

FILE HISTORY

17/854,914

INVENTORS: Bala Tripura Sundari Chodavarapu
Thirupathi Mangali
Jay Shukla
Anand Shukla
Dasaradhi Lakkaraju

TITLE: Lyophilized Compositions of Phenobarbital
Sodium Salt

APPLICATION NO: 17/854,914

FILED: 30 JUN 2022

COMPILED: 05 FEB 2025

17/854,914

Lyophilized Compositions of Phenobarbital Sodium Salt

Transaction History

Date	Transaction Description
06-30-2022	Patent Term Adjustment - Ready for Examination
06-30-2022	PTO-SB-69-Authorize EPO Access to Search Results
06-30-2022	Applicants have given acceptable permission for participating foreign
06-30-2022	Entity Status Set To Undiscounted (Initial Default Setting or Status Change)
06-30-2022	Initial Exam Team nn
07-21-2022	Applicant Has Filed a Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27
07-22-2022	Case Docketed to Examiner in GAU
07-22-2022	Application Dispatched from OIPE
07-22-2022	FITF set to YES - revise initial setting
07-25-2022	Email Notification
07-25-2022	Application Is Now Complete
07-25-2022	Filing Receipt
10-07-2022	Information Disclosure Statement (IDS) Filed
10-07-2022	Information Disclosure Statement (IDS) Filed
11-10-2022	Application ready for PDX access by participating foreign offices
11-10-2022	PG-Pub Issue Notification
11-11-2022	Email Notification

Electronic Acknowledgement Receipt	
EFS ID:	46092679
Application Number:	17854914
International Application Number:	
Confirmation Number:	1236
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:	104078.0001US2
Receipt Date:	30-JUN-2022
Filing Date:	
Time Stamp:	16:10:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$880
RAM confirmation Number	E20226TG16331398
Deposit Account	601823
Authorized User	Danielle Moroz
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees) 37 CFR 1.20 (Post Issuance fees) 37 CFR 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	ADS.pdf	2278006	no	9
			e10aae1f5fda72d62e6a951223951e022698ca12		
Warnings:					
Information:					
2		APP- FILED_2022-06-30_REV008.pdf	6825482	yes	98
			157d20fa7d4872cf8dff4580211571a6d648d5dc		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	54	
	Claims		55	58	
	Abstract		59	59	
	Drawings-other than black and white line drawings		60	98	
Warnings:					
Information:					
3	Oath or Declaration filed	Declaration_Chodavarapu_Signed.pdf	939567	no	1
			cad9906878198c2cf2a82743a47214915d6fc158		
Warnings:					
Information:					
4	Oath or Declaration filed	Declaration_Mangali_Signed.pdf	925855	no	1
			1d88dc0d4fb109af2b7e911d8213244eae8c5d3a		
Warnings:					
Information:					

5	Oath or Declaration filed	Declaration_Jay_Shukla_Signed.pdf	918558 9a1678ac210d93109cf6abf82458d45438aca685	no	1
Warnings:					
Information:					
6	Oath or Declaration filed	Declaration_Anand_Shukla_Signed.pdf	918348 c217b012984bc6a79e3043e7aaf889cefa3fc179	no	1
Warnings:					
Information:					
7	Oath or Declaration filed	Declaration_Lakkaraju_Signed.pdf	927594 73fb762ef11c490c49c2b1ce319d07af07ac2105	no	1
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	46461 dbefc1c0d7e93624dfc1eb32bea1f168c92d	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			13779871		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> 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. <u>National Stage of an International Application under 35 U.S.C. 371</u> 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. <u>New International Application Filed with the USPTO as a Receiving Office</u> 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.					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	104078.0001US2
		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.)
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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					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number		104078.0001US2	
		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 i	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 i	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 i	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.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	104078.0001US2
		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	104078.0001US2	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		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	104078.0001US2
		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)
	Continuation in part of	17025881	2020-09-18
Prior Application Status	Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
17025881	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).

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

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	104078.0001US2
		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.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	104078.0001US2
		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	
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
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.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	104078.0001US2
		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 ⁱ	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)	2022-06-30	
First Name	Martin	Last Name	Fessenmaier	Registration Number	46697
Additional Signature may be generated within this form by selecting the Add button. Add					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	104078.0001US2
		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

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 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 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 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.

LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT

Related Applications

[0001] This application is a continuation-in-part application of our copending and allowed US application with the serial number 17/025,881, filed 9/18/2020, which 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 (2EPM), 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 as 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 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.

[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 (2EPM), 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 (2EPM) 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 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 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 (O₂) gas from the water (*e.g.*, Water for Injection), it is also preferred that the water is sparged with nitrogen (N₂) 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
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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 (2EPM), 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

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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					
Test	Initial	Stability Data									
		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) 2EPM	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										
	2EPM: 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			
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

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

UV and PDA detector, an injector and a data processor is operated as follows:

[00119] 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

[00120] 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

[00121] 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

[00122] 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.

[00123] 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	NPH2031 A (Bulk Solution at 100 mg. mL Phenobarbital Sodium) Compounding at 2-8°C		NPH2031 A (Bulk Solution at 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	20	200	20	200
Sodium Chloride	NA	NA	9	90
WFI/DI Water	qs	qs	qs	qs

[00124] 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**).

[00125] 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				

[00126] 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				

[00127] 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	Initial	2 hrs		4 hrs		24 hrs	
			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								

[00128] 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**.

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[00129] 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 Clear Glass Vial; Stopper: 13 mm Lyo rubber stopper; Seal: 13 mm Flip off plastic with Al seal. API: Phenobarbital Sodium, USP Grade P								
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	9.6	9.6
% Assay Phenobarbital Sodium	98.0%-105.0 %	98.6	101.6	101.5	101.3	100.5	100.0	101.2
Related Substances 2EPMB:	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%	0.7	0.9	1.3	1.4	1.5	1.6	2.1
Note Book Reference		192039-150 to 158	192045- 25 to 45		192045-135 to 151		192051-84 to 122	
DOA: Date of Analysis; WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 3 minute after reconstitution; ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMB: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: o-Phenylbenzylguanidine; PEAU: Phenylethyladenine ;								

[00130] Table 11

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Product Name	Phenobarbital Sodium for Injection USP, 130 mg/vial		Batch#NPH2021 Fill Volume: 1.05 mL	Date Manufactured:01/20/2020
Vial Make	2 mL Clear Glass Vial			Date Initiated:02/14/2020
API Mfg.	Phenobarbital Sodium, USP Grade P. Re test Date: 11/16/2023			
Stopper Used	13 mm Grey Rubber stopper			Flip Off Seals:13mm Plastic with Aluminum Seal
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		24 Months
			DOA: 03/23/2020		DOA:05/20/20		DOA:09/04/20		DOA: 18-Mar-2022
			RT	ACC	RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH (100 mg/mL)	9.2-10.2	10.0	10.0	10.0	10.0	10.0	9.7	9.7	9.8
% Assay Phenobarbital Sodium	90.0%-105.0 %	100.3	99.7	99.3	100.0	99.6	99.1	98.3	99.8
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.7	0.7	0.9	0.9	1.1	1.0	1.3	1.4
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 151		192051-84 to 122		192099- 157,159,167,170
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: o-Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea ;									

[00131] Table 12

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Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial	Batch# NPHE2031A Fill Volume: 2.1 mL	Date Manufactured 06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		Date Initiated 06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV ₁		
Stopper Used	20 mm Igloo Bromobutyl Lyophilization Rubber stopper	Flip Off Seals 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)

Test	Spec.	Initial DOA: 06/05/20	3 Months DOA: 09/04/2020	
			RT	ACC
			WLP	WLP
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	BQL	BQL
Any unspecified degradation product @RRT 0.37	NMT 0.2%	BQL	0.06	0.05
Total degradation products	NMT 1.5 %	BQL	0.06	0.05
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3
Note Book Reference		192043-163 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: Phenylethylacetamide				

[00132] Table 13

Attmy Dkt No. 104078.0001US2

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial (Phenobarbital Sodium and 9% Saline/vial)	Batch# NPH2031B Fill Volume: 2.1 mL	Date Manufactured: 06/03/2020
Vial Make	10 mL Tubular Serum Bottle clear		Date Initiated: 06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV	Re test Date: 07/20/2024	
Stopper Used	20 mm Lyophilization Rubber stopper	Flip Off Seals: 20 mm Red Plastic top flip off with Aluminum Seal	
Configuration	Inverted	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months		6 Months		12 months
			DOA: 09/04/2020		DOA: 12/11/20		DOA: 11-Apr-22
			RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	9.6	9.6	9.5
% Assay Phenobarbital Sodium	90.0 -105.0	103.3	102.8	103.6	104.0	103.7	99.9
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	0.05	(BQL)
Any unspecified degradation product @PRT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5 %	BQL	0.06	0.05	0.06	0.10	BQL
Water Content by Karl Fischer	NMT 4.0%	0.8	0.9	1.1	NP	NP	1.2
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067-78 to 88		192034-137
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: Phenylethylaceturea							

[00133] Data for Osmolality, Particulate matter and assay for Sodium Chloride is disclosed in **Table 14.**

[00134] 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

[00135] Lyophilization parameters used for the 65 mg/vial, 100 mg/vial, 130 mg/vial and 200 mg/vial are disclosed in **Table 15**.

[00136] 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)

[00137] Six months stability data for Phenobarbital Sodium for Injection USP, 100 mg/vial is included in Table 16.

[00138] Table 16

Attny Dkt No. 104078.0001US2

Product Name	Phenobarbital Sodium for Injection USP, 100 mg/vial	Batch# NPH1980 Fill Volume 1.0 mL	Date Manufactured: 09/25/2019
Vial Make	5 mL Clear Untreated 5 mL Clear Treated		Date Initiated: 09/25/2019
API Mfg.	Phenobarbital Sodium, USP Grade P, C-TV., Re test Date:		
Stopper Used	13 mm Grey Butylrubber; 2 leg 1.3mm diameter Rubber stopper	Flip Off Seal: 13mm Rad Plastic top flip off with Aluminum Seal	
Configuration	Inverted	Stability	25°C, 60% RH (RT) & 40°C, 75% RH (ACC)

Test	Spec.	Initial DOA: 09/25/2019		1 Month DOA: 10/31/2019				3 Months DOA: 01/19/2020				6 Months DOA: 04/08/2020			
		UT	T	RT		ACC		RT		ACC		RT		ACC	
				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 (100 mg/mL)	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	90.5%- 105.0 %	99.4	97.6	98.6	99.0	99.0	100.4	99.1	99.7	97.0	96.9	97.7	98.3	97.1	97.6
% Impurity EPN&M	NMT 0.2%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
PEG	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%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total Impurities	NMT 2.0 %	0.06	0.06	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	0.9	1.1	1.3	1.2	1.1	1.6	1.4	1.6	1.2	1.5	2.0
Note Book Reference		192031-01 to 101		192031-102 to 123				192039-04 to 51				192045-06 to 85			
DOA: Date of Analysis WLP: White Lyophilized Powder, CCS: Clear Colorless Solution, 1 minute after reconstitution; UT: Untreated; T: Treated ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) EPN&M: 2-Ethyl-5-Phenylisoxazolidinone monohydrate, PEG: α-Phenylbutyrylglycine, PEAU: Phenylethylacetylurea															

[00139] 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	NPH1980 (Bulk Solution at 100 mg. mL Phenobarbital Sodium) Compounding at 2-8°		
	Fill Volume 1.0 mL		
	mg/mL (after reconstitution)	mg/vial	Batch Quantity (100 mL)
Phenobarbital Sodium	20	100	10.113 g
WFI/DI Water	qs	qs	Qs to 100 mL or 103.3 g

[00140] Representative chromatograms and/or corresponding calculations are shown in **Figs. 2A-2H, 3A-3L, 4A-4L, and Tables 2 and 3.**

[00141] The results for further extended stability studies are presented below in which commercially available phenobarbital sodium, USP Grade P was dissolved in water to produce an aqueous solution having a pH of between 9.2 and 10.2, and in which the aqueous solution was then filled into lyophilization vials in an amount of between 65 mg per vial and 200 mg per vial at a maximum concentration of phenobarbital of 100 mg/ml. Lyophilization was performed as in Table 15 noted above. Stability studies were then performed at standard conditions (RT: 25 °C, 60% relative humidity) and accelerated conditions (ACC: 40 °C, 75% relative humidity) for a period of up to 37 months.

[00142] After the storage conditions indicated in the tables below, the lyophilized product was then dissolved in water (or saline or dextrose) and subjected to analysis for degradation products of phenobarbital. Specifically, the inventors investigated the levels of degradation by quantifying the remaining phenobarbital and by quantifying 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU), as well as other unspecified degradation products. Remarkably, and as can be seen from the data below, the lyophilized amorphous phenobarbital had a storage stability at 25 °C and 60% relative humidity for up to and beyond three years and did readily dissolve upon reconstitution.

[00143] **Table 18** depicts exemplary results for 65 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%).

[00144] **Table 18 (65 mg/vial, up to 24 months)**

Product Name	Phenobarbital Sodium for Injection USP, 65 mg/vial	Batch# 54PH2020 Fill Volume: 1.05 mL	Date Manufactured: 01/20/2020
Vial Make	2 mL Flojigs Clear Blow Back Vial		Date Initiated: 02/14/2020
API Mfg	Phenobarbital Sodium, USP Grade P, C-IV:		
Stopper Used	13 mm Grey Birmaburst 1/2 leg Lympholization Rubber stopper (	Flip Off Seal: 13mm Red Plastic top flip off with Aluminum Seal.	
Configuration	Inverted	Stability	25°C, 60% RH (RT) & 40°C, 75% RH (ACC)

Test	Spec.	Initial DOA: 03/18/20	1 Month		3 Months		6 Months		24 months DOA: 18-MAR-2022	
			DOA: 03/23/2020		DOA: 05/26/20		DOA: 09/04/2020			
			RT	ACC	RT	ACC	RT	ACC	RT	
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	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	9.9	9.9	9.9	9.7
% Assay Phenobarbital Sodium	90.0%-105.0 %	98.6	101.6	101.5	101.3	100.5	100.0	101.2	101.2	101.2
Related Substances 2EPMMs	NMT 0.1%	BQL	ND	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.1%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.1%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.1%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.7	0.9	1.3	1.4	1.5	1.6	2.1		1.8
Note Book Reference		192039- 150 to 158	192045- 23 to 45		192045-135 to 151		192051-84 to 122		192099- 159, 160, 162, 170	
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%) 2EPMMs: 2-Ethyl-2-Phenylacetoamide, monochloride; PBG: p-Phenylglyoxal; PEAU: Phenylethylamine;										

[00145] Table 19 depicts exemplary results for 65 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

[00146] Table 19 (65 mg/vial, up to 37 months)

Product Name	Phenobarbital Sodium for Injection USP, 65 mg/mL			Batch#	NPH1907		Date Manufactured: 02/21/2019				
Vial Make	2 mL Vialax Clear Blow Back Vial							Date Initiated: 02/23/2019			
API Mfg	Phenobarbital Sodium, USP Grade P, C-IV										
Stopper Used	13 mm Gray Bromobutyl 2 leg Lyophilization Rubber stopper			Flip Off Seals:		13mm Red Plastic top flip off with Aluminum Seal					
Configuration	Inverted			Stability		25°C ± 2°C, 60 % RH ± 5% (RT) & 40°C ± 2°C, 75 % RH ± 5% (ACC)					

Test	Spec.	Initial DOA: 02/25/2019	1 Month DOA: 03/28/2019		3 Months DOA: 05/24/2019		6 Months DOA: 08/28/2019		12 Months DOA: 04/13/2020	30 Months
			RT	ACC	RT	ACC	RT	ACC	*RT	**RT
Description	White to almost white lyophilized powder	+	+	+	+	+	+	+	+	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH (0.5 MNaCl)	6.2-8.2	8.0	8.0	10.1	6.6	6.6	6.7	6.7	6.9	
% Assay Phenobarbital Sodium	98.0%-100.0%	98.1	99.4	99.1	99.7	97.4	100.0	99.3	98.0	
Related Substances (HPLC)	NMT 0.2%	NF	NF	NF	NF	NF	NF	NF	NF	
PBG	NMT 0.2%	NF	NF	NF	NF	NF	NF	NF	NF	
PEAU	NMT 0.2%	NF	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Any unspecified degradation products	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Total degradation products	NMT 1.0%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Water Content by Karl Fischer	NMT 3.0%	0.8	1.1	1.5	1.8	1.7	1.2	2.2	2.0	
Note Book Reference	192809 41,46,43,42		192806, 142, 143, 156, 157		192825, 45, 36, 51, 34		192811 8, 12, 14, 16, 17, 18		192804, 7 9, 11	
DATA: Date of Analysis W.P.: White Lyophilized Powder; CCS: Clear Colorless Solution; 1 minute after reconstitution; NF: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) HPLC: HPLC 2-Phenylisobarbital; related substances; PBG: o-Phenybutyrylgutamide; PEAU: Phenylethylurea * The samples were stored at 25°C ± 2°C, 60% RH ± 5%; ** The samples were stored from 20°C ± 2°C to 40°C ± 2°C and stored at 25°C ± 2°C, 60% RH ± 5%, at 18 months since prodn.										

[00147] Table 20 depicts exemplary results for 100 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%) or barely above quantitation limit.

[00148] Table 20 (100 mg/vial, up to 30 months)

Attny Dkt No. 104078.0001US2

Product Name	Phenobarbital Sodium for Injection USP, 100 mg/mL	Batch: 09PH1950 Full Volume: 10 mL	Date Manufactured: 09/25/2019
Vial Make	5 mL Clear Untreated 5 mL Clear Treated		Date Initiated: 09/25/2019
API Mfg.	Phenobarbital Sodium USP Grade F, C-IV		
Stopper Used	12 mm Grey Bromobutyl Tug Lyophilization Rubber stopper		
Configuration	Intended	Stability	25°C, 60% RH (RT) & 40°C, 75% RH (ACC)
	Flip Off Seal: 13mm Red Plastic top flip off with Aluminum Seal, Lot# NA		

Test	Spec	Initial DOA: 08/27/2019		1 Month DOA: 10/31/2019						3 Months DOA: 01/10/2020				6 Months DOA: 04/08/2020				36 Months DOA: 10-MAR-2022			
				RT		ACC		RT		ACC		RT		ACC		RT		ACC			
		UT	T	UT	T	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	WLP	WLP	WLP	WLP		
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS		
pH (136 mg/mL)	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	9.8	9.8	9.8	9.8		
% Assay of Phenobarbital	95.0%-103.0%	98.4	97.8	98.6	99.0	98.8	100.4	99.1	98.7	97.8	99.9	97.7	98.3	97.1	97.6	99.1	100.8				
% Impurity 2EPMM	NMT 0.1%	ND	ND	ND	ND	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL		
PBG	NMT 0.1%	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND		
PEAU	NMT 0.1%	BQL	BQL	ND	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL		
Any unspecified degradation product @RRT 0.37	NMT 0.1%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL		
Total Impurities	NMT 1.5%	0.06	0.06	0.05	0.05	0.05	0.05	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL		
Water Content by Karl Fischer	NMT 4.0%	0.7	0.6	1.0	0.9	1.1	1.3	1.2	1.1	1.6	1.4	1.6	1.2	1.5	2.0	2.1	1.8				
None Back Reference		192031-91 to 101		192031-169 to 183						192039-44 to 52				192045-48 to 85				192099-157,158,167,170,187,188,189,190			
DOA: Date of Analysis; WLP: Wate Lyophilized Powder; CCS: Clear Colorless Solution; 1: minute after reconstruction; UT: Untreated; T: Treated ND: Not Detected; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-5-phenylmaleimide monochloride; PBG: α-Phenyl-β-hydroxybutyrolactone; PEAU: Phenylethylacetolactone																					

[00149] Table 21 depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained at or below quantitation limit (0.05%).

[00150] Table 21 (130 mg/vial, up to 37 months)

Product Name	Phenobarbital Sodium for Injection USP, 130 mg/vial				Batch#NPH1912		Date Manufactured: 02/23/2019			
Vial Make	2 mL Fiolax Clear Blow Back Vial						Date Initiated: 02/25/2019			
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV.									
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper				Flip Off Seals: 13mm Red Plastic top flip off with Aluminum Seal					
Configuration	Inverted				Stability		15°C ± 2°C, 60 % RH ± 5% (RT) & 40°C ± 2°C, 75 % RH ± 5% (ACC)			
Test	Spec.	Initial DOA: 02/25/2019	1 Month DOA: 03/28/2019		3 Months DOA: 05/24/2019		6 Months DOA: 08/28/2019		18 Months DOA: 06/12/2020	37 Months DOA: 13-MAR-2022
			RT	ACC	RT	ACC	RT	ACC	RT	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (105 mg/mL)	8.2-10.2	8.8	10.0	9.9	9.8	9.1	9.3	9.8	10.0	9.3
% Assay Phenobarbital Sodium	90.0%-105.0 %	98.3	97.1	92.3	105.1	97.9	98.5	99.4	98.3	99.2
Related Substances 2EPB.D.1	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	ND	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	0.05	BQL	BQL
Total Degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	0.05	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.6	1.1	1.2	1.1	1.3	1.9	1.4	1.4	1.5
Note Book Reference	192019-41, 44, 45, 47		192019-122, 129, 125, 126		192025-24, 30, 31, 34		192031-8, 12, 14, 16, 17, 18		192051-2 to 11	192099-157, 159, 167, 170
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%); 2EPB.D.1: 2-Ethyl-5-Phenylsuccinonitrile, monohydrate; PBG: α-Phenylguanylguanidine; PEAU: Phenylethylacetylurea										

[00151] Table 22 depicts exemplary results for 130 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained below quantitation limit (0.05%).

[00152] Table 22 (130 mg/vial, up to 24 months)

Product Name	Phenobarbital Sodium for Injection USP, 130 mg/vial				Batch#NPH2021 Fill Volume: 1.65 mL		Date Manufactured:01/20/2020			
Vial Make	2 mL Fiolax Clear Elow Back Vial						Date Initiated 02/14/2020			
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV:									
Stopper Used	13 mm Grey Bromobutyl 2 leg Lyophilization Rubber stopper				Flip Off Seals: 13mm Red Plastic top flip off with Aluminum Seal					
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		24 Months	
			DOA: 03/23/2020		DOA: 05/23/20		DOA: 09/04/20		DOA: 18-Mar-2022	
			RT	ACC	RT	ACC	RT	ACC	RT	
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	WLP	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH (100 mg/mL)	9.2-10.2	10.0	10.0	10.0	10.0	10.0	9.7	9.7	9.8	
% Assay: Phenobarbital Sodium	90.0%-105.0 %	100.3	99.7	99.3	100.0	99.6	99.1	98.3	99.8	
Related Substances 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND	ND	ND	
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	ND	ND	
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Any unspecified degradation product	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	
Water Content by Karl Fischer	NMT 4.0%	0.7	0.7	0.9	0.9	1.1	1.0	1.3	1.4	
Note Book Reference		192039-150 to 158	192045- 23 to 45		192045-135 to 151		192051- 84 to 122		192059- 157,159,167,170	
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-Phenylsuccinamide, monohydrate; PBG: α-Phenyl-beta-benzamide; PEAU: Phenylethylaceturea ;										

[00153] Table 22 depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00154] Table 22 (200 mg/vial, up to 22 months)

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial	Batch# 01PH2031A Fill Volume: 2.1 mL	Date Manufactured: 06/09/2020
Vial Make	10 mL Tubular Serum Bottle clear		Date Initiated: 06/09/2020
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV		
Stoppers Used	20 mm Igloo Biotech/Lyophilization Rubber stopper		Flip Off Seals: 20 mm Red Plastic top flip off with Aluminum Seal
Configuration	Inverted	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months		6 months		12 months
			DOA: 09/04/2020		DOA: 12/11/2020		DOA: 11-Apr-2022
			RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.9	9.6	9.7	9.7	9.7	9.5
% Assay Phenobarbital Sodium	96.0 -105.0	100.1	98.1	101.0	100.8	102.5	98.2
Related Substances (% Area) 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product (RT 0.37)	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5 %	BQL	0.06	0.05	0.06	0.05	(BQL)
Water Content by Karl Fischer	NMT 3.0%	1.1	1.0	1.3	1.2	1.6	1.5
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067-78 to 88		192034-137
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: Phenylethylaceturea							

[00155] Table 23 depicts exemplary results for 200 mg per vial phenobarbital sodium stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%). In contrast to Table 22, this formulation was filled into the vial using a 9% saline solution. The final concentration of the saline after reconstitution in 10 mL of water for injection will be 0.9%.

