sparged with nitrogen (N_2) or other inert gas prior to the addition of the Phenobarbital Sodium solid. For effective sparging, a volume of about 100-200 ml water is sparged with nitrogen gas for at least 30 minutes. In exemplary protocols for producing either 65 mg, 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of Water for Injection is nitrogen sparged for 30 minutes. In additional embodiments, the water may also be cooled to approximately 2 to 8° C. In preferred embodiments, the water is cooled to approximately 2 to 8° C.

The addition of the Phenobarbital Sodium solid to the water (e.g., deionized nitrogen sparged water cooled to 2 to 8° C.) may be carried out using any suitable mixing. Preferably, the water (e.g., Water for Injection) is first added to a glass/stainless steel container for nitrogen sparging and cooling, and this prepped water remains in the glass/stainless steel container or a measured amount is transferred to a preferably weighed glass container/stainless steel container and the Phenobarbital Sodium solid is added thereto. For mixing, any suitable mixing may be used. For example, a magnetic stir bar may be added to the glass/stainless steel container. Upon addition of the Phenobarbital Sodium solid to the water, the mixture is stirred.

An additional consideration for stability of the Phenobarbital Sodium is maintaining a pH between 9.2 and 10.2 in the bulk solution of Phenobarbital Sodium. After dissolution of the Phenobarbital Sodium solid in the water, the pH is adjusted to within this range of 9.2 and 10.2. Accordingly, the pH of the water solubilized Phenobarbital Sodium is first measured upon dissolution. If the pH is higher than 10.2 or lower than 9.2, the pH is adjusted. For example, if necessary, the pH may be lowered to or between 9.2 and 10.2 using Hydrochloric acid (HCl) and the pH may be increased to or between 9.2 and 10.2 using Sodium Hydroxide (NaOH).

Following the pH measurement and any adjustment, the Phenobarbital Sodium solution is preferably filtered to remove any foreign particles. For example, the Phenobarbital Sodium solution may be filtered using a 0.2 μm (or 0.22 μm) membrane filter. For example, the membrane filter may be polyvinylidene difluoride (PVDF) or any other compatible filter membranes such as Polyethersulfone (PES) filter.

According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (e.g., nitrogen sparged Water for Injection cooled to 2 to 8° C.) having a pH of or between 9.2 and 10.2 and preferably filtered is ready for Lyophilization. Depending on the desired amount of the lyophilized Phenobarbital Sodium product, the Phenobarbital Sodium solution may be lyophilized in any amount or the solution may be aliquoted into sterile containers (e.g., vials). For example, in order to obtain a measured dose of lyophilized Phenobarbital Sodium in a container, the glass container, water, and Phenobarbital Sodium solid are weighed prior to mixing in order to determine an actual weight of the Phenobarbital Sodium after pH measurement and adjustment. For example, to produce 65 mg or 130 mg doses of lyophilized Phenobarbital Sodium, a batch may be dissolved, mixed, pH adjusted if necessary, and filtered and then aliquoted into single use dose vials for lyophilization. In a specific example, a 50 mL batch of Phenobarbital Sodium solution may be prepared where for 65 mg doses, 3.25 grams of Phenobarbital Sodium solid (e.g., USP Grade P) is added to 40 ml of water (e.g., nitrogen sparged Water for Injection cooled to 5 to 8° C.) and for 130 mg doses, 6.5 grams of the Phenobarbital Sodium is added to the 40 ml of water. Following dissolution, pH adjustment if necessary, adjusting final volume to 50.0 mL and filtering, 1 ml aliquots of this Phenobarbital Sodium solution are added to open (e.g., unstoppered) vials and then loosely stoppered (e.g., with lyophilization rubber stoppers) prior to lyophilization. Following lyophilization, each vial contains 65 mg or 130 mg of lyophilized Phenobarbital Sodium.

In further embodiments, following lyophilization, the vials may be completely closed (e.g., stoppered) under vacuum.

Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium.

Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution.

In one embodiment, the water is Water for Injection.

In another embodiment the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium.

In another embodiment, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium.

In another embodiment, the water is cooled to or between 2 to 8° C. prior to adding the Phenobarbital Sodium.

In another embodiment, the adjusting includes measuring the pH of the Phenobarbital Sodium solution, and if the pH is higher than 10.2, the adjusting includes adding Hydrochloric acid (HCl).

In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT).

In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium.

In another embodiment, the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

In another embodiment, the method further includes filtering the Phenobarbital Sodium solution prior to lyophilizing.

In another embodiment, the method further includes aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and after lyophilization, applying a closure to the vial under vacuum.

Another embodiment is directed to a method of treating an individual in need of Phenobarbital Sodium. The method

includes adding saline or dextrose to a composition containing lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual.

In another embodiment, the individual suffers from epilepsy.

In another embodiment, the individual is a newborn suffering from neonatal epilepsy.

In another embodiment, the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

In another embodiment, the administering includes intramuscular injection or intravenous injection.

Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to FIGS. **5**B-**5**C, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade PAPI shown comparatively in FIG. **5**D. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT.

In a comparison analysis, the presently disclosed lyophilized powder of Phenobarbital Sodium at 65 mg or 130 mg doses was reconstituted in water and assayed for impurities and stability along with marketed liquid formulation of Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL (Westward Pharmaceuticals). The formulation details for this comparative analysis are presented in Table 1. Representative chromatograms from HPLC analysis are shown in FIGS. **2**A-**2**H, **3**A-**3**L, and **4**A-**4**L.

TABLE 1

Formulation Details			
Dosage form		Liquid	Lyophilized
Components	Chemical name	mg/mL	mg/vial
Drug Substance	Phenobarbital Sodium	65 or 130	65 or 130
Inactive ingredients	Propylene Glycol	705	NA
	Benzyl alcohol	15.6	NA
	Ethanol	78.9	NA
	HCL	For pH adjustment	NA
	Water for Injection	QS (Quantity Supplied)	NA

Lyophilized Phenobarbital Sodium for Injection USP, 65 mg/vial and 130 mg/vial
Liquid Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL

With reference to Tables 2 and 3, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (Table 2) (FIGS. **3**A-**3**F, FIGS. **4**A-**4**F), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (Table 3) (FIGS. **3**G-**3**L, FIGS. **4**G-**4**L). In addition to the noted characteristics of each product, the products were assayed for the degradation products—phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both Tables 2 and 3, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25° C.) and under accelerated stability conditions (ACC) at 40° C. were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (Table 2). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (Table 3). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (Tables 2-3).

TABLE 2

65 mg/ml Liquid Formulation and 65 mg/vial Lyophilized Powder									
Product Name	Phenobarbital Sodium for Injection USP, 65 mg/mL (Marketed product)				Phenobarbital Sodium for Injection USP, 65 mg/Vial (Nivagen formulation- NPH1907)				
Formulation Type	Liquid				Lyophilized powder				
Stability Data	3 Months		6 Months		3 Months		6 Months		15 Months
	RT 25° C.,	ACC 40° C.,	RT 25° C.,	ACC 40° C.,	RT 25° C.,	ACC 40° C.,	RT 25° C.,	ACC 40° C.,	RT** 25° C.,

TABLE 2-continued

65 mg/ml Liquid Formulation and 65 mg/vial Lyophilized Powder											
Test	Initial	60% RH	75% RH	60% RH	75% RH	Initial	60% RH	75% RH	60% RH	75% RH	60% RH
Description	CCVS	CCVS	CCVS	CCVS	CCVS	WLP	WLP	WLP	WLP	WLP	WLP
Appearance after reconstitution	NA	NA	NA	NA	NA	CCS	CCS	CCS	CCS	CCS	CCS
Identification	$	$	$	$	$	$	$	$	$	$	$
pH*	9.3	9.8	9.7	9.6	9.6	9.8	9.6	9.6	9.7	9.7	9.8
% Assay of Phenobarbital Sodium	102.4	97.6	103.1	96.3	86.7	99.1	98.7	97.4	100.0	99.3	96.0
% degradation (Area percent) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND
PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	0.5	1.0	3.7	1.4	5.8	ND	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	BQL	BQL	0.1	BQL	0.3	BQL	BQL	BQL	0.07	0.06	0.04
Total degradation products	0.5	1.0	3.8	1.4	6.1	BQL	BQL	BQL	0.07	0.06	0.04

CCVS: Clear Colorless Viscous Solution;
CCS: Clear Colorless Solution;
WLP: White Lyophilized powder
$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.
BQL: Below Quantitation Limit; (QL-0.05%);
ND: Not Detected
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-phenylbutyrylguanidine,
PEAU: phenylethylacetylurea or Pheneturide
*pH of both liquid and lyophilized formulations are measured at 65 mg/mL concentration
**The samples were stored at 30 ± 2° C., 65% RH ± 5

Notably, the Lyophilized powder was stable even after 15 months, and no significant increase in the impurities was observed, rendering such formulation superior to known liquid formulations and enable easy administration.

TABLE 3

130 mg/mL Liquid Formulation and 130 mg/vial Lyophilized formulation											
	Product Name										
	Phenobarbital Sodium for Injection USP, 130 mg/mL (Marketed product)					Phenobarbital Sodium for Injection USP, 130 mg/vial (Nivagen formulation-NPH1912)					
	Formulation Type										
	Liquid					Lyophilized powder					
	Stability Data										
		3 Months		6 Months			3 Months		6 Months		15 Months
Test	Initial	RT 25° C., 60% RH	ACC 40° C., 75% RH	RT 25° C., 60% RH	ACC 40° C., 75% RH	Initial	RT 25° C., 60% RH	ACC 40° C., 75% RH	RT 25° C., 60% RH	ACC 40° C., 75% RH	RT** 25° C., 60% RH
Description	CCVS	CCVS	CCVS	CCVS	CCVS	WLP	WLP	WLP	WLP	WLP	WLP
Appearance after reconstitution	NA	NA	NA	NA	NA	CCS	CCS	CCS	CCS	CCS	CCS
Identification	$	$	$	$	$	$	$	$	$	$	$
pH*	9.5	9.9	9.9	9.8	9.7	9.8	9.8	9.8	9.8	9.8	10.0
% Assay of Phenobarbital Sodium	100.8	95.5	92.9	95.2	90.9	98.3	100.1	97.9	100.2	99.4	98.3
Related Substances (% Area) 2EPMM	ND	ND	BQL	BQL	BQL	ND	ND	ND	ND	ND	ND

TABLE 3-continued

130 mg/mL Liquid Formulation and 130 mg/vial Lyophilized formulation

PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	0.5	0.9	2.8	1.1	4.3	ND	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	ND	BQL	0.1	BQL	0.4	BQL	BQL	BQL	0.05	0.05	0.04
Total degradation products	0.5	0.9	2.9	1.1	4.7	BQL	BQL	BQL	0.05	0.05	0.04

CCVS: Clear Colorless Viscous Solution;
CCS: Clear Colorless Solution;
WLP: White Lyophilized powder
$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.
BQL: Below Quantitation Limit; (QL-0.05%);
ND: Not Detected
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-phenylbutyrylguanidine,
PEAU: phenylethylacetylurea or Pheneturide
*pH for liquid formulation is measured at 130 mg/mL and for lyophilized formulation at 100 mg/mL dilution
**The samples were stored at 30 ± 2° C., 65% RH ± 5

In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (e.g., 0.05% or less) of PEAU, 2 EPMM, or PBG.

According to contemplated embodiments, assaying the stability of the lyophilized Phenobarbital Sodium composition includes reconstituting the composition in water at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. For administration to an individual (e.g., a human patient) the lyophilized powder of Phenobarbital Sodium powder may be reconstituted in saline or dextrose as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution. In particular embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In preferred embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized Phenobarbital Sodium is a powder dose of 65 mg, 100 mg, 130 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection.

EXAMPLES

Lyophilization Microscopy. Lyophilization microscopy (FIGS. **1**A-**1**F) was performed using a Leica DM LP microscope equipped with a Linkam FDCS196 stage, TMS93 controller, vacuum pump, LNP unit, and a Spot Insight color camera. A 20×, 040 N.A. objective was used with crossed polarizers and a first order red compensator to view sample. Images were acquired using Spot Advanced software (v.4.5.9).

Lyophilization parameters for the lyophilization microscopy including a start temperature of −50° C. with heating at 1° C./minute to −40° C. followed by heating at 0.5° C./minute to −32.0° C.

HPLC Assays. High Performance Liquid Chromatography (HPLC) was used to assay Phenobarbital Sodium standards and sample solutions as disclosed herein (e.g., Tables 2, 3, FIGS. **3**A-**3**L, and **4**A-**4**L). Both Ultra High-Performance Liquid Chromatographic system (UHPLC) and High-Performance Liquid Chromatographic system (HPLC) (ThermoFisher/Waters) were used together with Data Acquisition Software (Empower 3), equipped with UV and Photodiode Array Detector (UV and PDA), column thermostat and auto sampler compartments or equivalent HPLC system and software.

An exemplary HPLC assay protocol is provided in the following:

Instruments/Apparatus: HPLC with UV detector/PDA Detector, Analytical balance, Sonicator, Volumetric flasks, Beakers, Pipettes.

Reagents, Solvents, Standards: Phenobarbital Reference Standard, Deionized water/Water for Injection, Potassium Monobasic Phosphate, Acetonitrile.

Preparation of Mobile Phase Solutions: Potassium phosphate monobasic (7 mM) and Acetonitrile (70:30) pH 4.5-6.5; Diluent: Mobile phase as a diluent.

Wash Solvent: Water:Acetonitrile (70:30)

CHROMATOGRAPHIC CONDITIONS: The liquid chromatography equipped with a UV and PDA detector, an injector and a data processor is operated as follows:

Parameters	Conditions
Column	L7 packaging column, 150 × 4.6 mm, Particle Size: 5 µm or equivalent
Flow rate	0.9-1.2 mL/min.
Detection Wavelength	254 ± 2 nm for assay and 210 ± 2 nm for Related Substances
Injection volume	10 µL
Run time	15 Minutes
Column Oven Temperature	30° C.
Sampler Cooler Temperature	25° C.

-continued

Parameters	Conditions
Retention Time	About 5 minutes for Phenobarbital
Pump Mode	Isocratic

Phenobarbital Assay Standard Solution: 0.2 mg/mL to 0.8 mg/mL in diluent; Phenobarbital Related Substances Standard Solution: 0.26 μg/mL to 15.6 μg/mL in diluent; Phenobarbital Related Substances resolution standard solution: 0.475 mg/mL Phenobarbital and about 1 μg/mL for related substances (2-Ethyl-2-Phenyl malonamide, monohydrate (2EPMM), Phenylbutyrylguanidine (PBG) and Phenylethylacetylurea (PEAU) in diluent; Phenobarbital Sodium Sample Solution for Assay: 0.26 mg/mL to 0.78 mg/mL in diluent

Phenobarbital Sodium related Substances sample solution: 0.52 mg/mL of Phenobarbital Sodium and related substances 2-Ethyl-2-Phenylmalonamide, monohydrate (2EPMM), Phenyl butyrylguanidine (PBG) and Phenylethylacetylurea (PEAU) and any unspecified degradation products at 0.26 μg/mL to 13.2 μg/mL

SYSTEM SUITABILITY REQUIREMENTS: The relative standard deviation of Phenobarbital peak from Six replication injections of related substances standard should not be more than 6.0%. The related standard deviation of Phenobarbital peak from five replicate injections in assay standard solution should not be more than 2.0%. Tailing factor for the Phenobarbital is not more than 2.0. USP Plate count for the Phenobarbital is not less than 2500. The S/N Ratio of the Sensitivity Standard Solution is NLT 10 for related substance test. The resolution between Phenobarbital peak and nearest impurity peak is NLT 1.5

Two alternative formulations are disclosed in Table 6. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

TABLE 6

Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

		NPH2031A (Bulk Solution @ 100 mg/ml Phenobarbital Sodium) Compounding at 2-8° C. Fill Volume: 2.1 mL		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8° C.	
Ingredients	Manufacturer	mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear			Wheaton Part#223686		
20 mm Igloo Bromobutyl stopper			Datwyler		
Seal 20 mm Filp-Cap, Red			Wheaton Part# 224203		

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (e.g., 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8° C. for 24 hrs and 3 to 4 hrs when stored at RT (see e.g., Tables 7, 8 and 9).

TABLE 7

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)

		Initial DOA:	Reconstituted Solution Stability after 20 hrs DOA: Jun. 6, 2020	
Test	Spec.	Jun. 5, 2020	2-8° C.	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS

TABLE 7-continued

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)

		Initial DOA:	Reconstituted Solution Stability after 20 hrs DOA: Jun. 6, 2020	
Test	Spec.	Jun. 5, 2020	2-8° C.	RT
pH (20 mg/mL)	9.2-10.2	9.9	9.7	9.8
% Assay Phenobarbital Sodium	90.0-105.0	100.1	100.1	100.1
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.24
Total degradation products	NMT 1.5%	BQL	0.09	0.27
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA
Note Book Reference		192045-163 to 189	192045-163-183	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 8

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)

			Reconstituted Solution Stability after 20 hrs	
Test	Specification	Initial	2-8° C.	RT
Description Appearance	WLP CCS	WLP CCS	WLP CCS	WLP CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.7	9.8
% Assay Phenobarbital Sodium	90.0-105.0	103.3	103.4	102.8
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	BQL
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.27
Total degradation products	NMT 1.5%	BQL	0.09	0.3

TABLE 8-continued

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)

			Reconstituted Solution Stability after 20 hrs	
Test	Specification	Initial	2-8° C.	RT
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA

WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 9

Reconstituted Solution Stability of Phenobarbital Sodium for injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)

		Time						
	Shelf life		2 hrs		4 hrs		24 hrs	
Tests	Specifications	Initial	2-8 C.	RT	2-8 C.	RT	2-8 C.	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.2-10.2	9.5	9.5	9.6	9.6	9.5	9.6	9.5
Assay of Phenobarbital Sodium	90.0%-105.0%	99.8	102.1	100.8	101.7	101.2	100.4	100.3
Related Substances (% Area)	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL
2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
PEAU	NMT 0.2%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Any unspecified degradation product @ RRT 0.37								
Total degradation products	NMT 1.5%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Osmolality mOsmol/Kg	To be reported	158	NP	NP	NP	NP	159	158

CCS: Clear colourless solution;
ND: Not detected;
BQL: Below Quantitation limit,
NP: Not performed;
2EPMM: 2-ethylphenylmalonamide monohydrate;
PBG: Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in Table 10. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in Table 11. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in Table 12. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in Table 13.

TABLE 10

Product Name	Phenobarbital Sodium for Injection USP, 65 mg/vial	Batch#NPH2020 Fill Volume: 1.05 mL	Date Manufactured: Jan. 20, 2020
Vial Make	2 mL Fiolax Clear Blow Back Vial (Schott, Article#1590892);		Date Initiated: Feb. 14, 2020
API Mfg.	Phenobarbital Sodium, USP Grade-P, C-IV: Siegfried USA, LLC Lot#1845X007; Re-test Date: Nov. 16, 2023		
Stopper Used	Aptar stelmi 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper (C1621 6730GC 6 TP3)		Flip Off Seals: Wheaton, 13 mm Red Plastic top flip off with Aluminum Seal, Lot#224202
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial	1 Month		3 Months		6 Months	
		DOA:	DOA: Mar. 29, 2020		DOA: May 20, 2020		DOA: Sep. 4, 2020	
Test	Spec.	Feb. 18, 2020	RT	ACC	RT	ACC	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.5	9.5
% Assay Phenobarbital Sodium	90.0%-105.0%	98.6	301.6	101.5	101.3	100.5	100.0	101.2

TABLE 10-continued

Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.6	0.9	1.3	1.4	1.5	1.5	2.1
Note Book Reference		192039-150 to 158	192046-23 to 45		192045-135 to 153		192051-84 to 122	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 11

Product Name	Phenobarbital Sodium for Injection USP, 65 mg/vial	Batch#NPH2020 Fill Volume: 1.05 mL	Date Manufactured: Jan. 20, 2020
Vial Make	2 mL Fiolax Clear Blow Back Vial (Schott, Article#1590892);		Date Initiated: Feb. 14, 2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV; Siegfried USA, LLC Lot#1845X007; Re-test Date: Nov. 16, 2023		
Stopper Used	Aptar stelmi 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper (C1621 6730GC 6 TP3)		Flip Off Seals: Wheaton, 13 mm Red Plastic top flip off with Aluminum Seal, Lot#224202
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

		Initial DOA:	1 Month DOA: Mar. 23, 2020		3 Months DOA: May 20, 2020		6 Months DOA: Sep. 4, 2020	
Test	Spec.	Feb. 18, 2020	RT	ACC	RT	ACC	RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.5	9.5
% Assay Phenobarbital Sodium	90.0%-105.0%	98.6	101.6	101.5	101.3	100.5	100.0	101.2
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.6	0.9	1.3	1.4	1.5	1.5	2.1
Note Book Reference		192039-150 to 158	192045-23 to 45		192045-135 to 153		192051-84 to 122	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 12

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial	Batch#NPH2031A Fill Volume: 2.1 mL		Date Manufactured: Jun. 3, 2020
Vial	10 mL Tubular Serum Bottle Clear			Date Initiated:
Make	Wheaton, Part# 223586; Batch#5192875);			Jun. 9, 2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1924X009; Re-test Date: Jul. 20, 2024			
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper		Flip Off Seals: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203	
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)	

		Initial DOA:	3 Months DOA: Sep. 4, 2020	
Test	Spec.	Jun. 5, 2020	RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7
% Assay Phenobarbital Sodium	90.0-105.0	100.1	98.1	101.0
Related Substances (% Area)	NMT 0.2%	ND	ND	ND
2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5%	BQL	0.09	0.09
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3
Note Book Reference		192045-163 to 189	192051-84 to 122	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

TABLE 13

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial	Batch#NPH2031A Fill Volume: 2.1 mL		Date Manufactured: Jun. 3, 2020
Vial	10 mL Tubular Serum Bottle Clear			Date Initiated:
Make	Wheaton, Part# 223586; Batch#5192875);			Jun. 9, 2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1924X009; Re-test Date: Jul. 20, 2024			
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper		Flip Off Seals: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal, Lot#224203	
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)	

		Initial DOA:	3 Months DOA: Sep. 4, 2020	
Test	Spec.	Jun. 5, 2020	RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5
% Assay Phenobarbital Sodium	90.0-105.0	103.3	102.8	103.6
Related Substances	NMT 0.2%	BQL	ND	ND

TABLE 13-continued

(% Area) 2EPMM				
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.00	0.05
Total degradation products	NMT 1.5%	BQL	0.1	0.08
Water Content by Karl Fischer	NMT 3.0%	0.8	0.9	1.1
Note Book Reference		192045-163 to 189	192051-84 to 122	

DOA: Date of Analysis;
WLP: White Lyophilized Powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected;
NMT: Not More Than;
BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-Phenylbutyrylguanidine;
PEAU: Phenylethylacetylurea

Data for Osmolality, Particulate matter and assay for Sodium Chloride is disclosed in Table 14.

TABLE 14

Phenobarbital Sodium for Injection, USP, 200 mg/vial in Water or Sodium Chloride - Osmolality, Particulate Matter and Assay for Sodium Chloride.

Batch No	Osmolality* (mOsmol/Kg) (Specification: To be reported) Reconstitution in 10 mL (20 mg/mL)	Particulate Matter (By Light Obscuration method) Ref: USP<788> ≥10 μM Specification: (NMT 6000 particles/vial)	≥25 μM Specification: (NMT 600 particles/vial	Assay of Sodium Chloride (titrimetric; Ref USP monograph for Sodium Chloride Injection Specification: (95.0%-105.0%)
NPH2031A (200 mg/vial)	148	80.0	0.67	NA
NPH2031B (200 mg/vial) (Phenobarbital Sodium 200 mg, 9% Sodium Chloride)	372	171	1.33	99.99
Water-Blank	0	NA	NA	NA
0.9% Sodium Chloride	270	NA	NA	NA

Lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial and 200 mg/vial are disclosed in Table 15.

TABLE 15

Lyophilization Cycle parameters.

		Lyophilization Cycle 1*				Lyophilization Cycle 2**			
Section	Phase	Condenser set point C.	Vacuum [mTorr]	Temperature ° C.	Hold Time [mm]	Condenser set point ° C.	Vacuum [mTorr]	Temperature ° C.	Hold Time [mm]
1	Loading		off	5	n.a.		off	−5	n.a.
2	Freezing		off	−5	5		off	−5	10
3	Freezing		off	−50	60		off	−52	120 (Ramp)

TABLE 15-continued

Lyophilization Cycle parameters.

		Lyophilization Cycle 1*				Lyophilization Cycle 2**			
Section	Phase	Condenser set point C.	Vacuum [mTorr]	Temperature ° C.	Hold Time [mm]	Condenser set point ° C.	Vacuum [mTorr]	Temperature ° C.	Hold Time [mm]
4	Freezing		off	−10	30		off	−52	180 (Hold)
5	Freezing		off	−50	120		n.a.	n.a.	n.a.
6	Evacuation	−50	75	−50	30	−60	50	−45	30
7	Primary drying		75	−50	400 (Hold)		50	−42	100 (Ramp)
8	Primary drying		75	−45	350 (Hold)		50	−42	1120 (Hold)
9	Primary drying		75	−43	300 (Hold)		n.a.	n.a.	n.a.
10	Primary drying		75	−35	250 (Hold)		n.a.	n.a.	n.a.
11	Primary drying		75	−20	60 (Hold)		n.a.	n.a.	n.a.
12	Primary drying		75	0	120 (Hold)		n.a.	n.a.	n.a.
13	secondary drying		75	50	120 (Hold)		50	35	100 (Ramp)
14	secondary drying		75	25	120 (Hold)		50	35	420 (Hold)

Lyophilization Cycle 1*: 65 mg/vial, 130 mg/vial and 100 mg/vial samples disclosed in Tables 1, 2, 3, 16 and 17

Lyophilization Cycle 2**: NPH2031A (200 mg/vial Phenobarbital Sodium) and NPH2031B (200 mg/vial in Phenobarbital Sodium and 90 mg/vial Sodium Chloride, NPH2020 (65 mg/vial) and NPH2021 (130 mg/vial)

Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

TABLE 16

Product Name	Phenobarbital Sodium for Injection USP, 100 mg/vial	Batch#NPH1980	Date Manufactured: Sep. 25, 2019
Vial Make	5 mL Clear Untreated Article#9621139054 5 mL Clear Treated Article#9621130486		Date Initiated: Sep. 30, 2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1845X006; Re-test Date: Nov. 16, 2023		
Stopper Used	Aptar stelmi 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper, Lot#G702/91884		Flip Off Seals: Wheaton, 13 mm Red Plastic top flip off with Aluminum Seal, Lot# NA
Configuration	Inverted	Stability	25° C., 60% RH (RT) & 40° C., 75% RH (ACC)

				1 Month				3 Months				6 Months			
		Initial		RT		ACC		RT		ACC		RT		ACC	
Test	Spec.	UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UT	T
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.5	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9
% Assay Phenobarbital Sodium	90.0%-105.0%	98.4	97.8	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9	97.7	98.3	97.2	97.6
Related Substances (% Area)	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	ND	ND	ND	ND
2EPMM															
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	0.05	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL

TABLE 16-continued

Water Content by Karl Fischer	NMT 3.0%	0.7	0.6	1.0	1.0	1.1	1.3	1.2	1.1	1.6	1.5	1.6	1.2	1.5	2.0
Note Book Reference		192031-91 to 101			192031-169 to 183				192039-44 to 52				192045-52 to 85		

WLP: White Lyophilized powder;
CCS: Clear Colorless Solution, 1 minute after reconstitution;
UT: Untreated;
T: Treated
ND: Not Detected;
NMT: Not More Than;
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate;
PBG: α-Phenylbutyrylguanidine;

TABLE 17

Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

Ingredients	Manufacturer/Lot number	Concentration (mg/mL)	Concentration (mg/vial)	Batch Quantity (100 mL)
Phenobarbital Sodium, USP Grade P C-IV	Siegfried USA, LLC Mat No: 300040 Lot# 1845X006 Retest date: Nov. 16, 2023	101.13 mg (~100 mg Phenobarbital Sodium after LOD correction	100 mg	10.113 g
Water for Injection	In house	Q.S. to 1 mL	NA	Q.S. to 100 mL or 103.3 g
100% Nitrogen	Airgas	NA	NA	NA
5 mL, untreated	Gerresheimer Article#9621139054	NA	NA	NA
5 mL, treated	Gerresheimer Article#9621130486	NA	NA	NA
13 mm Bromobutyl Lyophilization stoppers	Aptar-Stelmi C16216720GC6TP3	NA	NA	NA
Seal: 13 mm Seal, Flip-Cap, Red	Wheaton Unlined	NA	NA	NA

Diluents that can be used: Water for Injection, 0.9% Saline or 5% Dextrose
Proposed Reconstitution Volume: 5 mL

Representative chromatograms and/or corresponding calculations are shown in FIGS. **2A-211**, **3A-3L**, **4A-4L**, and Tables 2 and 3.

X-Ray Powder Diffraction. With reference to FIGS. **5A-5D**, XRPD was performed using the Rigaku Smart-Lab X-ray diffraction system configured for reflection Bragg-Brentano geometry using a line source X-ray beam. The x-ray source is a Cu Long Fine Focus tube that was operated at 40 kV and 44 mA. That source provides an incident beam profile at the sample that changes from a narrow line at high angles to a broad rectangle at low angles. Beam conditioning slits were used on the line X-ray source to ensure that the maximum beam size is less than 10 mm both along the line and normal to the line. The Bragg-Brentano geometry is a para-focusing geometry controlled by passive divergence and receiving slits with the sample itself acting as the focusing component for the optics. The inherent resolution of Bragg-Brentano geometry is governed in part by the diffractometer radius and the width of the receiving slit used. Typically, the Rigaku Smart-Lab is operated to give peak widths of 0.1° 2θ or less. The axial divergence of the X-ray beam is controlled by 5.0-degree Soller slits in both the incident and diffracted beam paths. The samples were placed in a low-background, silicon holder using light manual pressure to keep the sample surfaces flat and level with the reference surface of the holder. The samples were analyzed from 2 to 40° 2θ using a continuous scan of 6° 2θ per minute with an effective step size of 0.02° 2θ.

The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided with respect to certain embodiments herein is intended merely to better illuminate the full scope of the present disclosure, and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the claimed invention.

It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the full scope of the concepts disclosed herein. The disclosed subject matter, therefore, is not to be restricted except in the scope of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that

are not expressly referenced. Where the specification claims refers to at least one of something selected from the group consisting of A, B, C . . . and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc.

What is claimed is:

1. A method of producing a storage-stable form of lyophilized amorphous phenobarbital sodium composition, comprising:

adding phenobarbital sodium to water to form a phenobarbital sodium solution having a pH of between 9.2 and 10.2, wherein the phenobarbital sodium solution does not contain an organic solvent, and wherein the phenobarbital sodium solution optionally further comprises sodium chloride;

lyophilizing the phenobarbital sodium solution in a container under a protocol comprising a freezing step, a primary drying step, and a secondary drying step to thereby produce the lyophilized amorphous phenobarbital sodium composition;

wherein the freezing step comprises freezing the lyophilized amorphous phenobarbital sodium to a temperature of about −50° C. without application of vacuum;

wherein the primary drying step comprises application of vacuum at a pressure of between about 50 mTorr and 75 mTorr at a temperature of between about −50° C. and about 0° C. for at duration of at least 1,000 minutes;

wherein the secondary drying step comprises application of vacuum at a pressure of between about 50 mTorr and 75 mTorr at a temperature of between about 25° C. and about 50° C. for at duration of at least 200 minutes;

wherein the lyophilized amorphous phenobarbital sodium has an initial moisture content of equal or less than 1.5%; and

wherein the lyophilized amorphous phenobarbital sodium forms, upon storage over 3 months, no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution.

2. The method of claim **1**, wherein the sodium chloride is present in the phenobarbital sodium solution in an amount that, upon reconstitution of the lyophilized amorphous phenobarbital sodium in the aqueous solution, yields a sodium chloride concentration of 0.9% in the reconstituted solution.

3. The method of claim **1**, wherein the phenobarbital sodium solution in the container is present in an amount of about 65 mg, or about 100 mg, or about 130 mg, or about 200 mg.

4. The method of claim **1**, wherein the water is sparged with nitrogen.

5. The method of claim **1**, wherein the phenobarbital sodium solution does not contain a preservative.

6. The method of claim **1**, wherein the primary drying step is performed using at increasing temperatures that increase from about −50° C. to about 0° C. when the amount of phenobarbital sodium in the container is between 65 mg and 130 mg.

7. The method of claim **1**, wherein the primary drying step is performed using at constant temperature of about −42° C. when the amount of phenobarbital sodium in the container is 200 mg.

8. The method of claim **1**, wherein the secondary drying step is performed using at decreasing temperatures that decrease from about 50° C. to about 25° C. when the amount of phenobarbital sodium in the container is between 65 mg and 130 mg.

9. The method of claim **1**, wherein the secondary drying step is performed using at constant temperature of about 35° C. when the amount of phenobarbital sodium in the container is 200 mg.

10. The method of claim **1**, wherein the lyophilized amorphous phenobarbital sodium has an initial moisture content of equal or less than 1.2%.

11. The method of claim **1**, wherein the lyophilized amorphous phenobarbital sodium has an initial moisture content of equal or less than 1.0%.

12. The method of claim **1**, wherein the lyophilized amorphous phenobarbital sodium forms, upon storage over 3 months, no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution.

13. The method of claim **1**, wherein the lyophilized amorphous phenobarbital sodium forms, upon storage over 3 months, no detectable quantities of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution.

14. The method of claim **1**, wherein the storage is at 40° C. and 75% relative humidity.

15. The method of claim **1**, wherein the lyophilized amorphous phenobarbital sodium composition contains at least 98% lyophilized amorphous phenobarbital sodium.

* * * * *

Bibliographic Data

Application No: 17/025,881

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☑ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /CARLOS A AZPURU/ (Examiner's Signature) | (Initials)

Title: Lyophilized Compositions of Phenobarbital Sodium Salt

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
09/18/2020	424	1617	104078.0001US
RULE			

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CONTINUING DATA

This application has PRO of 62903511 09/20/2019

FOREIGN APPLICATIONS

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Electronic Acknowledgement Receipt	
EFS ID:	40605917
Application Number:	17025881
International Application Number:	
Confirmation Number:	8113
Title of Invention:	LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT
First Named Inventor/Applicant Name:	Bala Tripura Sundari CHODAVARAPU
Customer Number:	149344
Filer:	Martin Fessenmaier/Danielle Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	104078.0001US
Receipt Date:	18-SEP-2020
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Deposit Account	601823
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.21 (Miscellaneous fees and charges) 37 CFR 1.20 (Post Issuance fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.16 (National application filing, search, and examination fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	TrackOne Request	Track1_REQ.pdf	114760 688c82ff2e797444d8a20779f03417a35ff97253	no	2
Warnings:					
Information:					
2	Application Data Sheet	ADS.pdf	1874404 a0cec4b89311f7134f78f7bab57d47a9d3facd79	no	9
Warnings:					
Information:					
3		APP_2020-09-17_REV007.pdf	6691939 74e49f8bc7aca0596661f7c9054dacac5d1b9a7a	yes	79

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	36
Claims	37	39
Abstract	40	40
Drawings-other than black and white line drawings	41	79

Warnings:					
Information:					
4	Oath or Declaration filed	Declaration_Anand_Shukla_Signed.pdf	918348 c217b012984bc6a79e3043e7aaf889cefa3fc179	no	1
Warnings:					
Information:					

5	Oath or Declaration filed	Declaration_Chodavarapu_Signed.pdf	939567 cad9906878198c2cf2a82743a4721f4915d6f c158	no	1
Warnings:					
Information:					
6	Oath or Declaration filed	Declaration_Jay_Shukla_Signed.pdf	918558 9a1678ac210d93109a6ab82458df5438a ca685	no	1
Warnings:					
Information:					
7	Oath or Declaration filed	Declaration_Lakkaraju_Signed.pdf	927594 73fb762ef11c490c49c2b4ce319d07af07ac 2105	no	1
Warnings:					
Information:					
8	Oath or Declaration filed	Declaration_Mangali_Signed.pdf	925855 1d88dced4fb109af2b7e911d821324fecae8 c5d3a	no	1
Warnings:					
Information:					
9	Fee Worksheet (SB06)	fee-info.pdf	39941 ab5e4d1ee35fa7c4ff94a2397fd69caa010fe cec	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	13350966		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Bala Tripura Sundari Chodavarapu	Nonprovisional Application Number (if known):	
Title of Invention:	Lyophilized Compositions of Phenobarbital Sodium Salt		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Martin Fessenmaier/	Date September 18, 2020
Name (Print/Typed) Martin Fessenmaier	Practitioner Registration Number 46697

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☑ *Total of 1 forms are submitted.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Bala	Tripura Sundari	Chodavarapu	

Residence Information (Select One) • US Residency ○ Non US Residency ○ Active US Military Service

City	Davis	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle
Address 2	Suite 100

City	Sacramento	State/Province	CA
Postal Code	95827	Country	US

Inventor 2 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Thirupathi		Mangali	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Sacramento	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle
Address 2	Suite 100

City	Sacramento	State/Province	CA
Postal Code	95827	Country	US

Inventor 3 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Jay		Shukla	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

City	Sacramento	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle		
Address 2	Suite 100		
City	Sacramento	State/Province	CA
Postal Code	95827	Country	US

Inventor 4 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Anand		Shukla	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Denver	State/Province	CO	Country of Residence	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle		
Address 2	Suite 100		
City	Sacramento	State/Province	CA
Postal Code	95827	Country	US

Inventor 5 — Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Dasaradhi		Lakkaraju	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Sacramento	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	3050 Fite Circle		
Address 2	Suite 100		
City	Sacramento	State/Province	CA
Postal Code	95827	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. — Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Customer Number	149344		
Email Address	patents@umbergzipser.com	Add Email	Remove Email

Application Information:

Title of the Invention	Lyophilized Compositions of Phenobarbital Sodium Salt		
Attorney Docket Number	104078.0001US	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	39	Suggested Figure for Publication (if any)	

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	• Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	149344		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Claims benefit of provisional	62903511	2019-09-20

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 — Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

• Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Nivagen Pharmaceuticals, Inc.		
Mailing Address Information For Applicant:			
Address 1	3050 Fite Circle, Suite 100		
Address 2			
City	Sacramento	**State/Province**	CA
Country	US	Postal Code	95827
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☒

Organization Name	Nivagen Pharmaceuticals, Inc.

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1	3050 Fite Circle, Suite 100		
Address 2			
City	Sacramento	**State/Province**	CA
Country	US	Postal Code	95827
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Martin Fessenmaier/			Date (YYYY-MM-DD)	2020-09-18
First Name	Martin	Last Name	Fessenmaier	Registration Number	46697

Additional Signature may be generated within this form by selecting the Add button. Add

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	104078.0001US
	Application Number	
Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT

Related Applications

[0001] This application claims the benefit of United States Provisional Patent Application No. 62/903,511, filed on September 20, 2019, which is incorporated by reference in its entirety.

Field of the Invention

[0002] The present disclosure relates to compositions of storage-stable lyophilized Phenobarbital Sodium having high purity that are essentially void of impurities upon reconstitution in water.

Background of the Invention

[0003] The background description includes information that may be useful in understanding the present disclosure. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0004] All publications and patent applications herein are incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Where a definition or use of a term in an incorporated reference is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

[0005] Phenobarbital Sodium is a well-known barbiturate that is most commonly administered as an anti-convulsant for the treatment of seizures and may also be administered as a sedative, a sleep aide, or a pre-anesthetic. Phenobarbital Sodium is typically a liquid formulation administered intramuscularly (IM) or intravenously (IV) with crystalline granules or crystals dissolved in an aqueous solvent. For example, WO 2017/085687 to Parker et al. discloses a liquid formulation of Phenobarbital Sodium dissolved in water along with a C1-C4 alcohol and a glycol.

[0006] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, in water alone or in water with an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). While these degradation impurities may not directly compromise the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate.

[0007] Over the years of medical administration, efforts have been made to decrease the formation of the toxic degradation products in the Phenobarbital Sodium liquid formulation. For example, Gupta, V.D., (*J. Pharm Sci.*, 1984, 73:1661-1662) describes the effects of ethanol, glycerol, and propylene glycol on the stability of Phenobarbital Sodium in aqueous solutions. Specifically, Gupta discloses that ethanol has the best effect followed by propylene glycol and glycerol relative to water alone. Years after Gupta, Parker et al., (WO 2017/085687) focused on minimizing the total amount of water to reduce the hydrolysis and consequently the formation of the degradation products. Parker addresses the hydrolysis issue by limiting the amount of water (*e.g.*, to no more than 50 mg/mL) in the liquid formulation. Parker's minimized water formulations also include a C1-C4 alcohol such as ethanol and a glycol such as propylene glycol. However, while the amount of impurities in Parker's liquid formulation may have decreased compared to prior formulations, impurities such a PEAU are still present in undesirable amounts, particularly after extended storage.

[0008] In addition to the degradation impurities, the current marketed liquid formulation of Phenobarbital Sodium (*e.g.*, Phenobarbital Sodium for Injection USP, 65 mg/mL or130 mg/mL), includes organic solvents such as alcohol, which are not desirable in general and indeed not suitable for administration to newborns as described in the art, *e.g.*, Williams et al., 1998, "Evaluating Toxic Alcohol Poisoning in the Emergency Setting," *Laboratory Medicine*, Vol. 29,

No. 2; Wood et al., 2007, *J. of Perinatology*, 27:183-185; Kumar, 1985, "Adverse Drug Reactions in the Newborn," *Annals of Clin. And Lab. Sci*, Vol. 15, No. 3; and Cuzzolin, 2018, *J. Pediatric and Neonatal Individualized Med.*, doi:10.7363/070112.

[0009] Accordingly, there is still a need for a stable Phenobarbital Sodium formulation in a formulation that is storage stable and void or essentially void of degradation impurities upon solubilization in water.

Summary

[0010] Disclosed herein are compositions of, methods of producing, and use of a lyophilized Phenobarbital Sodium formulation. The contemplated composition is an amorphous lyophilized Phenobarbital Sodium with high stability and purity. The lyophilized composition may include no less than 98% Phenobarbital Sodium. The amorphous composition is a storage-stable form of lyophilized Phenobarbital Sodium.

[0011] The lyophilized amorphous formulation that was produced resulted in surprising, unexpected and desirable results. The quantity of undesirable and/or toxic degradation impurities that are produced from this formulation are less than those in current commercial products. And the stability of this formulation is superior to that of current commercial products. These results are particularly surprising and unexpected in view of the fact that conventional wisdom teaches that crystalline material is more stable than amorphous material (see *e.g.*, C. Ahlneck and G. Zografi "The Molecular Basis for Moisture Effects on the Physical and Chemical Stability of Drugs in the Solid-State," Int. J. Pharm. 1990, 62, 87-95). Thus, one of ordinary skill in the art would want to avoid using amorphous material in pharmaceutical formulations.

[0012] Preferably the percentage of the lyophilized formulation that is amorphous is at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95%. Alternatively, the percentage of the lyophilized formulation that is amorphous can be 100%. In addition, the percentage of the lyophilized formulation that is amorphous can be within any range between (and including) 20% to 100% (*e.g.*, 20%-100%, 25%-95%. etc.).

[0013] Methods for producing the storage-stable form of lyophilized Phenobarbital Sodium composition result in a lyophilized powder in which the impurity phenylethylacetylurea (PEAU)

is below detection limit and is never more than 0.2% of the specification limit even after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions (40 °C, 75% RH). In some embodiments, the method for producing the storage-stable lyophilized Phenobarbital Sodium includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, having a pH between 9.2 to 10.2, and lyophilizing the bulk solution. In some embodiments, the water is Water for Injection.

[0014] In preferred embodiments, the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (*e.g.*, Water for Injection) is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium.

[0015] For adjusting the pH of the Phenobarbital Sodium solution, the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition may also include measuring the pH of the Phenobarbital Sodium solution, wherein if the pH is higher than 10.2, the adjusting includes adding hydrochloric acid (HCl).

[0016] Typically, the resulting lyophilized Phenobarbital Sodium forms no more than 0.1% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months both at RT and accelerated stability conditions. More typically, the resulting lyophilized Phenobarbital Sodium forms no more than 0.05% PEAU when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and under accelerated stability conditions (40°C). Additionally, or alternatively, the resulting lyophilized Phenobarbital Sodium forms either an amount below the quantitative limit (BQL, 0.05%) or no detectable amount of PEAU, 2-ethyl-2-phenylmalonamide (2EPMM), or alpha-phenylbutyrylguanidine (PBG) when reconstituted in the aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at RT and accelerated stability conditions.

[0017] According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments,

the stability of the lyophilized Phenobarbital Sodium is determined by reconstituting the lyophilized Phenobarbital Sodium in an aqueous solution and measuring the amount of or the presence of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG).

[0018] Additional embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is filtered prior to lyophilization.

[0019] Further embodiments include the method for producing the storage-stable form of lyophilized Phenobarbital Sodium composition as disclosed in which the Phenobarbital Sodium solution is aliquoted into a vial prior to lyophilization, and after lyophilization, a closure is applied to the vial under vacuum.

[0020] Aspects of the present disclosure also include a method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution, in which the method includes adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2, and lyophilizing the Phenobarbital Sodium solution to form stable white lyophilized powder of Phenobarbital Sodium.

[0021] In preferred embodiments, the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (e.g., Water for Injection) is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium.

[0022] For adjusting the pH of the Phenobarbital Sodium solution, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution may also include measuring the pH of the Phenobarbital Sodium solution, wherein if the pH is higher than 10.2, the adjusting includes adding Hydrochloric acid (HCl).

[0023] In typical embodiments, the degradation products of Phenobarbital Sodium reconstituted in an aqueous solution include phenylethylacetylurea (PEAU), 2-ethyl-2-

phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and analysis of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and quantitating the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution.

[0024] In typical embodiments, the method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In some preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium, and in other preferred embodiments between 95% and 105% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no more than 0.2% PEAU, 2 EPMM, and/or PBG, and preferably has 0.05% or less PEAU and no detectable amount of 2 EPMM or PBG.

[0025] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. These methods include adding saline or dextrose to the lyophilized powder of Phenobarbital Sodium as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution and administering the Phenobarbital Sodium reconstituted solution to the individual. In some embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In particular embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized amorphous Phenobarbital Sodium is a powder dose of 65 mg, 130 mg, 100 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection.

[0026] Additional aspects of the present disclosure include a pharmaceutical product including a vial containing the white lyophilized powder of Phenobarbital Sodium for reconstitution prior to administration, in which the composition was lyophilized in the vial and the vial includes a closure positioned in order to seal the vial under vacuum after Lyophilization.

[0027] Therefore, the inventors also contemplate lyophilized Phenobarbital Sodium.

[0028] Various objects, features, aspects, and advantages will become more apparent from the following detailed description of preferred embodiments, along with the accompanying drawings.

Brief Description of Drawings

[0029] **Fig. 1A** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -50°C, as indicated.

[0030] **Fig. 1B** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -45.5°C as indicated.

[0031] **Fig. 1C** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -40.0°C as indicated.

[0032] **Fig. 1D** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -39.6°C as indicated.

[0033] **Fig. 1E** is a **polarized** light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -39.2°C as indicated.

[0034] **Fig. 1F is** a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during Lyophilization microscopy at -38.8°C as indicated.

[0035] **Fig. 2A** is a chromatogram from an injection of a "blank solution" for assay by high performance liquid chromatography (HPLC) at a detection wavelength of 210 nanometers (nm), as described herein.

[0036] **Fig. 2B** is a chromatogram from an injection of the "Sensitivity solution" of Phenobarbital for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0037] **Fig 2C** is a chromatogram from an injection of a "related substance" (RS) working standard at 0.2% impurity level) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0038] **Fig. 2D** is a chromatogram from an injection of 2-ethyl-2-phenylmalonamide (2EPMM) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0039] **Fig. 2E** is a chromatogram from an injection of alpha-phenylbutyrylguanidine (PBG) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0040] **Fig. 2F** is a chromatogram from an injection of phenylethylacetylurea (PEAU) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0041] **Fig. 2G** is a chromatogram from an injection of a "blank solution" for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0042] **Fig. 2H** is a chromatogram from an injection of an "assay working standard" for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0043] **Fig. 3A** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0044] **Fig. 3B** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0045] **Fig. 3C** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0046] **Fig. 3D** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0047] **Fig. 3E** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0048] **Fig. 3F** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0049] **Fig. 3G** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0050] **Fig. 3H** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0051] **Fig. 3I** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, as described herein.

[0052] **Fig. 3J** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0053] **Fig. 3K** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0054] **Fig. 3L** is a chromatogram from an injection of a marketed liquid formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0055] **Fig. 4A** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0056] **Fig. 4B** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0057] **Fig. 4C** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0058] **Fig. 4D** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0059] **Fig. 4E** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0060] **Fig. 4F** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 65 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0061] **Fig. 4G** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0062] **Fig. 4H** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0063] **Fig. 4I** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for assay by HPLC at a detection wavelength of 254 nm, according to embodiments of the present invention.

[0064] **Fig. 4J** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at initial time point for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0065] **Fig. 4K** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at room temperature (RT) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0066] **Fig. 4L** is a chromatogram from an injection of the disclosed reconstituted lyophilized formulation of Phenobarbital Sodium at 130 mg/mL at 6 months from initial time point at accelerated stability conditions (ACC) for related substances by HPLC at a detection wavelength of 210 nm, according to embodiments of the present invention.

[0067] **Fig. 5A** is an X-ray powder diffraction (XRPD) pattern of Phenobarbital Sodium Grade P

[0068] **Fig. 5B** is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 65 mg/vial.

[0069] **Fig. 5C** is an XRPD pattern of Phenobarbital Sodium for Injection, USP, 130 mg/vial.

[0070] **Fig. 5D** is a stack plot of the XRPD patterns of **Figs. 5A**, **5B**, and **5C**.

Detailed Description

[0071] The inventors have surprisingly discovered a method for making a storage-stable and highly purified Phenobarbital Sodium composition that is void of any detectable impurities in its lyophilized powder form and is essentially void of impurities upon reconstitution in water. The contemplated Phenobarbital Sodium composition is a lyophilized powder that is no less than 98% Phenobarbital Sodium and is stable (25 °C, 65% RH and 40 °C, 75% RH) for up to at least 6

months under accelerated conditions which is equivalent to 24 months at RT. Upon reconstitution *(e.g.* solubilization/resuspension) in water, the lyophilized Phenobarbital Sodium forms no more than 0.05% of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

[0072] The Phenobarbital Sodium composition as described herein refers to Phenobarbital Sodium having an IUPAC (International Union of Pure and Applied Chemistry) name of sodium 5-ethyl-4,6-dioxo-5-phenyl-1*H*-pyrimidin-2-olate, a Chemical Abstract Service (CAS) No. 57-30-7, and a molecular formula of $C_{12}H_{11}N_2NaO_3$.

[0073] In order to avoid hydrolysis of Phenobarbital Sodium and therefore the formation of its toxic degradation products, the inventors have unexpectedly discovered that a lyophilized Phenobarbital Sodium formed by the methods disclosed herein results in a storage-stable lyophilized powder of Phenobarbital Sodium. In particular, with reference to the polarized light photomicrographs of **Figs. 1A-1F** and the XRPD analysis shown in **Fig 5A-5D**, the storage-stable lyophilized powder of Phenobarbital Sodium has an amorphous structure. Without wishing to be bound by any theory or hypothesis, the lyophilized Phenobarbital Sodium produced following the methods according to embodiments of the present disclosure produces an amorphous structure that contributes to the observed stability of this composition upon reconstitution in water. Irrespective of the mechanism of action, the contemplated lyophilized Phenobarbital Sodium composition is stable and upon reconstitution in water, does not form significant (*e.g.,* not measurable or not detectable) amounts of the toxic degradation products—namely PEAU, 2EPMM, or PBG.

[0074] The contemplated method for producing a storage-stable lyophilized Phenobarbital Sodium composition includes adding purified Phenobarbital Sodium to water. Preferably the purified Phenobarbital Sodium solid is purchased from a chemical supplier (*e.g.,* Siegfried, USA) that adheres to the United States Pharmacopeia (USP) manufacturing and synthesis guidelines. The USP grade of the Phenobarbital Sodium is preferably USP "purified" or "practical" (P) grade indicating that it is a good quality chemical. As understood in the art, the USP grade (P) active pharmaceutical ingredient (API) of Phenobarbital Sodium is not suitable for administration because it is not sterile, is hygroscopic, and as such, maintaining anhydrous conditions of this grade of API is not feasible. Structurally, the analyzed USP grade P API (Siegfried, USA) is

polymorphous—containing both crystalline and non-crystalline material. With reference to **Fig. 5A**, an X-ray powder diffraction (XRPD) pattern is shown of this compound.

[0075] Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to Water for Injection and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O_2) gas from the water (*e.g.*, Water for Injection), it is also preferred that the water is sparged with nitrogen (N_2) or other inert gas prior to the addition of the Phenobarbital Sodium solid. For effective sparging, a volume of about 100-200 ml water is sparged with nitrogen gas for at least 30 minutes. In exemplary protocols for producing either 65 mg, 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of Water for Injection is nitrogen sparged for 30 minutes. In additional embodiments, the water may also be cooled to approximately 2 to 8°C. In preferred embodiments, the water is cooled to approximately 2 to 8°C.

