

FILE HISTORY

62/903,511

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TITLE: Lyophilized Compositions of Phenobarbital  
Sodium Salt

APPLICATION NO: 62/903,511

FILED: 20 SEP 2019

COMPILED: 05 FEB 2025

**62/903,511**

**Lyophilized Compositions of Phenobarbital Sodium Salt**

**Transaction History**

| <b>Date</b> | <b>Transaction Description</b>                                                                 |
|-------------|------------------------------------------------------------------------------------------------|
| 09-20-2019  | PTO-SB-69-Authorize EPO Access to Search Results                                               |
| 09-20-2019  | Applicants have given acceptable permission for participating foreign                          |
| 09-20-2019  | Entity Status Set To Undiscounted (Initial Default Setting or Status Change)                   |
| 09-20-2019  | Initial Exam Team nn                                                                           |
| 10-09-2019  | Application Dispatched from OIPE                                                               |
| 10-09-2019  | Applicant Has Filed a Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27 |
| 10-10-2019  | Application ready for PDX access by participating foreign offices                              |
| 10-10-2019  | Application Is Now Complete                                                                    |
| 10-10-2019  | Filing Receipt                                                                                 |
| 10-11-2019  | Email Notification                                                                             |
| 09-20-2020  | EXPIRED PROVISIONAL                                                                            |

| Electronic Acknowledgement Receipt   |                                                       |
|--------------------------------------|-------------------------------------------------------|
| EFS ID:                              | 37232546                                              |
| Application Number:                  | 62903511                                              |
| International Application Number:    |                                                       |
| Confirmation Number:                 | 5301                                                  |
| Title of Invention:                  | LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT |
| First Named Inventor/Applicant Name: | Bala Tripura Sundari Chodavarapu                      |
| Customer Number:                     | 149344                                                |
| Filer:                               | Nicole Ballew Chang/Danielle Moroz                    |
| Filer Authorized By:                 | Nicole Ballew Chang                                   |
| Attorney Docket Number:              | 104078.0001PRO                                        |
| Receipt Date:                        | 20-SEP-2019                                           |
| Filing Date:                         |                                                       |
| Time Stamp:                          | 17:45:33                                              |
| Application Type:                    | Provisional                                           |

**Payment information:**

|                                                                                                                |                  |
|----------------------------------------------------------------------------------------------------------------|------------------|
| Submitted with Payment                                                                                         | yes              |
| Payment Type                                                                                                   | CARD             |
| Payment was successfully received in RAM                                                                       | \$ 140           |
| RAM confirmation Number                                                                                        | E20199JH45489679 |
| Deposit Account                                                                                                |                  |
| Authorized User                                                                                                |                  |
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| File Listing:   |                                                     |                                                                      |                                                          |                  |                  |
| Document Number | Document Description                                | File Name                                                            | File Size(Bytes)/ Message Digest                         | Multi Part /.zip | Pages (if appl.) |
| 1               |                                                     | 2019-09-20_104078-0001PRO_LyophilizedPhenobarbitalSodium_REV0010.pdf | 756944<br><br>c6d0403cc6cd29f980790d7265d9818a12a5d5696  | yes              | 29               |
|                 | Multipart Description/PDF files in .zip description |                                                                      |                                                          |                  |                  |
|                 | Document Description                                |                                                                      | Start                                                    | End              |                  |
|                 | Specification                                       |                                                                      | 1                                                        | 24               |                  |
|                 | Claims                                              |                                                                      | 25                                                       | 28               |                  |
|                 | Abstract                                            |                                                                      | 29                                                       | 29               |                  |
| Warnings:       |                                                     |                                                                      |                                                          |                  |                  |
| Information:    |                                                     |                                                                      |                                                          |                  |                  |
| 2               | Drawings-other than black and white line drawings   | 2019-09-18_DRAWINGS_104078-0001PRO.pdf                               | 6677307<br><br>d223676d0d4d9f9169278da403a3c65d24df875a5 | no               | 39               |
| Warnings:       |                                                     |                                                                      |                                                          |                  |                  |
| Information:    |                                                     |                                                                      |                                                          |                  |                  |
| 3               | Provisional Cover Sheet (SB16)                      | ProvCvrSheet.pdf                                                     | 2048574<br><br>9c674f1b3d77e76f6668f3267c9f8071cd81b389  | no               | 4                |
| Warnings:       |                                                     |                                                                      |                                                          |                  |                  |
| Information:    |                                                     |                                                                      |                                                          |                  |                  |
| 4               | Application Data Sheet                              | ADS.pdf                                                              | 1874192<br><br>bd288c73a805a06c3c87cf92cfa90592e5d895f7  | no               | 9                |
| Warnings:       |                                                     |                                                                      |                                                          |                  |                  |
| Information:    |                                                     |                                                                      |                                                          |                  |                  |
| 5               | Fee Worksheet (SB06)                                | fee-info.pdf                                                         | 30137<br><br>c184f4516935216a70559f60b06c7a0556e70d76a3  | no               | 2                |

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| <b>Total Files Size (in bytes):</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 11387154 |
| <p>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.</p> <p><b><u>New Applications Under 35 U.S.C. 111</u></b><br/>         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.</p> <p><b><u>National Stage of an International Application under 35 U.S.C. 371</u></b><br/>         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.</p> <p><b><u>New International Application Filed with the USPTO as a Receiving Office</u></b><br/>         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.</p> |          |

## **LYOPHILIZED COMPOSITIONS OF PHENOBARBITAL SODIUM SALT**

### **Field of the Invention**

[0001] 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**

[0002] 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.

[0003] 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.

[0004] 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.

[0005] The stability of solubilized Phenobarbital Sodium has been a recurring problem because it readily hydrolyzes in water forming various degradation products. In particular, in water alone or in water with an increase in pH, Phenobarbital Sodium forms the degradation products phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and alpha-phenylbutyrylguanidine (PBG). While these degradation impurities may not directly compromise

the effectiveness of the Phenobarbital Sodium for its therapeutic activity, these degradation impurities are toxic and cause severe side effects. Specifically, PEAU was previously administered as Pheneturide for severely affected epileptics. However, the Food and Drug Administration (FDA) withdrew approval of Pheneturide due to its toxic effects. In particular, Pheneturide is reported to be a potent liver enzyme inducer that disrupts both calcium and folate metabolism. (Nayyar et al., 2012, *J. of Appl. Pharm Sci.*, 2:230-235.) Prior to its removal as an FDA-approved drug, patients treated with Pheneturide showed low levels of serum calcium and folate.

[0006] 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.

[0007] 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.

[0008] 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**

[0009] 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.

[0010] 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, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2, and lyophilizing the Phenobarbital Sodium solution. In some embodiments, the water is deionized water.

[0011] In preferred embodiments, the deionized water is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the deionized water is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (*e.g.*, deionized water) is cooled to or between 5 to 10°C prior to adding the Phenobarbital Sodium.

[0012] 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).

[0013] 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.

**[0014]** According to contemplated embodiments as disclosed herein, the amorphous lyophilized Phenobarbital Sodium composition is stable up to at least 6 months under accelerated stability conditions which is equivalent to 24 months at RT. In this respect, in some embodiments, the stability of the lyophilized Phenobarbital Sodium is determined by reconstituting the lyophilized Phenobarbital Sodium in an aqueous solution and measuring the amount of or the presence of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG).

**[0015]** 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.

**[0016]** 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.

**[0017]** 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 lyophilized Phenobarbital Sodium.

**[0018]** In preferred embodiments, the deionized water is sparged with nitrogen prior to adding the Phenobarbital Sodium. Typically, the deionized water is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium. In additional embodiments, the water (e.g., deionized water) is cooled to or between 5 to 10°C prior to adding the Phenobarbital Sodium.

**[0019]** 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).

**[0020]** 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 the measuring of the formation of the degradation products includes reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution, and measuring the amount of or presence of PEAU, 2 EPMM, and/or PBG in the reconstituted solution.

**[0021]** 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 the preferred embodiments, the reconstituted solution has no less than 98% 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.

**[0022]** 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 amorphous Phenobarbital Sodium powder 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 or 130 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection.

[0023] Additional aspects of the present disclosure include a pharmaceutical product including a vial containing the lyophilized amorphous Phenobarbital Sodium powder 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.

[0024] Therefore, the inventors also contemplate lyophilized amorphous Phenobarbital Sodium.

[0025] 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**

[0026] **Fig. 1A** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during lyophilization microscopy at  $-50^{\circ}\text{C}$ , as indicated.

[0027] **Fig. 1B** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during lyophilization microscopy at  $-45.5^{\circ}\text{C}$  as indicated.

[0028] **Fig. 1C** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during lyophilization microscopy at  $-40.0^{\circ}\text{C}$  as indicated.

[0029] **Fig. 1D** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during lyophilization microscopy at  $-39.6^{\circ}\text{C}$  as indicated.

[0030] **Fig. 1E** is a **polarized** light photomicrograph of the presently disclosed Phenobarbital Sodium in water during lyophilization microscopy at  $-39.2^{\circ}\text{C}$  as indicated.

[0031] **Fig. 1F** is a polarized light photomicrograph of the presently disclosed Phenobarbital Sodium in water during lyophilization microscopy at  $-38.8^{\circ}\text{C}$  as indicated.

[0032] **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.

[0033] **Fig. 2B** is a chromatogram from an injection of the “sensitivity solution” of Phenobarbital for assay by HPLC at a detection wavelength of 210 nm, as described herein.

[0034] **Fig. 2C** is a chromatogram from an injection of a “related substance” (RS) working standard at 0.2% impurity level) for assay by HPLC at a detection wavelength of 210 nm, as described herein.

[0035] **Fig. 2D** is a chromatogram from an injection of 2-ethyl-2-phenylmalonamide (2EPMM) for assay of related substances by HPLC at a detection wavelength of 210 nm, as described herein.

[0036] **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.

[0037] **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.

[0038] **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.

[0039] **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.

[0040] **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.

[0041] **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.

**[0042] 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.

**[0043] 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.

**[0044] 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.

**[0045] 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.

**[0046] 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.

**[0047] 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.

**[0048] 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.

**[0049] 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.

[0050] **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.

[0051] **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.

[0052] **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.

[0053] **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.

[0054] **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.

[0055] **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.

[0056] **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.

[0057] **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.

[0058] **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.

[0059] **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.

[0060] **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.

[0061] **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.

[0062] **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.

[0063] **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.

[0064] **Fig. 5A** is an X-ray powder diffraction (XRPD) pattern of Phenobarbital sodium Grade P

[0065] **Fig. 5B** is an XRPD pattern of Phenobarbital Sodium for injection USP 65 mg/vial.

[0066] Fig. 5C is an XRPD pattern of Phenobarbital Sodium for injection USP 130 mg/vial.

[0067] Fig. 5D is a stack plot of the XRPD patterns of Figs. 5A, 5B, and 5C.

#### **Detailed Description**

[0068] 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 does not form any detectable amounts of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG), and forms no more than 0.05% phenylethylacetylurea (PEAU).

[0069] 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  $C_{12}H_{11}N_2NaO_3$ .

[0070] 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 Phenobarbital Sodium powder. 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 Phenobarbital Sodium powder 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.

**[0071]** The contemplated method for producing a storage-stable lyophilized Phenobarbital Sodium composition includes adding purified Phenobarbital Sodium to water. Preferably the purified Phenobarbital Sodium solid is purchased from a chemical supplier (*e.g.*, Siegfried, USA) that adheres to the United States Pharmacopeia (USP) manufacturing and synthesis guidelines. The USP grade of the Phenobarbital Sodium is preferably USP “purified” or “practical” (P) grade indicating that it is a good quality chemical. As understood in the art, the USP grade (P) active pharmaceutical ingredient (API) of Phenobarbital Sodium is not suitable for administration because it is not sterile, is hygroscopic, and as such, maintaining anhydrous conditions of this grade of API is not feasible. Structurally, the analyzed USP grade P API (Siegfried, USA) is polymorphous—containing both crystalline and non-crystalline material. With reference to **Fig. 5A**, an X-ray powder diffraction (XRPD) pattern is shown of this compound.

**[0072]** Considering the need to avoid hydrolysis of the Phenobarbital Sodium, the Phenobarbital Sodium is preferably added to deionized water and later lyophilized to obtain a stable lyophilized finished product. In order to remove dissolved oxygen (O<sub>2</sub>) gas from the water (*e.g.*, deionized water), it is also preferred that the water is sparged with nitrogen (N<sub>2</sub>) 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 or 130 mg of lyophilized Phenobarbital Sodium, 100 milliliters (ml) of deionized water is nitrogen sparged for 30 minutes. In additional embodiments, the water may also be cooled to approximately 5 to 10°C. In preferred embodiments, the water is cooled to approximately 5 to 8°C.

**[0073]** The addition of the Phenobarbital Sodium solid to the water (*e.g.*, deionized nitrogen sparged water cooled to 5 to 8°C) may be carried out using any suitable mixing. Preferably, the water (*e.g.*, deionized water) is first added to a glass container for nitrogen sparging and cooling, and this prepped water remains in the glass 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 container. Upon addition of the Phenobarbital Sodium solid to the water, the mixture is stirred.

**[0074]** 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).

**[0075]** 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  $\mu\text{m}$  (or 0.22  $\mu\text{m}$ ) membrane filter. For example, the membrane filter may be polyvinylidene difluoride (PVDF) or any other compatible filter membranes.

**[0076]** According to aspects of the contemplated method, the Phenobarbital Sodium solution dissolved in the water (*e.g.*, nitrogen sparged deionized water cooled to 5 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, 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 deionized water 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, 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.

[0077] In further embodiments, following lyophilization, the vials may be completely closed (e.g., stoppered) under vacuum.

[0078] 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 (2EPM) 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.

[0079] In a comparison analysis, the presently disclosed lyophilized Phenobarbital Sodium at 65 mg or 130 mg powder 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**.

[0080] **Table 1:**

|  |
|--|
|  |
|--|

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

[0081] 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 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**).

[0082] 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) |                 |                  |                 |                  |
| Formulation Type                                                                                                                  |                                                                                       | Liquid                                                              |                  |                 |                  | Lyophilized powder                                                       |                 |                  |                 |                  |
| Test                                                                                                                              | Initial                                                                               | Stability Data                                                      |                  |                 |                  |                                                                          |                 |                  |                 |                  |
|                                                                                                                                   |                                                                                       | 3 Months                                                            |                  | 6 Months        |                  | Initial                                                                  | 3 Months        |                  | 6 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 |
| Description                                                                                                                       | CCVS                                                                                  | CCVS                                                                | CCVS             | CCVS            | CCVS             | WCA                                                                      | WCA             | WCA              | WCA             | WCA              |
| Appearance after reconstitution                                                                                                   | NA                                                                                    | NA                                                                  | NA               | NA              | NA               | 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              |
| % Assay of Phenobarbital                                                                                                          | 102.4                                                                                 | 97.6                                                                | 103.1            | 96.3            | 86.7             | 99.1                                                                     | 98.7            | 97.4             | 100.0           | 99.3             |
| % Impurity (Area percent) 2EPMM                                                                                                   | ND                                                                                    | ND                                                                  | BQL              | BQL             | BQL              | ND                                                                       | ND              | ND               | ND              | ND               |
| PBG                                                                                                                               | 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              |
| Any other Individual impurity                                                                                                     | BQL                                                                                   | BQL                                                                 | 0.1              | BQL             | 0.3              | BQL                                                                      | BQL             | BQL              | 0.07            | 0.06             |
| Total Impurities                                                                                                                  | 0.5                                                                                   | 1.0                                                                 | 3.8              | 1.4             | 6.1              | BQL                                                                      | BQL             | BQL              | 0.07            | 0.06             |
| CCVS: Clear Colorless Viscous Solution; CCS: Clear Colorless Solution; WCA: White Compact Aggregate                               |                                                                                       |                                                                     |                  |                 |                  |                                                                          |                 |                  |                 |                  |
| \$: 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: $\alpha$ -phenylbutyrylguanidine, PEAU: phenylethylacetylurea or Pheneturide |                                                                                       |                                                                     |                  |                 |                  |                                                                          |                 |                  |                 |                  |
| *                                                                                                                                 | pH of both liquid and lyophilized formulations are measured at 65 mg/mL concentration |                                                                     |                  |                 |                  |                                                                          |                 |                  |                 |                  |

[0083] Table 3

| 130 mg/mL Liquid Formulation and 130 mg/vial Lyophilized formulation                                                     |                                                                         |                       |                        |                       |                        |                                                                               |                       |                        |          |      |
|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------|------------------------|-----------------------|------------------------|-------------------------------------------------------------------------------|-----------------------|------------------------|----------|------|
| Product Name                                                                                                             | Phenobarbital Sodium for Injection USP,<br>130 mg/mL (Marketed product) |                       |                        |                       |                        | Phenobarbital Sodium for Injection USP,<br>130 mg/vial ( Nivagen formulation) |                       |                        |          |      |
| Formulation Type                                                                                                         | Liquid                                                                  |                       |                        |                       |                        | Lyophilized powder                                                            |                       |                        |          |      |
| Test                                                                                                                     | Stability Data                                                          |                       |                        |                       |                        |                                                                               |                       |                        |          |      |
|                                                                                                                          | Initial                                                                 | 3 Months              |                        | 6 Months              |                        | Initial                                                                       | 3 Months              |                        | 6 Months |      |
|                                                                                                                          |                                                                         | RT<br>25°C,<br>60% RH | ACC<br>40°C,<br>75% RH | RT<br>25°C,<br>60% RH | ACC<br>40°C,<br>75% RH |                                                                               | RT<br>25°C,<br>60% RH | ACC<br>40°C,<br>75% RH |          |      |
| Description                                                                                                              | CCVS                                                                    | CCVS                  | CCVS                   | CCVS                  | CCVS                   | WCA                                                                           | WCA                   | WCA                    | WCA      | WCA  |
| Appearance after reconstitution                                                                                          | NA                                                                      | NA                    | NA                     | NA                    | NA                     | 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  |
| % Assay of Phenobarbital                                                                                                 | 100.8                                                                   | 95.5                  | 92.9                   | 95.2                  | 90.9                   | 98.3                                                                          | 100.1                 | 97.9                   | 100.2    | 99.4 |
| % Impurity (Area percent) 2EPM                                                                                           | ND                                                                      | ND                    | BQL                    | BQL                   | BQL                    | ND                                                                            | ND                    | ND                     | ND       | ND   |
| PBG                                                                                                                      | 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  |
| Any other individual impurity                                                                                            | ND                                                                      | BQL                   | 0.1                    | BQL                   | 0.4                    | BQL                                                                           | BQL                   | BQL                    | 0.05     | 0.05 |
| Total Impurities                                                                                                         | 0.5                                                                     | 0.9                   | 2.9                    | 1.1                   | 4.7                    | BQL                                                                           | BQL                   | BQL                    | 0.05     | 0.05 |
| CCVS: Clear Colorless Viscous Solution; CCS: Clear Colorless Solution; WCA: White Compact Aggregate                      |                                                                         |                       |                        |                       |                        |                                                                               |                       |                        |          |      |
| \$: 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 for liquid formulation is measured at 130 mg/mL and for lyophilized formulation at 100 mg/mL dilution               |                                                                         |                       |                        |                       |                        |                                                                               |                       |                        |          |      |

[0084] 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.

[0085] 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 or 130 mg/mL.

[0086] 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 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 or 130 mg. In typical embodiments, the administering of the Phenobarbital Sodium reconstituted solution to the individual includes intramuscular injection or intravenous injection.

#### **Examples**

[0087] 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).

[0088] 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.

**[0089]** 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. The chromatography column was a Zorbax XDB-C8, 150 x 4.6 mm, particle size 5  $\mu$ m.

**[0090]** More specifically, the HPLC parameters and conditions for assaying the presence or absence of impurities in the referenced formulations, including control formulations are as set forth in **Table 4**. In particular, the HPLC mobile phase solution include: Mobile Phase (A), Wash Solvent C, and Diluent. Mobile Phase A solution: 1.904 g of Potassium Phosphate mono basic into a 2 liter (L) mobile phase bottle containing 1400 mL of deionized water; add 600 mL of Acetonitrile to the Potassium Phosphate solution and mix well. Filter the solution using Millipore filter apparatus equipped with (0.45  $\mu$ m) membrane filter or equivalent, under vacuum and sonicate to degas for two minutes prior to use. Wash Solvent C: Transfer 700 mL water and 300 mL Acetonitrile into 1 L bottle, mix well and filter the solution using Millipore filter apparatus equipped with (0.45  $\mu$ m) membrane filter or equivalent, under vacuum and sonicate to degas for 10 minutes prior to use. Diluent: Mobile Phase A solution.

**[0091]** **Table 4.**

| Parameters              | Conditions                                                                |
|-------------------------|---------------------------------------------------------------------------|
| Column                  | Zorbax XDB-C8, 150 X 4.6 mm, Particle Size: 5 $\mu$ m (P.No.: 993967-906) |
| Flow rate               | 1.0 mL/min.                                                               |
| Detection Wavelength    | 210 nm for related substances<br>254 nm for assay                         |
| Injection volume        | 10 $\mu$ L                                                                |
| Run time                | 15 Minutes                                                                |
| Column Oven Temperature | 30°C                                                                      |

|                            |                                   |
|----------------------------|-----------------------------------|
| Sampler Cooler Temperature | 25°C                              |
| Retention Time             | About 5 minutes for Phenobarbital |
| Pump Mode                  | Isocratic                         |

HPLC stock and standard solutions were prepared as follows. Phenobarbital Assay Reference Standard (RS) Stock Solution: (1900 ppm): (Solution-A).

Weigh accurately 47.5 mg of Phenobarbital reference standard and transfer it into a 25 mL volumetric flask. Add 2-3 mL of acetonitrile and sonicate to dissolve. Adjust the final volume with diluent and mix well.

[0092] Phenobarbital Assay Standard Solution: (475 ppm): (Solution-B). Pipette out accurately 5.0 mL Phenobarbital Standard Stock solution (Solution-A) to a 20 mL volumetric flask and adjust the final volume with diluent. Intermediate Stock Solution: (23.75 ppm): (Solution-C). Pipette out accurately 1.0 mL Phenobarbital assay solution (Solution-B) to a 20 mL volumetric flask and adjust the volume to 20.0 mL with diluent. Diluted Related Substances Standard (0.95 ppm): (Solution E). Pipette out accurately 1.0 mL Intermediate Stock Solution from (Solution-C) to a 25 mL volumetric flask and adjust the volume with diluent. Sensitivity Solution: (0.24ppm): (Solution-D). From (Solution -C), transfer accurately 1.0 mL Phenobarbital Intermediate Stock Solution into 100 mL volumetric flask and adjust the volume to 100.0 mL with diluent. Sample Stock Solution (2600 or 5200 ppm as Phenobarbital Sodium respectively): (Solution-E). Take 1 vial of Phenobarbital Sodium for injection (65 mg/vial or 130 mg/vial) and add 1.0 mL of water in vial. Shake well for about 2 minutes. Transfer the vial solution completely into 25 mL volumetric flask by rinsing with diluent and make up to the mark. Sample solution for assay (520 ppm as Phenobarbital Sodium). Further pipette out 2.0 mL (65 mg/vial sample stock solution) or 1 mL (130 mg/vial sample stock solution) of above stock solutions respectively into 10 mL volumetric flask and make the volume with diluent.

[0093] HPLC Injection Sequence for representative samples are shown in **Table 5**.

[0094] **Table 5.**

| Sr. No. | Solution Name        | Number of Injection |
|---------|----------------------|---------------------|
| 1       | Blank                | 1                   |
| 2       | Sensitivity Solution | 1                   |

|   |                                    |   |
|---|------------------------------------|---|
| 3 | RS Standard Solution               | 6 |
| 4 | Assay Standard Solution            | 5 |
| 5 | Test Solution                      | 1 |
| 6 | Bracketing RS Standard solution    | 1 |
| 7 | Bracketing Assay Standard Solution | 1 |

[0095] HPLC system suitability requirements were as follows: (1). The relative standard deviation (RSD) of Phenobarbital peak from six replicate injections in assay/RS standard solution is no more than (NMT) 2.0%. (2). Tailing factor for the Phenobarbital is NMT 2.0. (3). The USP Plate count for Phenobarbital is not less than (NLT) 2500. (4). The S/N Ratio of the Sensitivity Standard Solution is NLT 10.

[0096] Impurity calculations were determined as follows:

[0097] For Assays:

$$\frac{Au}{As} \times \frac{Ws}{25} \times \frac{5}{20} \times \frac{25}{V} \times \frac{10}{1} \times \frac{P}{LC} \times \frac{Mw1}{Mw2}$$

[0098] For Related Substances (Known or Unknown impurity):

$$\frac{Au}{As} \times \frac{Ws}{25} \times \frac{5}{20} \times \frac{25}{V} \times \frac{10}{1} \times \frac{P}{LC} \times \frac{Mw1}{Mw2} \times \frac{RRF}{1}$$

[0099] Total Impurities: Known Impurities + Total Unknown Impurities. Note: Any individual unknown impurity and total unknown impurity uses the Related Substances formula.

[00100] Specifically, for the data shown in **Tables 2** and **3**, the Related Substances were calculated as follows:

% Area (Impurity, Known or Unknown) = (Area of Impurity Peak/Area of Phenobarbital Peak) x 100.

**[00101]** For the above calculations as shown in **[0095 and 0096]**

Au: Peak area of Phenobarbital in sample solution.