[00156] Table 23 (200 mg/vial, up to 12 months)

Product Name	Phenobarbital Sodium for Injection USP, 200 mg/vial (Phenobarbital Sodium and 9% Saline/vial)	Batch#NPH2031B Fill Volume: 2.1 mL	Date Manufactured:06/09/2020
Vial Make	10 mL Tubular Serum Bottle clear	Date Initiated:06/09/2020	
API Mfg.	Phenobarbital Sodium, USP Grade P, C-IV		
Stopper Used	20 mm Igloo Bromocetyl Lyophilization Rubber stopper		Flip Off Seals:20 mm Red Plastic top flip off with Aluminum Seal
Configuration	Inverted	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)

Test	Spec.	Initial DOA: 06/05/20	3 Months		6 Months		12 months
			DOA: 09/04/2020		DOA: 12/11/20		DOA: 11-Apr-22
			RT	ACC	RT	ACC	RT
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL)	9.2-10.2	9.8	9.5	9.5	9.6	9.6	9.5
% Assay Phenobarbital Sodium	90.0-105.0	103.3	102.8	103.6	104.0	103.7	99.9
Related Substances (% Area) 2EPMM	NMT 0.2%	BQL	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	0.05	(BQL)
Any unspecified degradation product @RT 0.37	NMT 0.2%	BQL	0.06	0.05	0.06	0.05	(BQL)
Total degradation products	NMT 1.5 %	BQL	0.06	0.05	0.06	0.10	BQL
Water Content by Karl Fischer	NMT 4.0%	0.8	0.9	1.1	NP	NP	1.2
Note Book Reference		192045-163 to 189	192051- 84 to 122		192067-78 to 88		192034-137
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							

[00157] To further investigate if the nature of the reconstitution solution would have an adverse effect on stability after reconstitution, the inventors used 65 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose to a final concentration of 1 mg/ml. In an additional set of experiments, the inventors used 130 mg of lyophilized amorphous phenobarbital in a vial and dissolved the lyophilized material with 0.9% or 5% dextrose or water to a final concentration of 20 mg/ml. The so reconstituted solutions were then kept under refrigeration (2-8 °C) or at standard conditions (25 °C) for the indicated times in the tables below. The levels of degradation were determined by quantifying the remaining phenobarbital and by quantifying 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU), as well as other unspecified degradation products. Once more, under all tested conditions, the stability of the so reconstituted compositions was unexpectedly high.

[00158] **Table 24** depicts exemplary results for 65 mg per vial phenobarbital sodium reconstituted with 5% dextrose to 1 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below

quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00159] Table 24 (65 mg/vial, reconstituted to 1 mg/ml in 5% dextrose, up to 24 hrs)

Admixture Study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPH2620) (1 mg/mL dilution in 5% Dextrose)														
Specifications	Tests/Time	Initial	1 hrs		2.5 hrs		4 hrs		6 hrs		9 hrs		24 hrs	
			2-SC	RT	2-SC	RT	2-SC	RT	2-SC	RT	2-SC	RT	2-SC	RT
Complies	Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH To be reported	pH (1mg/mL dilution)	8.8	8.8	8.8	8.8	8.8	8.8	8.7	8.8	8.7	8.7	8.7	8.7	8.5
Assay 90%-105%	Assay of Phenobarbital Sodium	95.4	95.7	95.6	95.9	96.4	95.9	97.1	95.6	95.9	94.6	97.1	95.1	96.1
2EPMM NMT0.2%	Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG NMT0.2%	PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU NMT0.2%	PEAU	ND	ND	BQL	BQL	BQL	ND	BQL	BQL	ND	BQL	BQL	BQL	BQL
Unspecified degradation product NMT 0.2%	Any unspecified degradation product @ RRT 0.29	ND	ND	BDL	ND	BDL	ND	BDL	ND	0.02	BDL	0.02	BDL	0.03
	Any unspecified degradation product @ RRT 0.37	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.01	0.02	0.01	0.03	0.02	0.05
Osmolality To be reported NMT 1.5%	Osmolality (mOsmol/Kg)	254	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	255	253
	Total degradation products	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	0.08

CCS: Clear colourless solution; ND: Not detected; BDL: Below detection limit; BQL: Below Quantitation limit; NP: Not performed;
2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutyrylguanidine; PEAU: Phenylethylacetate; PEUA: Phenylethylacetate

CCS: Clear colorless solution; ND: Not detected; BDL: Below detection limit; BQL: Below Quantitation limit; NP: Not performed;
2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenobarbital sodium; PEAU: Phenylethylalacetate

[00160] Table 25 depicts exemplary results for 65 mg per vial phenobarbital sodium reconstituted with 0.9% saline to 1 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00161] Table 25 (65 mg/vial, reconstituted to 1 mg/ml in 0.9% saline, up to 24 hrs)

Specifications	Admixture study of Phenobarbital Sodium for Injection USP, 65 mg/vial (NPEH2026) (1 mg/mL dilution in 0.9% Saline)													
	Tests/Time	Initial	1 hr.		2.5 hrs		4 hrs		6 hrs		9 hrs		24 hrs	
			2-SC	RT	2-SC	RT	2-SC	RT	2-SC	RT	2-SC	RT	2-SC	RT
Concplies	Description	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH To be reported	pH (1mg/mL dilution)	9.0	8.8	8.9	9.0	9.0	8.9	8.9	8.8	8.9	8.7	8.8	8.5	8.4
Assay 90%-105%	Assay of Phenobarbital Sodium	95.8	96	94.3	95.4	95.6	95.5	95.2	95.8	93.9	94.6	95.4	95.2	95.3
2EPMM NMT 0.2%	Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG NMT 0.2%	PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU NMT 0.2%	PEAU	BQL	ND	BQL	BQL	BQL	BQL	BQL	BQL	ND	BQL	BQL	BQL	BQL
Unspecified degradation product NMT 0.2%	Any unspecified degradation product @ RRT 0.29	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
	Any unspecified degradation product @ RRT 0.37	0.02	0.02	0.03	0.02	0.03	0.02	0.04	0.02	0.04	0.03	0.05	0.03	0.1
NMT 1.5%	Total degradation products	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	0.05	BQL	0.1
Osmolality To be reported	Osmolality (mOsmol/Kg)	288	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	286	287
CCS: Clear colorless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutylguanine; PEAU: Phenylethylacetylurea; BQL: Below Quantitation limit (0.05%)														

[00162] Table 26 depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with 0.9% saline to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00163] Table 26 (130 mg/vial, reconstituted to 20 mg/ml in 0.9% saline, up to 24 hrs)

Admixture study of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In 0.9% Saline)													
Tests/Time	Initial	30 min		90 min		240 min		6 hrs		9.5 hrs		24 hrs	
		2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.4	9.4	9.3	9.4	9.3	9.4	9.4	9.4	9.4	9.4	9.2	9.4	9.3
Assay of Phenobarbital Sodium	104.1	103.6	102.4	103.3	102.7	103.2	102.9	103.4	102.9	99.5	103.3	103.3	101.3
Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	BQL	ND	BQL	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	BQL	0.03	0.04	0.03	0.05	0.03	0.07	0.03	0.09	0.03	0.13	0.04	0.24
Total degradation products	BQL	0.03	0.04	0.03	0.05	0.03	0.07	0.03	0.09	0.03	0.13	0.04	0.24
Osmolality (mOsmol/Kg)	418	NP	NP	NP	NP	NP	NP	NP	NP	420	418	417	419
CCS: Clear colourless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenobarbitalguandine; PEAU: Phenylethylacetyleurea													

[00164] Table 27 depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with 5% dextrose to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00165] Table 27 (130 mg/vial, reconstituted to 20 mg/ml in 5% saline, up to 24 hrs)

Admixture study of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution in 5% Dextrose)													
Tests/Time	Initial	36 min		96 min		4 hrs		6 hrs		9.5 hrs		24 hrs	
		2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT	2-8C	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.4	9.4	9.3	9.4	9.4	9.4	9.3	9.3	9.3	9.4	9.3	9.4	9.4
Assay of Phenobarbital Sodium	101	102	100	101.5	102	100.9	101.1	101.7	101.6	101.6	102.1	102.4	102.2
Related Substances (%Area) 2EPMM	ND	ND	ND	ND	ND	ND	BQL	ND	ND	ND	BQL	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	0.02	0.02	0.03	0.03	0.04	0.03	0.06	0.03	0.08	0.03	0.11	0.04	0.19
Total degradation products	0.02	0.02	0.03	0.03	0.04	0.03	0.06	0.03	0.08	0.03	0.11	0.04	0.19
Osmolality (mOsmol/Kg)	379	NP	NP	NP	NP	NP	NP	NP	NP	NP	379	380	377
CCS: Clear colourless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPMM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea													

[00166] Table 28 depicts exemplary results for 130 mg per vial phenobarbital sodium reconstituted with water to 20 mg/ml that was stored under refrigeration or at standard conditions. Under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00167] Table 28 (130 mg/vial, reconstituted to 20 mg/ml in water, up to 24 hrs)

Admixture study of Phenobarbital Sodium for Injection USP, 130 mg/vial (NPH2030) (20 mg/mL dilution In Water)							
Tests/Time	Initial	2 hrs		4 hrs		24 hrs	
		2-8C	RT	2-8C	RT	2-8C	RT
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (20 mg/mL dilution)	9.5	9.5	9.6	9.6	9.5	9.6	9.5
Assay of Phenobarbital Sodium	99.8	102.1	100.8	101.7	101.2	100.4	100.3
Related Substances (%Area) 2EPM	ND	ND	ND	ND	ND	ND	BQL
PBG	ND	ND	ND	ND	ND	ND	ND
PEAU	BQL	BQL	BQL	BQL	BQL	BQL	BQL
Any unspecified degradation product @ RRT 0.37	0.02	0.02	0.04	0.02	0.06	0.04	0.18
Total degradation products	0.02	0.02	0.04	0.02	0.06	0.04	0.18
Osmolality mOsmol/Kg	158	NP	NP	NP	NP	159	158
CCS: Clear colourless solution; ND: Not detected; BQL: Below Quantitation limit; NP: Not performed; 2EPM: 2-ethylphenylmalonamide monohydrate; PBG: Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea							

[00168] In further experiments, the inventors investigated if stable lyophilized phenobarbital preparations could be prepared (in crystalline and/or amorphous forms, depending on solvent) using one or more water miscible co-solvents. To that end, the inventors tested isopropanol, tert-butanol, ethanol, and acetonitrile as co-solvents. Most typically, the co-solvent(s) will be present in an amount of at least 1.0%, or at least 1.5%, or at least 2.0%, or at least 2.5%, or at least 3.0%, or at least 3.5%, or at least 4.0%, or at least 4.5%, or at least 5.0%, or at least 5.5%, or at least 6.0%, or at least 7.0%, or at least 8.0%, or at least 9.0%, or at least 10%, or at least 25%, or at least 50%, or at least 75%. Therefore, suitable quantities of co-solvent(s) include those between 1.0 and 3.0%, or between 2.5% and 5.0%, or between 3.0% and 7.5%, or between 5.0% and 10%, or between 10% and 25%, or between 25% and 50%, or between 50% and 75%, and even higher. For example, and as shown in more detail below, the concentration of the organic co-solvent was as high as 90%. Lyophilization conditions and results are shown below. **Tables 29A and 29B** depict formulation details used in the lyophilization and stability experiments. Two formulations were

prepared for each strength (65 mg and 130 mg), one with 5% Isopropanol and the other with 5% Tertiary Butanol, and other co-solvents (here acetonitrile and ethanol) were also evaluated. The organic solvent was added after the Phenobarbital Sodium was dissolved in water, mixed well and adjusted to final volume with water. Later the bulk solution is filled in vials and lyophilized using the Lyo cycle parameters shown in **Table 30**. After the Lyo cycle was completed, the finished product was analyzed for assay, related substances, pH, moisture content and residual solvents.

[00169] Table 29A – Formulations with t-butanol and isopropanol as organic co-solvent

Ingredients	Bulk Solution	CAS Number	Concentration in mL	Total volume (50 mL)
Phenobarbital Sodium, USP C-IV	65 mg/mL	NA	65.73 mg (~65 mg Phenobarbital Sodium after LOD correction)	3.287g
	130 mg/mL		131.469mg (~130 mg Phenobarbital sodium after LOD correction)	6.573g
Tertiary Butanol	5%	75-65-0	(0.05 ml or 0.039 g)	2.5 ml or 1.95g
Isopropanol		67-63-0	(0.05 ml or 0.0393 g)	2.5 ml or 1.963 g
DI Water/Water for Injection	N/A		Q.S. to 1 mL	Q.S. to 50 mL

[00170] Table 29B – Formulations with ethanol and acetonitrile as organic co-solvent

Ingredients	Bulk Solution Formulation prepared at 25°C	Total Volume (100 mL Batch Size)	
		NPH22035	NPH22034
Phenobarbital Sodium	130 mg/mL	13.38 g	13.38 g
Ethanol	Qs	-	Qs to total volume 100 mL
Acetonitrile	Qs	Qs to total volume 100 mL	-
Water for Injection/ DI water	10%	10 ml	10 ml

[00171] Table 30 – Lyophilization protocol

Section	Phase	Hold Time [min]	Temperature °C	Vacuum [mTorr]
1	Loading	n.a.	5	off
2	Freezing	5	-5	off
3	Freezing	60	-50	off
4	Freezing	30	-10	off
5	Freezing	120	-50	off
6	Evacuation	30	-50	75
7	Primary drying	400	-50	75
8	Primary drying	350	-45	75
9	Primary drying	300	-43	75
10	Primary drying	250	-35	75
11	Primary drying	60	-20	75
12	Primary drying	120	0	75
13	Secondary drying	120	50	75
14	Secondary drying	120	25	75

[00172] Table 31 depicts results for 65 mg and 130 mg per vial phenobarbital sodium (from a bulk solution containing 5% tert-butanol) stored at standard and accelerated conditions where under all tested conditions 2EPM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05%).

[00173] Table 31 (65/130 mg/vial, 5% tert-butanol, up to 3 months)

Product Name	Phenobarbital Sodium for Injection, USP Lyophilized Powder. Bulk solution prepared in 5% Tertiary Butanol				Date Manufactured:02/21/2019 Date Initiated:09/05/2019		
	Configuration	Inverted	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)			
Test	Spec.	NPH1965 (65 mg/vial)				NPH1967 (130 mg/vial)	
		Initial DOA: 9/07/2019	3 Months		Initial DOA: 12/20/2019	3 Months	
			DOA: 12/20/2019			DOA: 12/20/2019	
			RT	ACC		RT	ACC
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL) pH (100 mg/mL) for 130 mg/vial strength	9.2-10.2	9.7	9.7	9.7	9.8	9.8	9.8
% Assay Phenobarbital Sodium	90.0%-105 %	98.2	98.8	97.7	100.0	99.9	99.9
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL
Any other degradation product	NMT 0.2%	0.09	BQL	BQL	0.09	BQL	BQL
Total degradation products	NMT 1.5 %	0.09	BQL	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 4.0%	0.4	NP	NP	0.3	NP	NP
% Residual Solvent (Tertiary butanol)	To be reported	1.2	0.6	0.8	4.4	2.9	1.7
Note Book Reference		192031-46 to 52	192039-9 to 23		192031-46 to 52	192039-9 to 23	
LP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; DOA: Date of analysis ND: Not Detected; NP: Not performed; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α -Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea							

[00174] Table 32 depicts results for 65 mg and 130 mg per vial phenobarbital sodium (from a bulk solution containing 5% isopropanol) stored at standard and accelerated conditions where under all tested conditions 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Likewise, unspecified degradation products and total degradation products remained near or below quantitation limit (0.05).

[00175] Table 32 (65/130 mg/vial, 5% isopropanol, up to 3 months)

Product Name	Phenobarbital Sodium for Injection, USP Lyophilized Powder. Bulk solution prepared in 5% Isopropanol				Date			
					Manufactured:02/21/2019 Date Initiated:09/05/2019			
Configuration	Inverted	Stability	25°C, 60 % RH (RT) & 40°C, 75 % RH (ACC)					
Test	Spec.	NPH1966 (65 mg/vial)				NPH1968 (130 mg/vial)		
		Initial DOA: 9/07/2019	3 Months		Initial DOA: 9/07/2019	3 Months		
			DOA: 12/20/2019			DOA: 12/20/2019		
			RT	ACC		RT	ACC	
Description	WLP	WLP	WLP	WLP	WLP	WLP	WLP	
Appearance	CCS	CCS	CCS	CCS	CCS	CCS	CCS	
pH (65 mg/mL) pH (100 mg/mL) for 130 mg/vial strength	9.2-10.2	9.6	9.6	9.7	9.8	9.7	9.7	
% Assay Phenobarbital Sodium	90.0%-105 %	99.7	98.8	100.0	100.0	101.1	99.1	
Related Substances 2EPMM	NMT 0.2%	ND	ND	ND	ND	ND	ND	
PBG	NMT 0.2%	ND	ND	ND	ND	ND	ND	
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL	BQL	BQL	
Any other degradation product	NMT 0.2%	0.08	BQL	BQL	0.09	BQL	BQL	
Total degradation products	NMT 1.5 %	0.08	BQL	BQL	BQL	BQL	BQL	
Water Content by Karl Fischer	NMT 4.0%	0.3	NP	NP	0.3	NP	NP	
% Residual Solvent (Isopropanol)	To be reported	1.7	0.7	0.7	1.7	1.4	1.4	
Note Book Reference		192031-46 to 52	192039-9 to 23		192031-46 to 52	192039-9 to 23		
WLP: White Lyophilized Powder; CCS: Clear Colorless Solution, 1 minute after reconstitution; DOA: Date of analysis ND: Not Detected; NP: Not performed; NMT: Not More Than; BQL: Below Quantitation Limit (0.05%) 2EPMM: 2-Ethyl-2-Phenylmalonamide, monohydrate; PBG: α -Phenylbutyrylguanidine; PEAU: Phenylethylacetyleurea								

[00176] Table 33 depicts initial results for 65 mg and 130 mg per vial lyophilized phenobarbital sodium from respective bulk solutions containing ethanol or acetonitrile as co-solvent (to obtain 65 mg/ vial, 0.5 mL of the bulk solution was filled in the vials and for 130 mg/ vial strength, 1 ml of the bulk solution was filled in the vials prior to lyophilization). For all test products, 2EPMM, PBG, and PEAU remained undetectable or below quantitation limit (0.05%). Notably, unspecified degradation products and total degradation products also remained undetectable or below quantitation limit (0.05%).

[00177] Table 33 (65/130 mg/vial, acetonitrile or ethanol as co-solvents)

Test	Spec.	Initial		Initial	
		NPH22035 Formulation in Acetonitrile: Water		NPH22034 Formulation in Ethanol : Water	
		65 mg Fill volume (0.5 mL)	130 mg Fill Volume (1 mL)	65 mg Fill volume (0.5 mL)	130 mg Fill Volume (1 mL)
Description	WLP	WLP	WLP	WLP	WLP
Appearance	CCS	CCS	CCS	CCS	CCS
pH (65 mg/mL)	9.2-10.2	NA	NA	NA	NA
% Assay Phenobarbital Sodium	90.0%-105.0 %	103.6	101.2	100.2	98.3
Related Substances 2EPM	NMT 0.2%	ND	ND	ND	ND
PBG	NMT 0.2%	ND	ND	ND	ND
PEAU	NMT 0.2%	BQL	BQL	BQL	BQL
Any unspecified degradation product	NMT 0.2%	ND	ND	ND	ND
Total degradation products	NMT 1.5 %	BQL	BQL	BQL	BQL
Water Content by Karl Fischer	NMT 3.0%	0.4	0.4	0.2	0.2
Residual Solvent	To be reported	NA	NA	3.2	19.2
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%) 2EPM: 2-Ethyl-2- Phenylmalonamide, monohydrate; PBG: α -Phenylbutyrylguanidine; PEAU: Phenylethylacetylurea NA: Not available					

[00178] Notably, the results indicated that the above formulations were also storage stable over at least three months as evidenced by all known impurities below quantitation limit as shown in **Tables 31 and 32**. However, an unknown impurity was observed above LOQ level. Interestingly, the residual solvents tertiary butanol and isopropanol were not completely removed after the first cycle of secondary drying. Tertiary butanol and isopropanol were observed above 0.5% in the 65 mg and 130 mg strength products. The same vials were then subjected to additional secondary drying at 25 °C for 30 min and 50 °C for 120 min, and the samples were analyzed for residual solvent after the second cycle of secondary drying.

[00179] After the additional secondary drying steps, residual tert-butanol and isopropanol were observed at lower quantities, respectively. As can be readily seen, the organic solvents could be reduced in quantities, but were not completely removed, possibly suggesting that the tested organic solvents could form a bond in the crystal lattice of phenobarbital. However, further process modifications may possibly result in additional reduction of residual co-solvent, requiring

extensive experimentation. Similar formulations were prepared in organic solvents ethanol and acetonitrile. Here as well, the residual solvent ethanol was not completely removed, but further process modifications may possibly result in additional reduction of residual co-solvent, requiring extensive experimentation.

[00180] Organic solvents such as isopropanol, tertiary butanol, ethanol and acetonitrile were investigated as co-solvents during the lyophilization. Two co solvents tertiary butanol and Isopropanol were used as co-solvents at 5%. The 3M stability data for the formulation with IPA and tert-butanol indicates that although no known degradation products were observed above quantitation limit, the residual solvents could not be removed completely after lyophilization. When ethanol was used as a co solvent similar results were observed. In view of the fact that organic solvents are toxic to all age groups, and in particular to neonates and because residual solvents are typically trapped in the crystal lattice of the Phenobarbital, the lyophilized product with only water as solvent is preferred over formulations containing any organic co solvents.

[00181] 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 $0.1^\circ 2\theta$ 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 $40^\circ 2\theta$ using a continuous scan of $6^\circ 2\theta$ per minute with an effective step size of $0.02^\circ 2\theta$.

[00182] 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.

[00183] 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 product, comprising:
 - a container enclosing storage-stable lyophilized amorphous phenobarbital;
 - wherein the lyophilized amorphous phenobarbital is prepared under a lyophilization protocol that produces a lyophilized amorphous phenobarbital that has a stability such that, upon storage at 25 °C and 60% relative humidity for at least 22 months and reconstitution with water, less than 0.05% of degradation products from the phenobarbital are detectable in the reconstituted solution;
 - wherein the degradation products are selected from the group consisting of 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).
2. The product of claim 1, wherein upon storage at 25 °C and 60% relative humidity for at least 24 months and reconstitution with water, less than 0.05% of degradation products from the phenobarbital are detectable in the reconstituted solution.
3. The product of claim 1, wherein upon storage at 25 °C and 60% relative humidity for at least 30 months and reconstitution with water, less than 0.05% of degradation products from the phenobarbital are detectable in the reconstituted solution.
4. The product of claim 1, wherein upon storage at 25 °C and 60% relative humidity for at least 36 months and reconstitution with water, less than 0.05% of degradation products from the phenobarbital are detectable in the reconstituted solution.
5. The product of claim 1, wherein upon storage at 25 °C and 60% relative humidity for at least 30 months and reconstitution with water, the product comprises no more than 0.05% of total degradation products.
6. The product of claim 1, wherein the container encloses between 65 and 200 mg of lyophilized amorphous phenobarbital.

7. The product of claim 1, wherein the lyophilized amorphous phenobarbital contains no more than 1.8% water.
8. The product of claim 1, wherein the lyophilized amorphous phenobarbital contains no more than 1.5% water.
9. The product of claim 1, wherein the lyophilization protocol comprises a freezing step to a temperature of about -50 °C, a primary drying step at a pressure of between about 50mTorr and 75 mTorr and at a temperature of between about -50 °C and about 0 °C, and a secondary drying step at a pressure of between about 50 mTorr and 75 mTorr and at a temperature of between about 25 °C and about 50 °C.
10. The product of claim 9, wherein the freezing step is performed without application of a vacuum.
11. The product of claim 9, wherein the primary drying step is performed over a period of at least 1,000 minutes.
12. The product of claim 9, wherein the secondary drying step is performed over a period of at least 200 minutes.
13. The product of claim 1, wherein the lyophilized amorphous phenobarbital further comprises NaCl.
14. A method of preparing a pharmaceutical composition, comprising:
 - combining phenobarbital sodium with a water miscible organic solvent and water to a phenobarbital concentration of between 50 mg/ml and 150 mg/ml to thereby produce a phenobarbital solution;
 - wherein the water miscible organic solvent is selected from the group consisting of t-butanol, isopropanol, ethanol, or acetonitrile;
 - 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 phenobarbital sodium composition;

wherein the freezing step comprises freezing the phenobarbital solution to a temperature of about -50 °C without application of vacuum;
wherein the primary drying step comprises application of vacuum at a pressure of about 75 mTorr at a temperature of between about -50 °C and about -20 °C for at duration of at least 1,200 minutes;
wherein the secondary drying step comprises application of vacuum at a pressure of between about 25 mTorr and 50 mTorr at a temperature of between about 25 °C and about 50 °C for at duration of at least 200 minutes;
wherein the lyophilized phenobarbital sodium forms, upon storage over 3 months at room temperature, no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution.