[0076] The addition of the Phenobarbital Sodium solid to the water (*e.g.*, deionized nitrogen sparged water cooled to 2 to 8°C) may be carried out using any suitable mixing. Preferably, the water (*e.g.*, Water for Injection) is first added to a glass/stainless steel container for nitrogen sparging and cooling, and this prepped water remains in the glass/stainless steel container or a measured amount is transferred to a preferably weighed glass container/stainless steel container and the Phenobarbital Sodium solid is added thereto. For mixing, any suitable mixing may be used. For example, a magnetic stir bar may be added to the glass/stainless steel container. Upon addition of the Phenobarbital Sodium solid to the water, the mixture is stirred.

[0077] An additional consideration for stability of the Phenobarbital Sodium is maintaining a pH between 9.2 and 10.2 in the bulk solution of Phenobarbital Sodium. After dissolution of the Phenobarbital Sodium solid in the water, the pH is adjusted to within this range of 9.2 and 10.2. Accordingly, the pH of the water solubilized Phenobarbital Sodium is first measured upon dissolution. If the pH is higher than 10.2 or lower than 9.2, the pH is adjusted. For example, if necessary, the pH may be lowered to or between 9.2 and 10.2 using Hydrochloric acid (HCl) and the pH may be increased to or between 9.2 and 10.2 using Sodium Hydroxide (NaOH).

[0078] Following the pH measurement and any adjustment, the Phenobarbital Sodium solution is preferably filtered to remove any foreign particles. For example, the Phenobarbital Sodium

solution may be filtered using a 0.2 μm (or 0.22 μm) membrane filter. For example, the membrane filter may be polyvinylidene difluoride (PVDF) or any other compatible filter membranes such as Polyethersulfone (PES) filter.

[0079] According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (*e.g.*, nitrogen sparged Water for Injection cooled to 2 to 8°C) having a pH of or between 9.2 and 10.2 and preferably filtered is ready for Lyophilization. Depending on the desired amount of the lyophilized Phenobarbital Sodium product, the Phenobarbital Sodium solution may be lyophilized in any amount or the solution may be aliquoted into sterile containers (*e.g.*, vials). For example, in order to obtain a measured dose of lyophilized Phenobarbital Sodium in a container, the glass container, water, and Phenobarbital Sodium solid are weighed prior to mixing in order to determine an actual weight of the Phenobarbital Sodium after pH measurement and adjustment. For example, to produce 65 mg or 130 mg doses of lyophilized Phenobarbital Sodium, a batch may be dissolved, mixed, pH adjusted if necessary, and filtered and then aliquoted into single use dose vials for lyophilization. In a specific example, a 50 mL batch of Phenobarbital Sodium solution may be prepared where for 65 mg doses, 3.25 grams of Phenobarbital Sodium solid (*e.g.*, USP Grade P) is added to 40 ml of water (*e.g.*, nitrogen sparged Water for Injection cooled to 5 to 8°C) and for 130 mg doses, 6.5 grams of the Phenobarbital Sodium is added to the 40 ml of water. Following dissolution, pH adjustment if necessary, adjusting final volume to 50.0 mL and filtering, 1 ml aliquots of this Phenobarbital Sodium solution are added to open (*e.g.*, unstoppered) vials and then loosely stoppered (e.g., with lyophilization rubber stoppers) prior to lyophilization. Following lyophilization, each vial contains 65 mg or 130 mg of lyophilized Phenobarbital Sodium.

[0080] In further embodiments, following lyophilization, the vials may be completely closed (e.g., stoppered) under vacuum.

[0081] Another embodiment is directed to a pharmaceutical composition that consists of lyophilized amorphous Phenobarbital Sodium.

[0082] Another embodiment is directed to a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. The method comprising: includes adding Phenobarbital

Sodium to water to form a Phenobarbital Sodium solution, if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution.

[0083] In one embodiment, the water is Water for Injection.

[0084] In another embodiment the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium.

[0085] In another embodiment, the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium.

[0086] In another embodiment, the water is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium.

[0087] In another embodiment, the adjusting includes measuring the pH of the Phenobarbital Sodium solution, and if the pH is higher than 10.2, the adjusting includes adding Hydrochloric acid (HCl).

[0088] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

[0089] In another embodiment, the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

[0090] In another embodiment, the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

[0091] In another embodiment, the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT).

[0092] In another embodiment, the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium.

[0093] In another embodiment, the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

[0094] In another embodiment, the method further includes filtering the Phenobarbital Sodium solution prior to lyophilizing.

[0095] In another embodiment, the method further includes aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and after lyophilization, applying a closure to the vial under vacuum.

[0096] Another embodiment is directed to a method of treating an individual in need of Phenobarbital Sodium. The method includes adding saline or dextrose to a composition containing lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual.

[0097] In another embodiment, the individual suffers from epilepsy.

[0098] In another embodiment, the individual is a newborn suffering from neonatal epilepsy.

[0099] In another embodiment, the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

[00100] In another embodiment, the administering includes intramuscular injection or intravenous injection.

[00101] Surprisingly, the inventors have determined that the presently disclosed method produces a storage-stable lyophilized Phenobarbital Sodium that maintains its stability up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. With reference to **Figs. 5B-5C**, the lyophilized Phenobarbital Sodium is amorphous. In particular, the lyophilized Phenobarbital Sodium is non-crystalline unlike the USP grade P API shown comparatively in **Fig. 5D**. The lyophilized Phenobarbital Sodium is stable and ready for reconstitution in either water for injection, 0.9% Saline or 5% Dextrose for intravenous (IV) or intramuscular (IM) administration. The presently disclosed formulation does not contain any organic solvents or preservatives which is specifically advantageous for administration to newborns and neonates. Moreover, the resulting lyophilized Phenobarbital Sodium forms below the quantitation limit of 0.05% phenylethylacetylurea (PEAU), and no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in water after storage of the lyophilized Phenobarbital Sodium for up to 6 months under accelerated stability conditions which is equivalent to 24 months at RT.

[00102] In a comparison analysis, the presently disclosed lyophilized powder of Phenobarbital Sodium at 65 mg or 130 mg doses was reconstituted in water and assayed for impurities and stability along with marketed liquid formulation of Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL (Westward Pharmaceuticals). The formulation details for this comparative analysis are presented in **Table 1**. Representative chromatograms from HPLC analysis are shown in **Figs. 2A-2H, 3A-3L, and 4A-4L**.

[00103] Table 1

Lyophilized Phenobarbital Sodium for Injection USP, 65 mg/vial and 130 mg/vial
Liquid Phenobarbital Sodium for Injection USP, 65 mg/mL or 130 mg/mL

Formulation Details

Dosage form		Liquid	Lyophilized
Components	Chemical name	**mg/mL**	**mg/vial**
Drug Substance	Phenobarbital Sodium	65 or 130	65 or 130
Inactive ingredients	Propylene Glycol	705	NA
	Benzyl alcohol	15.6	NA
	Ethanol	78.9	NA

	HCL	For pH adjustment	NA
	Water for Injection	QS (Quantity Supplied)	NA

[00104] With reference to **Tables 2** and **3**, the presently disclosed 65 mg lyophilized Phenobarbital Sodium composition was reconstituted in water and compared to the 65 mg Liquid Phenobarbital Sodium for Injection USP (65 mg/mL marketed Liquid Formulation) (**Table 2**) (**Figs. 3A-3F**, **Figs. 4A-4F**), and the presently disclosed 130 mg lyophilized Phenobarbital Sodium for Injection USP (130 mg/vial) composition was reconstituted in water and compared to the 130 mg liquid Phenobarbital Sodium for Injection USP (130 mg/mL marketed Liquid Formulation) (**Table 3**) (**Figs. 3G-3L**, **Figs. 4G-4L**). In addition to the noted characteristics of each product, the products were assayed for the degradation products-- phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG) by HPLC analysis, as further described in the Examples. As indicated in both **Tables 2** and **3**, the initial amount of PEAU (phenylethylacetylurea) assayed in the 65 mg/mL and 130 mg/mL liquid formulations was 0.5% and 0.5%, respectively. Comparatively, no initial amount of PEAU was detected in either the 65 mg or 130 mg lyophilized Phenobarbital Sodium compositions. Furthermore, after 3 and 6 months from the date of manufacture, both the liquid and lyophilized formulations at 65 mg/mL and 130 mg/mL stored at room temperature (RT) (25°C) and under accelerated stability conditions (ACC) at 40°C were analyzed by HPLC for assay and related substances. Under these conditions, the amount of PEAU assayed in the 65 mg/mL liquid formulations at 3 months was 1.0% (RT) and 3.7% (ACC) and at 6 months was 1.4% (RT) and 5.8% (ACC) (**Table 2**). Similarly, the amount of PEAU assayed in 130 mg/mL liquid formulations at 3 months was 0.9% (RT) and 2.8% (ACC) and at 6 months was 1.1% (RT) and 4.3% (ACC) (**Table 3**). In contrast, for the presently disclosed lyophilized compositions, the amount of PEAU assayed at 3 and 6 months for the 65 mg and the 130 mg lyophilized Phenobarbital Sodium compositions was below quantitation limit (BQL) (0.05%) both at RT and ACC stability conditions (**Tables 2-3**).

[00105] Table 2

65 mg/ml Liquid Formulation and 65 mg/vial Lyophilized Powder												
Product Name		Phenobarbital Sodium for Injection USP, 65 mg/mL (Marketed product)					Phenobarbital Sodium for Injection USP, 65 mg/Vial (Nivagen formulation- NPH1907)					
Formulation Type		Liquid					Lyophilized powder					
	Stability Data											
Test	**Initial**	**3 Months**		**6 Months**			**Initial**	**3 Months**		**6 Months**		**15 Months**
		RT 25°C, 60% RH	**ACC 40°C, 75% RH**	**RT 25°C, 60% RH**	**ACC 40°C, 75% RH**			**RT 25°C, 60% RH**	**ACC 40°C, 75% RH**	**RT 25°C, 60% RH**	**ACC 40°C, 75% RH**	**RT** 25°C, 60% RH**
Description	CCVS	CCVS	CCVS	CCVS	CCVS		WLP	WLP	WLP	WLP	WLP	WLP
Appearance after reconstitution	NA	NA	NA	NA	NA		CCS	CCS	CCS	CCS	CCS	CCS
Identification	$	$	$	$	$		$	$	$	$	$	$
pH*	9.3	9.8	9.7	9.6	9.6		9.8	9.6	9.6	9.7	9.7	9.8
% Assay of Phenobarbital Sodium	102.4	97.6	103.1	96.3	86.7		99.1	98.7	97.4	100.0	99.3	96.0
% degradation (Area percent) 2EPMM	ND	ND	BQL	BQL	BQL		ND	ND	ND	ND	ND	ND
PBG	ND	ND	ND	ND	ND		ND	ND	ND	ND	ND	ND
PEAU	0.5	1.0	3.7	1.4	5.8		ND	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	BQL	BQL	0.1	BQL	0.3		BQL	BQL	BQL	0.07	0.06	0.04
Total degradation products	0.5	1.0	3.8	1.4	6.1		BQL	BQL	BQL	0.07	0.06	0.04
	CCVS: Clear Colorless Viscous Solution; CCS: Clear Colorless Solution; WLP: White Lyophilized powder											
	$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.											
	BQL: Below Quantitation Limit; (QL-0.05%); ND: Not Detected											
	2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-phenylbutyrylguanidine, PEAU: phenylethylacetylurea or Pheneturide											
*	pH of both liquid and lyophilized formulations are measured at 65 mg/mL concentration											
**	The samples were stored at 30±2°C,65%RH±5											

Notably, the Lyophilized powder was stable even after 15 months, and no significant increase in the impurities was observed, rendering such formulation superior to known liquid formulations and enable easy administration.

[00106] Table 3

130 mg/mL Liquid Formulation and 130 mg/vial Lyophilized formulation												
Product Name	Phenobarbital Sodium for Injection USP, 130 mg/mL (Marketed product)						Phenobarbital Sodium for Injection USP, 130 mg/vial (Nivagen formulation-NPH1912)					
Formulation Type	Liquid						Lyophilized powder					
Test	**Stability Data**											
	Initial	**3 Months**		**6 Months**			**Initial**	**3 Months**		**6 Months**		**15 Months**
		RT 25°C, 60% RH	**ACC 40°C, 75% RH**	**RT 25°C, 60% RH**	**ACC 40°C, 75% RH**			**RT 25°C, 60% RH**	**ACC 40°C, 75% RH**	**RT 25°C, 60% RH**	**ACC 40°C, 75% RH**	**RT** 25°C, 60% RH**
Description	CCVS	CCVS	CCVS	CCVS	CCVS		WLP	WLP	WLP	WLP	WLP	WLP
Appearance after reconstitution	NA	NA	NA	NA	NA		CCS	CCS	CCS	CCS	CCS	CCS
Identification	$	$	$	$	$		$	$	$	$	$	$
pH*	9.5	9.9	9.9	9.8	9.7		9.8	9.8	9.8	9.8	9.8	10.0
% Assay of Phenobarbital Sodium	100.8	95.5	92.9	95.2	90.9		98.3	100.1	97.9	100.2	99.4	98.3
Related Substances (% Area) 2EPMM	ND	ND	BQL	BQL	BQL		ND	ND	ND	ND	ND	ND
PBG	ND	ND	ND	ND	ND		ND	ND	ND	ND	ND	ND
PEAU	0.5	0.9	2.8	1.1	4.3		ND	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	ND	BQL	0.1	BQL	0.4		BQL	BQL	BQL	0.05	0.05	0.04
Total degradation products	0.5	0.9	2.9	1.1	4.7		BQL	BQL	BQL	0.05	0.05	0.04
	CCVS: Clear Colorless Viscous Solution; CCS: Clear Colorless Solution; WLP: White Lyophilized powder											
	$: In Assay analysis, the retention time of Phenobarbital in standard and sample solutions should be same.											
	BQL: Below Quantitation Limit; (QL-0.05%); ND: Not Detected											
	2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-phenylbutyrylguanidine, PEAU: phenylethylacetylurea or Pheneturide											
*	pH for liquid formulation is measured at 130 mg/mL and for lyophilized formulation at 100 mg/mL dilution											
**	The samples were stored at 30±2°C, 65% RH±5											

[00107] In typical embodiments, the method of reducing formation of degradation products of a lyophilized Phenobarbital Sodium composition reconstituted in water results in the reconstituted solution having no less than 96% Phenobarbital Sodium. In more typical embodiments, the reconstituted solution has no less than 97% Phenobarbital Sodium. In more preferred embodiments, the reconstituted solution has no less than 98% Phenobarbital Sodium. In additional or alternative embodiments, the reconstituted solution has no quantitative amount (*e.g.*, 0.05% or less) of PEAU, 2 EPMM, or PBG.

[00108] According to contemplated embodiments, assaying the stability of the lyophilized Phenobarbital Sodium composition includes reconstituting the composition in water at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

[00109] Further aspects of the present disclosure include methods of treating an individual in need of Phenobarbital Sodium. For administration to an individual (*e.g.*, a human patient) the lyophilized powder of Phenobarbital Sodium powder may be reconstituted in saline or dextrose as disclosed herein immediately prior to administration to form a Phenobarbital Sodium reconstituted solution. In particular embodiments, the individual in need of Phenobarbital Sodium suffers from epilepsy. In preferred embodiments, the individual in need of Phenobarbital Sodium is a newborn suffering from neonatal epilepsy. In other embodiments, the lyophilized Phenobarbital Sodium is a powder dose of 65 mg, 100 mg, 130 mg or 200 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection.

Examples

[00110] Lyophilization Microscopy. Lyophilization microscopy (**Figs. 1A-1F**) was performed using a Leica DM LP microscope equipped with a Linkam FDCS196 stage, TMS93 controller, vacuum pump, LNP unit, and a Spot Insight color camera. A 20x, 040 N.A. objective was used with crossed polarizers and a first order red compensator to view sample. Images were acquired using Spot Advanced software (v.4.5.9).

[00111] Lyophilization parameters for the lyophilization microscopy including a start temperature of -50°C with heating at 1°C/minute to -40°C followed by heating at 0.5°C/minute to -32.0°C.

[00112] HPLC Assays. High Performance Liquid Chromatography (HPLC) was used to assay Phenobarbital Sodium standards and sample solutions as disclosed herein (*e.g.*, **Tables 2**, **3**, **Figs. 2A-2H, 3A-3L, and 4A-4L**). Both Ultra High-Performance Liquid Chromatographic system (UHPLC) and High-Performance Liquid Chromatographic system (HPLC) (ThermoFisher/Waters) were used together with Data Acquisition Software (Empower 3), equipped with UV and Photodiode Array Detector (UV and PDA), column thermostat and auto sampler compartments or equivalent HPLC system and software.

[00113] An exemplary HPLC assay protocol is provided in the following:

[00114] Instruments / Apparatus: HPLC with UV detector / PDA Detector, Analytical balance, Sonicator, Volumetric flasks, Beakers, Pipettes.

[00115] Reagents, Solvents, Standards: Phenobarbital Reference Standard, Deionized water / Water for Injection, Potassium Monobasic Phosphate, Acetonitrile.

[00116] Preparation of Mobile Phase Solutions: Potassium phosphate monobasic (7 mM) and Acetonitrile (70:30) pH 4.5-6.5; Diluent: Mobile phase as a diluent.

[00117] Wash Solvent: Water: Acetonitrile (70:30)

[00118] CHROMATOGRAPHIC CONDITIONS: The liquid chromatography equipped with a UV and PDA detector, an injector and a data processor is operated as follows:

[00119]

Parameters	Conditions
Column	L7 packaging column , 150 X 4.6 mm, Particle Size : 5µm or equivalent
Flow rate	0.9- 1.2 mL /min.
Detection Wavelength	254± 2 nm for assay and 210± 2 nm for Related Substances
Injection volume	10 µL
Run time	15 Minutes
Column Oven Temperature	30°C
Sampler Cooler Temperature	25°C
Retention Time	About 5 minutes for Phenobarbital
Pump Mode	Isocratic

[00120] Phenobarbital Assay Standard Solution: 0.2 mg/mL to 0.8 mg/mL in diluent; Phenobarbital Related Substances Standard Solution: 0.26 µg/mL to 15.6 µg/mL in diluent; Phenobarbital Related Substances resolution standard solution: 0.475 mg/mL Phenobarbital and about 1 µg/mL for related substances (2-Ethyl-2-Phenyl malonamide, monohydrate (2EPMM), Phenylbutyrylguanidine (PBG) and Phenylethylacetylurea (PEAU) in diluent; Phenobarbital Sodium Sample Solution for Assay: 0.26 mg/mL to 0.78 mg/mL in diluent

[00121] Phenobarbital Sodium related Substances sample solution: 0.52 mg/mL of Phenobarbital Sodium and related substances 2-Ethyl-2-Phenylmalonamide, monohydrate (2EPMM), Phenyl butyrylguanidine (PBG) and Phenylethylacetylurea (PEAU) and any unspecified degradation products at 0.26 µg/mL to 13. 2 µg/mL

[00122] SYSTEM SUITABILITY REQUIREMENTS: The relative standard deviation of Phenobarbital peak from Six replication injections of related substances standard should not be more than 6.0%. The related standard deviation of Phenobarbital peak from five replicate injections in assay standard solution should not be more than 2.0%. Tailing factor for the Phenobarbital is not more than 2.0. USP Plate count for the Phenobarbital is not less than 2500. The S/N Ratio of the Sensitivity Standard Solution is NLT 10 for related substance test. The resolution between Phenobarbital peak and nearest impurity peak is NLT 1.5

[00123] Two alternative formulations are disclosed in **Table 6**. One of these formulations is 200 mg/vial, Phenobarbital Sodium reconstituted in 10 mL of Water for Injection or 5% Dextrose to obtain a concentration of 20 mg/mL. A second formulation is 200 mg/vial of Phenobarbital

Sodium along with 90 mg Sodium Chloride reconstituted in 10 mL of Water for Injection to obtain a concentration of 20 mg/mL Phenobarbital Sodium for Injection and 9 mg/mL or 0.9% Sodium Chloride.

[00124] Table 6. Phenobarbital Sodium for Injection, USP, 200 mg/vial in 10 mL vial. Formulation Details.

Reconstitution Volume 10 mL; Diluents that can be used are Water for Injection, 0.9% Saline or 5% Dextrose.

Ingredients	Manufacturer	NPH2031A (Bulk Solution @ 100 mg/mL Phenobarbital Sodium) Compounding at 2-8°C		NPH2031B (Bulk Solution @ 100 mg/mL Phenobarbital Sodium and 45 mg/mL Sodium Chloride) Compounding at 2-8°C	
		Fill Volume: 2.1 mL			
		mg/mL (after reconstitution)	mg/vial	mg/mL (after reconstitution)	mg/vial
Phenobarbital Sodium	Siegfried USA, LLC	20	200	20	200
Sodium Chloride	JT Baker	NA	NA	9	90
DI Water	In house	qs	qs	qs	qs
100% Nitrogen	Airgas	NA	NA	NA	NA
10 mL Tubular Serum Bottle clear	Wheaton Part#223686				
20 mm Igloo Bromobutyl stopper	Datwyler				
Seal 20 mm Filp-Cap, Red	Wheaton Part# 224203				

[00125] These formulations along with the previously disclosed formulations were developed to enable physicians and medical staff at hospitals to easily reconstitute to a desired concentration (*e.g.*, 20 mg/mL) and administer the medicine to patients in need thereof. The reconstituted solution is stable at 2-8°C for 24 hrs and 3 to 4 hrs when stored at RT (see *e.g.*, **Tables 7, 8 and 9**).

[00126] Table 7

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial (NPH2031A Phenobarbital Sodium @ 200 mg/vial) (Reconstitution in 10 mL Water)				
Test	Spec.	Initial DOA: 06/05/20	Reconstituted Solution Stability after 20 hrs DOA: 06/06/2020	
			2-8°C	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.7	9.8
% Assay Phenobarbital Sodium	90.0 -105.0	100.1	100.1	100.1
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.24
Total degradation products	NMT 1.5 %	BQL	0.09	0.27
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA
Note Book Reference		192045-163 to 189	192045- 163-183	
DOA: Date of Analysis; WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea				

[00127] Table 8

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 200 mg/vial in Sodium Chloride (NPH2031B Phenobarbital Sodium @ 200 mg/vial and Sodium Chloride @ 90 mg/vial) (Reconstitution in 10 mL Water)				
Test	Specification	Initial	Reconstituted Solution Stability after 20 hrs	
			2-8°C	RT
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.7	9.8
% Assay Phenobarbital Sodium	90.0 -105.0	103.3	103.4	102.8
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	BQL
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.03
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.27
Total degradation products	NMT 1.5 %	BQL	0.09	0.3
Water Content by Karl Fischer	NMT 3.0%	0.84	NA	NA
WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea				

[00128] Table 9

Reconstituted Solution Stability of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)								
Tests/Time	**Shelf life Specifications**		**2 hrs**		**4 hrs**		**24 hrs**	
		Initial	**2-8C**	**RT**	**2-8C**	**RT**	**2-8C**	**RT**
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.2-10.2	9.5	9.5	9.6	9.6	9.5	9.6	9.5
Assay of Phenobarbital Sodium	90.0%-105.0 %	99.8	102.1	100.8	101.7	101.2	100.4	100.3
Related Substances (%Area) 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	NMT 0.2%	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Total degradation products	NMT 1.5 %	0.015	0.02	0.04	0.02	0.06	0.04	0.18
Osmolality mOsmol/Kg	To be reported	158	NP	NP	NP	NP	159	158
CCS: Clear colourless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutyrylguanidine; PEAU:Phenylethylacetylurea								

[00129] Six months stability data for Phenobarbital Sodium for Injection, USP, 65 mg/vial is included in **Table 10**. Six months stability data for Phenobarbital Sodium for Injection, USP, 130 mg/vial is included in **Table 11**. Three months stability data for Phenobarbital Sodium for Injection, USP, 200 mg/vial is included in **Table 12**. Three months stability data for Phenobarbital Sodium for Injection, USP (Phenobarbital Sodium and 9% Saline), 200 mg/vial is included in **Table 13**.

[00130] Table 10

Product Name	**Phenobarbital Sodium for Injection USP**, 65 mg/vial	**Batch#**NPH2020 Fill Volume: 1.05 mL	**Date Manufactured**:01/20/2020
Vial Make	2 mL Fiolax Clear Blow Back Vial (Schott, Article#1590892);		**Date Initiated**:02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1845X007,		**Re test Date**: 11/16/2023
Stopper Used	Aptar stelmi 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper (C1621 6720GC 6 FP3)		**Flip Off Seals**:Wheaton,13mm Red Plastic top flip off with Aluminum Seal ,Lot#224202
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	**Spec.**	**Initial DOA: 02/18/20**	**1 Month**		**3 Months**		**6 Months**	
			DOA: 03/23/2020		**DOA:05/20/20**		**DOA: 08/04/2020**	
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.6	9.6
% Assay Phenobarbital Sodium	90.0%-105.0 %	98.6	101.6	101.5	101.3	100.5	100.0	101.2
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.6	0.9	1.2	1.4	1.5	2.5	2.4
Note Book Reference		192039-150 to 158	192045- 23 to 43		192045-135 to 151		192051-84 to 122	

DOA: Date of Analysis; WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%)
2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylureasoline; PEAU: Phenylethylacetylurea

[00131] Table 11

Product Name	**Phenobarbital Sodium for Injection USP**, 65 mg/vial	**Batch#**NPH2020 Fill Volume: 1.05 mL	**Date Manufactured**:01/20/2020
Vial Make	2 mL Fiolax Clear Blow Back Vial (Schott, Article#1590892);		**Date Initiated**:02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1845X097.		**Re test Date**: 11/16/2023
Stopper Used	Aptar stelmi 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper (C1621 6326GC 6 TP2)	**Flip Off Seals**:Wheaton,13mm Red Plastic top flip off with Aluminum Seal ,Lot#224202	
Configuration	Inverted **Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)	

Test	**Spec**	**Initial DOA: 02/18/20**	**1 Month**		**3 Months**		**6 Months**	
			DOA: 03/23/2020		**DOA:05/20/20**		**DOA: 09/04/2020**	
			RT	**ACC**	**RT**	**ACC**	**RT**	**ACC**
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	9.9	9.9	9.9	9.9	9.9	9.8	9.6
% Assay Phenobarbital Sodium	90.0%-105.0 %	98.6	101.6	101.5	101.3	100.5	100.0	101.2
Related Substances (% Area) 2EPhM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.6	0.9	1.1	1.4	1.5	1.5	2.1
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 153		192051-84 to 122	

DOA: Date of Analysis; WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution;
ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%);
2EPhM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea

[00132] Table 12

Product Name	**Phenobarbital Sodium for Injection USP,** 200 mg/vial	**Batch#**NPH2031A Fill Volume: 2.1 mL	**Date Manufactured**:06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear (Wheaton, Part# 223686; Batch#5192875);		**Date Initiated**:06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1924X009,	**Re test Date**: 07/20/2024	
Stopper Used	Datwyler 20 mm Igloo Bromobutyl Lyophilization Rubber stopper	**Flip Off Seals**:Wheaton,20 mm Red Plastic top flip off with Aluminum Seal , Lot#2224203	
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months	
			DOA: 09/04/2020	
			RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7
% Assay Phenobarbital Sodium	90.0 -105.0	100.1	98.1	101.0
Related Substances (% Area) 2EPMM	NMT 0.2%	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5 %	BQL	0.09	0.09
Water Content by Karl Fischer	NMT 5.0%	1.1	1.0	1.3
Note Book Reference		192045-163 to 189	192051 - 84 to 122	

DOA: Date of Analysis; WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; ND: Not Detected; NMT: Not More Than; BQL- Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea

[00133] Table 13

Product Name	**Phenobarbital Sodium for Injection USP,** 200 mg/vial (Phenobarbital Sodium and 9% Saline/vial)	**Batch#**NPH2031E Fill Volume: 2.1 mL	**Date Manufactured**:06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear (Wheaton, Part# 223686; Batch#3192875);		**Date Initiated**:06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1924X009,		**Re test Date**: 03/20/2024
Stopper Used	Daltnyter 20 mm Igloo Bromobutyl Lyophilization Rubber stopper		**Flip Off Seals**: Wheaton, 20 mm Red Plastic top flip off with Aluminum Seal , Lot#2242203
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months DOA: 09/04/2020	
			RT	ACC
Description	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5
% Assay Phenobarbital Sodium	90.0 -105.0	103.3	102.8	103.6
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND
PBG	NMT 0.2%	ND	ND	ND
PEAU	NMT 0.2%	BQL	0.03	0.04
Any unspecified degradation product	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5 %	BQL	0.1	0.08
Water Content by Karl Fischer	NMT 3.0%	0.8	0.9	1.1
Note Book Reference		192045-163 to 189	192051- 84 to 123	
DOA: Date of Analysis; WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea				

[00134] Data for Osmolality, Particulate matter and assay for Sodium Chloride is disclosed in **Table 14**.

[00135] Table 14. Phenobarbital Sodium for Injection, USP, 200 mg/vial in Water or Sodium Chloride – Osmolality, Particulate Matter and Assay for Sodium Chloride.

Batch No	Osmolality* (mOsmol/Kg) (Specification: To be reported) Reconstitution in 10 mL (20 mg/mL)	Particulate Matter (By Light Obscuration method) Ref: USP<788>		Assay of Sodium Chloride (titrimetric; Ref USP monograph for Sodium Chloride Injection
		≥10 µM Specification: (NMT 6000 particles/vial)	≥25 µM Specification: (NMT 600 particles/vial	Specification: (95.0%-105.0%)
NPH2031A (200 mg/vial)	148	80.0	0.67	NA
NPH2031B (200 mg/vial) (Phenobarbital Sodium 200 mg, 9% Sodium Chloride)	372	171	1.33	99.99
Water -Blank	0	NA	NA	NA
0.9% Sodium Chloride	270	NA	NA	NA

[00136] Lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial and 200 mg/vial are disclosed in **Table 15**.

[00137] Table 15. Lyophilization Cycle parameters.

Section	Phase	Lyophilization Cycle 1*				Lyophilization Cycle 2**			
		Condenser set point C	Vacuum [mTorr]	Temperature °C	Hold Time [mm]	Condenser set point °C	Vacuum [mTorr]	Temperature °C	Hold Time [mm]
1	Loading		off	5	n.a.		off	-5	n.a.
2	Freezing		off	-5	5		off	-5	10
3	Freezing		off	-50	60		off	-52	120 (Ramp)
4	Freezing		off	-10	30		off	-52	180 (Hold)
5	Freezing		off	-50	120		n.a.	n.a.	n.a.
6	Evacuation	-50	75	-50	30	-60	50	-45	30
7	Primary drying		75	-50	400 (Hold)		50	-42	100 (Ramp)
8	Primary drying		75	-45	350 (Hold)		50	-42	1120 (Hold)
9	Primary drying		75	-43	300 (Hold)		n.a.	n.a.	n.a.
10	Primary drying		75	-35	250 (Hold)		n.a.	n.a.	n.a.
11	Primary drying		75	-20	60 (Hold)		n.a.	n.a.	n.a.
12	Primary drying		75	0	120 (Hold)		n.a.	n.a.	n.a.
13	secondary drying		75	50	120 (Hold)		50	35	100 (Ramp)
14	secondary drying		75	25	120 (Hold)		50	35	420 (Hold)

Lyophilization Cycle 1*: 65 mg/vial, 130 mg/vial and 100 mg/vial samples disclosed in Tables 1, 2, 3, 16 and 17

Lyophilization Cycle 2: NPH2031A (200 mg/vial Phenobarbital Sodium) and NPH2031B (200 mg/vial in Phenobarbital Sodium and 90 mg/vial Sodium Chloride, NPH2020 (65 mg/vial) and NPH2021 (130 mg/vial)**

[00138] Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in **Table 16**.

[00139] Table 16

Product Name	**Phenobarbital Sodium for Injection USP**, 100 mg/vial	**Batch#**NPH1980	**Date Manufactured:**09/25/2019
Vial Make	5 mL Clear Untreated Article#9621139054 5 mL Clear Treated Article#9621130486		**Date Initiated**:09/30/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV: Siegfried USA, LLC Lot#1845X006, **Re test Date**: 11/16/2023		
Stopper Used	Aptar stelmi 13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper, Lot#0702/9188+	**Flip Off Seals**:Wheaton,13mm Red Plastic top flip off with Aluminum Seal Lot# NA	
Configuration	Inverted	**Stability**	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial		1 Month				3 Months				6 Months			
				RT		ACC		RT		ACC		RT		ACC	
		UT	T	UT	T	UT	T	UT	T	UT	T	UT	T	UT	T
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH	9.2-10.2	9.7	9.7	9.6	9.7	9.6	9.6	9.7	9.7	9.7	9.7	9.8	9.9	9.8	9.9
% Assay of Phenobarbital Sodium	90.0%-105.0%	98.4	97.6	98.6	99.0	98.0	100.4	99.1	98.7	97.0	96.9	97.7	96.3	97.2	97.6
Related Substances (% Area) 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	0.08	0.08	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5 %	0.08	0.08	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.6	1.0	1.0	1.1	1.3	1.2	1.1	1.6	1.5	1.6	1.2	1.5	2.0
Note Book Reference		192031-91 to 101		192031-169 to 183				192039-44 to 52				192045-52 to 85			
WLP: White Lyophilized powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; UT: Untreated; T: Treated ND: Not Detected; NMT: Not More Than; 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α-Phenylbutyrylguanidine															

[00140] Table 17. Phenobarbital Sodium for Injection, USP, 100 mg/vial Formulation Details.

Diluents that can be used: Water for Injection, 0.9% Saline or 5% Dextrose

Proposed Reconstitution Volume: 5 mL

Ingredients	Manufacturer/Lot number	Concentration (mg/mL)	Concentration (mg/vial)	Batch Quantity (100 mL)
Phenobarbital Sodium, USP Grade P C-IV	Siegfried USA, LLC Mat No: 300040 Lot# 1845X006 Retest date: 11/16/2023	101.13 mg (~100 mg Phenobarbital Sodium after LOD correction)	100 mg	10.113 g
Water for Injection	In house	Q.S. to 1 mL	NA	Q.S. to 100 mL or 103.3g
100% Nitrogen	Airgas	NA	NA	NA
5 mL, untreated	Gerresheimer Article#9621130054	NA	NA	NA
5 mL, treated	Gerresheimer Article#9621130486	NA	NA	NA
13mm Bromobutyl Lyophilization stoppers	Aptar-Stelmi C16316720GC6TP3	NA	NA	NA
Seal 13 mm Seal, Flip-Cap, Red	Wheaton Unlimit	NA	NA	NA

[00141] Representative chromatograms and/or corresponding calculations are shown in **Figs. 2A-2H, 3A-3L, 4A-4L,** and **Tables 2** and **3**.

[00142] X-Ray Powder Diffraction. With reference to **Figs. 5A-5D**, XRPD was performed using the Rigaku Smart-Lab X-ray diffraction system configured for reflection Bragg-Brentano geometry using a line source X-ray beam. The x-ray source is a Cu Long Fine Focus tube that was operated at 40 kV and 44 mA. That source provides an incident beam profile at the sample that changes from a narrow line at high angles to a broad rectangle at low angles. Beam conditioning slits were used on the line X-ray source to ensure that the maximum beam size is less than 10mm both along the line and normal to the line. The Bragg-Brentano geometry is a para-focusing geometry controlled by passive divergence and receiving slits with the sample itself acting as the focusing component for the optics. The inherent resolution of Bragg-Brentano geometry is governed in part by the diffractometer radius and the width of the receiving slit used. Typically, the Rigaku Smart-Lab is operated to give peak widths of 0.1 °2θ or less. The axial divergence of the X-ray beam is controlled by 5.0-degree Soller slits in both the incident and diffracted beam paths. The samples were placed in a low-background, silicon holder using light manual pressure to keep the sample surfaces flat and level with the reference surface of the holder. The samples were analyzed from 2 to 40 °2θ using a continuous scan of 6 °2θ per minute with an effective step size of 0.02 °2θ.

[00143] The recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.*, "such as") provided with respect to certain embodiments herein is intended merely to better illuminate the full scope of the present disclosure, and does not pose a limitation on the scope of the invention otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the claimed invention.

[00144] It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the full scope of the concepts disclosed herein. The disclosed subject matter, therefore, is not to be restricted except in the scope of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced. Where the specification claims refers to at least one of something selected from the group consisting of A, B, C ... and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium.

2. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising:

adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution;

if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and

lyophilizing the Phenobarbital Sodium solution.

3. The method of claim 2, wherein the water is Water for Injection.

4. The method of claim 3, wherein the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium.

5. The method of claim 4, wherein the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium.

6. The method of claim 2, wherein the water is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium.

7. The method of claim 2, wherein the adjusting comprises measuring the pH of the Phenobarbital Sodium solution, and wherein if the pH is higher than 10.2, the adjusting comprises adding Hydrochloric acid (HCl).

8. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

9. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

10. The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

11. The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT).

12. The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium.

13. The method of claim 2, wherein the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.

14. The method of claim 2, further comprising filtering the Phenobarbital Sodium solution prior to lyophilizing.

15. The method of claim 2, further comprising:

aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and

after lyophilization, applying a closure to the vial under vacuum.

16. A method of treating an individual in need of Phenobarbital Sodium, the method comprising:

adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and

administering the Phenobarbital Sodium solution to the individual.

17. The method of claim 16, wherein the individual suffers from epilepsy.

18. The method of claim 17, wherein the individual is a newborn suffering from neonatal epilepsy.

19. The method of claim 16, wherein the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

20. The method of claim 16, wherein the administering comprises intramuscular injection or intravenous injection.

ABSTRACT

A composition of, method for producing, and use of an amorphous lyophilized Phenobarbital Sodium having high purity are presented. The amorphous lyophilized Phenobarbital Sodium is storage-stable being essentially void of impurities (*e.g.*, phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG)) upon reconstitution in water.

Fig. 1A

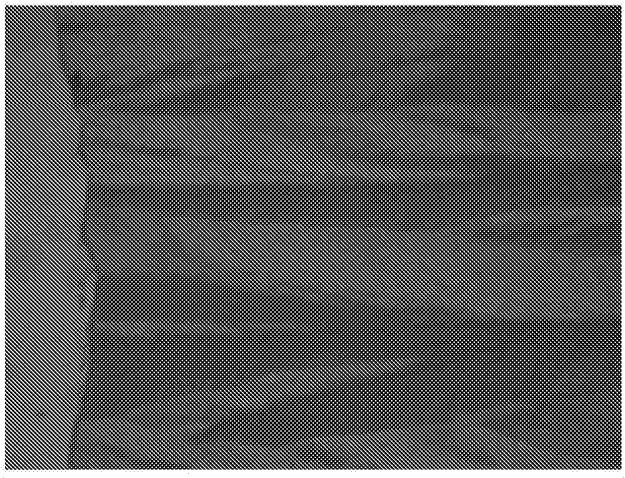


Fig. 1B

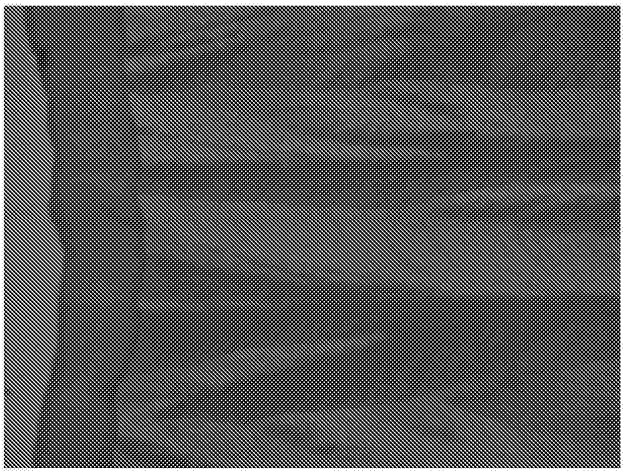


Fig. 1C

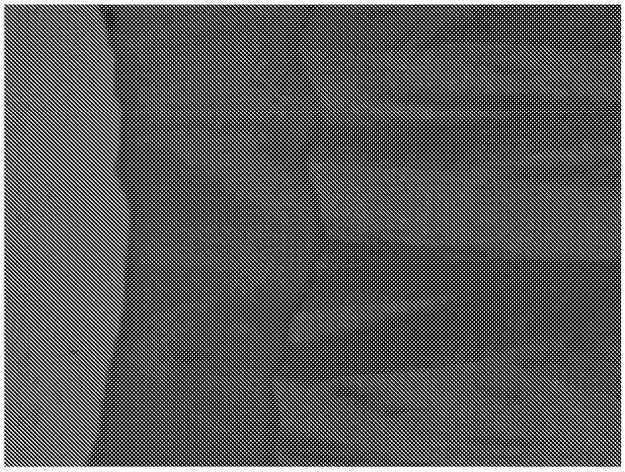


Fig. 1D



Fig. 1E

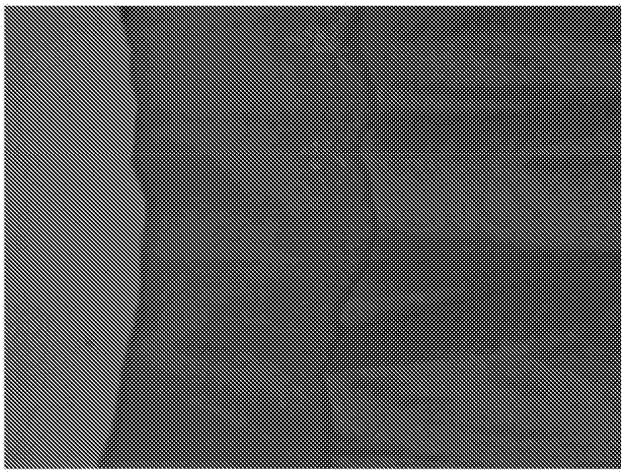


Fig. 1F

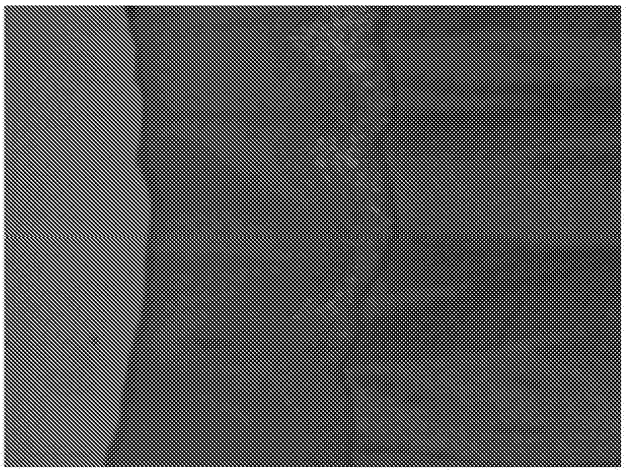


Fig. 2A

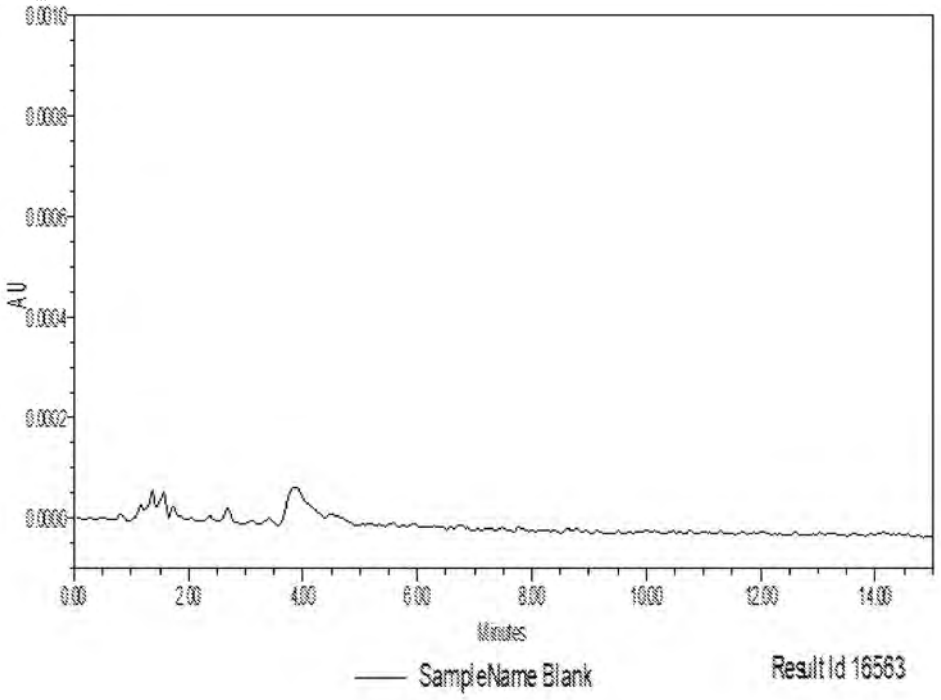
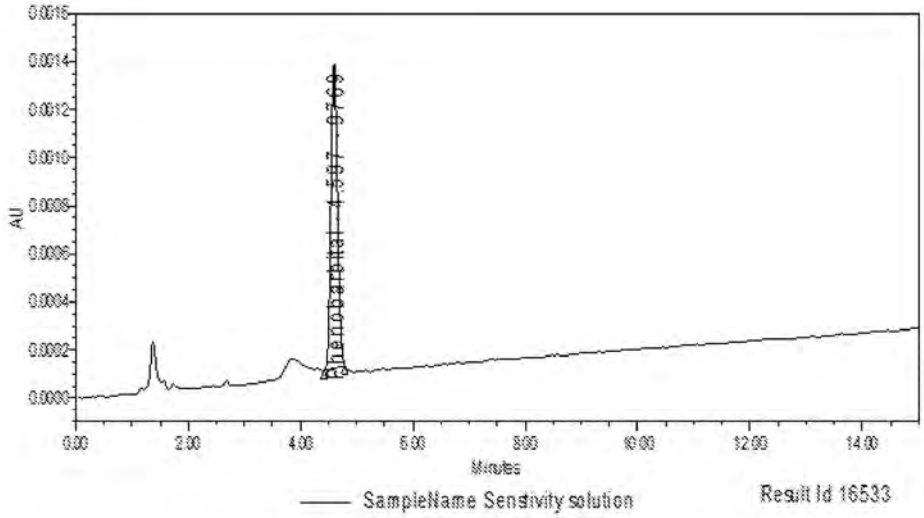
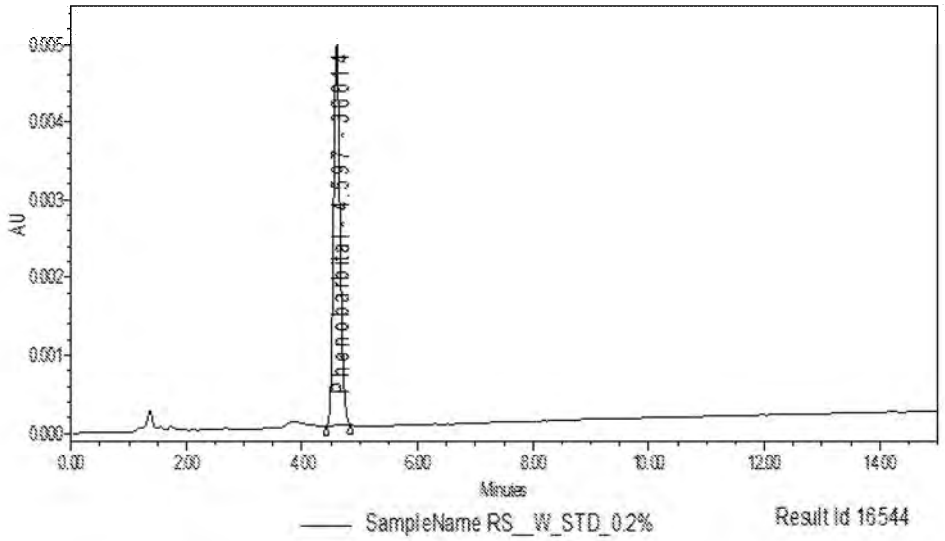

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Fig. 2B



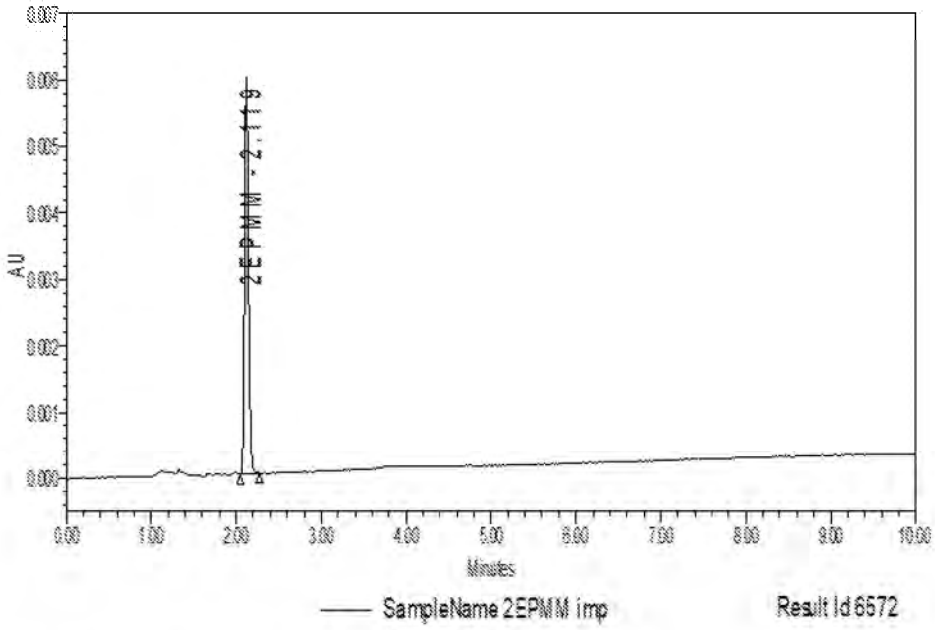
	Peak Name	RT	Area	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	9769	1054.848570	7881.1	1.1

Fig. 2C



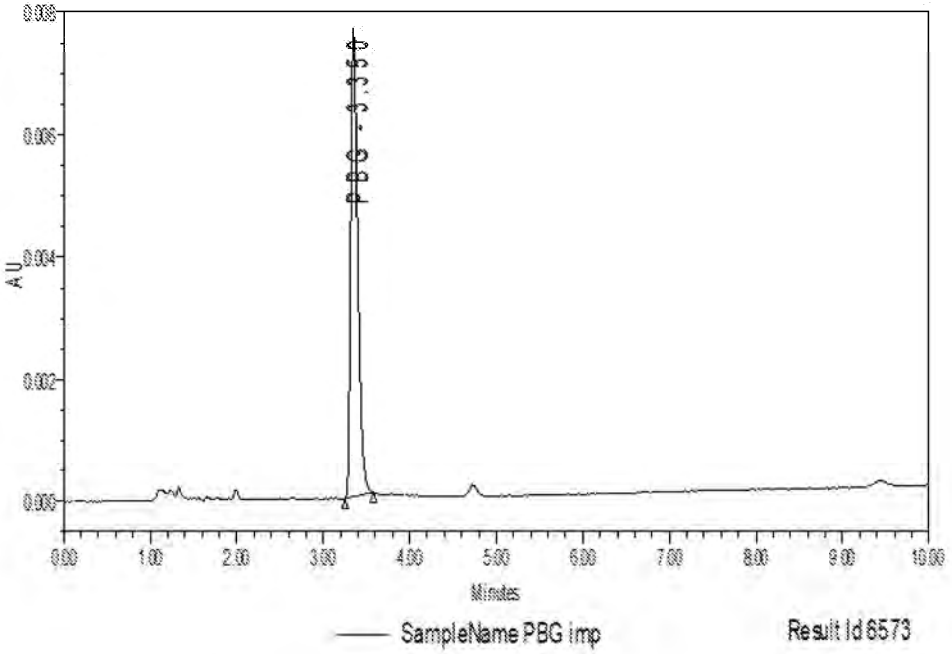
	Peak Name	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	38614	0.001	2906.846635	7746.3	1.2

Fig. 2D



	PeakName	RT	Area	% Area	sih	USP Plate Count	USP Tailing	PurityA Angle	PurityA Threshold
1	2EPMM	2.119	18797	100.00	1472	10573.6	1.2	0.674	1.833

Fig. 2E



	PeakName	RT	Area	% Area	sin	USP Plate Count	USP Tailing	Purity Angle	Purity Threshold
1	PBG	3.350	41776	100.00	2050	9801.9	1.5	21.648	62.962

Fig. 2F

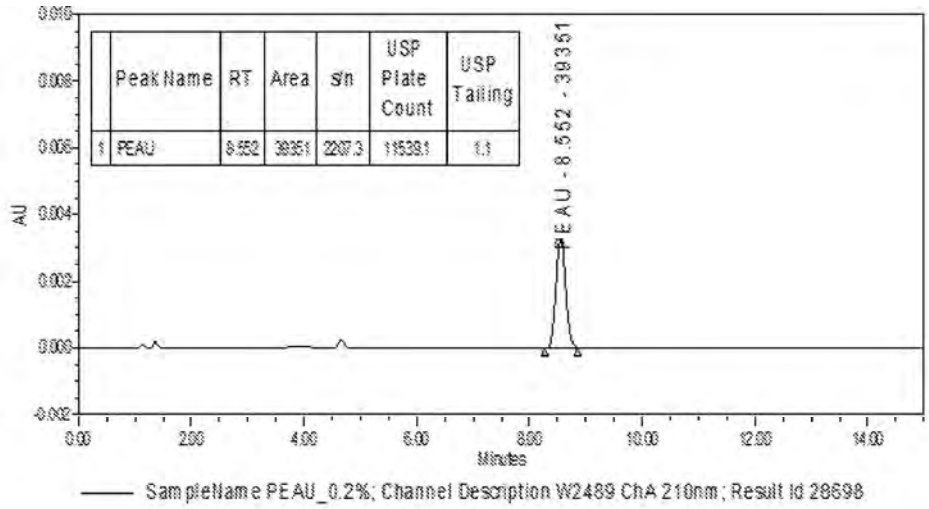

Peak Name
RT
Area
S/n
USP Plate Count
USP Tailing
1
PEAU
8.552
39351
2207.3
115381
1.1
PEAU - 8.552 - 39351
AU
Minutes
SampleName PEAU_0.2%; Channel Description W2489 ChA 210nm; Result Id 28698