As: Average peak area of Phenobarbital in standard solution.

Ws: Weight of Phenobarbital standard in milligrams (mg).

V: Volume of sample solution.

LC: Label Claim of Phenobarbital Sodium.

P: Purity of Phenobarbital Standard.

Mw1: Molecular weight of Phenobarbital Sodium (254.22).

Mw2: Molecular weight of Phenobarbital Base (232.24).

RRF: Relative Response Factor for known and unknown impurity.

**[00102]** Representative chromatograms and/or corresponding calculations are shown in **Figs. 2A-2H, 3A-3L, 4A-4L, and Tables 2 and 3.**

**[00103]** 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 °2θ using a continuous scan of 6 °2θ per minute with an effective step size of 0.02 °2θ.

**[00104]** 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.

**[00105]** 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 composition consisting essentially of lyophilized amorphous Phenobarbital Sodium.
2. The composition of claim 1, wherein the lyophilized amorphous Phenobarbital Sodium is no less than 98.5% of the composition.
3. A method of producing a storage-stable form of lyophilized Phenobarbital sodium that forms no more than 0.2% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution, the method comprising:
  - adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution;
  - if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and
  - lyophilizing the Phenobarbital Sodium solution.
4. The method of claim 3, wherein the water is deionized water.
5. The method of claim 4, wherein the deionized water is sparged with nitrogen prior to adding the Phenobarbital Sodium.
6. The method of claim 5, wherein the deionized water is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital Sodium.
7. The method of any one of claims 3-6, wherein the water is cooled to or between 5 to 10°C prior to adding the Phenobarbital Sodium.
8. The method of claim 3, wherein the adjusting comprises measuring the pH of the Phenobarbital Sodium solution, and wherein if the pH is higher than 10.2, the adjusting comprises adding Hydrochloric acid (HCl).
9. The method of claim 3, wherein the lyophilized Phenobarbital Sodium forms no more than 0.1% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage

of the lyophilized Phenobarbital Sodium for up to 6 months at RT and ACC stability storage conditions.

10. The method of claim 3, wherein the lyophilized Phenobarbital Sodium forms no more than 0.05% phenylethylacetylurea (PEAU) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at RT and ACC stability storage conditions.
11. The method of claim 3, wherein the lyophilized Phenobarbital Sodium forms no detectable amount of 2-ethyl-2-phenylmalonamide (2EPMM) or alpha-phenylbutyrylguanidine (PBG) when reconstituted in an aqueous solution after storage of the lyophilized Phenobarbital Sodium for up to 6 months at RT and ACC stability storage conditions.
12. The method of claim 3, wherein the lyophilized Phenobarbital Sodium is stable up to at least 6 months at ACC stability storage conditions which is equivalent to 24 months at RT.
13. The method of claim 12, wherein the stability of the lyophilized Phenobarbital Sodium is determined by adding the lyophilized Phenobarbital Sodium to an aqueous solution to form a reconstituted lyophilized Phenobarbital Sodium and measuring amount of phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG) in the reconstituted lyophilize Phenobarbital Sodium.
14. The method of claim 3, wherein the Phenobarbital Sodium solution is at a concentration of 65 mg/mL or 130 mg/mL.
15. The method of claim 3, further comprising filtering the Phenobarbital Sodium solution prior to lyophilizing.
16. The method of claim 3, further comprising:
  - aliquoting the Phenobarbital Sodium solution into a vial prior to lyophilization; and
  - after lyophilization, applying a closure to the vial under vacuum.

17. A method of reducing formation of degradation products of Phenobarbital Sodium reconstituted in an aqueous solution, the method comprising:

adding Phenobarbital Sodium to water to form a Phenobarbital Sodium solution;

if necessary, adjusting the pH of the Phenobarbital Sodium solution to or between 9.2 to 10.2; and

Lyophilizing the Phenobarbital Sodium solution to form stable lyophilized Phenobarbital sodium.

18. The method of claim 17, wherein the water is deionized water.

19. The method of claim 18, wherein the deionized water is sparged with nitrogen prior to adding the Phenobarbital Sodium.

20. The method of claim 18, wherein the deionized water is sparged with nitrogen for at least 30 minutes prior to adding the Phenobarbital sodium.

21. The method of any one of claims 17-20, wherein the water is cooled to or between 5 to 10°C prior to adding the Phenobarbital Sodium.

22. The method of claim 17, wherein the adjusting comprises measuring the pH of the Phenobarbital Sodium solution, and wherein if the pH is higher than 10.2, the adjusting comprises adding Hydrochloric acid (HCl).

23. The method of claim 17, wherein the degradation products are phenylethylacetylurea (PEAU), 2-ethyl-2-phenylmalonamide (2EPMM), and/or alpha-phenylbutyrylguanidine (PBG), and measuring formation of the degradation products comprises:

reconstituting the stable lyophilized Phenobarbital Sodium in an aqueous solution to form a reconstituted solution; and

measuring amount of PEAU, 2 EPMM, and/or PBG in the reconstituted solution.

24. The method of claim 23, wherein the reconstituted solution comprises no less than 96% Phenobarbital Sodium.
25. The composition of claim 23, wherein the reconstituted solution comprises no less than 97% Phenobarbital Sodium.
26. The composition of claim 23, wherein the reconstituted solution comprises no less than 98% Phenobarbital Sodium.
27. The composition of claim 23, wherein the reconstituted solution comprises no more than 0.20% PEAU, 2 EPMM, and/or PBG after storage of the stable lyophilized Phenobarbital Sodium for up to 6 months when stored at RT and ACC stability conditions.
28. A method of treating an individual in need of Phenobarbital Sodium, the method comprising:
  - adding saline or dextrose to the composition of claim 1 immediately prior to administration to form a Phenobarbital Sodium solution; and
  - administering the Phenobarbital Sodium solution to the individual.
29. The method of claim 28, wherein the individual suffers from epilepsy.
30. The method of claim 29, wherein the individual is a newborn suffering from neonatal epilepsy.
31. The method of claim 28, wherein the composition is a powder dose of 65 mg or 130 mg.
32. The method of claim 28, wherein the administering comprises intramuscular injection or intravenous injection.
33. A pharmaceutical product comprising:
  - a vial containing the composition of claim 1 for reconstitution prior to administration, the composition having been lyophilized in the vial, wherein the vial comprises a closure having been placed to seal the vial after lyophilization under vacuum.
34. A lyophilized amorphous Phenobarbital Sodium.

#### **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

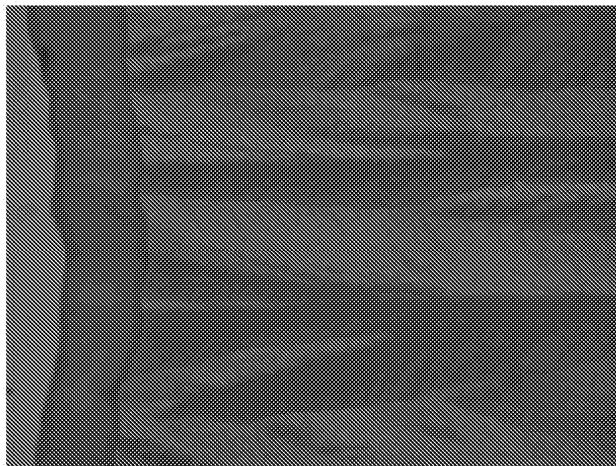


Fig. 1C

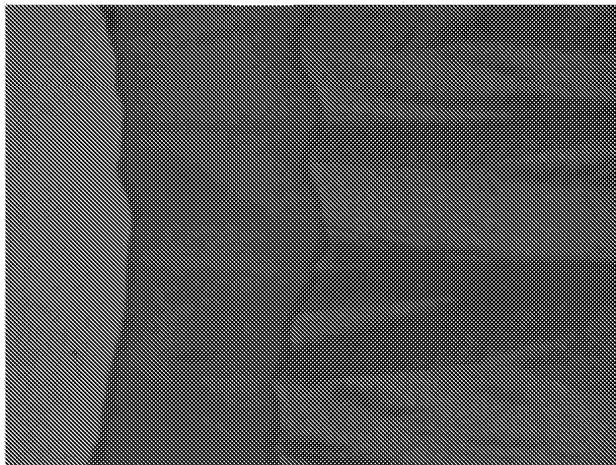


Fig. 1D

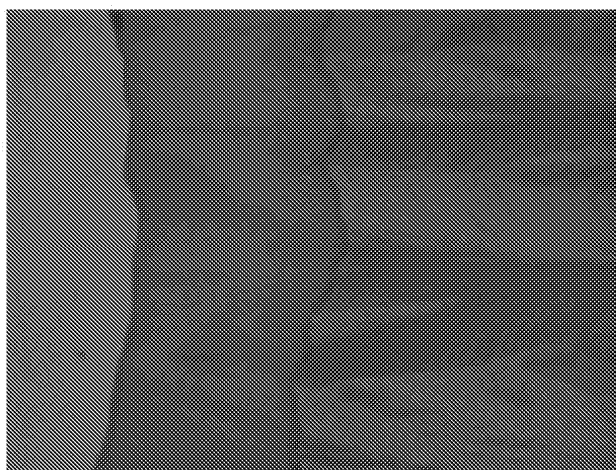


Fig. 1E

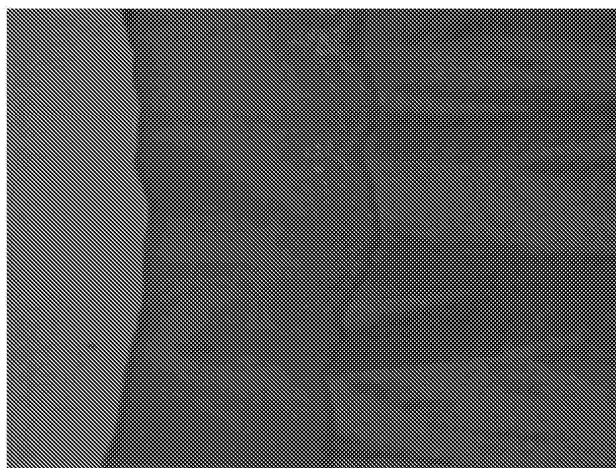


Fig. 1F

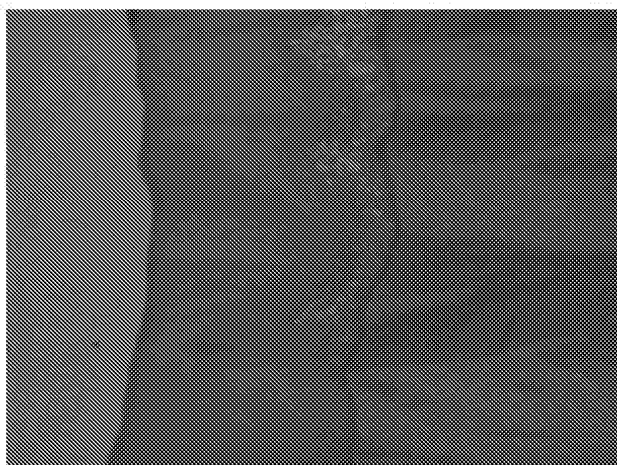


Fig. 2A

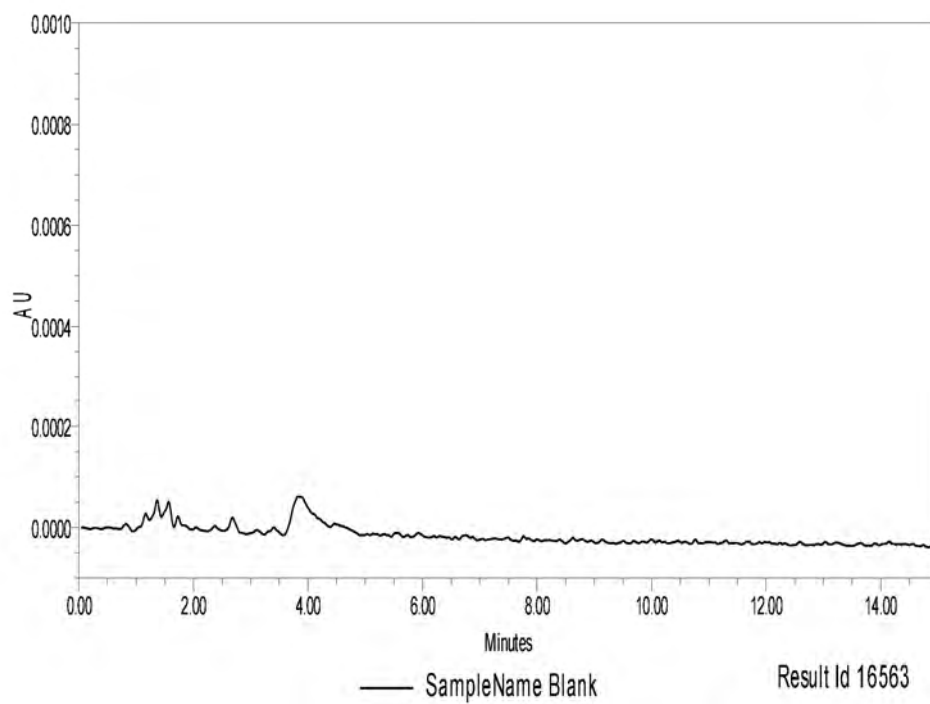
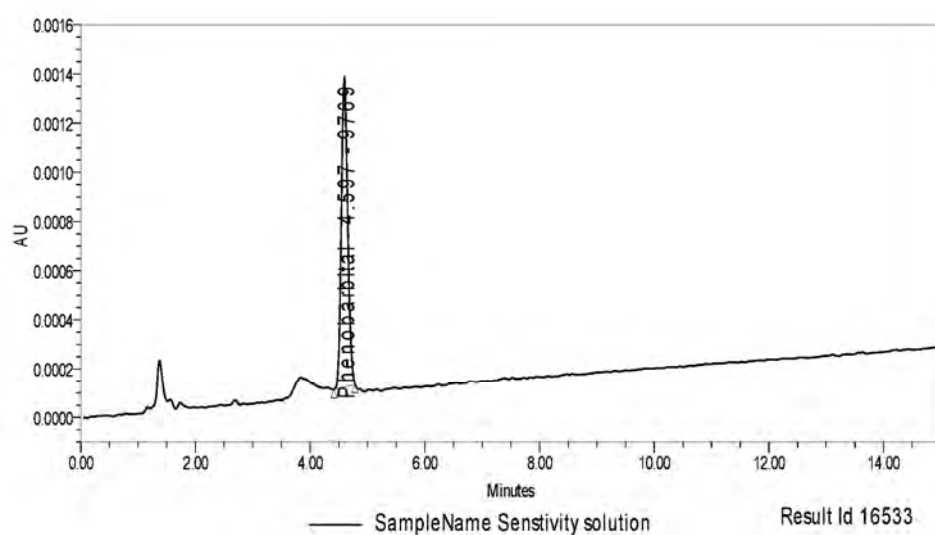
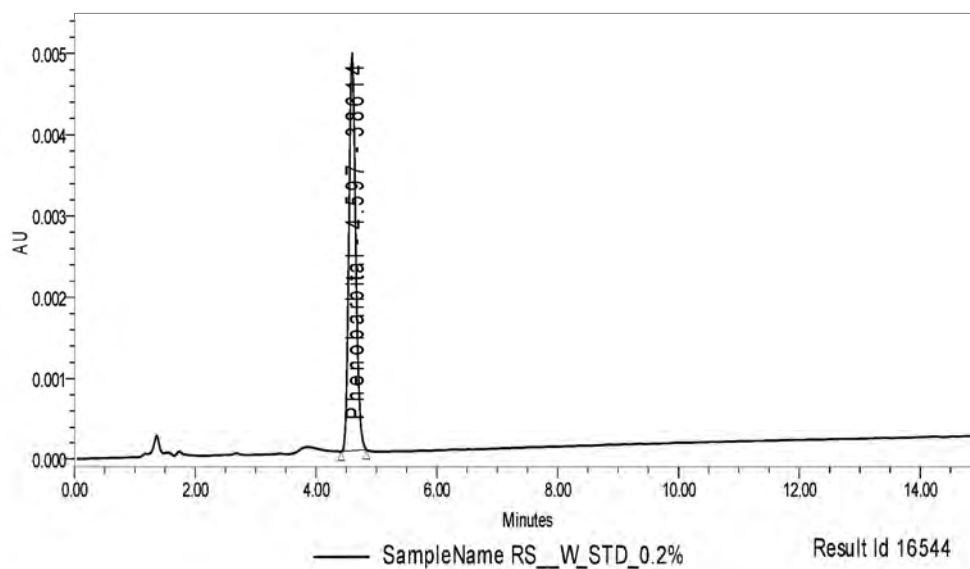


Fig. 2B



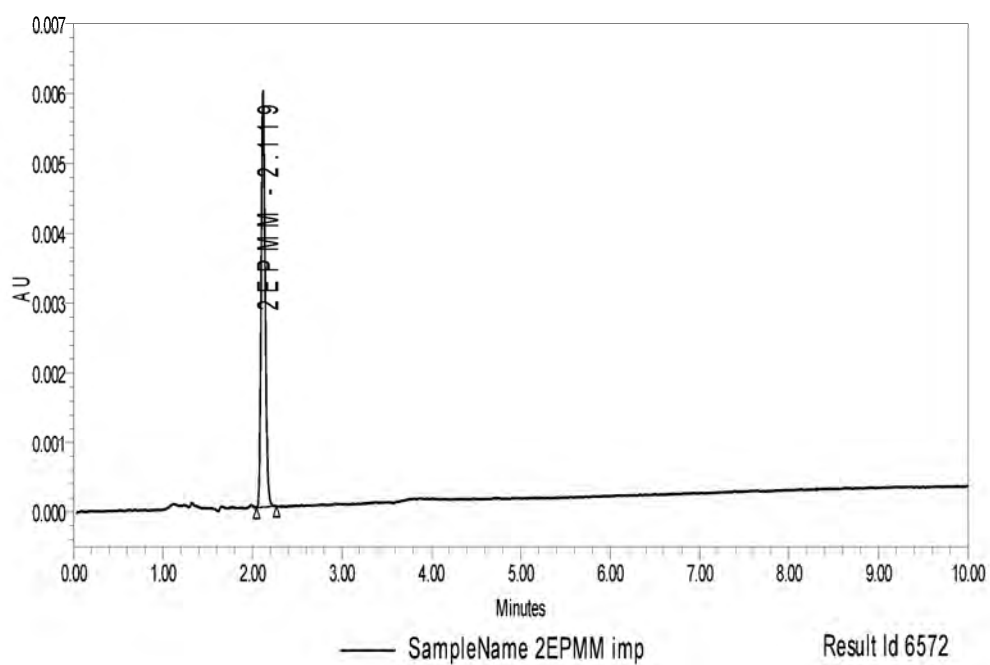
|   | PeakName      | RT    | Area | s/n         | USP<br>Plate<br>Count | USP<br>Tailing |
|---|---------------|-------|------|-------------|-----------------------|----------------|
| 1 | Phenobarbital | 4.597 | 9769 | 1054.848570 | 7861.1                | 1.1            |

Fig. 2C



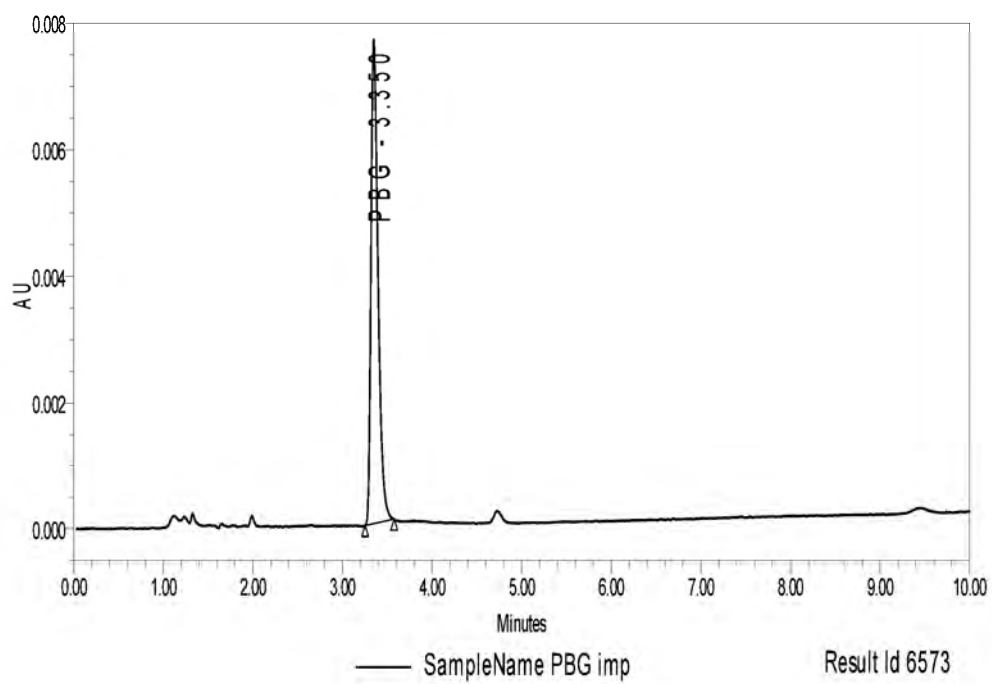
|   | Peak Name     | RT    | Area  | Amount | s/n         | USP<br>Plate<br>Count | USP<br>Tailing |
|---|---------------|-------|-------|--------|-------------|-----------------------|----------------|
| 1 | Phenobarbital | 4.597 | 38614 | 0.001  | 2906.846635 | 7746.3                | 1.2            |

Fig. 2D



|   | Peak Name | RT    | Area  | % Area | s/n  | USP<br>Plate<br>Count | USP<br>Tailing | Purity1<br>Angle | Purity1<br>Threshold |
|---|-----------|-------|-------|--------|------|-----------------------|----------------|------------------|----------------------|
| 1 | 2EPMM     | 2.119 | 18797 | 100.00 | 1472 | 10573.6               | 1.2            | 0.674            | 1.833                |

Fig. 2E



|   | PeakName | RT    | Area  | % Area | s/n  | USP<br>Plate<br>Count | USP<br>Tailing | Purity1<br>Angle | Purity1<br>Threshold |
|---|----------|-------|-------|--------|------|-----------------------|----------------|------------------|----------------------|
| 1 | PBG      | 3.350 | 41776 | 100.00 | 2090 | 8801.9                | 1.5            | 21.648           | 62.982               |