15. The method of claim 14, wherein the lyophilized phenobarbital sodium forms, upon storage over 3 months at room temperature, no detectable quantities of 2-ethyl-2-phenylmalonamide (2EPMM) when reconstituted in an aqueous solution.
16. The method of claim 14, wherein the lyophilized phenobarbital sodium forms, upon storage over 3 months at room temperature, no detectable quantities of alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution.
17. The method of claim 14, wherein the lyophilized phenobarbital sodium forms, upon storage over 3 months at room temperature, less than 0.05% of total degradation products when reconstituted in an aqueous solution.
18. The method of claim 14, wherein the lyophilized amorphous sodium contains no more than 4.4% residual tert-butanol or no more than 1.7% residual isopropanol.
19. The method of claim 14, further comprising an additional secondary drying step at a temperature of between about 25 °C and about 50 °C for at duration of at least 100 minutes.
20. The method of claim 19, wherein the lyophilized phenobarbital sodium contains after the additional secondary drying step no more than 3.4% residual tert-butanol or no more than 0.9% residual isopropanol.

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21. The method of claim 14, wherein the organic solvent in the phenobarbital sodium solution has a concentration of between 1% and 90%.

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

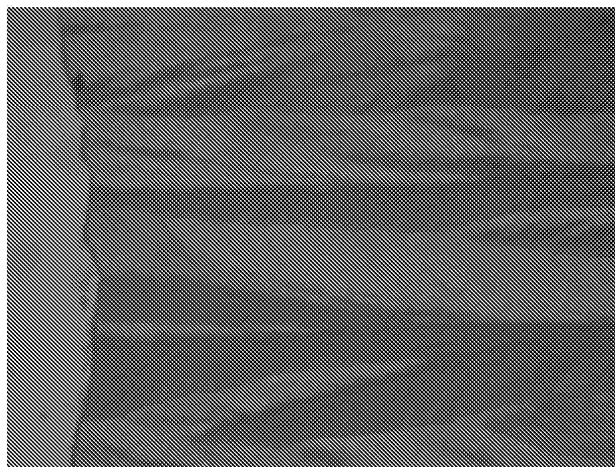


Fig. 1B

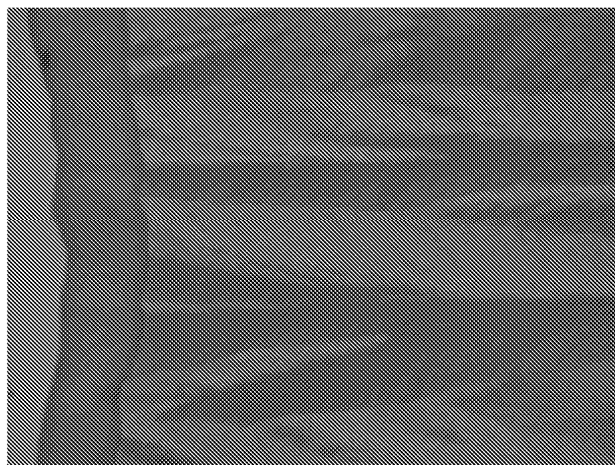


Fig. 1C

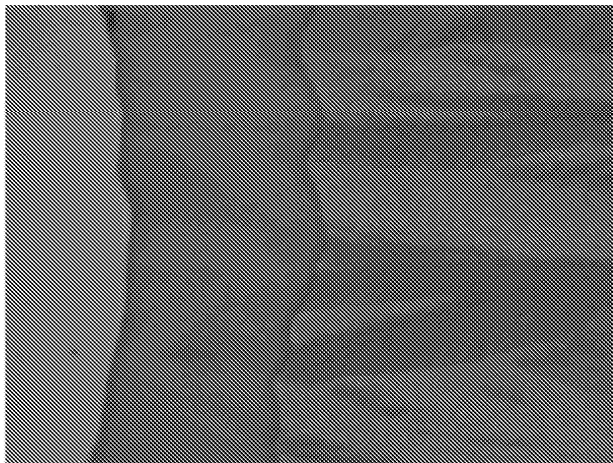


Fig. 1D

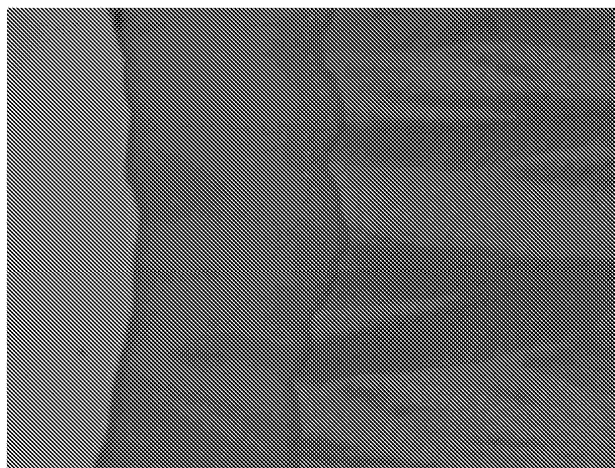


Fig. 1E

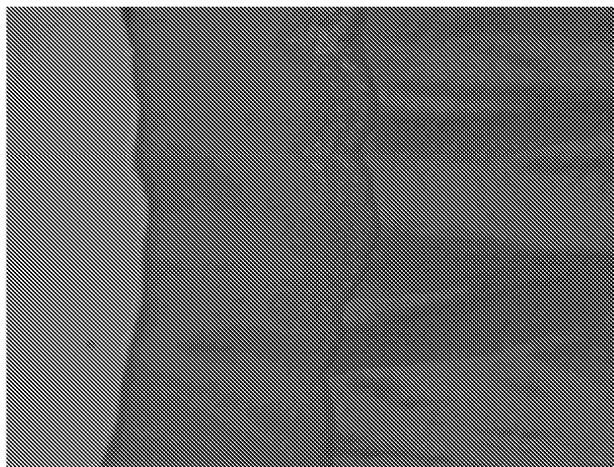


Fig. 1F

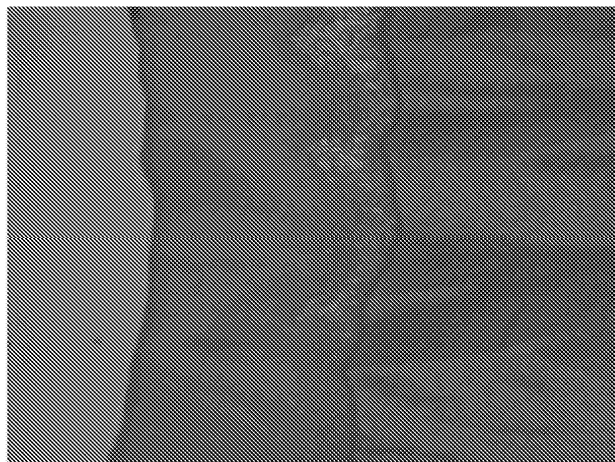


Fig. 2A

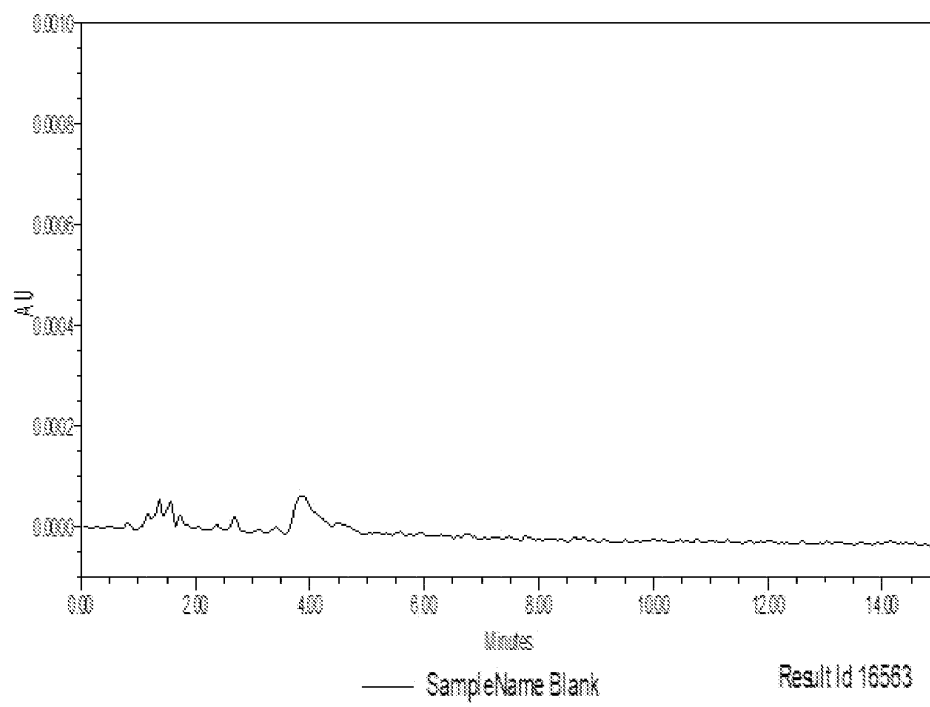
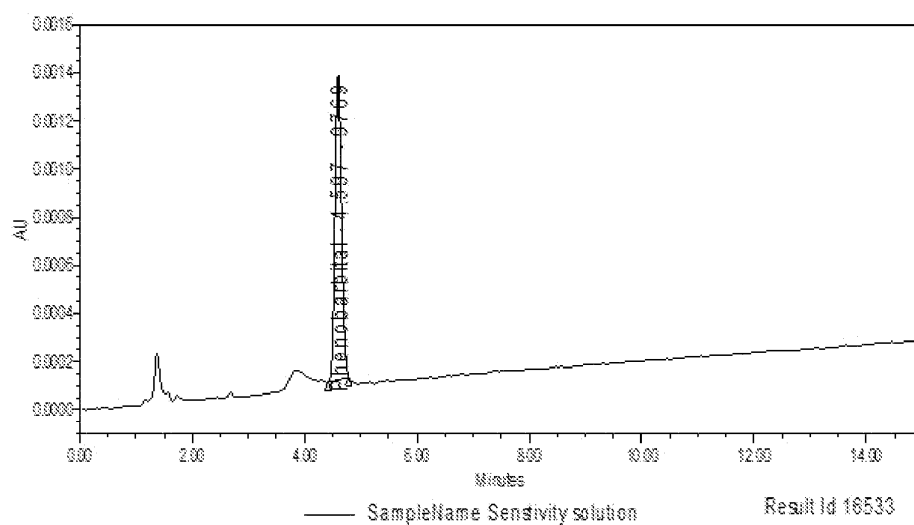
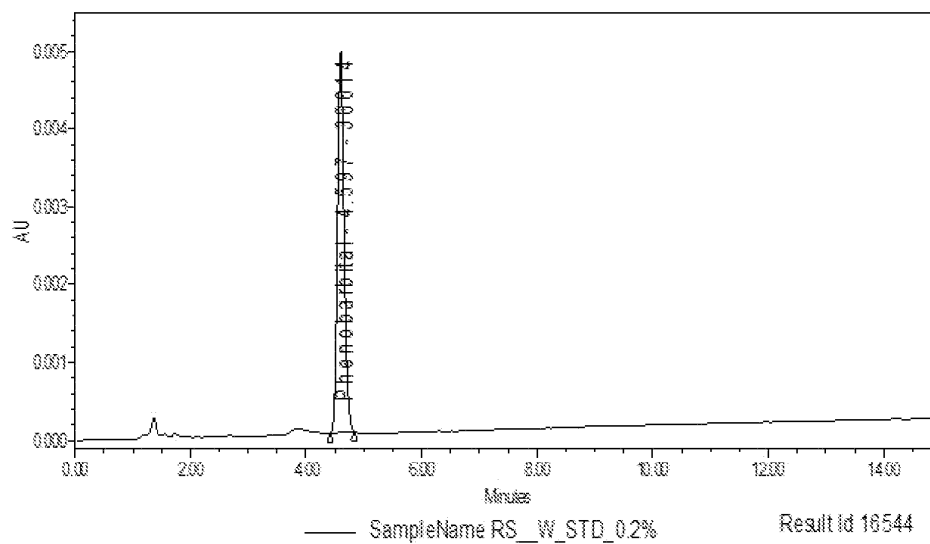


Fig. 2B



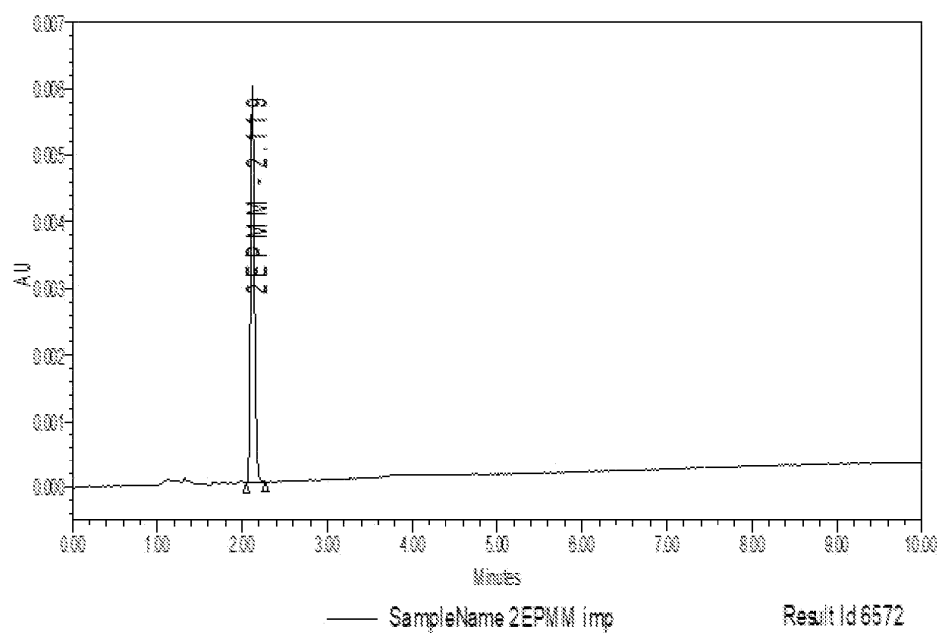
	PeakName	RT	Area	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.587	9769	1054.848570	7861.1	1.1

Fig. 2C



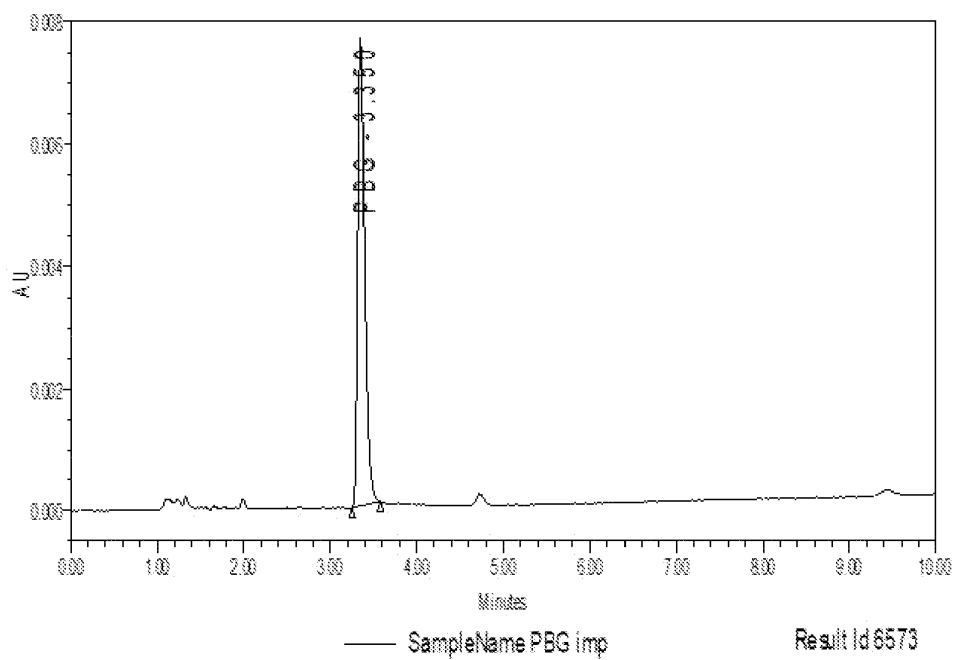
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1	Phenobarbital	4.597	38614	0.001	2906.846635	7746.3	1.2

Fig. 2D



	PeakName	RT	Area	% Area	sh	USP Plate Count	USP Tailing	Purity/ Angle	Purity/ Threshold
1	2EPNM	2.119	18797	100.00	1472	10573.6	1.2	0.674	1.833

Fig. 2E



	PeakName	RT	Area	%Area	sh	USP Rate Count	USP Tailing	Purity/ Angle	Purity/ Threshold
1	PBG	3.350	41776	100.00	2090	88019	1.5	21.646	62.962

Fig. 2F

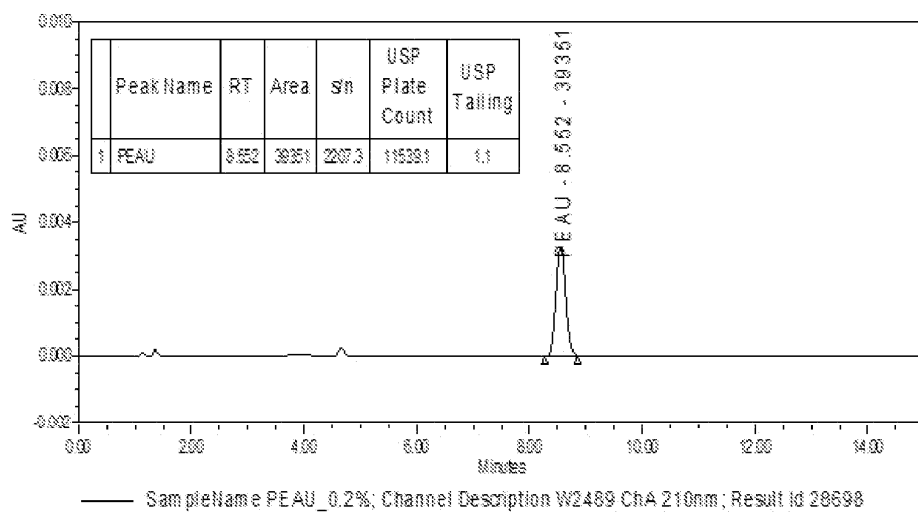


Fig. 2G

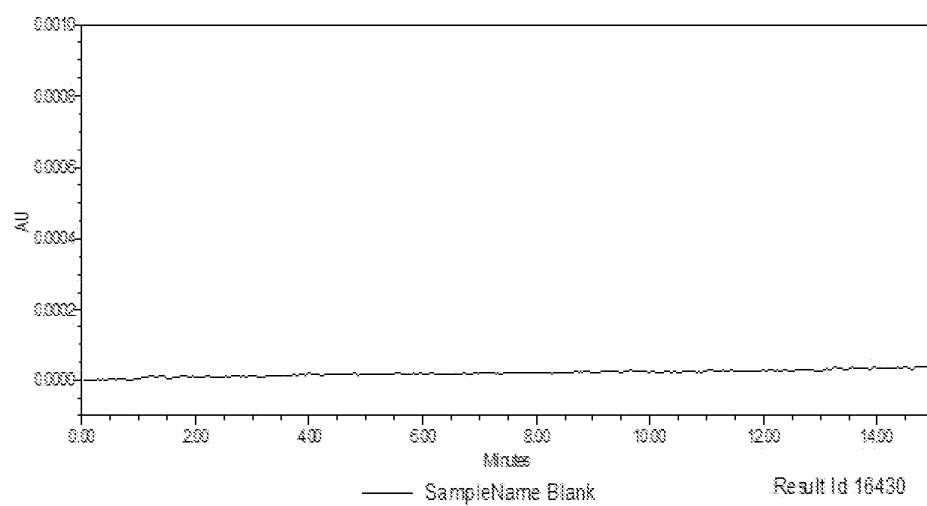
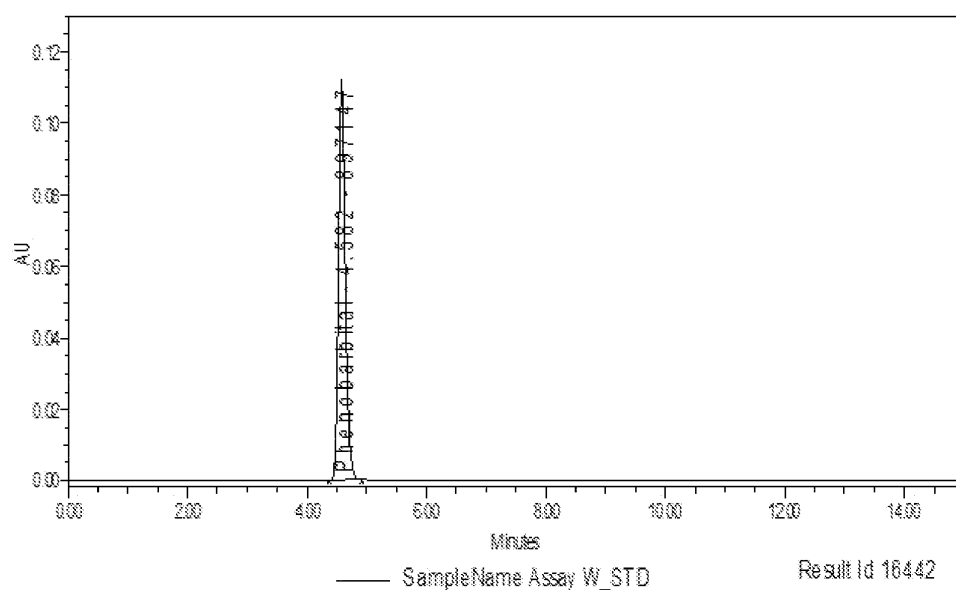
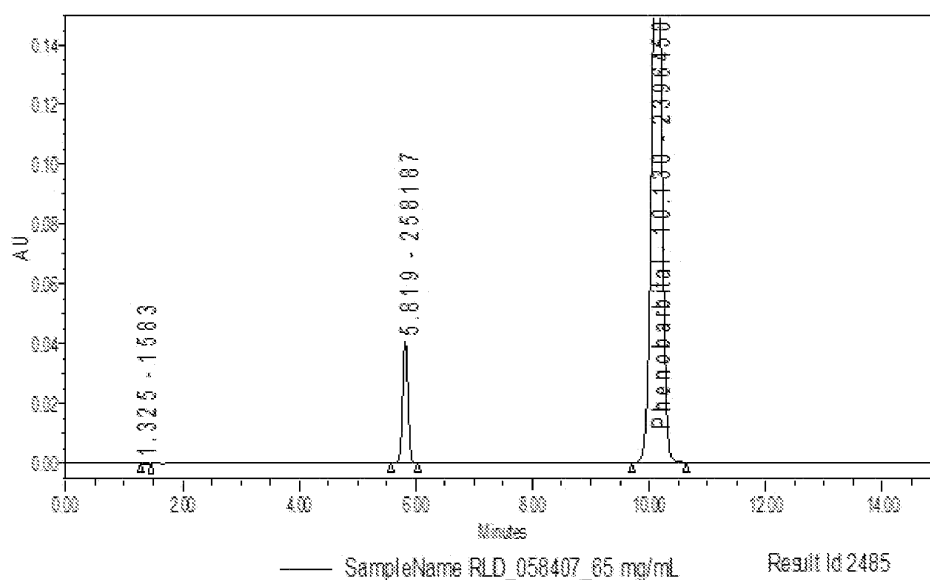


Fig. 2H



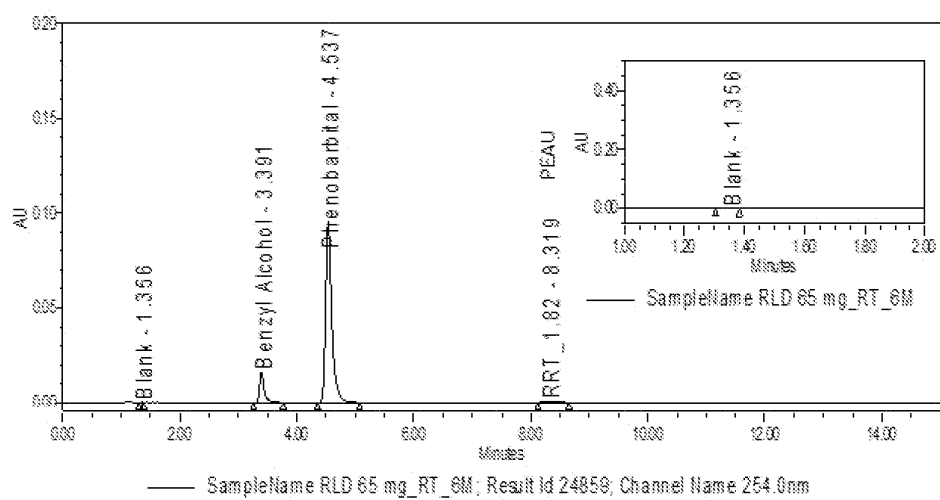
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.582	897147	0.476	50940.058185	7493.0	1.2