Fig. 2G

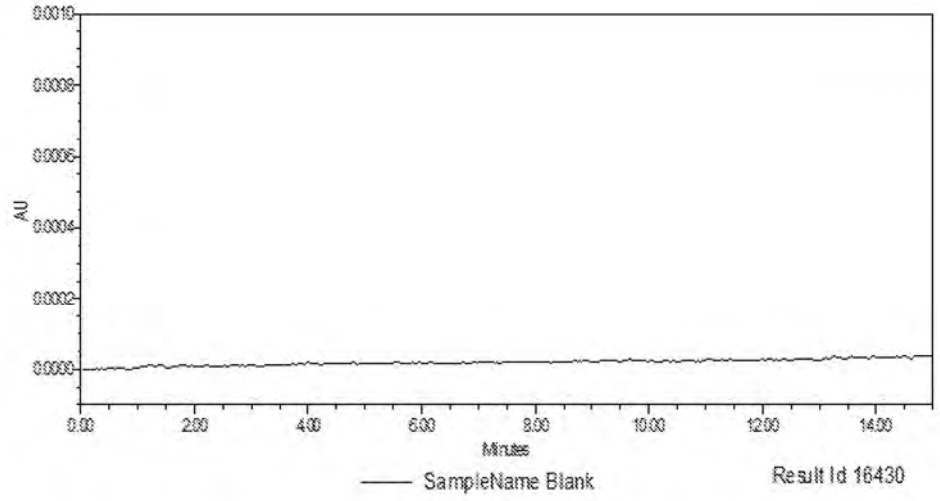
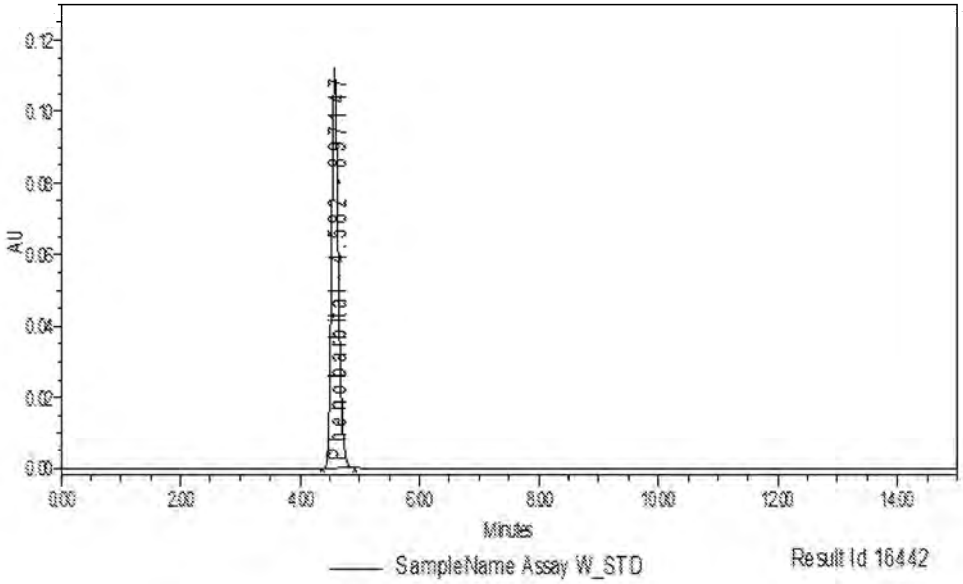
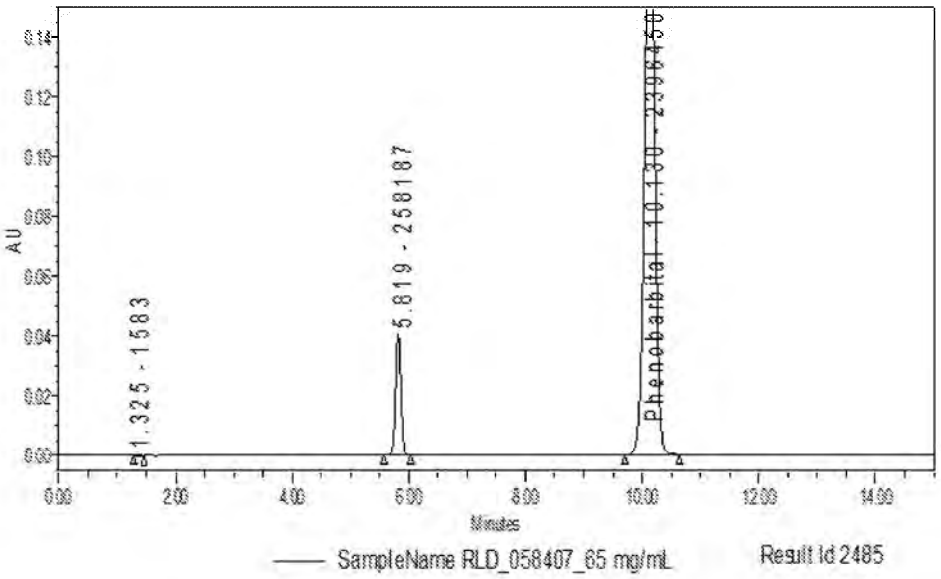

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Fig. 2H



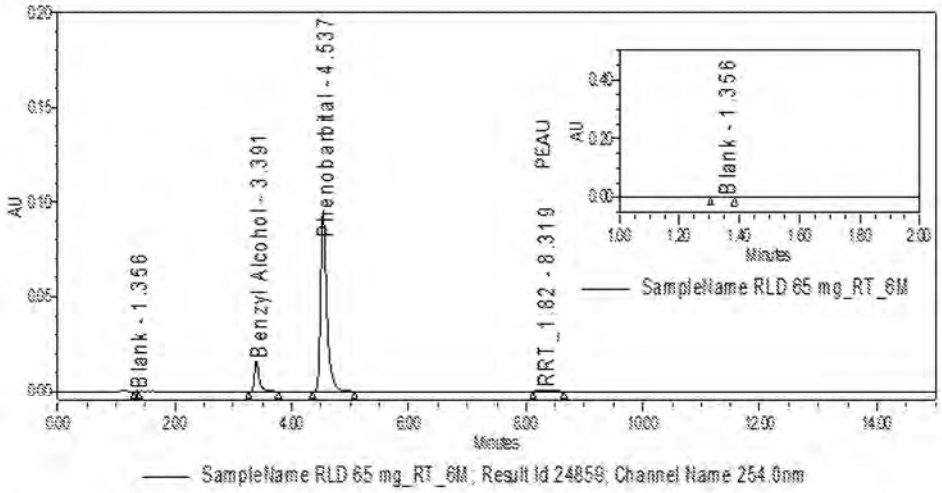
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.582	897147	0.476	50940.058185	7493.0	1.2

Fig. 3A



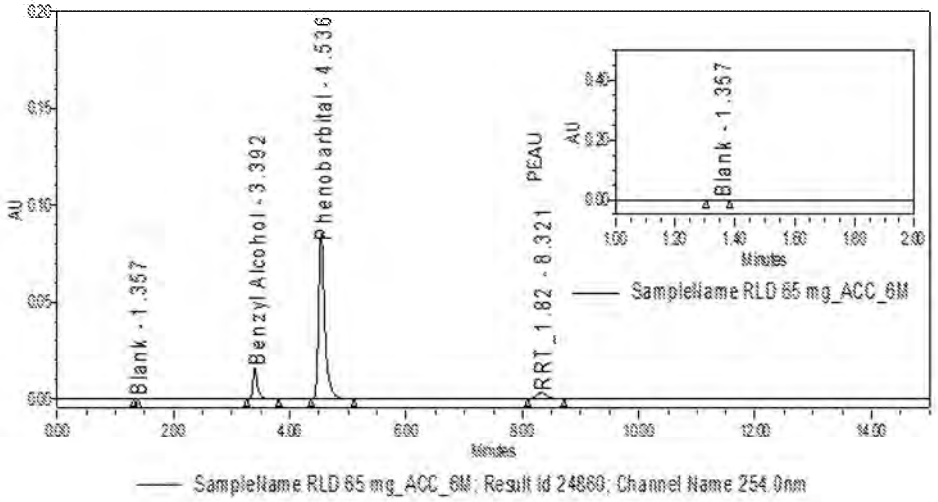
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.130	2396458	60.823	17.9	17534.1	1.0	112.1

Fig. 3B



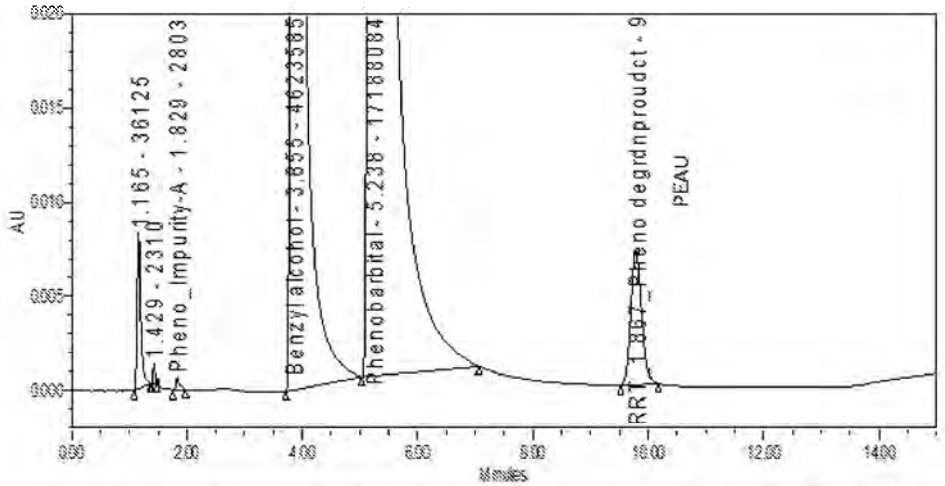
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	87091	10.96	14.994	mg/mL	105.2	23.7	1.7
2	Blank	1.356	828	0.10	0.068	mg/mL			1.0
3	Phenobarbital	4.537	697184	87.71	57.200	mg/mL	96.3	7.2	1.5
4	RRT_1.82	8.319	9745	1.23	0.800	mg/mL		15.0	1.3

Fig. 3C



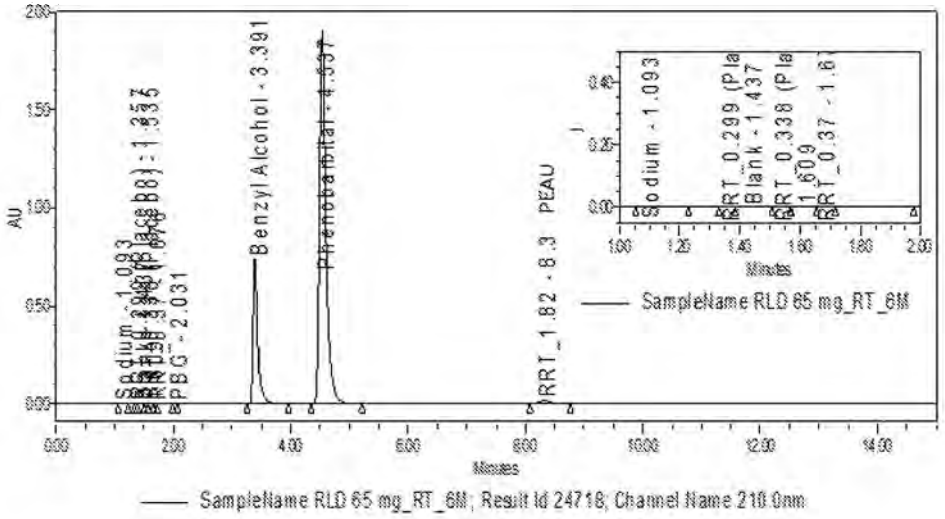
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	84435	11.25	14.537	mg/mL	102.0	23.7	1.7
2	Blank	1.357	798	0.11	0.065	mg/mL			1.1
3	Phenobarbital	4.536	627538	83.64	51.486	mg/mL	86.7	7.2	1.5
4	RRT_1.82	8.321	37484	5.00	3.075	mg/mL		14.6	1.2

Fig. 3D



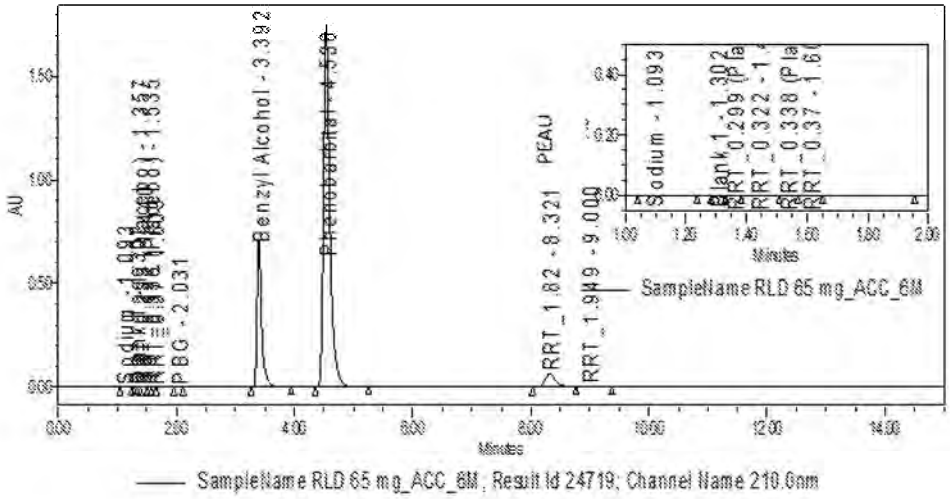
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.855	4623585	21.07	17.1	396.1	12312.6	1.5
2	Pheno_Impurity-A	1.829	2803	0.01	5.2	0.3	7668.2	1.6
3	Phenobarbital	5.238	17188084	78.32	8.0	1048.9	11239.0	1.4
4	RRT_1.867_Pheno degrdnproudct	9.781	92807	0.42	16.5	3.5	13191.8	1.2

Fig. 3E



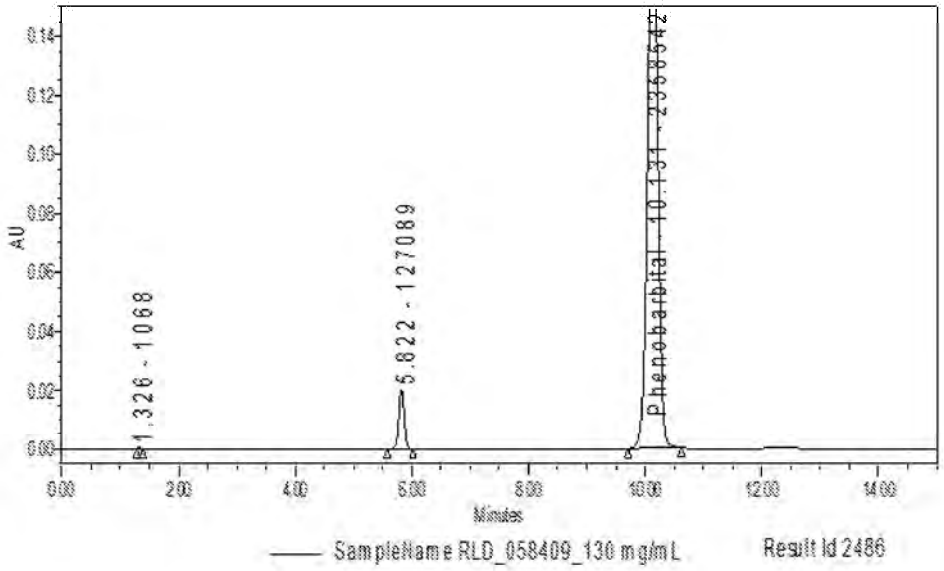
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	3972837	21.25	16.272	mg/mL	13.8	1.7
2	Phenobarbital	4.537	14515521	77.64	56.435	mg/mL	7.1	1.5
3	RRT_1.82	8.321	200110	1.07	0.778	mg/mL	14.6	1.3

Fig. 3F



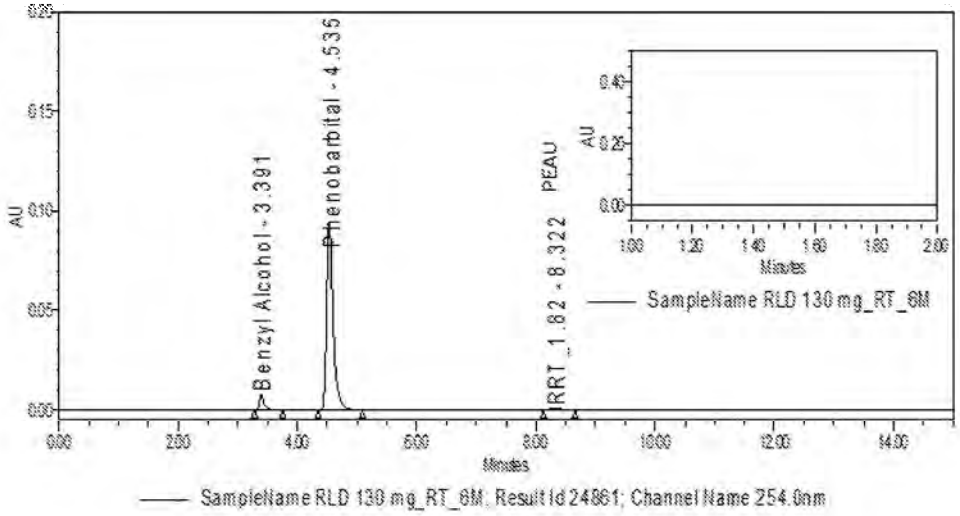
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	3833550	21.50	15.701	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13183528	73.94	51.257	mg/mL	7.1	1.5
3	RRT_1.82	8.321	762556	4.28	2.965	mg/mL	14.6	1.3
4	RRT_1.949	9.000	42716	0.24	0.166	mg/mL	1.9	1.3

Fig. 3G



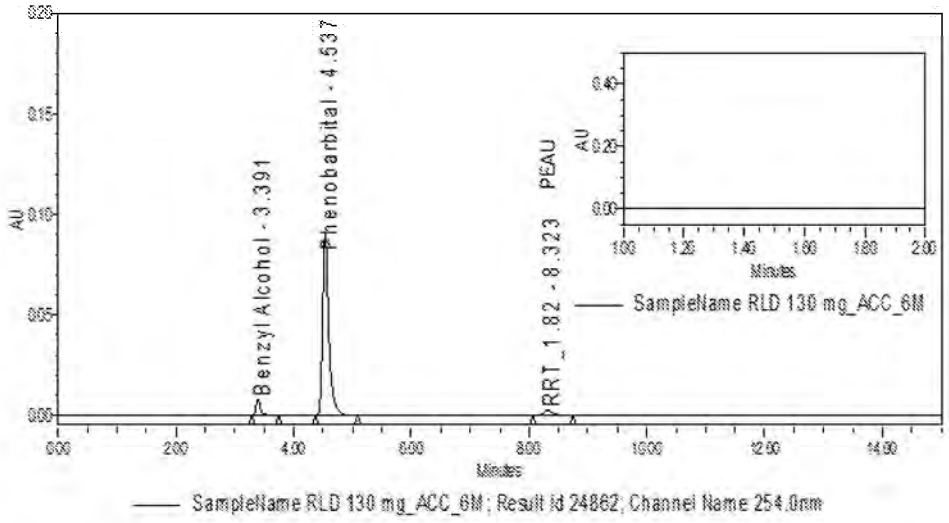
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.131	2358542	119.721	17.9	17563.1	1.0	110.3

Fig. 3H



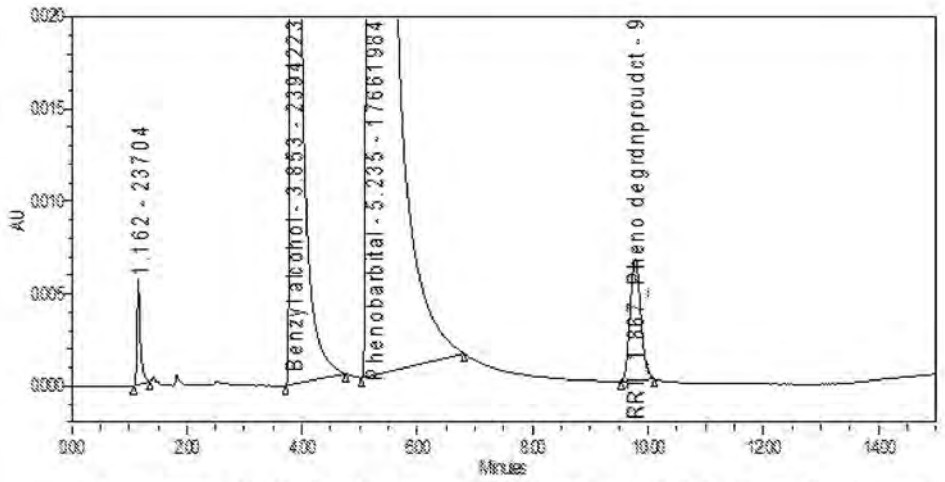
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43232	5.84	14.886	mg/mL	104.5		1.7
2	Phenobarbital	4.535	688747	93.10	113.015	mg/mL	95.2	7.2	1.5
3	RRT_1.82	8.322	7837	1.06	1.286	mg/mL		14.5	1.2

Fig. 3I



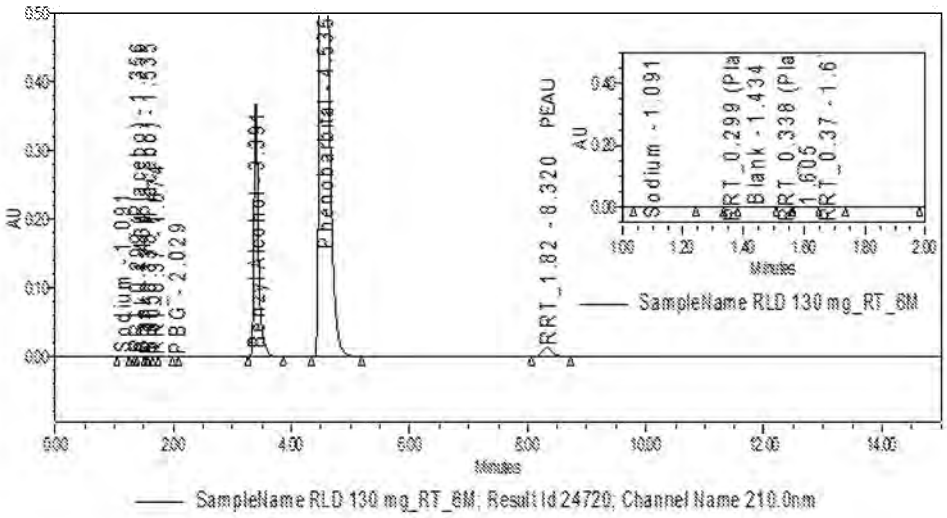
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43440	5.84	14.958	mg/mL	105.0		1.7
2	Phenobarbital	4.537	657548	89.99	107.895	mg/mL	90.9	7.2	1.5
3	RRT_1.82	8.323	29742	4.07	4.880	mg/mL		14.6	1.2

Fig. 3J



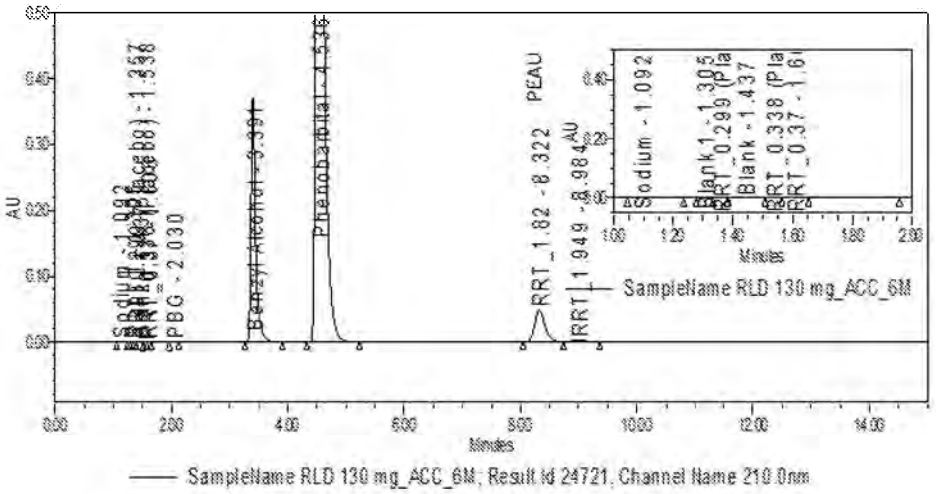
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3853	2394223	11.97	20.8	223.9	12438.0	1.5
2	Phenobarbital	5235	17661984	87.59	8.0	1144.4	11214.3	1.4
3	RRT_1.867_Pheno degrdnproudct	9.776	83649	0.41	16.6	3.5	19612.7	1.1

Fig. 3K



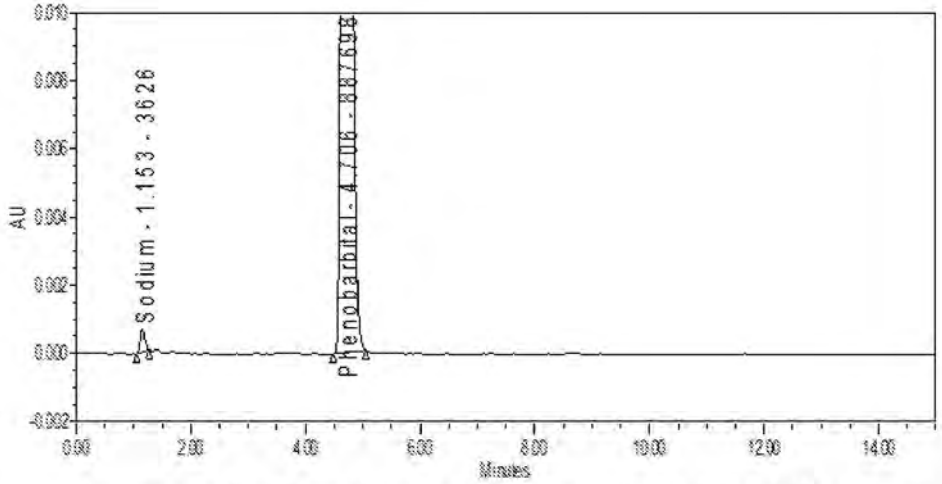
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1963213	11.91	16.081	mg/mL	13.4	1.7
2	Phenobarbital	4.535	14347574	87.08	111.565	mg/mL	7.1	1.5
3	RRT_1.82	8.320	162620	0.99	1.265	mg/mL	14.6	1.3

Fig. 3L



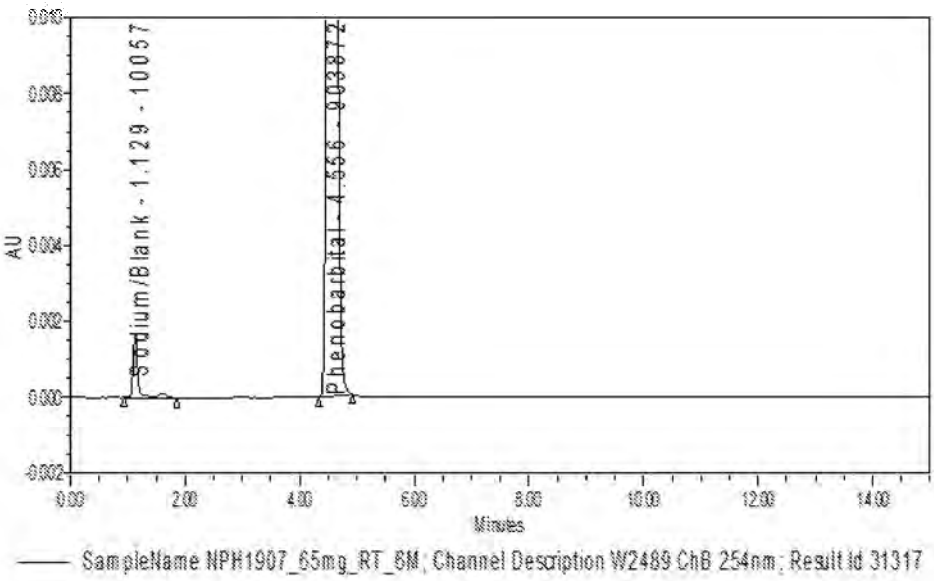
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1984788	12.10	16.258	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13768702	83.93	107.064	mg/mL	7.1	1.5
3	RRT_1.82	8.322	594916	3.63	4.626	mg/mL	14.6	1.2
4	RRT_1.949	8.984	48228	0.29	0.375	mg/mL	1.8	1.3

Fig. 4A



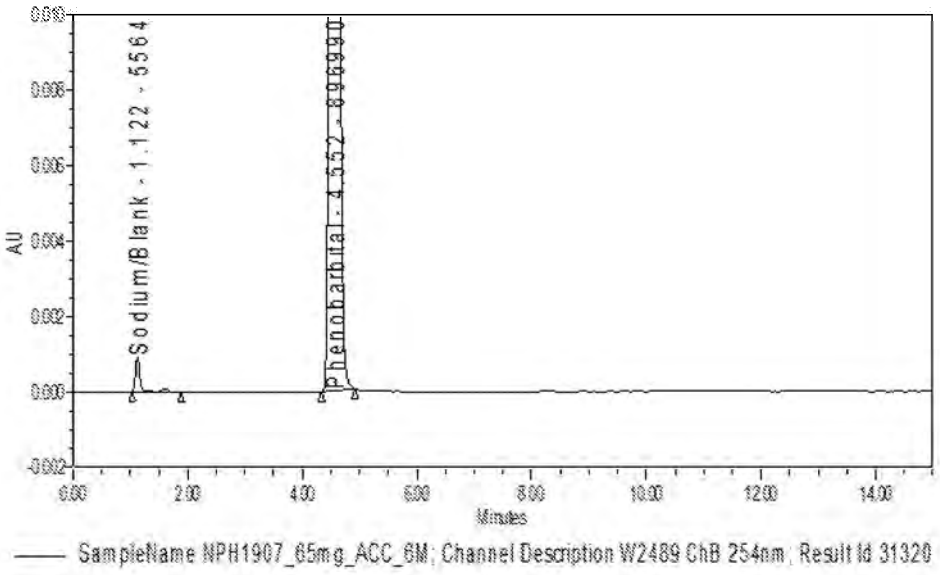
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.706	887598	58.858	mg/mL	99.1	19.3	52343.5	7952.5	1.2
2	Sodium	1.153	3626					318.4	943.9	1.1

Fig. 4B



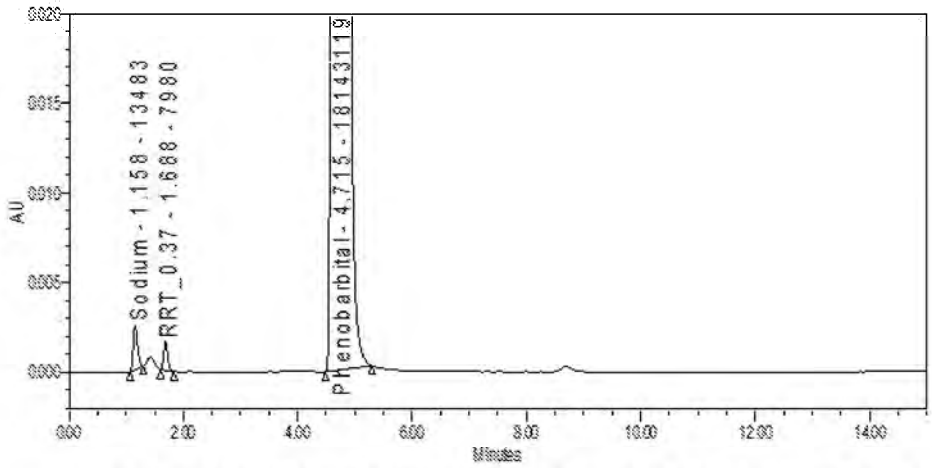
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.556	903872	59.368	mg/mL	100.0	20.8	44922.6	8704.0	1.1
2	Sodium/Blank	1.129	10057	0.661	mg/mL			616.7	1292.0	1.3

Fig. 4C



	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	S/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.552	896990	58.936	mg/mL	99.3	21.1	48295.1	8573.3	1.1
2	Sodium/Blank	1.122	5564	0.366	mg/mL			364.9	1275.7	1.3

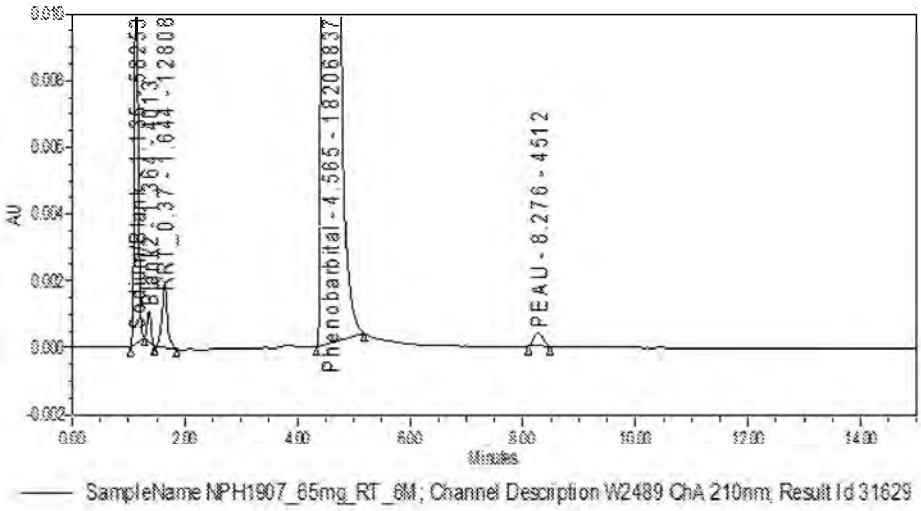
Fig. 4D



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14043

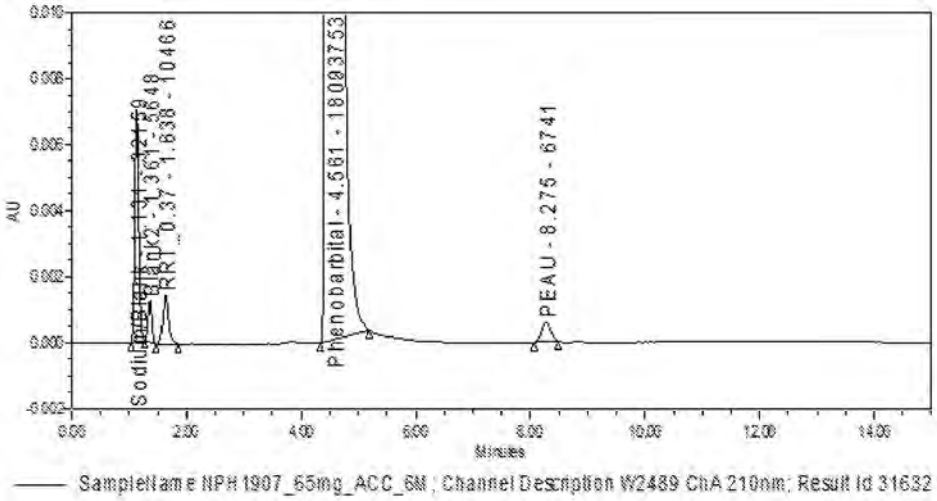
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.715	18143119	99.88	58.872	mg/mL	17.3	1973101.3	7634.1	1.2
2	RRT_0.37	1.688	7980	0.04	0.026	mg/mL	3.7	772.4	2602.8	1.2
3	Sodium	1.158	13483	0.07	0.044	mg/mL		1197.5	1039.2	1.2

Fig. 4E



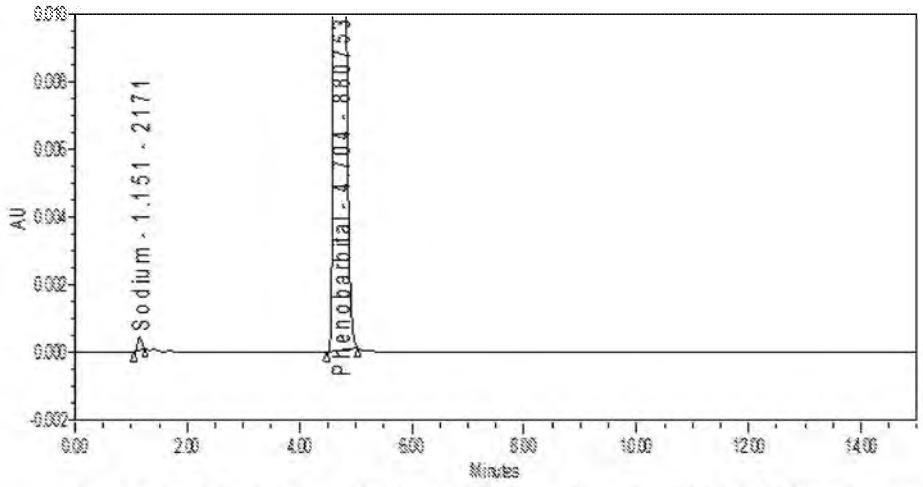
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.364	4513	0.02			1.9	826.1	2241.7	1.1
2	PEAU	8.276	4512	0.02	0.013	mg/mL	14.8	278.0	12299.1	1.1
3	Phenobarbital	4.565	18206837	99.56	53.971	mg/mL	15.2	16166754	6239.9	1.1
4	RRT_0.37	1.644	12808	0.07	0.038	mg/mL	1.9	1278.5	1540.7	1.1
5	SodiumBlank	1.135	58253	0.32	0.173	mg/mL		3406.1	1363.0	1.1

Fig. 4F



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.361	5848	0.03			1.9	899.0	2143.9	1.0
2	PEAU	8.275	6741	0.04	0.020	mg/mL	14.5	427.7	11916.8	1.0
3	Phenobarbital	4.581	18093753	99.70	53.635	mg/mL	15.2	1693108.6	8445.9	1.1
4	RRT_0.37	1.638	10466	0.06	0.031	mg/mL	1.9	1664.2	1482.5	1.1
5	Sodium/Blank	1.131	32159	0.18	0.095	mg/mL		4912.0	1362.2	1.1

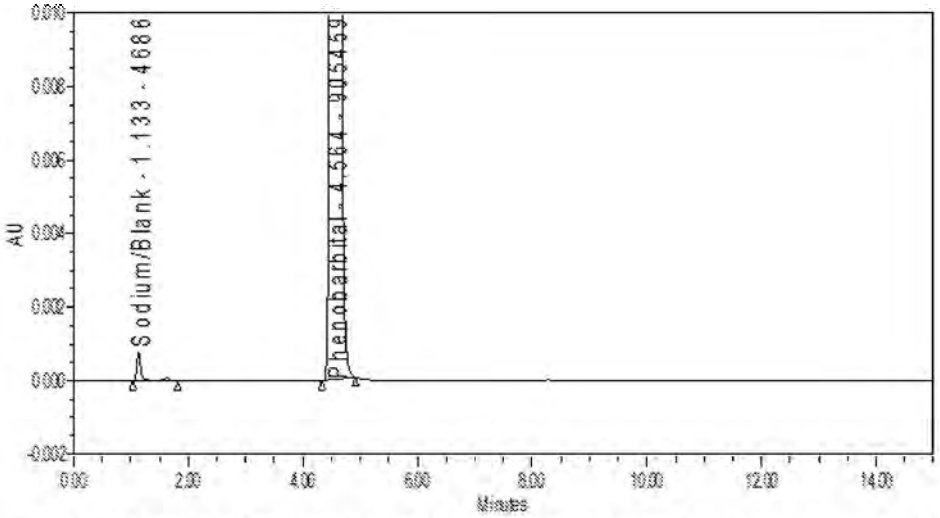
Fig. 4G



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13998

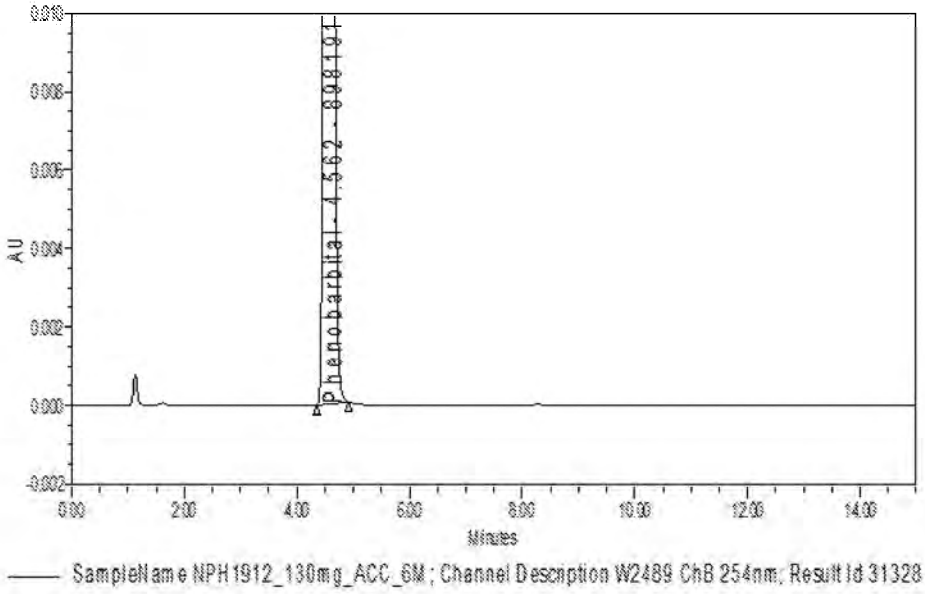
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.704	880753	116.796	mg/mL	98.3	19.3	40192.1	7866.8	1.2
2	Sodium	1.151	2171					148.3	959.0	1.0

Fig. 4H



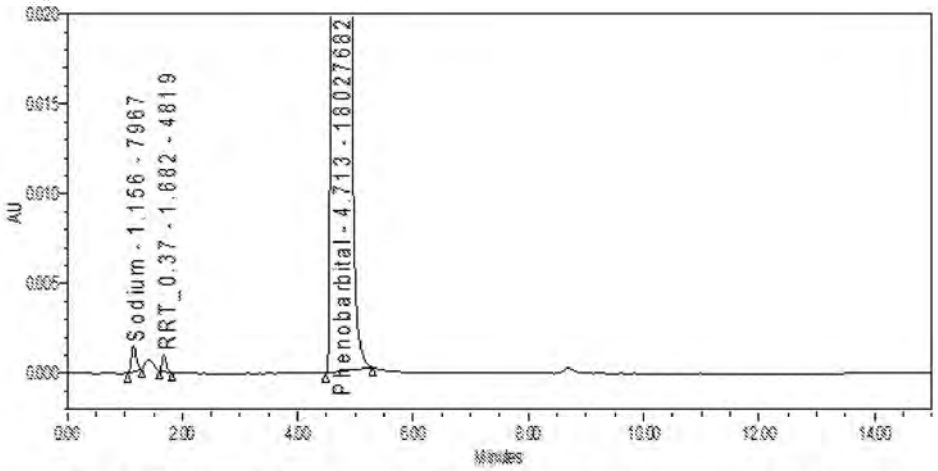
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.564	905459	118.985	mg/mL	100.2	20.7	55858.2	8639.9	1.1
2	Sodium/Blank	1.133	4686	0.616	mg/mL			358.4	1316.2	1.4

Fig. 4I



	Peak Name	RT	Area	Amount	Units	Assay	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.562	298191	118.000	mg/mL	99.4	553756	8698.8	1.1

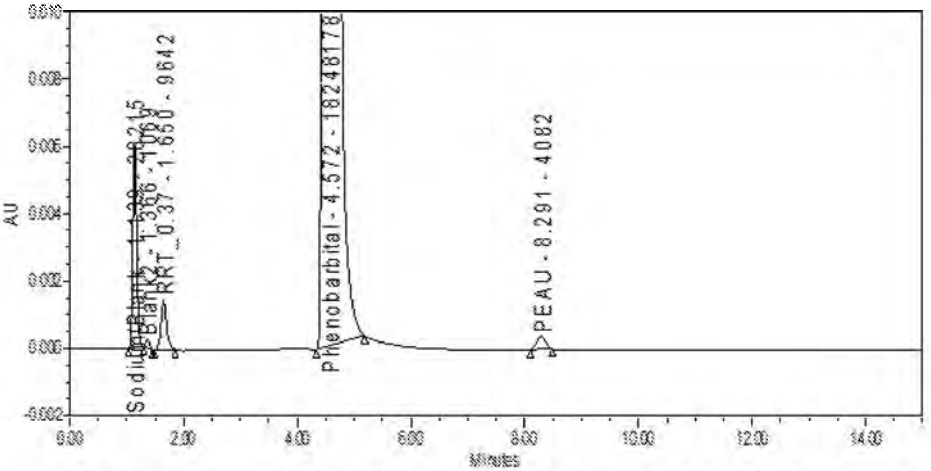
Fig. 4J



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14048

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.713	18027682	99.93	116.995	mg/mL	17.0	1001025.6	7849.3	1.2
2	RRT_0.37	1.682	4819	0.03	0.031	mg/mL	3.6	403.7	2401.3	1.2
3	Sodium	1.156	7967	0.04	0.052	mg/mL		649.1	941.5	1.1

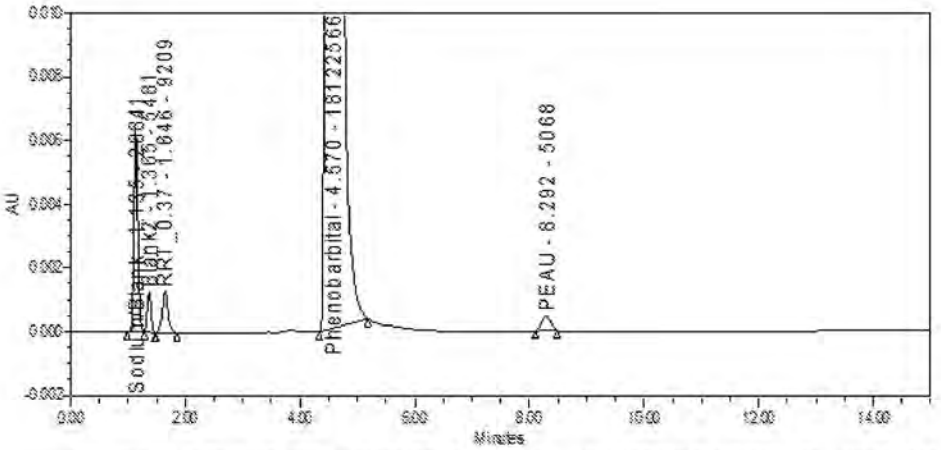
Fig. 4K



SampleName NPH1912_130mg_RT_6M; Channel Description W2489 ChA 210nm; Result Id 31637

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.366	1069	0.01			1.9	143.5	2247.2	1.1
2	PEAU	8.291	4082	0.02	0.024	mg/mL	14.8	213.9	12463.8	1.0
3	Phenobarbital	4.572	18248178	99.76	106.167	mg/mL	15.9	1373502.2	8426.5	1.1
4	RRT_0.37	1.650	9642	0.05	0.057	mg/mL	2.0	832.7	1618.4	1.1
5	SodiumBlank	1.139	28215	0.15	0.167	mg/mL		3438.2	1392.8	1.1

Fig. 4L



SampleName NPH1912_130mg_ACC_6M; Channel Description W2489 ChA 210nm; Result Id 31640

	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.365	5481	0.03			1.9	687.2	2149.1	1.1
2	PEAU	8.292	5068	0.03	0.030	mg/mL	14.8	256.0	12320.6	1.0
3	Phenobarbital	4.570	18122568	99.73	107.442	mg/mL	15.1	930658.2	8330.4	1.1
4	RRT_0.37	1.646	9209	0.05	0.055	mg/mL	1.8	725.3	14810	1.1
5	Sodium/Blank	1.135	28641	0.16	0.171	mg/mL		3440.5	1382.6	1.1

Fig. 5A

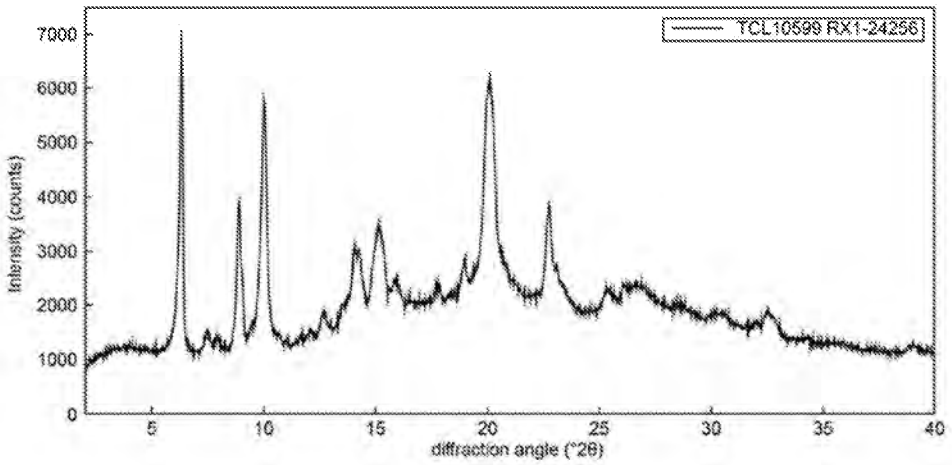

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4000
3000
2000
1000
0
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 5B

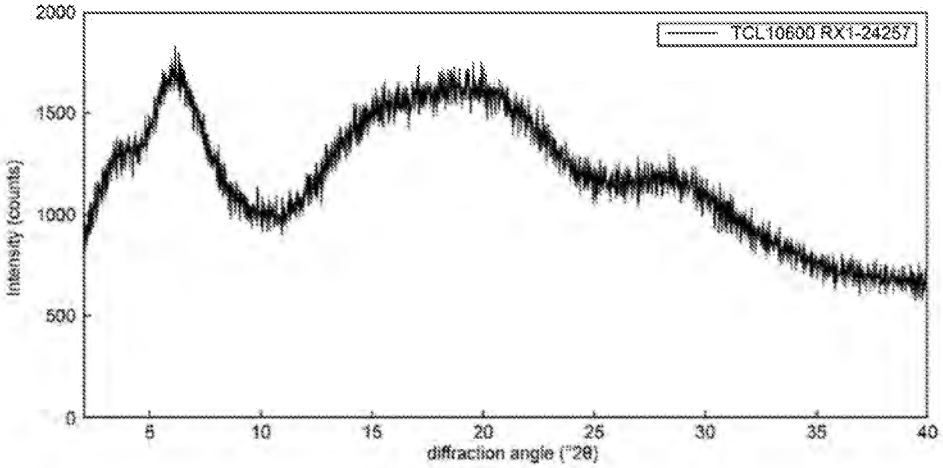

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1500
1000
500
0
Intensity (counts)
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10
15
20
25
30
35
40
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Fig. 5C

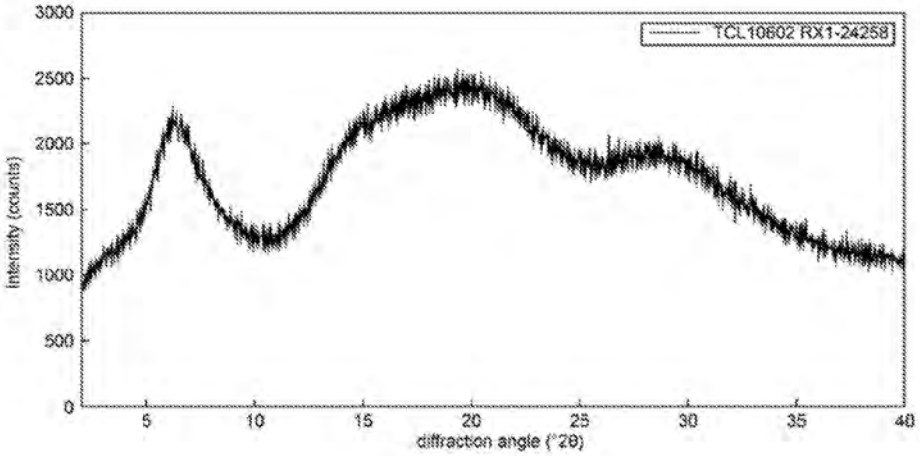

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1500
2000
2500
3000
5
10
15
20
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30
35
40

Fig. 5D

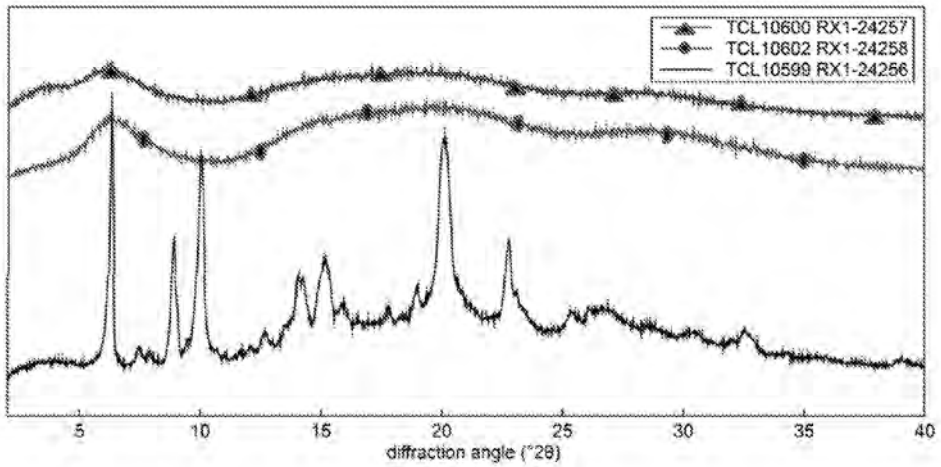

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TCL10602 RX1-24258
TCL10599 RX1-24256
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10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 1A