Fig. 2F

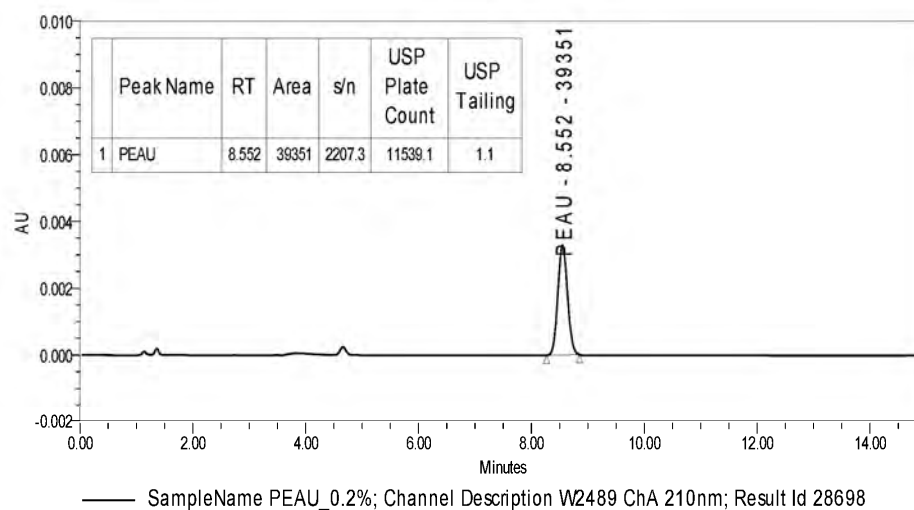


Fig. 2G

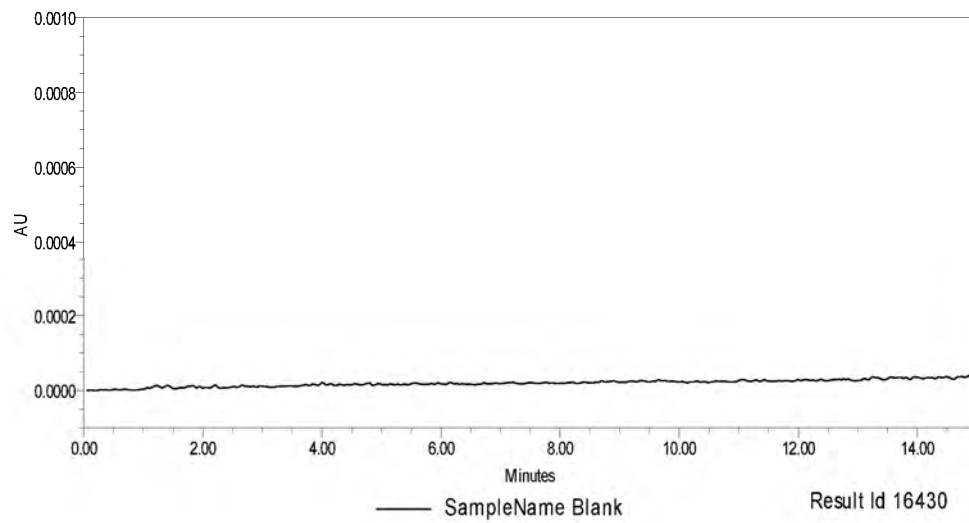
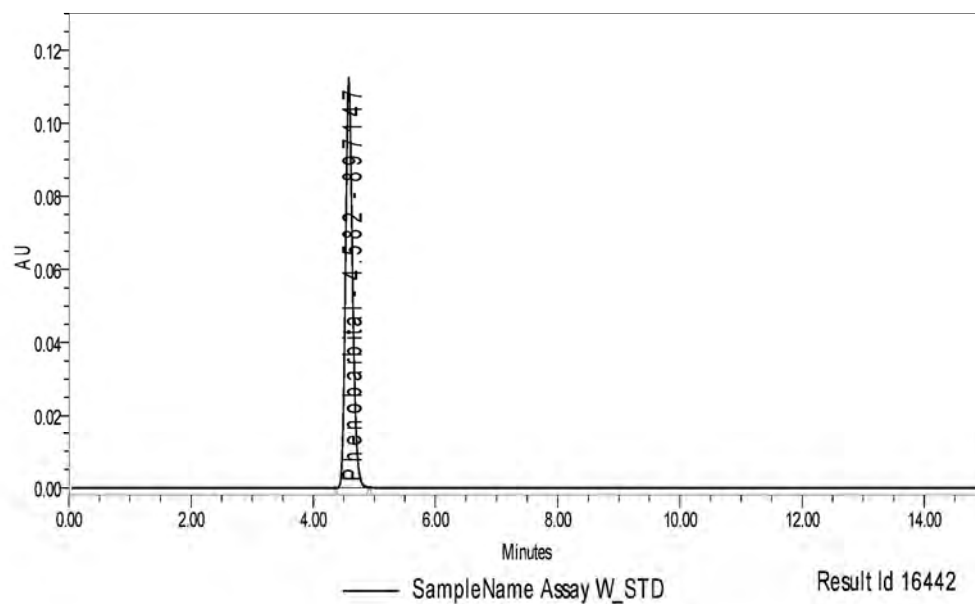
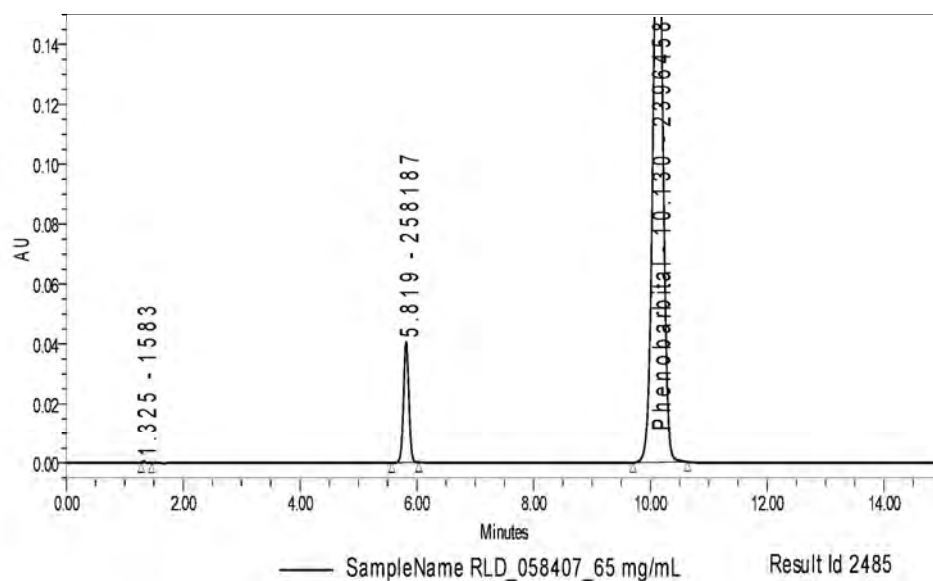


Fig. 2H



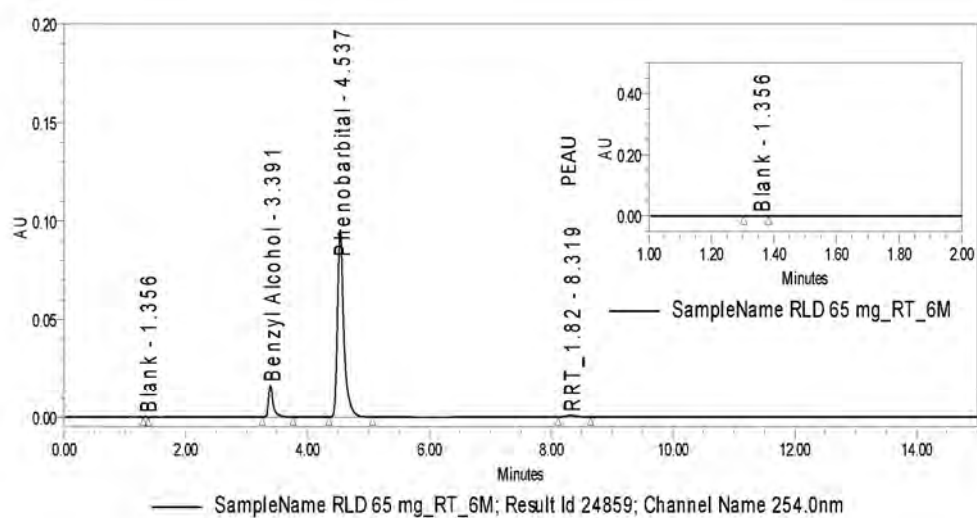
|   | Peak Name     | RT    | Area   | Amount | s/n          | USP<br>Plate<br>Count | USP<br>Tailing |
|---|---------------|-------|--------|--------|--------------|-----------------------|----------------|
| 1 | Phenobarbital | 4.582 | 897147 | 0.476  | 50940.058185 | 7493.0                | 1.2            |

Fig. 3A



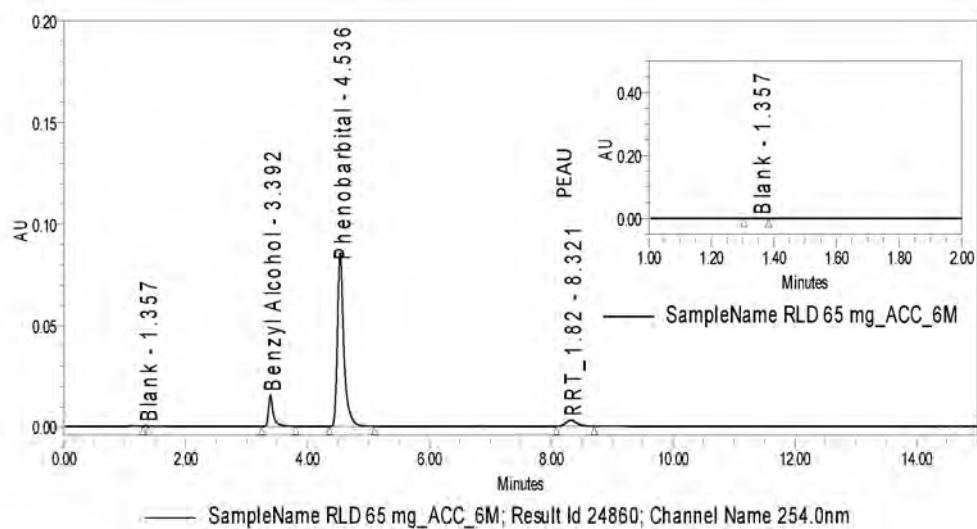
|   | Peak Name     | RT     | Area    | Amount | USP Resolution | USP Plate Count | USP Tailing | Assay |
|---|---------------|--------|---------|--------|----------------|-----------------|-------------|-------|
| 1 | Phenobarbital | 10.130 | 2396458 | 60.823 | 17.9           | 17534.1         | 1.0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

Fig. 3B



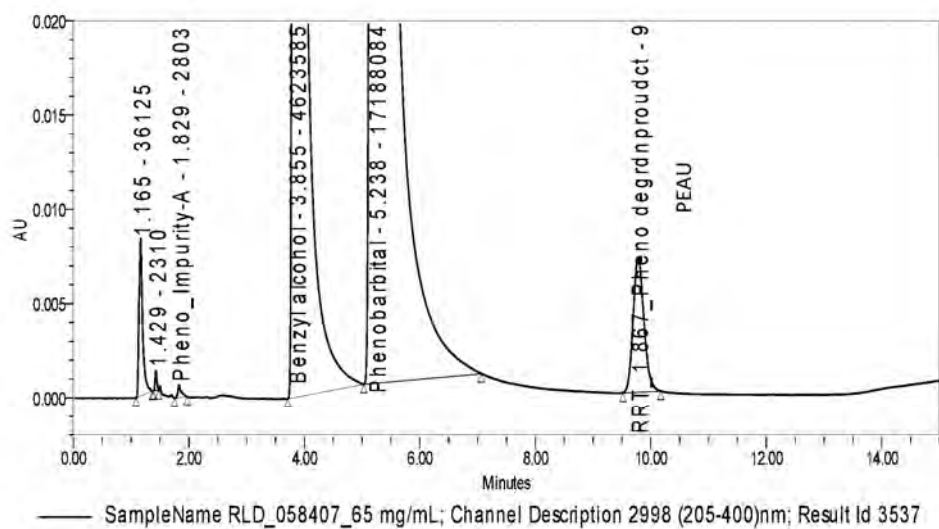
|   | PeakName       | RT    | Area   | % Area | Amount | Units | Assay | USP Resolution | USP Tailing |
|---|----------------|-------|--------|--------|--------|-------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.391 | 87091  | 10.96  | 14.994 | mg/mL | 105.2 | 23.7           | 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



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

Fig. 3D



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

Fig. 3E

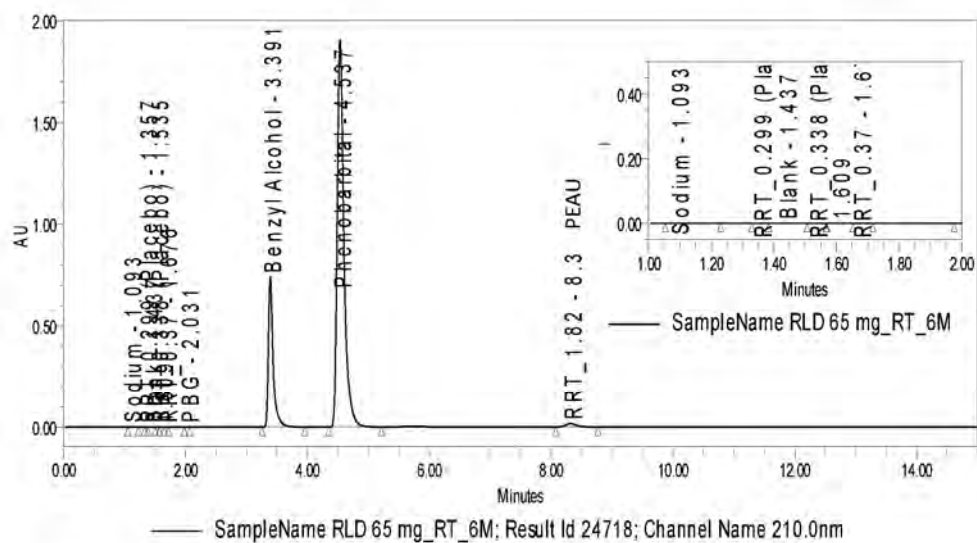
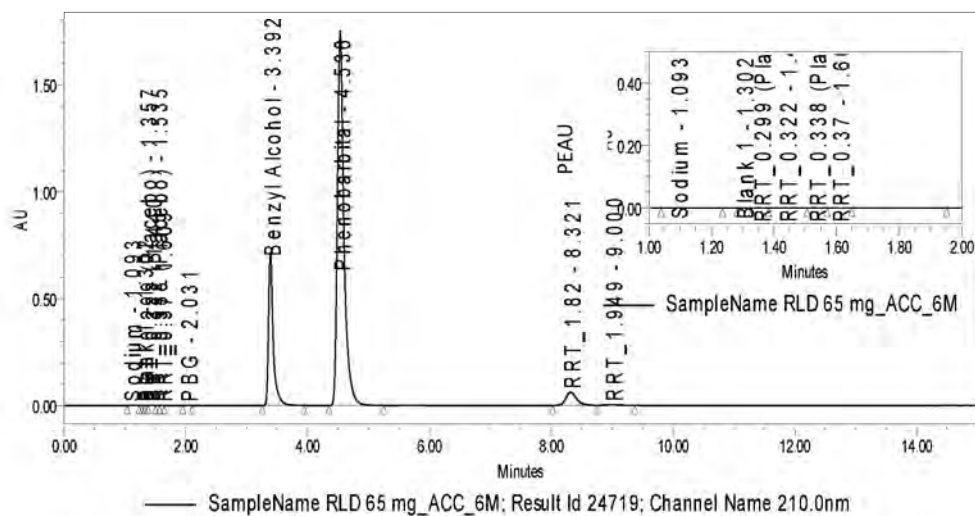
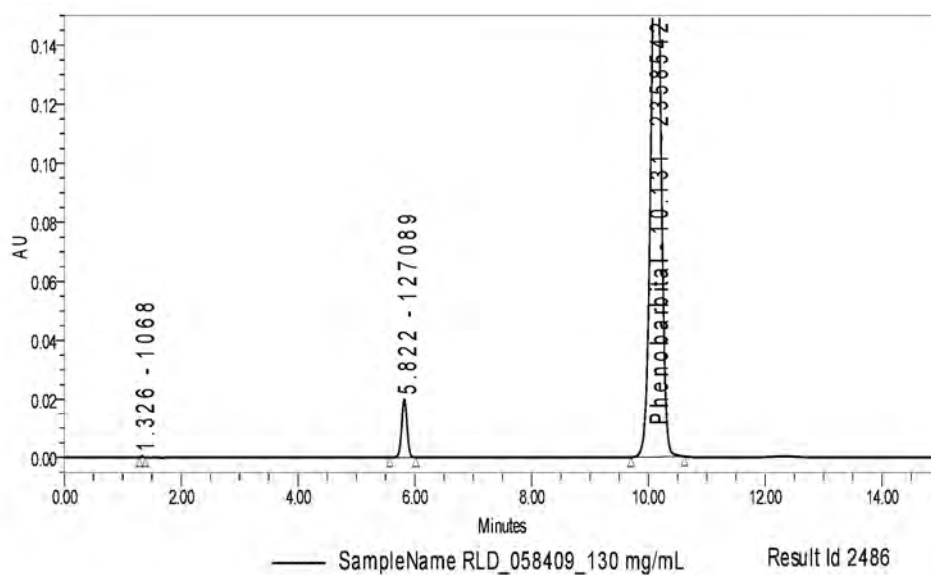


Fig. 3F



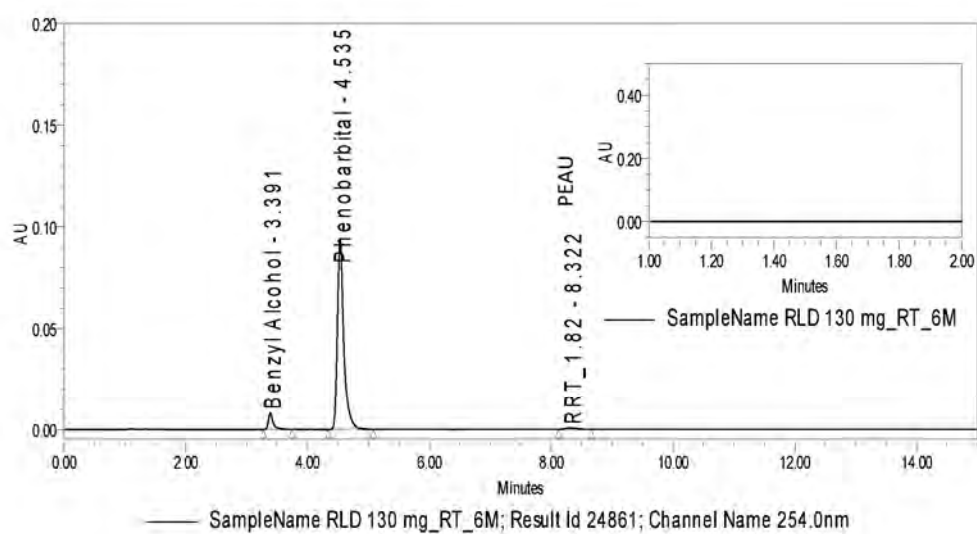
|   | Peak Name      | RT    | Area     | % Area | Amount | Units | USP Resolution | USP Tailing |
|---|----------------|-------|----------|--------|--------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.392 | 3833550  | 21.50  | 15.701 | mg/mL | 12.8           | 1.7         |
| 2 | 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



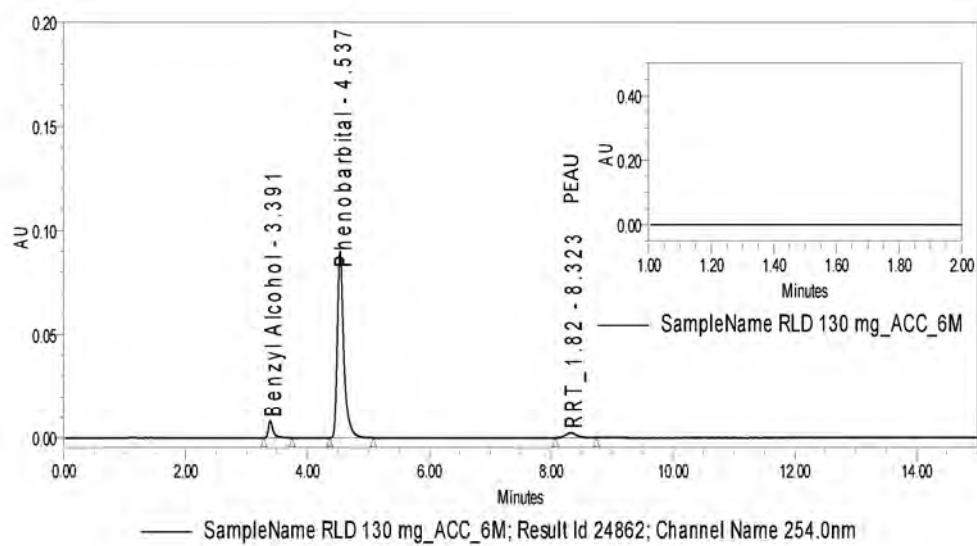
|   | PeakName      | RT     | Area    | Amount  | USP<br>Resolution | USP<br>Plate<br>Count | USP<br>Tailing | Assay |
|---|---------------|--------|---------|---------|-------------------|-----------------------|----------------|-------|
| 1 | Phenobarbital | 10.131 | 2358542 | 119.721 | 17.9              | 17563.1               | 1.0            | 110.3 |

Fig. 3H



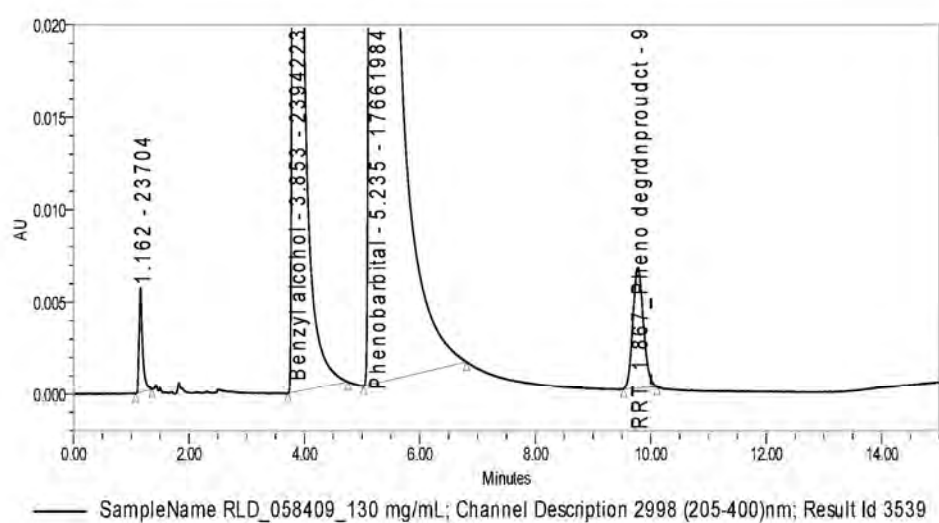
|   | PeakName       | RT    | Area   | % Area | Amount  | Units | Assay | USP Resolution | USP Tailing |
|---|----------------|-------|--------|--------|---------|-------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.391 | 43232  | 5.84   | 14.886  | mg/mL | 104.5 |              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

Fig. 3I



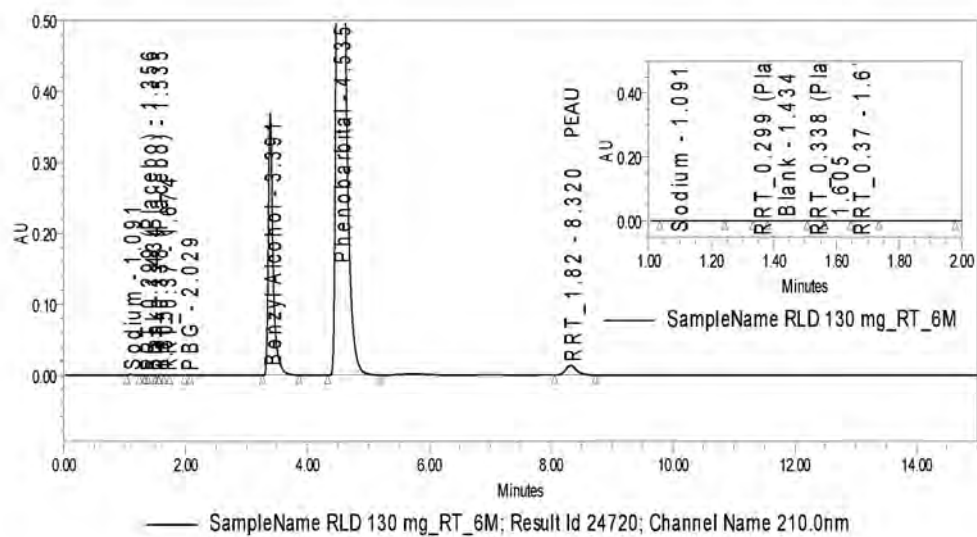
|   | Peak Name      | RT    | Area   | % Area | Amount  | Units | Assay | USP Resolution | USP Tailing |
|---|----------------|-------|--------|--------|---------|-------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.391 | 43440  | 5.94   | 14.958  | mg/mL | 105.0 |              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

Fig. 3J



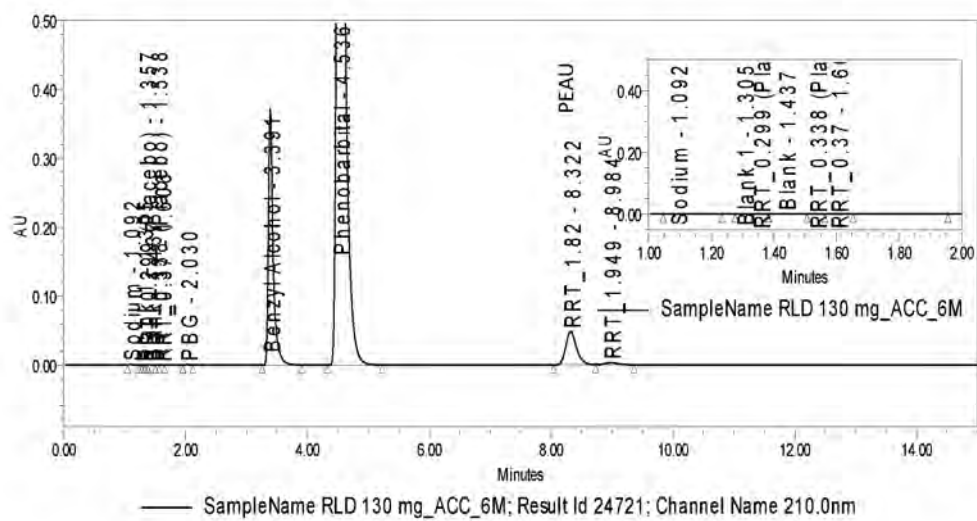
|   | Peak Name                    | RT    | Area     | % Area | USP Resolution | s/n    | USP Plate Count | USP Tailing |
|---|------------------------------|-------|----------|--------|----------------|--------|-----------------|-------------|
| 1 | Benzyl alcohol               | 3.853 | 2394223  | 11.87  | 20.8           | 223.9  | 12438.0         | 1.5         |
| 2 | Phenobarbital                | 5.235 | 17661984 | 87.59  | 8.0            | 1144.4 | 11214.3         | 1.4         |
| 3 | RRT_1.867_Pheno degrdnprodct | 9.776 | 83640    | 0.41   | 16.6           | 3.5    | 13612.7         | 1.1         |