Fig. 3A



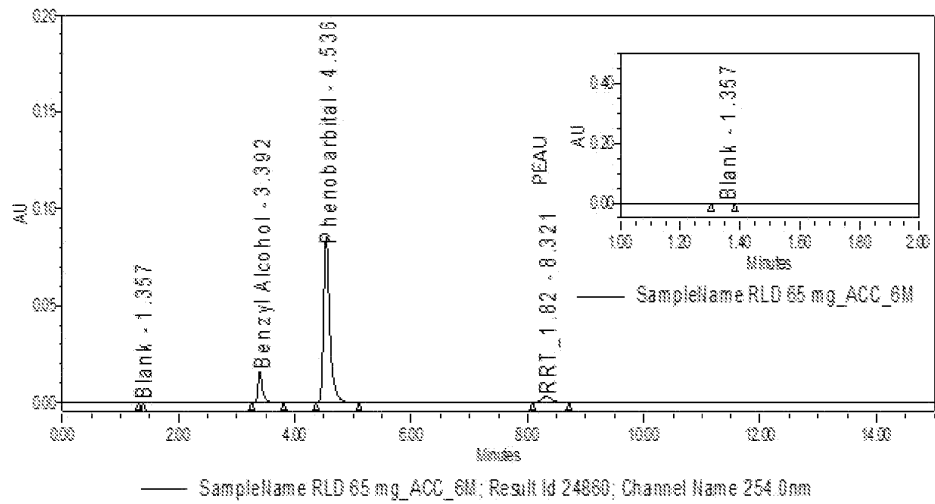
	PeakName	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.130	2396458	60.823	17.9	17534.1	1.0	112.1

Fig. 3B



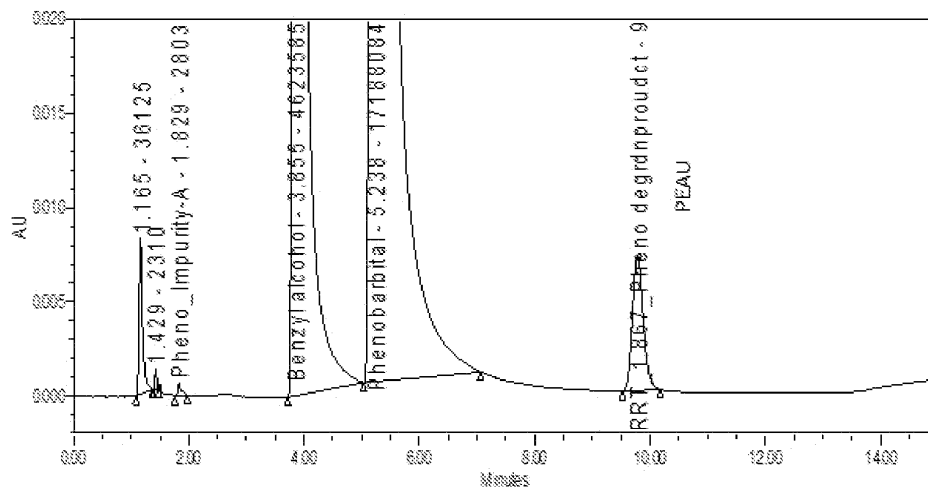
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	87091	10.96	14.994	mg/mL	105.2	23.7	1.7
2	Blank	1.356	828	0.10	0.068	mg/mL			1.0
3	Phenobarbital	4.537	697184	87.71	57.200	mg/mL	96.3	7.2	1.5
4	RRT_1.82	8.319	9745	1.23	0.800	mg/mL		15.0	1.3

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

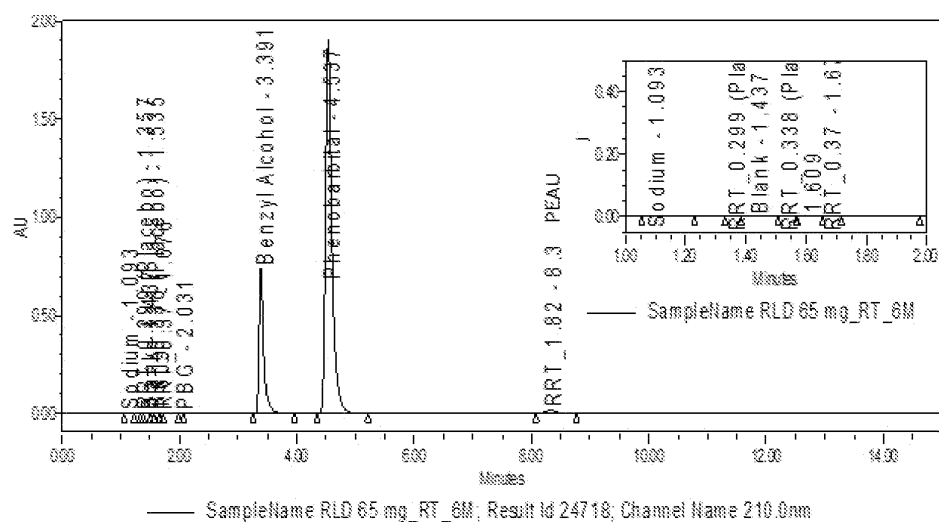
Fig. 3D



SampleName RLD_058407_65 mg/mL; Channel Description 2998 (205-400)nm; Result Id 3537

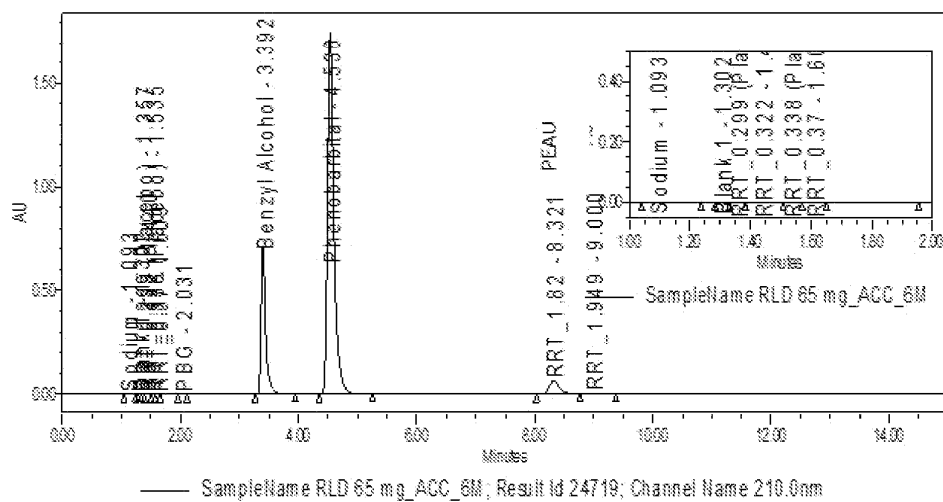
	Peak Name	RT	Area	% Area	USP Resolution	sn	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.855	4623585	21.07	17.1	390.1	12312.6	1.5
2	Pheno_impurityA	1.829	2803	0.01	5.2	0.3	7608.2	1.6
3	Phenobarbital	5.238	17188084	78.32	8.0	1015.9	11239.0	1.4
4	RR_1.867_Phenol degradation product	9.781	92997	0.42	16.5	3.5	13191.8	1.2

Fig. 3E



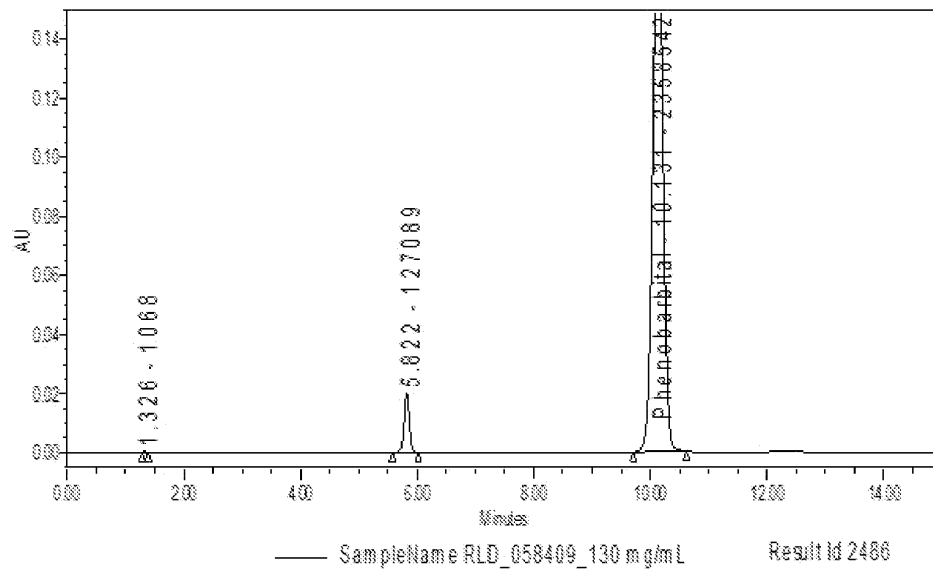
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	3972837	21.25	16.272	mg/mL	13.8	1.7
2	Phenobarbital	4.537	14515521	77.64	56.435	mg/mL	7.1	1.5
3	RRT_1.82	8.321	200110	1.07	0.778	mg/mL	14.5	1.3

Fig. 3F



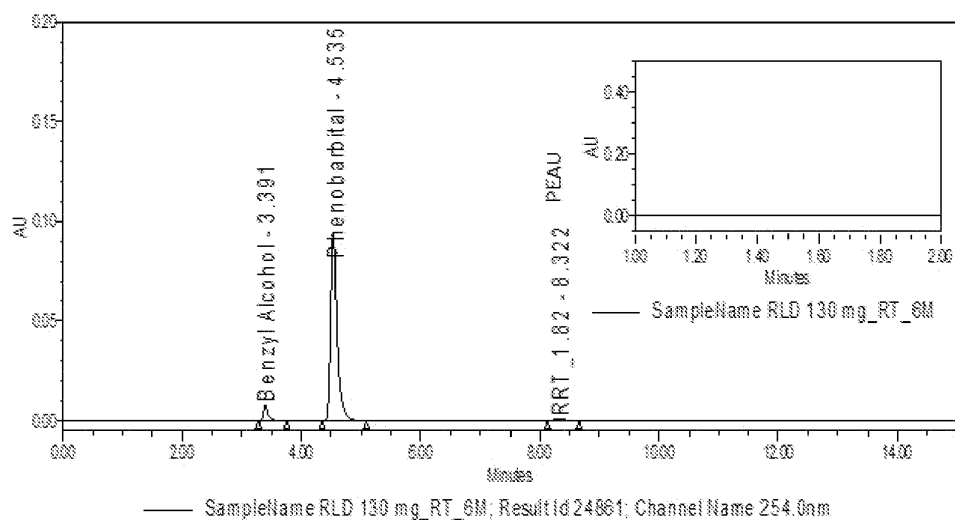
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	3833550	21.50	15.701	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13183528	73.94	51.257	mg/mL	7.1	1.5
3	RRT_1.82	8.321	762556	4.28	2.965	mg/mL	14.6	1.3
4	RRT_1.949	9.000	42716	0.24	0.165	mg/mL	1.9	1.3

Fig. 3G



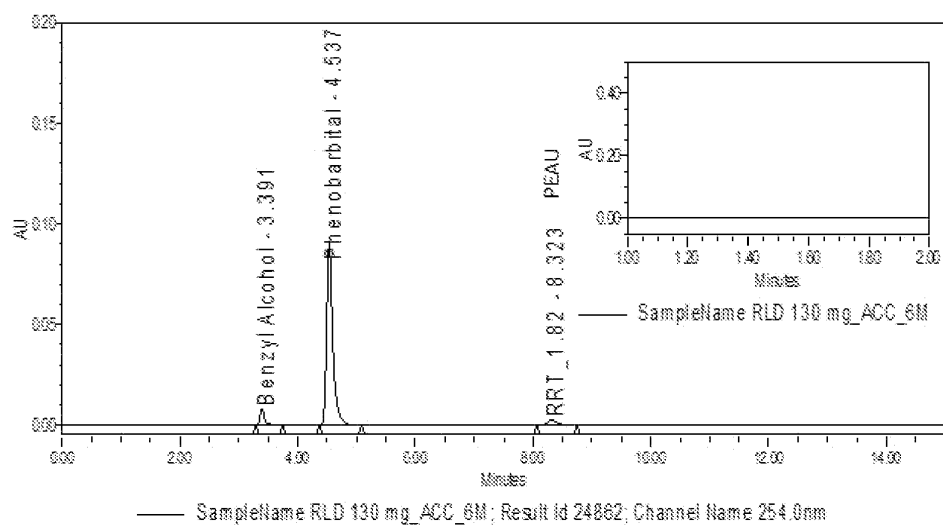
	PeakName	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.131	2358542	119.721	17.9	17563.1	1.0	110.3

Fig. 3H



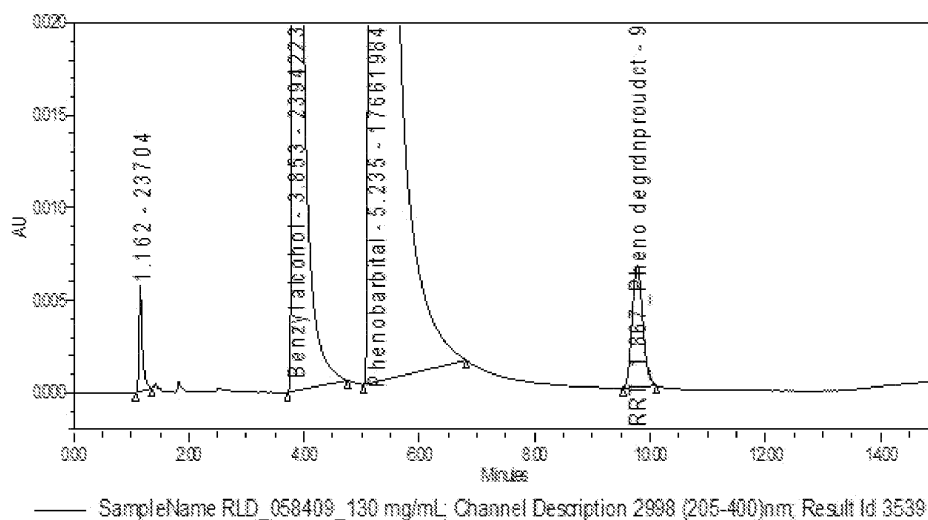
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43232	5.84	14.886	mg/mL	104.5		1.7
2	Phenobarbital	4.535	688747	93.10	113.015	mg/mL	95.2	7.2	1.5
3	RRT_1.82	8.322	7837	1.06	1.286	mg/mL		14.5	1.2

Fig. 3I



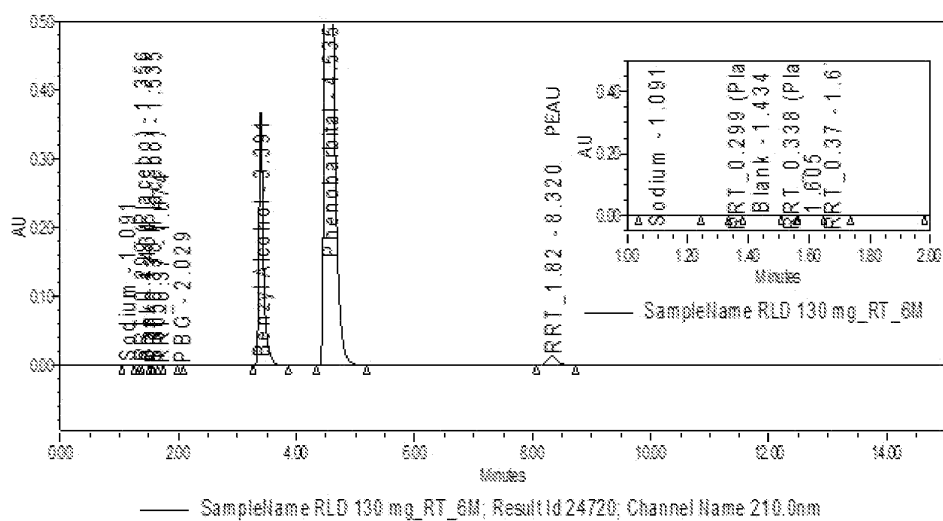
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43440	5.94	14.958	mg/mL	105.0		1.7
2	Phenobarbital	4.537	657548	89.99	107.895	mg/mL	90.9	7.2	1.5
3	RRT_1.82	8.323	29742	4.07	4.880	mg/mL		14.6	1.2

Fig. 3J



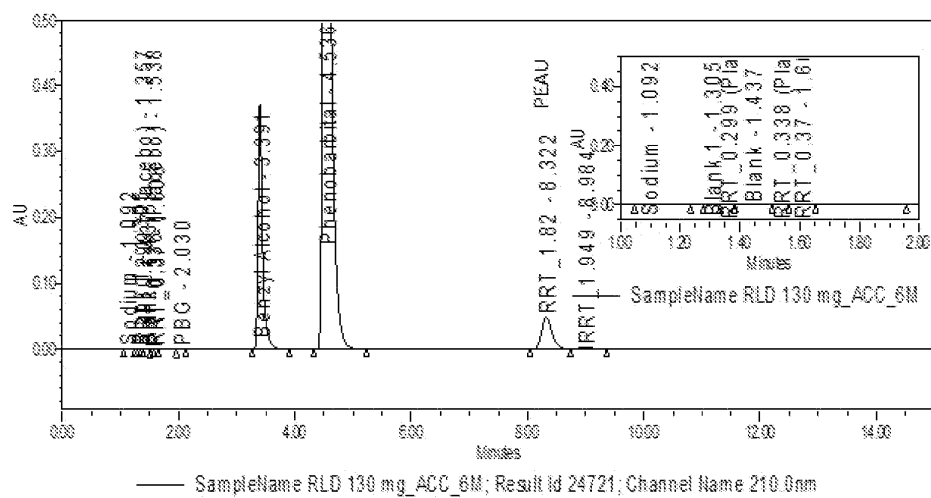
	PeakName	RT	Area	%Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzylalcohol	3.853	2394223	11.87	20.8	223.9	12436.0	1.5
2	Phenobarbital	5.235	17661984	87.99	9.0	1144.4	11214.3	1.4
3	RRT_1.967_Phenobarbital degradation product	9.776	63640	0.41	16.6	3.5	19512.7	1.1

Fig. 3K



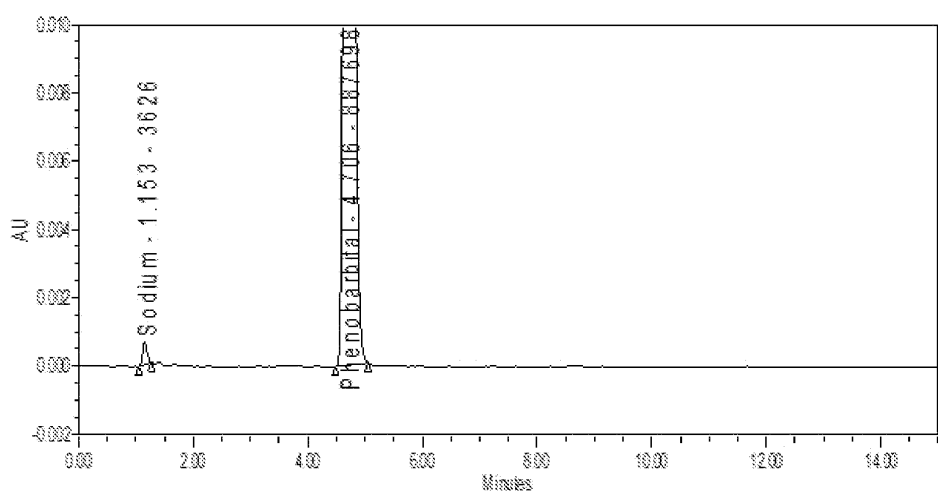
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1963213	11.91	16.081	mg/mL	13.4	1.7
2	Phenobarbital	4.535	14347574	87.06	111.585	mg/mL	7.1	1.5
3	RRT_1.82	8.320	162820	0.99	1.265	mg/mL	14.6	1.3

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

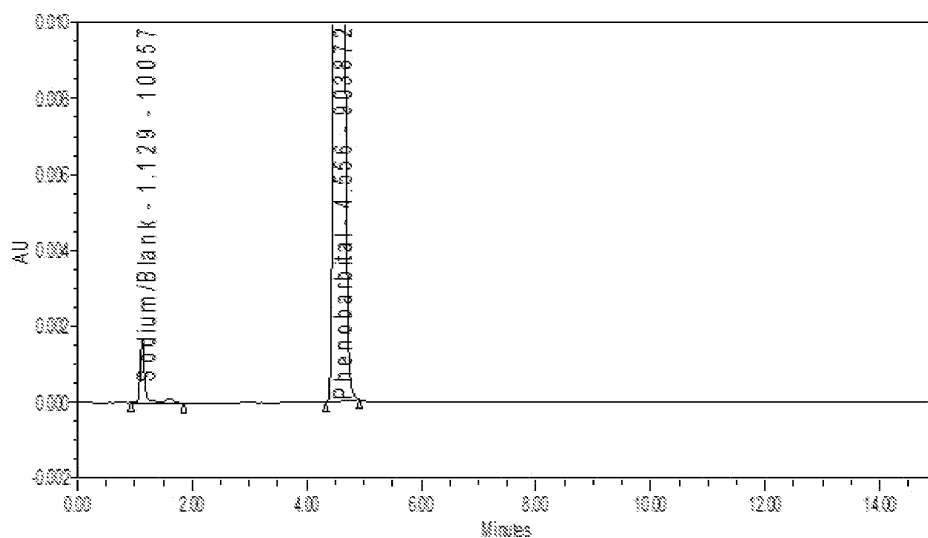
Fig. 4A



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

	PeakName	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	7892.5	1.2
2	Sodium	1.153	3625					318.4	943.9	1.1

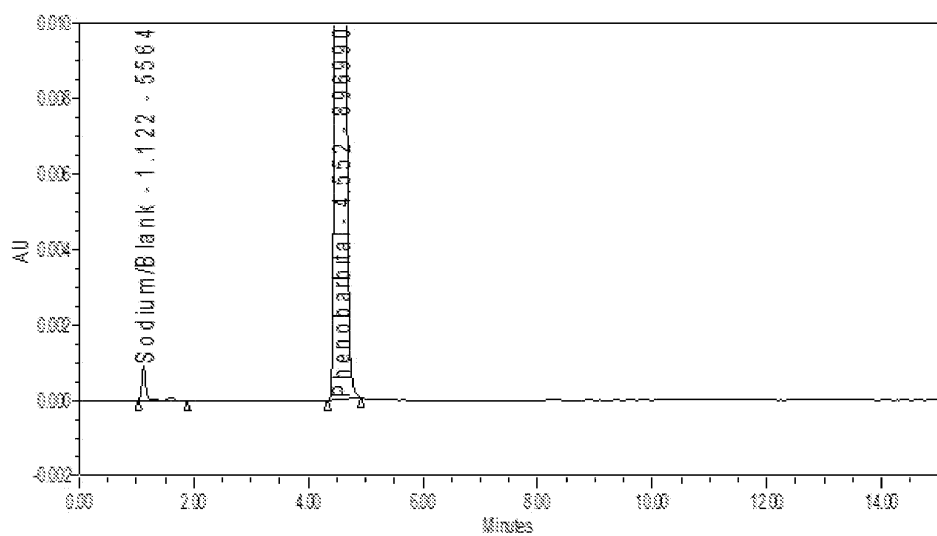
Fig. 4B



SampleName NPH1907_65mg_RT_6M; Channel Description W2489 ChB 254nm; Result Id 31317

	PeakName	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	44622.6	8704.0	1.1
2	Sodium/Blank	1.129	10057	0.661	mg/mL			616.7	1292.0	1.3