Fig. 1B

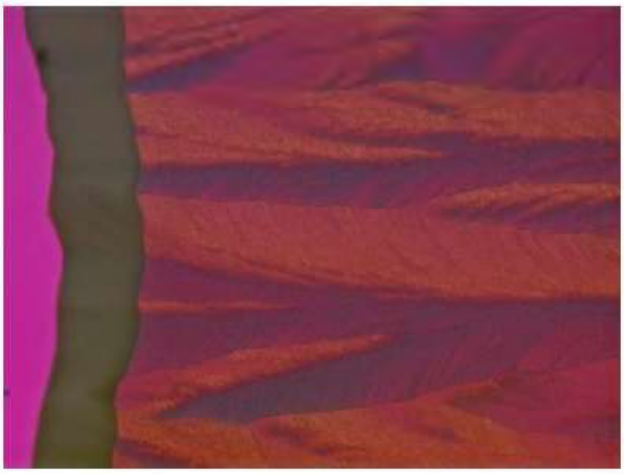


Fig. 1C



Fig. 1D



Fig. 1E

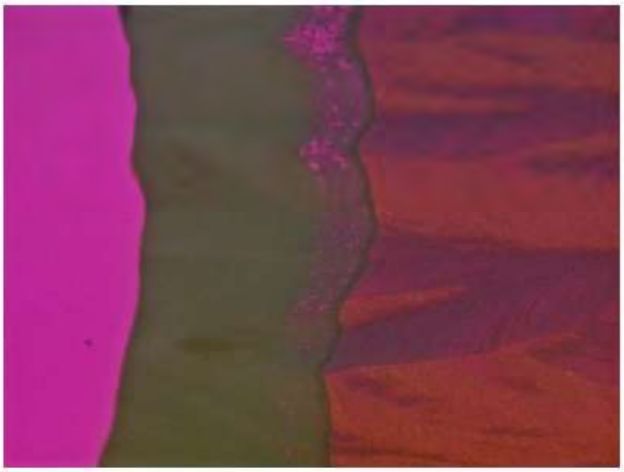


Fig. 1F

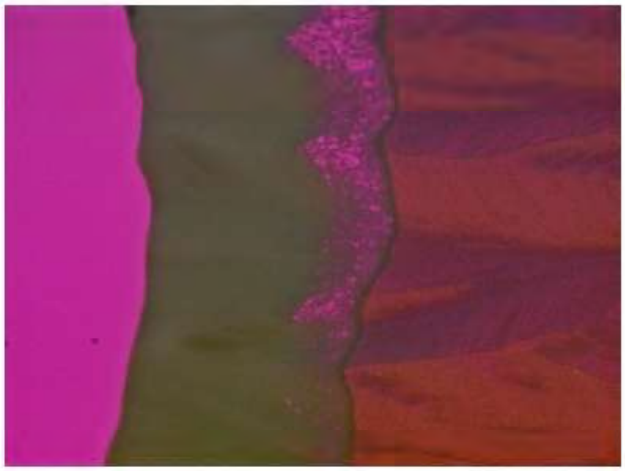


Fig. 2A

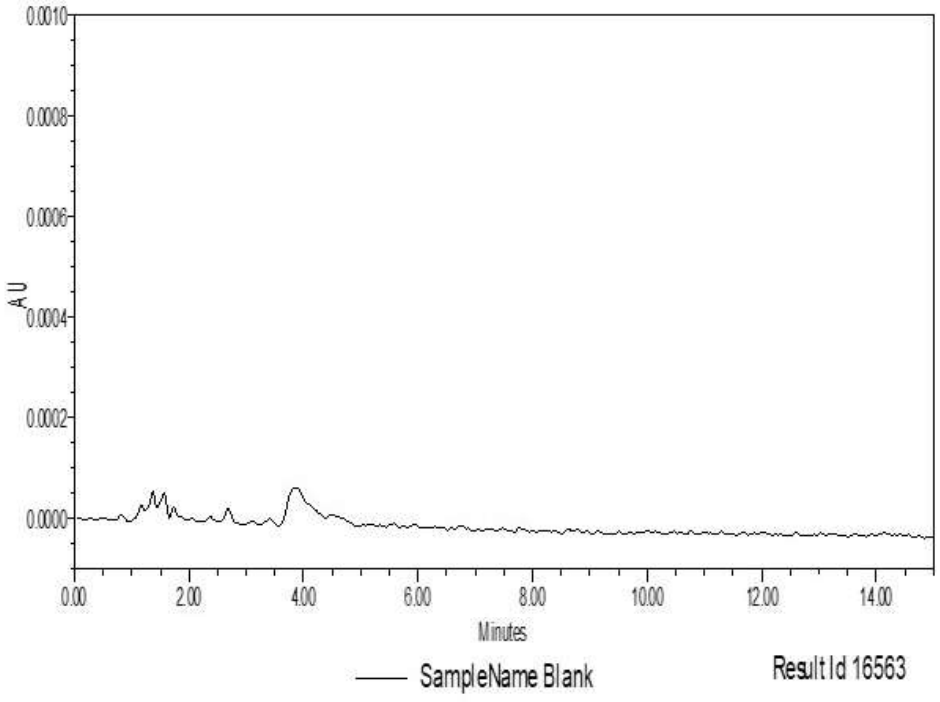
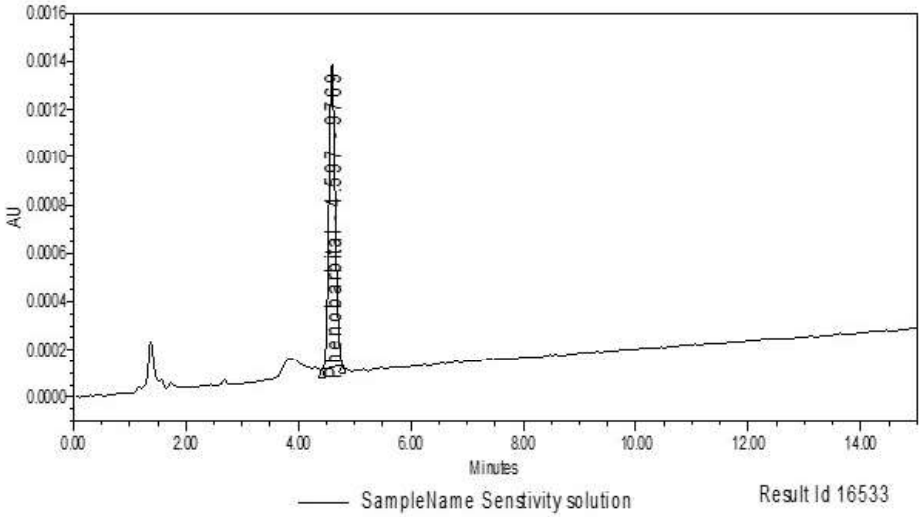
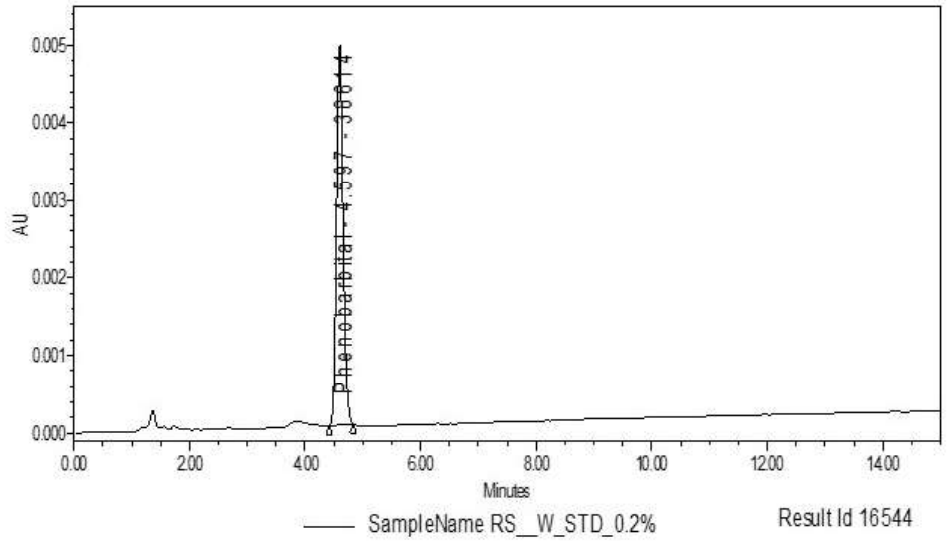

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Fig. 2B



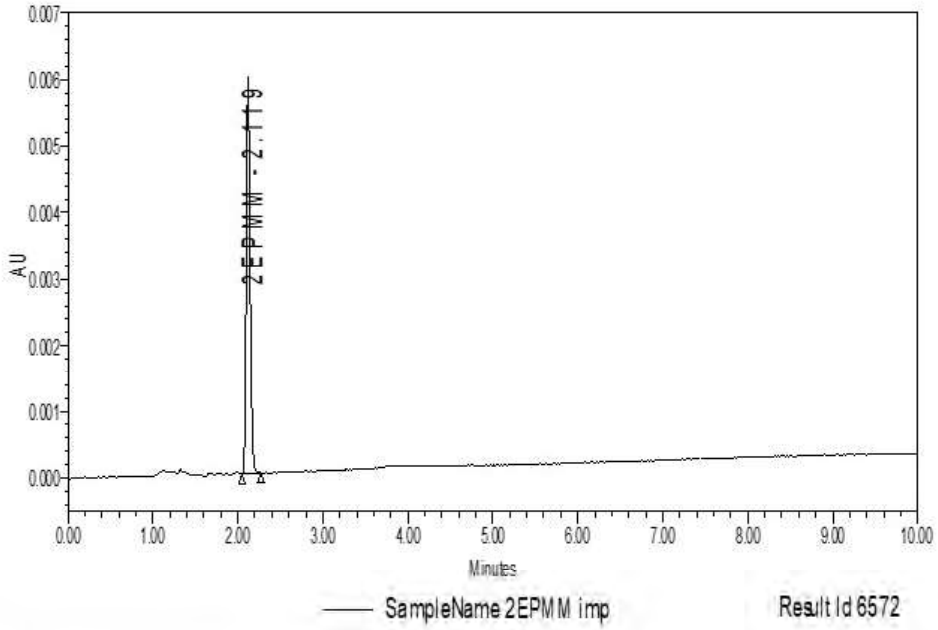
	Peak Name	RT	Area	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	9769	1054.848570	7861.1	1.1

Fig. 2C



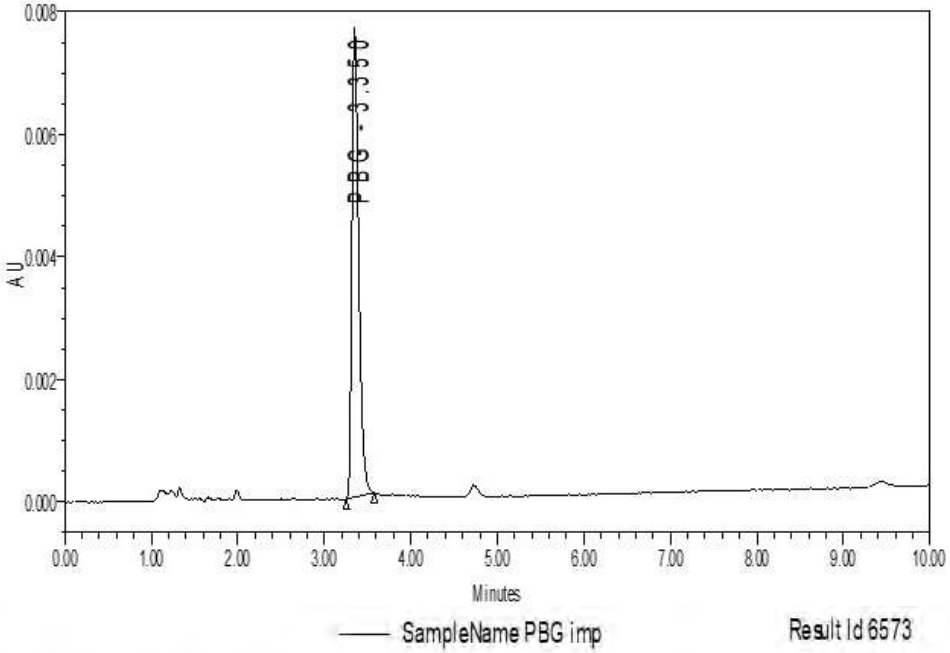
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	38614	0.001	2906.846635	7746.3	1.2

Fig. 2D



	PeakName	RT	Area	% Area	s/n	USP Plate Count	USP Tailing	Purity Angle	Purity Threshold
1	2EPMM	2.119	18797	100.00	1472	10573.6	1.2	0.674	1.833

Fig. 2E



	PeakName	RT	Area	% Area	s/n	USP Plate Count	USP Tailing	Purity Angle	Purity Threshold
1	PBG	3.350	41776	100.00	2090	8801.9	1.5	21.648	62.982

Fig. 2F

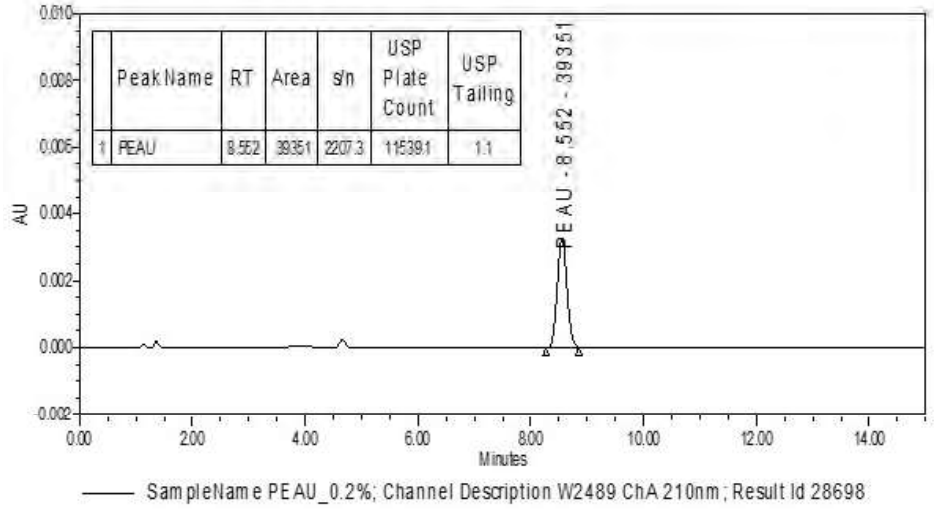

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s/n
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Minutes
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SampleName PEAU_0.2%; Channel Description W2489 ChA 210nm; Result Id 28698

Fig. 2G

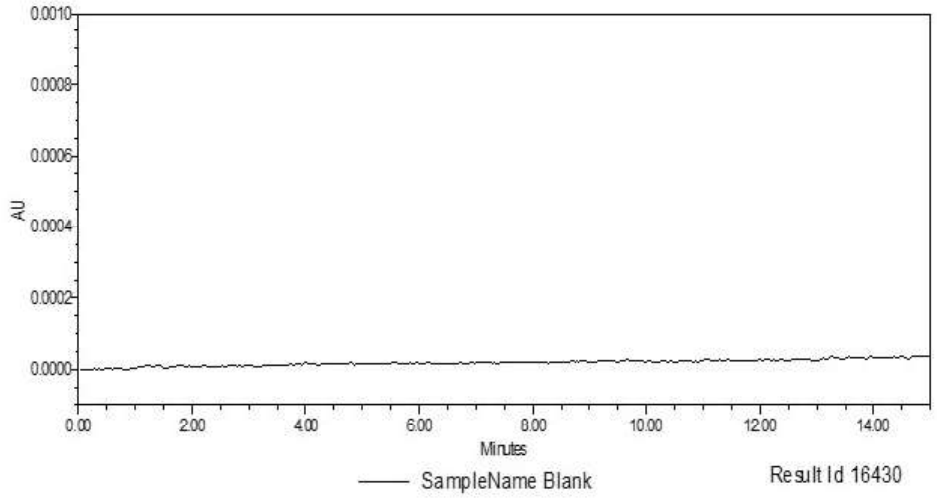
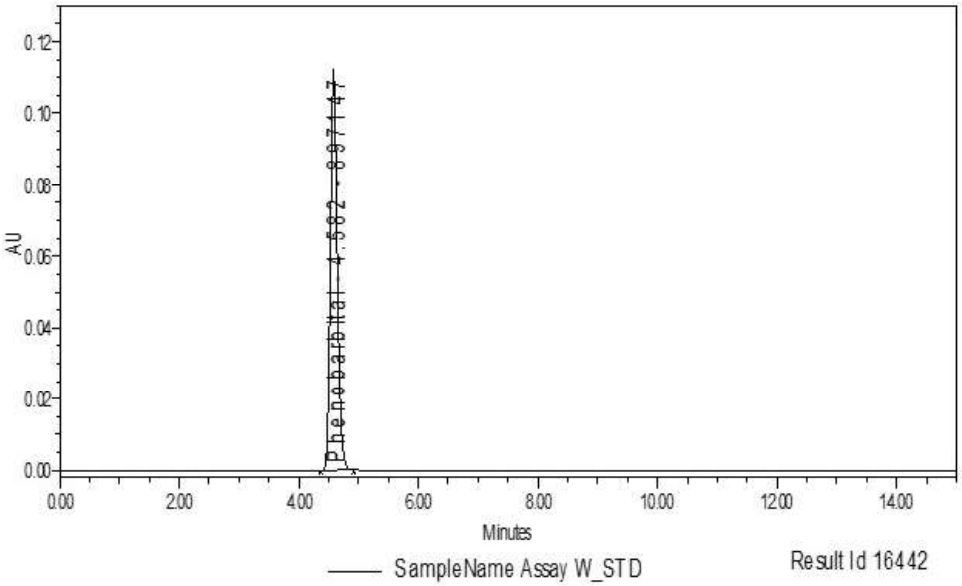
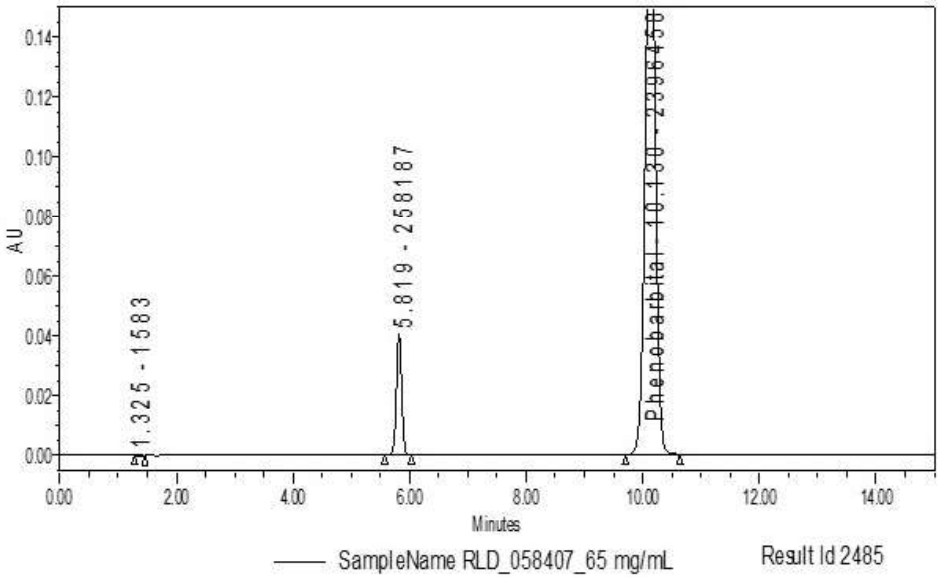

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Fig. 2H



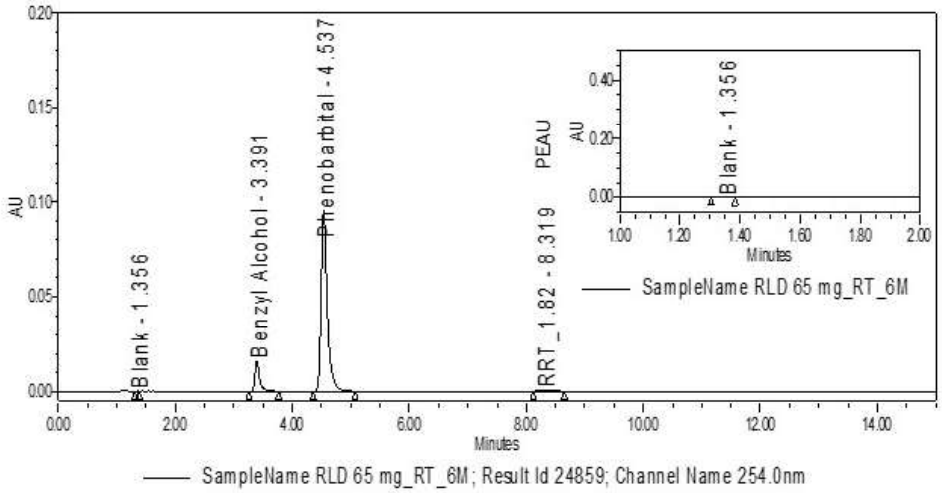
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.582	897147	0.476	50940.058185	7493.0	1.2

Fig. 3A



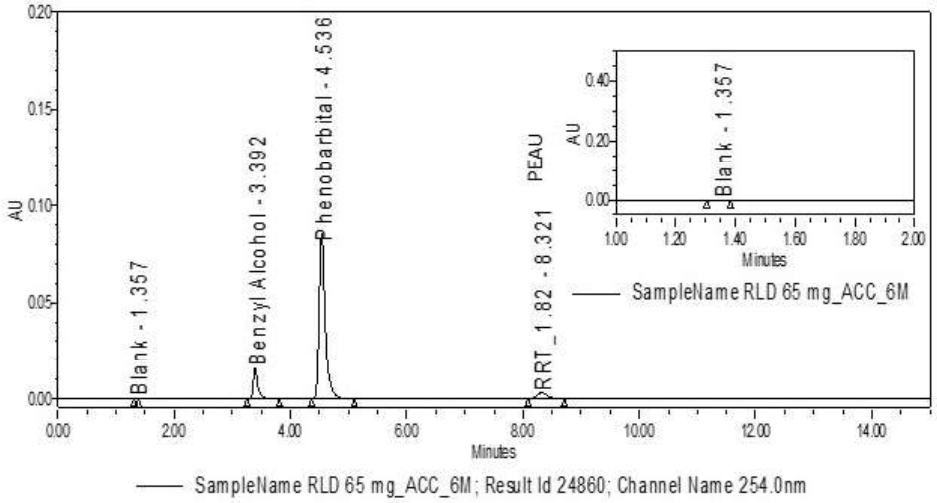
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.130	2396458	60.823	17.9	17534.1	1.0	112.1

Fig. 3B



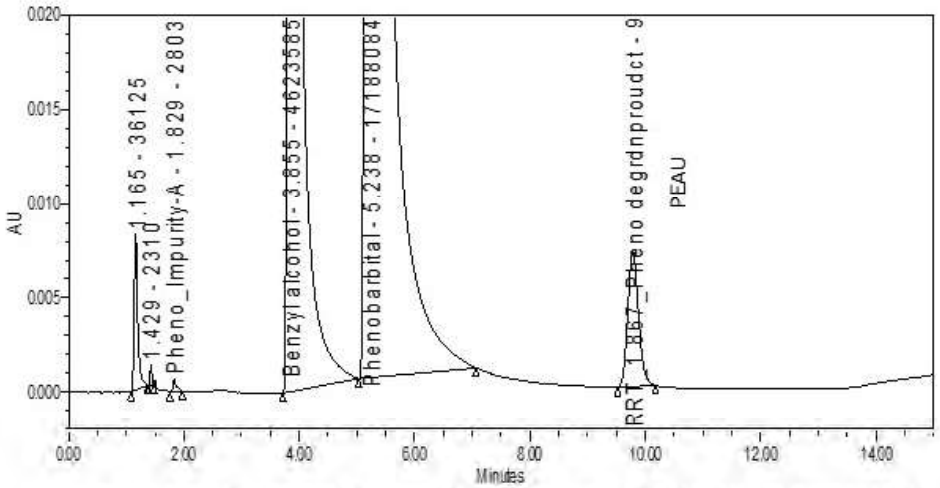
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	87091	10.96	14.994	mg/mL	105.2	23.7	1.7
2	Blank	1.356	828	0.10	0.068	mg/mL			1.0
3	Phenobarbital	4.537	697184	87.71	57.200	mg/mL	96.3	7.2	1.5
4	RRT_1.82	8.319	9745	1.23	0.800	mg/mL		15.0	1.3

Fig. 3C



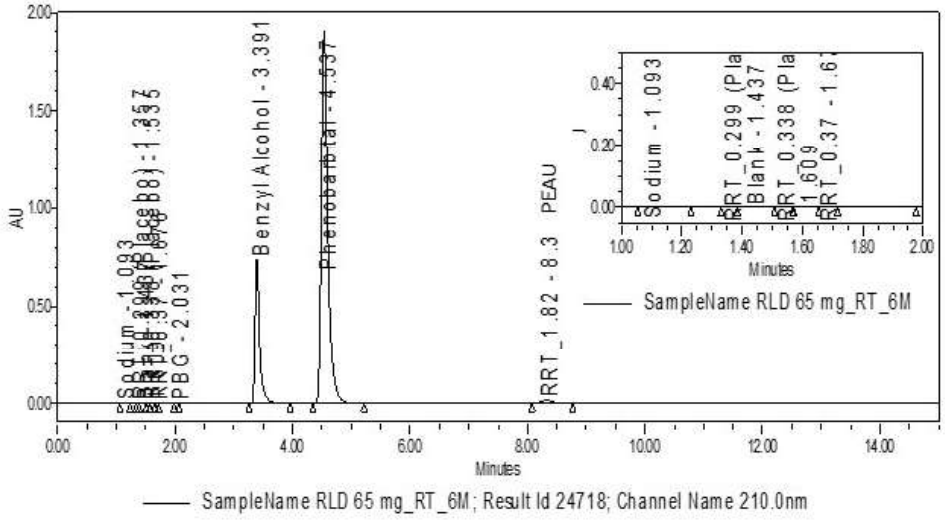
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	84435	11.25	14.537	mg/mL	102.0	23.7	1.7
2	Blank	1.357	798	0.11	0.065	mg/mL			1.1
3	Phenobarbital	4.536	627538	83.64	51.486	mg/mL	86.7	7.2	1.5
4	RRT_1.82	8.321	37484	5.00	3.075	mg/mL		14.6	1.2

Fig. 3D



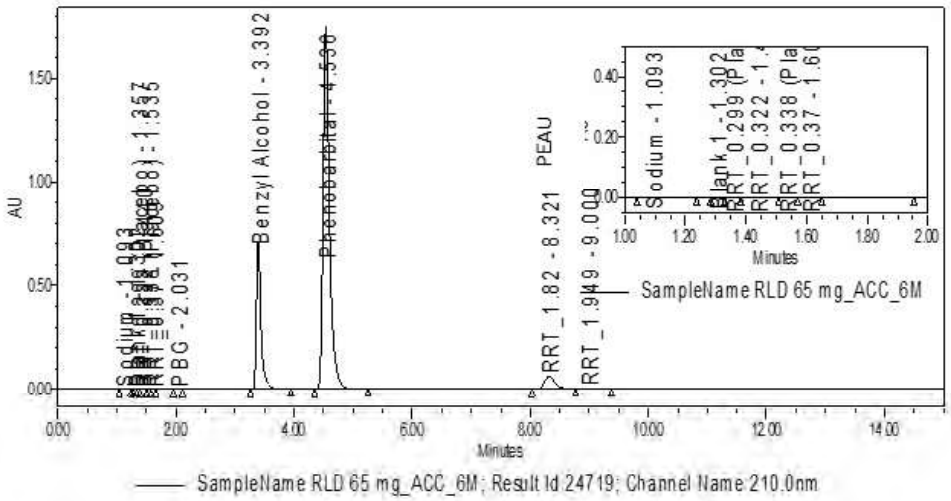
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.855	4623585	21.07	17.1	390.1	12312.8	1.5
2	Pheno_Impurity-A	1.829	2803	0.01	5.2	0.3	7608.2	1.6
3	Phenobarbital	5.238	17188084	78.32	8.0	1018.9	11239.0	1.4
4	RRT_1.867_Pheno degrdnproudct	9.781	92937	0.42	16.5	3.5	13191.8	1.2

Fig. 3E



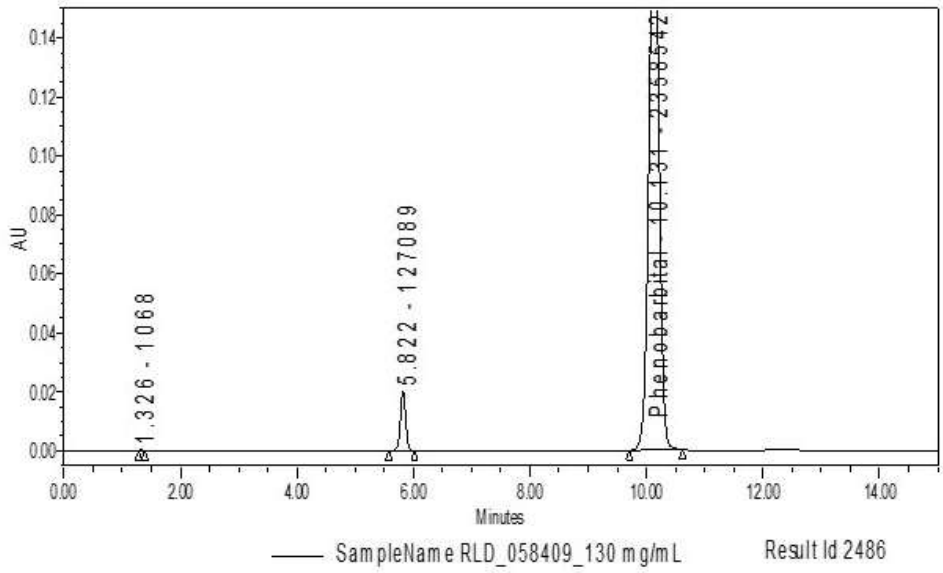
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	3972837	21.25	16.272	mg/mL	13.8	1.7
2	Phenobarbital	4.537	14515521	77.64	56.435	mg/mL	7.1	1.5
3	RRT_1.82	8.321	200110	1.07	0.778	mg/mL	14.6	1.3

Fig. 3F



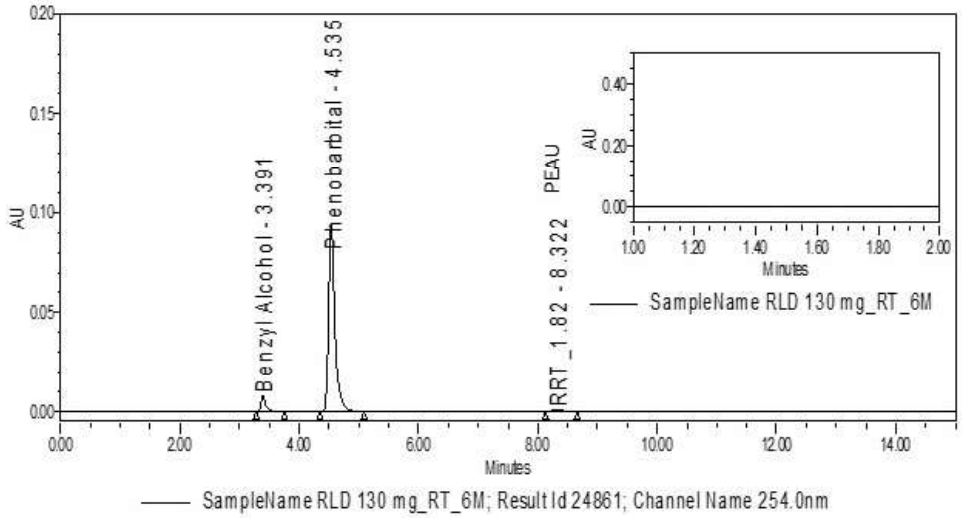
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	3833550	21.50	15.701	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13183528	73.94	51.257	mg/mL	7.1	1.5
3	RRT_1.82	8.321	762556	4.28	2.965	mg/mL	14.6	1.3
4	RRT_1.949	9.000	42716	0.24	0.166	mg/mL	1.9	1.3

Fig. 3G



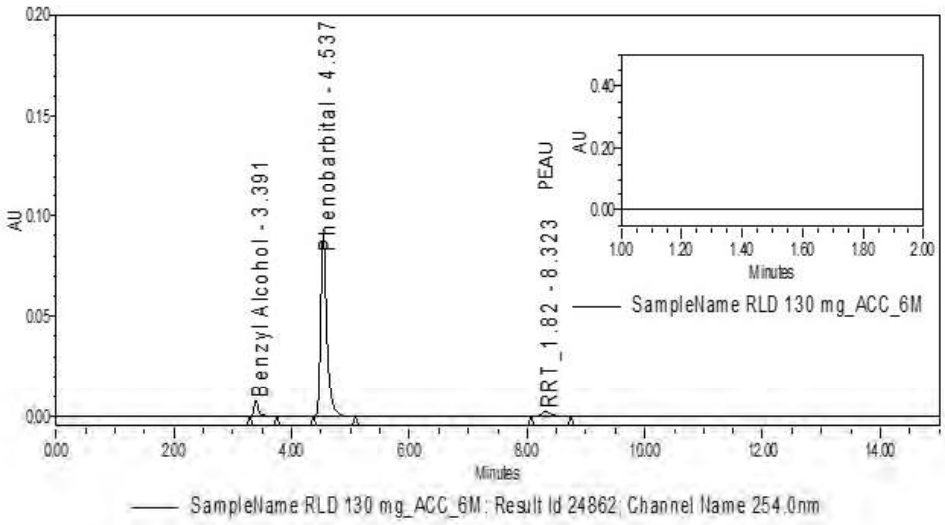
	Peak Name	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.131	2358542	119.721	17.9	17563.1	1.0	110.3

Fig. 3H



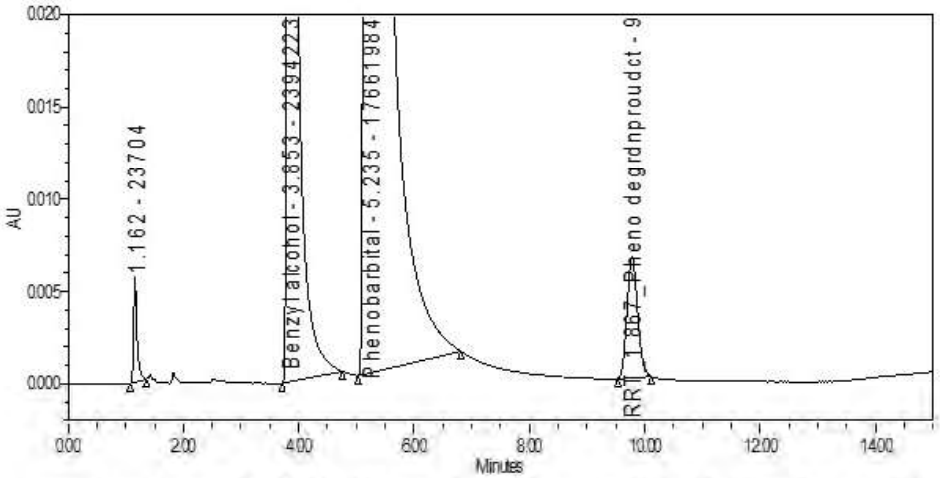
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43232	5.84	14.886	mg/mL	104.5		1.7
2	Phenobarbital	4.535	688747	93.10	113.015	mg/mL	95.2	7.2	1.5
3	RRT_1.82	8.322	7837	1.06	1.286	mg/mL		14.5	1.2

Fig. 3I



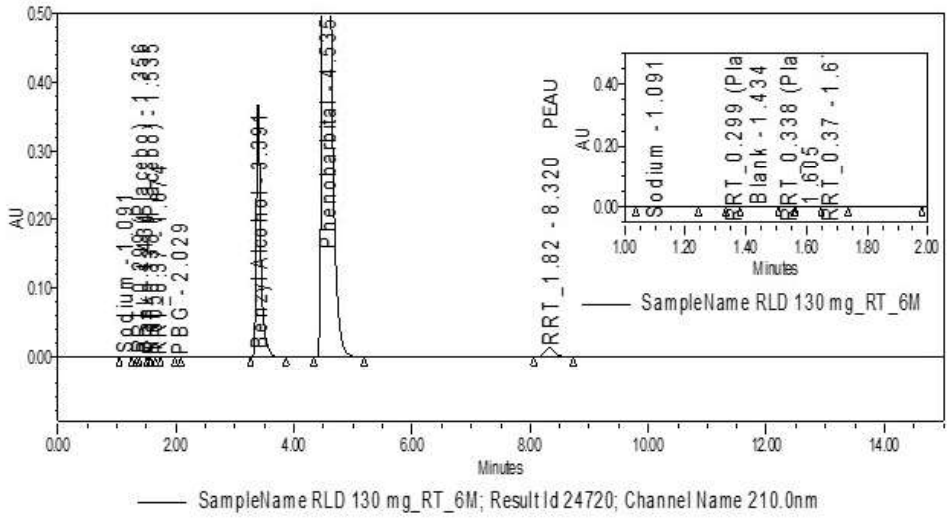
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43440	5.94	14.958	mg/mL	105.0		1.7
2	Phenobarbital	4.537	657548	89.99	107.895	mg/mL	90.9	7.2	1.5
3	RRT_1.82	8.323	29742	4.07	4.880	mg/mL		14.6	1.2

Fig. 3J



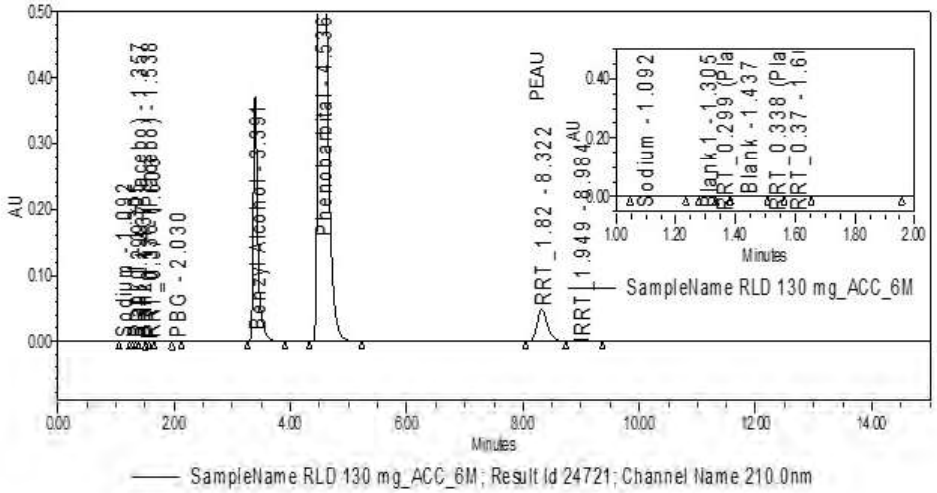
	Peak Name	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.853	2394223	11.87	20.8	223.9	12438.0	1.5
2	Phenobarbital	5.235	17661984	87.59	8.0	1144.4	11214.3	1.4
3	RRT_1.867_Pheno degrdnproudct	9.776	83640	0.41	16.6	3.5	13612.7	1.1

Fig. 3K



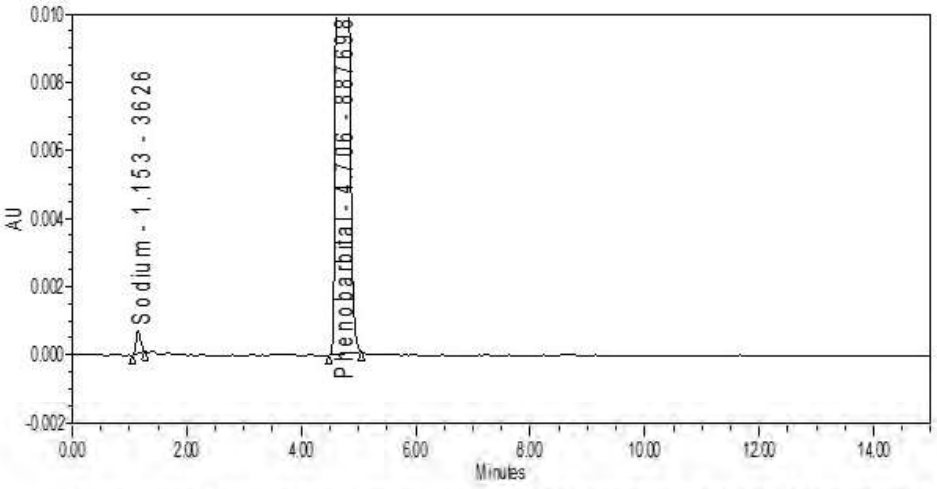
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1963213	11.91	16.081	mg/mL	13.4	1.7
2	Phenobarbital	4.535	14347574	87.06	111.565	mg/mL	7.1	1.5
3	RRT_1.82	8.320	162620	0.99	1.265	mg/mL	14.6	1.3

Fig. 3L



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1984788	12.10	16.258	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13768702	83.93	107.064	mg/mL	7.1	1.5
3	RRT_1.82	8.322	594916	3.63	4.626	mg/mL	14.6	1.2
4	RRT_1.949	8.984	48228	0.29	0.375	mg/mL	1.8	1.3

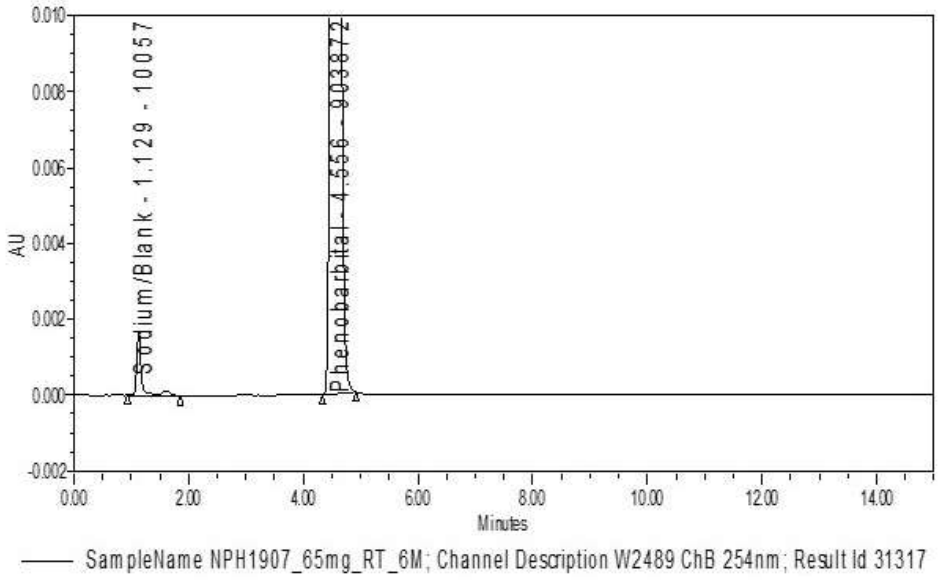
Fig. 4A



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13991

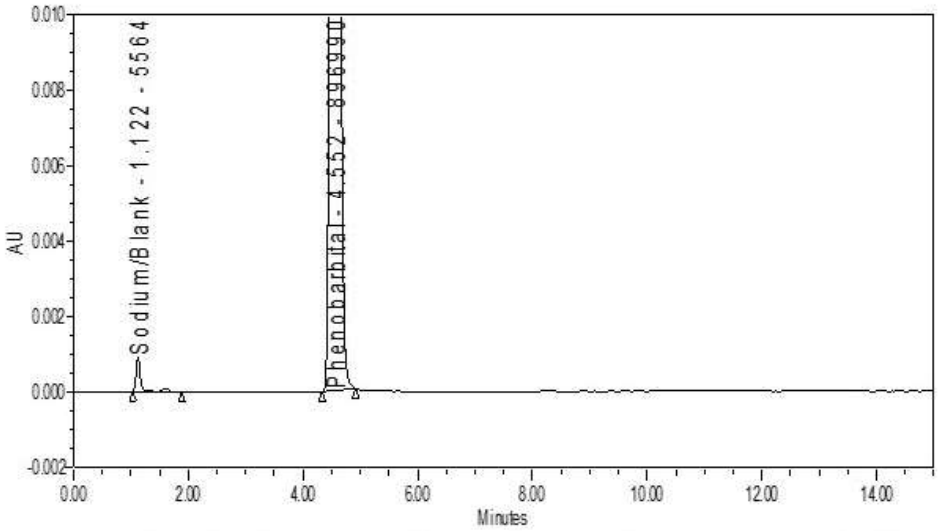
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.706	887698	58.858	mg/mL	99.1	19.3	52343.5	7952.5	1.2
2	Sodium	1.153	3626					318.4	943.9	1.1

Fig. 4B



	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.556	903872	59.388	mg/mL	100.0	20.8	44822.6	8704.0	1.1
2	Sodium/Blank	1.129	10057	0.661	mg/mL			616.7	1292.0	1.3

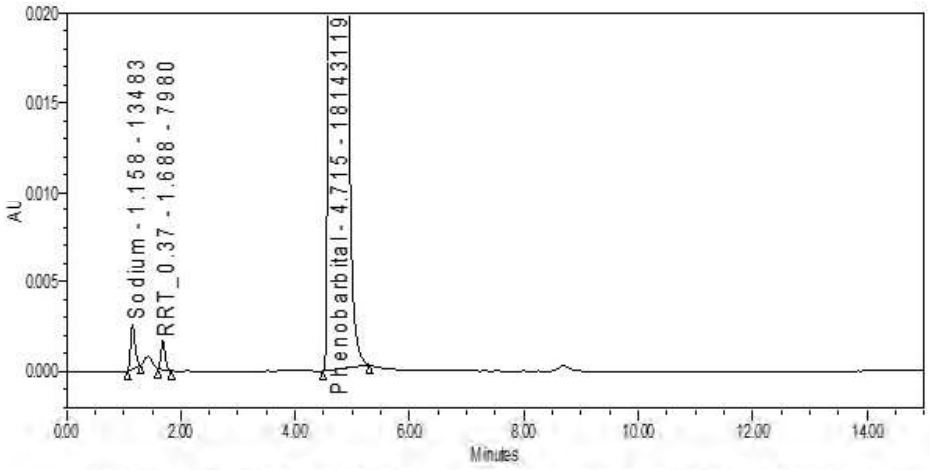
Fig. 4C



SampleName NPH1907_65mg_ACC_6M; Channel Description W2489 ChB 254nm; Result Id 31320

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.552	896990	58.936	mg/mL	99.3	21.1	48295.1	8573.3	1.1
2	Sodium/Blank	1.122	5564	0.366	mg/mL			364.9	1276.7	1.3

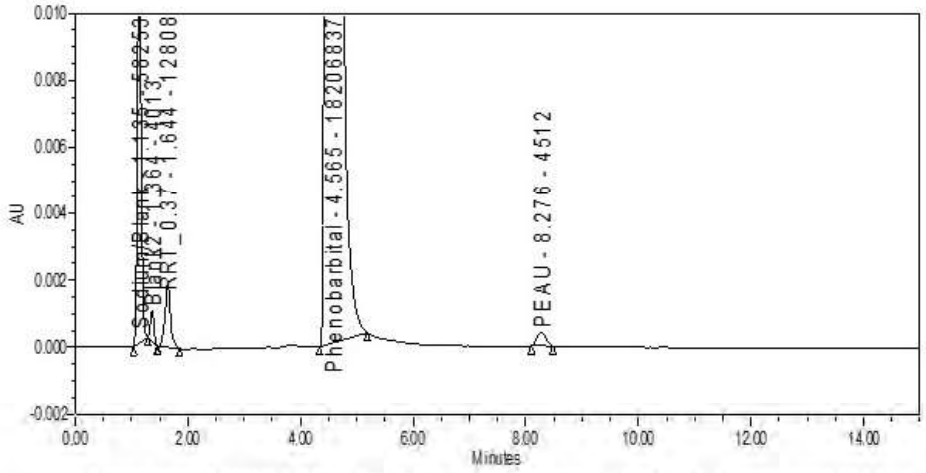
Fig. 4D



SampleName #NPH1907_Lyo_65mg/mL_Initial; Channel Description W2489 ChA 210nm; Result Id 14043

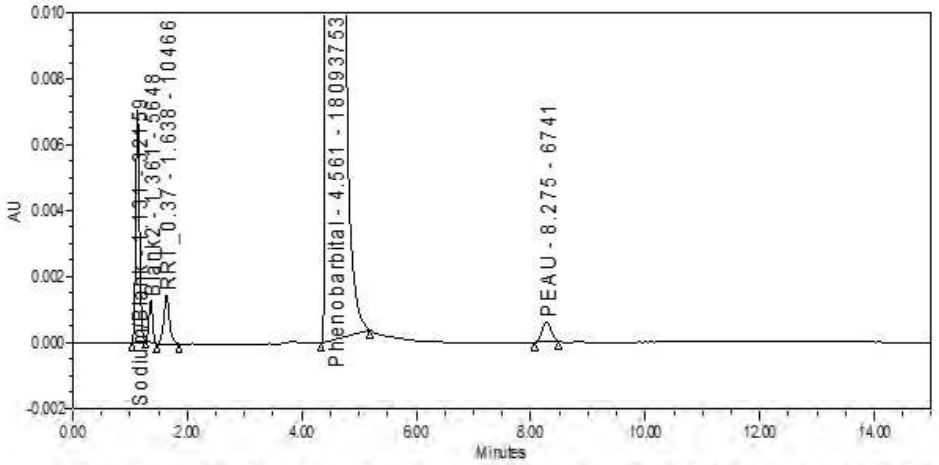
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.715	18143119	99.88	58.872	mg/mL	17.3	1073101.3	7604.1	1.2
2	RRT_0.37	1.688	7980	0.04	0.026	mg/mL	3.7	772.4	2602.6	1.2
3	Sodium	1.158	13483	0.07	0.044	mg/mL		1197.5	1039.2	1.2

Fig. 4E



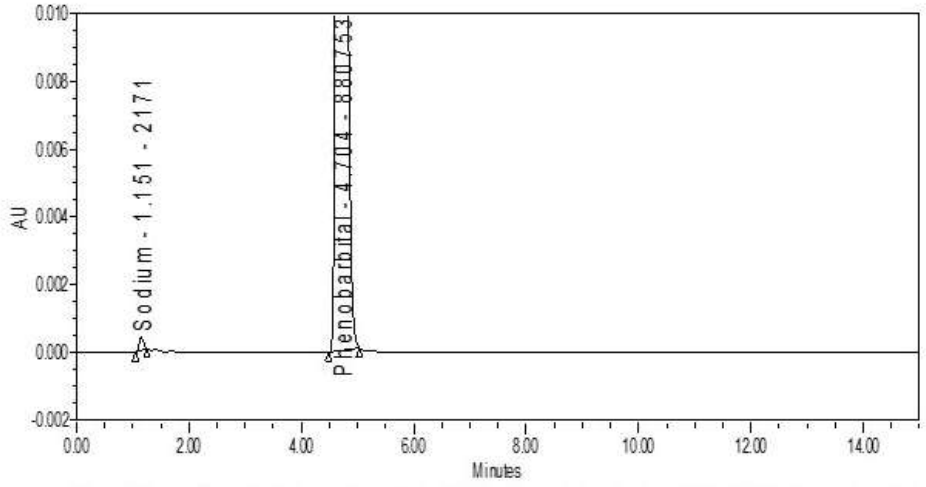
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.354	4013	0.02			1.9	626.1	2241.7	1.1
2	PEAU	8.276	4512	0.02	0.013	mg/mL	14.8	278.0	12299.1	1.1
3	Phenobarbital	4.565	18206837	99.56	53.971	mg/mL	15.2	1616675.4	8239.9	1.1
4	RRT_0.37	1.644	12808	0.07	0.038	mg/mL	1.9	1270.5	1640.7	1.1
5	Sodium/Blank	1.135	58253	0.32	0.173	mg/mL		8406.1	1363.0	1.1

Fig. 4F



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.361	5648	0.03			1.9	899.0	2143.9	1.0
2	PEAU	8.275	6741	0.04	0.020	mg/mL	14.6	427.7	11918.8	1.0
3	Phenobarbital	4.561	18093753	99.70	53.636	mg/mL	15.2	1693108.6	8445.9	1.1
4	RRT_0.37	1.638	10466	0.06	0.031	mg/mL	1.9	1064.2	1482.5	1.1
5	Sodium/Blank	1.131	32159	0.18	0.095	mg/mL		4912.0	1362.2	1.1