Fig. 3K



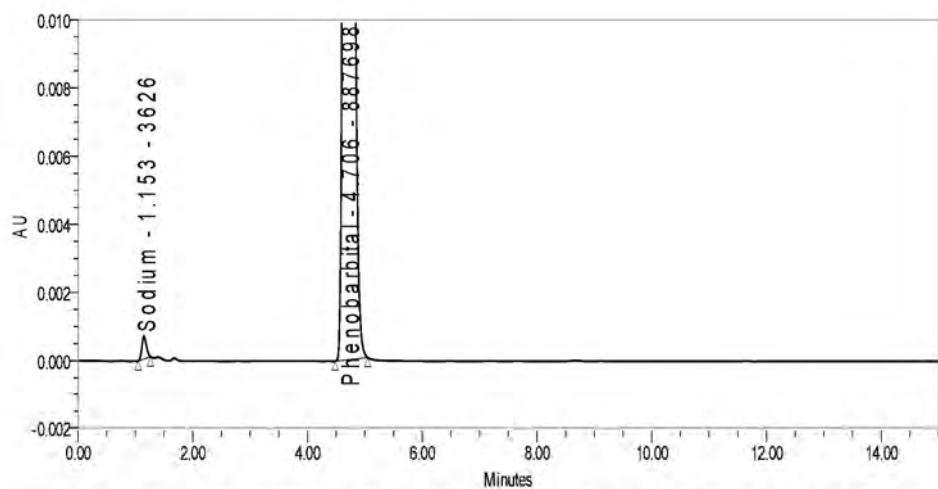
|   | PeakName       | RT    | Area     | % Area | Amount  | Units | USP Resolution | USP Tailing |
|---|----------------|-------|----------|--------|---------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.391 | 1963213  | 11.91  | 16.081  | mg/mL | 13.4           | 1.7         |
| 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



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

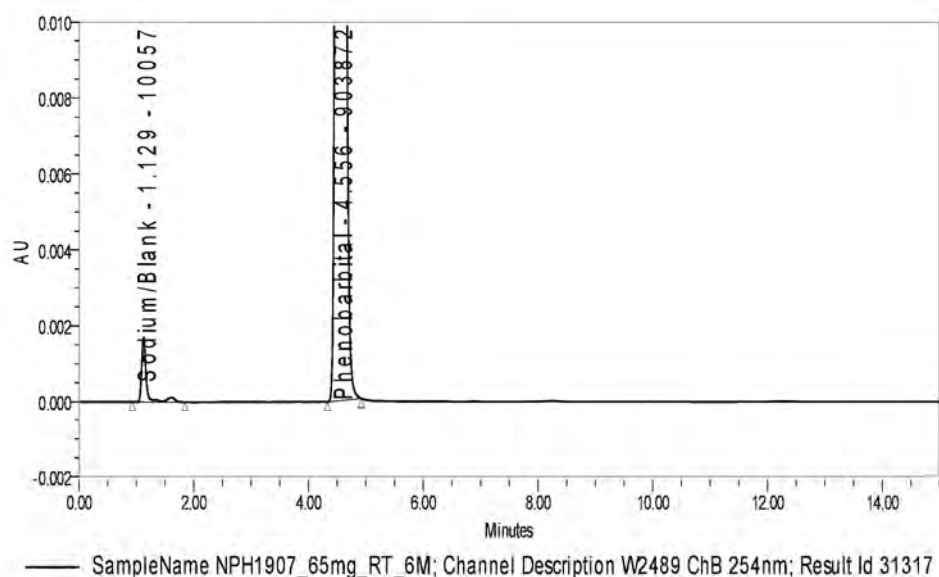
Fig. 4A



SampleName #NPH1907\_Lyo\_65mg/mL\_Initial; Channel Description W2489 ChB 254nm; Result Id 13991

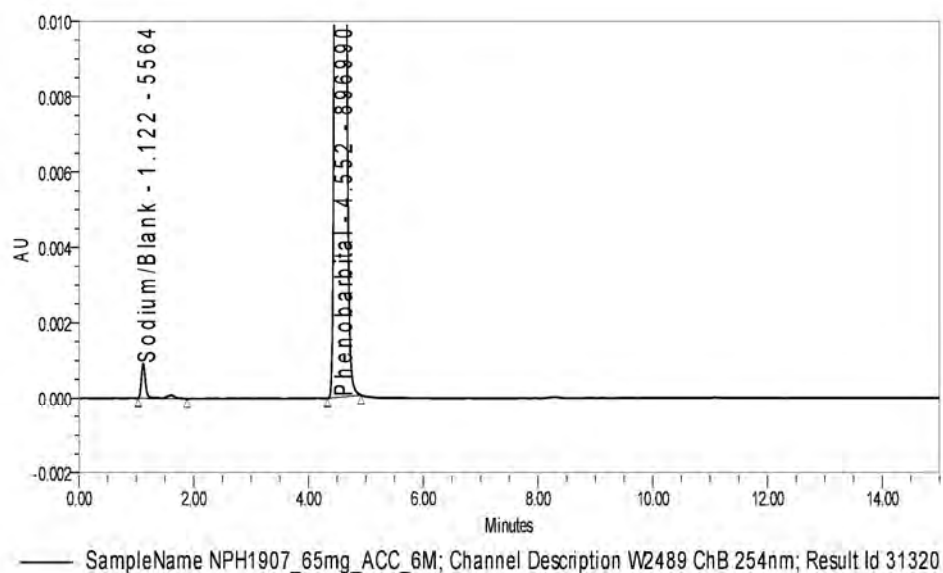
|   | Peak Name     | RT    | Area   | Amount | Units | Assay | USP Resolution | s/n     | USP Plate Count | USP Tailing |
|---|---------------|-------|--------|--------|-------|-------|----------------|---------|-----------------|-------------|
| 1 | Phenobarbital | 4.706 | 887698 | 58.858 | mg/mL | 99.1  | 19.3           | 52343.5 | 7952.5          | 1.2         |
| 2 | Sodium        | 1.153 | 3626   |        |       |       |                | 318.4   | 943.9           | 1.1         |

Fig. 4B



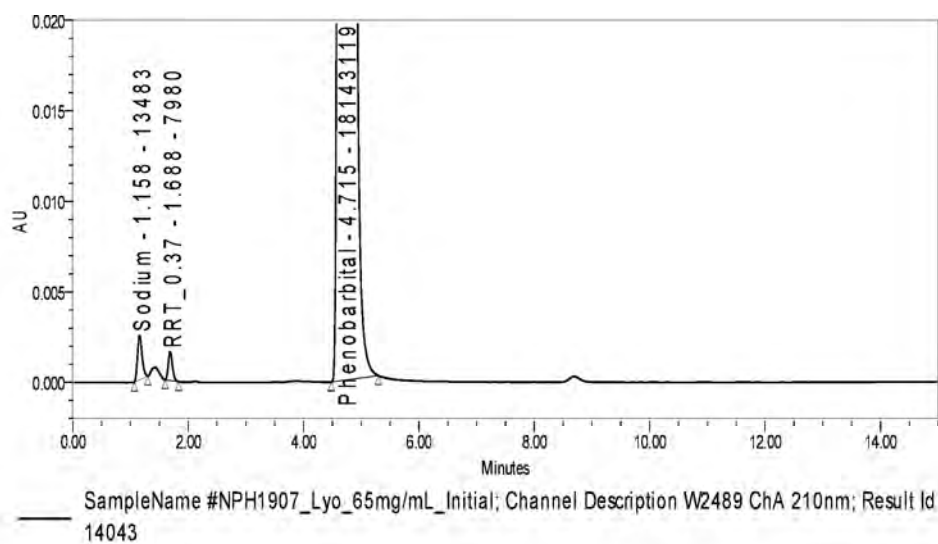
|   | PeakName      | RT    | Area   | Amount | Units | Assay | USP Resolution | s/n     | USP Plate Count | USP Tailing |
|---|---------------|-------|--------|--------|-------|-------|----------------|---------|-----------------|-------------|
| 1 | Phenobarbital | 4.556 | 903872 | 59.388 | mg/mL | 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



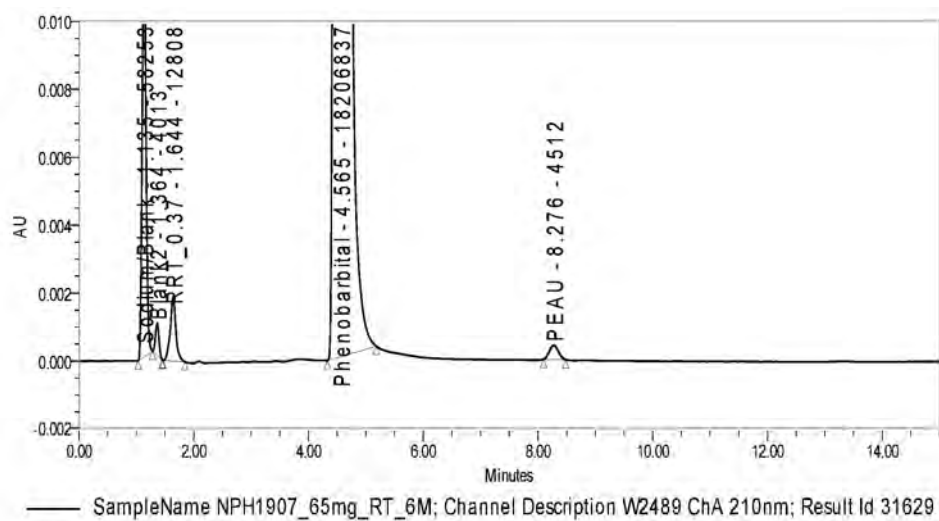
|   | PeakName      | RT    | Area   | Amount | Units | Assay | USP Resolution | s/n     | USP Plate Count | USP Tailing |
|---|---------------|-------|--------|--------|-------|-------|----------------|---------|-----------------|-------------|
| 1 | Phenobarbital | 4.552 | 896990 | 58.936 | mg/mL | 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



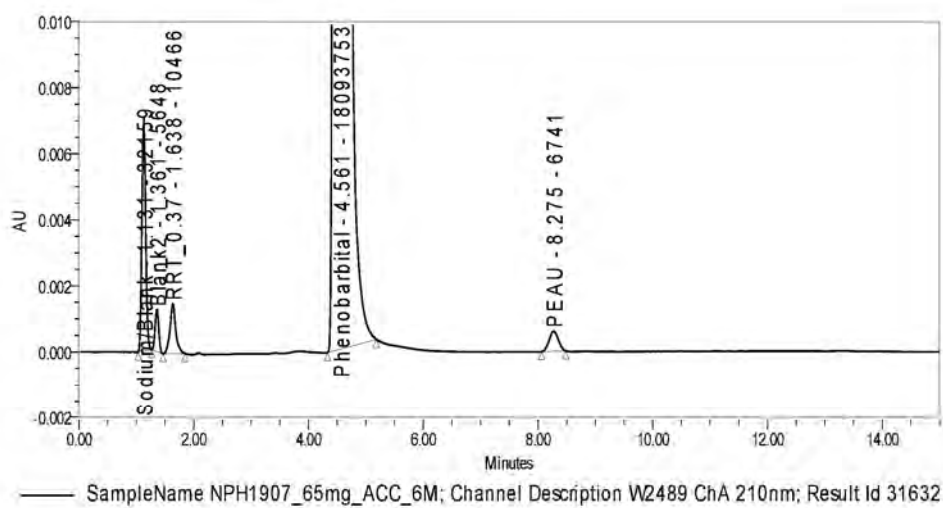
|   | Peak Name     | RT    | Area     | % Area | Amount | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|--------|-------|----------------|-----------|-----------------|-------------|
| 1 | Phenobarbital | 4.715 | 18143119 | 99.88  | 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



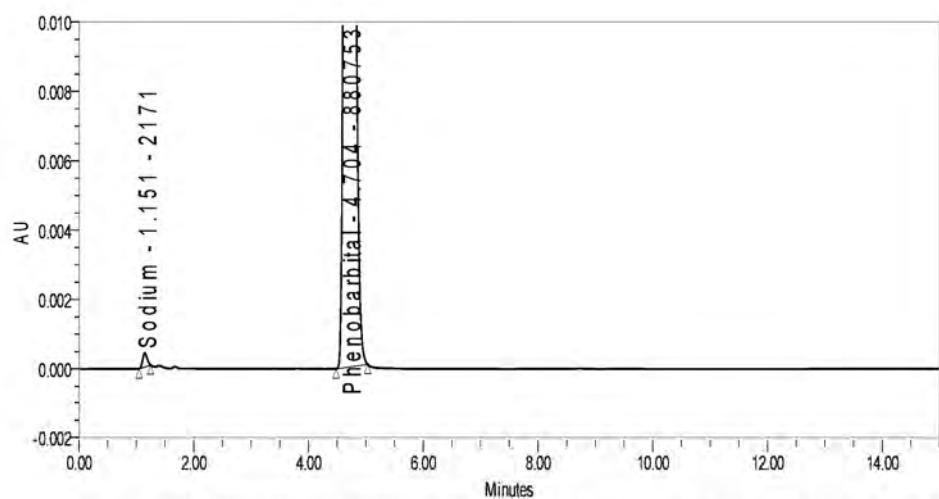
|   | PeakName      | RT    | Area     | % Area | Amount | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|--------|-------|----------------|-----------|-----------------|-------------|
| 1 | Blank2        | 1.364 | 4013     | 0.02   |        |       | 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 | Sodium/Blank  | 1.135 | 58253    | 0.32   | 0.173  | mg/mL |                | 8406.1    | 1363.0          | 1.1         |

Fig. 4F



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

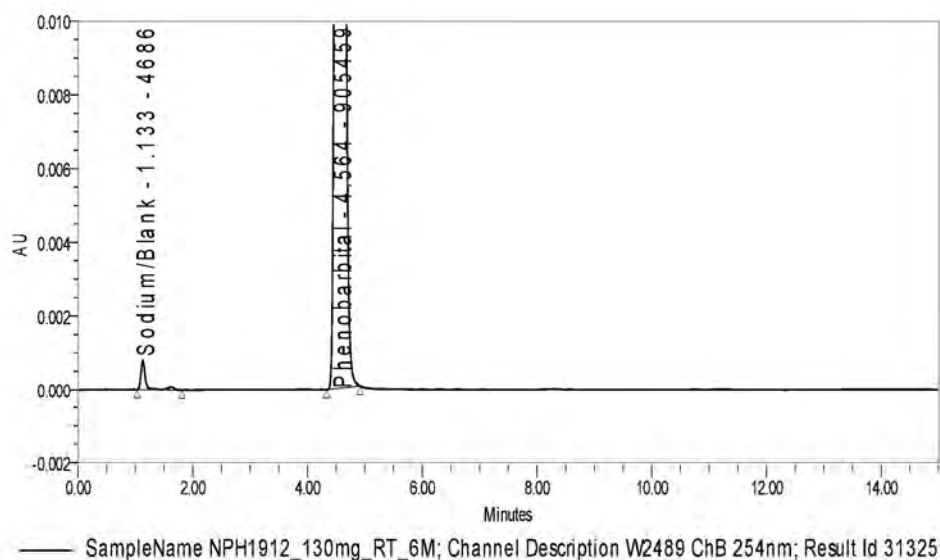
Fig. 4G



SampleName #NPH1912\_Lyo\_130mg/mL\_Initial; Channel Description W2489 ChB 254nm; Result Id 13996

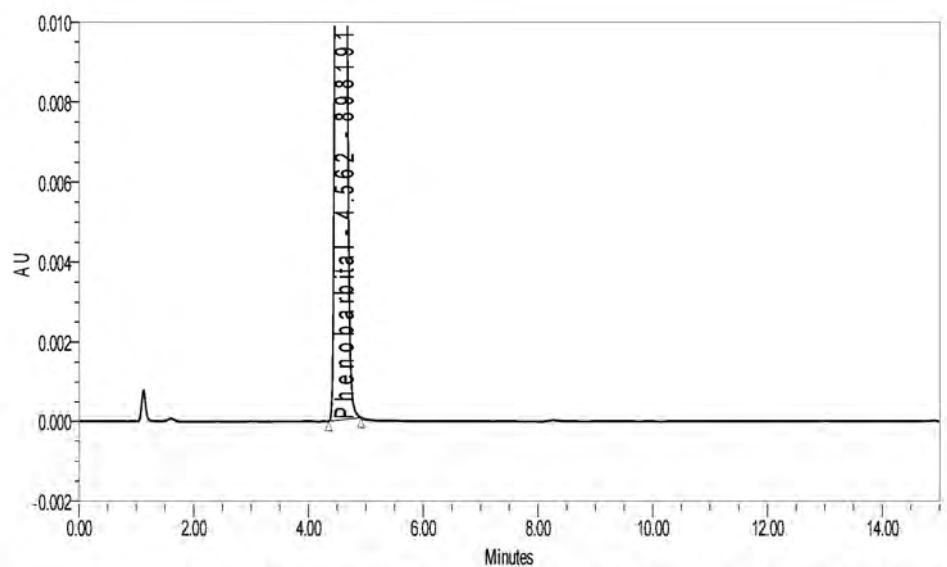
|   | Peak Name     | RT    | Area   | Amount  | Units | Assay | USP Resolution | s/n     | USP Plate Count | USP Tailing |
|---|---------------|-------|--------|---------|-------|-------|----------------|---------|-----------------|-------------|
| 1 | Phenobarbital | 4.704 | 880753 | 116.796 | mg/mL | 98.3  | 19.3           | 40192.1 | 7866.8          | 1.2         |
| 2 | Sodium        | 1.151 | 2171   |         |       |       |                | 148.3   | 959.0           | 1.0         |

Fig. 4H



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

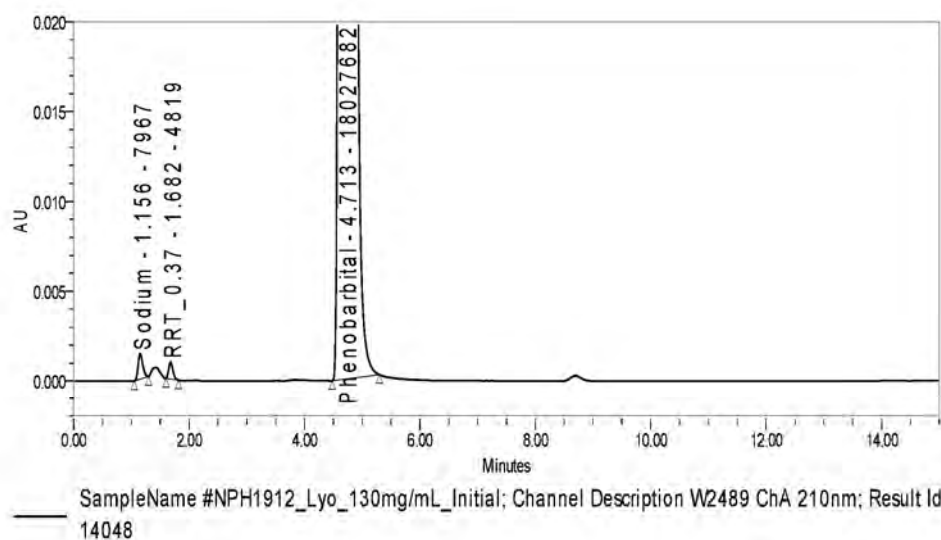
Fig. 4I



— SampleName NPH1912\_130mg\_ACC\_6M; Channel Description W2489 ChB 254nm; Result Id 31328

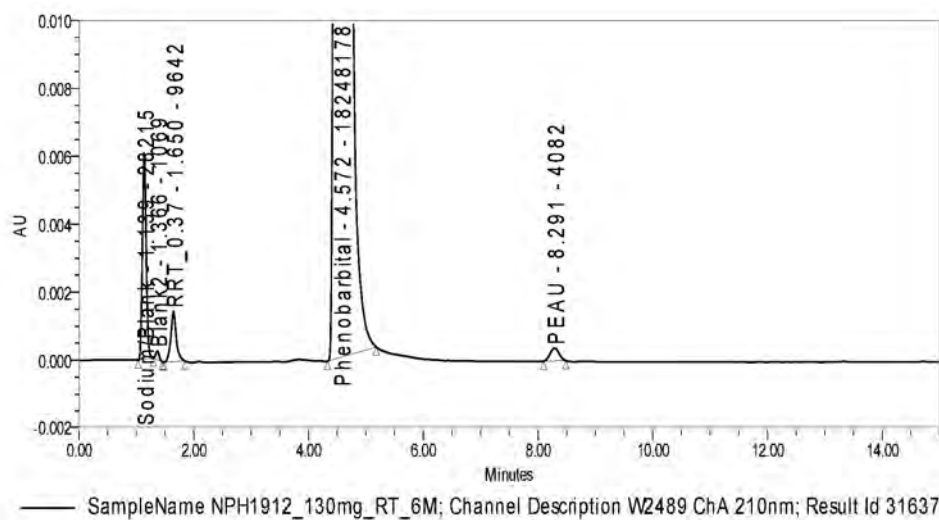
|   | Peak Name     | RT    | Area   | Amount  | Units | Assay | s/n     | USP<br>Plate<br>Count | USP<br>Tailing |
|---|---------------|-------|--------|---------|-------|-------|---------|-----------------------|----------------|
| 1 | Phenobarbital | 4.562 | 898191 | 118.030 | mg/mL | 99.4  | 55375.6 | 8693.8                | 1.1            |

Fig. 4J



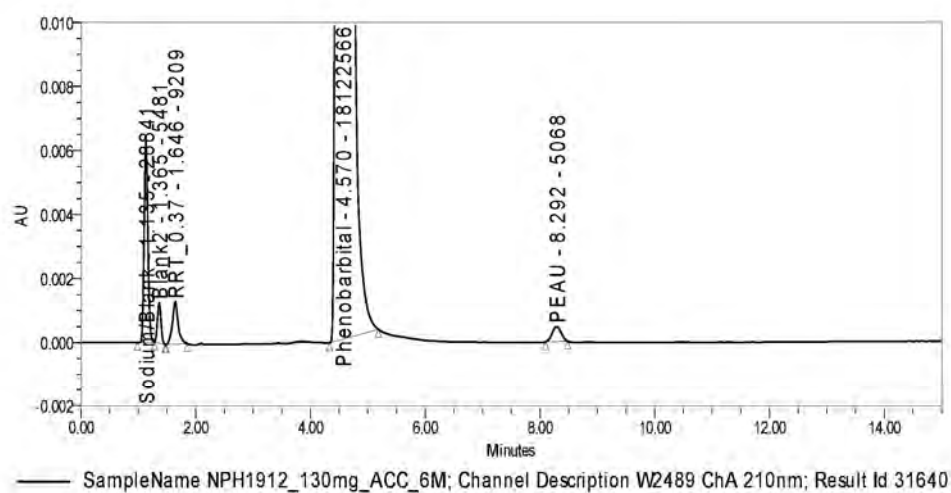
|   | PeakName      | RT    | Area     | % Area | Amount  | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|---------|-------|----------------|-----------|-----------------|-------------|
| 1 | Phenobarbital | 4.713 | 18027682 | 99.93  | 116.995 | mg/mL | 17.0           | 1001026.6 | 7649.3          | 1.2         |
| 2 | RRT_0.37      | 1.682 | 4819     | 0.03   | 0.031   | mg/mL | 3.6            | 433.7     | 2401.3          | 1.2         |
| 3 | Sodium        | 1.156 | 7967     | 0.04   | 0.052   | mg/mL |                | 649.1     | 941.5           | 1.1         |

Fig. 4K



|   | Peak Name     | RT    | Area     | % Area | Amount  | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|---------|-------|----------------|-----------|-----------------|-------------|
| 1 | Blank2        | 1.366 | 1069     | 0.01   |         |       | 1.9            | 143.5     | 2247.2          | 1.1         |
| 2 | PEAU          | 8.291 | 4082     | 0.02   | 0.024   | mg/mL | 14.8           | 213.9     | 12463.8         | 1.0         |
| 3 | Phenobarbital | 4.572 | 18248178 | 99.76  | 108.187 | mg/mL | 15.9           | 1373502.2 | 8426.5          | 1.1         |
| 4 | RRT_0.37      | 1.650 | 9642     | 0.05   | 0.057   | mg/mL | 2.0            | 832.7     | 1618.4          | 1.1         |
| 5 | Sodium/Blank  | 1.139 | 28215    | 0.15   | 0.167   | mg/mL |                | 3438.2    | 1382.8          | 1.1         |

Fig. 4L



|   | PeakName      | RT    | Area     | % Area | Amount  | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|---------|-------|----------------|-----------|-----------------|-------------|
| 1 | Blank2        | 1.365 | 5481     | 0.03   |         |       | 1.9            | 687.2     | 2149.1          | 1.1         |
| 2 | PEAU          | 8.292 | 5068     | 0.03   | 0.030   | mg/mL | 14.8           | 256.0     | 12320.6         | 1.0         |
| 3 | Phenobarbital | 4.570 | 18122566 | 99.73  | 107.442 | mg/mL | 15.1           | 1320858.2 | 8330.4          | 1.1         |
| 4 | RRT_0.37      | 1.646 | 9209     | 0.05   | 0.055   | mg/mL | 1.8            | 725.3     | 1481.0          | 1.1         |
| 5 | Sodium/Blank  | 1.135 | 28841    | 0.16   | 0.171   | mg/mL |                | 3440.5    | 1392.6          | 1.1         |