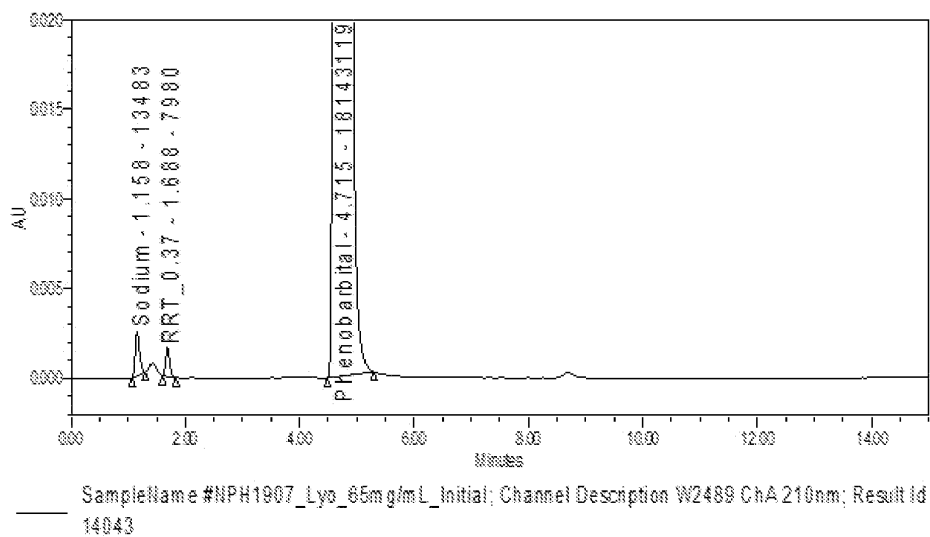
Fig. 4C



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

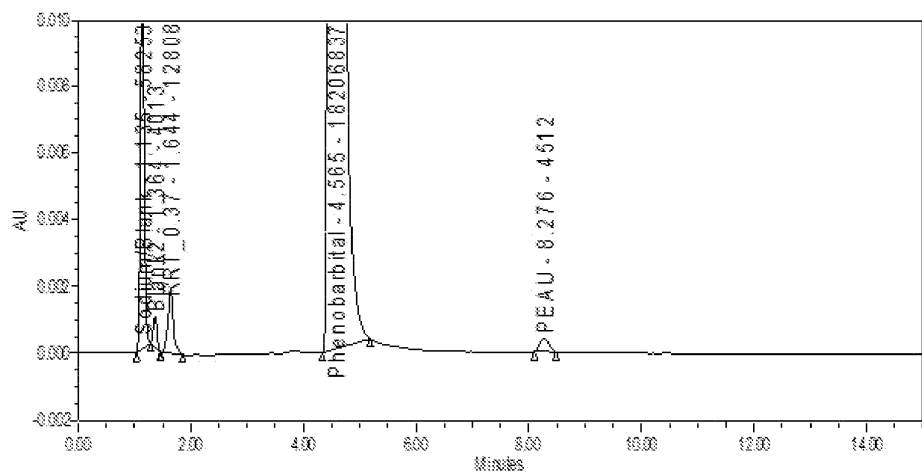
	Peak Name	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.552	896890	58.936	mg/mL	99.3	21.1	48295.1	8573.3	1.1
2	Sodium/Blank	1.122	5564	0.366	mg/mL			364.9	1275.7	1.3

Fig. 4D



	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.715	18143119	99.98	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

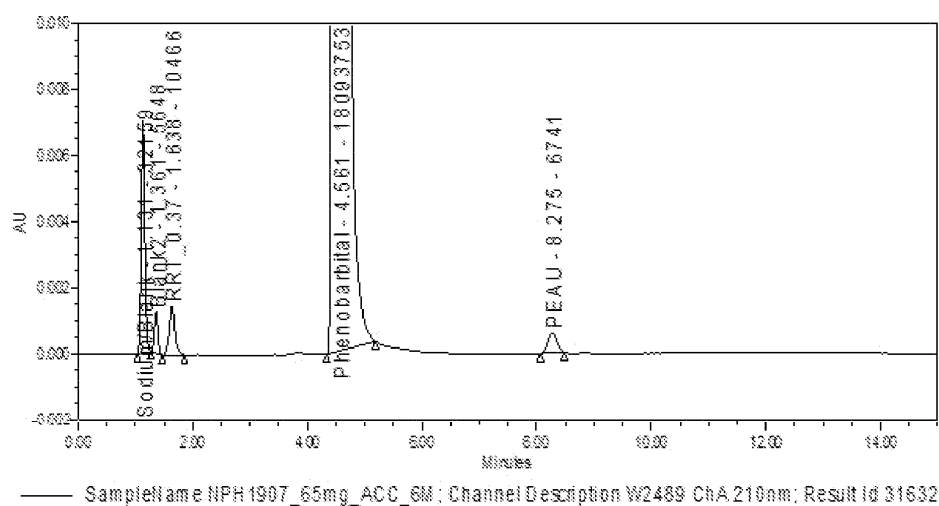
Fig. 4E



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

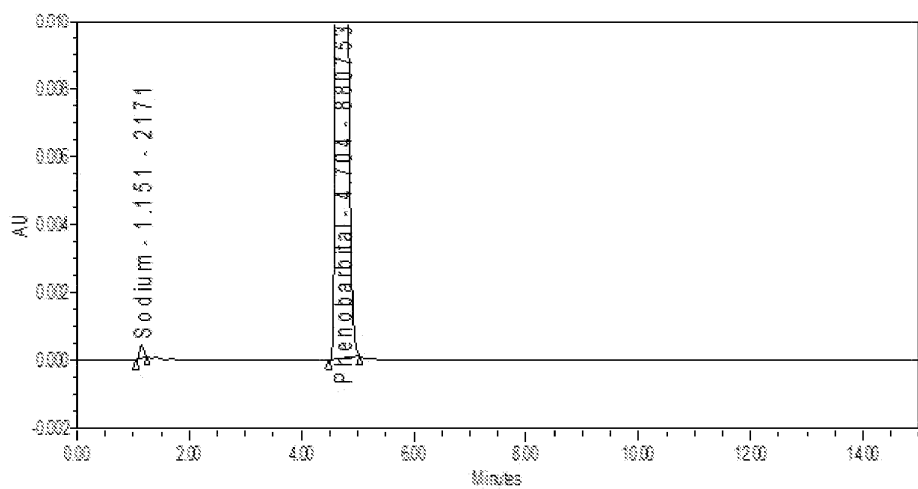
	PeakName	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.364	4010	0.02			19	625.1	2241.7	1.1
2	PEAU	8.276	4512	0.02	0.013	mg/mL	14.8	278.0	62299.1	1.1
3	Phenobarbital	4.565	18206837	98.56	53.971	mg/mL	15.2	9516675.4	82389.9	1.1
4	RRT_0.37	1.644	12606	0.07	0.036	mg/mL	1.9	1278.5	1640.7	1.1
5	SodiumBlank	1.135	50253	0.32	0.173	mg/mL		6406.1	13633.0	1.1

Fig. 4F



	PeakName	RT	Area	% Area	Amount	Units	USP Resolution	sn	USP Plate Count	USP Tailing
1	Blank2	1.361	5546	0.03			1.9	899.0	2140.9	1.0
2	PEAU	8.275	6741	0.04	0.020	mg/mL	14.6	427.7	11816.8	1.0
3	Phenobarbital	4.561	18093753	99.79	53.636	mg/mL	15.2	1033106.6	8445.9	1.1
4	RRT_0.37	1.638	10496	0.06	0.021	mg/mL	1.9	1054.2	1482.5	1.1
5	SodiumBlank	1.131	32199	0.18	0.095	mg/mL		4912.0	1362.2	1.1

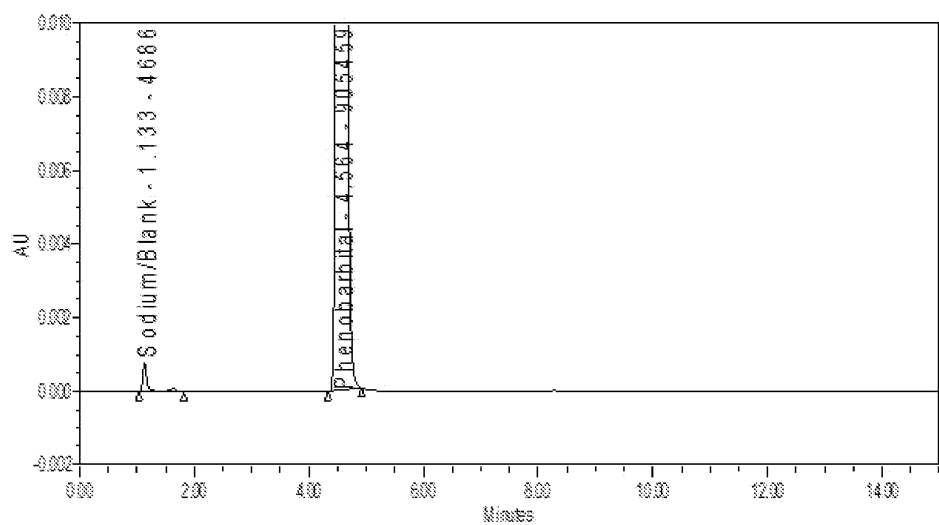
Fig. 4G



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	193	40192.1	7866.8	1.2
2	Sodium	1.151	2171					148.3	9590	1.0

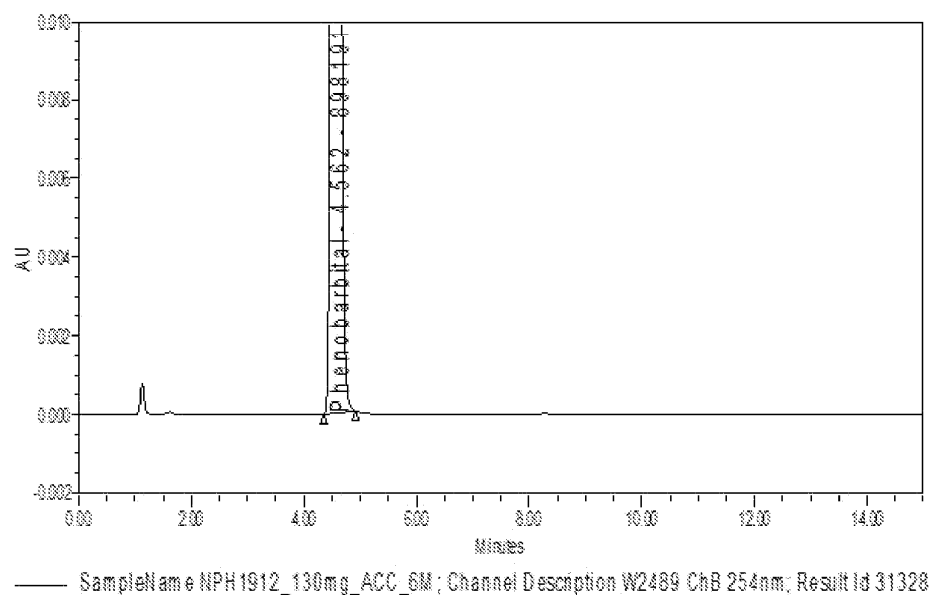
Fig. 4H



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

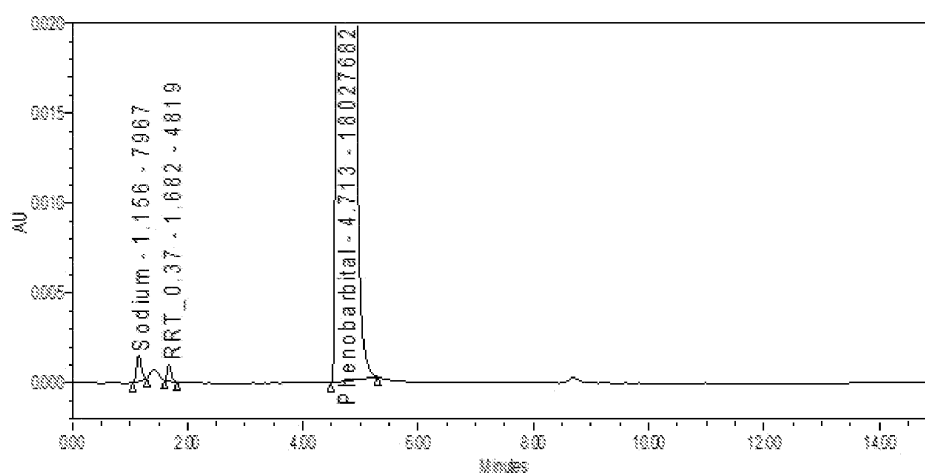
	PeakName	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.564	905459	116.985	mg/mL	100.2	20.7	55858.2	3639.9	1.1
2	Sodium/Blank	1.133	4686	0.616	mg/mL			358.4	1396.2	1.4

Fig. 4I



	Peak Name	RT	Area	Amount	Units	Assay	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.562	896191	118.030	mg/mL	99.4	502755	86938	1.1

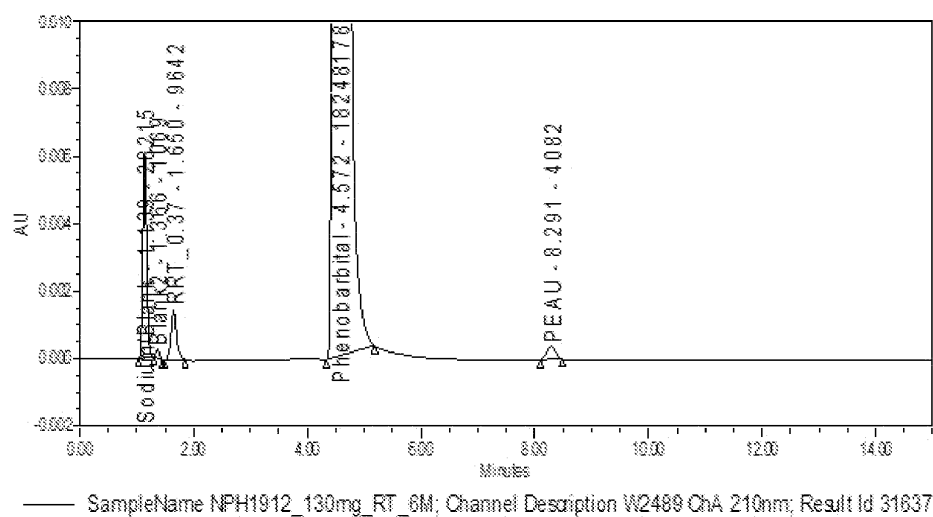
Fig. 4J



SampleName #NPH1912_Lyo_130mg/mL_Initial; Channel Description WZ489 ChA 210nm; Result Id 14048

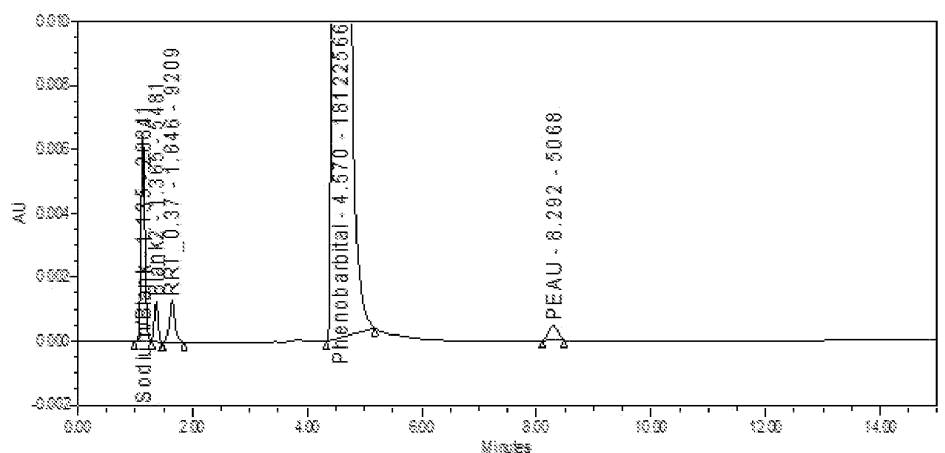
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.713	18027682	99.93	116.995	mg/mL	17.0	1001025.6	7649.3	1.2
2	RRT_0.37	1.682	4819	0.03	0.031	mg/mL	36	493.7	2491.3	1.2
3	Sodium	1.156	7967	0.04	0.052	mg/mL		649.1	941.5	1.1

Fig. 4K



	PeakName	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.386	1069	0.01			19	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	10248178	99.76	106.187	mg/mL	15.9	1373502.2	8426.5	1.1
4	RRT_0.37	1.650	9642	0.05	0.057	mg/mL	20	632.7	1818.4	1.1
5	SodiumBlank	1.139	28215	0.15	0.167	mg/mL		3438.2	1362.8	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	1.365	5481	0.03			1.9	687.2	2449.1	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	132358.2	6330.4	1.1
4	ERT_0.37	1.646	9209	0.05	0.055	mg/mL	1.8	725.3	1481.0	1.1
5	Sodium Blank	1.135	28641	0.16	0.171	mg/mL		3440.5	1382.8	1.1

Fig. 5A

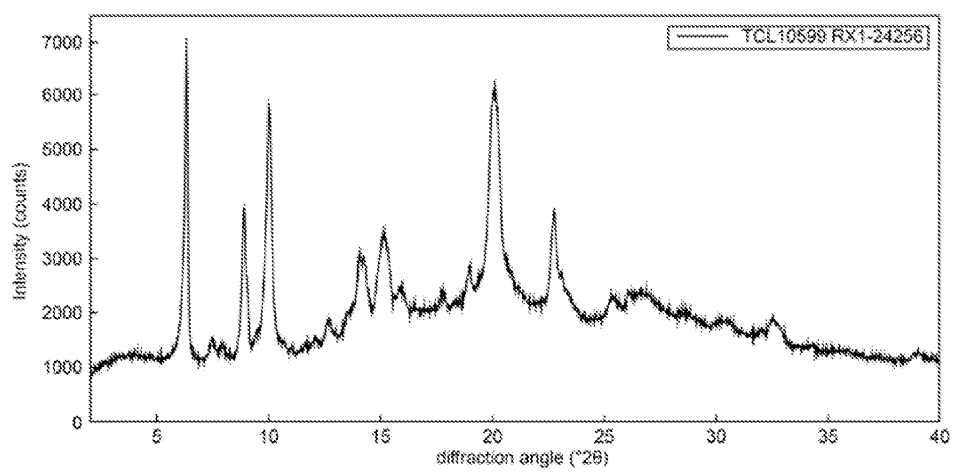


Fig. 5B

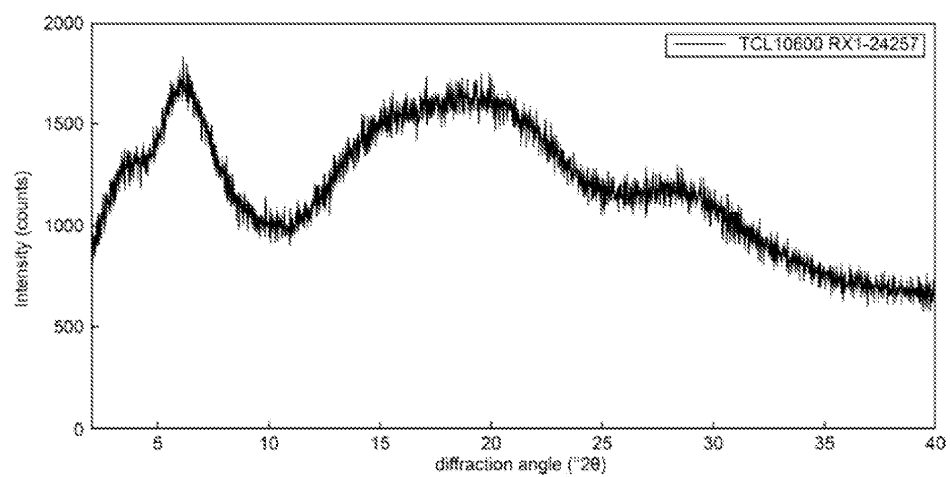


Fig. 5C

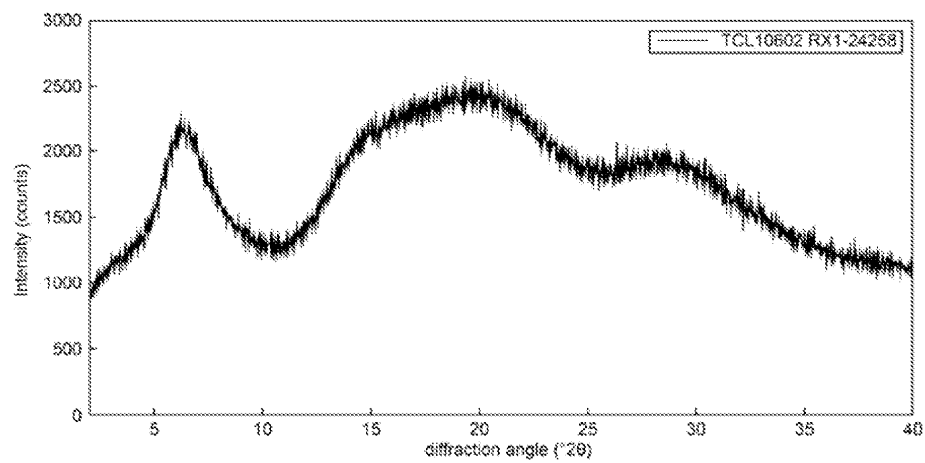


Fig. 5D

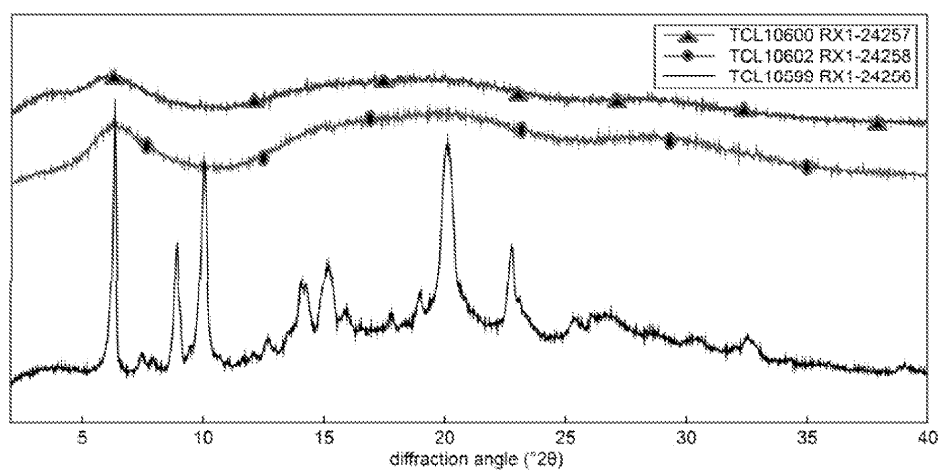


Fig. 1A



Fig. 1B



Fig. 1C



Fig. 1D



Fig. 1E



Fig. 1F



Fig. 2A

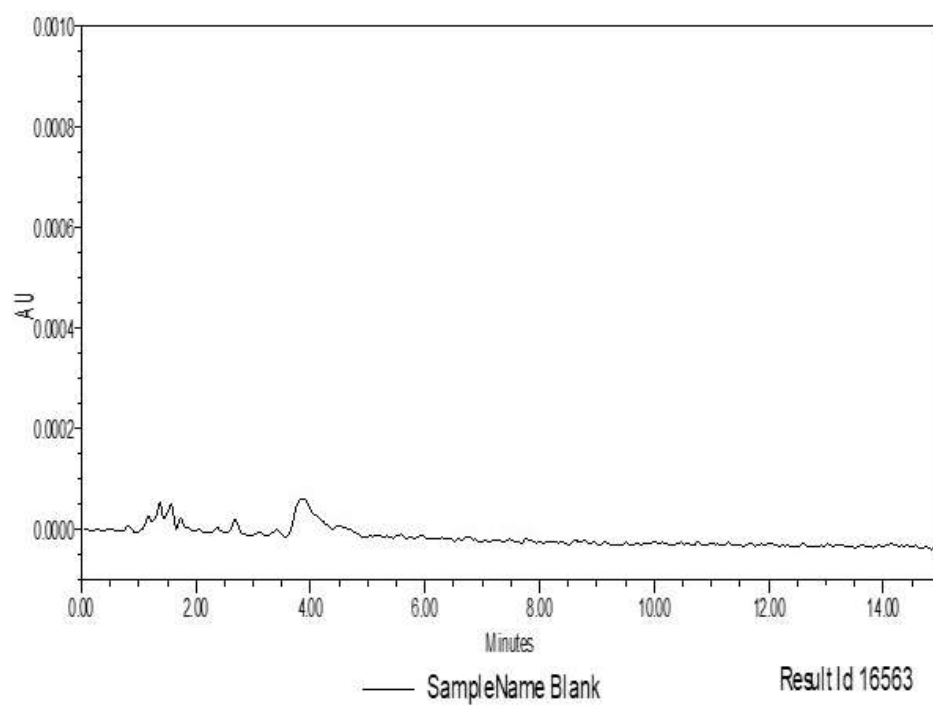
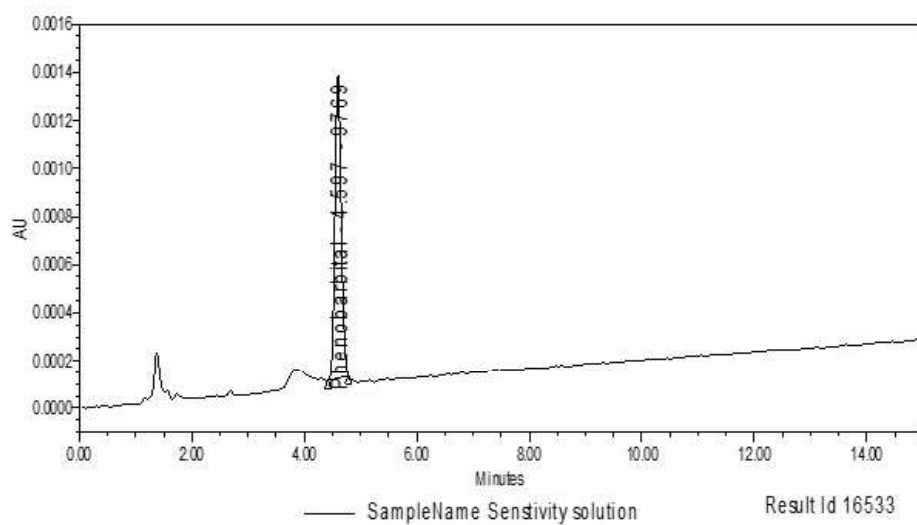
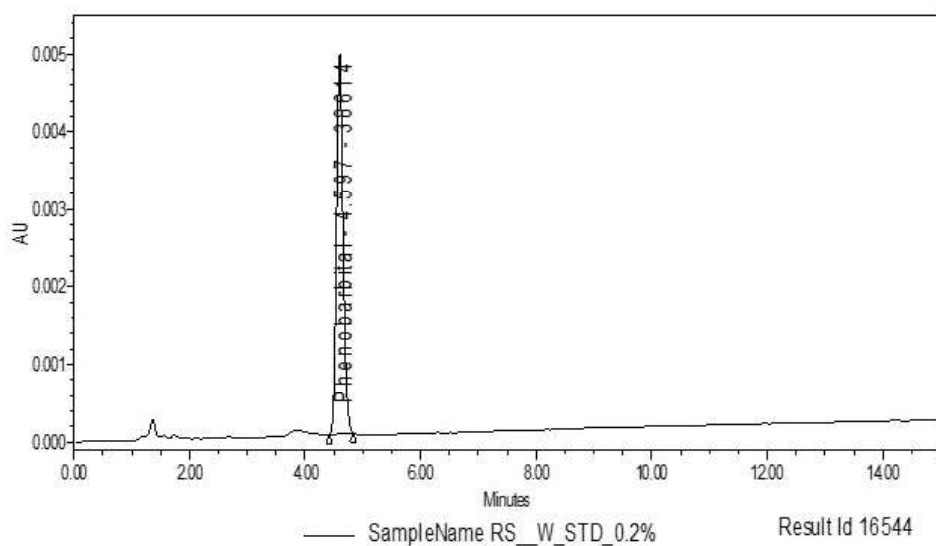