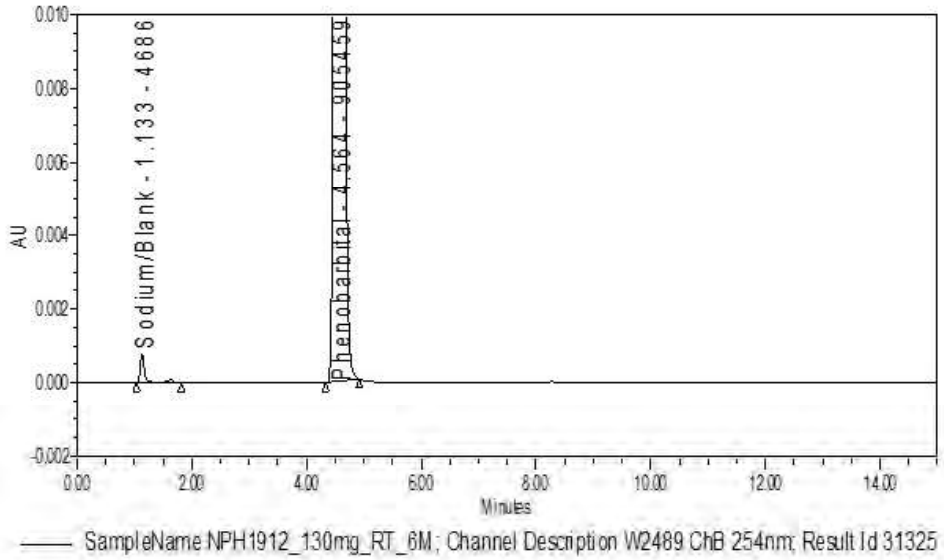
Fig. 4G



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChB 254nm; Result Id 13996

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.704	880753	116.796	mg/mL	98.3	19.3	40192.1	7866.8	1.2
2	Sodium	1.151	2171					148.3	959.0	1.0

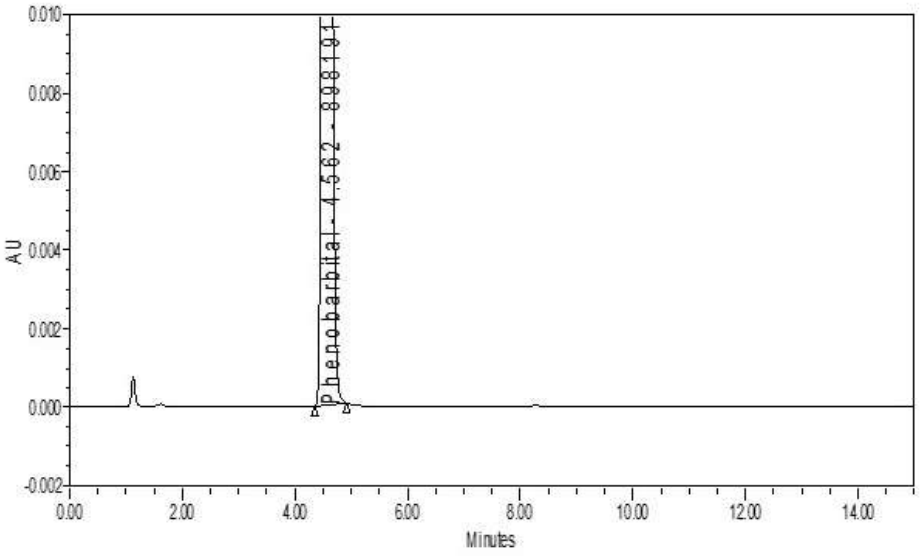
Fig. 4H



SampleName NPH1912_130mg_RT_6M; Channel Description W2489 ChB 254nm; Result Id 31325

	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.564	905459	118.985	mg/mL	100.2	20.7	55858.2	8639.9	1.1
2	Sodium/Blank	1.133	4686	0.616	mg/mL			358.4	1316.2	1.4

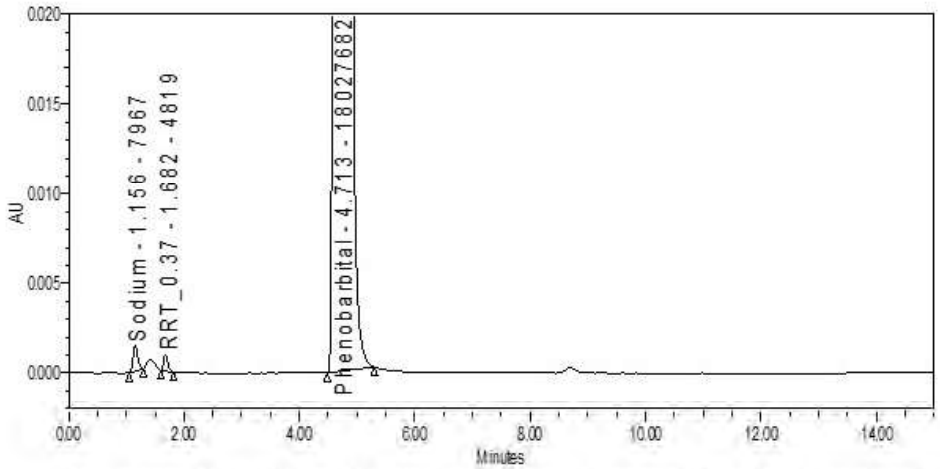
Fig. 4I



SampleName NPH1912_130mg_ACC_6M; Channel Description W2489 ChB 254nm; Result Id 31328

	Peak Name	RT	Area	Amount	Units	Assay	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.562	898191	118.030	mg/mL	99.4	55375.6	8693.8	1.1

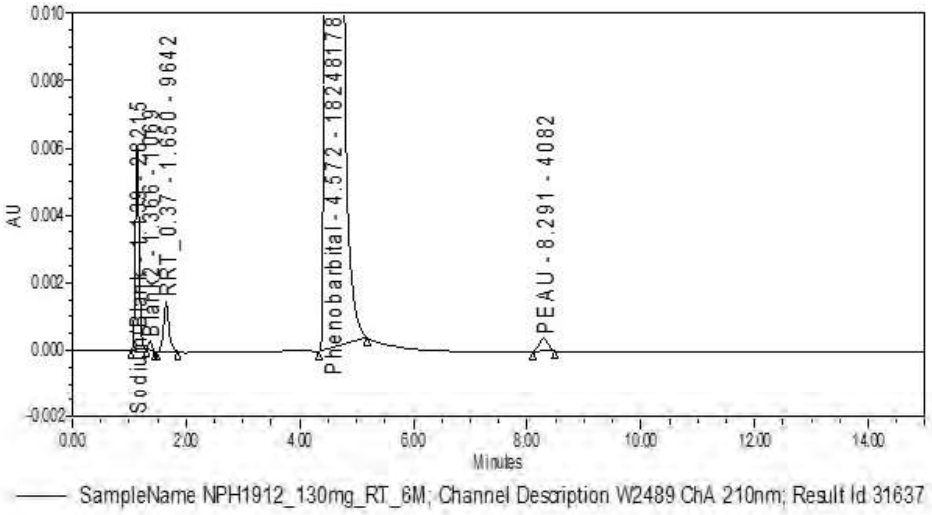
Fig. 4J



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description W2489 ChA 210nm ; Result Id 14048

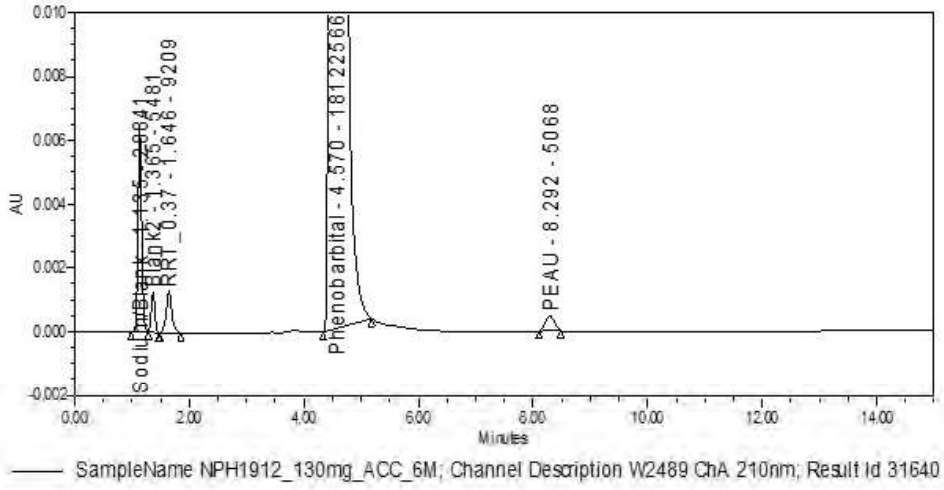
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.713	18027682	99.93	116.995	mg/mL	17.0	1001026.6	7649.3	1.2
2	RRT_0.37	1.682	4819	0.03	0.031	mg/mL	3.6	433.7	2401.3	1.2
3	Sodium	1.156	7967	0.04	0.052	mg/mL		649.1	941.5	1.1

Fig. 4K



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.366	1069	0.01			1.9	143.5	2247.2	1.1
2	PEAU	8.291	4082	0.02	0.024	mg/mL	14.8	213.9	12463.8	1.0
3	Phenobarbital	4.572	18248178	99.76	108.187	mg/mL	15.9	1373502.2	8426.5	1.1
4	RRT_0.37	1.650	9642	0.05	0.057	mg/mL	2.0	832.7	1618.4	1.1
5	Sodium/Blank	1.139	28215	0.15	0.167	mg/mL		3438.2	1382.8	1.1

Fig. 4L



	PeakName	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.365	5481	0.03			1.9	687.2	2149.1	1.1
2	PEAU	8.292	5068	0.03	0.030	mg/mL	14.8	256.0	12320.6	1.0
3	Phenobarbital	4.570	18122566	99.73	107.442	mg/mL	15.1	1320858.2	8330.4	1.1
4	RRT_0.37	1.646	9209	0.05	0.055	mg/mL	1.8	725.3	1481.0	1.1
5	Sodium/Blank	1.135	28841	0.16	0.171	mg/mL		3440.5	1392.6	1.1

Fig. 5A

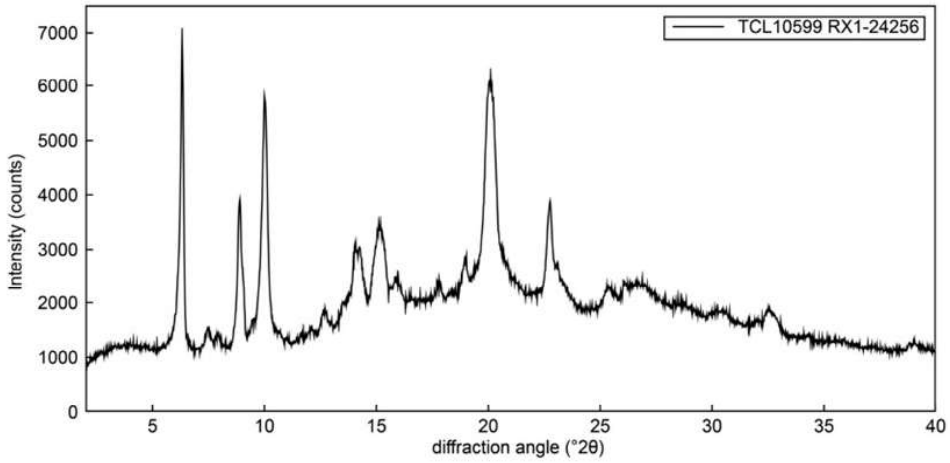

TCL10599 RX1-24256
Intensity (counts)
diffraction angle (°2θ)
0
1000
2000
3000
4000
5000
6000
7000
5
10
15
20
25
30
35
40

Fig. 5B

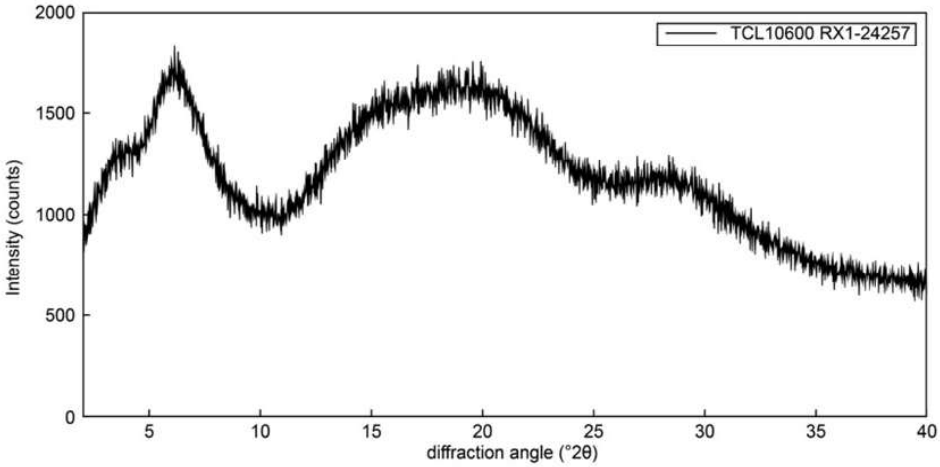

TCL10600 RX1-24257
Intensity (counts)
2000
1500
1000
500
0
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

Fig. 5C

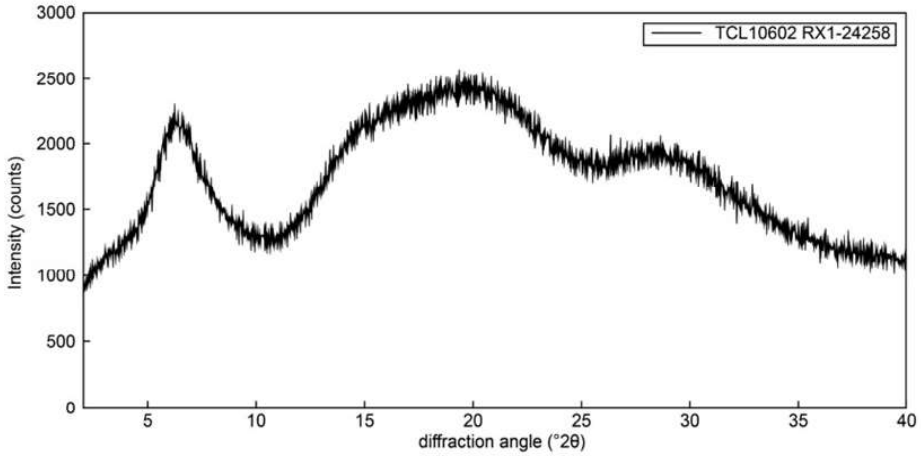
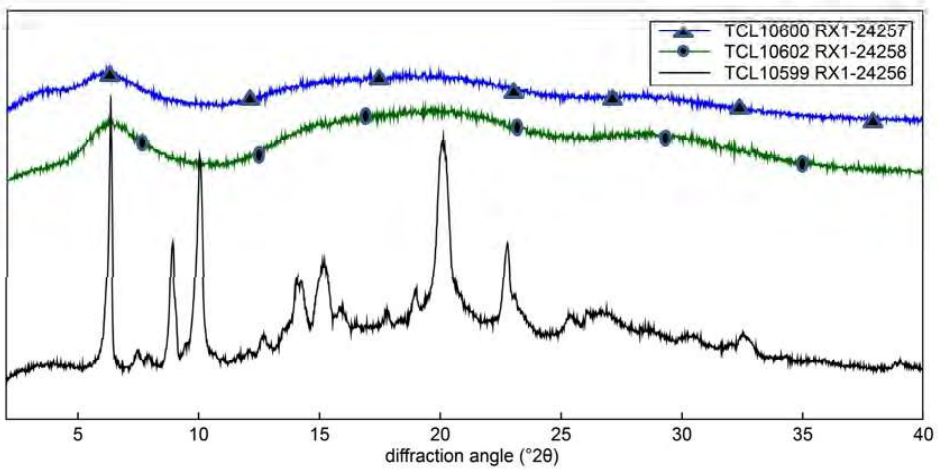

TCL10602 RX1-24258
Intensity (counts)
diffraction angle (°2θ)
0
500
1000
1500
2000
2500
3000
5
10
15
20
25
30
35
40

Fig. 5D


TCL10600 RX1-24257
TCL10602 RX1-24258
TCL10599 RX1-24256
5
10
15
20
25
30
35
40
diffraction angle (°2θ)

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Lyophilized Compositions of Phenobarbital Sodium Salt

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [x] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application

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LEGAL NAME OF INVENTOR

Inventor: Anand Shukla Date (Optional): _____

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Bala Tripura Sundari Chodavarapu Date (Optional) : _____

Signature: Bala Tripura Sundari Chodavarapu

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Jay Shukla Date (Optional) : _____

Signature: Jay Shukla

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LEGAL NAME OF INVENTOR

Inventor: Dasaradhi Lakkaraju Date (Optional): _____

Signature: Dasaradhi Lakkaraju

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LEGAL NAME OF INVENTOR

Inventor: Thirupathi Mangali Date (Optional): _____

Signature: Thirupathi Mangali

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Application Number:					
Filing Date:					
Title of Invention:	LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT				
First Named Inventor/Applicant Name:	Bala Tripura Sundari CHODAVARAPU				
Filer:	Martin Fessenmaier/Danielle Moroz				
Attorney Docket Number:	104078.0001US				
Filed as Small Entity					
Filing Fees for Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a)					
Description		**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:					
UTILITY FILING FEE (ELECTRONIC FILING)		4011	1	75	75
UTILITY SEARCH FEE		2111	1	330	330
UTILITY EXAMINATION FEE		2311	1	380	380
REQUEST FOR PRIORITIZED EXAMINATION		2817	1	2000	2000
Pages:					
Claims:					
Miscellaneous-Filing:					

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2855**

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Document Date - 2020-09-18

Document Title - Applicant Communication Re: Entity Status Set to Undiscounted (Initial Default Setting or Status Change)

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Document Date - 2020-09-28

Document Title - Applicant Communication Re: Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
17/025,881	09/18/2020	1615	785	104078.0001US	20	2

CONFIRMATION NO. 8113

149344
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

FILING RECEIPT

OC000000120226855

Date Mailed: 09/29/2020

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Inventor(s)

Bala Tripura Sundari Chodavarapu, Davis, CA;
Thirupathi Mangali, Sacramento, CA;
Jay Shukla, Sacramento, CA;
Anand Shukla, Denver, CO;
Dasaradhi Lakkaraju, Sacramento, CA;

Applicant(s)

Nivagen Pharmaceuticals, Inc., Sacramento, CA;

Assignment For Published Patent Application

Nivagen Pharmaceuticals, Inc., Sacramento, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 62/903,511 09/20/2019

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 09/28/2020
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/025,881**
Projected Publication Date: 03/25/2021
Non-Publication Request: No
Early Publication Request: No
** **SMALL ENTITY** **
Title

Lyophilized Compositions of Phenobarbital Sodium Salt

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/025,881	09/18/2020	Bala Tripura Sundari Chodavarapu	104078.0001US	8113

149344 7590 10/21/2020

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
ART UNIT	PAPER NUMBER
1615	

NOTIFICATION DATE	DELIVERY MODE
10/21/2020	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@umbergzipser.com
rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 17/025,881	**Applicant(s)** Chodavarapu et al.	
	Examiner DIANE C GOODWYN	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 18 September 2020 IS **GRANTED** .

The above-identified application has met the requirements for prioritized examination

A. ☑ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination**. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims** , or a multiple dependent claim;

C. filing a **request for continued examination** ;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to DIANE GOODWYN at (571) 272-6735. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/DIANE C GOODWYN/ Paralegal Specialist, OPET	

U.S. Patent and Trademark Office
PTO-2298 (Rev. 02-2012)

To: rdean@umbergzipser.com,patents@umbergzipser.com,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 149344

Oct 22, 2020 03:50:24 AM

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Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614
UNITED STATES

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The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

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Application	Document	Mailroom Date	Attorney Docket No.
17025881	TRACK1.GRANT	10/21/2020	104078.0001US

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/025,881	09/18/2020	Bala Tripura Sundari Chodavarapu	104078.0001US	8113

149344 7590 11/30/2020

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

EXAMINER	
ZHANG, YANZHI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
11/30/2020	ELECTRONIC

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rdean@umbergzipser.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 17/025,881	Applicant(s) Chodavarapu et al.	
	Examiner YANZHI ZHANG	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 09/18/20.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) ____ is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☑ Claim(s) 1-20 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on ____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. ____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date ____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date ____.

4) ☐ Other: ____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Status

This action is a response to papers filed on September 18, 2020. Claims 1-20 are pending in the application and under consideration on the merit.

Priority

This application claims priority benefit from U.S. Provisional Patent Application 62/903.511 filed September 20, 2019.

Claim Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Claim 1 is rejected under 35 U.S.C. 102(a)(1) as anticipated by Sun et al ("Sun", US 20100035904 A1, publication-date: February 11, 2010).

Claim 1 embraces a pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium.

Sun is directed to phenobarbital salts; methods of making; and methods of use thereof (title). Sun discloses that **phenobarbital sodium** is a known salt freely soluble in water in contrast to the free acid form ([0004], the same drug in the instant claim 1). Sun also discloses

non-crystalline or **amorphous forms of phenobarbital** salts including phenobarbital sodium ([0011], the same physical form in the instant claim 1).

Sun, by disclosing all the essential elements, anticipates claim 1.

Regarding the limitation of "lyophilized" amorphous in claim 1, it is inconsequential whether the amorphous phenobarbital sodium is obtained by lyophilization or by other means because the term "lyophilized" is considered a process. According to MPEP 2113(I): PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. In this case, the product itself is amorphous phenobarbital sodium.

Claim Rejections - 35 U.S.C. 102 or 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 16-20 are rejected under 35 U.S.C. 102(a)(1) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Kelly et al ("Kelly", non-patent literature, Critical Care Trauma Centre, pp. 1-3, last update: October 11, 2018, only pertinent pages).

Claims 16-20 embrace a method of treating an individual in need of Phenobarbital Sodium, the method comprising: adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a

Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual.

Kelly is directed to **phenobarbital sodium** for **intravenous** (IV) direct injection or infusion (title, and the section of Administration on page 1, read on the limitation of the drug in the instant claim 16 and the administering routes in the instant claim 20). Kelly discloses that the drug, anticonvulsant, sedative, is diluted to 10mL with sodium chloride 0.9%, dextrose 5% or Ringer's Lactate and is used to treat seizures (i.e. epilepsy) (the section of Classification on page 1, read on the limitations of the instant claims 16-17). Kelly also discloses the loading dose is 10 - 15 mg/kg IV or 1000 mg in 250 mL for infusion (the section of Dose and Administration on page 1, read on the limitation of the instant claim 19).

Kelly, by disclosing all the essential elements, anticipates claim 1.

Regarding the limitation of "lyophilized amorphous" phenobarbital sodium in claim 16, Kelly teaches the same drug, in the same liquid carrier. Thus, it is believed the same drug has the same biological effect, whether the drug is in crystal or amorphous form, absent evidence to the contrary.

Regarding the limitation of the individual is a newborn suffering from neonatal epilepsy in claim 18, it is believed that one of ordinary skilled in the art have the knowledge for treating infants because the use of phenobarbital in so called "brain orientated neonatal intensive care" has become established in 1984 (see relevant art section).

Claim Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims the examiner presumes that the subject matter of the various claims was commonly owned as of the effective filing date of the claimed invention(s) absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and effective filing dates of each claim that was not commonly owned as of the effective filing date of the later invention in order for the examiner to consider the applicability of 35 U.S.C. 102(b)(2)(C) for any potential 35 U.S.C. 102(a)(2) prior art against the later invention.

The factual inquiries for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 2, 6, 8-13, and 15 are rejected under 35 U.S.C. 103 as obvious over Sun et al ("Sun", US 20100035904 A1, publication date: February 11, 2010) in view of Snyder (non-patent literature, Drug discovery and development, pp. 1-5, March 7, 2017) and Dietz et al ("Dietz", non-patent literature, titled: Phenobarbital Stability in different dosage forms: alternatives for Elixirs, Pharmaceutical Research, vol. 5, No. 12; pp.803-805, 1988).

Claims 2-15 embrace a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenyl ethyl acetyl urea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the

phenobarbital sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution.

In addition, claim 2 uses the open-ended transitional phrase "comprising". Thus, it allows for the presence of additional unrecited components.

The step of adjusting pH in claim 2 is treated as an optional step (not required) due to the phrase of "if necessary" in line 5. Prior art without step of adjusting pH still read on claim 2.

Sun is directed to phenobarbital salts; **methods of making**; and methods of use thereof (title). Sun teaches non-crystalline or **amorphous forms of phenobarbital** salts including phenobarbital sodium ([0011], the same drug as the instant claim 2). Sun also teaches that preparation of phenobarbital sodium salt is achieved by dissolving phenobarbital and sodium hydroxide in acetone followed by removal of the acetone ([0055]). Sun further teaches that the concentration of phenobarbital in selected buffers or **pH conditions** will be determined using a **stability indicating assay** that distinguishes the active agent from its degradation products, and also detects any degradation that may appear in the salt solution ([0060], read on the limitation of the instant claim 12). Sun recognizes that phenobarbital sodium is a known salt freely soluble in water in contrast to the free acid form, but phenobarbital sodium is hygroscopic and degrades when exposed to humid environments ([0004]).

While teaching preparation of amorphous phenobarbital sodium by solvent removal, Sun does not expressly teach the solvent is water, nor removal solvent by lyophilization. These deficiencies are cured by Snyder.

Snyder is directed to Lyophilization: the Basics (title). Snyder teaches that **lyophilization** is defined as a freeze-drying process to **remove water from a product** after it is frozen and placed under a vacuum (the 1st paragraph on page 1/5, implying the solvent of water).

Snyder indicates that if the bulk drug ingredients are not stable in liquid or frozen form due to chemical reactions, degradation, aggregation, biological growth, heat sensitivity, lyophilization is necessary (the 3rd paragraph on page 1/5). Snyder indicates that lyophilization enables longer shelf life (enhancing stability), makes it much easier to process the product including removing water without having to heat the product excessively and reconstituting the product rapidly and easily (the 1st paragraph on page 2/5). Snyder also teaches that the lyophilization process involves the following steps (the last paragraph on page 3/5):

1. Fill tray with liquid solution (implying the 1st step of adding a drug to water to form the liquid solution in the instant claim 1),

2. Carry trays over to dryer and load

3. Lyophilization (including those three stages)

4. Remove tray from dryer and remove powder from try into another bag or sealed **container** (interpreted as a vial, read on the limitation in the instant claim 15).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose lyophilization as taught by Snyder as the particular means for an aqueous drug solution because the particular option identified by Snyder are predictable solutions to the problem of drying a unstable drug like phenobarbital sodium as evidenced by Dietz, who teaches that the aqueous solution of phenobarbital sodium degrades fastest (see a heat facilitated degradation profile in Fig. 1 on page 804 and the average percentage in Table 1 on page 805). The person of ordinary skill in the art would have a reasonable expectation to be of success in choosing the option. See MPEP 2141, part (III)(A) and (D). Additionally, one of ordinary skill in the art would take advantages of lyophilization taught by Snyder as set forth above.

Regarding the preamble of "no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution" in claim 2, "no more than 0.1% phenylethylacetylurea" in claim 8, "no more than 0.05% phenylethylacetylurea" in claim 9, no detectable amount of 2-ethyl-2-phenylmalonamide, etc. in claim 10, and stable up to at least 6 months at accelerated stability conditions in claim 11; these are considered properties of the lyophilized Phenobarbital sodium. The lyophilized Phenobarbital sodium as set forth in the rejection above would meet these limitation. In the absence of the USPTO to have at its disposal the tools or facilities deemed necessary to make physical determinations of this sort, Applicants have the burden to show that this, in fact, is not the case.

Regarding the optional step of adjusting pH in claim 1 and concentrations in claim 13, Dietz teaches that **sodium phenobarbital** (438 mg) is dissolved in 100ml with a buffer containing 40% (v/v) propylene glycol having a final pH of 5.4, and an aqueous solution of sodium phenobarbital having a final pH of 8 (the 1st and 2nd paragraph on page 803). Dietz also teaches various concentrations for studying emulsion dosage forms (Table II). The principal of law is "[Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). This rule is limited to cases in which the optimized variable is a "result-effective variable." *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). In this case, Sun and Dietz teach different pH in different conditions, indicating that pH is a result-effective variable. It would have been obvious to optimize the pH of an aqueous solution of sodium phenobarbital to achieve desired effect, absent evidence to the contrary.

Regarding the water is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium in claim 6, Dietz teaches that heat facilitating degradation of Phenobarbital Sodium. It would have been obvious to cool the water to slow down the degradation.

Claims 3-5, 7, and 14 are rejected under 35 U.S.C. 103 as obvious over Sun et al ("Sun", US 20100035904 A1, publication date: February 11, 2010) in view of Snyder (non-patent literature, Drug discovery and development, pp. 1-5, March 7, 2017) and Dietz et al ("Dietz", non-patent literature, Pharmaceutical Research, vol. 5, No. 12; pp.803-805, 1988) as applied to claims 2, 6, 8-13, and 15 in further view of Roskos et al ("Roskos", US 6077545 A, date issued: June 20, 2000).

The teaching of Sun and Snyder have been discussed as applied to claims 2, 6, 8-13, and 15. Sun and Snyder do not expressly teach the water is water for injection (WFI), nor nitrogen purge. These deficiencies are cured by Roskos.

Roskos is directed to an improved diluent for the preparation of cisplatin suspensions from a lyophilized powder (abstract). Roskos teaches that lyophilized CDDP (a drug for cancer) is intended for reconstitution into a solution and the standard vehicle for such solution reconstitution is **Water for Injection** (WFI) (col. 3, lines 4-6.readon the limitation of the instant claim 3). Roskos teaches that the solution of example 1 is sparged with nitrogen for 30 minutes (gas flushing), when the required amount of epinephrine is added, and the mixture is stirred under a nitrogen blanket until the epinephrine dissolved. **pH is adjusted** with HCl and/or NaOH (Table of col. 5) if necessary, and additional WFI was added to achieve the final desired volume. The solution was **sparged with nitrogen** for an additional 30 minutes, and then sterile **filtered** through a 0.22 micron filter. Filtered solution was filled into 5 ml vials, the vial headspace was

flushed with nitrogen, and the vials are stoppered (interpreted as sealed) (col. 5, lines 45-58, read on the limitations of the instant claims 3-5, 7, and 14).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose nitrogen sparge and filtering prior to adding the drug as taught by Roskos as the particular means to ensure the drug is stable and meet the Food and drug administration requirements. The person of ordinary skill in the art would have a reasonable expectation to be of success in choosing the steps because Roskos provides the exact solution of processing a stable lyophilized drug product. See MPEP 2141, part (III)(A) and (G). In addition, selection of any order of performing process steps is prima facie obvious in the absence of unexpected results (see MPEP 2144).

Relevant Art

Staudt (non-patent literature, titled Phenobarbital in newborn infants: Overview, Monatsschr Kinderheilkd; vol. 132, issue 4, pp.194-202; Apr., 1984) is provided, but not cited, to show the state of art at the time when the invention was filed.

It should be noted that the original article is in German. The abstract in English is provided (downloaded from https://pubmed.ncbi.nlm.nih.gov/6374432/).

CONCLUSION

No claim is allowed.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YANZHI ZHANG whose telephone number is (571)272-3117. The examiner can normally be reached on Monday-Friday 8am-5pm.

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
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*	B	US-6077545-A	06-2000	Roskos; Kathleen V.	A61K9/0019	424/649
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Staudt, title: Phenobarbital in newborn infants: Overview, Monatsschr Kinderheilkd; vol. 132, issue 4, pp.194-202; Apr., 1984 (Year: 1984)
	V	Kelly et al, title: phenobarbital sodium, Critical Care Trauma Centre, last update: October 11, 2018. (Year: 2018)
	W	Dietz et al, title: Phenobarbital Stability in different dosage forms: alternatives for Elixirs, Pharmaceutical Research, vol. 5, No. 12; pp.803-805, 1988 (Year: 1988)
	X	Snyder, title: Lyophilization: the Basics; Drug discovery and development, pp. 1-5, March 7, 2017 (Year: 2017)

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Review Monatsschr Kinderheilkd. 1984 Apr;132(4):194-202

[Phenobarbital in newborn infants. Overview]

[Article in German]

F Staudt

PMID: 6374432

Abstract

Over the past years the use of phenobarbital in so called "brain orientated neonatal intensive care" has gradually become established. It is the recommended drug for the treatment of seizures in term neonates. It also should be given to neonates who are being treated with curare like muscle relaxants and whose EEG may show paroxysmal activity. It is recommended to administer phenobarbital before curare is given. This may result in more effective mechanical ventilation. Seizures occurring in the premature baby can hardly be influenced. The prophylactic treatment of premature infants to avoid intraventricular haemorrhage is controversial. It is, however, generally accepted that full term babies with neonatal asphyxia should receive phenobarbital. Bacterial meningitis is also an indication for its use in a similar manner. A loading dose of 15-20 mg/kg body weight given intravenously is recommended. The plasma concentration of phenobarbital will usually reach therapeutic levels (15-30 micrograms/ml) within a few minutes of the injection and will hardly change during the following 48 hours. No other anticonvulsant drug should be used until the phenobarbital plasma level exceeds 40 micrograms/ml. As maintenance therapy a dose of 3-4 mg/kg/day is recommended. Due to the long plasma half-life (69-165 h) accumulation of the drug may be possible. It can be avoided if the dose does not exceed 5 mg/kg/day. The duration of therapy depends on the condition of the baby. In general early discontinuation after 1-2 weeks should be possible.

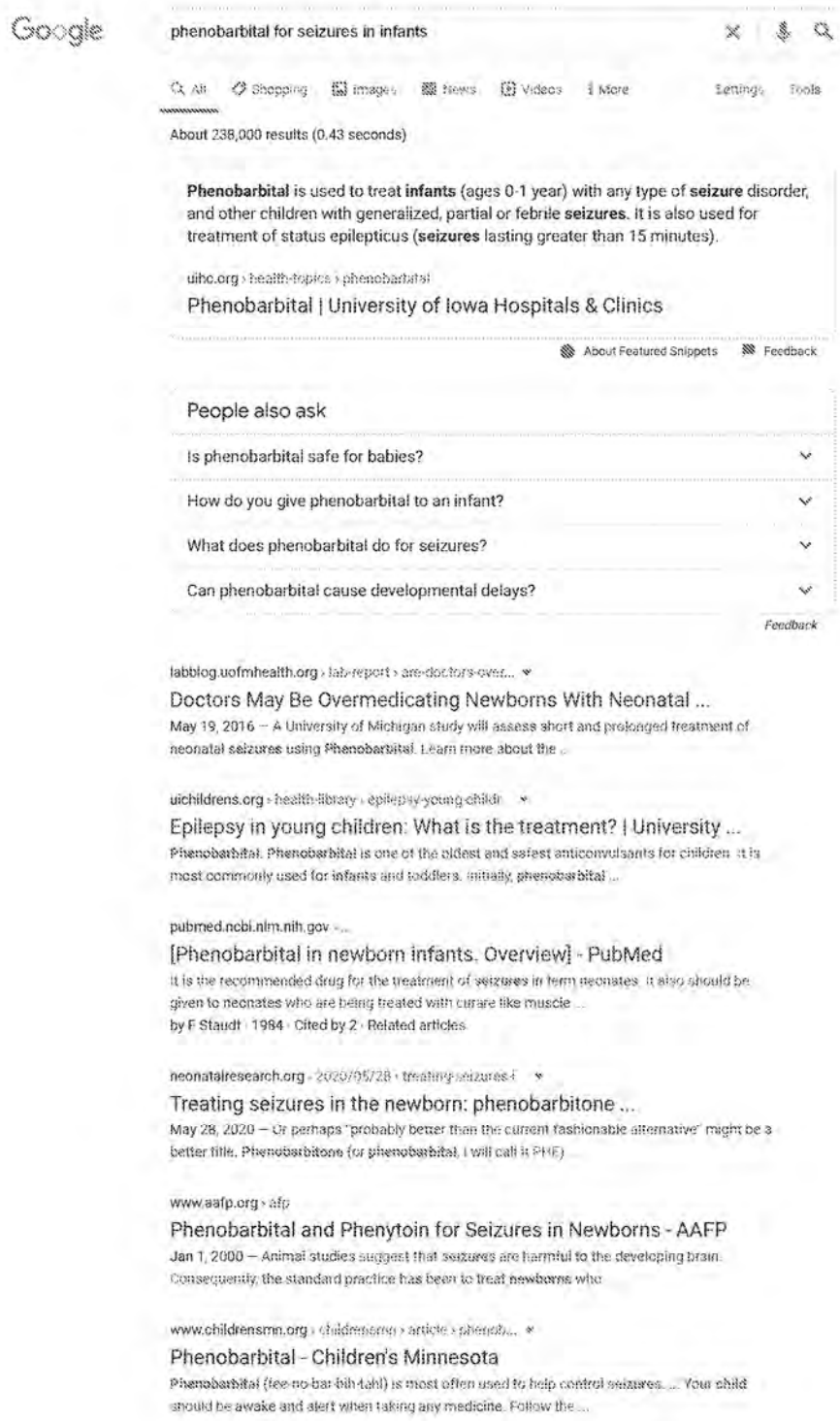
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Phenobarbital is used to treat infants (ages 0-1 year) with any type of seizure disorder, and other children with generalized, partial or febrile seizures. It is also used for treatment of status epilepticus (seizures lasting greater than 15 minutes).
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May 28, 2020 – Or perhaps "probably better than the current fashionable alternative" might be a better title. Phenobarbitone (or phenobarbital, I will call it PHE)
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Phenobarbital and Phenytoin for Seizures in Newborns - AAFP
Jan 1, 2000 – Animal studies suggest that seizures are harmful to the developing brain. Consequently, the standard practice has been to treat newborns who
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It has traditionally been considered the first choice to treat neonatal seizures (seizures in newborn infants). Most studies have found that phenobarbital controls

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Phenobarbital - AboutKidsHealth

Mar 13, 2010 — Your child needs to take the medicine called phenobarbital. It is a medication used to control or prevent certain types of seizures. You may

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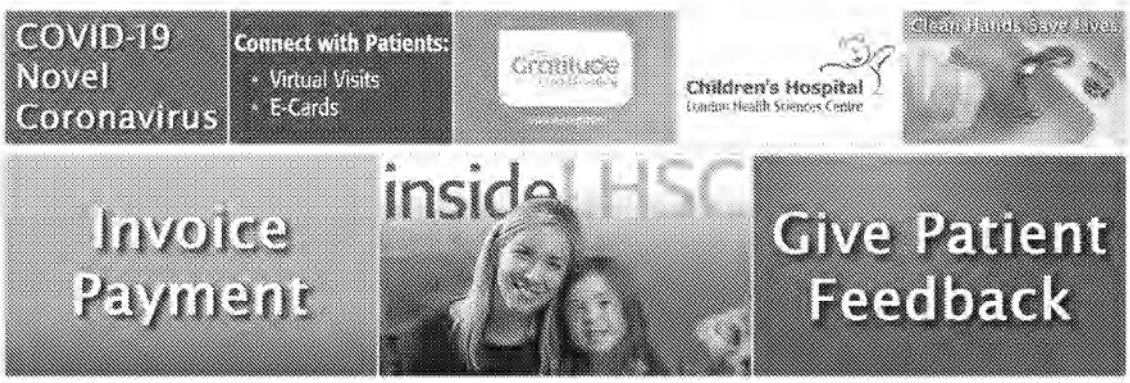
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PHENOBARBITAL SODIUM

Name:	**PHENOBARBITAL SODIUM**
Classification:	***barbiturate; anticonvulsant*** • sedative • used to treat seizures that fail to respond to phenytoin **This is a Tier 3 drug and only approved physicians may order**
Dose:	• **For Refractory Status Epilepticus:** • **Loading Dose:** 10 - 15 mg/kg IV (reduce to 5-10 mg/kg IV for patients with hypotension). Administer slowly over 1 hour. • **Infusion:** Start at 0.5 - 1 mg/kg/hour and titrate slowly to a maximum dose of 0.5 - 10 mg/kg/hour as required to maintain a desired interburst interval (period of suppression on a continuous EEG
Administration:	**IV direct:** • undiluted **OR** diluted to 10mL with sodium chloride 0.9%, dextrose 5% or Ringer's Lactate • **Do not administer faster than 50 mg/minute** **IV Infusion:** 1000 mg in 250 mL (4 mg/mL) sodium chloride 0.9%, dextrose 5% or Ringer's Lactate

Adverse Effects:	• **respiratory depression** • laryngospasm, bronchospasm, angioedema • apnea especially if administered too rapidly • **bradycardia** • **hypotension and cardiovascular depression;** caution in patients with cardiovascular disease • solution is very alkaline; extravasation may produce tissue necrosis and thrombophlebitis • intra-arterial injection may cause severe pain with reactions ranging from transient pain to gangrene • skin rashes
Drug Interactions:	• phenobarbital + beta adrenergic blockers (eg. propranolol) = decreased beta blocker effect • phenobarbital + haloperidol = decreased haloperidol effect • phenobarbital + meperidine = increased meperidine CNS depression (increased production of normeperidine) • phenobarbital + theophylline = decreased theophylline effect
Monitoring Therapy:	• respiratory rate and breath sounds; rapid IV administration may cause laryngospasm or bronchospasm • blood pressure • continuous HR and rhythm • ICP and CPP if indicated • Continous EEG • Mechanical ventilation with continuous End Tidal CO2 and pulse oximetry monitoring • **serum concentrations**, therapeutic 65-170 uM/L (pre-dose), toxic >215 uM/L administration site
CCTC Protocol:	• May be administered IV direct or by IV infusion by a nurse in Adult Critical Care provided that an MD administered the first dose • Administer via Central Venous Line • Continuous infusions must be administered by infusion device and the pump library must be enabled

Lynne Kelly, Pharmacist, CCTC
Brenda Morgan, Clinical Nurse Specialist, CCTC
Last Update: October 11, 2018



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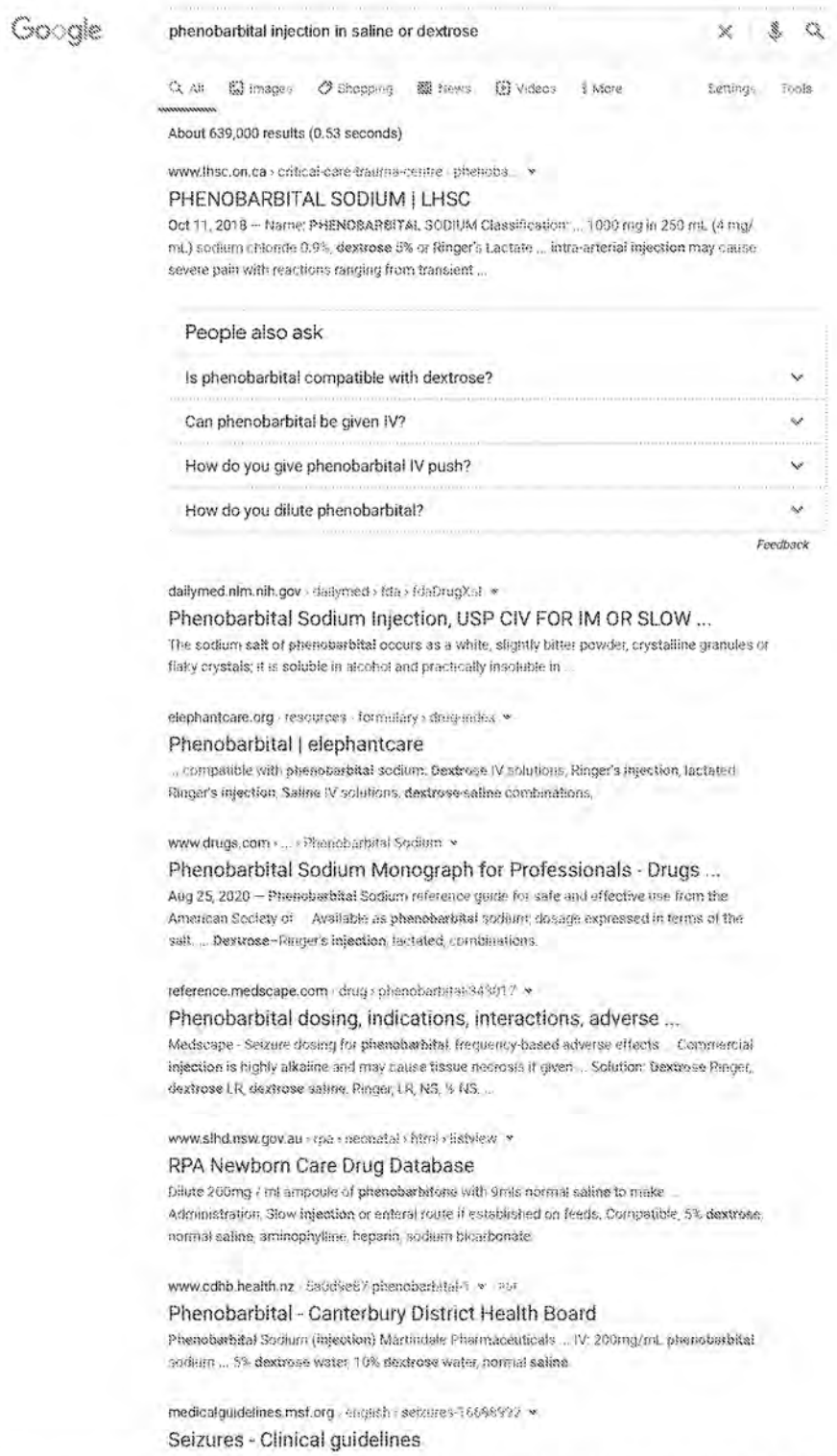
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Seizures - Clinical guidelines

Child weighing 8 kg: 120 mg (15 mg x 8 kg), i.e. 0.6 ml of phenobarbital in 20 ml
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Neonatal Drug Formulary

D5, 5 % dextrose • NS, 0.9% saline ... intravenous (IV): Slow IV injection over 3-5 minutes ... Vial, 1000mg (1g) powder for injection. Dose: ... 10% or 5% Dextrose (D5 or D10) ... Neonatal seizures NOT responding to phenobarbitone alone.

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Pharmaceutical Research, Vol. 5, No. 12, 1988

Technical Note

Phenobarbital Stability in Different Dosage Forms: Alternatives for Elixirs

Nancy J. Dietz,[1] Peter J. Cascella,[2,3] Joel E. Houglum,[2] Gary S. Chappell,[2] and Ronald M. Sieve[1]

Received March 21, 1988; accepted June 26, 1988

KEY WORDS: phenobarbital; stability; solubility; emulsions; solutions; elixirs; high-performance liquid chromatographic (HPLC) analysis.

INTRODUCTION

The only oral solution dosage form of phenobarbital currently marketed is an elixir. An elixir is a hydroalcoholic dosage form used as a vehicle because ethanol enhances solubility and promotes the stability of phenobarbital by reducing the rate of hydrolysis of the ionized species (1,2). Advantages over solid dosage forms may include increased bioavailability and ease of administration.

The use of alcohol may, however, present problems in drug therapy because of the synergistic action of alcohol with other drugs. These therapeutic problems are of particular concern in elderly patients (3–5). Emulsions may possess the same advantage of other liquid dosage forms while eliminating the alcohol.

The present study evaluated the stability of phenobarbital as an elixir, emulsion, aqueous solution, and aqueous solution with propylene glycol.

EXPERIMENTAL

Preparation of Dosage Forms

Phenobarbital Emulsions. Cholesterol (100 mg), phenobarbital (400 mg), Span 85 (1 ml), and corn oil (30 ml) were added to a flask, stirred, and heated (70°C) until all the phenobarbital was dissolved. Sorenson buffer (65 ml, 2/15 *M*, pH 5) containing 40% (v/v) propylene glycol (final pH 5.4) was added to Tween 85 (2 ml). The aqueous and oil phases were heated to 70°C and mixed. The preparation was cooled to room temperature and adjusted to 100 ml with Sorensen buffer, shaken, heated to 70°C, and homogenized three times with a hand homogenizer. A blank emulsion containing propylene glycol was also prepared. Another phenobarbital emulsion was also prepared in the same manner without propylene glycol.

Phenobarbital Solutions. A concentration of sodium phenobarbital equivalent to the concentration of the free acid used in the emulsions was used. Sodium phenobarbitral (438 mg) was diluted to 100 ml with Sorenson buffer (2/15 *M*, pH 5) containing 40% (v/v) propylene glycol (final pH 5.4).

An aqueous solution of sodium phenobarbital without propylene glycol was also prepared in Sorenson buffer (2/15 *M*, pH 8). All preparations were stored in amber glass containers.

Phenobarbital Elixir. A commercially prepared elixir (20 mg/5 ml, Lilly, Lot 9NN12A) was used throughout the experiment.

High-Performance Liquid Chromatographic (HPLC) Assay

One milliliter of sample (emulsion, elixir, or solution) was mixed with methanol (9 ml), vortexed, and centrifuged (International Equipment Company, Needham Heights, Mass.) at 3000 rpm. Mixtures were then syringe filtered using a nylon filter (0.45-μm) membrane (Anspec H3404, P.O. Box 7730, Ann Arbor, Mich.).

Clear filtrate (20 μl) was injected onto the HPLC system, which consisted of a Model 825 pump (Instrument Specialities Company, 4700 Superior Street, Lincoln, Neb.), Model 226 UV (254-nm) detector, and BD-40 recorder (Kipp and Zonen, P.O. Box 507, 2600 AM Delft, Delft, Holland). The column was an ODS-Ultrasphere (Alltech Associates, Inc., Applied Science Labs, 205 Waukegan Road, Deerfield, Ill.) (5 μm, 4.6-mm ID × 15 cm) and the mobile phase was 55% methanol in 1/10 *M* acetic acid (flow, 1.2 ml/min). The retention time of phenobarbital was 3 min. A standard consisting of phenobarbital (4 mg/ml) in methanol was prepared daily. Calculations were based upon the average peak height of sample to the average peak height obtained from injections of standard solution which bracketed the sample injections. To establish linearity a stock solution of phenobarbital (0.5 mg/ml) in methanol was prepared and then diluted further with methanol to give varying concentrations of phenobarbital (0.5, 0.4, 0.2, 0.1, and 0.05 mg/ml). The entire procedure was repeated once.

Linear least-squares was performed on all individual (*r*

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= 0.99) peak heights. The intercept was not significantly different from zero ($P \geq 0.01$).

Recovery studies were performed on the emulsions prepared with and without propylene glycol. Three samples (1 ml) of each dosage form were assayed with duplicate injections. A mixture of 1 ml of emulsion without phenobarbital and 1 ml of phenobarbital (4 mg/ml in methanol) was qs'd to 10 ml with methanol and used as the standard for the emulsion dosage forms. The average recovery for the emulsion with propylene glycol was 102% (±2%); that of the emulsion without propylene glycol was 100% (±1%). A t test (two tailed) was performed on the average peak height for each dosage form and standard. There was no significant difference for either emulsion compared to the standard ($P \geq 0.01$). The peak height of the commercially prepared elixir was 110% (±1%) and significantly different from that of a standard of 0.4 mg/ml phenobarbital in methanol ($P < 0.01$). This may be a reflection of a higher concentration in the elixir than the label claim. Since this study is concerned with the breakdown of phenobarbital over time, all values in the stability study were expressed as percentage remaining.

A phenobarbital emulsion (4 mg/ml, pH 5, Sorenson buffer, 40% propylene glycol) was prepared to determine the precision of the assay. Seven samples of the emulsion were extracted and injected onto the HPLC in triplicate. An ANOVA between extractions was performed, with no significant difference between extractions ($F = 4.21$, $P \geq 0.01$). The coefficient of variation between extractions was 1.4%.

To determine the reproducibility of the emulsion preparation procedure, four emulsions containing propylene glycol were prepared (4 mg phenobarbital/ml). Each emulsion was extracted once and injected four times. No significant difference ($F = 0.84$, $P \geq 0.01$) was observed between emulsions.

Homogeneity of variance was evaluated for each ANOVA using Bartlett's test for multiple sample variances. No significant difference between variances was detected at the 1% level.

RESULTS AND DISCUSSION

A solution of sodium phenobarbital equivalent to 40 mg of free acid was prepared in a pH 8 Sorenson buffer and heated for various times at 98°C to establish if degradation products would interfere with the peak height of the parent compound. Figure 1 illustrates a typical chromatogram obtained. The peak (B) representing phenobarbital (retention time of 3 min) diminishes and other peaks (A and C) appear. The height of A and C increase with time, while C diminishes.

Three preparations of each dosage form (pH 8 solution, propylene glycol solution, and two different emulsions) were used for the stability study. Only one commercially purchased elixir was used throughout the experiment. A fresh standard was prepared daily.

Table I summarizes the average percentage remaining for each of the dosage forms.

The emulsions prepared without propylene glycol showed a rapid decline of phenobarbital concentration with time followed by a period in which the concentration was stable. This initial decline was accompanied by the formation of a precipitate which was not readily redispersed. After 4 weeks the remaining phenobarbital in the preparation appeared stable. The emulsions with propylene glycol, the propylene glycol solution, and the elixir (but not the aqueous solution) all appear to be stable. Assuming a first-order degradation process, a linear least-squares analysis was performed on the log of the percentage remaining as a function of time. This was calculated for each preparation of each dosage form. The average first-order half-lives obtained from each preparation within a dosage form were 693 (±240), 990 (±163), 770 (±27), and 130 (±11) weeks for the propylene glycol emulsion, elixir, propylene glycol solution, and aqueous solution, respectively. With the exception of the aqueous solution, it is not possible to reject the hypothesis that the slopes of the individual percentage remaining versus time plot within each dosage form are equal to zero ($P > 0.01$). This would suggest that the emulsion, elixir, and propylene glycol are all quite stable over the length of the study. For this reason, it is inappropriate to compare the half-lives of these preparations as an indicator of stability relative to one another. This does not negate the fact, however, that all three dosage forms appear to be quite stable.

