

Physical and Chemical Stability of Phenobarbital 1 mg/mL and 50 mg/mL Oral Suspensions (SuspendIt™)

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Introduction

Phenobarbital is a barbiturate that may be used in children for all forms of epilepsy, except typical absence seizures, and status epilepticus¹. In the United States, phenobarbital *per os* is commercially available as tablets (mainly) and the oral solutions (4 mg/mL) include sucrose and/or alcohol, excipients not recommended in paediatrics². An alternative, child-appropriate extemporaneous preparation was developed for phenobarbital 1 mg/mL and 50 mg/mL. The corresponding Beyond-Use Dates (BUDs) were determined by testing the physical and chemical stability of the oral suspensions.

Methodology

Phenobarbital 1 mg/mL and 50 mg/mL were prepared by adding the active pharmaceutical ingredient to the proprietary suspending vehicle SuspendIt™, in accordance to the formula displayed in Table 1. Phenobarbital USP (Lot C177782) and SuspendIt™ (Lot 7287309) were obtained from PCCA (Houston, TX). A batch of 1 L was prepared for each strength and distributed into 50-mL amber plastic bottles. The study samples were stored for 182 days in a laboratory refrigerator at a temperature of 5°C ± 3°C; and in an environmentally controlled chamber at a temperature of 25°C ± 2°C and relative humidity of 60% ± 5%. The physical characterization consisted in observing all samples for appearance/color and odor, and testing for pH (Horiba LaquaTwin pH meter) and density (Fisher Scientific grease pycnometer). The chemical characterization consisted in a validated, stability-indicating Ultra-High Performance Liquid Chromatography (UHPLC) assay testing (Waters Acquity). At pre-determined time points (0, 7, 14, 28, 42, 63, 91, 118, and 182 days), a study sample (one unopened bottle) of each strength was withdrawn from the storage conditions, shaken vigorously and tested for physical and chemical stability (Figure 1). The determinations obtained on day 0 were set as the baseline for all the calculations.



Ingredients	Quantity
Phenobarbital	50 g
Vehicle (SuspendIt™)	qs 1000 mL

Table 1. Formula for the extemporaneous preparation of phenobarbital 50 mg/mL oral suspension.

Figure 1. Samples of phenobarbital 1 mg/mL (left) and 50 mg/mL (right) oral suspensions (50 mL) on day 182 of the study.

For the chemical characterization, the chromatographic assay method was validated by evaluating the system suitability, linearity, accuracy, precision, robustness, solution stability, and specificity. To ensure that the UHPLC assay testing was stability-indicating, forced degradation studies were performed on the phenobarbital 1 mg/mL and 50 mg/mL oral suspensions by exposing a sample of each strength, as well as a placebo sample (Table 1, phenobarbital excluded), to thermal degradation and oxidation degradation.

References

1. Paediatric Formulary Committee (2016) *BNF for Children*. London: BMJ Group and Pharmaceutical Press, p. 203-4.
2. Clinical Pharmacology (2017) *Phenobarbital: US Drug Products*. Available at: <https://www.clinicalpharmacology-ip.com/default.aspx> (Accessed: 22 May 2017).
3. The United States Pharmacopeial Convention (2016c) 'General Requirements / <2> Oral Drug Products – Product Quality Tests'. *USP 39 – NF 34*. Rockville: USP, p.77.
4. Kupiec, T.C., Skinner, R. and Lanier, L. (2008) 'Stability Versus Potency Testing: The Madness is in the Method', *International Journal of Pharmaceutical Compounding*, 12 (1), p. 50-53.

Results and Discussion

Considering the physical characterization, the phenobarbital 1 mg/mL oral suspensions exhibited a homogeneous faint yellow color, translucent appearance (Figure 1) and a characteristic odor throughout the study. The range of densities (0.975 g/mL - 1.000 g/mL at 5°C and 0.986 g/mL - 1.002 g/mL at 25°C/60%) and the range of pH (4.84-5.32 at 5°C and 4.84-5.19 at 25°C/60%) were within the limits. The phenobarbital 50 mg/mL oral suspensions, on the other hand, exhibited a homogeneous white color, opaque appearance (Figure 1) and a characteristic odor as well. The range of densities (0.980 g/mL - 1.011 g/mL at 5°C and 0.984 g/mL - 1.014 g/mL at 25°C/60%) and the range of pH (4.77-5.09 at 5°C and 4.77-5.23 at 25°C/60%) were also within the limits.