Fig. 2B



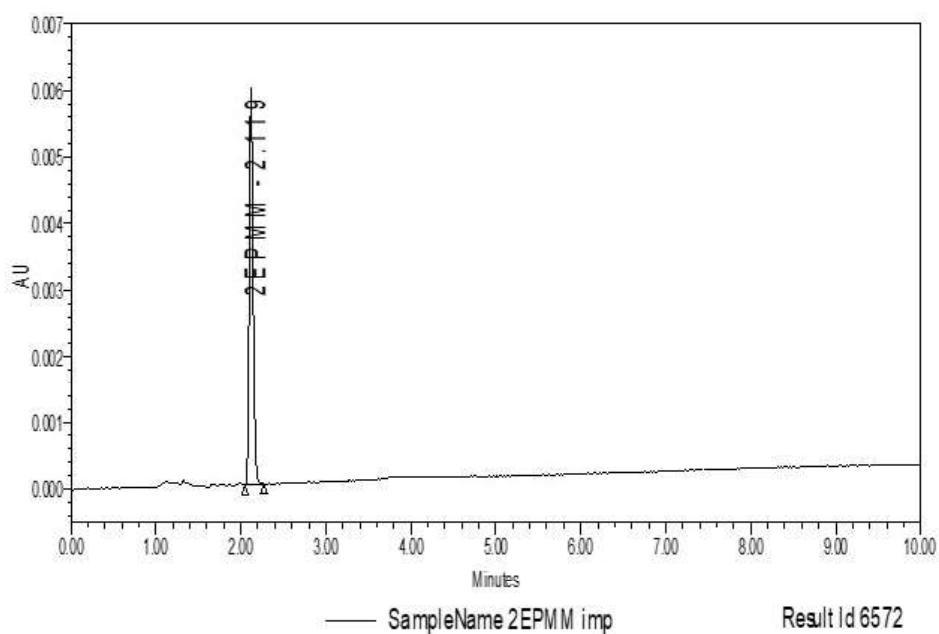
	Peak Name	RT	Area	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	9769	1054.848570	7861.1	1.1

Fig. 2C



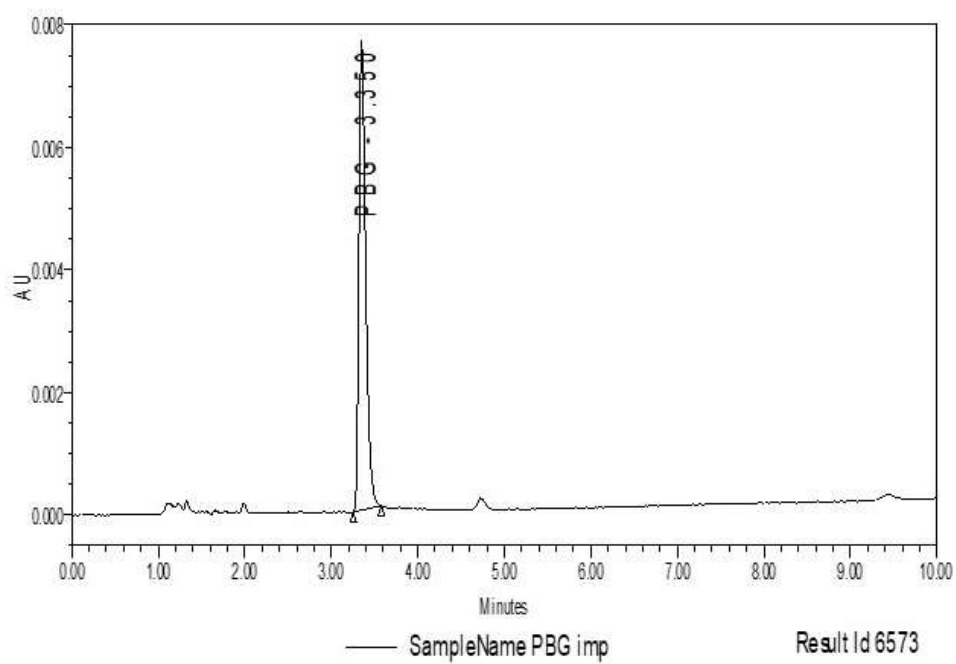
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.597	38614	0.001	2906.846635	7746.3	1.2

Fig. 2D



	PeakName	RT	Area	% Area	s/h	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/h	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

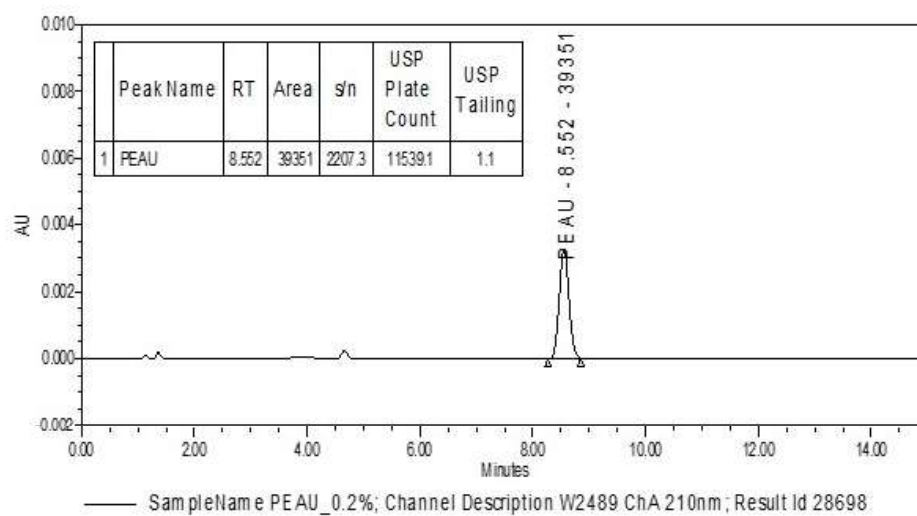


Fig. 2G

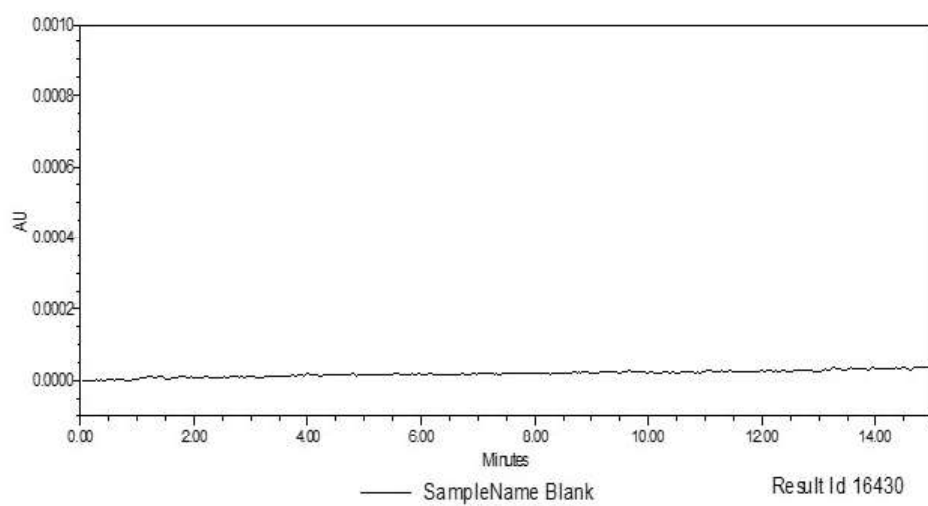
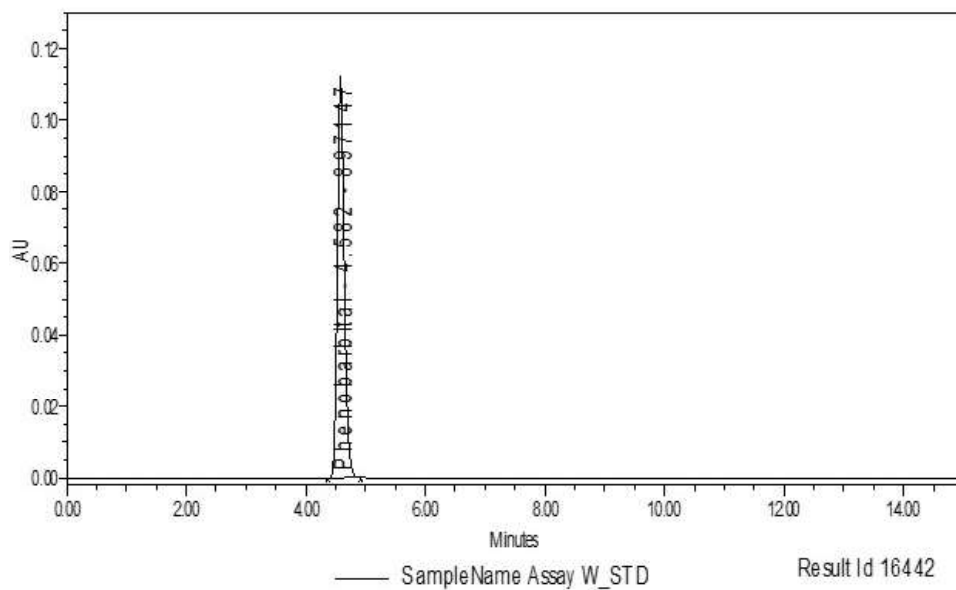
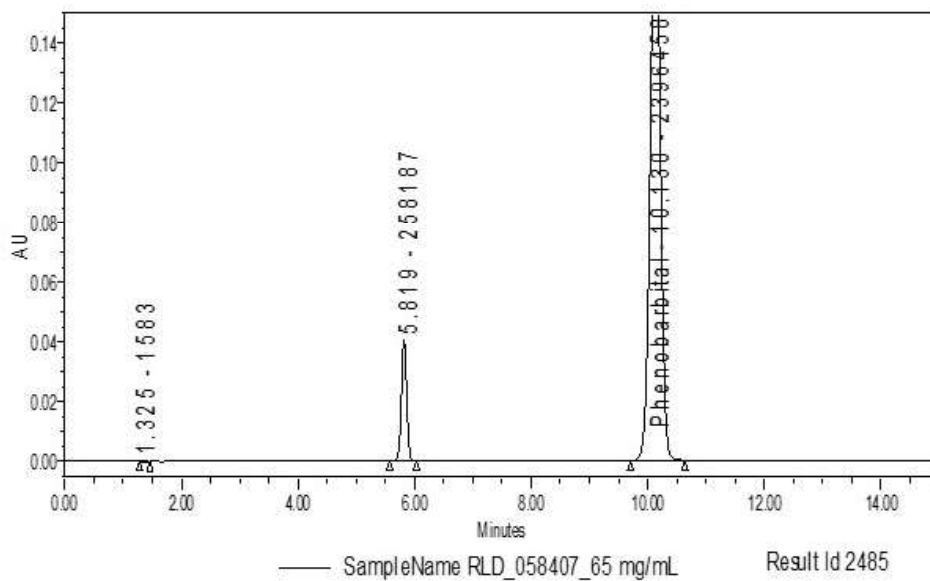


Fig. 2H



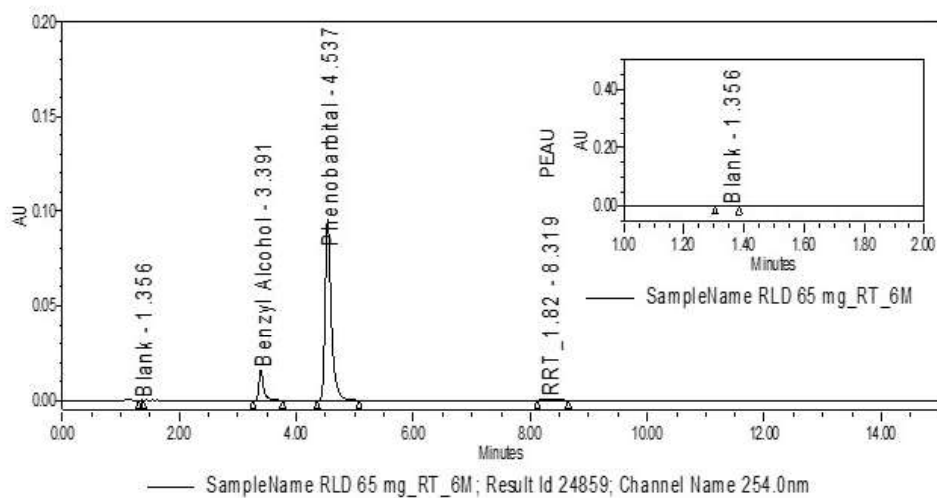
	PeakName	RT	Area	Amount	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.582	897147	0.476	50940.058185	7493.0	1.2

Fig. 3A



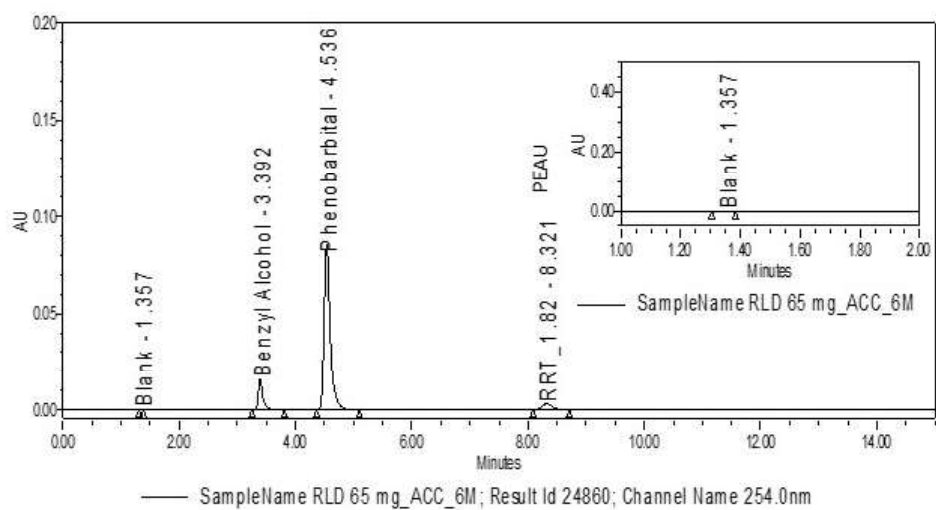
	PeakName	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.130	2396458	60.823	17.9	17534.1	1.0	112.1

Fig. 3B



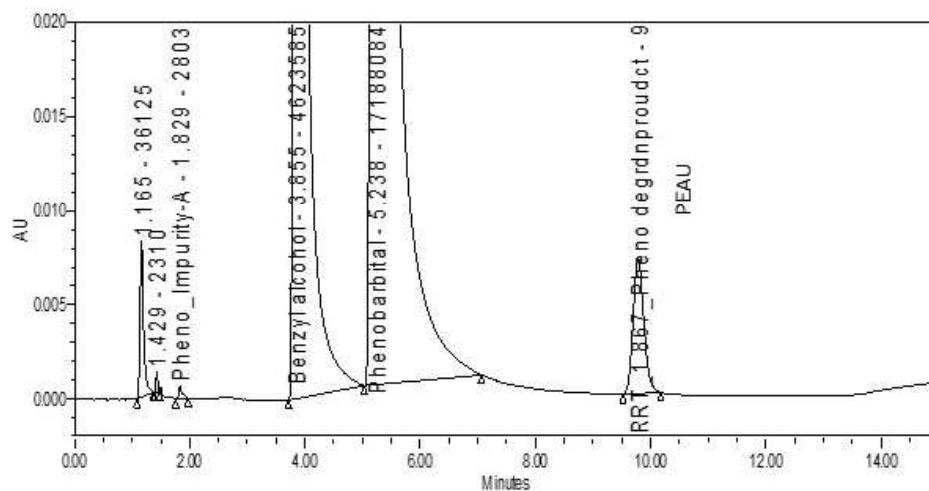
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	87091	10.96	14.994	mg/mL	105.2	23.7	1.7
2	Blank	1.356	828	0.10	0.068	mg/mL			1.0
3	Phenobarbital	4.537	697184	87.71	57.200	mg/mL	96.3	7.2	1.5
4	RRT_1.82	8.319	9745	1.23	0.800	mg/mL		15.0	1.3

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

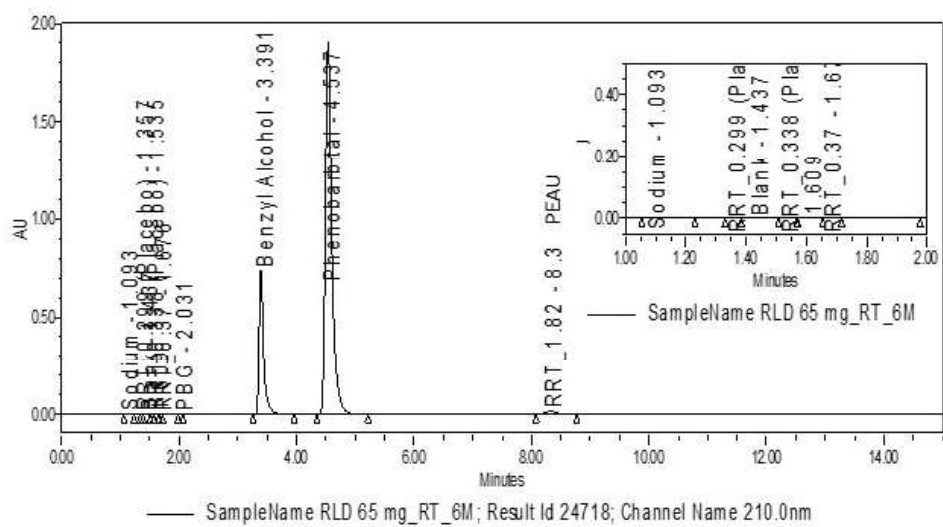
Fig. 3D



— SampleName RLD_058407_65 mg/mL; Channel Description 2998 (205-400)nm; Result Id 3537

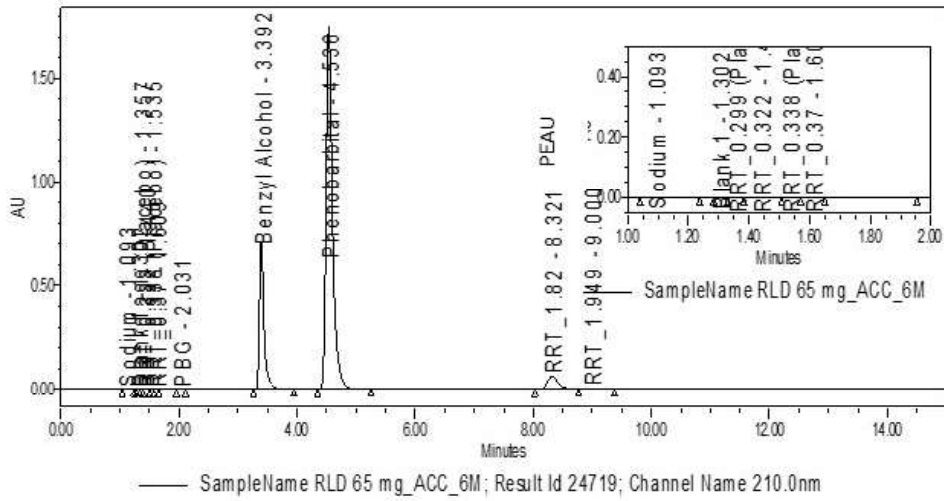
	PeakName	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.855	4623585	21.07	17.1	390.1	12312.8	1.5
2	Pheno_ImpurityA	1.829	2803	0.01	5.2	0.3	7608.2	1.6
3	Phenobarbital	5.238	17188084	78.32	8.0	1018.9	11239.0	1.4
4	RRT_1.867_Phenodegrinproduct	9.781	92937	0.42	16.5	3.5	13191.8	1.2

Fig. 3E



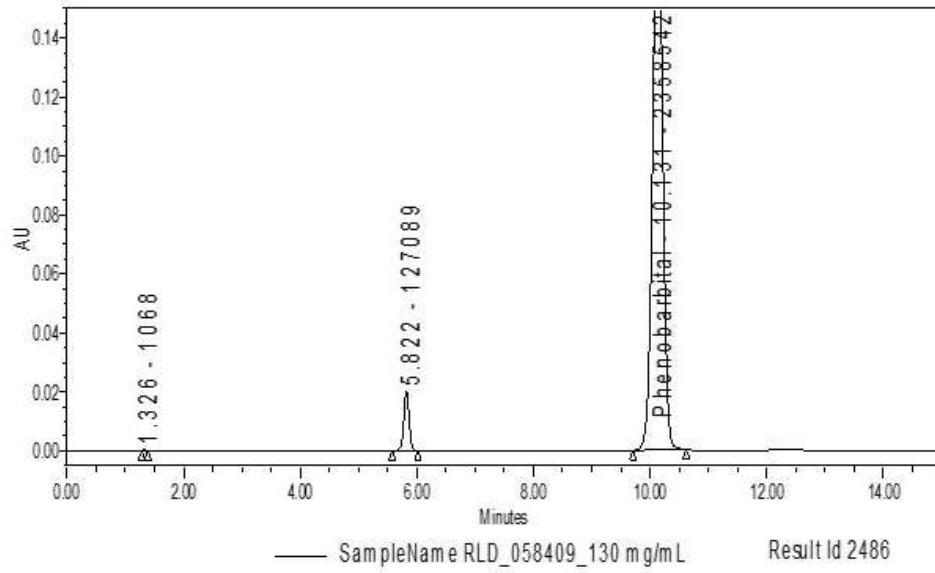
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	3972837	21.25	16.272	mg/mL	13.8	1.7
2	Phenobarbital	4.537	14515521	77.64	56.435	mg/mL	7.1	1.5
3	RRT_1.82	8.321	200110	1.07	0.778	mg/mL	14.6	1.3