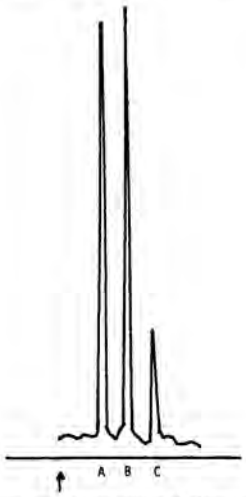


Fig. 1. A representative chromatogram of phenobarbital after heating to facilitate degradation. The arrow indicates the time of injection. Peaks A and C represent breakdown products, while peak B is phenobarbital.

The oil and water phases for the two emulsions were separated by centrifugation and 1 ml of each phase was assayed for phenobarbital. The results are summarized in Table II. A t test indicates no significant differences ($P > 0.01$) between the oil phases of the two emulsions but a difference between the aqueous phases ($P < 0.01$). The emulsion with propylene glycol contains 25% of the total phenobarbital in the oil phase. The total recovered phenobarbital from both phases was 42 mg/10 ml (105% recovery). The emulsion without propylene glycol contains 42% of the total phenobarbital in the oil phase but the total recovered phenobarbital from both phases was 24 mg/10 ml (60% recovery). This

Table I. Average Percentage Remaining Dosage Form

Week	Emulsion[a]	Emulsion[b]	Elixir[c]	Solution[d]	Solution[e]
1	100	100	100	100	100
2	100	95	97	97	94
4	100	66	97	96	95
6	96	67	94	96	95
8	97	69	—	95	93
10	98	68	—	96	91
12	98	68	—	95	90
17	94	—	97	—	—
55	105	—	100	101	77
56	105	—	101	101	76

[a] Emulsion with propylene glycol.
[b] Emulsion without propylene glycol.
[c] Commercially available elixir.
[d] Propylene glycol solution.
[e] Aqueous solution (pH 8).

suggests that the propylene glycol raised the solubility of the phenobarbital in the aqueous phase. The 60% recovery from the emulsion without propylene glycol is due to precipitation of the phenobarbital from the aqueous phase.

In conclusion we have used a rapid HPLC assay to evaluate the stability of phenobarbital in a number of different dosage forms. Using this assay we have demonstrated that phenobarbital is stable in an elixir, an emulsion, and a propylene glycol solution. The stability of the propylene glycol emulsion is attributed both to the solubilization of the drug in the oil phase and to the use of propylene glycol in the aqueous phase. Increasing the phase volume ratio of oil/water should increase the percentage of the drug in the oil phase, as may altering the quantity or nature of the surface active agents. This study also supports the hypothesis that it may be possible to maintain stability of drugs prone to degradation in aqueous solutions by dispersing them in an emulsion as an alternative to an elixir. Our lab is evaluating emulsions of other drugs to determine if the emulsion dosage form can enhance the bioavailability of these drugs.

Table II. Concentration (mg/ml) of Phenobarbital in Emulsion Dosage Forms

	Emulsion A[a]		Emulsion B[b]	
Sample	Oil phase	Water phase	Oil phase	Water phase
1	3.48	4.56	3.48	1.92
2	3.49	4.68	3.76	1.62
3	2.92	4.68	3.52	2.12
Mean	3.30	4.64	3.59	1.88
SD	0.33	0.69	0.15	0.25

[a] Emulsion with propylene glycol.
[b] Emulsion without propylene glycol.

ACKNOWLEDGMENTS

This study was supported in part by the APS Pharmaceutical Analysis and Control Section Undergraduate Award in Pharmaceutical Analysis (1986) and South Dakota State University Research Support Fund (314815).

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Lyophilization: The Basics

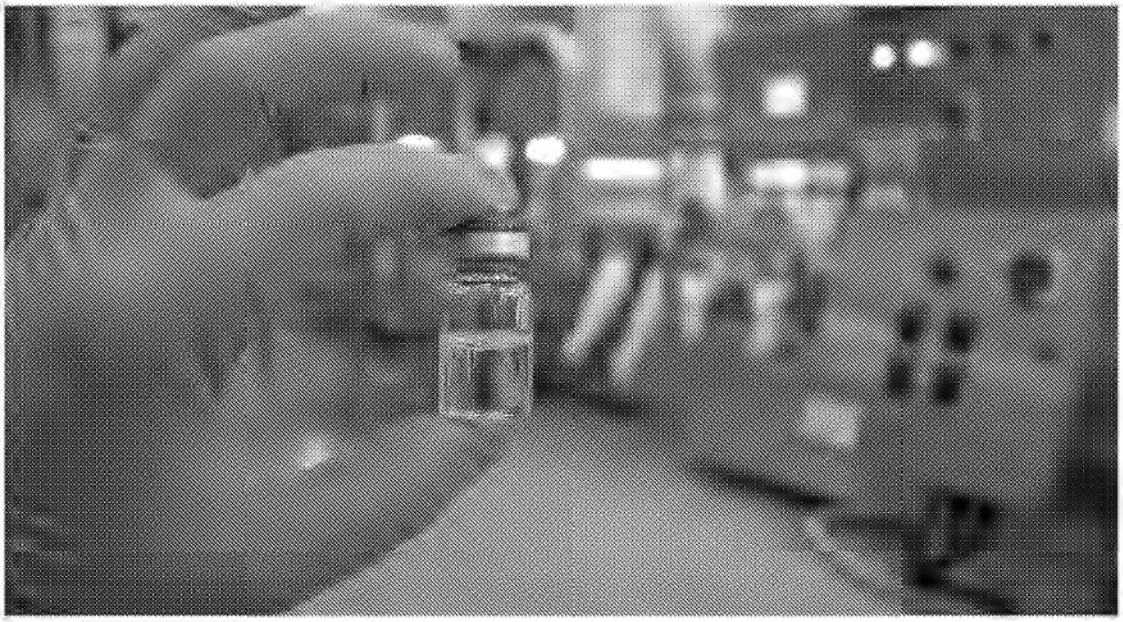
By Meg Snyder | March 7, 2017

Lyophilization: The Basics

Lyophilization, defined as a freeze-drying process that removes water from a product after it is frozen and placed under a vacuum, is often messy, but filled with possibilities for potential applications.

Some of the typical pharmaceutical products that would undergo lyophilization include bulk pharmaceutical/biopharmaceutical ingredient (chemical or biologics found in nature), protein, collagen, peptide, oligonucleotide, chemical API, enzymes, and mAbs.

"If the bulk drug ingredients are not stable in liquid or frozen form, lyophilization is necessary. This can be due to chemical reactions, degradation, aggregation, biological growth, heat sensitivity, etc. Lyophilization enables longer shelf life, often as long as two-five years and makes it much easier to transport the product. In addition, products can be stored at room temperature," said Cherish Robinson, Product Specialist, Gore & Associates, Gore PharmBIO Products, detailing why lyophilization—despite some of its challenges—is unmistakably important.



Advantages & Disadvantages of Lyophilization

Some of the advantages of lyophilization, according to the FDA, include:

- Processing a liquid with ease (and thereby simplifying aseptic handling)
- Enhancing the stability of a dry powder as well as the product stability in a dry state
- Removing water without having to heat the product excessively
- Dissolution of reconstituted product (rapidly and easily)

The FDA also lists some of the disadvantages of lyophilization:

- Handling and processing time increases
- Sterile diluent needed upon reconstitution
- Equipment becomes costly and complex

"One of the biggest problems in lyophilization is the mess it can create," said Robinson.

In addition to the process being messy, Robinson details a few other challenges of lyophilization:

- Expensive

The filling of vials that are to be lyophilized can also be challenging, specifically having an open system from filling all the way through the end of the process (and the resulting potential for contaminants to enter the vials).

At present, 80 percent of the market lyophilizes in vials.

"Consider using a closed tray in lyophilization chambers. Using a closed tray can prevent product flyout during the filling, transportation, and lyophilization process, which reduces dryer cleaning time and validation of cleaning procedure," said Robinson.

Lyophilization: The Process

Typically, lyophilization occurs in three stages:

1. **Freezing**
2. **Primary drying**
3. **Secondary drying**

"Freezing takes place in stage one of the lyophilization process. It can take place in the freeze dryer. Some customers freeze in a freezer instead. Freezing temperatures are around -40°C," Robinson explained.

There is no thawing in the second stage, she adds. "The product goes from frozen state to dry powder through the process of sublimation."

"Think of lyophilization as basically freeze-drying—it is a dehydration process typically used to preserve a perishable material or make the material more convenient for transport. Freeze-drying works by freezing the liquid material and then reducing the surrounding pressure to allow the frozen water in the material to sublimate directly from the solid phase to the gas phase. This leaves us with a dry powder."

Depending on the type of product and quantity, it can take 12-72 hours to go through all of these stages.

As to the lyophilization process, Robinson broke it down into the following steps:

- Fill tray with liquid solution
- Carry trays over to dryer and load
- Lyophilization (including those three stages)
- Remove tray from dryer and remove powder from try into another bag or sealed container

Regulatory Oversight & Financial Investment

Generally speaking, cleaning protocols involve a lot of oversight. Cleaning validation, for example, is something that the FDA reviews.

Robinson recommends looking for products that help protect the inside of the lyophilization dryers "by containment inside closed and even single-use disposable trays, which can ease the cleaning headaches." Open stainless steel trays—which are effective and often used—necessitate longer and more rigorous cleaning protocols.

In addition, it's important to note that the lyophilization process, itself, is the most expensive operating unit in the production process, according to Robinson.

"Freeze dryers, themselves, are a $2-3 million investment—that equipment is the same regardless if a disposable or reusable SS tray is used. You can have dryers with or without CIP/SIP features," said Robinson.



- Growth in freeze drying equipment used for pharma/biopharma/biotechnology segment, 13.5% CAGR 2013-20181
- Growth in CMOs used for pharma/biopharma/biotechnology segment, 10.5% CAGR 2013-20181
- More complex drug formulations that are not stable in liquid form
- Growth in Oligonucleotides and Peptides, which degrade in liquid form
- Topics being discussed for bulk lyophilization are continuous processing and buffer free solutions

"For bulk drug product, lyophilization improvements are continuing in tray handling, dryer loading, dryer cleaning, and dryer removal," said Robinson, noting that much of the discussion in lyophilization (at present) relates to vials. "Dryer cleaning is a big concern, because of next-batch contamination. This can be a problem and good cleaning protocols are examined to ensure you are not contaminating batch-to-batch."

The Market Today

According to BCC Research, 16 percent of the top 100 pharmaceutical drugs are lyophilized and 35 percent of biologic drugs are lyophilized.

With more than 30 percent of the FDA-approved parenterals lyophilized and soon more than half injectable drugs to require lyophilization—Markets and Markets reports in their 2020 global forecast—there is ample room for standardization and expansion of this freeze-drying process in pharmaceuticals.

We recommend

Recognizing T2D management beyond glycemic control

.

Sequential afatinib and osimertinib in patients with EGFR mutation-positive NSCLC: final analysis of the GioTag study

MJ Hochmair, et al, Future Oncology, 2020

Unmatched A1C reductions found in trials

.

NUT carcinoma FAQs for your patients: diagnosis, treatment, our open/recruiting clinical trials

MyStudyWindow, 2020

NUT carcinoma clinical phase 1 trial: A study to find the maximum dose of BET inhibitor that is tolerated by patients with different types of advanced solid tumours, including NUT carcinoma

MyStudyWindow, 2020

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Electronic Acknowledgement Receipt	
EFS ID:	41262548
Application Number:	17025881
International Application Number:	
Confirmation Number:	8113
Title of Invention:	Lyophilized Compositions of Phenobarbital Sodium Salt
First Named Inventor/Applicant Name:	Bala Tripura Sundari Chodavarapu
Customer Number:	149344
Filer:	Martin Fessenmaier/Danielle Moroz
Filer Authorized By:	Martin Fessenmaier
Attorney Docket Number:	104078.0001US
Receipt Date:	01-DEC-2020
Filing Date:	18-SEP-2020
Time Stamp:	15:41:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

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Payment Type	CARD
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RAM confirmation Number	E2020B1F42222635
Deposit Account	601823
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Warnings:					
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6	Information Disclosure Statement (IDS) Form (SB08)	IDS-01.pdf	1053585 596a37621a7b493a4cbc32188676416911c7d9a1	no	4
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	17025881
	Filing Date	2020-09-18
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	1617
	Examiner Name	Yanzhi ZHANG
	Attorney Docket Number	104078.0001US

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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See attached certification statement.

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A certification statement is not submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Martin Fessenmaier/	Date (YYYY-MM-DD)	2020-12-01
Name/Print	Martin Fessenmaier	Registration Number	46697

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(Not for submission under 37 CFR 1.99)

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Filing Date	2020-09-18
First Named Inventor	Bala Tripura Sundari Chodavarapu
Art Unit	1617
Examiner Name	Yanzhi ZHANG
Attorney Docket Number	104078.0001US

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	1	104940149	CN	A	2015-09-30	Sun		X
	2	2017085687	WO	A1	2017-05-26	WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED		☐

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	Application Number	17025881
	Filing Date	2020-09-18
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	1617
	Examiner Name	Yanzhi ZHANG
	Attorney Docket Number	104078.0001US

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	GUPTA, V. Das, "Effect of Ethanol, Glycerol, and Propylene Glycol on the Stability of Phenobarbital Sodium," Journal of Pharmaceutical Sciences, 1984 November 1; 73(11):1661-1662. Abstract only	
	2	NAYYAR et al., "Phenytoin-Folate Interactions: How Far is Safe Folate Supplementation in Phenytoin Treated Epileptic Patients?" Journal of Applied Pharmaceutical Science, 2012; 02(06):230-235.	

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(72)发明人 孙莉新

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A61K 47/26(2006.01)
A61P 29/00(2006.01)

权利要求书2页 说明书6页

(54)发明名称

一种复方氨林巴比妥注射冻干粉针剂及其制备方法

(57)摘要

本发明公开了一种复方氨林巴比妥注射冻干粉针剂及其制备方法，其处方组成为氨基比林、安替比林、巴比妥、甘露醇、丙二醇、亚硫酸钠、乳糖、右旋糖苷。相对于现有技术，本发明制备的复方氨林巴比妥注射冻干粉针剂复溶性好、质量稳定、肌肉注射引起的疼痛感轻，且本发明提供的制备工艺简单、易控、生产效率高、生产能耗低。

CN 104940149 A

1. 一种用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂，其特征在于包括氨基比林、安替比林、巴比妥、甘露醇、丙二醇、亚硫酸钠、乳糖、右旋糖苷，

其中各成分组成为：

氨基比林	0.05-0.15 重量份、
安替比林	30-50 重量份、
巴比妥	16-20 重量份、
甘露醇	70-110 重量份、
丙二醇	45-65 重量份、
亚硫酸钠	15-35 重量份、
乳糖	10-30 重量份、
右旋糖酐	30-50 重量份。

2. 根据权利要求 1 所述的用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂，其特征在于各成分组成为：

氨基比林	0.05 重量份、
安替比林	30 重量份、
巴比妥	16 重量份、
甘露醇	70 重量份、
丙二醇	45 重量份、
亚硫酸钠	15 重量份、
乳糖	10 重量份、
右旋糖酐	30 重量份。

3. 根据权利要求 1 所述的用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂，其特征在于各成分组成为：

氨基比林	0.15 重量份、
安替比林	50 重量份、

巴比妥	20 重量份、
甘露醇	110 重量份、
丙二醇	65 重量份、
亚硫酸钠	35 重量份、
乳糖	30 重量份、
右旋糖酐	50 重量份。

4. 根据权利要求 1 所述的用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂，其特征在于各成分组成为：

氨基比林	0.1 重量份、
安替比林	40 重量份、
巴比妥	18 重量份、
甘露醇	90 重量份、
丙二醇	55 重量份、
亚硫酸钠	25 重量份、
乳糖	20 重量份、
右旋糖酐	40 重量份。

5. 一种权利要求 1-4 之一所述的用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂的制备方法，其特征在于，包括以下步骤

A. 按生产处方备料，原辅料分别按处方量称取，备用；

B. 将处方量的甘露醇、丙二醇、乳糖溶于 60% 的 60±5℃的注射用水中，加入 0.1% 活性炭，过滤得 A1 液；

C. 将氨基比林、安替比林、巴比妥、亚硫酸钠、右旋糖酐依次溶于 60% 的 60±5℃的注射用水中，加入 0.1% 活性炭，过滤得 B1 液；

D. 取步骤 B 得到的 A 液 1，加到步骤 C 得到的 B1 液，混合均匀后，微孔滤膜过滤；

E，将步骤 D 中过滤后的溶液置于 -55℃下预冻 7 小时；然后在温度 -15℃时升华干燥 30 小时；再将温度升至 25℃进行再干燥，时间为 15 小时；加塞、压盖、包装。

一种复方氨林巴比妥注射冻干粉针剂及其制备方法

技术领域

[0001] 本发明涉及一种用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂及其制备方法，属于医药制剂领域。

背景技术

[0002] 安痛定注射液又称复方氨林巴比妥注射液，为无色或微黄色的澄明液体。主要用于急性高热时的紧急退热，对发热时的头痛症状也有缓解作用。用于治疗紧急发热时的退热、发热时的头痛、关节痛、神经痛、风湿痛与痛经等病症的片剂、注射液药物。为复方制剂，其中氨基比林和安替比林同属于吡唑酮类解热镇痛药，能抑制下视丘前列腺素的合成和释放，恢复体温调节中枢感受神经元的正常反应性而起退热作用；同时还通过抑制前列腺素等的合成而起镇痛作用。氨基比林并能抑制炎症局部组织中前列腺素的合成和释放，稳定溶酶体膜，影响吞噬细胞的吞噬作用而起到抗炎作用。合用巴比妥，可加强镇痛作用。

[0003] 中国专利文献CN101129328A公开的复方氨林巴比妥注射液组成为氨基比林、安替比林、巴比妥、乙二胺四乙酸二钠和注射用水。CN104324034A公开的注射用复方氨基比林的药物组合物组成为氨基比林；安替比林、巴比妥、PLGA、PEG、PVP、甘露醇、甘氨酸、泊洛沙姆、乙二醇。虽然上述注射剂具有复溶性好、稳定性佳，载药量高、临床试验安全性好等特点，克服了现有技术中复溶性差、稳定性差的不足之处，但其存在肌肉注射导致的肌肉疼痛问题不容忽视。安痛定的肌肉注射引发的肌肉、骨骼疼痛、臀部红肿、脓肿，肢端坏死等不良反应已有多篇文献报道。

[0004] 针对这一问题，虽然众多文献“改进肌肉注射方法减轻局部疼痛的探讨（黄英英，等，南方护理杂志1998年5月第5卷第3期）”中已有报道，通过调整肌肉注射时的操作手法会部分减轻患者局部疼痛，但是该方法无法 从制剂本身的角度对肌肉疼痛进行舒缓，只能从很轻微的程度上减轻由于药物组成带来的制剂本身存在的导致肌肉注射疼痛的问题。因而，针对安痛定制剂自身进行研究，从制剂角度根本减轻或避免其肌肉注射导致的疼痛等不良反应，已经是迫切继续解决的技术问题。

发明内容

[0005] 因此，本发明所要解决的技术问题在于克服现有复方氨林巴比妥注射剂易引起的肌肉疼痛的技术缺陷，从而提出一种肌肉注射疼痛感低、且产品稳定、复溶性好的复方氨林巴比妥注射冻干粉针剂及制备方法。

[0006] 为此，本发明提供一种用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂，包括氨基比林、安替比林、巴比妥、甘露醇、丙二醇、亚硫酸钠、乳糖、右旋糖苷。

[0007] 其中各成分组成为：

[0008]

氨基比林	0.05-0.15 重量份、
安替比林	30-50 重量份、
巴比妥	16-20 重量份、
甘露醇	70-110 重量份、
丙二醇	45-65 重量份、
亚硫酸钠	15-35 重量份、
乳糖	10-30 重量份、
右旋糖酐	30-50 重量份。

[0009] 本发明用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂原料组成优选为：

[0010]

氨基比林	0.05 重量份、
安替比林	30 重量份、
巴比妥	16 重量份、
甘露醇	70 重量份、
丙二醇	45 重量份、

[0011]

亚硫酸钠	15 重量份、
乳糖	10 重量份、
右旋糖酐	30 重量份。

[0012] 本发明用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂原料组成优选为：

[0013]

氨基比林	0.15 重量份、
安替比林	50 重量份、
巴比妥	20 重量份、
甘露醇	110 重量份、
丙二醇	65 重量份、
亚硫酸钠	35 重量份、
乳糖	30 重量份、
右旋糖酐	50 重量份。

[0014] 本发明用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂原料组成优选为：

[0015]

氨基比林	0.15 重量份、
安替比林	50 重量份、
巴比妥	20 重量份、
甘露醇	110 重量份、
丙二醇	65 重量份、
亚硫酸钠	35 重量份、
乳糖	30 重量份、
右旋糖酐	50 重量份。

[0016] 本发明还提供了所述用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂的制备方法：

[0017] A. 按生产处方备料，原辅料分别按处方量称取，备用；

[0018] B. 将处方量的甘露醇、丙二醇、乳糖溶于 60％的 60±5℃的注射用水中，加入 0.1％活性炭，过滤得 A1 液；

[0019] C. 将氨基比林、安替比林、巴比妥、亚硫酸钠、右旋糖酐依次溶于 60％的 60±5℃的注射用水中，加入 0.1％活性炭，过滤得 B1 液；

[0020] D. 取步骤 B 得到的 A 液 1，加到步骤 C 得到的 B1 液，混合均匀后，微孔滤膜过滤；

[0021] E：将步骤 D 中过滤后的溶液置于 -55℃下预冻 7 小时；然后在温度 -15℃时升华干燥 30 小时；再将温度升至 25℃进行再干燥，时间为 15 小时；加塞、压盖、包装。

[0022] 本发明的上述技术方案相比现有技术具有以下优点，通过筛选冻干粉针剂中辅料的种类以及原辅料的用量，本发明提供了一种采用简单的制备工艺即可达到复溶性好、质量稳定、肌肉注射引起的疼痛感轻的复方氨林巴比妥注射冻干粉针剂。本发明制备的产品稳定性好，杂质等各项目指标的稳定性显著优于现有产品，尤为重要的是引发的肌肉疼痛感几乎为零，且本发明提供的制备工艺简单、易控、生产效率高、生产能耗低。

具体实施方式

[0023] 在本发明中，若非特指，所有的份、百分比均为重量或体积单位，所有的设备和原料等均可从市场购得或是本行业常用的。下述实施例中的方法，如无特别说明，均为本领域的常规方法。

[0024] 实施例 1：用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂

[0025]

氨基比林	0.05g、
安替比林	30g、
巴比妥	16g、
甘露醇	70g、
丙二醇	45g、

[0026]

亚硫酸钠	15g、
乳糖	10g、
右旋糖酐	30g。

[0027] 实施例 2：用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂

[0028]

氨基比林	0.15g、
安替比林	50g、
巴比妥	20g、
甘露醇	110g、
丙二醇	65g、
亚硫酸钠	35g、
乳糖	30g、
右旋糖酐	50g。

[0029] 实施例 3：用于治疗急性高热的复方氨林巴比妥注射冻干粉针剂

[0030]

氨基比林	0.15g、
安替比林	50g、
巴比妥	20g、
甘露醇	110g、
丙二醇	65g、
亚硫酸钠	35g、
乳糖	30g、
右旋糖酐	50g。

[0031] 实施例 1-3 均采用以下方法进行制备：

[0032] A. 按生产处方备料，原辅料分别按处方量称取，备用；

[0033] B. 将处方量的甘露醇、丙二醇、乳糖溶于 60％的 60±5℃的注射用水中，加入 0.1％活性炭，过滤得 A1 液；

[0034] C. 将氨基比林、安替比林、巴比妥、亚硫酸钠、右旋糖酐依次溶于 60％的 60±5℃的注射用水中，加入 0.1％活性炭，过滤得 B1 液；

[0035] D. 取步骤 B 得到的 A 液 1，加到步骤 C 得到的 B1 液，混合均匀后，微 孔滤膜过滤；

[0036] E：将步骤 D 中过滤后的溶液置于 -55℃下预冻 7 小时；然后在温度 -15℃时升华干燥 30 小时；再将温度升至 25℃进行再干燥，时间为 15 小时；加塞、压盖、包装。

[0037] 对比例 1：按 CN101129328A 实施例 1 方法进行制备

[0038] 对比例 2：按 CN104324034A 实施例 1 方法进行制备

[0039] 实验例 1 稳定性对比研究结果

[0040] 将本发明实施例 3 中的复方氨林巴比妥注射冻干粉针剂与 CN101129328A、CN104324034A 实施例 1 制备的产品进行溶解程度的考察，测定各项指标，结果见表 1。

[0041] 表 1

[0042]

试验条件	溶解程度		
	实施例 3	对比例 1	对比例 2
澄清度	澄清	基本澄清	澄清
速度	快	快	较快
不溶颗粒	无	略显	基本无

[0043] 由表 1结果可知，在澄清度、溶解速度、不溶颗粒多少等参考指标下，本发明制得的样品中均明显优于对比例的产品，说明本发明制得的产品的质量更加稳定、可控。

[0044] 实验例 2 稳定性对比研究结果

[0045] 将本发明实施例 3 中的复方氨林巴比妥注射冻干粉针剂与 CN101129328A、CN104324034A 实施例 1 制备的产品进行加速稳定性试验研究，测定各项指标，结果见表 2、表 3。

[0046] 表 2

[0047]

取样时间	实施例 3	对比例 1	对比例 2
0 天	澄清、无颗粒	基本澄清、略有颗粒	澄清、无颗粒
加速 1 月	澄清、无颗粒	基本澄清、略有颗粒	澄清、无颗粒
加速 2 月	澄清、无颗粒	基本澄清、颗粒增多	澄清、基本无颗粒
加速 3 月	澄清、无颗粒	基本澄清、颗粒增多	澄清、基本无颗粒

[0048] 由表 2结果可知，在加速试验条件下，本发明制得的样品外观等方面明显比对比例 1 产品更具有优势，与对比例 2 相比更优或者相当，说明本发明制得的产品的质量更加稳定、可控

[0049] 实验例 3 疼痛程度对比研究结果

[0050] 注射过程由专人操作，推药均匀，速度一致，排除注射者水平高低不一的因素，并在同一病人身上用不同实验例的药物进行注射，排除不同病人疼痛阈值不同的因素。注射后立即询问被注射者的疼痛程度，根据主诉很痛 (++)、较痛 (+)、不痛 (-) 三种标准记录，进行对照分析，结果见表 3。

[0051] 表 3

[0052]

实验药物	注射例数	疼痛程度		
		++	+	-
实施例 3	150	0	15	135
对比例 1	150	27	102	21
对比例 2	150	48	87	15

[0053] 由表 3结果可见，注射本发明实施例 3 的冻干粉针剂产生的肌肉疼痛感明显轻于对比例 1 或对比例 2 产生的肌肉疼痛感，即本发明的制剂在减轻由于制剂本身引起的肌肉疼痛这一不良反应方面，产生了非常理想的效果。

[0054] 显然，上述实施例仅仅是为清楚地说明所作的举例，而并非对实施方式的限定。对于所属领域的普通技术人员来说，在上述说明的基础上还可以做出其它不同形式的变化或变动。这里无需也无法对所有的实施方式予以穷举。而由此所引伸出的显而易见的变化或变动仍处于本发明创造的保护范围之中。

CN104940149A 9/30/2015 Compound aminopyrine antipyrine barbital injection freeze-dried powder injection and preparation method thereof

Status: Filed

Abstract: The invention discloses compound aminopyrine antipyrine barbital injection freeze-dried powder injection and a preparation method thereof. The compound aminopyrine antipyrine barbital injection freeze-dried powder injection comprises aminopyrine, antipyrine, barbital, mannitol, propylene glycol, sodium sulfite, lactose and dextran. Compared with the prior art, the compound aminopyrine antipyrine barbital injection freeze-dried powder injection is good in redissolving property, and stable in quality, and can relieve pain caused by intramuscular injection, the preparation process provided by the invention is simple and easy to control, the production efficiency is high and production energy consumption is low.

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Priority Date: 2015-06-08

Description: [0001] Technical Field [0002] The invention relates to a method for the treatment of acute thermal compound ammonia forest barbiturics injection lyophilized powder for injection and its preparation method, which belongs to the field of pharmaceutical formulations. [0003] Background Art [0004] Antondin injection also called compound ammonia forest barbiturics injection, is colorless or yellowish clear liquid of. Acute a high heat is mainly used for the emergency tuire, the heating of the headache symptoms also relieve function. Used for the treatment of emergency of the antipyretic, of the headache, arthralgia, neuralgia, rheumatalgia tablet of disease with dysmenorrhea, injection drug. For compound preparation, wherein aminopyrin and with antipyrine the pyrazole ketone jiere analgesic, can inhibit 视丘 prostandin of the synthesis and release, restoration of thermoregulatory center feel neuronal normal reactive, antipyretic effect; at the same time also by inhibiting prostandin such as the synthesis of analgesic activity. Aminopyrin and can inhibit the local tissue inflammation in synthesis and prostaglandin release, stable lysosome membrane, phagocytosis of influence phagocytic and anti-inflammatory effect. Shared barbiturics, analgesic effect can be strengthened. [0005] Chinese Patent literature CN101129328A the disclosed compound ammonia forest barbiturics injection is aminopyrin, antipyrine, barbiturics, ethylenediaminetetraacetic acid disodium salt and water for injection. CN104324034A open for injection of a compound aminopyrin pharmaceutical composition for aminopyrin; antipyrine, barbiturics, PLGA, PEG, PVP, mannitol, glycine, Poloxamer, ethylene glycol. Although the above-mentioned injection has the advantages of good reply solubleness, good stability, high drug loading amount, clinical test good safety and the like, has overcome the poor soluble duplicates the prior art, the shortcoming of poor stability, but the muscle injection of muscle pain problems are not to be ignored. Antondin intramuscular injection-induced muscle, bone pain, buttock inflammation, abscess, acromelic necrosis have adverse reactions such as literature report of the article. [0006] In view of this, while many literature "improved muscle injection method of reducing local pain (黄英英 , and other, the south care magazine 1998 year 5 month section 5 roll section 3 a view to)" have been reported in, intramuscular injection, by adjusting the paddle will parts reduce local pain of the patient, however, the method can not the angle of from the preparation itself to alleviate the muscle pain, can only from a very minor extent alleviate the preparation of the

pharmaceutical composition itself has resulted in the problem of pain intramuscular injection. Therefore, study against antondin preparation itself, in terms of preparation of the fundamental reduce or avoid pain caused by muscle injection and other adverse reactions, it is urgent to solve the technical problem. [0007] Content of the invention [0008] Therefore, the invention solves the technical problem of overcoming the existing compound ammonia forest barbiturics injection can easily cause muscle pain technical defect, so as to propose a low pain intramuscular injection, and the product is stable, good re-soluble compound ammonia forest barbiturics injection lyophilized powder for injection and preparation method. [0009] To this end, the present invention provides a used for the treatment of acute thermal compound ammonia forest barbiturics injection lyophilized powder for injection, including aminopyrin, antipyrine, barbiturics, mannitol, propylene glycol, sodium sulfite, lactose, dextran, [0010] Wherein each a packet as: [0011] [0012] The invention is used for treating acute hyperthermia compound ammonia forest barbiturics injection of the raw material is preferably a lyophilized powder: [0013] [0014] [0015] The invention is used for treating acute hyperthermia compound ammonia forest barbiturics injection of the raw material is preferably a lyophilized powder: [0016] [0017] The invention is used for treating acute hyperthermia compound ammonia forest barbiturics injection of the raw material is preferably a lyophilized powder: [0018] [0019] The invention also provides the means for the treatment of acute thermal compound ammonia forest barbiturics injection freeze-dried injection preparation method: [0020] A. According to the production of prescription material, according to the prescription quantity of the original product weighed respectively, spare; [0021] B. The amount of mannitol, propylene glycol, milk sugar dissolved in 60% of water in the injection 60 ±5 °C, by adding 0.1% of activated carbon, filtering to obtain A1 liquid; [0022] C. The aminopyrin, antipyrine, barbiturics, sodium sulfite, dextran are sequentially dissolved in 60% of water in the injection 60 ±5 °C, by adding 0.1% of activated carbon, filtering to obtain B1 liquid; [0023] D. Taking steps of B A liquid 1, obtained C to step B1 liquid, after mixing, microporous membrane filter; [0024] E: after filtering in step D the solution is placed in a -55 the frozen under 7 hours; then at the temperature -15 the sublimation drying the 30 hours; then the temperature rises to the 25 for re-drying, time is 15 hours; gace, gland, packing. [0025] The technical proposal of this invention has the following advantages compared with the prior art, freeze dry powder injection through the screening type of the original and in the consumption of the auxiliary, the present invention provides a simple process for the preparation of good reply solubleness can be achieved, the quality is stable, quick pain caused by muscle injection of compound ammonia forest barbiturics injection lyophilized powder for injection. The product prepared in this invention has good stability, the impurity such as the stability of the various items index significantly superior to the existing product, what is particularly important is the muscle pain is almost zero, and the present invention provides the preparation process is simple, is easy to control, with high production efficiency, low power consumption. [0026] Mode of execution [0027] In the present invention, if 非特指 , all the parts, percentages are weight or volume unit, all of the equipment and raw materials, etc. or can be bought from the market of the industry. The method in the following embodiment, if there is no special note, in the field of all the conventional method. [0028] Embodiment 1: used for the treatment of acute thermal compound ammonia forest barbiturics injection freeze-dried injection [0029] [0030] [0031] Embodiment 2: used for the treatment of acute thermal compound ammonia forest barbiturics injection freeze-dried injection [0032] [0033] Embodiment 3: used for the treatment of acute thermal compound ammonia forest barbiturics injection freeze-dried injection [0034] [0035] Embodiment 1-3 are prepared by the following method: [0036] A. According to the production of prescription material, according to the prescription quantity of the original product

weighed respectively, spare; [0037] B. The amount of mannitol, propylene glycol, milk sugar dissolved in 60% of water in the injection 60 ±5 °C, by adding 0.1% of activated carbon, filtering to obtain A1 liquid; [0038] C. The aminopyrin, antipyrine, barbiturics, sodium sulfite, dextran are sequentially dissolved in 60% of water in the injection 60 ±5 °C, by adding 0.1% of activated carbon, filtering to obtain B1 liquid; [0039] D. Taking steps of B A liquid 1, obtained C to step B1 liquid, after mixing, microporous membrane filter; [0040] E: after filtering in step D the solution is placed in a -55 the frozen under 7 hours; then at the temperature -15 the sublimation drying the 30 hours; then the temperature rises to the 25 for re-drying, time is 15 hours; gace, gland, packing. [0041] The ratio 1:by CN101129328A embodiment 1 method for preparation [0042] The ratio 2:by CN104324034A embodiment 1 method for preparation [0043] Experimental example 1 stability study results [0044] The the embodiment of the invention 3 compound ammonia forest barbiturics injection of freeze-dried powder injection and CN101129328A, CN104324034A embodiment 1 preparation of a product inspection of the dissolving degree, determine the various indicators, results see table 1. [0045] Table 1 [0046] [0047] From table 1 it can be seen , in clarity, dissolving speed, insoluble particles, such as the reference index number, in the sample of the prepared by the invention is obviously superior to the product of the proportion, of the invention make the quality of the product is more stable, controllable. [0048] Experimental example 2 stability study results [0049] The the embodiment of the invention 3 compound ammonia forest barbiturics injection of freeze-dried powder injection and CN101129328A, CN104324034A embodiment 1 preparation of the accelerated stability test research products, measuring various indicators, results see table 2, table 3. [0050] Table 2 [0051] Sampling time Embodiment 3 The proportion 1 The ratio 2 0 days To clarify, particle-free Basic clarification, slightly particles To clarify, particle-free Accelerating 1 month To clarify, particle-free Basic clarification, slightly particles To clarify, particle-free Accelerate the 2 month To clarify, particle-free Basic clarification, particle increased To clarify, the basic particle-free Accelerating 3 months To clarify, particle-free Basic clarification, particle increased To clarify, the basic particle-free [0052] From table 2 it can be seen , in the acceleration test conditions, the appearance of the sample prepared by the invention is the proportion of such aspects as of comparison 1 product has more advantages, with the ratio 2 or more excellent compared with a considerable, of the invention make the quality of the product is more stable, controllable [0053] Experimental example 3 the results of the comparative study of pain intensity [0054] Operation by hand the injection process, uniform are communicated, the same speed, different from the factors of the level of the injector, and in the same on the body of the patient for injection of different 实验例 , from different patients pain threshold of different factors. Inquiry is immediately after the injection of pain intensity of the injector, according to very painful (++) difficulties, a pain (+), (-) and three standard record, for contrast analysis, results see table 3. [0055] Table 3 [0056] [0057] From table 3 we can see the results , injection the embodiment of the invention 3 freeze-dried powder injection of the pain of muscles generated by the lighter-than-the proportion is 1 or the proportion 2 muscle pain is generated, that is, the formulations of the present invention in reducing the pain of the muscle of the formulation itself caused by a bad response to this, the effect of a very ideal. [0058] Obviously, the above embodiment is merely to clearly describe the example of, but not limited to the mode of execution. The common in the field of the technical personnel, in the above-mentioned statement can also be made on the basis of other different forms of change or changes. Here also is not required for all embodiments of to be exhaustive. By this the obvious extension of the change or changes in the creation of this invention are still in the scope of protection.

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Forward Patent Citations:

Claims: claim 1: 1. A used for the treatment of acute thermal compound ammonia forest barbiturics injection lyophilized powder for injection, characterized in that to include aminopyrin, antipyrine, barbiturics, mannitol, propylene glycol, sodium sulfite, lactose, dextran, Wherein each a packet as:; claim 2: 2. Used for the treatment of acute hyperthermia freeze-dried powder injection of compound ammonia forest barbiturics injection according to Claim 1, characterized in that each thereof into packets become:; claim 3: 3. Used for the treatment of acute hyperthermia freeze-dried powder injection of compound ammonia forest barbiturics injection according to Claim 1, characterized in that each thereof into packets become:; claim 4: 4. Used for the treatment of acute hyperthermia freeze-dried powder injection of compound ammonia forest barbiturics injection according to Claim 1, characterized in that each thereof into packets become:; claim 5: 5. A claim 1-4 之一所述 heat used for the treatment of acute of compound ammonia forest barbiturics injection freeze-dried injection preparation method, characterized in that comprises the following steps A. According to the production of prescription material, according to the prescription quantity of the original product weighed respectively, spare; B. The amount of mannitol, propylene glycol, milk sugar dissolved in 60% of water in the injection 60 ±5 °C, by adding 0.1% of activated carbon, filtering to obtain A1 liquid; C. The aminopyrin, antipyrine, barbiturics, sodium sulfite, dextran are sequentially dissolved in 60% of water in the injection 60 ±5 °C, by adding 0.1% of activated carbon, filtering to obtain B1 liquid; D. Taking steps of B A liquid 1, obtained C to step B1 liquid, after mixing, microporous membrane filter; E: after filtering in step D the solution is placed in a -55 the frozen under 7 hours; then at the temperature -15 the sublimation drying the 30 hours; then the temperature rises to the 25 for re-drying, time is 15 hours; gace, gland, packing.

Independent Claims:

First Claim: claim 1: 1. A used for the treatment of acute thermal compound ammonia forest barbiturics injection lyophilized powder for injection, characterized in that to include aminopyrin, antipyrine, barbiturics, mannitol, propylene glycol, sodium sulfite, lactose, dextran, Wherein each a packet as:

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(54) Title: STABLE FORMULATION OF PHENOBARBITAL SODIUM INJECTION

(57) Abstract: Stable phenobarbital sodium solutions for injection that do not generate impurities during extended storage. These solutions include phenobarbital sodium in an amount of 15 to 200 mg/mL; a C1-C4 alcohol such as ethanol in an amount of 105 to 160 mg/mL; and a glycol such as propylene glycol in an amount of between 620 and 830 mg/mL and have a pH of between 9 and 12 which is adjusted to that range by adding acid or base, as required. No more than 50 mg/mL water is present including any water introduced by the acid or base. The solutions contain no more than 0.8% of phenyl ethyl acetyl urea impurity as well as no detectable amount of phenyl butyric acid after two years storage at room temperature.

STABLE FORMULATION OF PHENOBARBITAL SODIUM INJECTION

This application claims the benefit of US provisional application no. 62/258,000 filed November 20, 2015, the entire content of which is expressly incorporated herein by reference thereto.

BACKGROUND

The present invention relates to a phenobarbital sodium solution formulation that is more stable under various stress conditions then prior art formulations and that includes a reduced impurity profile and faster dissolution rate.

A number of phenobarbital injection USP products are currently available on the US and international markets for various treatments, including as a medication for partial and generalized tonic-clonic seizures as well as for treatment of neonatal seizures. The injectable form is primarily used to control status epilepticus.

To prepare phenobarbital sodium formulations for injection, the compound is typically dissolved in a solvent. While the compound is freely soluble in water with solubility reported to be as high as 333 mg/mL to 1 g/mL), the presence of hydroxyl ions in the formulation from the water results in a hydrolysis pathway that can destroy the phenobarbital ring complex. This destruction results in the possible formation of impurities including harmful degradants or precipitates. Furthermore, some of the impurities do not possess a chromophore and therefore are not capable of detection by standard UV-Vis detectors with HPLC analytical methodology. Thus, it is desired to minimize or preferably eliminate any impurities in commercial phenobarbital sodium injection formulations.

The solution to the problem then easily becomes removal of water from the formulation. This is easier said than done as it is highly difficult to dissolve phenobarbital sodium in any organic solvent alone, even when utilizing an aggressive turbulent flow for mixing the active and solvent together. Instead, the prior art generally suggests that a common method for minimizing phenobarbital degradation in solution dosage forms is to dissolve the drug in a mixed solvent of water with organic solvents such as alcohol, sorbitol, propylene glycol, glycerol, polyethylene glycol, and others. This assumes and requires the inclusion of some water for dissolution purposes. As phenobarbital sodium is not as soluble in solvents such as, e.g., ethanol, with solubility reported to only be as high as 100 mg/mL, some water is typically included in formulations that include ethanol or other liquids as

primary solvents. The water content, in general, is on the order of 8 to 12% by weight or more of such solvent mixtures.

The typical impurities for phenobarbital solutions that include water as part of the solvent system are phenyl ethyl acetyl urea (PEAU) and phenyl butyric acid (PBA). Currently, the limits for such impurities in commercially marketed pharmaceutical products are up to 10% of PEAU and up to 1.0% of PBA. The impurities are measured after storage of the solution at room temperature for 2 years. As an accelerated test, the impurities are measured after storage of the solution at a temperature of 40°C for three months. Room temperature is defined as "near 25°C" and is typically understood as being between the ordinary temperatures of approximately 18.3°C to 26.7°C of the atmosphere in a laboratory.

Other possible degradation products of phenobarbital sodium can result from other conditions, such as reactions with base, oxidation or subjecting the compound to heat. These degradation products are illustrated in Table 1 below:

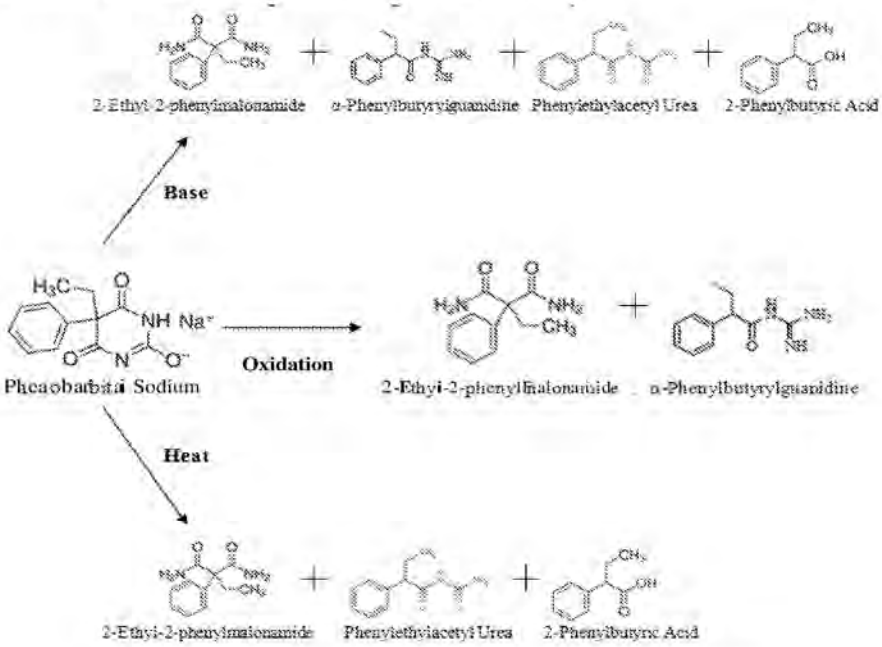


Table 1: Degradation Products of Phenobarbital Sodium

The following prior art documents are cited as particular examples of solvent mixtures that have been used for phenobarbital sodium solutions or for other pharmaceuticals that cannot be solubilized in water.

US patent 6,627,211, which discloses a solvent mixture for transmucosal delivery of an anticonvulsant agent, such as a diazepam, wherein the solvent mixture comprises, e.g., 30% of a C1-C5 aliphatic alcohol such as ethanol, 60%> of a glycol such as propylene glycol and 10% water along with a biological surfactant of a bile salt or lecithin to assist in the transmucosal permeation of the anticonvulsant agent.

US patent 5,141,961, which discloses a process for solubilizing various pharmaceuticals that are difficult to solubilize in water. These pharmaceuticals are solubilized in a mixture of a polyethylene glycol and a polyvinylpyrrolidone. A typical formulation includes 20% to 70% of propylene glycol along with 1 to 28%> of a polyvinylpyrrolidone and a water content that is 8%> or less. A solvent of a C1-C4 aliphatic alcohol, typically ethanol, can be used in an amount of 1 to 50% to prepare mixtures of the ingredients but thereafter is evaporated from the formulation.

US patent publication 2006/0153905 discloses transdermal or transmucosal pharmaceutical formulations that include at least one pharmacologically active ingredient, and a solvent system having a monoalkyl ether of diethylene glycol and a glycol present in specified ratios, and a mixture of water and alcohol. The document discloses the use of 6%> propylene glycol and 47% ethanol with water and other components.

PCT publication WO 2006/125774 discloses an oral formulation of topiramate that has a low water content to prevent hydrolysis of the active and to extend the storage life of the formulation. The water content of such formulations is no more than 5%. The solvents that are used include ethanol, propylene glycol, or polyethylene glycols, alone or in various combinations. These solutions also contain various preservatives and antioxidants in order to form stable solutions at pH values of 5 to 8.

An article by Gupta, V.D., Effect of ethanol, glycerol and propylene glycol on the stability of Phenobarbital Sodium, J. Pharm. Sci., 1984, 73:1661-2, reports on the effects that these solvents have on the stability of phenobarbital solutions. For stabilization, Gupta discloses that ethanol had the best effect followed by propylene glycol and glycerol compared to the stability of phenobarbital in water alone. The preferred solutions included 20% of ethanol, propylene glycol or glycerol in water. As noted herein, however, such a large amount of water is not desirable from the standpoint that it will likely cause hydrolysis of the phenobarbital ring and the generation of undesirable impurities.

A number of other prior art documents disclose the stability of phenobarbital in various aqueous solutions that can contain propylene glycol, ethanol, or other solvents. As

noted, however, such aqueous solutions are not desirable in pharmaceutical products due to the generation of impurities over time.

An article by Williams, N.A. et al., "Excess free energy approach to the estimation of solubility in mixed solvent systems III: Ethanol-propylene glycol-water mixtures," J. Pharm Sci (Jan, 1984), 73(1): 18-23, describes the applicability of the Wohl excess free energy expression to describe the solubility of phenobarbital in various mixtures including ethanol or propylene glycol combined together or with water. Williams concludes that the equation does not satisfactorily describe solubility for phenobarbital in ethanol/propylene glycol solutions even though solubility is fairly high because the assumptions made in the derivation of the equation do not hold, but that the equation is acceptable for describing the solubility of solutions that contain water.

As noted, the inclusion of significant amounts of water in a phenobarbital sodium formulations is not desirable as it will likely result in the formation of undesirable amounts of impurities. Thus, there is a need for formulations that contain or generate relatively low amounts of such impurities. The present invention now addresses the need for stable, essentially impurity-free formulations.

SUMMARY OF THE INVENTION

The present invention now provides, for the first time, phenobarbital solutions for injection that are extremely stable and that do not generate any significant amounts of impurities during extended storage. Generally, these phenobarbital solutions include a phenobarbital salt, preferably phenobarbital sodium, in an amount of 15 to 200 mg/mL and in particular 25 to 150 mg/mL; a C1-C4 alcohol, preferably ethanol, in an amount of 105 to 160 mg/mL and in particular 125 to 150 mg/mL; and a glycol such as propylene glycol in an amount of between 620 and 830 mg/mL and in particular 675 to 810 mg/mL. Advantageously, these solutions have a pH of between 9 and 12 and in particular between 9.2 and 10.2 which is adjusted to that range by adding a sufficient amount of acid or base, as required. These solutions contain no more than 50 mg/mL water including any water introduced by the acid or base that is added to provide the desired pH. The enhanced stability of these solutions is demonstrated by the fact that they contain no more than 0.8% of PEAU impurity after two years storage at room temperature. Furthermore, these solutions do not contain a detectable amount of PBA impurity after the same periods of two years storage at room temperature.

The present invention provides a substantial reduction of impurities due to the greatly enhanced stability of such solutions compared to conventional or currently available commercial solutions of phenobarbital sodium for injection. This reduction of impurities is based on the careful selection and balance of the solvent systems disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

In the following detailed description, numerous specific details are set forth by way of examples in order to provide a thorough understanding of the relevant teachings. It should be apparent to those skilled in the art, however, that the present teachings may be practiced without such details. In other instances, well known methods, procedures and/or, formulation details have been described at a relatively high-level, without detail, in order to avoid unnecessarily obscuring aspects of the present teachings.

The invention may be more fully understood by reference to the following definitions.

When the singular forms "a," "an" and "the" or like terms are used herein, they will be understood to include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like. The word "or" and like terms mean any one member of a particular list and also includes any combination of members of that list.

When used herein the term "about" will compensate for variability allowed for in the pharmaceutical industry and inherent in pharmaceutical products, such as differences in product strength and bioavailability due to manufacturing variations and time-induced product degradation. The term allows for any variation which in the practice of pharmaceuticals would allow the product being evaluated to be considered pharmaceutically equivalent or bioequivalent, or both if the context requires, to the recited strength of a claimed product. Alternatively, the term can allow for up to 5, 10, 15 or 20% variation from the stated value. Where particular values are described in the application and claims, unless otherwise stated, the term "about" is implicit and in this context means within an acceptable error range for the particular value.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps. The term "consisting essentially of means that other additives or components that impart a material change to the invention are not encompassed by the claims. For example, a stable formulation consisting essentially of recited components would exclude other additives

that are conventionally used for imparting stability or anti-oxidant properties to the formulation, as these additives are not needed based on the components that are specifically recited to be present.

When ranges are given by specifying the lower end of a range separately from the upper end of the range, it will be understood that the range can be defined by selectively combining any one of the lower end variables with any one of the upper end variables that is mathematically possible. Also, when reciting ranges between certain values, the endpoints are considered to be included in the recited range.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts that are pharmaceutically acceptable, as defined above, and that possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-l-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-l-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like. The preferred phenobarbital salt is phenobarbital sodium.

The term "pharmaceutical solution" or "solution" refers to a mixture with a pharmaceutically suitable excipient, diluent or carrier selected with regard to the intended

route of administration and standard pharmaceutical practice. The excipient, diluent and/or carrier must be "acceptable" in the sense of being compatible with the other ingredients of the solution and not deleterious to the recipient thereof. Acceptable excipients, diluents, and carriers for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins (A.R. Gennaro edit. 2005). The choice of pharmaceutical excipient, diluent, and carrier can be selected with regard to the intended route of administration and standard pharmaceutical practice. The most preferred excipients, diluents and carriers are disclosed herein and in the examples.

The present formulations are designated as "stable" if they provide the same or less total impurities when exposed to a wider range of system parameters, i.e., oxygen head space, pH, and temperature. In particular, the stable formulations of the present invention have been found to exhibit 1% or less, preferably 0.8% or less of hydrolysis impurities.

As a skilled artisan would know, "hydrolysis impurities" refers to impurities that result from hydrolysis of the phenobarbital ring as precipitates or other degradation products. The typical impurities for phenobarbital solutions are PEAU and PBA. As noted herein, current limits for such impurities in commercial products are up to 10% of PEAU and up to 1% of PBA. The impurities are measured after storage of the solution at room temperature for 2 years.

As noted herein, the phenobarbital solutions of the invention include the phenobarbital salt, phenobarbital sodium. This is a well-known and conventionally used active which is established for various treatments. The general amount of this compound to be included in solutions for injection is from about 15 to about 200 mg/mL, including the endpoints although any other amount in the recited ranges should be suitable. The upper end of the range is a maximum concentration that does not precipitate in the particular formulation, while on the lower end, the minimum amount to be used would be one that provides a pharmacological effect without requiring repeated injections of lower concentrations to achieve such an effect. More specifically, the amount may be between 30 and 135 mg/mL and in particular between 40 and 130 mg/mL, with the most preferred amounts being between formulations that contain 30, 55, 65, 90 or 130 mg/mL.

The solvent mixture comprises two major components, namely an alcohol and a glycol. The alcohol is preferably a C1-C4 alcohol, and preferably is an aliphatic alcohol. The most preferred alcohol is ethanol, as it is well understood by skilled artisans and has been commonly used in many different formulations in the art. The amount of alcohol may be

between about 125 to about 160 mg/mL. Preferably, the amount should be between 135 and 150 mg/mL with a target amount of about 140 mg/mL.