Fig. 5A

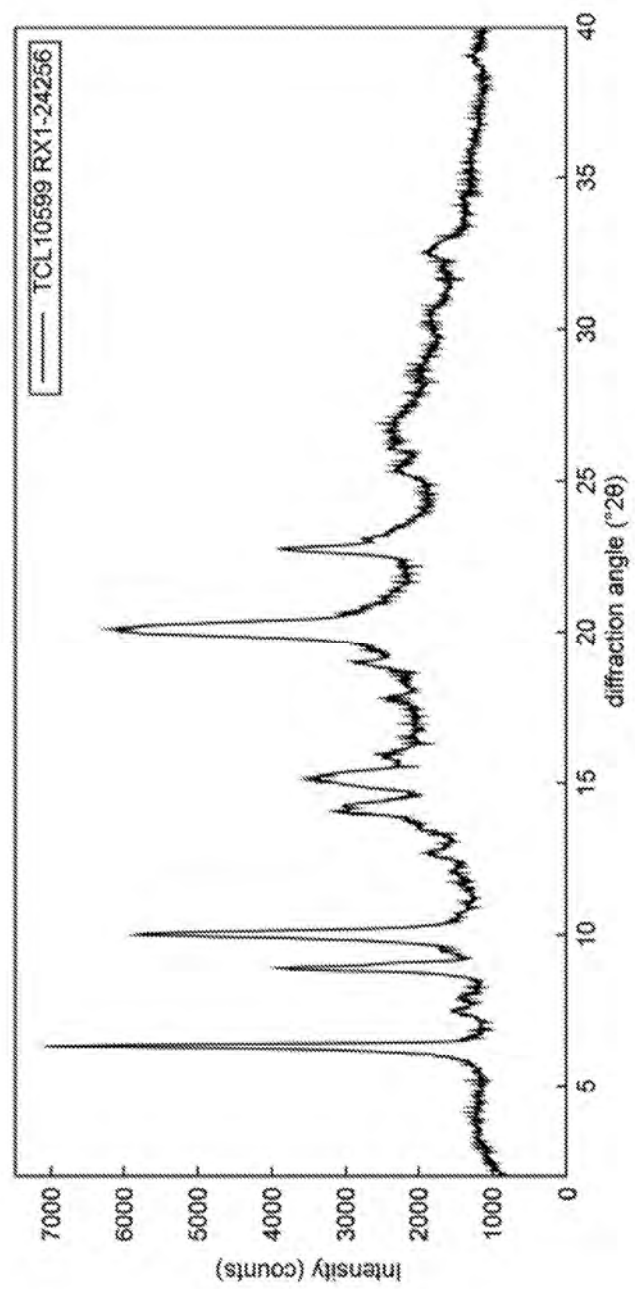


Fig. 5B

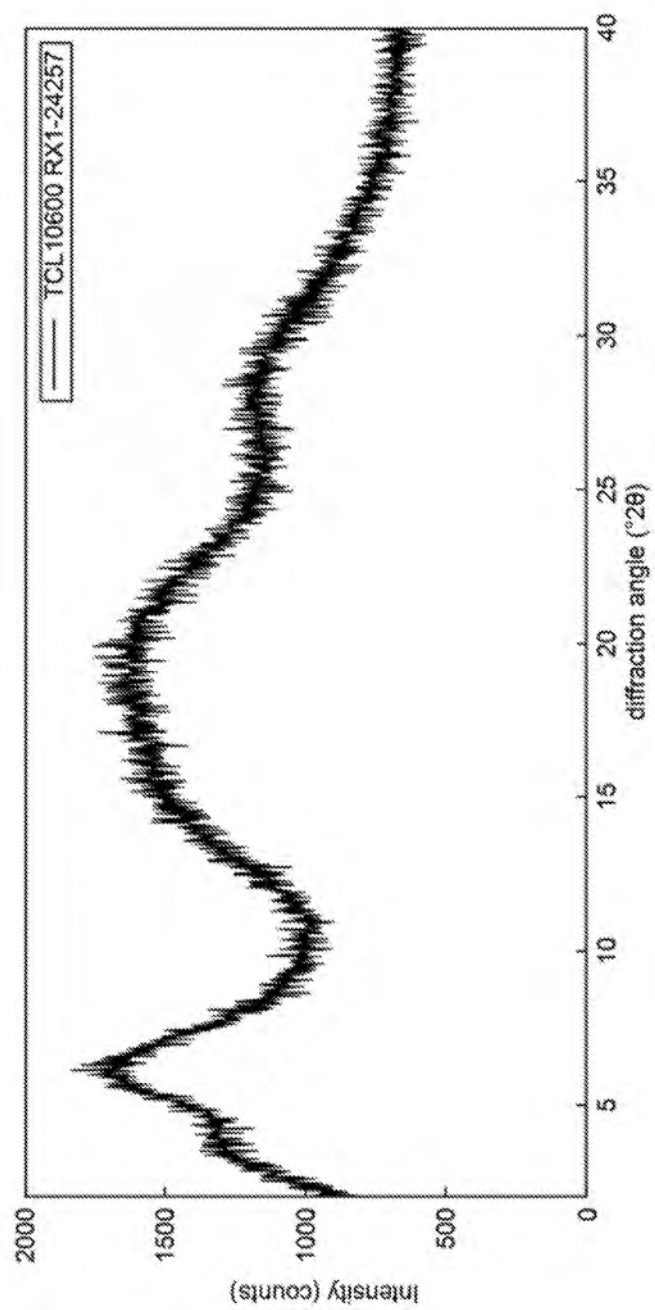


Fig. 5C

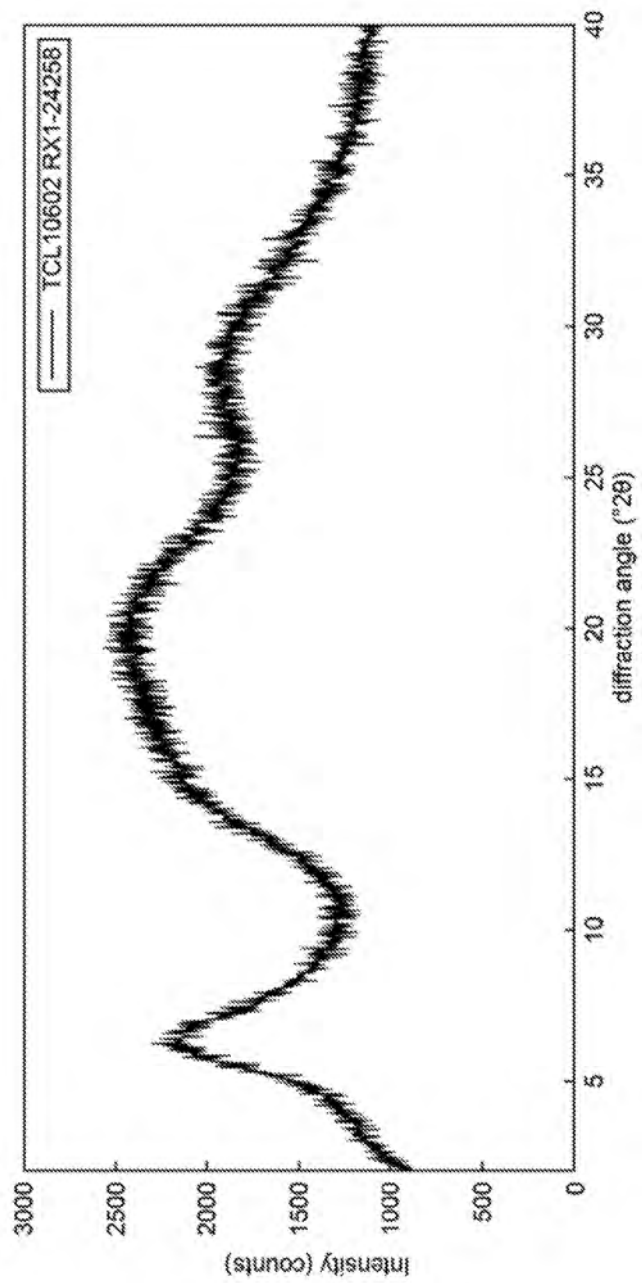


Fig. 5D

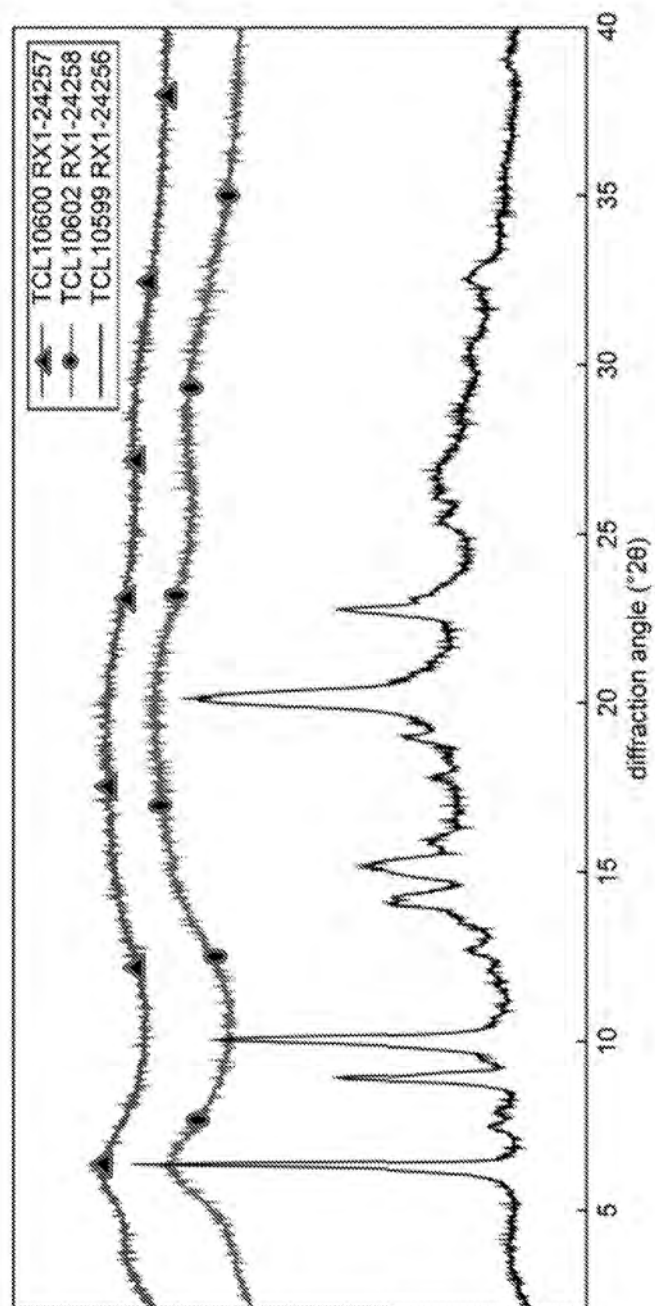


Fig. 1A



Fig. 1B



Fig. 1C



Fig. 1D



Fig. 1E



Fig. 1F

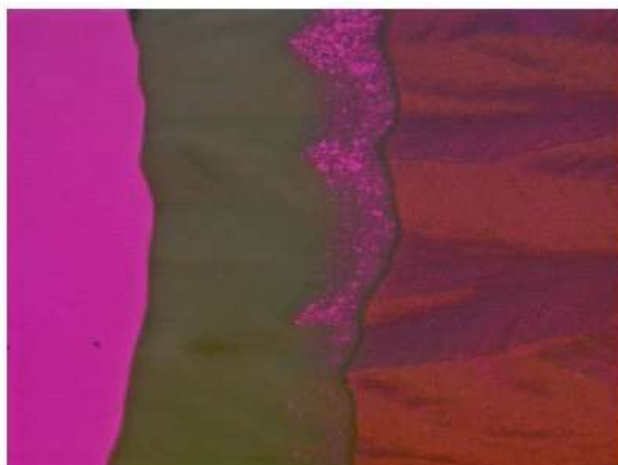


Fig. 2A

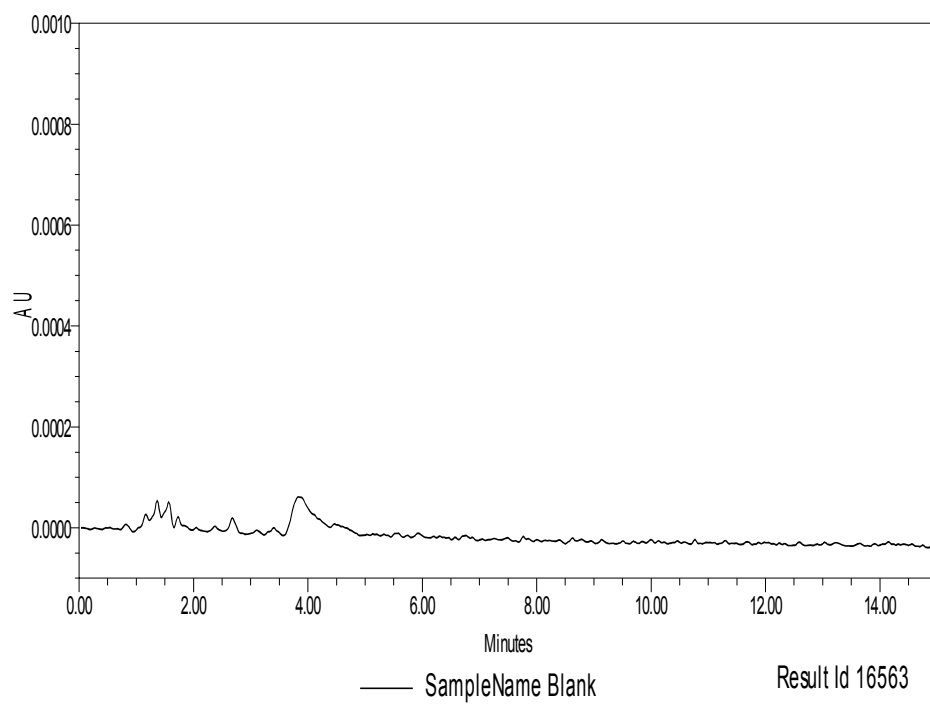
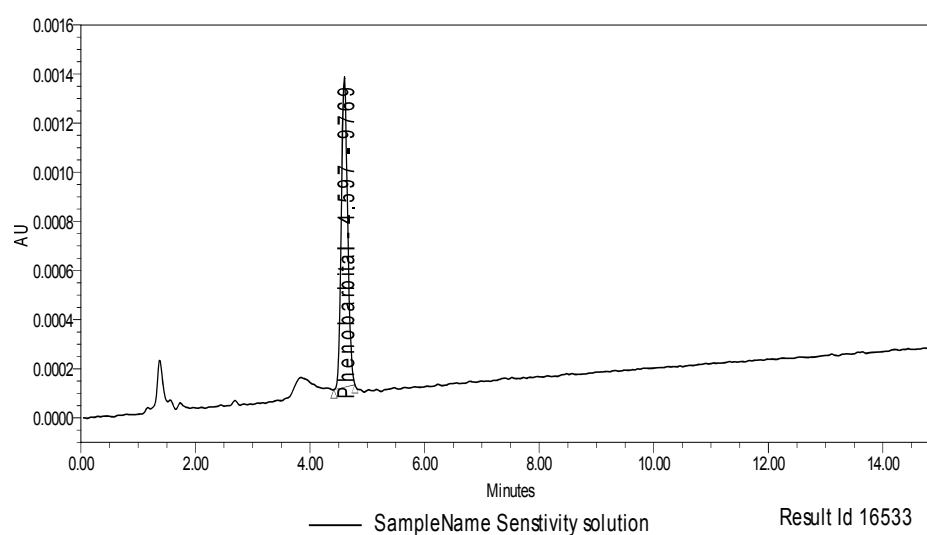
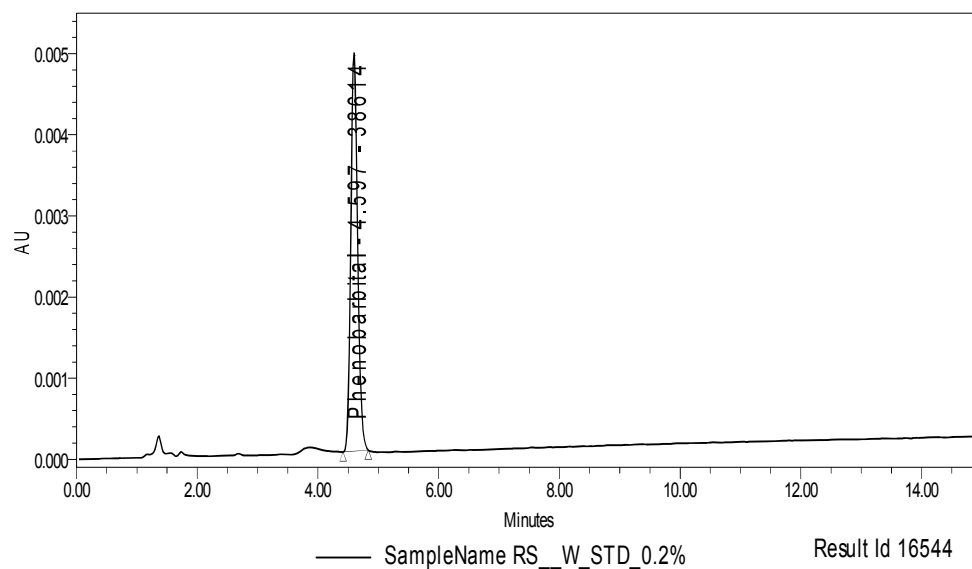


Fig. 2B



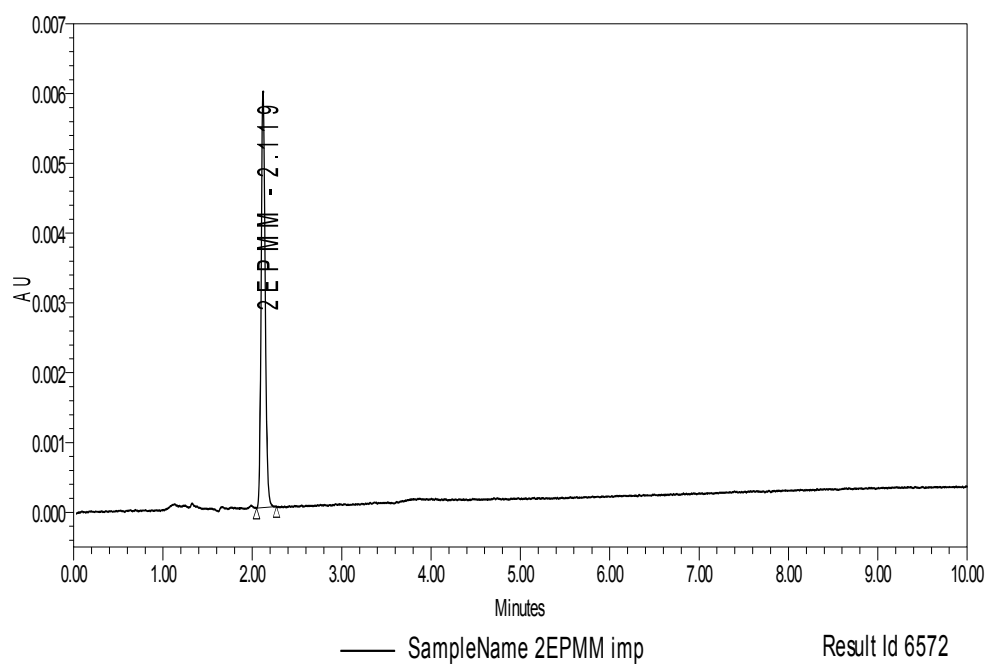
|   | PeakName      | RT    | Area | s/n         | USP<br>Plate<br>Count | USP<br>Tailing |
|---|---------------|-------|------|-------------|-----------------------|----------------|
| 1 | Phenobarbital | 4.597 | 9769 | 1054.848570 | 7861.1                | 1.1            |

Fig. 2C



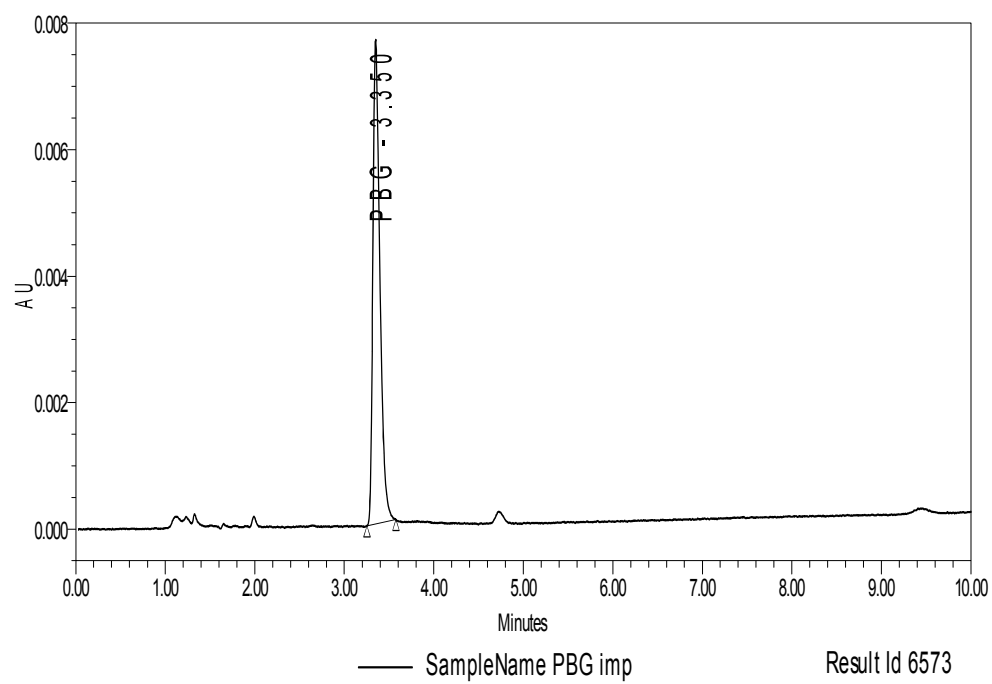
|   | Peak Name     | RT    | Area  | Amount | s/n         | USP<br>Plate<br>Count | USP<br>Tailing |
|---|---------------|-------|-------|--------|-------------|-----------------------|----------------|
| 1 | Phenobarbital | 4.597 | 38614 | 0.001  | 2906.846635 | 7746.3                | 1.2            |

Fig. 2D



|   | Peak Name | RT    | Area  | % Area | s/n  | USP<br>Plate<br>Count | USP<br>Tailing | Purity1<br>Angle | Purity1<br>Threshold |
|---|-----------|-------|-------|--------|------|-----------------------|----------------|------------------|----------------------|
| 1 | 2EPMM     | 2.119 | 18797 | 100.00 | 1472 | 10573.6               | 1.2            | 0.674            | 1.833                |

Fig. 2E



|   | PeakName | RT    | Area  | % Area | s/n  | USP<br>Plate<br>Count | USP<br>Tailing | Purity1<br>Angle | Purity1<br>Threshold |
|---|----------|-------|-------|--------|------|-----------------------|----------------|------------------|----------------------|
| 1 | PBG      | 3.350 | 41776 | 100.00 | 2090 | 8801.9                | 1.5            | 21.648           | 62.982               |