Fig. 3F



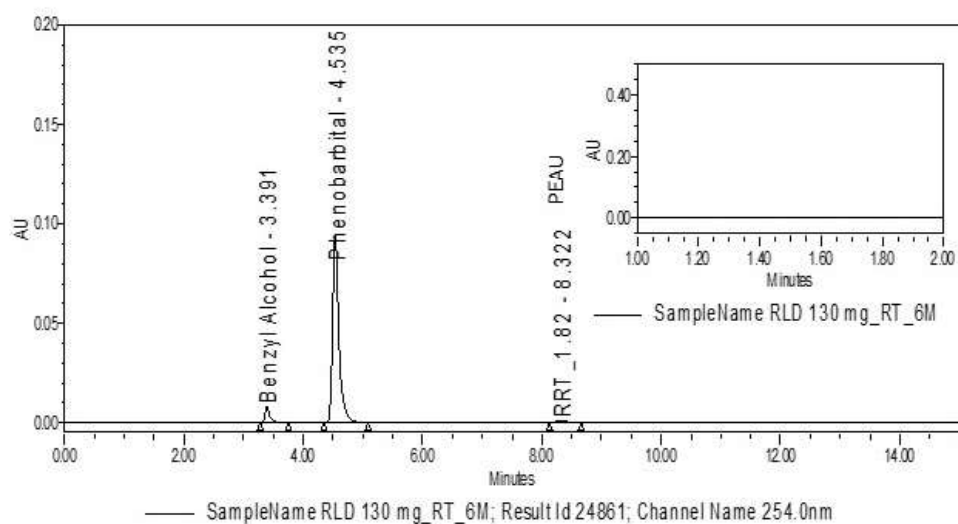
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.392	3833550	21.50	15.701	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13183528	73.94	51.257	mg/mL	7.1	1.5
3	RRT_1.82	8.321	762556	4.28	2.965	mg/mL	14.6	1.3
4	RRT_1.949	9.000	42716	0.24	0.166	mg/mL	1.9	1.3

Fig. 3G



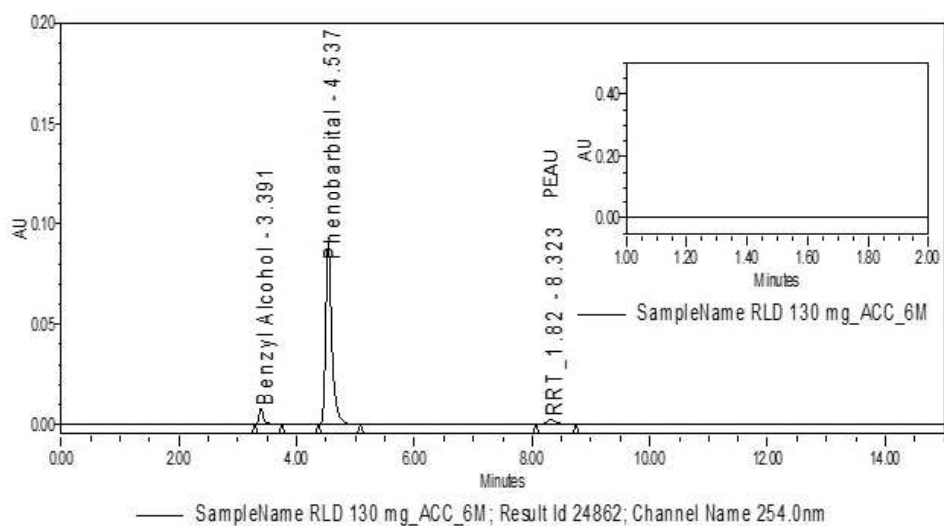
	PeakName	RT	Area	Amount	USP Resolution	USP Plate Count	USP Tailing	Assay
1	Phenobarbital	10.131	2358542	119.721	17.9	17563.1	1.0	110.3

Fig. 3H



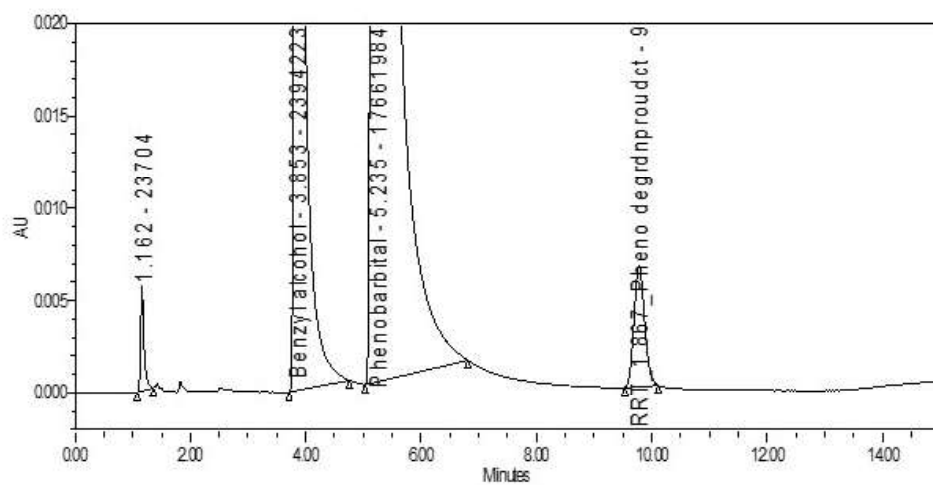
	Peak Name	RT	Area	% Area	Amount	Units	Assay	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	43232	5.84	14.886	mg/mL	104.5		1.7
2	Phenobarbital	4.535	688747	93.10	113.015	mg/mL	95.2	7.2	1.5
3	RRT_1.82	8.322	7837	1.06	1.286	mg/mL		14.5	1.2

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

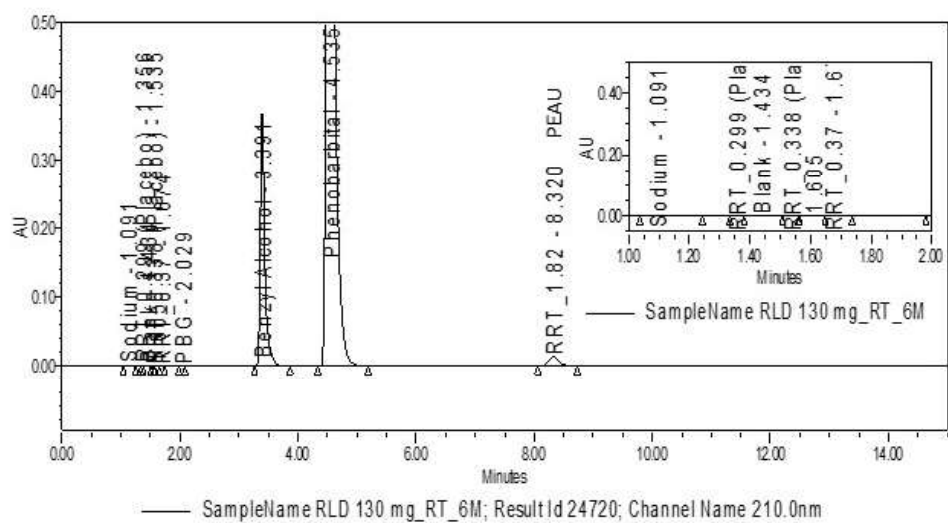
Fig. 3J



SampleName RLD_058409_130 mg/mL; Channel Description 2998 (205-400)nm; Result Id 3539

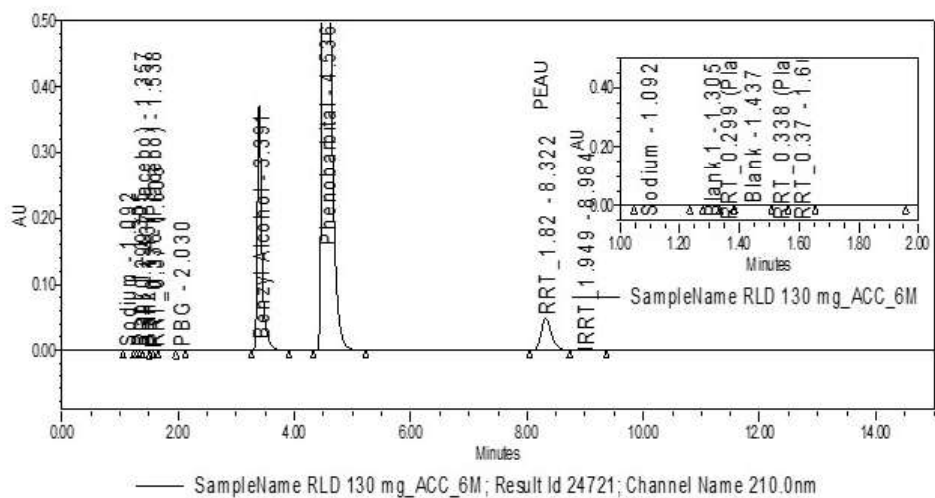
	PeakName	RT	Area	% Area	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Benzyl alcohol	3.853	2394223	11.87	20.8	2239	12438.0	15
2	Phenobarbital	5.235	17661984	87.59	8.0	1144.4	11214.3	14
3	RR1.867_Pheno degrdnprouct	9.776	83640	0.41	16.6	3.5	13612.7	11

Fig. 3K



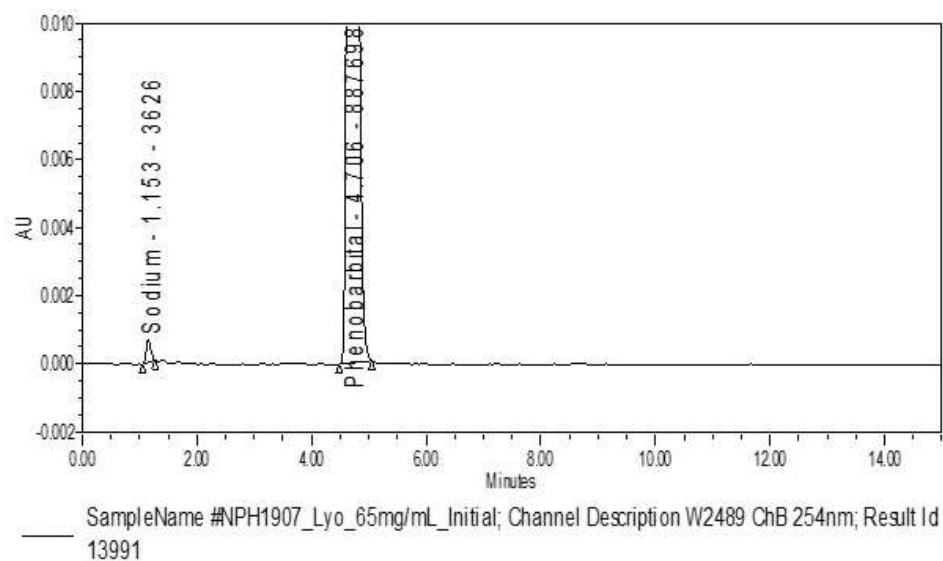
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1963213	11.91	16.081	mg/mL	13.4	1.7
2	Phenobarbital	4.535	14347574	87.06	111.565	mg/mL	7.1	1.5
3	RRT_1.82	8.320	162620	0.99	1.265	mg/mL	14.6	1.3

Fig. 3L



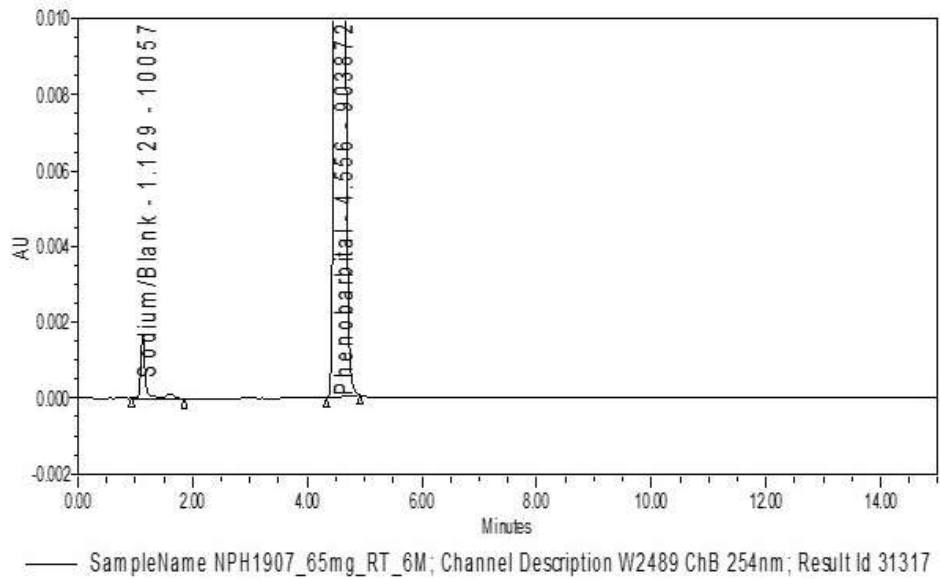
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	USP Tailing
1	Benzyl Alcohol	3.391	1984788	12.10	16.258	mg/mL	12.8	1.7
2	Phenobarbital	4.536	13768702	83.93	107.064	mg/mL	7.1	1.5
3	RRT_1.82	8.322	594916	3.63	4.626	mg/mL	14.6	1.2
4	RRT_1.949	8.984	48228	0.29	0.375	mg/mL	1.8	1.3

Fig. 4A



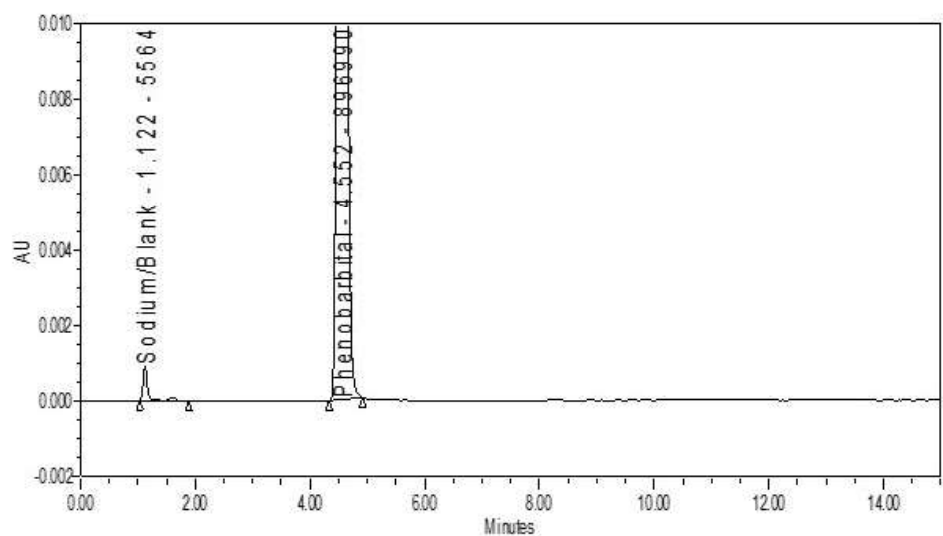
	PeakName	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.706	887698	58.858	mg/mL	99.1	193	52343.5	7952.5	1.2
2	Sodium	1.153	3626					318.4	943.9	1.1

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			616.7	1292.0	1.3

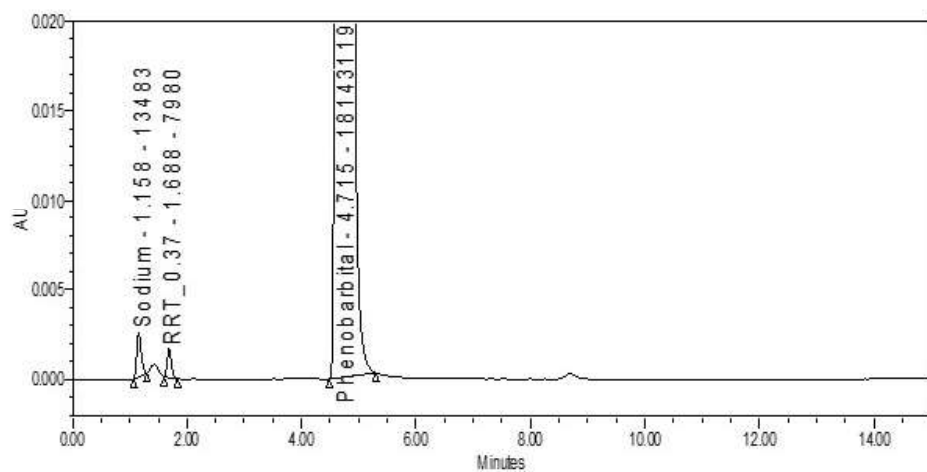
Fig. 4C



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	1275.7	1.3

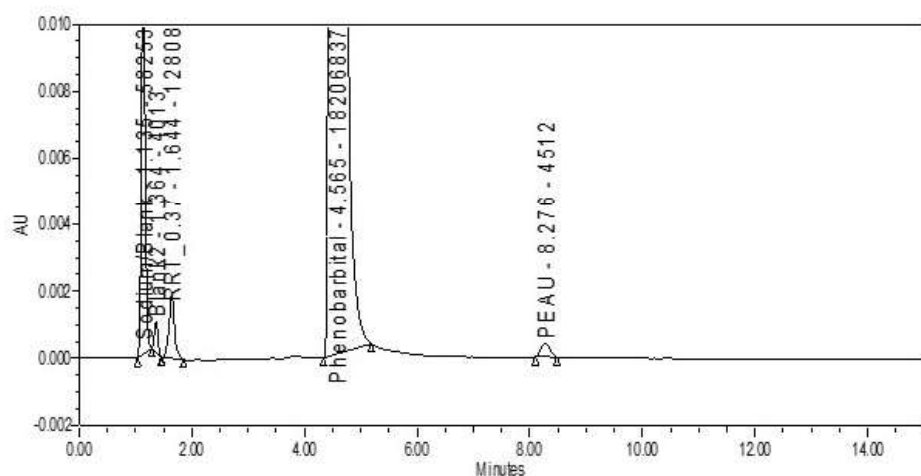
Fig. 4D



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	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

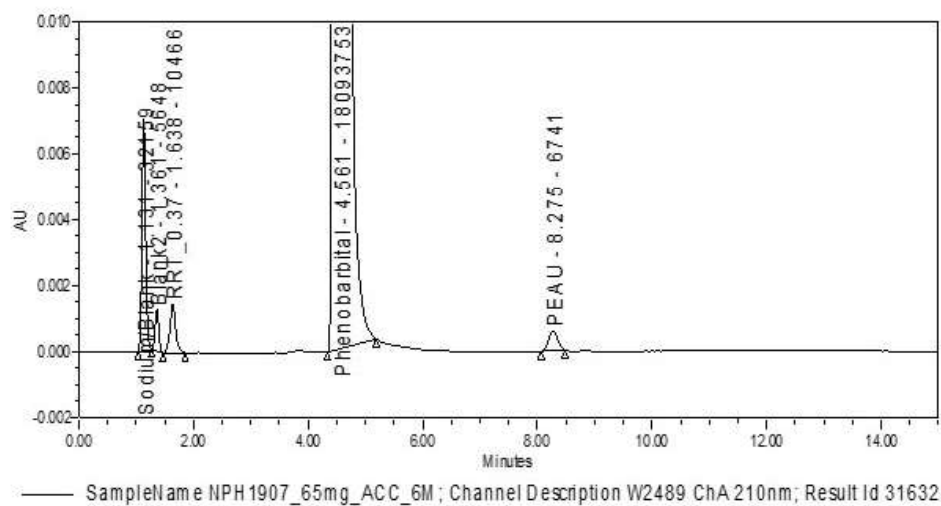
Fig. 4E



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

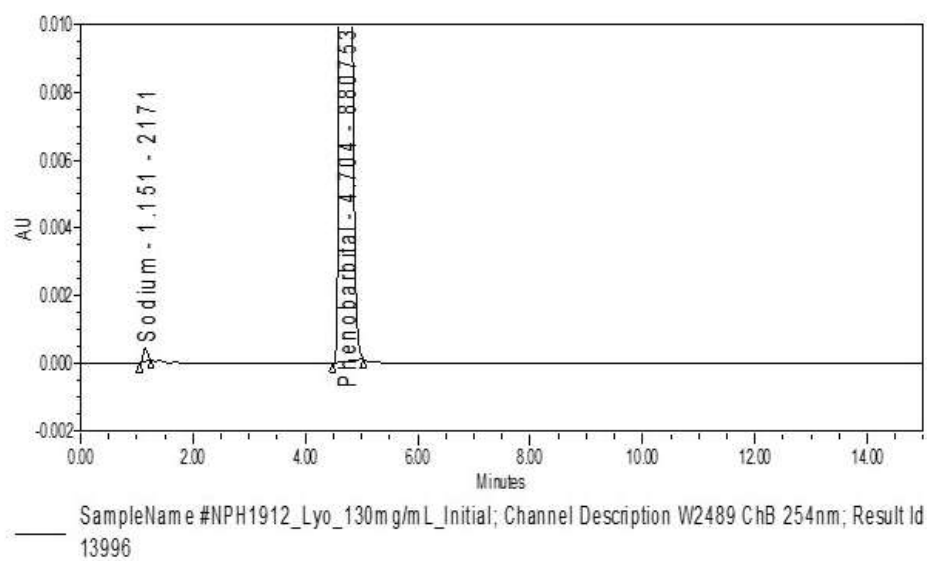
	PeakName	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.364	4013	0.02			1.9	626.1	2241.7	1.1
2	PEAU	8.276	4512	0.02	0.013	mg/mL	14.8	278.0	12299.1	1.1
3	Phenobarbital	4.565	18206837	99.56	53.971	mg/mL	15.2	1616675.4	8239.9	1.1
4	RRT_0.37	1.644	12808	0.07	0.038	mg/mL	1.9	1270.5	1640.7	1.1
5	SodiumBlank	1.135	58253	0.32	0.173	mg/mL		8406.1	1363.0	1.1

Fig. 4F



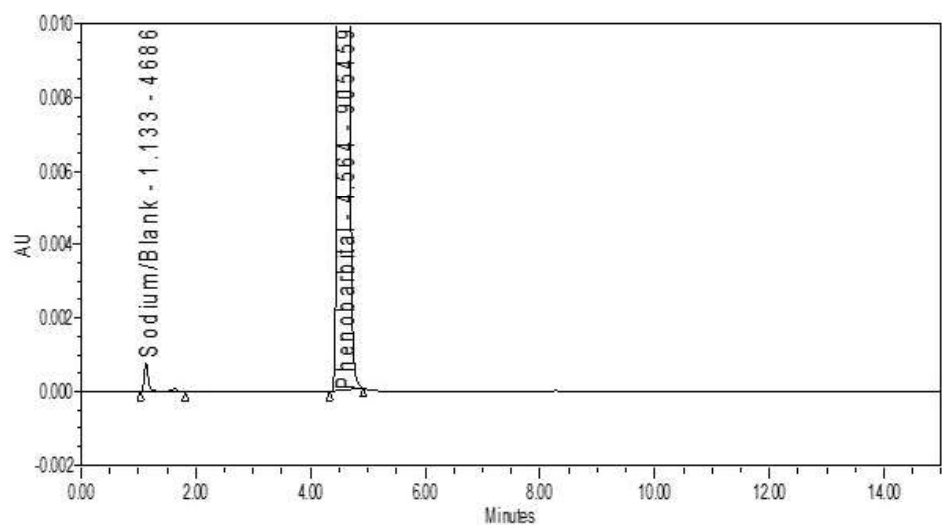
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Blank2	1.361	5648	0.03			1.9	899.0	2143.9	1.0
2	PEAU	8.275	6741	0.04	0.020	mg/mL	14.6	427.7	11918.8	1.0
3	Phenobarbital	4.561	18093753	99.70	53.636	mg/mL	15.2	1693108.6	8445.9	1.1
4	RRT_0.37	1.638	10466	0.06	0.031	mg/mL	1.9	1064.2	1482.5	1.1
5	SodiumBlank	1.131	32159	0.18	0.095	mg/mL		4912.0	1362.2	1.1