The glycol is preferably propylene glycol, which is another solvent that is well understood by skilled artisans and commonly used in many different formulations in the art. The amount of the glycol may be between about 620 and 830 mg/mL. Preferably, the amount is between 700 and 810 mg/mL with the most preferred amounts being determined by routine testing of the formulation provided that it is in the general range described herein. Often, the amount is between 725 and 785 mg/mL and the most preferred amount is between about 750 and about 760 mg/mL.

Advantageously, these solutions have a pH of between 9 and 12, and preferably from 9.2 to 10.2, with the pH of the solution adjusted to that range by adding a sufficient amount of acid or base, as required. While any acid or base can be used for this purpose, it has been found that hydrochloric acid and sodium hydroxide are eminently suitable and are preferred due to their well-known nature.

In contrast to the prior art, the phenobarbital sodium solutions of the present invention provide a substantial reduction of PEAU and PBA impurities. To assist in maintaining the impurities at such low levels, the solutions of the invention contains no more than 50 mg/mL water and preferably 40 mg/mL or less including the water that is introduced by the acid or base that is added to provide the desired pH. The enhanced stability of these solutions is demonstrated by the fact that the solution contains no more than 0.8% of PEAU impurity after two years storage at room temperature. Furthermore, these solutions do not contain a detectable amount of PBA after the same period.

The preferred concentrations of phenobarbital sodium range from 30 to 135 mg/mL. These amounts can be effectively and easily dissolved in the preferred 50-50 mixture of ethanol and propylene glycol to form a stable solution containing very small amounts of water. This reduction in water content leads to the prevention or significant reduction of impurities as the amount of water is insufficient to cause any significant hydrolysis of the phenobarbital ring. As noted, the amount of PEAU impurity is at least about 8 to 9 times lower than that which is currently allowed in commercial products while any amount of PBA is effectively eliminated from these solutions. Also, the reduced amount of impurity formation in the pH range of 9 to 12 and preferably from 9.2 to 10.2 would reduce the propensity for loss of mass balance in an analytical test method utilizing a UV-Vis detector.

These compositions do not need to contain and are typically free from including any preservatives, anti-oxidants, wetting agents, emulsifying agents, surfactants or dispersing

agents. If desired, such components can be added in conventional amounts but it is preferred that they not be present. The same is true of other additives for the prevention of the action of microorganisms: there is no need for the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like, but they can be added if desired.

Additionally, it is preferred that the solution not contain any other drug active. This assists in avoiding impurities. In more preferred embodiments, the solutions consist essentially of or even consist of the recited components.

And while the present formulations are described in terms of concentrations of the various components, the formulations are distinct from the prior art even when the relative percentages of the components is considered. Converting the concentrations of the ingredients to percentages, it is seen that the present invention utilizes a solvent solution that is between about 40 and about 60% of ethanol and about 60 to about 40% of propylene glycol for dissolution of the phenobarbital sodium API. Preferably, equal amounts of each solvent are used. While the solvent solution does contain a small amount of water, in an amount of 5.0% or less and preferably 3.5% or less, water is not intentionally added to the solvent solution. It is instead introduced from the addition of the acid or base used to adjust the pH of the solution to the preferred value of 9.2 to 10.2.

Accordingly, the preferred formulations of the invention are those wherein:

(a) the phenobarbital sodium is present in an amount of 25 mg/mL;
the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL;
the polypropylene glycol is present in an amount of about 809 mg/mL; and
wherein the solution contains no more than 40 mg/mL water;

(b) the phenobarbital sodium is present in an amount of 55 mg/mL;
the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL;
the polypropylene glycol is present in an amount of between 779 mg/mL; and
wherein the solution contains no more than 40 mg/mL water;

(c) the phenobarbital sodium is present in an amount of 90 mg/mL;
the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL;
the polypropylene glycol is present in an amount of about 754 mg/mL; and
wherein the solution contains no more than 40 mg/mL water;

(d) the phenobarbital sodium is present in an amount of 150 mg/mL; and
the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL;
the polypropylene glycol is present in an amount of about 694 mg/mL; and

wherein the solution contains no more than 40 mg/mL water.

Other concentrations of the phenobarbital sodium, such as 30, 65 or 130 mg/mL can be used. In all of the foregoing formulations, the preferred C1-C4 alcohol is ethanol and is present in an amount of between about 120 and 160 mg/mL, the polypropylene glycol is present in an amount of about 620 to 830 mg/mL: and the water is typically present at about 36 mg/mL or less.

Another embodiment of the invention relates to a method of making an injection solution of phenobarbital sodium by admixing from solvents together with the active agent and then adjusting the pH to the desired range as necessary. The method then calls for filling an appropriate container, such as a pre-filled syringe, vial, or the like, with about 0.5 to about 20 mL of the solution. After admixing the components solutions and filling the appropriate container, the product is subject to sterilizing and the container is sealed. The invention calls for providing a headspace in the sealed container consisting of less than 10% by volume of oxygen content and preferably below 5% by volume by adding nitrogen to the container. As noted, this is achieved by adding nitrogen to the container during filling with the solution.

EXAMPLES

The present invention is now further identified and defined by the following examples, which illustrate the most preferred embodiments.

Example 1: Comparison of Phenobarbital Sodium Injection Formulations of the Present Invention and Prior Art Marketed Formulations.

Table 2: Formulations

Purpose	Raw Material	Currently Marketed Formulations	Inventive Formulations			
Active	Phenobarbital Sodium, USP	65 mg/mL and 130 mg/mL	25 mg/mL	55 mg/mL	90 mg/mL	150 mg/mL
Co-Solvent	Ethanol, Dehydrated, USP	105.5 mg/mL	140 mg/mL	140 mg/mL	140 mg/mL	140 mg/mL
Co-Solvent	Propylene Glycol, USP[A]	702.4 mg/mL	QS to 100% Approx. 809 mg/mL	QS to 100% Approx. 779 mg/mL	Q.S. to 100% Approx. 754 mg/mL	QS to 100% Approx. 694 mg/mL
Preservative	Benzyl Alcohol	15.63 mg/mL	N/A	N/A	N/A	N/A

pH Adjuster	1:5 Hydrochloric Acid, NF	As required to adjust pH	As required to adjust pH	As required to adjust pH	As required to adjust pH	As required to adjust pH
	1:10 Sodium Hydroxide, NF	As required to adjust pH	As required to adjust pH	As required to adjust pH	As required to adjust pH	As required to adjust pH
Diluent	Water for Injection[B], USP	QS to 100% About 8% to 12% w/w	36 mg/mL 3.53%[C]	36 mg/mL 3.53%[C]	36 mg/mL 3.53%[C]	36 mg/mL 3.53%[C]

[A] The amount of Propylene Glycol addition is based on a calculation utilizing the density.
[B] The water for injection (WFI) amount is as follows:
Propylene Glycol [mg/mL] = Density [mg/mL] - summation of all other ingredients [mg/mL].
Batch record will read "Q.S. to final batch weight".
[C] WFI concentration is listed with the inclusion of water (acid) added by pH adjustment.

In general, the solutions of the present invention contain much less water than prior art formulations and do not need to include a preservative. Basically, the relative amount of propylene glycol would be between 66 and 82%, the amount of ethanol would be between 10 and 16%, and the amount of water would be less than 5% and preferably 3.5% or less. These values do not always add up to 100% due to the miscibility of the components in each other.

Tables 3 to 5 below illustrate the properties and performance of prior art formulations, one of which contains 65 mg/mL phenobarbital sodium and the other of which contains 130 mg/mL. Table 3 shows the water content, pH and assay percentage for those formulations, while Table 4 shows accelerated degradation data at 40°C for the 65 mg/mL solution and Table 5 shows accelerated degradation data at 40°C for the 130 mg/mL solution. Various headspace oxygen contents were used, typically at 21% (atmospheric content) or at 5% (reduced content due to nitrogen flushing of the container during filling).

Table 3: Prior Art 65 mg/mL (11.6% Water) Accelerated Degradation at 40°C Data

Sample ID	Storage Temp °C	Oxygen High/Low	Duration (Month)	Assay	pH	2-Phenylburtyric Acid (PBA) %	Phenylethylacetyl Urea (PEAU) %	Total % Impurities
PB3-7	25	21%	0	95.4	9.4	ND	0.05	0.1
PB3-19	40	21%	1	92.2	9.4	ND	2.00	2.0
PB3-20	40	21%	2	88.9	9.4	0.20	4.80	5.0
PB3-21	40	21%	3	86.0	9.4	0.38	5.52	5.9
PB3-13	25	5%	0	94.3	9.5	ND	0.05	0.1
PB3-23	40	5%	1	92.8	9.4	ND	1.90	1.9
PB3-24	40	5%	2	91.0	9.4	0.10	4.20	4.3
PB3-25	40	5%	3	78.8	9.4	1.81	9.12	10.9

Table 4: Prior Art 130 mg/mL (8% Water) Accelerated Degradation at 40°C Data

Sample ID	Storage Temp °C	Oxygen High/Low	Duration (Months)	Assay	pH	PBA %	PEAU %	Total %
PB3-41	25	21%	0	96.6	9.8	ND	ND	ND
PB3-53	40	21%	1	94.5	9.6	ND	0.60	0.6
PB3-54	40	21%	2	94.2	9.6	ND	1.13	1.1
PB3-55	40	21%	3	91.9	9.6	ND	1.77	1.8
PB3-47	25	5%	0	98.7	9.6	ND	ND	ND
PB3-57	40	5%	1	97.4	9.5	ND	0.70	0.7
PB3-58	40	5%	2	95.4	9.5	ND	1.23	1.2
PB3-59	40	5%	3	96.5	9.6	ND	1.78	1.8

The results in Table 3 shows an impurity level for the 65 mg/mL solution 5.5% PEAU and 0.4% PBA for a total impurity level of 5.9%> after three months storage at 40°C in a container having 21%> oxygen in the headspace, and an impurity level of 9.1%> PEAU and 1.8% PBA for a total impurity level of 10.9%> after three months storage at 40°C in a container having 5%> oxygen in the headspace. Similarly, the results for the 130 mg/mL solution in Table 4 show an impurity level of 1.8% PEAU and no detectable PBA for a total impurity level of 1.8% after three months storage at 40°C in a container having 21% oxygen in the headspace, and the same values three months storage at 40°C in a container having 5% oxygen in the headspace. The results are worse for the 65 mg/mL formulation because it contained 11.6% water while the 130 mg/mL formulation contained only 8% water.

Tables 5 to 7 illustrate test results for a solution of 55 mg/mL phenobarbital sodium solution according to the invention that contains only 3.5% water

Table 5: 90 mg/mL formulation (3.5% water) 3 Month 40°C Data (pH of 10.2)

Test ID #	Oxygen	Temp	Month	pH	Other Imp	PEMA	PEAU	PBA	Total
PB13-23	21%	40°C	3	10.2	0.05	<LOQ	0.77	0.07	**0.9%**
PB13-27	<5%	40°C	3	10.2	<LOQ	ND	0.63	ND	**0.6%**
Formulation also contains 140 mg/mL ethanol and 754 mg/mL propylene glycol.									

Table 6: 90 mg/mL formulation (3.5 % water) 3 Month 40°C Data (pH of 9.85)

Test ID #	Oxygen	Temp	Month	pH	Other Imp	PEMA	PEAU	PBA	Total
PB13-67	21%	40°C	3	9.85	<LOQ	ND	0.79	ND	**0.8%**
PB13-71	<5%	40°C	3	9.85	0.05	ND	0.71	ND	**0.8%**
Formulation also contains 140 mg/mL ethanol and 754 mg/mL propylene glycol.									

Table 7: 90 mg/mL formulation (3.5% water) 3 Month 40°C Data (pH of 9.5)

Test ID #	Oxygen	Temp	Month	Other Imp	PEMA	PEAU	PBA	Total
PB13-111	21%	40°C	3	ND	ND	0.82	ND	**0.8%**
PB13-115	<5%	40°C	3	ND	ND	0.74	ND	**0.7%**
Formulation also contains 140 mg/mL ethanol and 754 mg/mL propylene glycol.								

The results show significantly reduced impurity levels. In Table 5, the formulation that was exposed to atmospheric oxygen (21%) exhibited only 0.77% of PEAU and 0.07% of PBA impurities. For the same solution in a low oxygen environment, the impurity levels were reduced to 0.63 for PEAU and PBA was not even detected. Thus, these two products provided total impurity levels of 0.9 and 0.6% respectively.

Table 6 shows similar excellent results. The formulation that was exposed to atmospheric oxygen (21%) exhibited only *0.79%* of PEAU and PBA was not detected. For the same solution in a low oxygen environment (5%), the impurity levels were reduced to 0.71 for PEAU and PBA was again not even detected. Thus, these two products each provided a total impurity level of 0.8%.

In Table 7, the formulation that was exposed to atmospheric oxygen (21%) exhibited only 0.82% of PEAU, while the same solution in a low oxygen environment exhibited 0.74% of PEAU. PBA was not even detected for either formulation. Thus, these two products provided total impurity levels of 0.8 and 0.7% respectively.

The results for each formulation in Tables 5 to 7 are more than 10 times lower than the maximum amount allowable for commercial products of phenobarbital solutions. These unexpected and significant improvements in impurity levels are obtained due to the 50/50 Ethanol/PEG dissolution solution and the reduced amount of water added only as a pH adjustment after an almost complete PEG to final volume.

In Table 8 and 9, the results of three batches each of the preferred 55mg/mL and 90mg/mL invention, respectively, are shown to demonstrate the decrease in impurities under normal conditions. The results of these studies showed no detectable amounts of PBA were formed and the PEAU controlled to 0.7%.

Table 8: Preferred 55 mg/mL Formulation (3.5% Water) Stability Data at 25°C Storage

Batch	Duration (Month)	Assay	2-Phenylburtyric Acid (PBA) %	Phenylethylacetyl Urea (PEAU) %	Total % Impurities
A	0	99.9%	ND	ND	<LOQ
A	**6**	**100.3%**	ND	0.19%	0.2%
A	12	100.1%	ND	**0.37%**	0.4%

A	24	100.7%	ND	0.68%	0.7%
B	0	100.5%	ND	ND	<LOQ
B	6	100.5%	ND	0.20%	0.2%
B	12	100.7%	ND	0.38%	0.4%
B	24	100.9%	ND	0.69%	0.7%
C	0	99.9%	ND	ND	<LOQ
C	6	101.7%	ND	0.20%	0.2%
C	12	100.5%	ND	0.37%	0.4%
C	24	100.9%	ND	0.66%	0.7%

Formulation also contains 140 mg/mL ethanol and 779 mg/mL propylene glycol.

Table 9: Preferred 90 mg/mL Formulation (3.5% Water) Stability Data at 25°C Storage

Batch	Duration (Month)	Assay	2-Phenylburtyric Acid (PBA) %	Phenylethylacetyl Urea (PEAU) %	Total % Impurities
A	0	100.7%	ND	ND	<LOQ
A	6	100.8%	ND	0.21%	0.2%
A	12	100.5%	ND	0.38%	0.4%
A	24	101.5%	ND	0.69%	0.7%
B	0	99.8%	ND	ND	<LOQ
B	6	100.9%	ND	0.20%	0.2%
B	12	100.4%	ND	0.36%	0.4%
B	24	100.0%	ND	0.65%	0.7%
C	0	99.1%	ND	ND	<LOQ
C	6	100.3%	ND	0.22%	0.2%
C	12	99.4%	ND	0.39%	0.4%
C	24	100.2%	ND	0.70%	0.7%

Formulation also contains 140 mg/mL ethanol and 754 mg/mL propylene glycol.

All patents, patent applications, publications, test methods, protocols, literature, and other materials cited herein are hereby incorporated by reference in their entireties.

Those skilled in the art will appreciate that the present invention has a wide range of applications and that it fulfills the needs of the prior art described herein and meets the above-stated objects. While there has been shown and described preferred embodiments of the invention, it will be evident to those skilled in the art that various modifications and changes may be made thereto without departing from the spirit and the scope of the invention as set forth in the appended claims and equivalents thereof.

THE CLAIMS

What is claimed is:

1. A phenobarbital sodium solution for injection comprising:
phenobarbital sodium in an amount of 15 to 200 mg/mL;
a C1-C4 alcohol in an amount of 105 to 160 mg/mL; and
propylene glycol in an amount of between 620 and 830 mg/mL;
wherein the solution has a pH of between 9 and 12 which is adjusted to that range by adding a sufficient amount of acid or base, as required;
wherein the solution contains no more than 50 mg/mL water including any water introduced by the acid or base that is added to provide the desired pH; and
wherein the solution contains no more than 0.8% of phenyl ethyl acetyl urea (PEAU) impurity after two years storage at room temperature.

2. The solution of claim 1, wherein:
the phenobarbital sodium is present in an amount of 25 to 150 mg/mL;
the C1-C4 alcohol is present in an amount of 125 to 150 mg/mL; and
the propylene glycol is present in an amount of between 675 and 800 mg/mL; and
the solution has a pH of between 9.2 and 10.2.

3. The solution of claim 1, wherein:
the phenobarbital sodium is present in an amount of 25 to 90 mg/mL;
the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL; and
the polypropylene glycol is present in an amount of between 730 and 830 mg/mL;
wherein the solution contains no more than 40 mg/mL water.

4. The solution of claim 1, wherein:
the phenobarbital sodium is present in an amount of 90 to 150 mg/mL;
the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL; and
the polypropylene glycol is present in an amount of between 660 and 730 mg/mL;
wherein the solution contains no more than 40 mg/mL water.

5. The solution of any preceding claim which is free of preservatives or antioxidants.

6. The solution of any preceding claim which does not contain a detectable amount of phenyl butyric acid (PBA) after two years storage at room temperature.

7. The solution of any preceding claim which does not contain any other drug active.

8. The solution of claim any preceding claim which consists of the recited components.

9. The solution of claim 1 specifically as the following formulations:

(a) the phenobarbital sodium is present in an amount of 25 mg/mL; the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL; the polypropylene glycol is present in an amount of about 809 mg/mL; and wherein the solution contains no more than 40 mg/mL water; or

(b) the phenobarbital sodium is present in an amount of 55 mg/mL; the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL; the polypropylene glycol is present in an amount of between 779 mg/mL; and wherein the solution contains no more than 40 mg/mL water; or

(c) the phenobarbital sodium is present in an amount of 90 mg/mL; the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL; the polypropylene glycol is present in an amount of about 754 mg/mL; and wherein the solution contains no more than 40 mg/mL water; or

(d) the phenobarbital sodium is present in an amount of 150 mg/mL; and the C1-C4 alcohol is ethanol and is present in an amount of about 140 mg/mL; the polypropylene glycol is present in an amount of about 694 mg/mL; and wherein the solution contains no more than 40 mg/mL water.

10. A sealed container that includes therein about 0.5 to about 20 mL of the phenobarbital sodium solution of any one of claims 1 to 9.

11. The sealed container of claim 10 which is a syringe or vial and which is sterilized.

12. The sealed container of claim 10 or 11 which has a headspace that has an oxygen content of less than 10% by volume or less than 5% by volume.

13. A method for making the phenobarbital sodium solution according to any one of claims 1 to 9 which comprises admixing the phenobarbital sodium with the alcohol and glycol and then adjusting the pH to the desired range as necessary by the addition of the acid or base.

14. The method of claim 13 which further comprises filling a container with about 0.5 to about 20 mL of the solution; sterilizing the solution; and sealing the container.

15. The method of claim 13 or 14 which further comprises providing a headspace in the sealed container that contains oxygen in an amount of less than 10% by volume or less than 5% by volume by adding nitrogen to the container.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/056973

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/10 A61K9/08 A61K31/515
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , BIOSIS, EMBASE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TORRELLAS A ET AL: "Pituitary-adrenal responses to sub-chronic treatment with phenobarbital and/or phenytoin (diphenylhydantoin) in rats", PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, ELSEVIER, US, vol. 15, no. 2, 1 August 1981 (1981-08-01), pages 235-241, XP023804979, ISSN: 0091-3057, DOI: 10.1016/0091-3057(81)90182-9 [retrieved on 1981-08-01] page 235, right-hand column, lines 1-12 -----	1-15
A	RU 2 463 052 C1 (VC 41598 [RU]) 10 October 2012 (2012-10-10) page 5, lines 39-50 figure 1; example 2 claims -----	1-15

☐ Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
RU 2463052 C1	10-10-2012	----------	

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NOTES | VOLUME 73, ISSUE 11, P1661-1662, NOVEMBER 01, 1984

Effect of Ethanol, Glycerol, and Propylene Glycol on the Stability of Phenobarbital Sodium

V. Das Gupta DOI: https://doi.org/10.1002/jps.2600731149

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Abstract

The effects of ethanol, glycerol, propylene glycol, phosphate buffer, and ionic strength on the stability of phenobarbital sodium have been studied. Ethanol had the maximum stabilization effect followed by propylene glycol and glycerol when compared with the stability in water. The estimated half-lives at 50°C (pH ~ 8) were 78, 95, 109, and 127 d in water and 20% aqueous solutions of glycerol, propylene glycol, and ethanol, respectively. The effects of phosphate buffer and ionic strength were negligible.

phrases

Phenobarbital sodium—stability, effects of ethanol, glycerol, and propylene glycol •
Stability—phenobarbital, effect of solvents

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Phenytoin-Folate Interactions: How Far is Safe Folate Supplementation in Phenytoin Treated Epileptic Patients?

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ABSTRACT

Chronic administration of phenytoin has been associated to have a number of adverse effects. Falling serum folate levels is one such most often reported adverse drug sequelae of long term phenytoin usage. Folates administered at pharmacological doses, on the other hand, have been blamed for a decrease in the serum concentration of phenytoin, severe enough to precipitate seizures. This review substantiated with references from various studies focuses on the folic acid-phenytoin interaction and discusses the feasibility of using folate supplements to avoid such inadvertent drug sequelae in epileptic patients kept on chronic treatment with phenytoin.

Keywords: Phenytoin, anti-convulsant, folate metabolism, seizures.

INTRODUCTION

Epilepsy is described as a chronic neurological disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness (Sridharan, 2002). A recent meta-analysis of published and unpublished studies puts an overall prevalence rate of epilepsy in India at 5.59 per 1,000 populations (Sridharan, 1999). Despite the tremendous advances in the management of epilepsy, phenytoin still remains the drug of choice (Scheinfeld, 2003; Hassessian, 2003) however; the long term administration of phenytoin has been seen to lead to a number of adverse effects (Hassell, 2000, Ciancio, 1972). Falling serum folic acid levels is one such most commonly reported adverse drug sequela of long term usage of phenytoin (Brunet, 1996). While the details of these interactions remain obscure, several potential mechanisms have been proposed as explanations. One of the first hypotheses suggested that phenytoin increased the pH of the small intestine inhibiting the intestinal conjugase activity impairing the intestinal absorption of folates by the anti-convulsant drugs. Other hypotheses include direct competition between folate and phenytoin for uptake sites, inhibition of folate inter-converting enzymes by phenytoin, increased catabolism of folates by phenytoin induction of folate catabolic enzymes and inhibition of central appetite centers by phenytoin decreasing food intake and thereby leading to decreased tissue folate concentrations.

Folates administered at pharmacological doses, on the other hand, have been blamed for a decrease in the serum concentration of phenytoin, possibly due to direct competition between folate and phenytoin for uptake sites, severe enough to precipitate seizures. Numerous studies conducted in the past have proposed different reasons for falling serum folate levels on long term administration of phenytoin (Majola, 2000; Reynolds, 1971. Sener, 2006; Linnebank, 2011). This review focuses on a concise overview of the mechanisms that have been proposed in the literature regarding the deficiency of folic acid seen and also, discusses the feasibility of using folate supplements to avoid such inadvertent drug sequelae in epileptic patients kept on chronic treatment with phenytoin while simultaneously preventing the precipitation of seizures.

Phenytoin Use and Folate Deficiency: A Brief Overview of the proposed Hypotheses

Phenytoin administered at therapeutic dosages has been shown to deplete plasma folate concentrations in humans (Pisciotta, 1982). This has been later confirmed in other studies as well. While the details of these interactions remain obscure, several potential mechanisms have been proposed as explanations. One of the first hypotheses suggested that phenytoin increased the pH of the small intestine inhibiting the intestinal conjugase activity (Hoffbrand, 1968) impairing the intestinal absorption of folates by the anti-convulsant drugs (Meynell, 1966, Dahlke, 1967). Eighty percent of the folates are present in the diet in the form of non-absorbable polyglutamates (Butterworth, 1963) which are deconjugated by the intestinal enzyme conjugase into absorbable monoglutamates during absorption (Rosenberg, 1967). The phenytoin-generated increase in gut pH was hypothesized to decrease the driving force of the proton pump which supplied the energy for at least one folate transporter in the gut (Schron, 1991). Other hypotheses that have been stated in the literature in this regard include direct competition between folate and phenytoin for uptake sites (Rosenberg, 1979), inhibition of folate inter-converting enzymes by phenytoin (Carl, 1983), increased catabolism of folates by phenytoin induction of folate catabolic enzymes (Chanarin, 1979) and inhibition of central appetite centers by phenytoin decreasing food intake and thereby leading to decreased tissue folate concentrations (Hoppner, 1989). The fact that anti-convulsant drugs are known to induce hepatic enzymes led to a further series of hypotheses. Richens and Waters suggested that folate deficiency in long term phenytoin users might arise due to induction of enzymes involved in folate metabolism. Maxwell et al proposed that folate deficiency in phenytoin users might be a result of an increase in the demand for the folate co-enzymes required either for the anti-convulsant drug hydroxylations or, for other hepatic enzymes induced by these drugs.

Phenytoin and Folate Interaction: A Review of Different Studies

In a study published in 1966 in the British Medical Journal by Malpas JS, Spray GH and Witts LJ (Malpas, 1966) on serum folic acid and vitamin B_{12} levels in anti-convulsant therapy, the results substantiated the earlier work of the association of megaloblastic anemia with anti-convulsant therapy as reported first by Mannheimer, Pakesch, Reimer and Vetter (1952). The finding of normal levels of vitamin B_{12} and the correction of anemia following folic acid therapy suggested the role of anti-convulsants on folic acid metabolism. Further evidence for this had been the demonstration of macrocytosis or low serum folic acid levels in about half the patients who had been on anti-convulsant drugs (Hawkins, 1958; Klipstein, 1964).

In another original report published in the British Medical Journal in 1967 by Wells DG and Casey HJ (Wells, 1967), low CSF folate levels were observed in treated epileptic patients which was found to be significantly different from that of a control group irrespective of whether the results were analyzed using a log-normal or a Gaussian distribution.

In another study detailed in the British Pharmacological Society conducted by Richens A and Waters AH (Richens, 1971) based on the acute effects of phenytoin on serum folate concentration, in the results, five of the six subjects showed a gradual fall in the concentration of serum folate during the 4 days of treatment and four subjects had developed a subnormal value by day 3. Six days after stopping the drug, serum folate returned almost to control levels, however, red cell folate concentrations were seen to fall only slightly. These findings suggested that the acute fall in the serum folate concentration was due largely to a disturbance in the folate metabolism caused by the administration of phenytoin, the exact mechanism, however, for this remained unexplained. It was proposed, however, that phenytoin might inhibit intestinal conjugase and thereby impair the absorption of polyglutamates.

In a study published in 1971 in the Journal of Neurology, Neurosurgery and Psychiatry based on folate metabolism in epileptic and psychiatric patients by Reynolds EH, Preece J and Johnson AL (Reynolds, 1971), significant lowering of serum folate and red cell folate levels was observed in epileptic patients with psychiatric illness, and a less significant fall in red cell folate levels was found in non-epileptic psychiatric patients. A significant correlation was found between serum and red cell folate values in control, epileptic, and non-epileptic patients. In the epileptic patients there was a significant association between low serum and red cell folate levels and the presence of psychiatric illness.

In a study published in 1972 in the British Medical Journal by Maxwell JD, Hunter John, Stewart DA, Ardeman Simon and Williams Roger (Maxwell, 1972) to find out the role of hepatic enzyme induction behind folate deficiency after anti-convulsant drugs, serum and red cell folate levels were found to be reduced in children with epilepsy attending a residential school. Also, the degree of folate deficiency was significantly related to increased hepatic microsomal enzyme activity as assessed from increased urinary excretion of D-glucaric acid and also, correlated with the daily dose of anti-convulsant taken. Anti-convulsant drugs have long been known to have enzyme inducing properties and decreased levels of folate suggested that folate depletion resulted

from increased demand for the co-factor after induction of drug metabolizing enzymes. As folate deficiency was ultimately proposed to have an impact on drug metabolism, this hypothesis explained why blood phenytoin levels decreased and fit control worsened after correction of folate deficiency in epileptic patients.

In another study published in the Gut in 1972 by Houlihan CM, Scott JM, Boyle PH and Weir DG (Houlihan, 1972) on the effect of phenytoin on the absorption of synthetic folic acid polyglutamate, the study concluded that phenytoin had no adverse effect on the absorption of synthetic polyglutamate in vivo substantiating the work of Baugh and Krumdieck (1969) that showed in vitro that phenytoin did not inhibit the intestinal folate deconjugase enzyme(s) necessary for the breakdown of the folate polyglutamates, a process which occurs before or during folate absorption.

In a study published in 1973 in the Journal of Clinical Pharmacology by Latham AN, Millbank L, Richens A, Rowe DJF (Latham, 1973), on the liver enzyme induction by anti-convulsant drugs, and its relationship to disturbed calcium and folic acid metabolism, serum calcium and folate levels estimated in epileptic patients and related to the urinary excretion of D-glucaric acid. Calcium and folate levels were lowest in those patients who were receiving treatment with pheneturide. This group of patients also excreted a significantly greater amount of D-glucaric acid in their urine, suggesting that pheneturide is a potent liver enzyme inducer and is more powerful in this respect than phenobarbitone, phenytoin, or primidone. The study also supported the hypothesis that the disturbance of both calcium and folate metabolism is caused by liver enzyme induction.

In a study published in 1979 in the Journal of Clinical Investigation by Kelly Deirdre, Weir Berenice Donald and Scott John (Kelly, 1979) on the effect of anti-convulsant drugs on the rate of folate catabolism in mice, it was shown that the rate of catabolism of folate was actually increased after anti-convulsant, in particular phenytoin therapy. For the study, an experimental animal model using mice was developed to determine the rate of catabolism of radioactive hydrogen replaced pteroylglutamic acid by the quantitative estimation of p-aminobenzoylglutamic acid and acetamidobenzoylglutamic acid in the urine. Administration of intramuscular phenobarbitone on the other hand did not affect the rate of catabolism when compared with the controls.

In another review published in 1983 in Therapeutic Drug Monitoring on Phenytoin and folic acid: individualized drug-drug interaction by Berg MJ, Rivey MP, Vern BA, Fischer LJ, Schottelius DD (Berg, 1983), the effect of folic acid supplementation on the disposition of phenytoin and the resultant loss of seizure control in a male folate-deficient epileptic was reported. Due to the increase in tonic-clonic seizures after the initiation of folic acid, the sodium phenytoin dosage was increased until control was achieved. Because of these dosage changes, the Vmax and Km were calculated before and after initiation of the folic acid. The Vmax remained relatively the same, but the Km decreased after folate supplementation. In a Phenytoin-folic acid review published in Drug Intelligence and Clinical Pharmacy in 1984 by Rivey MP, Schottelius DD and Berg MJ (Berg, 1984), it was concluded that the nutrient-drug interaction between folate and phenytoin was a two-way interaction. Folate deficiency resulting from long-term phenytoin therapy was a common occurrence, but progression of the deficiency to a megaloblastic anemia was rare. However, there were data to suggest non-anemic folate deficiency may be detrimental to the patient. Several mechanisms were proposed to explain the ability of phenytoin to deplete body folate. The supplementation of folic acid to folate-deficient patients taking phenytoin was shown to result in lowered serum concentrations of phenytoin, and possibly loss of control of the seizure disorder. Folate appeared to be associated with the hepatic metabolism of phenytoin, although the effect of folic acid supplementation on phenytoin elimination kinetics was suggested to be individualized. In another review published in The Annals of Pharmacotherapy in 1995 regarding the dual and interdependent drug-nutrient interaction between phenytoin and folic acid by Lewis DP, Van Dyke DC, Willhite LA, Stumbo PJ and Berg MJ (Lewis, 1995), all human studies examining the effects of phenytoin on serum folate concentrations and folic acid supplementation on serum phenytoin concentrations were selected. Case reports were included because of the extensive length of the time needed to study this drug interaction. The information was retrieved from a MEDLINE search of English language literature conducted from 1983 to 1995. Data extracted included gender, dosing, serum folate concentrations, pharmacokinetics and adverse events. The results arrived revealed a decrease in the serum folate concentrations when phenytoin therapy was initiated alone with no folate supplementation. Also, it was found that folic acid supplementation in folate deficient patients with epilepsy changed the pharmacokinetics of phenytoin usually leading to lower serum phenytoin concentrations and possible seizure breakthrough. Folate is hypothesized to be a co-factor in phenytoin metabolism and has been proposed to be responsible for the pseudo-steady-state, a concentration where phenytoin appears to be at a steady state but in reality is not. With simultaneous initiation of phenytoin and folic acid therapy was observed prevention of decreased folate and phenytoin achieving steady state concentrations sooner. It was finally concluded that folic acid supplementation should be initiated each time phenytoin therapy commences because of the hypothesized co-factor mechanism, decreased adverse effects associated with folate deficiency and better seizure control with no perturbation of phenytoin pharmacokinetics.

In a study published in 1997 in Journal of Nutrition by Franklin Carl G, Farlyn Hudson Z and Byron McGuire S Jr. (Carl, 1997) titled Phenytoin-Induced Depletion of Folate in Rats Originates in Liver and Involves a Mechanism That Does Not Discriminate Folate Form studying the mechanism of decrease in plasma concentrations of folate in epileptic patients on the anti-convulsant phenytoin, phenytoin administration was found to have minimal effect on folate concentration as well as the composition of the folate pool in intestinal mucosa. Phenytoin administration did, however, cause a depletion of total hepatic folate, causing the pentaglutamate derivatives of each of the pteridine derivatives to

decline rapidly, with the formyl and dihydro derivatives of the pteridine moiety falling more rapidly than the methyl and methylene / tetrahydro derivatives. The monoglutamate of the methylene / un-substituted tetrahydro derivative increased significantly with time of phenytoin treatment. The mono- and di-glutamate derivatives of the methyltetrahydrofolate increased transiently and significantly in the bile, and the polyglutamate chain length increased significantly in the brain with time of phenytoin treatment. The study concluded that phenytoin inhibits the formation of polyglutamyl folates in rat liver.

In another study published in the Seizure in 2006 by Sener Ufuk, Zorlu Yasar, Karaguzel Oguz, Ozdamar Ozlem, Coker Isik and Topbas Murat (Sener, 2006) on the effects of common anti-epileptic drug monotherapy on serum levels of homocysteine, vitamin B_{12}, folic acid and vitamin B_6, the study revealed that patients receiving phenytoin had significantly lower folic acid levels. A negative correlation between homocysteine and folic acid concentrations was also seen in epileptic patients on anti-epileptic therapy. The duration of anti-epileptic drug use was also correlated to the decrease of folic acid levels In a study published in 2007 in the Indian Journal of Clinical Biochemistry by Itemobong Ekaidem S, Monday Akpanabiatu I, Friday Uboh E and Offiong Eka U (Itemobong, 2007) titled effect of folic acid and vitamin B_{12} administration on phenytoin induced toxicity in rats: the effects of folic acid and vitamin B_{12} on liver integrity of growing Wistar albino rats following therapeutic dose of phenytoin administration were investigated. The activities of serum AST, ALT, ALP were investigated. Serum total protein level and lipid profile were also measured as indices of biochemical changes. The ingestion of phenytoin alone in rats significantly reduced serum protein, while AST, ALT activities increased. Supplementation of phenytoin with oral administration of folic acid resulted in a significant reversal in serum total protein and suppression in serum AST and ALT activities. Vitamin B_{12} supplementation did not afford any significant protection against the effect of phenytoin ingestion but rather phenytoin toxicity was exacerbated in this study. However, the combined effects of vitamin B_{12} and folic acid ameliorated the effects of phenytoin on serum enzymes of experimental rats. The effect of combination of phenytoin with folic acid or folic acid and vitamin B_{12} was an interesting finding. Supplementation of phenytoin with folic acid or combination of these vitamins was recommended for the purpose of ameliorating the adverse biochemical changes which are associated with phenytoin therapy.

In a recent population-based case–control study published in 2007 in the British Journal of Gynaecology: An International Journal of Obstetrics and Gynaecology by Kjær D, Horvath-Puho' E, Christensen J, Vestergaard M, Czeizel A, Sorensen H, Olsen J (Kjær, 2008) entitled Antiepileptic drug use, folic acid supplementation, and congenital abnormalities with an objective to investigate whether folic acid supplementation in early pregnancy modifies the association between the prevalence of congenital abnormalities in the offspring and maternal use of carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), and primidone (PRI) at The Hungarian Case–Control Surveillance of Congenital Abnormalities (HCCSCA) (1980–1996) and its information on children from the Hungarian Congenital Abnormality Registry and the Hungarian National Birth Registry. Children with congenital abnormalities and unaffected children were included. Information on drug exposure and background variables for the mothers were collected from antenatal logbooks, discharge summaries, and structured questionnaires completed by the mothers at the time of HCCSCA registration. The results arrived at revealed that compared with children unexposed to AEDs and folic acid, the odds ratio of congenital abnormalities was 1.47 (95% CI 1.13–1.90) in children exposed to AEDs without folic acid supplementation and 1.27 (95% CI 0.85–1.89) for children exposed to AEDs with folic acid supplementation. The results indicated that the risk of congenital abnormalities in children exposed in-utero to CBZ, PB, PHT, and PRI was reduced but not eliminated by folic acid supplementation at 5–12 weeks from LMP. The statistical precision in the study was limited due to rarity of the exposures, and further studies were warranted.

Risk of folate supplementation in precipitation of breakthrough seizures

The link between epilepsy and folic acid supplementation is however found to be controversial. The well-known teratogenic effects of anti-convulsant drugs are explained on the basis of decreased blood folate levels and have been seen to be prevented with folic acid supplementation during the peri-conceptional period. However, folate supplementation in phenytoin treated patients, as in phenytoin treated pregnant epileptic patients to prevent the risk of neural tube defects and other common teratogenic effects of anti-convulsant drugs, is also not considered to be safe because of the risk of precipitation of seizures in an otherwise stabilized epileptic patients.

In 1976, Smithells et al (Smithells, 1976) suggested that folate deficiency might cause neural tube defects because the mothers of infants with neural tube defects had low blood folate levels. Smithells and co-workers (Smithells, 1983) later found that folic acid supplementation during the peri-conceptional period could potentially reduce the risk of neural tube defects. In 1991, the UK Medical Research Council Vitamin Study (MRC Vitamin Study Research Group, 1991) also supported this hypothesis. There is also accumulating evidence that folic acid supplementation in peri-conceptional period might prevent other major birth defects including congenital heart disease, oro-facial clefts and anomalies of the urinary tract (Botto, 2004, Bailey, 2005, Czeizel, 1998, Myers, 2001). However, this is still controversial since there are also studies that do not show any correlation between folate fortification and the incidence of these birth defects (Botto, 2004).

In 2002, the UK Food Standards Agency decided against the introduction of mandatory folic acid fortification. One reason for this was issue of freedom of choice but interestingly, worry for the possible adverse effects, particularly masking of the diagnosis of vitamin B12 deficiency by prevention of anemia and precipitation of neurologic complications was the main cause (Bailey, 2005, Czeizel, 1998, Myers, 2001, Wald, 2001, Davis, 2002, Abramsky,

2002, Reynolds, 2002). Other issues that were raised were the possible drug interactions particularly with the anti-convulsant medication itself leading to the precipitation of fresh episodes of seizures in an otherwise well-controlled, epileptic patient because of reduction in seizure threshold by lowering serum phenytoin levels, breakthrough seizures; (Campbell, 1996, Ralston, 1970, Grant, 1970, Gibberd, 1981, Chien, 1975, Guidolin, 1998) hypersensitivity reactions, cancer promotion and increase of twinning rate (Bailey, 2005, Czeizel, 1998, Myers, 2001, Wald, 2001, Davis, 2002, Abramsky, 2002, Reynolds, 2002, Campbell, 1996). Another question was that of fetal death as it is a well-known fact that epilepsy with seizures during pregnancy leads to a 2-2.5 folds increase in fetal loss compared to normal subjects (Yerbi, 1997, Czeizel, Bod, 1992) although special care and monitoring during pregnancy may significantly decrease this (Cseh, 1991).

Infact, folic acid was long ago considered as a neurotoxin (Baxter, 1973) and a convulsant (Olney, 1981) if provided in high doses for therapeutic reasons. Chanarin et al (Chanarin, 1960) in 1960 were the first to raise the possibility of a decrease in the efficacy of anti-convulsant medications in case of therapeutic use of folic acid supplementation. Later, Chien et al (Guidolin, 1998) found that some subjects with epilepsy were more sensitive to the therapeutic doses of folic acid administered under certain circumstances. Strauss and Bernstein (Strauss, 1975) also found increased seizure frequency in certain epileptic females treated with anti-epileptic drug, phenytoin. However, Boss et al (Boss, 1980) did not find any hazards of oral doses as high as 1000 mg/day of folic acid. Later, Dansky et al (Dansky, 1987) were also unable to detect any impairment of seizure control in pregnant epileptics using valproic acid along with folic acid supplementation. These differences in the observations are explained on the basis of an intact blood-brain barrier that is said to restrict the entry of folic acid in the brain while on the other hand, after damage of the same, a toxic effect of folic acid might be seen (Hommes, 1973).

Controlled trials of folate therapy for upto 3 months produced conflicting results. There is enough experimental evidence however that folate derivatives have excitatory properties especially when the blood-brain barrier mechanism for the vitamin is circumvented (Reynolds, 1976, Reynolds, 1972, Hommes, 1979). In laboratory animals, intravenous infusions of the sodium salt of folate will only induce seizures in very large doses but if the blood-brain barrier is damaged locally by trauma or, a heat lesion, the dose required for an epileptogenic effect is much lower (Hommes, 1973, Miller, 1979). If the blood-brain barrier on the other hand is circumvented by an intra-ventricular or, intra-cortical administration, all folate derivatives have been seen to be highly epileptogenic (Hommes, 1973, Miller, 1979). Furthermore, the vitamin enhances the kindling model of epilepsy and can be used to kindle seizures directly (Davis, 1973). How exactly folates lead to excitation is unknown but they may do so by blocking or reversing GABA-mediated inhibitions (Reynolds, 2002). Epileptic phenomena produced by folates resemble those induced by disinhibitory compounds such as bicuculline, penicillin or picrotoxin (Spaans, 1970).

The risk of aggravating epileptic seizures is small however because of a restricted entry of the folates by the intact blood-brain barrier but increases gradually with increasing doses given over prolonged periods (Reynolds, 1970).

DISCUSSION

Numerous studies conducted in the past have proposed different reasons for falling serum folate levels on long term administration of phenytoin. While the details of these interactions remain obscure, several potential mechanisms have been proposed as explanations. Folic acid administered at pharmacological doses has been, on the other hand, blamed for a decrease in the serum concentration of phenytoin, possibly due to direct competition between folate and phenytoin for uptake sites, severe enough to precipitate seizures. The use of folic acid as an adjuvant to phenytoin/anti-epileptic therapy therefore mandates further analysis to overcome phenytoin, and folate deficiency associated possible adverse effects of long-term administration of phenytoin while simultaneously regulating the sera levels of folic acid within the safe limits to avoid the precipitation of seizures in this set of medically regulated epileptic patients.

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Electronic Patent Application Fee Transmittal				
Application Number:	17025881			
Filing Date:	18-Sep-2020			
Title of Invention:	Lyophilized Compositions of Phenobarbital Sodium Salt			
First Named Inventor/Applicant Name:	Bala Tripura Sundari Chodavarapu			
Filer:	Martin Fessenmaier/Danielle Moroz			
Attorney Docket Number:	104078.0001US			
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Description	**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:				
Pages:				
Claims:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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SUBMISSION- INFORMATION DISCLOSURE STMT	2806	1	130	130
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Electronic Acknowledgement Receipt	
EFS ID:	41918370
Application Number:	17025881
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Title of Invention:	Lyophilized Compositions of Phenobarbital Sodium Salt
First Named Inventor/Applicant Name:	Bala Tripura Sundari Chodavarapu
Customer Number:	149344
Filer:	Martin Fessenmaier/Danielle Moroz
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Appl No.:	17/025,881
First Inventor:	Bala Tripura Sundari Chodavarapu
Filing Date:	2020-09-18
Art Unit:	1617
Examiner:	Yanzhi ZHANG
Attorney Docket No.:	104078.0001US
Title	Lyophilized Compositions of Phenobarbital Sodium Salt

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO OFFICE ACTION

Sir:

This paper responds to the Office Action dated 30 November 2020. Please enter the amendments shown herein.

- Claim amendments begin on page 2.
- Remarks begin on page 5.

AMENDMENTS TO THE CLAIMS

This listing of claims represents the current version of claims before the Office:

1. (presently amended) A pharmaceutical composition comprising a storage-stable form of lyophilized amorphous Phenobarbital Sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution.
2. (presently amended) A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising:

   adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution with a pH at or between 9.2 to 10.2; and

   ~~if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and~~

   lyophilizing the Phenobarbital Sodium solution to produce the storage-stable form of Phenobarbital Sodium.
3. (original) The method of claim 2, wherein the water is Water for Injection.
4. (original) The method of claim 3, wherein the Water for Injection is sparged with nitrogen prior to adding the Phenobarbital Sodium.
5. (original) The method of claim 4, wherein the Water for Injection is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium.
6. (original) The method of claim 2, wherein the water is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium.
7. (presently amended) The method of claim 2, wherein the forming of the Phenobarbital Sodium solution with the pH at or between 9.2 to 10.2 ~~the adjusting~~ comprises measuring the pH of the Phenobarbital Sodium solution, and wherein if the pH is higher than 10.2, the forming ~~adjusting~~ comprises adding Hydrochloric acid (HCl).
8. (original) The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).

9. (original) The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).
10. (original) The method of claim 2, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at room temperature (RT) and accelerated stability conditions (ACC).
11. (original) The method of claim 2, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT).
12. (original) The method of claim 11, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and analyzing to quantitate the amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium.
13. (original) The method of claim 2, wherein the Phenobarbital Sodium solution is at a concentration of 65 mg/mL, 100 mg/mL, 130 mg/mL or 200 mg/mL.
14. (original) The method of claim 2, further comprising filtering the Phenobarbital Sodium solution prior to lyophilizing.
15. (original) The method of claim 2, further comprising:

    aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and

    after lyophilization, applying a closure to the vial under vacuum.
16. (presently amended) A method of treating an individual in need of Phenobarbital Sodium, the method comprising:

    adding saline or dextrose to a composition comprising a storage-stable form of lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution with no more than 0.2% phenylethylacetylurea (PEAU); and

    administering the Phenobarbital Sodium solution to the individual,

wherein the efficacy of the treating is not diminished, and the side effects caused by degradation products of the Phenobarbital Sodium are not increased as a consequence of an extended storage duration of the Phenobarbital Sodium of at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT).

17. (original) The method of claim 16, wherein the individual suffers from epilepsy.

18. (original) The method of claim 17, wherein the individual is a newborn suffering from neonatal epilepsy.

19. (original) The method of claim 16, wherein the composition is a powder dose of 65 mg, 100, 130 mg or 200 mg.

20. (original) The method of claim 16, wherein the administering comprises intramuscular injection or intravenous injection.

21. (new) The method as in claim 2, wherein the lyophilizing comprises freezing, evacuating, and primary drying at a temperature below 0 °C, followed by evacuating and secondary drying at a stable or declining temperature above 0 °C.

22. (new) A pharmaceutical composition comprising a storage-stable form of lyophilized Phenobarbital Sodium of claim 2.

23. (new) A method of treating an individual in need of Phenobarbital Sodium, the method comprising:

adding saline or dextrose to a composition comprising a storage-stable form of lyophilized Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution with no more than 0.2% phenylethylacetylurea (PEAU), the lyophilized Phenobarbital Sodium of claim 2; and

administering the Phenobarbital Sodium solution to the individual.

REMARKS/ARGUMENTS

The Office action dated 30 November 2020 has been received and carefully considered. By this amendment, claims 1, 2, 7, and 16 are amended. New claims 21-23 have been added. After entry of this Amendment, claims 1-23 will be pending. With these amendments, no new matter is added. In view of these amendments and the following remarks, Applicants respectfully request reconsideration.

Claim Amendments/New Claims

Independent claims 1, 2, and 16 have been amended to clarify that lyophilized amorphous Phenobarbital Sodium is provided in a storage-stable form that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution. This is disclosed at least in para [0082]. No new matter has been added.

35 U.S.C. §102

The Office rejected claim 1 under 35 U.S.C. §102(b) as being anticipated by Sun et al (US 20100035904). In view of the amendments herein, and arguments below, Applicant respectfully disagrees.

As amended, claim 1 requires the limitations of the composition "*comprising a storage-stable form of lyophilized amorphous Phenobarbital Sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution*". These limitations are not taught or suggest by the cited reference.

As described in the specification, the life cycle of the pharmaceutical composition of the present invention consists generally of three steps:

- manufacturing step, in turn including
    - adding the Phenobarbital Sodium to water in a predefined manner to form a Phenobarbital Sodium solution, and
    - lyophilizing the solution to produce a dry storage-stable form of the composition;

- extended storage step of the dry Phenobarbital Sodium for at least 6 months at accelerated stability conditions (ACC), which is equivalent to 24 months at room temperature (RT), and

- a step of reconstituting the liquid form of the Phenobarbital Sodium suitable for injection.

The invention is aimed at defining the first liquid solution of the initial formulation of Phenobarbital Sodium and the process of its subsequent lyophilization during its manufacturing step, so as to minimize degradation of the dry from of the Phenobarbital Sodium during the second step of extended storage. Removing of initially added water from the product formulation via lyophilization prior to storage is aimed to preclude formation of toxic additives such as phenylethylacetylurea (PEAU) during the second phase of long-term storage. This in turn assures no toxic substances in the reconstituted Phenobarbital Sodium solution in the third step, which otherwise may cause severe side effects when treating an individual with the pharmaceutical composition of the invention.

The present invention compares favorably with conventional formulations of Phenobarbital Sodium, which are stored in a liquid form. Having water present in the formulation necessitates adding of excipients and stabilizers, which conventionally cause formation of toxic substances such as PEAU. In contrast with conventional formulations, absence of water in the formulation of the present invention during long-term storage obviates the need for these additional substances and therefore inherently provides a more acceptable, substantially less toxic product during the third step of administration to a patient in need of such formulation. This is particularly important in pediatric and especially neonate patient populations as these populations are especially vulnerable to even small amounts of toxic additives.

Distinction is therefore made between the first liquid solution of the Phenobarbital Sodium containing water during manufacture thereof and the second liquid solution of the Phenobarbital Sodium containing water during its administration. Any prior art reference discussing the second liquid solution is not relevant to the first liquid solution as it does not

affect a potential for formation of degradation products during the extended storage of the composition.

Additional limitations of the presently amended claim 1, along with the notion of the Phenobarbital Sodium being *lyophilized* are not merely reflective of the process of producing the Phenobarbital Sodium as alleged by the Office Action. The structure of the composition is not merely the initial compound but necessarily the products of its degradation over time. Amended claim 1 describes this unanticipated and unique structure of lyophilized amorphous Phenobarbital Sodium in a storage-stable high-purity form by specifying that it forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution.

Traditional Phenobarbital Sodium in a dry form would not be anticipated to have a long storage life without degradation unless it is produced as a crystalline material ("*conventional wisdom teaches that crystalline material is more stable than amorphous material*" – para [0011]). As described throughout the specification, a number of unexpected and desirable results were obtained using a multitude of method steps of producing the lyophilized amorphous Phenobarbital Sodium. These unexpected results must be a consequence of a unique structure of the Phenobarbital Sodium formed during the processing thereof as described in the specification.

Thus, for at least these reasons, the cited reference fails to teach or suggest each and every limitation of claim 1, and Applicant respectfully requests the above rejection be withdrawn.

35 U.S.C. §102 and §103

The Office rejected claims 16-20 under 35 U.S.C. §102(a)(1) or §103 as anticipated or being obvious over Kelly (non-patent literature). In view of the amendments herein, and arguments below, Applicant respectfully disagrees.

As amended, claim 16 requires the limitations of providing a "*composition comprising a storage-stable form of lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution with no more than 0.2% phenylethylacetylurea (PEAU)*". Claim 16 contains a further limitation of "*the efficacy of the*

treating is not diminished, and the side effects caused by degradation products of the Phenobarbital Sodium are not increased as a consequence of an extended storage duration of the Phenobarbital Sodium of at least 6 months at accelerated stability conditions (ACC) which is equivalent to 24 months at room temperature (RT)". These limitations are not taught, suggested, or motivated by the cited Kelly reference alone or in combination with other references.

The Office Action admits that Kelly does not disclose providing the Phenobarbital Sodium in lyophilized amorphous form as taught by the present invention but asserts that it does not affect its biological effect. As discussed at least in the para [0006] of the specification, "*the stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products*", which are toxic and may cause side severe effects. Kelly is silent about maintaining the efficacy of the treatment as well as avoiding side effects over the storage life of the Phenobarbital Sodium. The present invention describes novel methods of producing and use of the Phenobarbital Sodium in a lyophilized amorphous form that preserves the treatment efficacy and guards against the formation of toxic degradation products during the extensive storage duration of the product and therefore provides for maintaining the same biological effect no matter whether the product is used immediately after its manufacture or as long as 24 months thereafter.