Fig. 2F

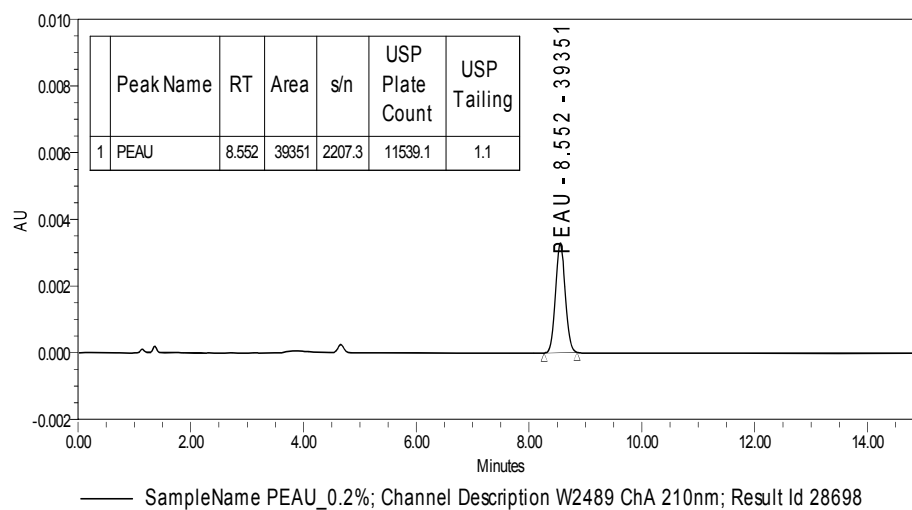


Fig. 2G

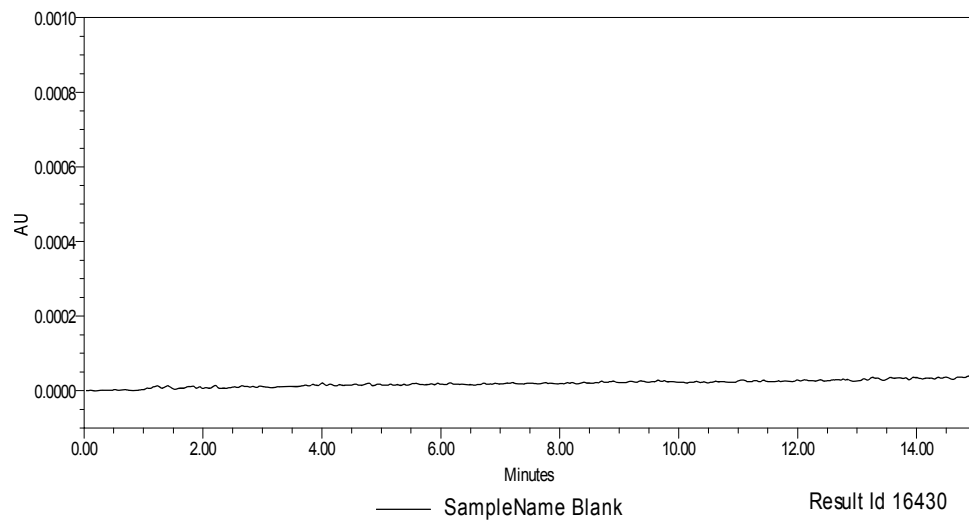
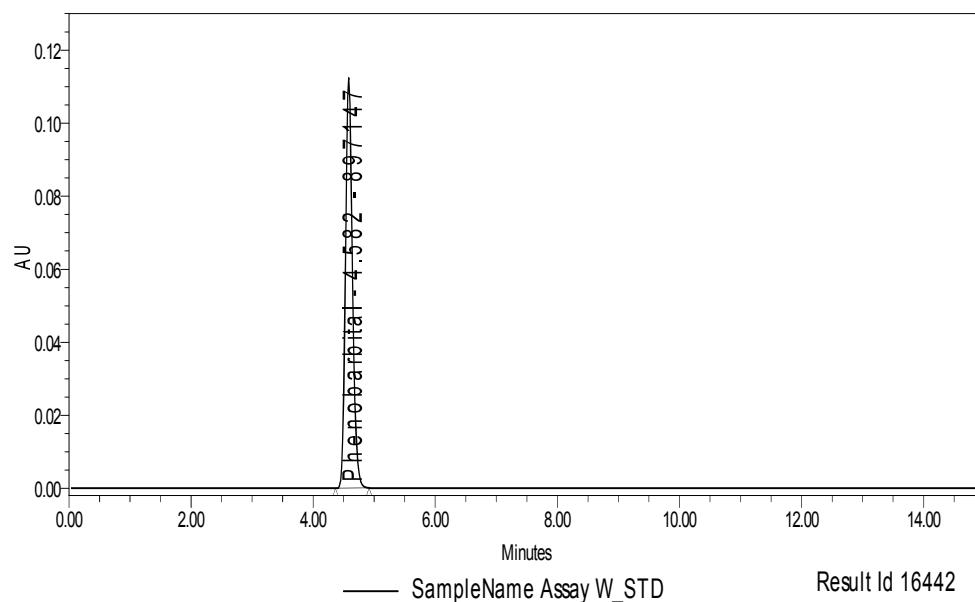
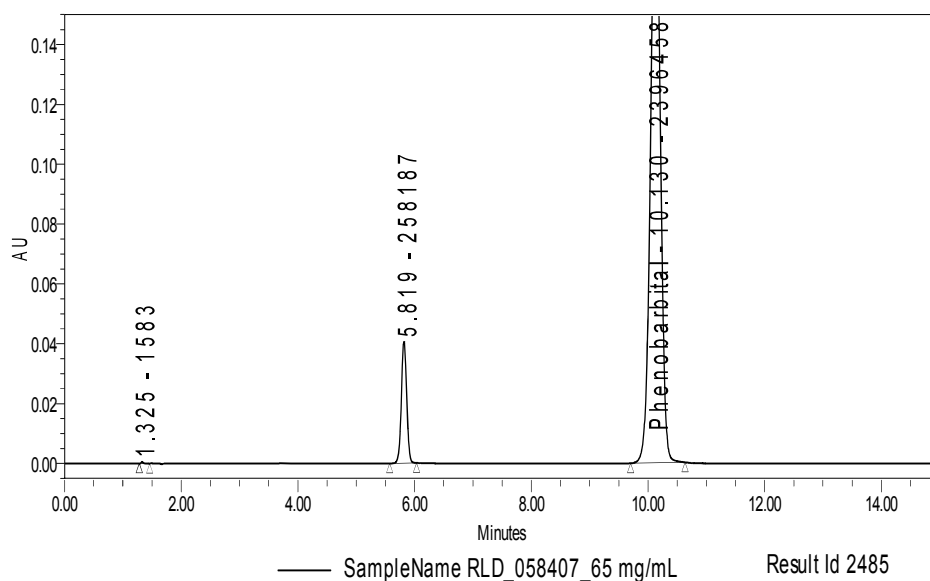


Fig. 2H



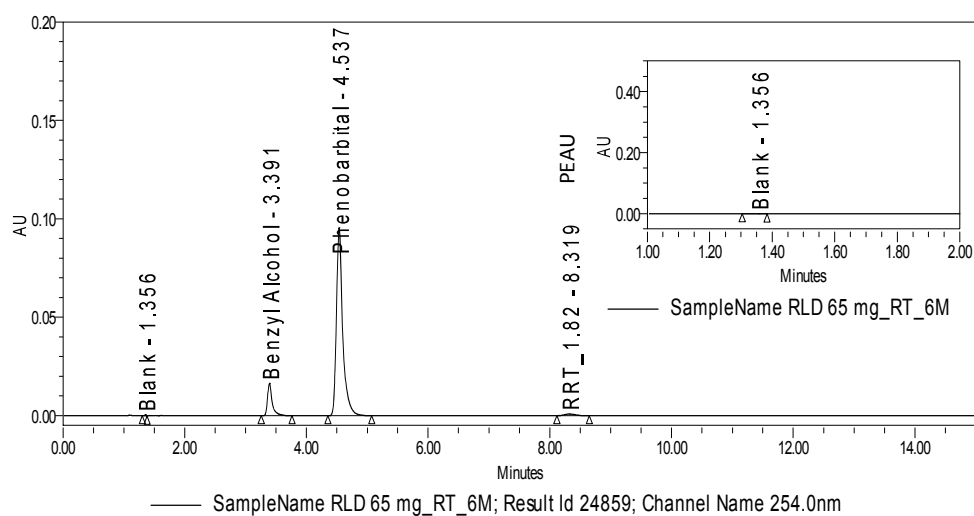
|   | Peak Name     | RT    | Area   | Amount | s/n          | USP<br>Plate<br>Count | USP<br>Tailing |
|---|---------------|-------|--------|--------|--------------|-----------------------|----------------|
| 1 | Phenobarbital | 4.582 | 897147 | 0.476  | 50940.058185 | 7493.0                | 1.2            |

Fig. 3A



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

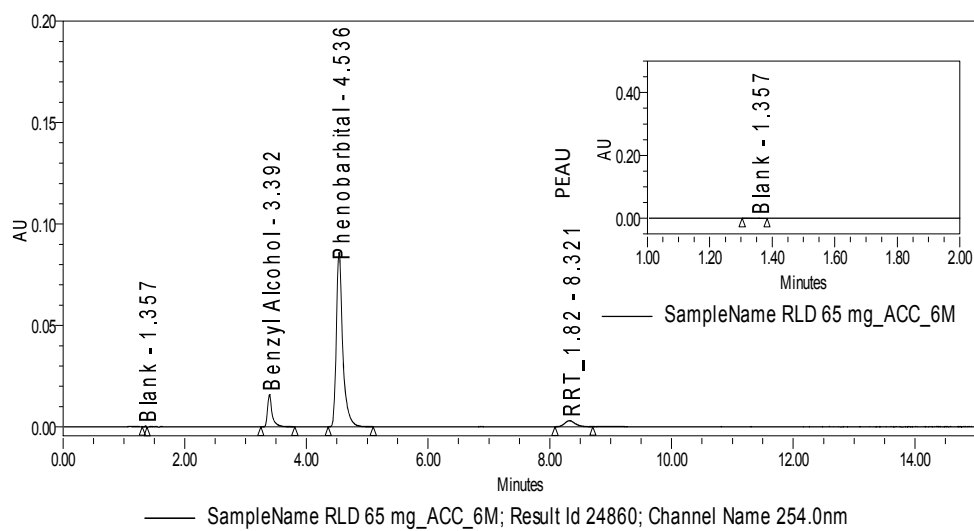
Fig. 3B



SampleName RLD 65 mg\_RT\_6M; Result Id 24859; Channel Name 254.0nm

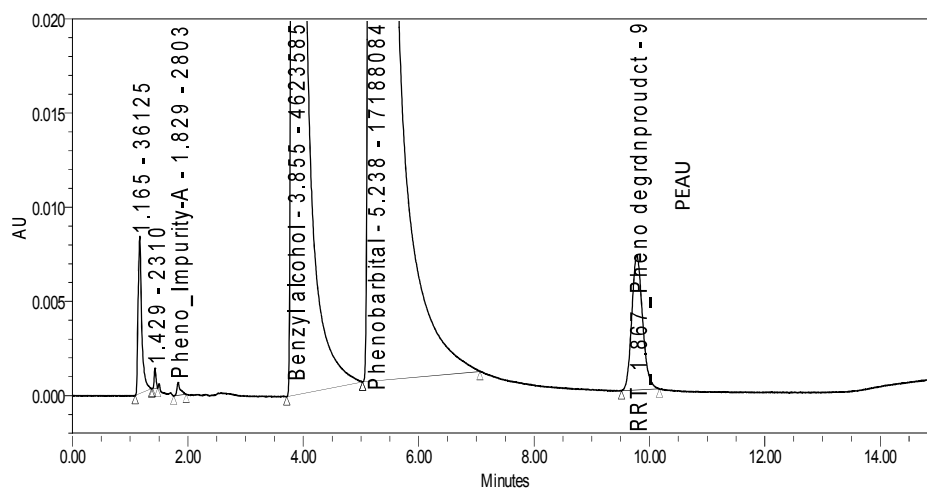
|   | Peak Name      | RT    | Area   | % Area | Amount | Units | Assay | USP Resolution | USP Tailing |
|---|----------------|-------|--------|--------|--------|-------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.391 | 87091  | 10.96  | 14.994 | mg/mL | 105.2 | 23.7           | 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         |

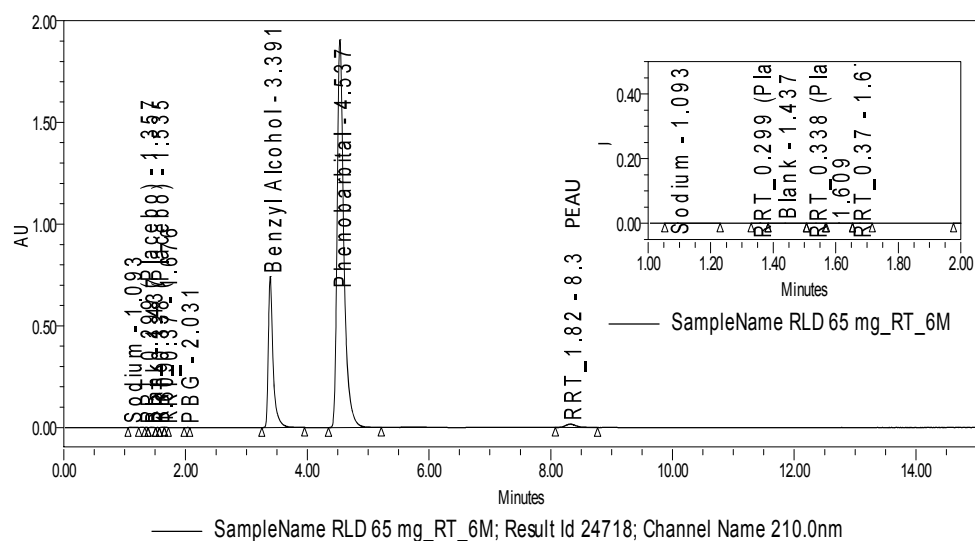
Fig. 3D



SampleName RLD\_058407\_65 mg/mL; Channel Description 2998 (205-400)nm; Result Id 3537

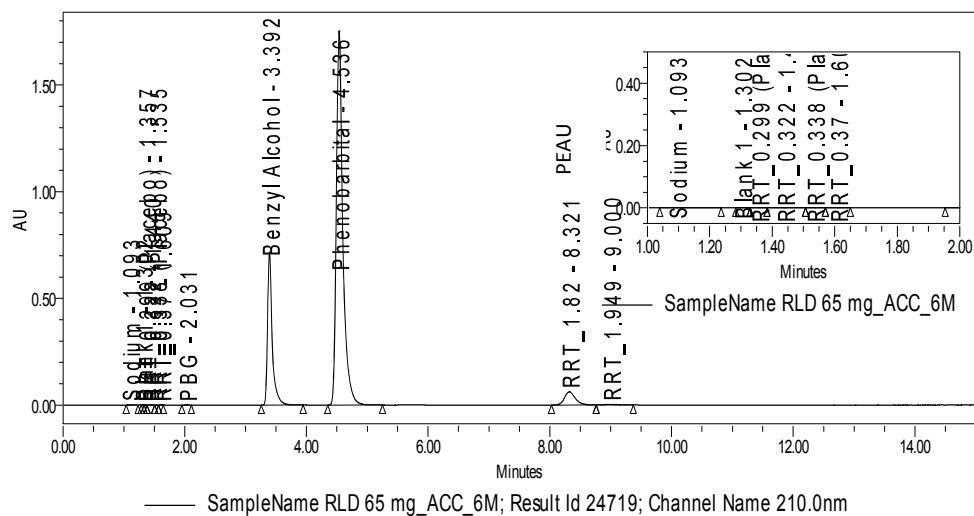
|   | Peak Name                   | RT    | Area     | % Area | USP Resolution | s/n    | USP Plate Count | USP Tailing |
|---|-----------------------------|-------|----------|--------|----------------|--------|-----------------|-------------|
| 1 | Benzyl alcohol              | 3.855 | 4623585  | 21.07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

Fig. 3E



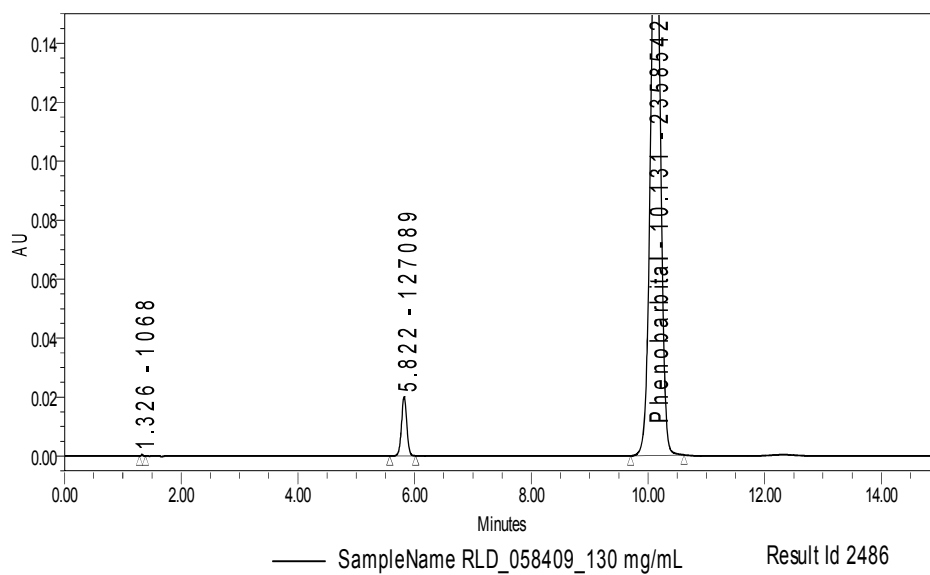
|   | Peak Name      | RT    | Area     | % Area | Amount | Units | USP Resolution | USP Tailing |
|---|----------------|-------|----------|--------|--------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.391 | 3972837  | 21.25  | 16.272 | mg/mL | 13.8           | 1.7         |
| 2 | 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



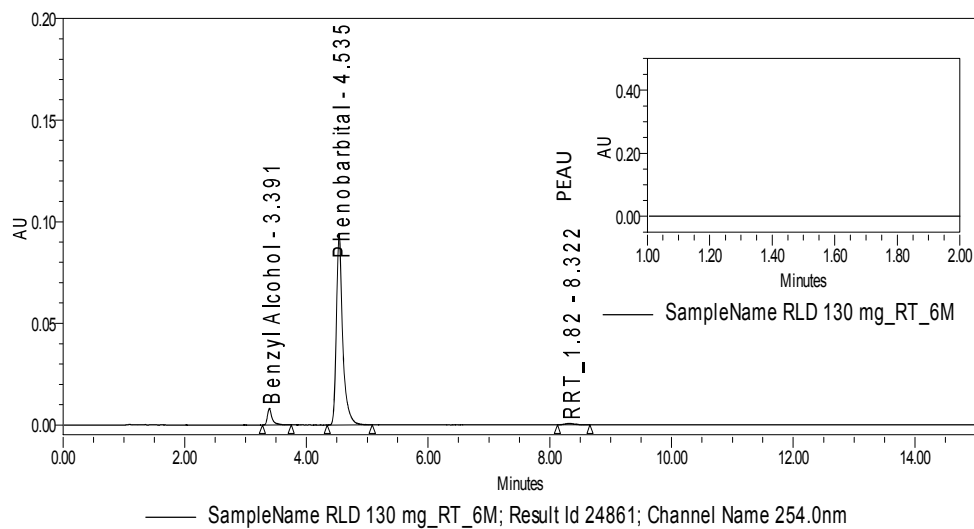
|   | Peak Name      | RT    | Area     | % Area | Amount | Units | USP Resolution | USP Tailing |
|---|----------------|-------|----------|--------|--------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.392 | 3833550  | 21.50  | 15.701 | mg/mL | 12.8           | 1.7         |
| 2 | 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



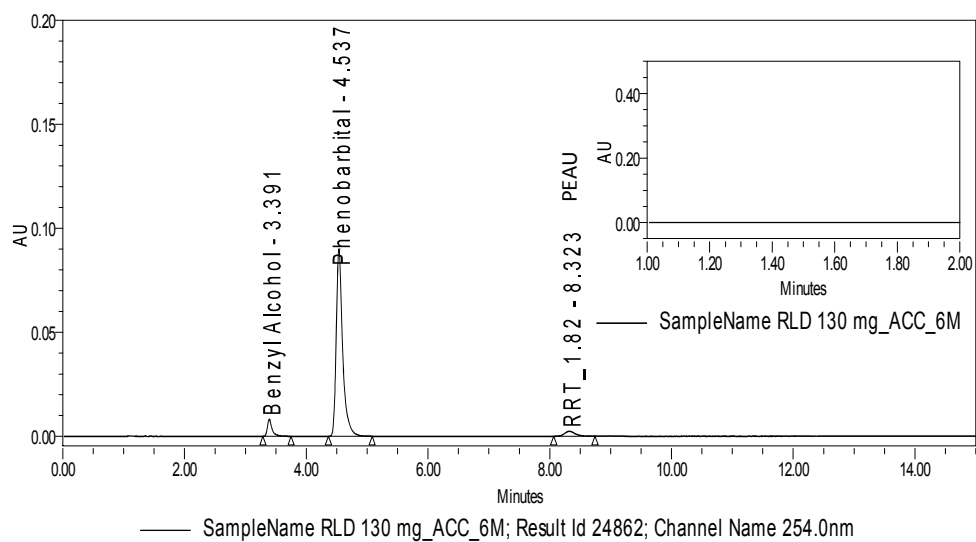
|   | PeakName      | RT     | Area    | Amount  | USP<br>Resolution | USP<br>Plate<br>Count | USP<br>Tailing | Assay |
|---|---------------|--------|---------|---------|-------------------|-----------------------|----------------|-------|
| 1 | Phenobarbital | 10.131 | 2358542 | 119.721 | 17.9              | 17563.1               | 1.0            | 110.3 |

Fig. 3H



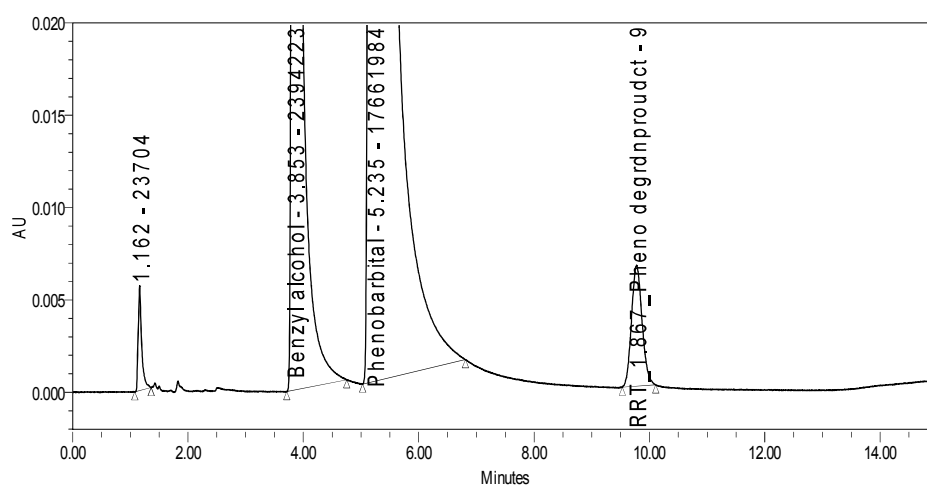
|   | Peak Name      | RT    | Area   | % Area | Amount  | Units | Assay | USP Resolution | USP Tailing |
|---|----------------|-------|--------|--------|---------|-------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.391 | 43232  | 5.84   | 14.886  | mg/mL | 104.5 |                | 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         |

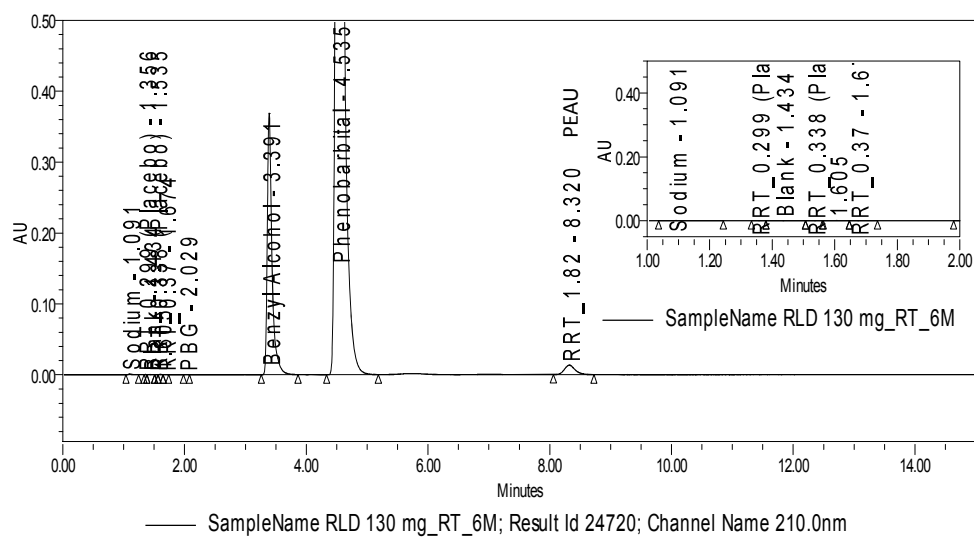
Fig. 3J



SampleName RLD\_058409\_130 mg/mL; Channel Description 2998 (205-400)nm; Result Id 3539

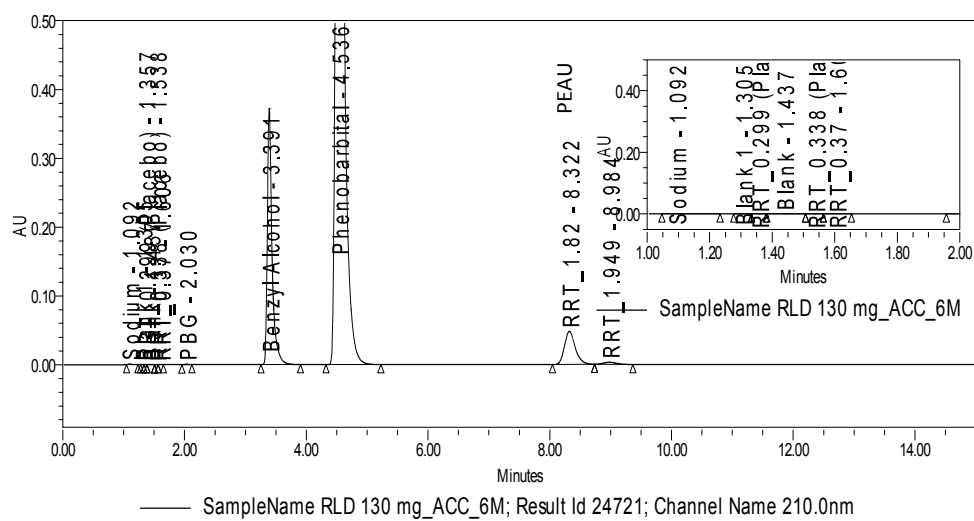
|   | Peak Name                    | RT    | Area     | % Area | USP Resolution | s/n    | USP Plate Count | USP Tailing |
|---|------------------------------|-------|----------|--------|----------------|--------|-----------------|-------------|
| 1 | Benzyl alcohol               | 3.853 | 2394223  | 11.87  | 20.8           | 223.9  | 12438.0         | 1.5         |
| 2 | Phenobarbital                | 5.235 | 17661984 | 87.59  | 8.0            | 1144.4 | 11214.3         | 1.4         |
| 3 | RRT_1.867_Pheno degrdnprodct | 9.776 | 83640    | 0.41   | 16.6           | 3.5    | 13612.7         | 1.1         |