Fig. 4G



	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

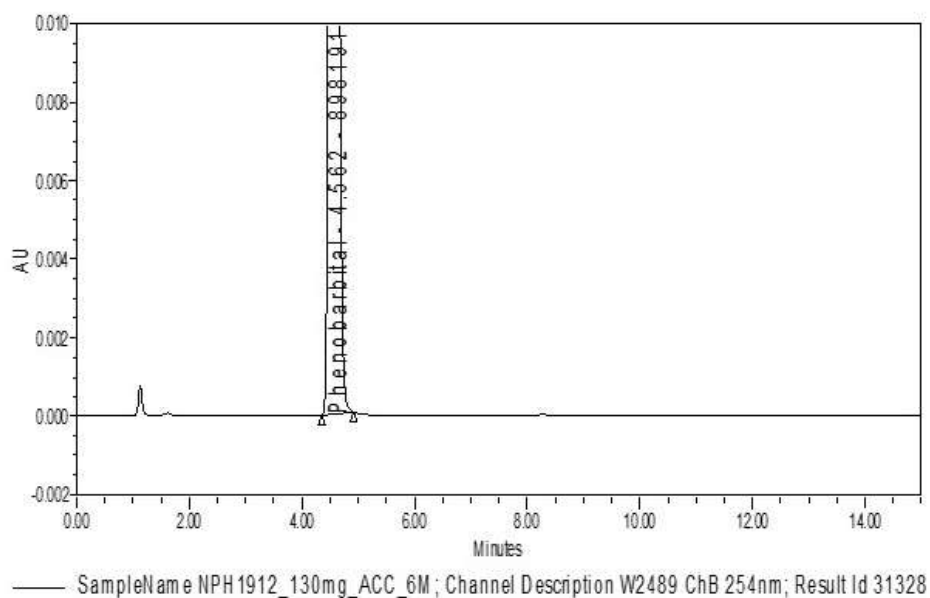
Fig. 4H



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

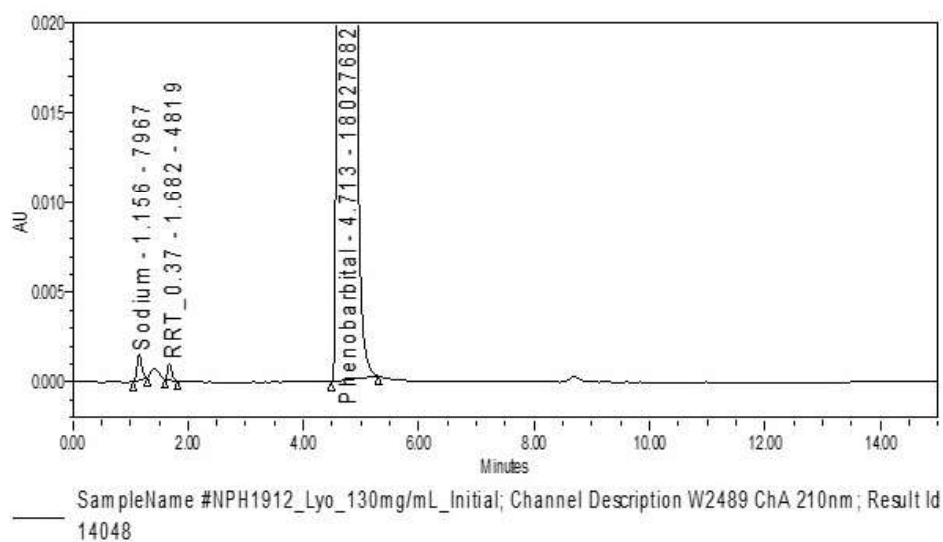
	PeakName	RT	Area	Amount	Units	Assay	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.564	905459	118.985	mg/mL	100.2	20.7	55858.2	8639.9	1.1
2	Sodium/Blank	1.133	4686	0.616	mg/mL			358.4	1316.2	1.4

Fig. 4I



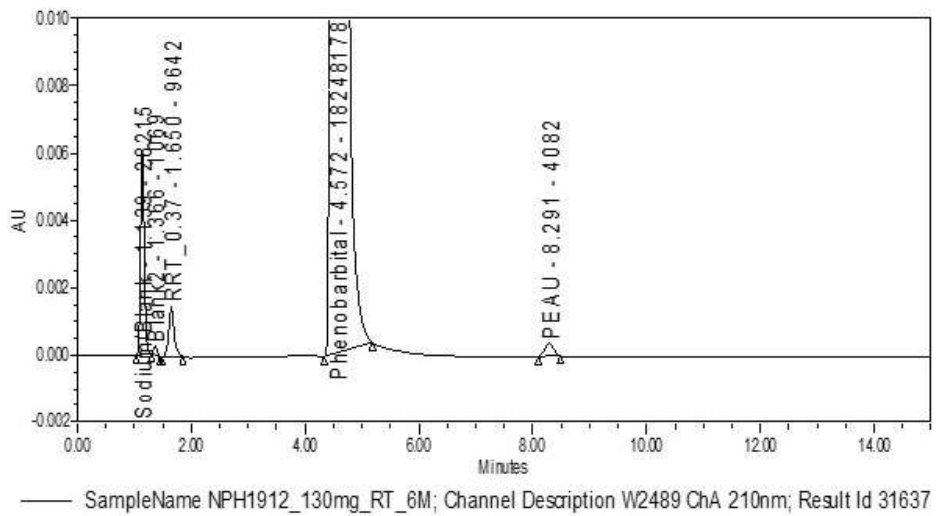
	PeakName	RT	Area	Amount	Units	Assay	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.562	898191	118.030	mg/mL	99.4	55375.6	8698.8	1.1

Fig. 4J



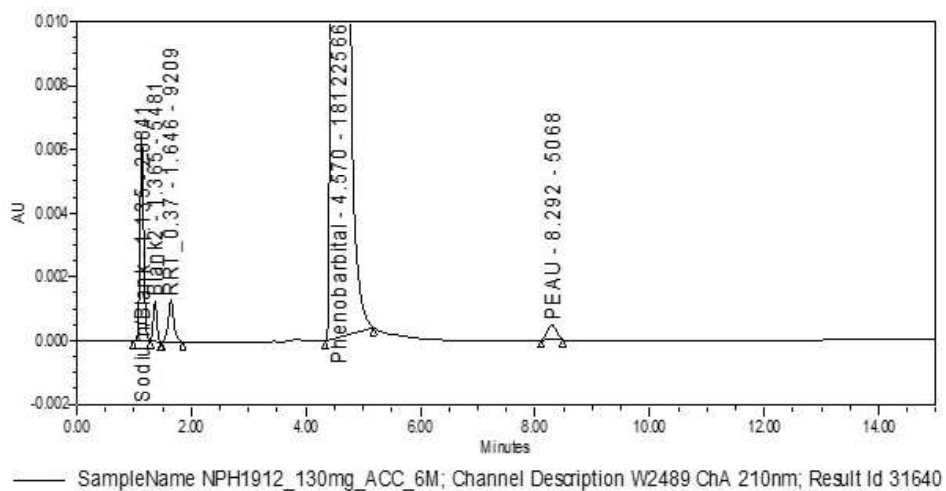
	Peak Name	RT	Area	% Area	Amount	Units	USP Resolution	s/n	USP Plate Count	USP Tailing
1	Phenobarbital	4.713	18027682	99.93	116.995	mg/mL	17.0	1001026.6	7649.3	1.2
2	RRT_0.37	1.682	4819	0.03	0.031	mg/mL	36	433.7	2401.3	1.2
3	Sodium	1.156	7967	0.04	0.052	mg/mL		649.1	941.5	1.1

Fig. 4K



	PeakName	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	SodiumBlank	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	18122586	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	SodiumBlank	1.135	28841	0.16	0.171	mg/mL		3440.5	1392.6	1.1

Fig. 5A

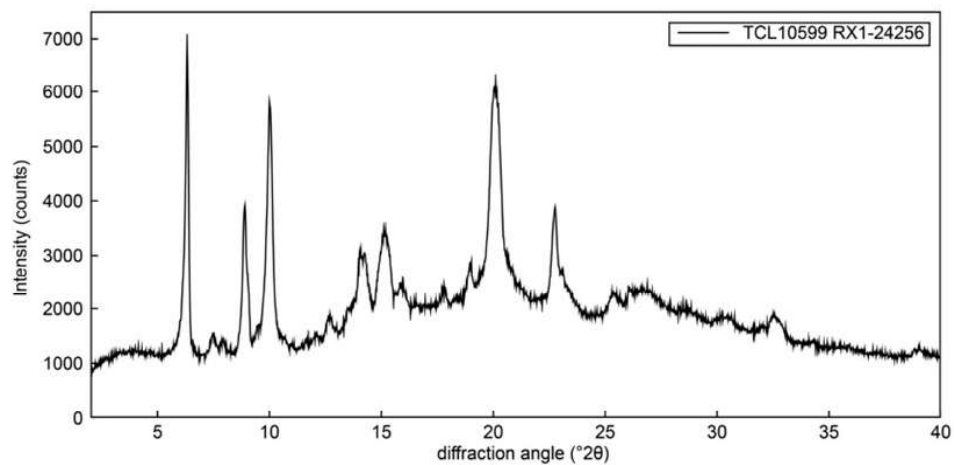


Fig. 5B

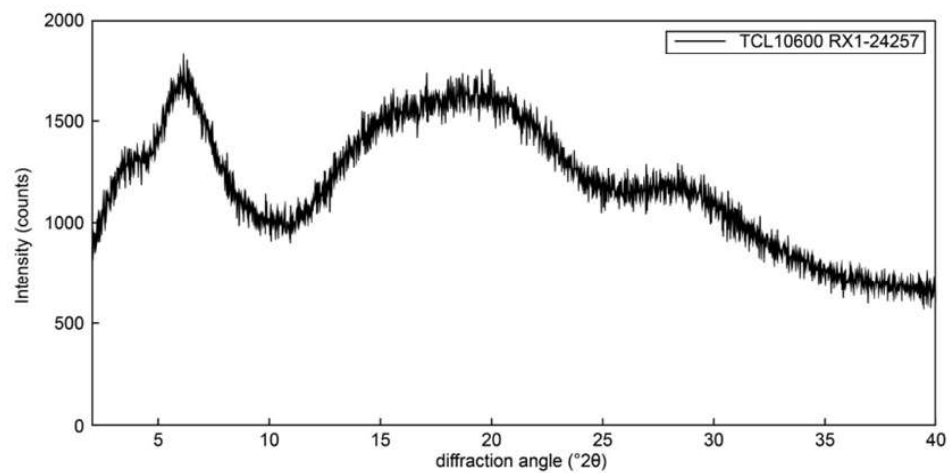


Fig. 5C

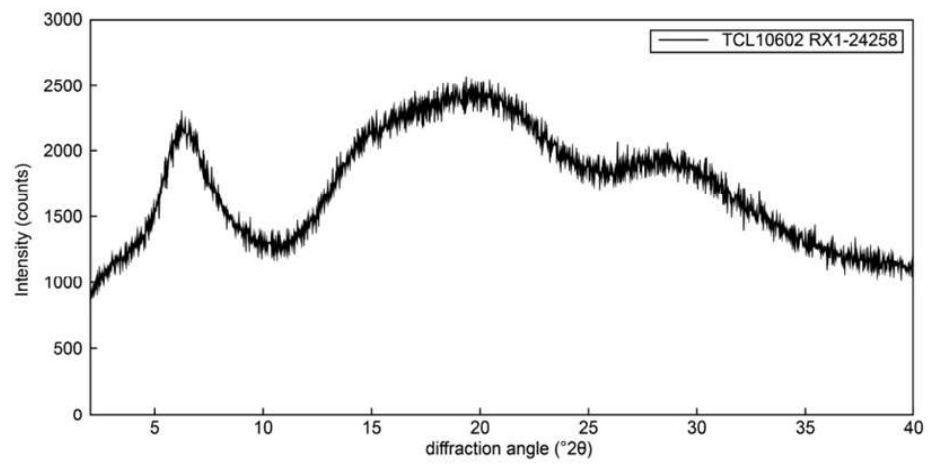
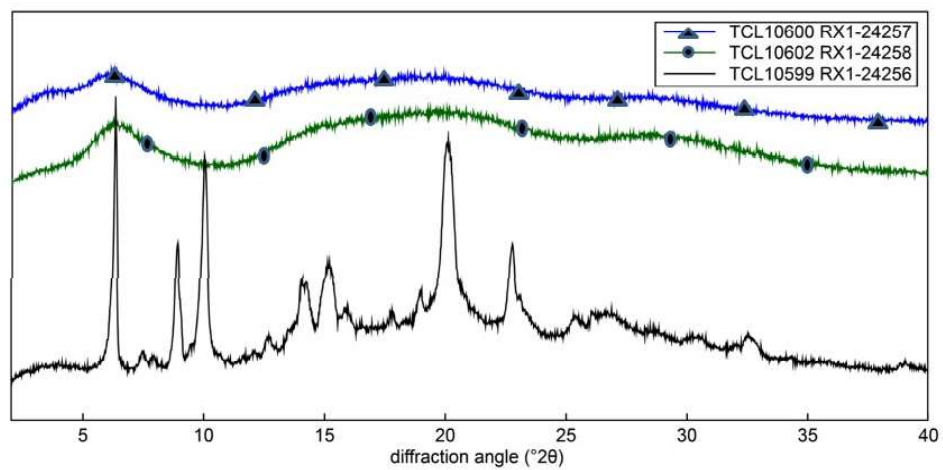


Fig. 5D



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: ☒ 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. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both. WARNING: Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.	
LEGAL NAME OF INVENTOR Inventor: <u>Bala Tripura Sundari Chodavarapu</u> Date (Optional) : _____ Signature: <u>Bala Tripura Sundari Chodavarapu</u>	
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: <u>Thirupathi Mangali</u> Date (Optional) : _____ Signature: <u>Thirupathi Mangali</u>	
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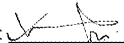
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LEGAL NAME OF INVENTOR Inventor: <u>Jay Shukla</u> Date (Optional) : _____ Signature: <u>Jay Shukla</u>	
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LEGAL NAME OF INVENTOR Inventor: <u>Anand Shukla</u> Date (Optional) : _____ Signature:  _____	
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LEGAL NAME OF INVENTOR Inventor: <u>Dasaradhi Lakkaraju</u> Date (Optional) : _____ Signature: <u>Dasaradhi Lakkaraju</u>	
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Electronic Patent Application Fee Transmittal				
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:		104078.0001US2		
Filed as Small Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	80	80
UTILITY SEARCH FEE	2111	1	350	350
UTILITY EXAMINATION FEE	2311	1	400	400
Pages:				
Claims:				
CLAIMS IN EXCESS OF 20	2202	1	50	50
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				880

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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
17/854,914	06/30/2022		880	104078.0001US2	21	2

CONFIRMATION NO. 1236

FILING RECEIPT



0000000135345579

149344
Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

Date Mailed: 07/25/2022

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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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 application is a CIP of 17/025,881 09/18/2020 PAT 11406598
which 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: 07/21/2022

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/854,914**

Projected Publication Date: 11/03/2022

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

Lyophilized Compositions of Phenobarbital Sodium Salt

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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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.

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page 2 of 4

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Title 35, United States Code, Section 184
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Electronic Acknowledgement Receipt	
EFS ID:	46777947
Application Number:	17854914
International Application Number:	
Confirmation Number:	1236
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:	104078.0001US2
Receipt Date:	07-OCT-2022
Filing Date:	30-JUN-2022
Time Stamp:	15:33:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no				
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Information:	
Total Files Size (in bytes):	1283702
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	17854914
	Filing Date	2022-06-30
	First Named Inventor	Bala Tripura Sundari Chodavarapu
	Art Unit	
	Examiner Name	
	Attorney Docket Number	104078.0001US2

CERTIFICATION STATEMENT			
Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):			
That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).			
OR			
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See attached certification statement.			
The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.			
☒ A certification statement is not submitted herewith.			
SIGNATURE			
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 Ph.D./	Date (YYYY-MM-DD)	2022-10-07
Name/Print	Martin Fessenmaier Ph.D.	Registration Number	46697
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Doc code: IDS

Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-22)

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17854914
	Filing Date		2022-06-30
	First Named Inventor	Bala Tripura Sundari Chodavarapu	
	Art Unit		
	Examiner Name		
	Attorney Docket Number	104078.0001US2	

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	2	20170143719	A1	2017-05-25	Parker et al.			
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	1	104940149	CN	A	2015-09-30	Sun		×
	2	2017085687	WO	A1	2017-05-26	WEST-WARD PHARMACEUTICALS INTERNATIONAL LIMITED		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17854914
	Filing Date		2022-06-30
	First Named Inventor	Bala Tripura Sundari Chodavarapu	
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	1	BARDAT et al., "Moisture Measurement: A New Method for Monitoring Freeze-drying Cycles," Journal of Parenteral Science & Technology, 1993 November-December; 47(6):293-299.	
	2	DIETZ et al., "Phenobarbital Stability in Different Dosage Forms: Alternatives for Elixirs," Pharmaceutical Research, 1988; 5(12):803-805.	
	3	FDA, "Lyophilization of Parenteral: Guide to Inspections of Lyophilization of Parenterals," published 2014-11-11; 22 pgs.	
	4	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.	
	5	JATUL, Bernard B., "The Stability of Solutions of Phenobarbital Sodium," A Dissertation Presented to the Graduate Council of the University of Florida, 1943 February; 170 pgs.	
	6	KELLY et al., "Phenobarbital Sodium," London Health Sciences Centre; Last Update: 2018 October 11; 4 pgs. Retrieved from the internet on 2020 November 18: https://www.lhsc.on.ca/critical-care-trauma-centre/phenobarbital-sodium .	
	7	NAHATA et al., "Stability of phenobarbital sodium diluted in 0.9% sodium chloride injection," American Journal of Hospital Pharmacy, 1986 February; 43:384-385.	
	8	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.	
	9	SNYDER, Meg, "Lyophilization: The Basics - Drug Discovery and Development," 2017 March 7; pgs. 1-5. Retrieved from the internet on 2020 November 19: https://www.drugdiscoverytrends.com/lyophilization-the-basics/#:~:text=Some of the advantages of,to heat the product excessively .	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number		17854914
	Filing Date		2022-06-30
	First Named Inventor	Bala Tripura Sundari Chodavarapu	
	Art Unit		
	Examiner Name		
	Attorney Docket Number		104078.0001US2

	10	STAUDT, "Phenobarbital in newborn infants: Overview," Monatsschr Kinderheilkd, 1984 April; 132(4):194-202. Abstract only.
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Examiner Signature		Date Considered
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Other Prior Art

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/854,914	06/30/2022	Bala Tripura Sundari Chodavarapu	104078.0001US2

CONFIRMATION NO. 1236

149344

Umberg Zipser LLP
1920 Main Street Suite 750
Irvine, CA 92614

PUBLICATION NOTICE



OC000000136804603

Title:Lyophilized Compositions of Phenobarbital Sodium Salt

Publication No.US-2022-0354794-A1

Publication Date:11/10/2022

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The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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APPLICATION #
17/854,914

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104078.0001US2

Title of Invention

Lyophilized Compositions of Phenobarbital Sodium Salt

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1236	FILED BY	LEONARDO QUINTANA
PATENT CENTER #	66718048	FILING DATE	06/30/2022
CUSTOMER #	149344	FIRST NAMED INVENTOR	Bala Tripura Sundari Chodavarapu
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Martin Fessenmaier

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
104078-0001US2_Preliminary_Amendment_as_filed.pdf	5	-	126 KB
104078-0001US2_Preliminary_Amendment_as_filed-A.PE.pdf (1-1)	1	Preliminary Amendment	110 KB
104078-0001US2_Preliminary_Amendment_as_filed-CLM.pdf (2-4)	3	Claims	92 KB
104078-0001US2_Preliminary_Amendment_as_filed-REM.pdf (5-5)	1	Applicant Arguments/Remarks Made in an Amendment	87 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
104078- 0001US2_Preliminary_Amend ment_as_filed.pdf	E3E3CB9FDB7456BE6FC896104C0FF6185485A367E8673C657 0FB7FB7BD1B4448AA9969F334DF8471CA997682DF885C1580 8E86D2CD387FBD6DBB5645A5D430A2
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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl No.:	17/854,914	Examiner:	Not Yet Determined
First Inventor:	Bala Tripura Sundari Chodavarapu	Art Unit:	Not Yet Determined
Filing Date:	2022-06-30	Docket No.:	104078.0001US2
Title	Lyophilized Compositions of Phenobarbital Sodium Salt		

PRELIMINARY AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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:

1-21. (canceled)

22. (new) A pharmaceutical product, comprising:

- a container enclosing sterile storage stable lyophilized amorphous phenobarbital;
wherein the lyophilized phenobarbital is storage stable such that, upon storage at 25 °C and 60% relative humidity for 3 months and reconstitution with water, less than 0.05% of degradation products from the phenobarbital are detectable in the reconstituted solution;
- wherein the degradation products are selected from the group consisting of 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU); and
- wherein the lyophilized phenobarbital is stored under vacuum in the container.

23. (new) The product of claim 22, wherein no more than 0.05% total degradation products, including 2EPMM, PBG, and PEAU, are detectable in the reconstituted solution.

24. (new) The product of claim 22, wherein the lyophilized amorphous phenobarbital contains no more than 1.8% water.

25. (new) The product of claim 22, wherein the lyophilized amorphous phenobarbital contains no more than 1.5% water.

26. (new) The product of claim 22, wherein at least 90% of total lyophilized phenobarbital is amorphous phenobarbital.

27. (new) The product of claim 22, wherein the lyophilized amorphous phenobarbital is storage stable such that, upon storage at 25 °C and 60% relative humidity for 6 months and reconstitution with water, less than 0.05% of degradation products from the phenobarbital are detectable in the reconstituted solution.

28. (new) The product of claim 27, wherein no more than 0.05% total degradation products, including 2EPMM, PBG, and PEAU, are detectable in the reconstituted solution.
29. (new) The product of claim 22, wherein the container contains 65 mg of the sterile storage stable lyophilized amorphous phenobarbital.
30. (new) The product of claim 22, wherein the container contains 130 mg of the sterile storage stable lyophilized amorphous phenobarbital.
31. (new) The product of claim 22, wherein the container contains 65-200 mg of the sterile storage stable lyophilized amorphous phenobarbital.
32. (new) The product of claim 22, wherein the lyophilized amorphous phenobarbital is storage stable such that, upon storage at 40 °C and 75% relative humidity for 3 months and reconstitution with water, less than 0.05% of degradation products from the phenobarbital are detectable in the reconstituted solution.
33. (new) The product of claim 32, wherein no more than 0.1% total degradation products, including 2EPMM, PBG, and PEAU, are detectable in the reconstituted solution.
34. (new) The product of claim 22, wherein the lyophilized amorphous phenobarbital is storage stable such that, upon storage at 40 °C and 75% relative humidity for 6 months and reconstitution with water, less than 0.05% of degradation products from the phenobarbital are detectable in the reconstituted solution.
35. (new) A method of preparing a phenobarbital solution in an aqueous carrier, comprising:
reconstituting the pharmaceutical product of claim 22 in the container in an aqueous carrier to produce a clear colorless solution comprising the phenobarbital;
wherein the clear colorless solution comprises, upon reconstitution, initial quantities of degradation products from the phenobarbital in an amount of less than 0.05%; and
wherein the degradation products are selected from the group consisting of 2-ethyl-2-phenylmalonamide (2EPMM), alpha-phenylbutyrylguanidine (PBG), and phenylethylacetylurea (PEAU).

36. (new) The method of claim 35, wherein the clear colorless solution comprises, upon reconstitution, initial quantities of total degradation products, including 2EPMM, PBG, and PEAU, in an amount of no more than 0.05%.
37. (new) The method of claim 35, wherein the aqueous carrier is water for injection, a 0.9% saline solution, or a 5% dextrose solution.
38. (new) The method of claim 35, wherein the clear colorless solution comprises the phenobarbital at a concentration of 20 mg/mL.
39. (new) The method of claim 35, wherein the clear colorless solution contains, upon storage for 20 hours at 25 °C and 60% relative humidity, less than 0.05% of degradation products from the phenobarbital.
40. (new) The method of claim 39, wherein the clear colorless solution contains, upon storage for 20 hours at 25 °C and 60% relative humidity, no more than 0.3% total degradation products, including 2EPMM, PBG, and PEAU.
41. (new) The method of claim 37, wherein the clear colorless solution has, upon reconstitution, an initial pH of between 9.5 and 9.9.

Preliminary Amendment
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REMARKS/ARGUMENTS

Claim Amendments

By this amendment, claims 1-21 are canceled and new claims 22-41 are added. All newly added claims find corresponding support in the parent application (US 17/025,881, now US 11,406,598) as originally filed. With these amendments, no new matter is added.

Request For Allowance

Claims 22-41 are pending in this application. Applicant requests allowance of all pending claims.

Respectfully submitted,
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Date: August 8, 2024

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 17/854,914	
APPLICATION AS FILED - PART I							
(Column 1)		(Column 2)		SMALL ENTITY		OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	80		N/A	
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	350		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	400		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	21	minus 20 = *	1	x 50 = 50			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2	minus 3 = *		x 240 = 0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
				TOTAL		TOTAL	
* If the difference in column 1 is less than zero, enter "0" in column 2.				880			
APPLICATION AS AMENDED - PART II							
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		x =
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		x =
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
				TOTAL ADD'L FEE		TOTAL ADD'L FEE	
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)
	Total (37 CFR 1.16(i))	*	Minus **	=	x =		x =
	Independent (37 CFR 1.16(h))	*	Minus ***	=	x =		x =
	Application Size Fee (37 CFR 1.16(s))						
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
				TOTAL ADD'L FEE		TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.							