In addition, the present invention has improved the ease of use of the composition as its liquid form prior to administration can be simply reconstituted by adding water and without any further steps.

Thus, for at least these reasons and the discussion above regarding claim 1, the cited references, alone or in combination, fails to teach, suggest or motivate each and every limitation of claim 16, and Applicant respectfully requests the above rejection be withdrawn. The rejection of claims 17-20 should also be withdrawn at least due in part to their dependence on claim 16.

35 U.S.C. §103

The Office rejected claims 2, 6, 8-13, and 15 under 35 U.S.C. §103(a) as being obvious over Sun in view of Snyder and Dietz. In view of the amendments and arguments herein, Applicant respectfully disagrees. As discussed above, the combination of Sun and Snyder fails

to teach, suggest or motivate each and every limitation of claim 2, from which claims 6, 8-13, and 15 depend. The addition of Dietz fails to remedy the above-identified deficiencies. Thus, the rejection of claims 6, 8-13, and 15 should be withdrawn at least due in part to their dependence on claim 2.

More specifically, amended claim 2 no longer refers to achieving the cited range of pH for the Phenobarbital Sodium solution as an optional step. It clearly specifies that this solution has to be provided in the specified range of pH prior to the step of lyophilization thereof, which is needed to achieve the result of improved storage-stable form of the composition. As the prior art does not disclose providing the Phenobarbital Sodium solution in this pH range, it does no longer read on presently amended claim 2.

Moreover, Sun teaches methods of making various forms of Phenobarbital salts and studying their solubility in aqueous media after reconstituting thereof in water - with various pH conditions adjusted for using a suitable stability-indicating assay (cited para [0060] of Sun). The present invention, in comparison with Sun, teaches providing the Phenobarbital Sodium solution in the desired pH range prior to lyophilization thereof, and certainly prior to subsequent reconstituting in water, which is not fairly disclosed or suggested by Sun.

As discussed above, the notion of specifying any water-related parameter of the first Phenobarbital Sodium solution (prior to lyophilization) is not taught by any of the cited references and is not obvious for at least the reason that the water is removed from the solution as a result of lyophilization. As stated in the specification, the association of the various water-related parameters of the first solution and achieving the storage-stable form of the compound after lyophilization was unexpected and surprising, especially given no presence of conventional stabilizers or solubilizers aimed at improving stability of the formulation.

Snyder describes a general notion of using lyophilization as a freeze-drying method of treating bulk drug ingredients that are not stable in a liquid form to enable their longer shelf life. Snyder is silent as to the desired pH range of the drug solution prior to the initiation of the lyophilization process, or about any other water-related parameters as described in depth in the

specification, for example providing the water for adding the Phenobarbital Sodium in a predetermined temperature range as specified in claim 6.

Diets uses heating to facilitate the degradation of the Phenobarbital Sodium solution. This is done to study various liquid solutions of the Phenobarbital salt at the point of their use for treatment purposes and therefore have no useful guidance for preparing the aqueous solution of the Phenobarbital Sodium prior to lyophilization. Cooling the water to the desired temperature range before lyophilization is not suggested by Dietz to slow down the degradation of the dry form of the Phenobarbital Sodium during extended storage as asserted by the Office Action.

The Office further rejected claims 3-5, 7, and 14 under 35 U.S.C. §103(a) as being obvious over Sun in view of Snyder and Dietz and further in view of Roskos. In view of the amendments and arguments herein, Applicant respectfully disagrees. As discussed above, the combination of cited references fails to teach, suggest or motivate each and every limitation of claim 2, from which claims 3-5, 7, and 14 depend. The addition of Roskos fails to remedy the above-identified deficiencies. Thus, the rejection of claims 3-5, 7, and 14 should be withdrawn at least due in part to their dependence on claim 2.

Roskos describes lyophilization of cisplafin (CDDP), an anticancer drug, to form a powder to be reconstituted later and used as a chemotherapy agent. The chemical composition and, as a consequence, the storage degradation properties of cisplafin are dramatically different from that of Phenobarbital Sodium. Therefore, there is no motivation to combine Roskos with other cited references discussing Phenobarbital salts to make the present invention obvious.

As to claim 7, the cited pH adjustment of Roskos described in Table of col. 5 refers to the examples of various diluents used for reconstituting cisplafin from its lyophilized form, not as part of formulating the solution to be subjected to lyophilization. In addition, the cited target pH level is 4.0, which is well outside the range of 9.2 to 10.2 specified in claims 2 and 7.

The same deficiency is present with regard to claim 5 and the discussion of using nitrogen flushing in Roskos – it pertains to the diluent preparation used to reconstitute the drug from the dry powder form, and not to the preparation of solution subjected to subsequent lyophilization as taught by the present invention. As a result, there is no motivation to use the

nitrogen flushing of the diluent of one drug after its storage in a dry form (as discussed in Roskos) to apply to a liquid solution being prepared for lyophilization to achieve the goal of creating a storage-stable form of the other drug (as described in the present invention).

New claim 21 is added describing specific lyophilization parameters leading to the desired outcome of the method of the invention. Of particular importance is the step of conducting secondary drying at a stable or declining temperature above 0 degrees C, as seen in table 15 of the specification.

New claim 22 defines a new composition comprising a lyophilized amorphous form of Phenobarbital Sodium made according to the methods of the present invention described in claim 2.

Finally, a new claim 23 describes the use of the lyophilized amorphous form of Phenobarbital Sodium made according to the methods of the present invention described in claim 2 for treating an individual in need of Phenobarbital Sodium.

Request For Allowance

Claims 1-23 are pending in this application. Applicant requests allowance of all pending claims.

Respectfully submitted,
Umberg Zipser LLP

Date: February 12, 2021

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Electronic Patent Application Fee Transmittal				
Application Number:	17025881			
Filing Date:	18-Sep-2020			
Title of Invention:	Lyophilized Compositions of Phenobarbital Sodium Salt			
First Named Inventor/Applicant Name:	Bala Tripura Sundari Chodavarapu			
Filer:	Martin Fessenmaier/Danielle Moroz			
Attorney Docket Number:	104078.0001US			
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	**Fee Code**	**Quantity**	**Amount**	**Sub-Total in USD($)**
Basic Filing:				
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	2202	3	50	150
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	150

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Application	Document	Mailroom Date	Attorney Docket No.
17025881	CTFR	02/26/2021	104078.0001US
	892	02/26/2021	104078.0001US
	1449	02/26/2021	104078.0001US

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/025,881	09/18/2020	Bala Tripura Sundari Chodavarapu	104078.0001US	8113

149344 7590 02/26/2021

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EXAMINER	
ZHANG, YANZHI	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
02/26/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 17/025,881	Applicant(s) Chodavarapu et al.	
	Examiner YANZHI ZHANG	Art Unit 1617	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 02/12/21.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-23 is/are pending in the application.

5a) Of the above claim(s) ____ is/are withdrawn from consideration.

6) ☐ Claim(s) ____ is/are allowed.

7) ☑ Claim(s) 1-23 is/are rejected.

8) ☐ Claim(s) ____ is/are objected to.

9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on ____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. ____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date ____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date ____.

4) ☐ Other: ____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claim Status

This action is a response to papers filed on Feb. 12, 2021. Claims 1-2, 7, and 16 have been amended; claims 21-23, newly added. No claim has been canceled. Accordingly, claims 1-23 are pending in the application and under consideration on the merit.

Information Disclosure Statement

The Information Disclosure Statements filed 12/01/20 are in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statements in English are fully considered by the examiner. The foreign language references, are only considered to the extent where an English translation available or examiner understands that language. A signed copy of form 1449 is enclosed herewith.

Applicant's arguments filed 12/12/2021 have been fully considered, but they are not found persuasive. The present rejection is maintained from the office action dated 11/30/2020, but has been modified to address Applicant's amended claims of 02/12/2021.

Maintained Claim Rejections - 35 U.S.C. 102

The text of those sections of Title 35 of the U.S. Code not included in this action can be found in a prior Office action.

Claim 1 is rejected under 35 U.S.C. 102(a)(1) as anticipated by Sun et al ("Sun", US 20100035904 A1, publication-date: February 11, 2010).

Claim 1 embraces a pharmaceutical composition comprising lyophilized amorphous Phenobarbital Sodium.

Sun is directed to phenobarbital salts; methods of making; and methods of use thereof (title). Sun discloses that **phenobarbital sodium** is a known salt freely soluble in water in contrast to the free acid form ([0004], the same drug in the instant claim 1). Sun also discloses non-crystalline or **amorphous forms of phenobarbital** salts including phenobarbital sodium ([0011], the same physical form in the instant claim 1).

Sun, by disclosing all the essential elements, anticipates claim 1.

Regarding the newly added limitation of "a storage-stable form of" lyophilized amorphous in claims 1 and 22, a chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure and the same lyophilized amorphous, the properties e.g. storage-stable and the amount of phenyl ethyl acetylurea (PEAU) when reconstituted in an aqueous solution applicant claims are necessarily present. *In re Spada*, 911 F.2d 705,709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

In the absence of the USPTO to have at its disposal the tools or facilities deemed necessary to make physical determinations of this sort, Applicants have the burden to show that this, in fact, is not the case.

Response to Arguments

Applicant's arguments filed 02/12/2021 have been considered, but they are not found persuasive.

Applicant argues that these new limitations are not taught or suggest by the cited reference.

In response, as set forth in the rejection above, these "new limitations" are considered inherent the properties and are necessarily present unless there is evidence showing that this, in fact, is not the case.

Claim Rejections - 35 U.S.C. 103

The text of those sections of Title 35 of the U.S. Code not included in this action can be found in a prior Office action.

Claims 2, 6, 8-13, 15, and 21-22 are rejected under 35 U.S.C. 103 as obvious over Sun et al ("Sun", US 20100035904 A1, publication date: February 11, 2010) in view of Parker et al ("Parker", US 20170143719 A1, publication date: May 25, 2017) and Snyder (non-patent literature, Drug discovery and development, pp. 1-5, March 7, 2017).

Claims 2, 6, 8-13, 15, and 21-22 embrace a method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenyl ethyl acetyl urea (PEAU) when reconstituted in an aqueous solution, the method comprising: adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution; if necessary, adjusting the pH of the phenobarbital sodium solution to or between 9.2 to 10.2; and lyophilizing the Phenobarbital Sodium solution and a method of using thereof.

In addition, claims 2 and 22 (composition) use the open-ended transitional phrase "comprising". Thus, they allow for the presence of additional unrecited steps or components.

Sun is directed to phenobarbital salts; **methods of making**; and methods of use thereof (title). Sun teaches non-crystalline or **amorphous forms** of phenobarbital salts including **phenobarbital sodium** ([0011], the same drug in the same form as the instant claim 2). Sun also

teaches that preparation of phenobarbital sodium salt is achieved by dissolving phenobarbital and sodium hydroxide in acetone followed by removal of the acetone ([0055]). Sun further teaches that the concentration of phenobarbital in selected buffers or **pH conditions** will be determined using a **stability indicating assay** that distinguishes the active agent from its degradation products, and also detects any degradation that may appear in the salt solution ([0060], read on the limitation of the instant claim 12). Sun recognizes that phenobarbital sodium is a known salt freely soluble in water in contrast to the free acid form, but phenobarbital sodium is hygroscopic and degrades when exposed to humid environments ([0004]).

While teaching preparation of amorphous phenobarbital sodium by adjusting pH conditions and solvent removal, Sun does not expressly teach the specific pH range as claimed nor aqueous solvent (water) by lyophilization. These deficiencies are cured by Parker and Snyder, respectively.

Parker is directed to **stable formulation** of phenobarbital sodium injection (title, read on the limitation of the instant claim 22). Parker teaches that stable phenobarbital sodium **solutions for injection** include phenobarbital sodium in an amount of 15 to 200 mg/mL; a C1-C4 alcohol in an amount of 105 to 160 mg/mL; and propylene glycol in an amount of between 620 and 830 mg/mL and have a **pH** of between **9 and 12** which is adjusted to that range by adding acid or base, as required. Parker teaches that the solutions for injection do not generate impurities including phenyl ethyl acetyl urea (PEAU) and phenyl butyric acid (PBA, [0006]) during extended storage (abstract, read on the pH range in the instant claim 2).

Snyder is directed to Lyophilization: the Basics (title). Snyder teaches that **lyophilization** is defined as a freeze-drying process to **remove water from a product** after it is frozen and placed under a vacuum (the 1st paragraph on page 1/5, implying the solvent of water).

Snyder indicates that if the bulk drug ingredients are not stable in liquid or frozen form due to chemical reactions, degradation, aggregation, biological growth, heat sensitivity, lyophilization is necessary (the 3rd paragraph on page 1/5). Snyder indicates that lyophilization enables longer shelf life (enhancing stability), makes it much easier to process the product including removing water without having to heat the product excessively and reconstituting the product rapidly and easily (the 1st paragraph on page 2/5). Snyder also teaches that the lyophilization process involves the following steps (the last paragraph on page 3/5):

1. Fill tray with liquid solution (implying the 1st step of adding a drug to water to form the liquid solution in the instant claim 1),

2. Carry trays over to dryer and load

3. Lyophilization (including those three stages)

4. Remove tray from dryer and remove powder from try into another bag or sealed **container** (interpreted as a vial, read on the limitation in the instant claim 15).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose lyophilization as taught by Snyder as the particular means for an aqueous drug solution because the particular option identified by Snyder are predictable solutions to the problem of drying a unstable drug like phenobarbital sodium as evidenced by Dietz, who teaches that the aqueous solution of phenobarbital sodium degrades fastest (see a heat facilitated degradation profile in Fig. 1 on page 804 and the average percentage in Table 1 on page 805). The person of ordinary skill in the art would have a reasonable expectation to be of success in choosing the option. See MPEP 2141, part (III)(A) and (D). Additionally, one of ordinary skill in the art would take advantages of lyophilization taught by Snyder as set forth above.

Regarding the preamble of "no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution" in claim 2, "no more than 0.1% phenylethylacetylurea" in claim 8, "no more than 0.05% phenylethylacetylurea" in claim 9, no detectable amount of 2-ethyl-2-phenylmalonamide, etc. in claim 10, and stable up to at least 6 months at accelerated stability conditions in claim 11; these are considered properties of the lyophilized Phenobarbital sodium. The lyophilized Phenobarbital sodium as set forth in the rejection above would meet these limitation. In the absence of the USPTO to have at its disposal the tools or facilities deemed necessary to make physical determinations of this sort, Applicants have the burden to show that this, in fact, is not the case.

Regarding the optional step of adjusting pH in claim 1 and concentrations in claim 13, Dietz teaches that **sodium phenobarbital** (438 mg) is dissolved in 100ml with a buffer containing 40% (v/v) propylene glycol having a final pH of 5.4, and an aqueous solution of sodium phenobarbital having a final pH of 8 (the 1st and 2nd paragraph on page 803). Dietz also teaches various concentrations for studying emulsion dosage forms (Table II). The principal of law is "[Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). This rule is limited to cases in which the optimized variable is a "result-effective variable." *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). In this case, Sun and Dietz teach different pH in different conditions, indicating that pH is a result-effective variable. It would have been obvious to optimize the pH of an aqueous solution of sodium phenobarbital to achieve desired effect, absent evidence to the contrary.

Regarding the water is cooled to or between 2 to 8°C prior to adding the Phenobarbital Sodium in claim 6, Dietz teaches that heat facilitating degradation of Phenobarbital Sodium. It would have been obvious to cool the water to slow down the degradation.

Claims 3-5, 7, and 14 are rejected under 35 U.S.C. 103 as obvious over Sun et al ("Sun", US 20100035904 A1, publication date: February 11, 2010) in view of Parker et al ("Parker", US 20170143719 A1, publication date: May 25, 2017) and Snyder (non-patent literature, Drug discovery and development, pp. 1-5, March 7, 2017) as applied to claims 2, 6, 8-13, 15, and 21-22 in further view of Roskos et al ("Roskos", US 6077545 A, date issued: June 20, 2000).

The teaching of Sun and Snyder have been discussed as applied to claims 2, 6, 8-13, and 15. Sun and Snyder do not expressly teach the water is water for injection (WFI), nor nitrogen purge. These deficiencies are cured by Roskos.

Roskos is directed to an improved diluent for the preparation of cisplatin suspensions from a lyophilized powder (abstract). Roskos teaches that lyophilized CDDP (a drug for cancer) is intended for reconstitution into a solution and the standard vehicle for such solution reconstitution is **Water for Injection** (WFI) (col. 3, lines 4-6, read on the limitation of the instant claim 3). Roskos teaches that the solution of example 1 is sparged with nitrogen for 30 minutes (gas flushing), when the required amount of epinephrine is added, and the mixture is stirred under a nitrogen blanket until the epinephrine dissolved, **pH is adjusted** with HCl and/or NaOH (Table of col. 5) if necessary, and additional WFI was added to achieve the final desired volume. The solution was **sparged with nitrogen** for an additional 30 minutes, and then sterile **filtered** through a 0.22 micron filter. Filtered solution was filled into 5 ml vials, the vial

headspace was flushed with nitrogen, and the vials are stoppered (interpreted as sealed) (col. 5, lines 45-58, read on the limitations of the instant claims 3-5, 7, and 14).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose nitrogen sparge and filtering prior to adding the drug as taught by Roskos as the particular means to ensure the drug is stable and meet the Food and drug administration requirements. The person of ordinary skill in the art would have a reasonable expectation to be of success in choosing the steps because Roskos provides the exact solution of processing a stable lyophilized drug product. See MPEP 2141, part (III)(A) and (G). In addition, selection of any order of performing process steps is prima facie obvious in the absence of unexpected results (see MPEP 2144).

Response to Arguments

Applicant's arguments filed 02/12/2021 have been considered to the extent that they might apply to the new grounds of rejection set forth above, but they are not found persuasive.

Dietz is no longer a prior art. Thus, arguments pertinent to Dietz is not addressed.

Applicant argues that the present invention, in comparison with Sun, teaches providing the Phenobarbital Sodium solution in the desired pH range prior to lyophilization thereof, and certainly prior to subsequent reconstituting in water, which is not fairly disclosed or suggested by Sun.

In response, first, applicant is reminded that the rejections are based on combinations of references. Applicant cannot show nonobviousness by attacking references individually. Second, it is noted applicant agrees that Sun teaches methods of making various forms of phenobarbital

salts and studying their solubility in aqueous media after reconstituting thereof in water. It should be mentioned that Sun also studies their stability, which is done by using a seven day toluene slurry. Each salt (about 10-20 mg) is slurried in 250 microliters of toluene at ambient temperature for seven days in a 4 ml vial ([0049]). The pH range of Sun or Snyder is not only applicable to prior to lyophilization thereof, but also to prior to subsequent reconstituting in water, too.

It is known that phenobarbital sodium is an old and well-studied drug as evidenced by a dissertation by Jatul (the full dissertation is attached for applicant's review), who discloses nature of deterioration (page 2 of Jatul), factors in deterioration. Jatul discusses the effect of heating (at temperatures from 60 to 127°C, pages 91-117 of Jatul)

Applicant also argues that Roskos describes lyophilization of cisplatin (CDDP), an anticancer drug, to form a powder to be reconstituted later and used as a chemotherapy agent. The chemical composition and, as a consequence, the storage degradation properties of cisplatin are dramatically different from that of Phenobarbital Sodium. Therefore, there is no motivation to combine Roskos with other cited references discussing Phenobarbital salts to make the present invention obvious.

In response to applicant's argument that there is no motivation to combine Roskos with other cited references discussing Phenobarbital salts to make the present invention obvious, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In this case, Roskos is introduced for the

preparation of cisplatin suspensions from a lyophilized powder. This is the exact issue of the instant claims 3-5, 7, and 14.

Claim Rejections - 35 U.S.C. 103

The text of those sections of Title 35 of the U.S. Code not included in this action can be found in a prior Office action.

Claims 16-20 are rejected under 35 U.S.C. 103 as obvious over Kelly et al ("Kelly", non-patent literature, Critical Care Trauma Centre, pp. 1-3, last update: October 11, 2018) and Sun et al ("Sun", US 20100035904 A1, publication-date: February 11, 2010).

Claims 16-20 embrace a method of treating an individual in need of Phenobarbital Sodium, the method comprising: adding saline or dextrose to a composition comprising lyophilized amorphous Phenobarbital Sodium immediately prior to administration to form a Phenobarbital Sodium solution; and administering the Phenobarbital Sodium solution to the individual.

Kelly is directed to **phenobarbital sodium** for **intravenous** (IV) direct injection or infusion (title, and the section of Administration on page 1, read on the limitation of the drug in the instant claim 16 and the administering routes in the instant claim 20). Kelly discloses that the drug, anticonvulsant, sedative, is diluted to 10mL with sodium chloride 0.9%, dextrose 5% or Ringer's Lactate and is used to treat seizures (i.e. epilepsy) (the section of Classification on page 1, read on the limitations of the instant claims 16-17). Kelly also discloses the loading dose is 10 - 15 mg/kg IV or 1000 mg in 250 mL for infusion (the section of Dose and Administration on page 1, read on the limitation of the instant claims 19 and 23).

While teaching phenobarbital sodium for intravenous Kelly does not expressly teach phenobarbital sodium is a lyophilized amorphous product as claimed. This deficiency is cured by Sun.

Sun is directed to phenobarbital salts; methods of making; and methods of use thereof (title). Sun discloses that **phenobarbital sodium** is a known salt freely soluble in water in contrast to the free acid form ([0004], the same drug in the instant claim 1). Sun also discloses non-crystalline or **amorphous forms** of phenobarbital salts including phenobarbital sodium ([0011], the same physical form in the instant claim 16).

It would have been obvious for one of ordinary skill in the art, as of the effective filing date of the claimed invention, to choose amorphous form of phenobarbital sodium as taught by Sun as the particular drug to be incorporated into the method of Kelly because all of the particular options identified by Sun are predictable solutions to the drug formulations,. The person of ordinary skill in the art would have a reasonable expectation to be of success in choosing any of those options. See MPEP 2143, part (I)(B) or (E).

Response to Arguments

Applicant's arguments filed 02/12/2021 have been considered to the extent that they might apply to the new grounds of rejection set forth above, but they are not found persuasive.

Applicant argues that these new limitations are not taught, suggested, or motivated by the cited Kelly reference alone or in combination with other references.

In response, as set forth in the rejection above, these "new limitations" including storage-stable form, no more than 0.2% PEAU, treating is not diminished, etc. are considered inherent the properties and are necessarily present because Kelly teaches the same drug, same route of

administration, while Sun teaches the same amorphous form. Applicants have the burden to show that this, in fact, is not the case.

Relevant Art

Nahata et al (non-patent literature, titled Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection; Am J Hosp Pharm, 1986 Feb; vol. 43(2), pp.384-5; abstract only) is provided, but not cited, to show the state of art at the time when the invention was filed.

Examiner's Notes:

The full text of Nahata et al was ordered on 02/17/21 (see attached office action appendix). However, due to COVID-19, the process was slow. Thus, only abstract is provided.

CONCLUSION

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YANZHI ZHANG whose telephone number is (571)272-3117. The examiner can normally be reached on Monday-Friday 8am-5pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 5712720646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/YANZHI ZHANG/

Primary Examiner, Art Unit 1617

Notice of References Cited	Application/Control No. 17/025,881	Applicant(s)/Patent Under Reexamination Chodavarapu et al.	
	Examiner YANZHI ZHANG	Art Unit 1617	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20170143719-A1	05-2017	Parker; Michael G.	A61K47/10	1/1
	B					
	C					
	D					
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	F					
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Nahata et al, title: Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection; Am J Hosp Pharm, 1986 Feb; vol. 43(2), pp.384-5; abstract only) (Year: 1986)
	V	Jatul, title: The stability of solutions of phenobarbital sodium; A dissertation presented to the graduate council of the University of Florid, Feb. 1943 (Year: 1943)
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection

Milap C. Nahata, Pharm.D. ✉, Thomas F. Hipple, Steven D. Strausbaugh

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Abstract

The stability of phenobarbital sodium diluted to 10 mg/mL in 0.9% sodium chloride injection was studied at an unadjusted pH (8.5) and an adjusted pH (10.0) at 4°C over a four-week period.

The phenobarbital concentrations were measured before dilution and at 1, 2, 3, 7, 14, and 28 days using high-performance liquid chromatography.

The observed phenobarbital concentrations ranged from 98.0 to 106.0% of initial concentration at the unadjusted pH and from 96.7 to 108.5% of initial concentration at the adjusted pH.

The diluted phenobarbital sodium was stable over a four-week period at 4°C without the need for pH adjustment.

Keywords: Additives, Anxiolytics, sedatives and hypnotics, Concentration, Diluents, Dilutions, Hydrogen ion concentration, Incompatibilities, Injections, Phenobarbital sodium, Sodium chloride, Stability

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THE STABILITY OF SOLUTIONS OF PHENOBARBITAL SODIUM

By
BERNARD B. JATUL

A DISSERTATION PRESENTED TO THE GRADUATE COUNCIL OF
THE UNIVERSITY OF FLORIDA
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

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TABLE OF CONTENTS

		Page
	ACKNOWLEDGMENT	ii
I.	INTRODUCTION	1
II.	REVIEW OF THE LITERATURE	2
	A. DETERIORATION AND STABILIZATION OF BARBITURATE SOLUTIONS	2
	1. Nature of the Deterioration	2
	2. Factors in the Deterioration	16
	a. Hydrogen Ion Concentration	16
	b. Temperature	19
	3. Stabilization of Barbiturate Solutions	25
	a. Adjustment of Hydrogen Ion Concentration	25
	b. Amines as Stabilizing Agents	25
	c. Amides as Stabilizing Agents	29
	d. Use of Urethane in Conjunction with Other Agents	30
	e. Other Nitrogen Compounds as Stabilizing Agents	33
	f. Glycols as Stabilizing Agents	34
	g. Miscellaneous Stabilizing Agents	36
	B. METHODS OF ASSAYING BARBITURIC ACID DERIVATIVES	38
	1. Procedures Employing Immiscible Solvents	38
	a. The U. S. P. XI and U. S. P. XII Methods	38
	b. Method of Rotondaro	39
	c. Method of van Itallie and Steenhauer	42
	d. Method of Glycart	42
	2. Procedures Employing Indicators	44
	3. Conductimetric Titration	45
	4. Procedures in Which Undissociated Barbiturates Are Formed	45
	a. Mercury Salts	46
	b. Silver Salts	48
	5. Colorimetric Methods	52
	a. Method of Zwikker	52
	b. Method of Oettel	52
	c. Method of Koppanyi, et al.	53

III. EXPERIMENTAL PART 54

A. SCOPE OF INVESTIGATION 54

B. ANALYTICAL METHODS AND CONTROL 55

1. Materials Used 55

2. Determination of Moisture 55

3. pH Determination 56

4. Determination of Volume of Precipitate 57

5. Use of the Autoclave 58

C. A COMPARISON OF METHODS OF DRYING PHENOBARBITAL SODIUM PREPARATORY TO ASSAY 59

D. EVALUATION OF REPORTED METHODS OF ASSAY 65

1. Comparison of U. S. P. XI and Rotondaro Assays of Phenobarbital Sodium U. S. P. XI 66

2. Comparison of Modified Rotondaro Assays of Phenobarbital and Phenobarbital Sodium 73

3. A Study of Assays Employing Silver Nitrate 79

4. Von Mabitsch Titration of Phenobarbital 85

5. Comparison of Assays of a Deteriorated Solution of Phenobarbital Sodium U. S. P. XI 87

E. A STUDY OF A NUMBER OF FACTORS IN THE DETERIORATION OF SOLUTIONS OF PHENOBARBITAL SODIUM U. S. P. XI 91

1. Effect of Heating a 5% w/v Solution of Phenobarbital Sodium U. S. P. XI at 60° C. 97

2. Effect of Heating 5, 10, and 20% w/v Solutions of Phenobarbital Sodium U. S. P. XI at 80° C. 100

3. Effect of Heating 5, 10, and 20% w/v Solutions of Phenobarbital Sodium U. S. P. XI at 100° C. 107

4. Effect of Heating 5, 10, and 20% w/v Solutions of Phenobarbital Sodium U. S. P. XI at 115° C. 112

5. Effect of Heating 5, 10, and 20% w/v Solutions of Phenobarbital Sodium U. S. P. XI at 127° C. 117

F. RELATION OF pH TO THE DETERIORATION OF SOLUTIONS OF PHENOBARBITAL SODIUM 123

1. The Use of Monosodium and Disodium Phosphates 123

2. The Use of Sodium Carbonate 127

G. EVALUATION OF SEVERAL SUGGESTED STABILIZING AGENTS ON SOLUTIONS OF PHENOBARBITAL AND PHENOBARBITAL SODIUM. 130

1. An Experiment on the Stability of Elixir of Phenobarbital U. S. P. XI and Several Modifications .. 130

2. An Experiment on the Stability of Phenobarbital Sodium U. S. P. XI in the Presence of Alcohol, Glycerin, and Antipyrine 133

3. An Experiment on the Stability of Solutions of Phenobarbital Sodium U. S. P. XI Containing Dextrose. 135

IV. DISCUSSION OF RESULTS 139

V. SUMMARY AND CONCLUSIONS 148

VI. BIBLIOGRAPHY 157

BIOGRAPHICAL ITEMS 164

I. INTRODUCTION

Since the introduction of diethyl barbituric acid into medicine by Fischer and von Mering (1) in 1903, barbituric acid derivatives have assumed a leading place amongst the medicines which assist in alleviating the ills of mankind. These medicinals are now more widely used than any other class of hypnotics. For oral use, they are generally dispensed in the dry state or in elixir form. However, for parenteral injection, it has usually been necessary to employ aqueous solutions. Since barbiturates as a class rapidly decompose in aqueous media, they are administered soon after preparation of the solution. This instability has prompted a number of workers to conduct research relative to the nature of the phenomena and to methods of its retardation.

The present work was carried out to extend the knowledge regarding the deterioration and stabilization of barbiturate solutions, limiting the research to one derivative, namely, phenylethyl barbituric acid. Methods of assay applicable to the problem have been studied and compared. Experiments were conducted to investigate a number of factors in the decomposition and to evaluate and amplify several reported methods of stabilization.

REVIEW OF THE LITERATURE

A. DETERIORATION AND STABILIZATION OF BARBITURATE SOLUTIONS

1. Nature of the Deterioration

In 1927, Steenhauer (2) found that aqueous solutions of sodium diethylbarbiturate, when heated at 100° C., suffered hydrolysis into carbon dioxide and diethylacetylurea. The latter compound crystallized out on cooling. Confirmation of these findings came from Madsen (3) in 1934, and Bailey (4) in 1936. Bailey (4) separated the crystals formed in solutions of sodium barbital which had been autoclaved. The crystals were washed with water and then extracted with a chloroform-ether mixture. The compound obtained from the latter was recrystallized from boiling water. The colorless needles resulting melted at 207° C. (corr.). No ammonia was formed when the compound was heated with strong alkaline solutions, whether aqueous or alcoholic. Ammonia was formed after long heating with 50% sulfuric acid and subsequent treatment with alkali. The fact that nitrogen was formed in this sulfuric acid solution when treated with excess alkaline hypobromite showed the presence of urea. Analysis yielded the following results:

Hydrogen	8.92	Nitrogen	17.69
Carbon	53.44	Oxygen	20.01 (by difference).

The simplest empirical formula derived from the above data is $C_7H_{14}N_2O_2$. The molecular weight was found to be 155, when determined by cryoscopic means with camphor as the solvent. Urea and an oily liquid, which was practically insoluble in water, were the products of hydrolysis formed by refluxing this compound with 50% sulfuric acid. The oily liquid

was diethyl acetic acid. The oily liquid had an acid reaction, a boiling point of slightly over 190° C., and a density less than that of water. Pittig in 1880 gave the boiling point of diethylacetic acid as 194-195° C. and stated that it was lighter than water. This information, together with other considerations, led Bailey (4) to conclude that crystalline precipitate was diethylacetylurea. Its molecular weight is 168.

No ammonia is produced by heating diethylacetylurea with strong alkaline solutions because of its great stability. Lassaigne's test cannot be performed because the compound tends to volatilise rather than decompose when dropped on boiling sodium.

According to Fischer and Dilthey (5), ureides of dialkylacetic acid are frequently formed as by-products in the preparation of ureides of dialkylmalonic acid in the presence of sulfuric acid. They are also formed by heating the ureides of dialkylmalonic acid. A third method of preparation is based on the action of phosphorus oxychloride on a mixture of dialkylmalonic acid and urea. These three methods are probably one and the same, namely, the decomposition of dialkylmalonylurea. Fischer and Dilthey (5) remarked that dimethylacetylurea could not be prepared by any of the aforesaid mentioned methods. Furthermore, it was unknown at that time (1904).

Diethylacetylurea was first described by the von Meissen brothers (6) who stated that it was formed by heating diethylbarbituric acid to 102° C. They indicated that the melting point was 207.5° C. (corr.) and that it was hydrolyzed into diethylacetic acid and urea only on prolonged heating with concentrated hydrochloric acid. Fischer and

Dilthey (5) prepared diethylacetylurea by heating a mixture of urea and diethylmalonic acid to which phosphorus oxychloride had been added. The product was crystallized from hot water. They found that the melting point was 207.5° C. The structure of the compound was learned from its cleavage into urea and diethylacetic acid upon heating with concentrated hydrochloric acid in a sealed tube for seventeen hours. The diethylacetic acid separated as an oil. To identify the latter product, its silver salt was prepared. The silver content was determined and found to correspond to that of silver diethylacetate. The presence of urea was shown by preparing the nitrate salt in order to free it from the hydrochloric acid solution, regenerating the urea molecule, and then analyzing for nitrogen content. The nitrogen content and the melting point were those of urea.

Diethylacetylurea dissolves in approximately 120 parts of hot water. It is practically insoluble in cold water, moderately soluble in chloroform and ether, and very soluble in alcohol. It is insoluble in both cold dilute acids and alkalies.

Methods of preparing dipropylacetylurea and methylethylacetylurea were also given by Fischer and Dilthey (5). From qualitative tests on purified precipitates formed in solutions of other barbiturates, Bailey (4) found that the disubstituted acetylurea, corresponding to the barbiturate employed, was produced in each case.

In addition to the diethylacetylurea, Bailey (4) found that the following compounds resulted from the hydrolysis of solutions of diethylbarbiturate:

Gases: carbon dioxide and ammonia

Substances in solution: urea, sodium diethylacetate, sodium diethylmalonate, sodium bicarbonate, and sodium carbonate.

From the products formed, Bailey (4) deduced that the barbituric acid molecule is hydrolyzed in two ways:

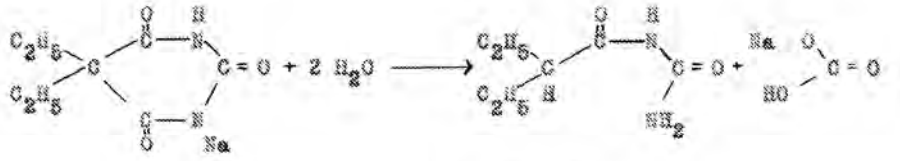
(1) loss of one molecule of carbon dioxide, opening the ring to form diethylacetylurea;

(2) cleavage of the ring to form diethylmalonic acid or its salt and urea. The diethylmalonic acid then loses one molecule of carbon dioxide to give diethylacetic acid or its salt. The urea molecule decomposes slowly into carbon dioxide and ammonia.

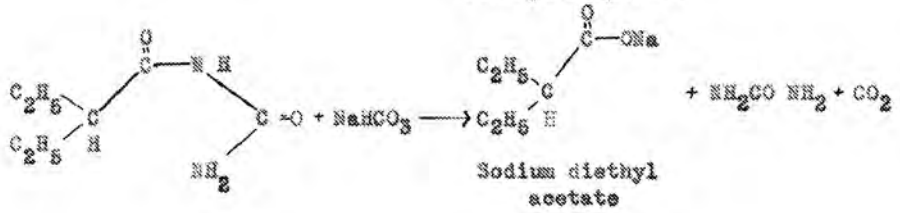
Earlier, Madsen (3) had reported that diethylacetylurea hydrolyzed in considerable quantity into diethylacetic acid and urea, and latter hydrolyzing further in a small degree to carbon dioxide and ammonia.

Bailey (4) suggested that neither reactions proceeded to completion, so that both final and intermediate products are obtained. Bailey (4) presented the equations which follow.

(1)

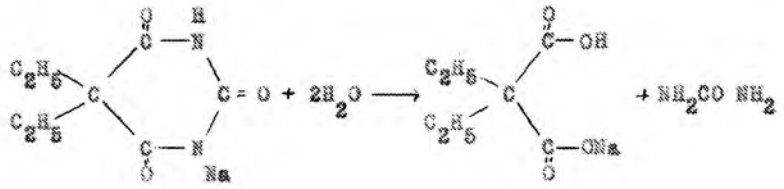


Diethylacetylurea

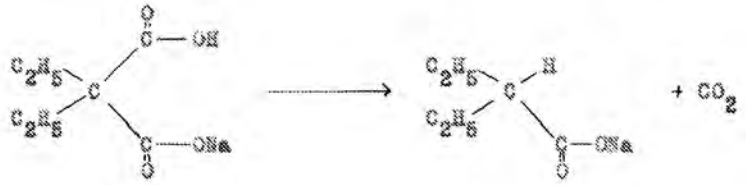


Sodium diethyl acetate

(2)



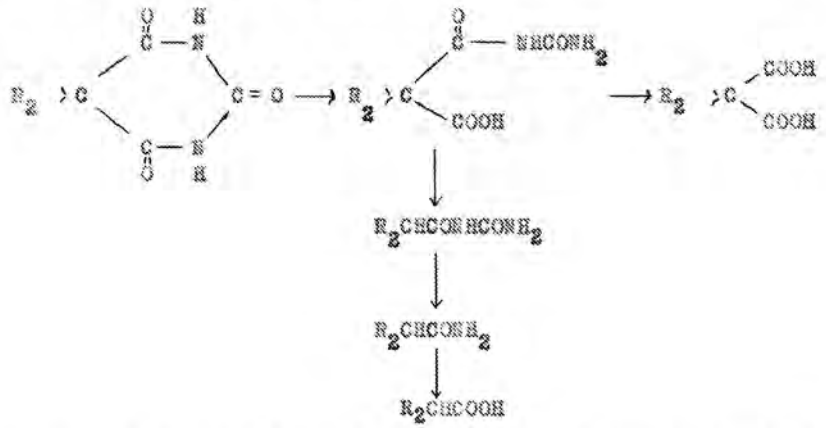
Primary Sodium diethylmalonate



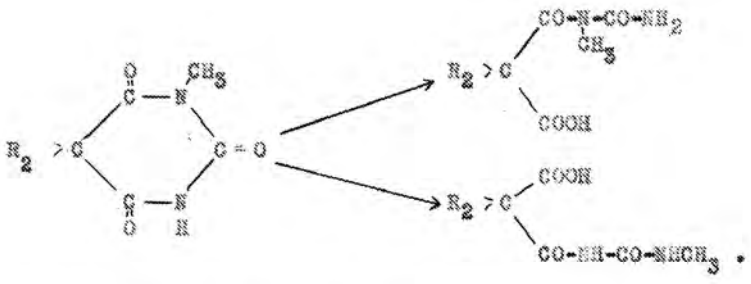
Sodium diethylacetate



Aspelund and Skoglund (7) outlined the course of deterioration of substituted barbituric acids as follows:



Trisubstituted barbituric acids may break down in either of two ways.



Aspelund and Skoglund (7) separated the decomposition products from one another, as they occurred in deteriorated solutions of barbiturates, by filtration and extraction with ether at successive pH levels. The results obtained are summarized in Table 1 and Table 2 showing the percentage yields of the different products obtained.

TABLE 1

PERCENTAGE YIELDS OF DECOMPOSITION PRODUCTS OBTAINED FROM DETERIORATED BARBITURATE SOLUTIONS WHICH WERE BOILED FOR THREE HOURS*

Name of the Barbituric Acid	Original Barbituric Acid	Substituted Malonuric Acid	Substituted Acetureide	Substituted Acetic Acid
Diethyl b.a.	45	30	7	-
Ethyl-allyl-b.a.	29	15	34	-
Diallyl b.a.	14	7	24	12
Isopropyl-allyl b.a.	83	1.5	4	-
Phenyl-ethyl b.a.	67	-	11	12
Phenyl-ethyl-N-methyl b.a.	30	0.3	34	7
Cyclohexenyl-methyl-N-methyl b.a.	23	4	48	-
Ethyl-allyl-N-Methyl b.a.	28	25	32	-

*Results obtained by Aspelund and Skoglund (7)

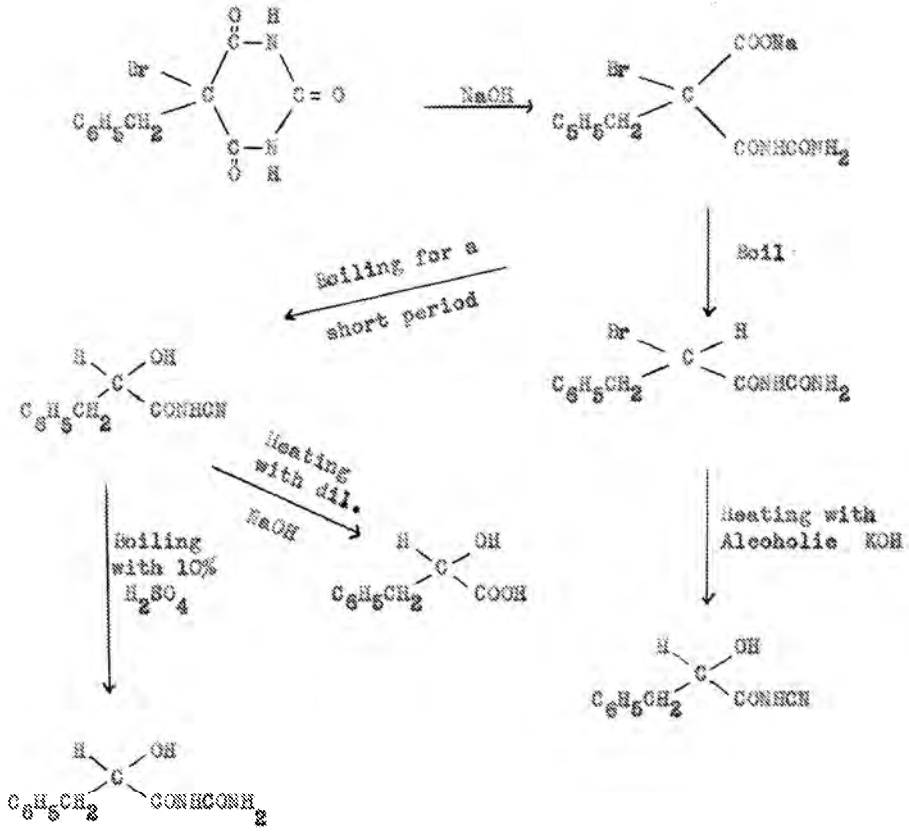
TABLE 2

PERCENTAGE YIELDS OF SUBSTITUTED MALONURIC ACID OBTAINED FROM DETERIORATED BARBITURATE SOLUTIONS WHICH HAD BEEN STANDING FOR EIGHT DAYS*

Name of the Barbituric Acid	Percentage Yield of Substituted Malonuric Acid
Diethyl b.a.	0.5
Ethyl-allyl b.a.	2.0
Diallyl b.a.	4.0
Isopropyl-allyl b.a.	traces
Phenyl-ethyl b.a.	1
Phenyl-ethyl-N-methyl b.a.	24
Cyclohexenyl-methyl-N-methyl b.a.	12
Ethyl-allyl-N-methyl b.a.	2.5

*Results obtained by Aspelund and Skoglund (7)

Aspelund (8) stated that the instability of the malonylurea ring in barbiturates is probably due to the negative hydroxyl group. He studied the decomposition of 5,5-bromobenzyl barbituric acid. The results obtained are outlined by the equations which follow.



Aspelund and Lindh (9) made a study of the chemistry of the decomposition products of 5,5-bromoalkyl-N-alkyl barbituric acids. The results obtained are outlined by the equations which follow.

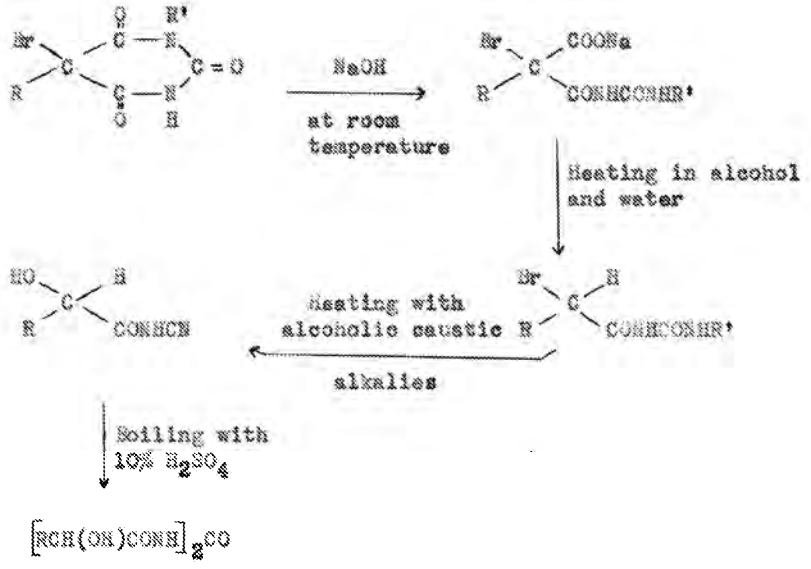


TABLE 3

MELTING POINTS OF DECOMPOSITION PRODUCTS OBTAINED FROM DETERIORATED BARBITURATE SOLUTIONS

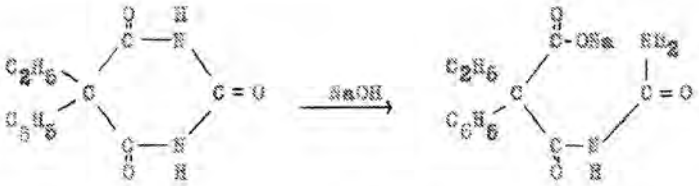
Decomposition Product	m. p. °C.	Worker
Phenylethylacetylurea	160	Smiley (4)
Phenylmethylacetyl urea	158	Smiley (4)
N-methyl-cyclohexenyl-methylacetylurea	97-101	Smiley (4)
Butylethylacetylurea	154	Smiley (4)
Diethylacetylurea	206-207	Smiley (4)
Diethylmalonuric acid	161-162	Neilsen (10)
Phenylethylacetic acid	44-45	Neilsen (11)

Although they may keep for 8-15 days as Wetzel (12) claimed, solutions of sodium phenylethyl barbiturate also undergo an analogous hydrolysis into phenylethylacetylurea (m. p. 146°-147° C.) and carbon dioxide. Nielsen (13) found that phenylethylacetylurea was precipitated when he refluxed 20% solutions of sodium phenobarbital for periods of 1/2 to 1 hour. Heating for 3 to 6 hours resulted in hydrolysis of part of the phenylethylacetylurea into phenylethylacetic acid and urea. Aspelund and Skoglund (14) stated that phenylethylmalonuric acid was very unstable.

The formation of free phenylethyl barbituric acid is also a possibility. It is to be noted that the solubility of this acid in water is about 1 : 1000, whereas the solubility of free diethyl barbituric acid in water is about 1 : 150. Therefore, the appearance of a precipitate of the free barbituric acid in solutions of sodium phenobarbital is a greater possibility than in solutions of sodium barbital. According to Woodward (15), Nielsen (13) has provided evidence that free phenylethyl barbituric may be formed in solutions of sodium phenobarbital on prolonged standing. Both liberation of the latter acid and hydrolysis take place at the same time. When determining phenylethylacetylurea formed in solutions, Nielsen (13) had difficulty in obtaining deposits and filtrates free from simultaneously formed phenylethyl barbituric acid. The acid was freed by the carbon dioxide absorbed from the atmosphere. To prevent deterioration by carbon dioxide, Cazzani (17) suggested that the solution be saturated with nitrogen. Nielsen (13) prevented the formation of the free acid by adjusting the

pH of the solutions with standard sodium hydroxide. Presumably the sodium hydroxide was employed in a manner so as to redissolve any liberated acid.

Mesnard (1) reiterated that solutions of sodium phenylethyl barbiturate hydrolyze into phenylethylbarbituric acid and sodium hydroxide. The decomposition of phenylethyl barbituric acid follows due to the action of sodium hydroxide, forming products without therapeutic value. Mesnard (18) gave the following:



The rapidity of hydrolysis of some barbiturate solutions is indicated by the length of time during which they are suitable for parenteral administration. The hydrolysis of evipal-sodium is rapid. Cazzani (17) stated that aqueous solutions should not be used 2 to 3 hours after their preparation. According to Eli Lilly & Company (19, 20) solutions of sodium amytal and of sodium pentobarbital should not be used thirty minutes after their preparation. Abbott Laboratories (21) stated that solutions of sodium ethyl (1-methyl butyl) thiobarbiturate can not be safely allowed to stand longer than 4 hours. Aspelund and Skoglund (14) found that 5-substituted barbituric acids were more easily decomposed than the 5,5 disubstituted barbituric acids. They stated that the sodium salts of isopropylallyl barbituric acid and cyclohexylethyl barbituric acid and perhaps of diethyl barbituric acid

are stable in aqueous solution for a definite length of time.

2. Factors in the Deterioration

a. Hydrogen Ion Concentration

In 1933, Nielsen (13) found the rate of hydrolysis of solutions of sodium phenylethyl barbiturate was decreased when there was an increase in hydrogen ion concentration. The amount of hydrolysis occurring was followed by determining the quantity of carbon dioxide and phenylethylacetylurea formed. Nielsen (13) stated that the determination of the chloroform-soluble urea derivative introduces an error due to its high solubility in the original solution and due to the formation of free phenylethyl barbituric acid by the carbonic acid released during the hydrolysis. Presumably, Nielsen (13) extracts the urea derivative with chloroform, thus explaining the above mentioned error. The solubility of phenylethyl barbituric acid in chloroform is 1 Gm. in 40 cc.(22). The results obtained by Nielsen (13) are summarized in Table 4.

TABLE 4

RELATION OF pH TO DECOMPOSITION OCCURRING IN 10% SOLUTIONS CONTAINING BOTH PHENOBARBITAL SODIUM AND PHENOBARBITAL AT 18.6 (±1)° C.

pH	Number of days required for 1% decomposition
8.9	30
9.4	22
9.9	18

A 10% solution of phenobarbital sodium saturated with the free acid has a pH of 8.9. Berasain and Vitali (23) stated that the pH of a 10% w/v solution of the sodium salt was 9.6.

Berasain and Vitali (23) prepared 10% w/v solutions of phenobarbital sodium in buffer solutions instead of water. The pH values of the solutions prepared are indicated in Table 5. However, they failed to state what proportions of the respective buffer solutions were used.

TABLE 5

EFFECT OF BUFFERS ON THE pH OF 10% SOLUTIONS OF PHENOBARBITAL SODIUM

Buffer	Originator	pH obtained
NaOH and glycocoll	Sorensen	9.71, 9.39, 8.39, 8.57, 8.24
KH_2PO_4 and NaOH	Clark and Lubs	8.00, 7.80, 7.60, 7.40, 7.20
Veronal and HCl	Michaelis	9.40, 8.80, 8.00, 7.60
Sodium citrate and NaOH	Clark and Lubs	7.00

In another experiment, phenobarbital was used to neutralize the free alkali and to lower the pH. The latter and the buffered solutions were subjected to heating by steam for fifteen minutes. A precipitate was formed in each case but the quantity was less in those solutions, having a pH less than 9.00. The precipitate appeared as white, small flakes, flocculent at first and then as needles, grouped in a radiating fashion.

Tomski and Waller (24) investigated the effect of varying amounts of sodium carbonate on the hydrolysis of solutions of sodium phenylethyl

barbiturate. One (1) cc., 2 cc., and 3 cc. portions of N/10 sodium carbonate were added to 5 cc. portions of a solution of sodium phenobarbital. Blank solutions were also made using water instead of the sodium carbonate solution. All the solutions were heated for sixty minutes at 80° C. Each blank solution showed a loss in percentage of 2.6. The results which Tomski and Waller (24) obtained are summarized in Table 8.

TABLE 8

LOSS IN PERCENTAGE ON HEATING A SOLUTION PHENOBARBITAL SODIUM IN THE PRESENCE OF SODIUM CARBONATE

cc. N/10 Na_2CO_3	Loss in Percentage
1	5.6
2	10
3	15

Madsen (3) found that solutions of sodium diethylbarbiturate hydrolyzed at a slower rate upon an increase in hydrogen ion concentration. He calculated the degree of hydrolysis by determining the amount of diethylacetylurea and carbon dioxide formed. The results secured by Madsen (3) are given in Tables 7 and 8.

TABLE 7

EFFECT OF HEAT ON 10% SOLUTIONS OF SODIUM DIETHYLBARBITURATE

Temperature	Duration of Heating	Per cent Decomposed	pH Change
100° C.	1 hour	2.5	10.1 to 9.8
80°	2 hours	1.0	10.1 to 9.6
60°	5 hours	0.23	-

TABLE 8

EFFECT OF HEAT ON 10% SOLUTIONS OF SODIUM DIETHYLBARBITURATE WITH A pH OF 9.9

Temperature	Duration of Heating	Per cent Decomposed
100° C.	1 hour	1.6
80°	2 hours	0.32

Bailey (4) discovered from a study of solutions prepared from different samples of sodium barbital that some showed precipitates on heating at 100° C. while others required a slightly higher temperature to bring about the same result. Upon determing the pH values of all the solutions, he found that those which decomposed at 100° C. had a slightly higher pH value. This was apparently due to the excess alkali used