Fig. 3K



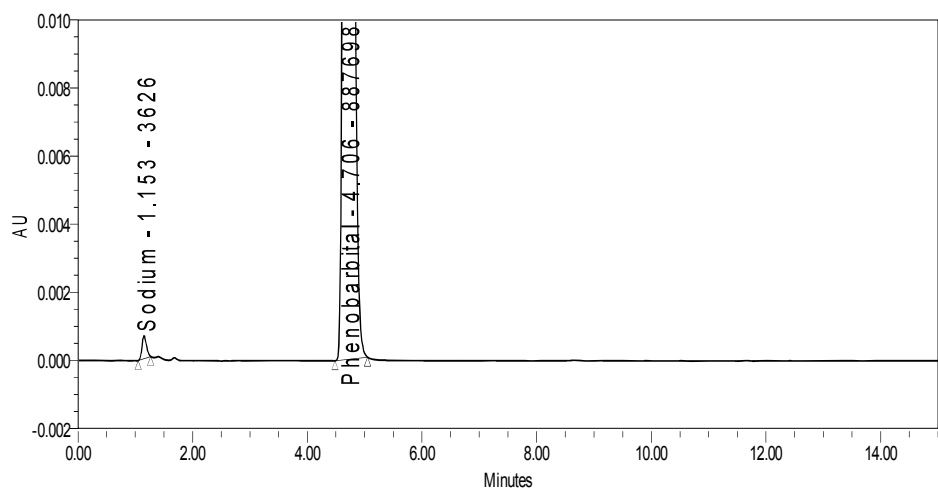
|   | Peak Name      | RT    | Area     | % Area | Amount  | Units | USP Resolution | USP Tailing |
|---|----------------|-------|----------|--------|---------|-------|----------------|-------------|
| 1 | Benzyl Alcohol | 3.391 | 1963213  | 11.91  | 16.081  | mg/mL | 13.4           | 1.7         |
|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

Fig. 3L



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

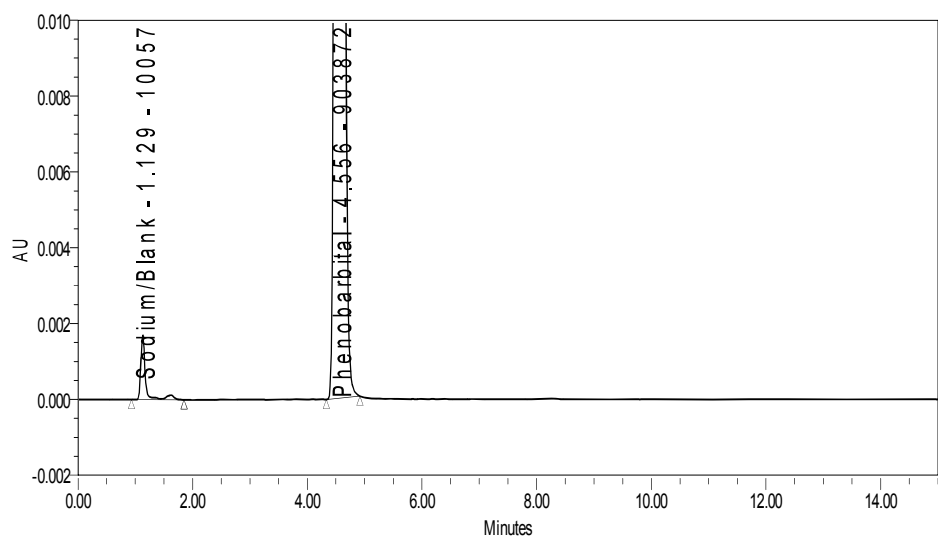
Fig. 4A



SampleName #NPH1907\_Lyo\_65mg/mL\_Initial; Channel Description W2489 ChB 254nm; Result Id 13991

|   | Peak Name     | RT    | Area   | Amount | Units | Assay | USP Resolution | s/n     | USP Plate Count | USP Tailing |
|---|---------------|-------|--------|--------|-------|-------|----------------|---------|-----------------|-------------|
| 1 | Phenobarbital | 4.706 | 887698 | 58.858 | mg/mL | 99.1  | 19.3           | 52343.5 | 7952.5          | 1.2         |
| 2 | Sodium        | 1.153 | 3626   |        |       |       |                | 318.4   | 943.9           | 1.1         |

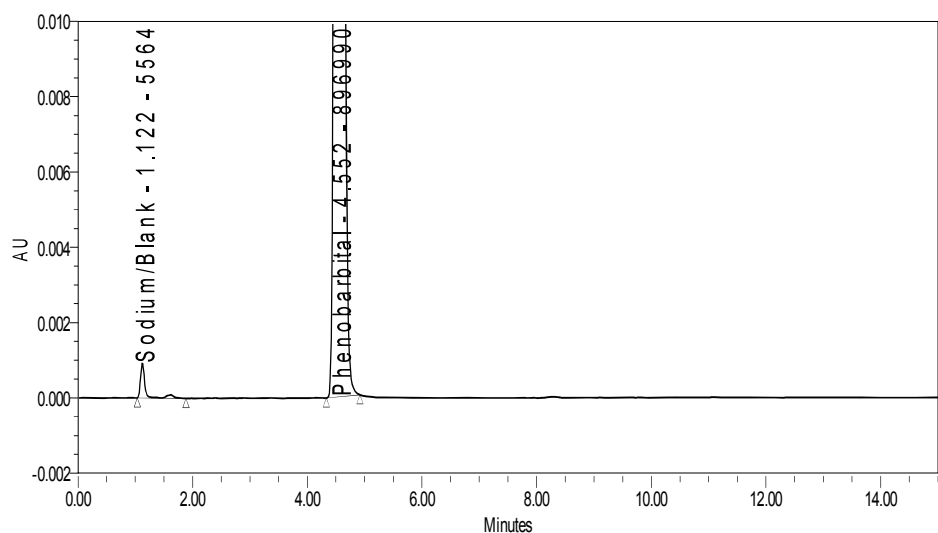
Fig. 4B



SampleName NPH1907\_65mg\_RT\_6M; Channel Description W2489 ChB 254nm; Result Id 31317

|   | 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         |

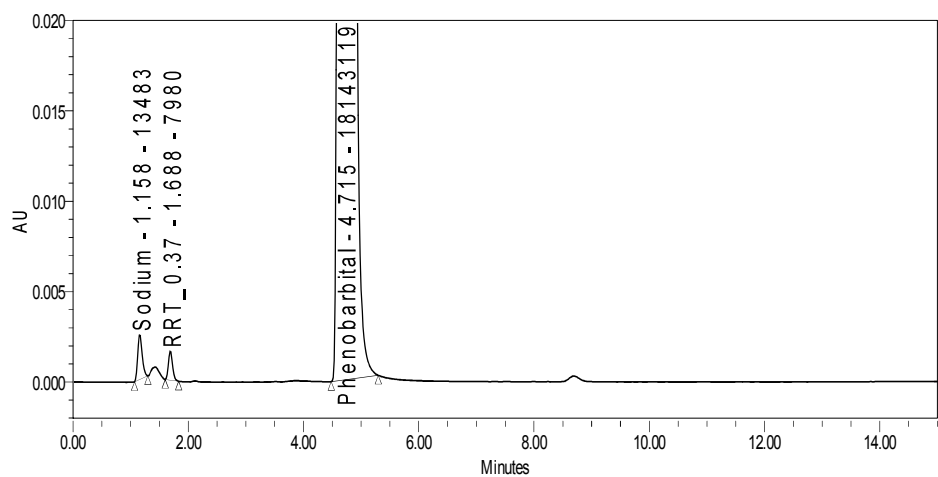
Fig. 4C



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         |

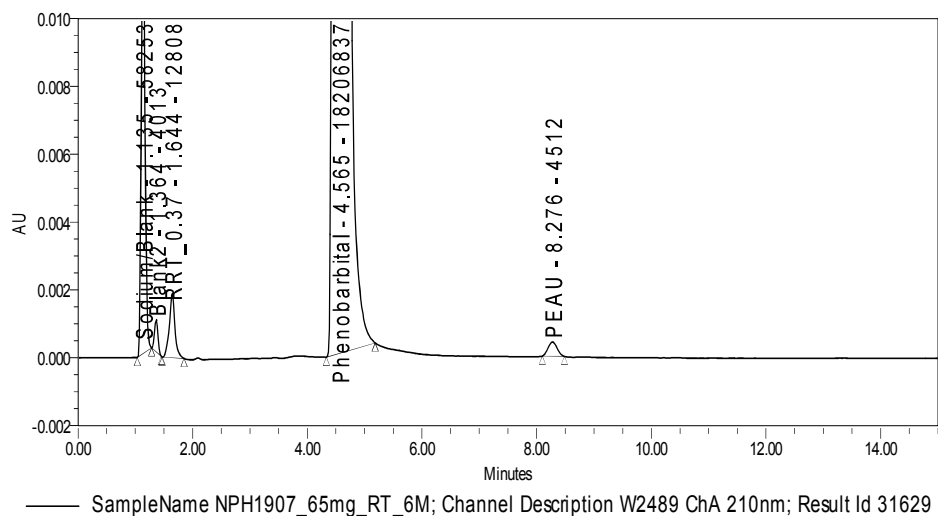
Fig. 4D



SampleName #NPH1907\_Lyo\_65mg/mL\_Initial; Channel Description W2489 ChA 210nm; Result Id 14043

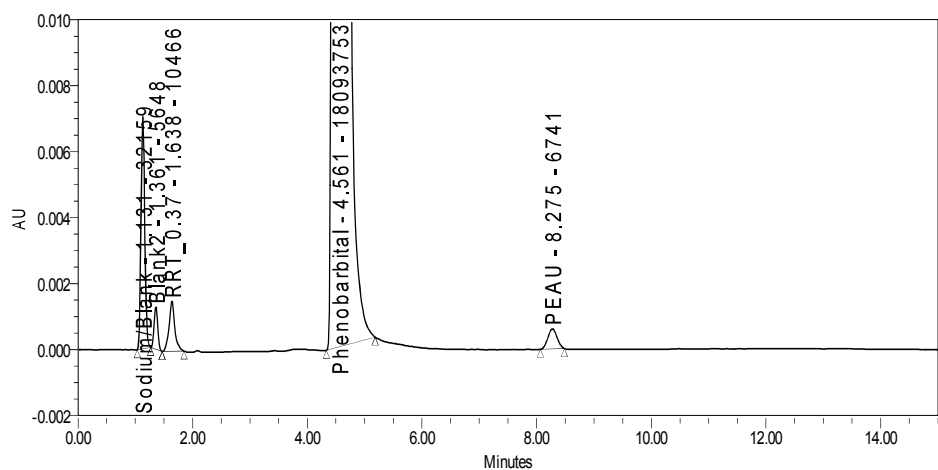
|   | Peak Name     | RT    | Area     | % Area | Amount | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|--------|-------|----------------|-----------|-----------------|-------------|
| 1 | Phenobarbital | 4.715 | 18143119 | 99.88  | 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



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

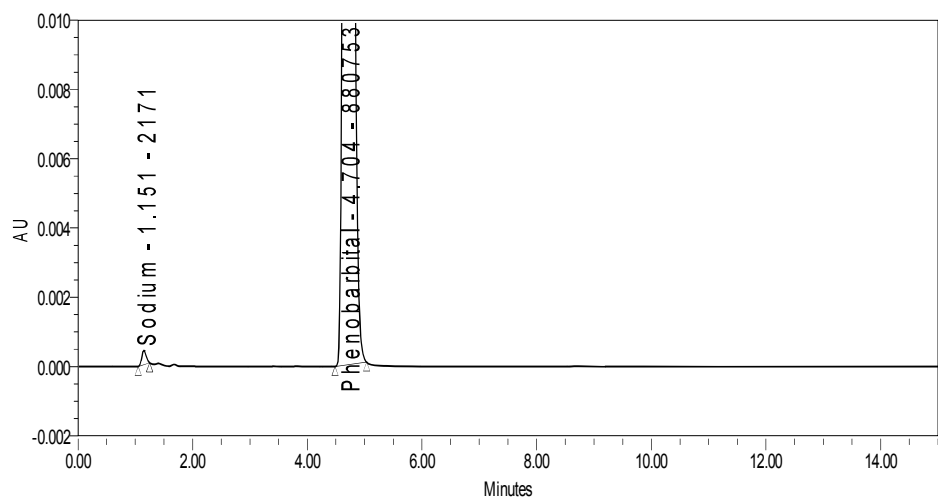
Fig. 4F



— SampleName NPH1907\_65mg\_ACC\_6M; Channel Description W2489 ChA 210nm; Result Id 31632

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

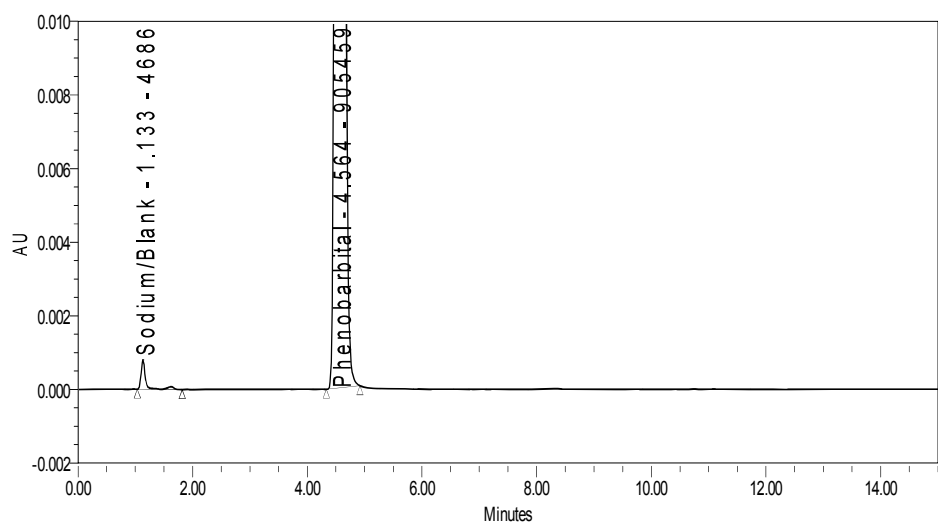
Fig. 4G



SampleName #NPH1912\_Lyo\_130mg/mL\_Initial; Channel Description W2489 ChB 254nm; Result Id 13996

|   | Peak Name     | RT    | Area   | Amount  | Units | Assay | USP Resolution | s/n     | USP Plate Count | USP Tailing |
|---|---------------|-------|--------|---------|-------|-------|----------------|---------|-----------------|-------------|
| 1 | Phenobarbital | 4.704 | 880753 | 116.796 | mg/mL | 98.3  | 19.3           | 40192.1 | 7866.8          | 1.2         |
| 2 | Sodium        | 1.151 | 2171   |         |       |       |                | 148.3   | 959.0           | 1.0         |

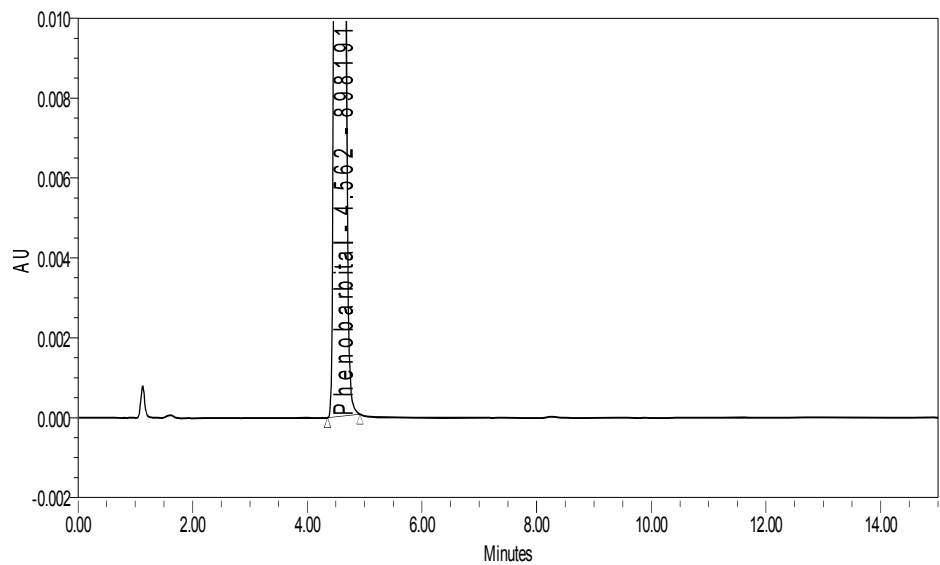
Fig. 4H



SampleName NPH1912\_130mg\_RT\_6M; Channel Description W2489 ChB 254nm; Result Id 31325

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

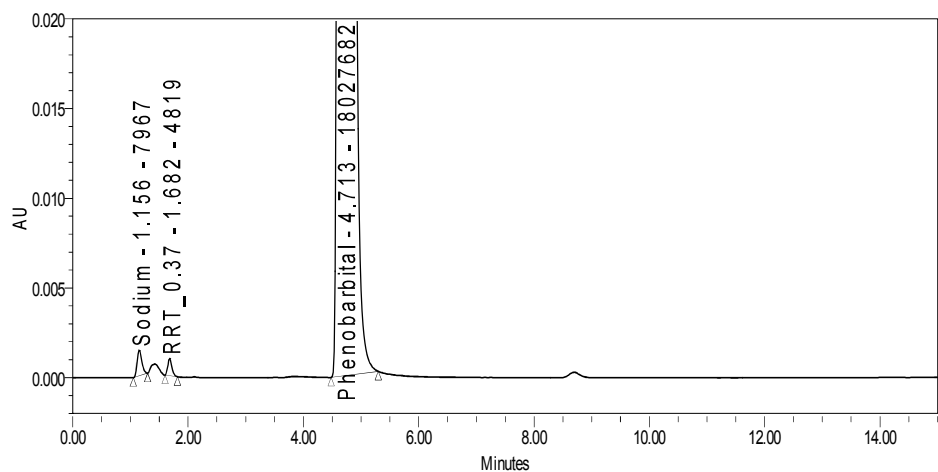
Fig. 4I



SampleName NPH1912\_130mg\_ACC\_6M; Channel Description W2489 ChB 254nm; Result Id 31328

|   | Peak Name     | RT    | Area   | Amount  | Units | Assay | s/n     | USP Plate Count | USP Tailing |
|---|---------------|-------|--------|---------|-------|-------|---------|-----------------|-------------|
| 1 | Phenobarbital | 4.562 | 898191 | 118.030 | mg/mL | 99.4  | 55375.6 | 8693.8          | 1.1         |

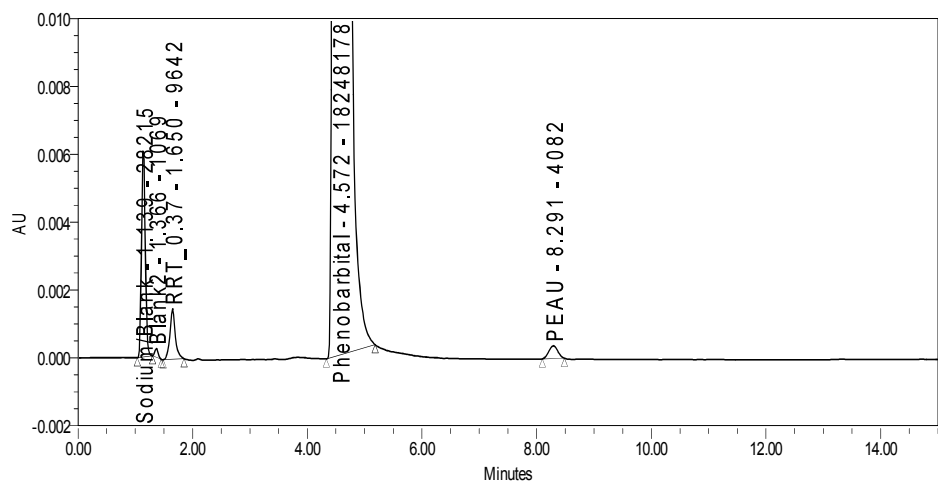
Fig. 4J



SampleName #NPH1912\_Lyo\_130mg/mL\_Initial; Channel Description W2489 ChA 210nm; Result Id 14048

|   | Peak Name     | RT    | Area     | % Area | Amount  | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|---------|-------|----------------|-----------|-----------------|-------------|
| 1 | Phenobarbital | 4.713 | 18027682 | 99.93  | 116.995 | mg/mL | 17.0           | 1001026.6 | 7649.3          | 1.2         |
| 2 | RRT_0.37      | 1.682 | 4819     | 0.03   | 0.031   | mg/mL | 3.6            | 433.7     | 2401.3          | 1.2         |
| 3 | Sodium        | 1.156 | 7967     | 0.04   | 0.052   | mg/mL |                | 649.1     | 941.5           | 1.1         |

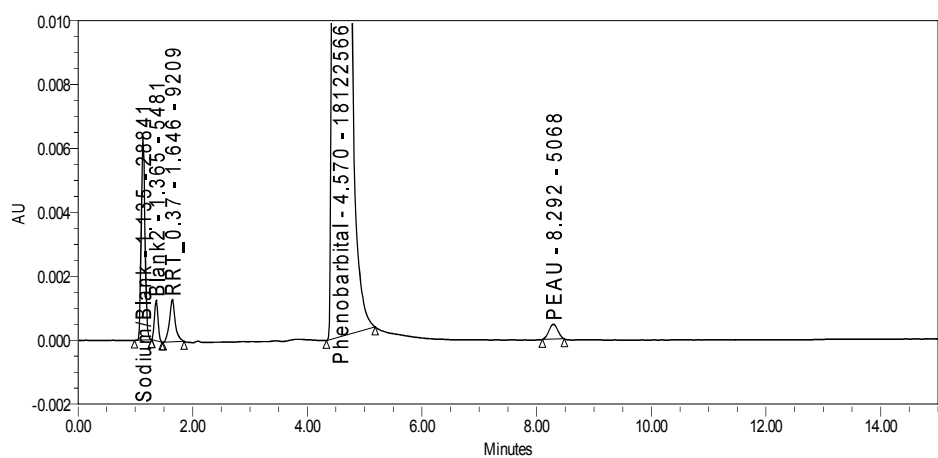
Fig. 4K



SampleName NPH1912\_130mg\_RT\_6M; Channel Description W2489 ChA 210nm; Result Id 31637

|   | Peak Name     | RT    | Area     | % Area | Amount  | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|---------|-------|----------------|-----------|-----------------|-------------|
| 1 | Blank2        | 1.366 | 1069     | 0.01   |         |       | 1.9            | 143.5     | 2247.2          | 1.1         |
| 2 | PEAU          | 8.291 | 4082     | 0.02   | 0.024   | mg/mL | 14.8           | 213.9     | 12463.8         | 1.0         |
| 3 | Phenobarbital | 4.572 | 18248178 | 99.76  | 108.187 | mg/mL | 15.9           | 1373502.2 | 8426.5          | 1.1         |
| 4 | RRT_0.37      | 1.650 | 9642     | 0.05   | 0.057   | mg/mL | 2.0            | 832.7     | 1618.4          | 1.1         |
| 5 | Sodium/Blank  | 1.139 | 28215    | 0.15   | 0.167   | mg/mL |                | 3438.2    | 1382.8          | 1.1         |

Fig. 4L



SampleName NPH1912\_130mg\_ACC\_6M; Channel Description W2489 ChA 210nm; Result Id 31640

|   | Peak Name     | RT    | Area     | % Area | Amount  | Units | USP Resolution | s/n       | USP Plate Count | USP Tailing |
|---|---------------|-------|----------|--------|---------|-------|----------------|-----------|-----------------|-------------|
| 1 | Blank2        | 1.365 | 5481     | 0.03   |         |       | 1.9            | 687.2     | 2149.1          | 1.1         |
| 2 | PEAU          | 8.292 | 5068     | 0.03   | 0.030   | mg/mL | 14.8           | 256.0     | 12320.6         | 1.0         |
| 3 | Phenobarbital | 4.570 | 18122566 | 99.73  | 107.442 | mg/mL | 15.1           | 1320858.2 | 8330.4          | 1.1         |
| 4 | RRT_0.37      | 1.646 | 9209     | 0.05   | 0.055   | mg/mL | 1.8            | 725.3     | 1481.0          | 1.1         |
| 5 | Sodium/Blank  | 1.135 | 28841    | 0.16   | 0.171   | mg/mL |                | 3440.5    | 1392.6          | 1.1         |

Fig. 5A

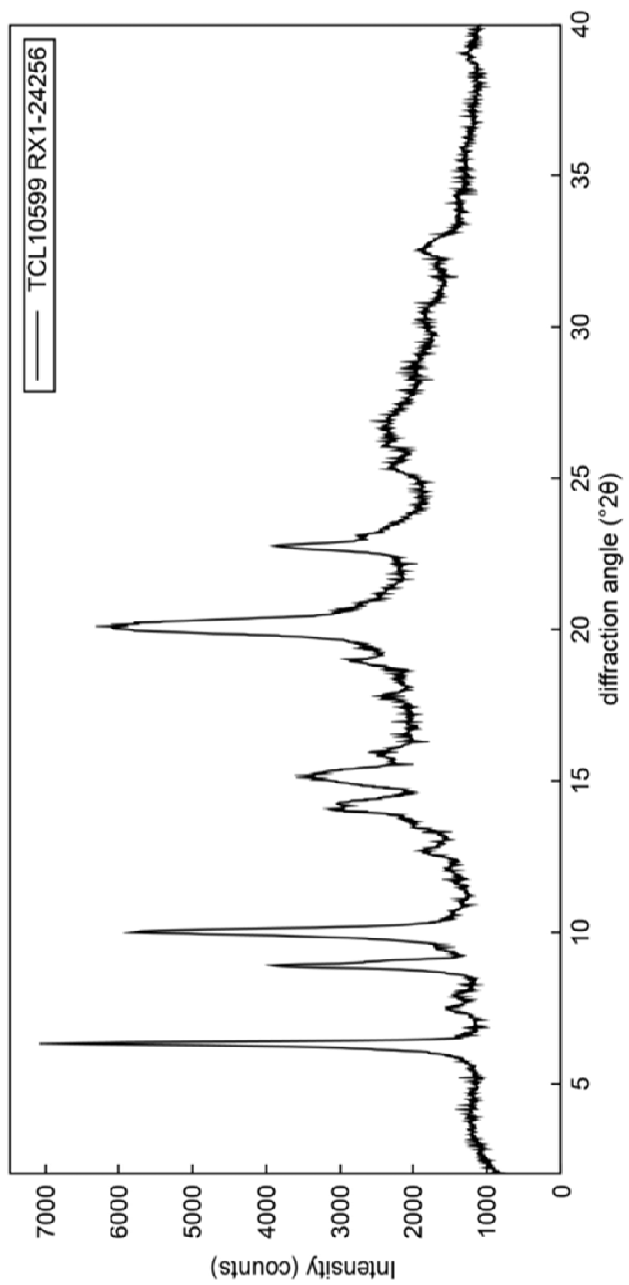


Fig. 5B

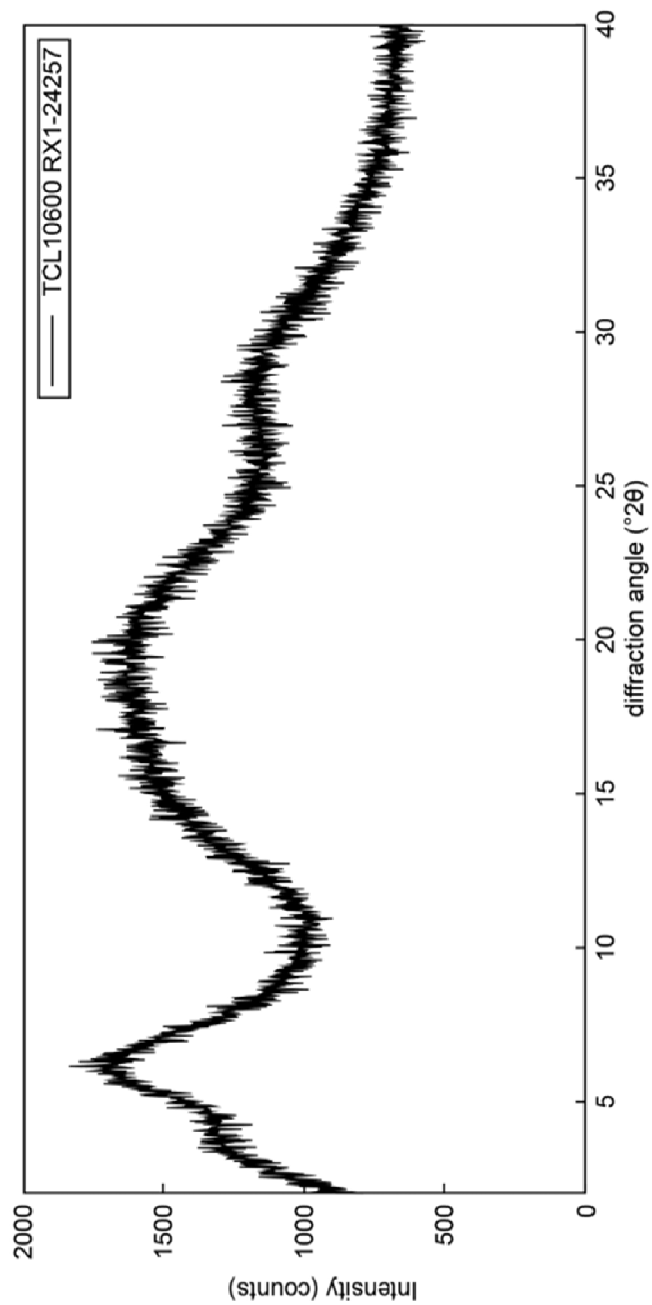


Fig. 5C

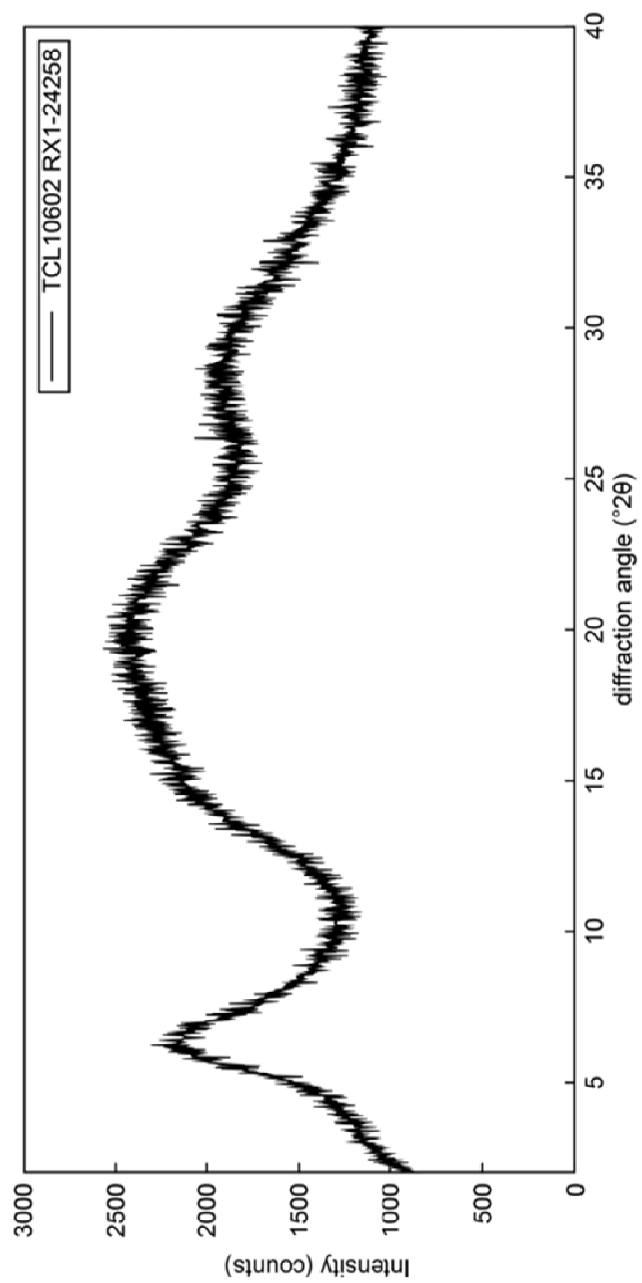
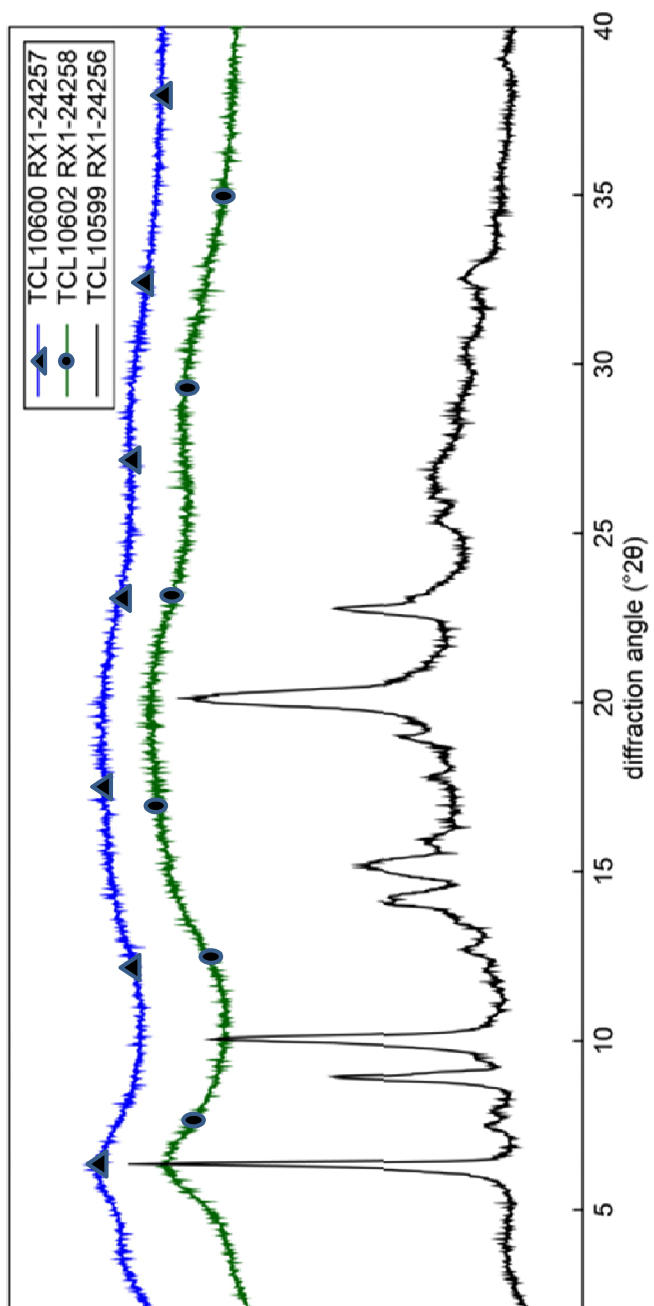


Fig. 5D



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| <b>Title of Invention</b>                                                                                                            |                 | Lyophilized Compositions of Phenobarbital Sodium Salt |                                               |       |                                       |
| Attorney Docket Number (if applicable)                                                                                               |                 | 104078.0001PRO                                        |                                               |       |                                       |
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|------------|-----------------------|-----------|-------------------|--------------------------------------|-------|
| Signature  | /Nicole Ballew Chang/ |           | Date (YYYY-MM-DD) | 2019-09-20                           |       |
| First Name | Nicole                | Last Name | Ballew Chang      | Registration Number (If appropriate) | 51611 |

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| <b>Application Data Sheet 37 CFR 1.76</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                       | Attorney Docket Number | 104078.0001PRO |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                       | Application Number     |                |
| Title of Invention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Lyophilized Compositions of Phenobarbital Sodium Salt |                        |                |
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| Inventor                                                                                                                                                                 | 1                            |                 |             |                      | Remove |
| Legal Name                                                                                                                                                               |                              |                 |             |                      |        |
| Prefix                                                                                                                                                                   | Given Name                   | Middle Name     | Family Name | Suffix               |        |
|                                                                                                                                                                          | Bala                         | Tripura Sundari | Chodavarapu |                      |        |
| Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service |                              |                 |             |                      |        |
| City                                                                                                                                                                     | Sacramento                   | State/Province  | CA          | Country of Residence | US     |
| Mailing Address of Inventor:                                                                                                                                             |                              |                 |             |                      |        |
| Address 1                                                                                                                                                                | 3050, Fite Circle, Suite 100 |                 |             |                      |        |
| Address 2                                                                                                                                                                |                              |                 |             |                      |        |
| 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) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service |                              |                 |             |                      |        |
| City                                                                                                                                                                     | Sacramento                   | State/Province  | CA          | Country of Residence | US     |
| Mailing Address of Inventor:                                                                                                                                             |                              |                 |             |                      |        |
| Address 1                                                                                                                                                                | 3050, Fite Circle, Suite 100 |                 |             |                      |        |
| Address 2                                                                                                                                                                |                              |                 |             |                      |        |
| 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) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service |                              |                 |             |                      |        |

|                                                                                                                                                                          |            |                                                       |                |                                       |    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-------------------------------------------------------|----------------|---------------------------------------|----|
| <b>Application Data Sheet 37 CFR 1.76</b>                                                                                                                                |            | Attorney Docket Number                                | 104078.0001PRO |                                       |    |
|                                                                                                                                                                          |            | Application Number                                    |                |                                       |    |
| Title of Invention                                                                                                                                                       |            | Lyophilized Compositions of Phenobarbital Sodium Salt |                |                                       |    |
| City                                                                                                                                                                     | Sacramento | State/Province                                        | CA             | Country of Residence                  | US |
| <b>Mailing Address of Inventor:</b>                                                                                                                                      |            |                                                       |                |                                       |    |
| Address 1                                                                                                                                                                |            | 3050, Fite Circle, Suite 100                          |                |                                       |    |
| Address 2                                                                                                                                                                |            |                                                       |                |                                       |    |
| City                                                                                                                                                                     | Sacramento | State/Province                                        | CA             |                                       |    |
| Postal Code                                                                                                                                                              | 95827      | Country i                                             | US             |                                       |    |
| Inventor                                                                                                                                                                 | 4          |                                                       |                | <input type="button" value="Remove"/> |    |
| Legal Name                                                                                                                                                               |            |                                                       |                |                                       |    |
| Prefix                                                                                                                                                                   | Given Name | Middle Name                                           | Family Name    | Suffix                                |    |
|                                                                                                                                                                          | Anand      |                                                       | Shukla         |                                       |    |
| Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service |            |                                                       |                |                                       |    |
| City                                                                                                                                                                     | Sacramento | State/Province                                        | CA             | Country of Residence                  | US |
| <b>Mailing Address of Inventor:</b>                                                                                                                                      |            |                                                       |                |                                       |    |
| Address 1                                                                                                                                                                |            | 3050, Fite Circle, Suite 100                          |                |                                       |    |
| Address 2                                                                                                                                                                |            |                                                       |                |                                       |    |
| City                                                                                                                                                                     | Sacramento | State/Province                                        | CA             |                                       |    |
| Postal Code                                                                                                                                                              | 95827      | Country i                                             | US             |                                       |    |
| Inventor                                                                                                                                                                 | 5          |                                                       |                | <input type="button" value="Remove"/> |    |
| Legal Name                                                                                                                                                               |            |                                                       |                |                                       |    |
| Prefix                                                                                                                                                                   | Given Name | Middle Name                                           | Family Name    | Suffix                                |    |
|                                                                                                                                                                          | Dasaradhi  |                                                       | Lakkaraju      |                                       |    |
| Residence Information (Select One) <input checked="" type="radio"/> US Residency <input type="radio"/> Non US Residency <input type="radio"/> Active US Military Service |            |                                                       |                |                                       |    |
| City                                                                                                                                                                     | Sacramento | State/Province                                        | CA             | Country of Residence                  | US |
| <b>Mailing Address of Inventor:</b>                                                                                                                                      |            |                                                       |                |                                       |    |
| Address 1                                                                                                                                                                |            | 3050, Fite Circle, Suite 100                          |                |                                       |    |
| Address 2                                                                                                                                                                |            |                                                       |                |                                       |    |
| 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 <input type="button" value="Add"/> button.      |            |                                                       |                |                                       |    |

**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.

|                                           |                                                       |                        |                |
|-------------------------------------------|-------------------------------------------------------|------------------------|----------------|
| <b>Application Data Sheet 37 CFR 1.76</b> |                                                       | Attorney Docket Number | 104078.0001PRO |
|                                           |                                                       | 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                  | 104078.0001PRO                                        | Small Entity Status Claimed               | <input checked="" type="checkbox"/> |
| Application Type                        | Provisional                                           |                                           |                                     |
| 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:

|                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> Request Early Publication (Fee required at time of Request 37 CFR 1.219)                                                                                                                                                                                                                                                                                                                      |
| <input type="checkbox"/> <b>Request Not to Publish.</b> 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 <b>has not and will not</b> 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:                                                                                                                                                                                                                                                                                                                                                                                                                                              | <input checked="" type="radio"/> Customer Number | US Patent Practitioner | <input type="radio"/> Limited Recognition (37 CFR 11.9) |
| Customer Number                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 149344                                           |                        |                                                         |

|                                           |                                                       |                        |                |
|-------------------------------------------|-------------------------------------------------------|------------------------|----------------|
| <b>Application Data Sheet 37 CFR 1.76</b> |                                                       | Attorney Docket Number | 104078.0001PRO |
|                                           |                                                       | 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                                                                                              | <div style="border: 1px solid black; width: 150px; height: 20px; display: flex; align-items: center; justify-content: center;">▼</div> | <a href="#" style="border: 1px solid black; padding: 2px 5px;">Remove</a> |                                                                          |
| Application Number                                                                                                    | Continuity Type                                                                                                                        | Prior Application Number                                                  | Filing or 371(c) Date (YYYY-MM-DD)                                       |
| <div style="border: 1px solid black; width: 150px; height: 20px;"></div>                                              | <div style="border: 1px solid black; width: 150px; height: 20px; display: flex; align-items: center; justify-content: center;">▼</div> | <div style="border: 1px solid black; width: 150px; height: 20px;"></div>  | <div style="border: 1px solid black; width: 150px; height: 20px;"></div> |
| Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the <b>Add</b> button. |                                                                                                                                        |                                                                           | <a href="#" style="border: 1px solid black; padding: 2px 5px;">Add</a>   |

### 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)<sup>i</sup> 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 <sup>j</sup>                                                     | Filing Date (YYYY-MM-DD)                                                 | Access Code <sup>k</sup> (if applicable)                                 |
| <div style="border: 1px solid black; width: 150px; height: 20px;"></div>                               | <div style="border: 1px solid black; width: 150px; height: 20px;"></div> | <div style="border: 1px solid black; width: 150px; height: 20px;"></div> | <div style="border: 1px solid black; width: 150px; height: 20px;"></div> |
| Additional Foreign Priority Data may be generated within this form by selecting the <b>Add</b> button. |                                                                          |                                                                          | <a href="#" style="border: 1px solid black; padding: 2px 5px;">Add</a>   |

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> 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.<br>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. |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                           |                                                       |                        |                |
|-------------------------------------------|-------------------------------------------------------|------------------------|----------------|
| <b>Application Data Sheet 37 CFR 1.76</b> |                                                       | Attorney Docket Number | 104078.0001PRO |
|                                           |                                                       | 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.

|                                           |                                                       |                        |                |
|-------------------------------------------|-------------------------------------------------------|------------------------|----------------|
| <b>Application Data Sheet 37 CFR 1.76</b> |                                                       | Attorney Docket Number | 104078.0001PRO |
|                                           |                                                       | 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.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |   |                                                                |                   |
| <b>Applicant</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 1 | <input type="button" value="Remove"/>                          |                   |
| <p>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.</p> |   |                                                                |                   |
| <input type="button" value="Clear"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |   |                                                                |                   |
| <input checked="" type="radio"/> Assignee                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |   | <input type="radio"/> Legal Representative under 35 U.S.C. 117 |                   |
| <input type="radio"/> Joint Inventor                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |   |                                                                |                   |
| Person to whom the inventor is obligated to assign.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |   | Person who shows sufficient proprietary interest               |                   |
| If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |   |                                                                |                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |   |                                                                |                   |
| Name of the Deceased or Legally Incapacitated Inventor:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |   |                                                                |                   |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |   |                                                                |                   |
| If the Applicant is an Organization check here. <input checked="" type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |   |                                                                |                   |
| Organization Name                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |   | Nivagen Pharmaceuticals, Inc.                                  |                   |
| <b>Mailing Address Information For Applicant:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |   |                                                                |                   |
| Address 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |   | 3050, Fite Circle, Suite 100                                   |                   |
| Address 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |   |                                                                |                   |
| City                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |   | Sacramento                                                     | State/Province CA |
| Country US                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |   | Postal Code                                                    | 95827             |
| Phone Number                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |   | Fax Number                                                     |                   |
| Email Address                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |   |                                                                |                   |
| Additional Applicant Data may be generated within this form by selecting the Add button.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |   |                                                                |                   |
| <input type="button" value="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. |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                           |                                                       |                        |                |
|-------------------------------------------|-------------------------------------------------------|------------------------|----------------|
| <b>Application Data Sheet 37 CFR 1.76</b> |                                                       | Attorney Docket Number | 104078.0001PRO |
|                                           |                                                       | Application Number     |                |
| Title of Invention                        | Lyophilized Compositions of Phenobarbital Sodium Salt |                        |                |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                        |            |                |             |        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|----------------|-------------|--------|
| <b>Assignee</b>                                                                                                                                                                                                                                                                                                                                                                                                                                        | 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. |            |                |             |        |
| <a href="#">Remove</a>                                                                                                                                                                                                                                                                                                                                                                                                                                 |            |                |             |        |
| If the Assignee or Non-Applicant Assignee is an Organization check here. <input type="checkbox"/>                                                                                                                                                                                                                                                                                                                                                      |            |                |             |        |
| Prefix                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Given Name | Middle Name    | Family Name | Suffix |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                        |            |                |             |        |
| <b>Mailing Address Information For Assignee including Non-Applicant Assignee:</b>                                                                                                                                                                                                                                                                                                                                                                      |            |                |             |        |
| Address 1                                                                                                                                                                                                                                                                                                                                                                                                                                              |            |                |             |        |
| Address 2                                                                                                                                                                                                                                                                                                                                                                                                                                              |            |                |             |        |
| City                                                                                                                                                                                                                                                                                                                                                                                                                                                   |            | State/Province |             |        |
| Country                                                                                                                                                                                                                                                                                                                                                                                                                                                |            | Postal Code    |             |        |
| Phone Number                                                                                                                                                                                                                                                                                                                                                                                                                                           |            | Fax Number     |             |        |
| Email Address                                                                                                                                                                                                                                                                                                                                                                                                                                          |            |                |             |        |
| Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. <a href="#">Add</a>                                                                                                                                                                                                                                                                                                                  |            |                |             |        |

**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.

|                                                                                                         |                       |           |                   |                     |
|---------------------------------------------------------------------------------------------------------|-----------------------|-----------|-------------------|---------------------|
| <b>Signature</b>                                                                                        | /Nicole Ballew Chang/ |           | Date (YYYY-MM-DD) | 2019-09-20          |
| First Name                                                                                              | Nicole                | Last Name | Ballew Chang      | Registration Number |
|                                                                                                         |                       |           |                   | 61611               |
| Additional Signature may be generated within this form by selecting the Add button. <a href="#">Add</a> |                       |           |                   |                     |

|                                           |                                                       |                        |                |
|-------------------------------------------|-------------------------------------------------------|------------------------|----------------|
| <b>Application Data Sheet 37 CFR 1.76</b> |                                                       | Attorney Docket Number | 104078.0001PRO |
|                                           |                                                       | Application Number     |                |
| Title of Invention                        | Lyophilized Compositions of Phenobarbital Sodium Salt |                        |                |

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

## Privacy Act Statement

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| 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:                                        |          | Nicole Ballew Chang/Danielle Moroz                    |        |                      |
| Attorney Docket Number:                       |          | 104078.0001PRO                                        |        |                      |
| Filed as Small Entity                         |          |                                                       |        |                      |
| Filing Fees for Provisional                   |          |                                                       |        |                      |
| Description                                   | Fee Code | Quantity                                              | Amount | Sub-Total in USD(\$) |
| Basic Filing:                                 |          |                                                       |        |                      |
| PROVISIONAL APPLICATION FILING FEE            | 2005     | 1                                                     | 140    | 140                  |
| Pages:                                        |          |                                                       |        |                      |
| Claims:                                       |          |                                                       |        |                      |
| Miscellaneous-Filing:                         |          |                                                       |        |                      |
| Petition:                                     |          |                                                       |        |                      |
| Patent-Appeals-and-Interference:              |          |                                                       |        |                      |
| Post-Allowance-and-Post-Issuance:             |          |                                                       |        |                      |

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|--------------------|----------|----------|--------|----------------------|
| Extension-of-Time: |          |          |        |                      |
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# File History Content Report

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Document Date - 2019-09-20

Document Title - Applicant Communication Re: Entity Status Set to Undiscounted  
(Initial Default Setting or Status Change)

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Document Date - 2019-10-09

Document Title - Applicant Communication Re: Verified Statement of Small Entity Status in Compliance with 37 CFR 1.27

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| APPLICATION<br>NUMBER | FILING or<br>371(c) DATE | GRP ART<br>UNIT | FIL FEE REC'D | ATTY DOCKET NO | TOT CLAIMS | IND CLAIMS |
|-----------------------|--------------------------|-----------------|---------------|----------------|------------|------------|
| 62/903,511            | 09/20/2019               |                 | 140           | 104078.0001PRO |            |            |

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

CONFIRMATION NO. 5301  
FILING RECEIPT



Date Mailed: 10/10/2019

Receipt is acknowledged of this provisional patent application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. 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)**

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**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:** 10/09/2019

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 62/903,511**

**Projected Publication Date:** None, application is not eligible for pre-grant publication

page 1 of 3

**Non-Publication Request:** No

**Early Publication Request:** No

**\*\* SMALL ENTITY \*\***

**Title**

Lyophilized Compositions of Phenobarbital Sodium Salt

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

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