Considering the chemical characterization, the UHPLC assay testing met all the necessary criteria for the method validation and forced degradation studies; it is therefore stability-indicating for the phenobarbital 1 mg/mL and 50 mg/mL oral suspensions. The most common mistake in determining a BUD is failure to use a stability-indicating analytical method⁴. The assay testing measured the main chromatographic peak (Figure 2) and provided the mean concentration of phenobarbital per time point. The percent potency was calculated taking into account the baseline measurements on day 0. The potency of the oral suspensions remained within the specifications of ±10% variation in limits (90% to 110%)³ for the duration of the study, as follows:

- Phenobarbital 1 mg/mL: 98.39% - 102.06% (refrigerated conditions) and 99.66% - 101.72% (room temperature).
- Phenobarbital 50 mg/mL: 95.40% - 100.00% (refrigerated conditions) and 96.73% - 100.85% (room temperature; Figure 3).

As a result, the phenobarbital oral suspensions from 1 mg/mL up to 50 mg/mL (bracketed study) are physically and chemically stable at 5°C and 25°C/60%, in amber plastic bottles, for 182 days.

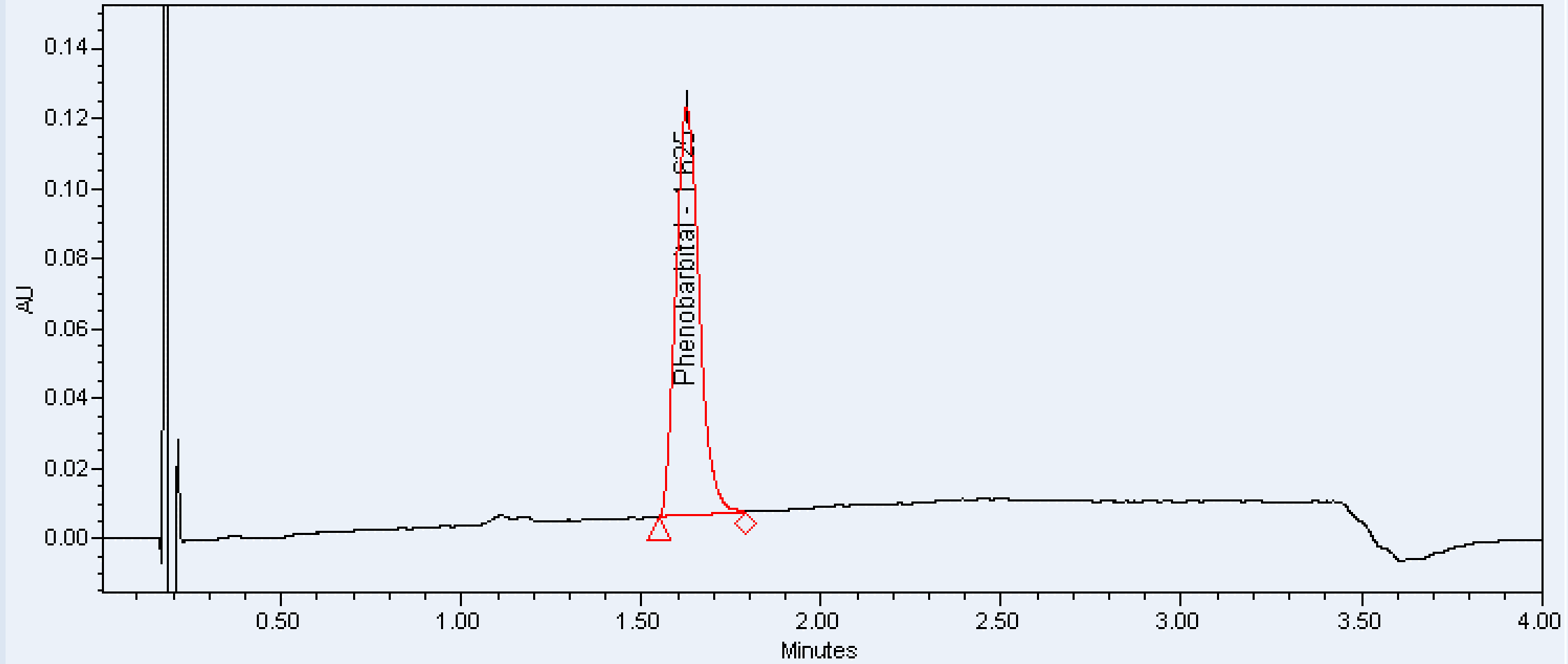


Figure 2. Chromatogram of the phenobarbital 50 mg/mL oral suspension stored at room temperature on day 182 of the study.

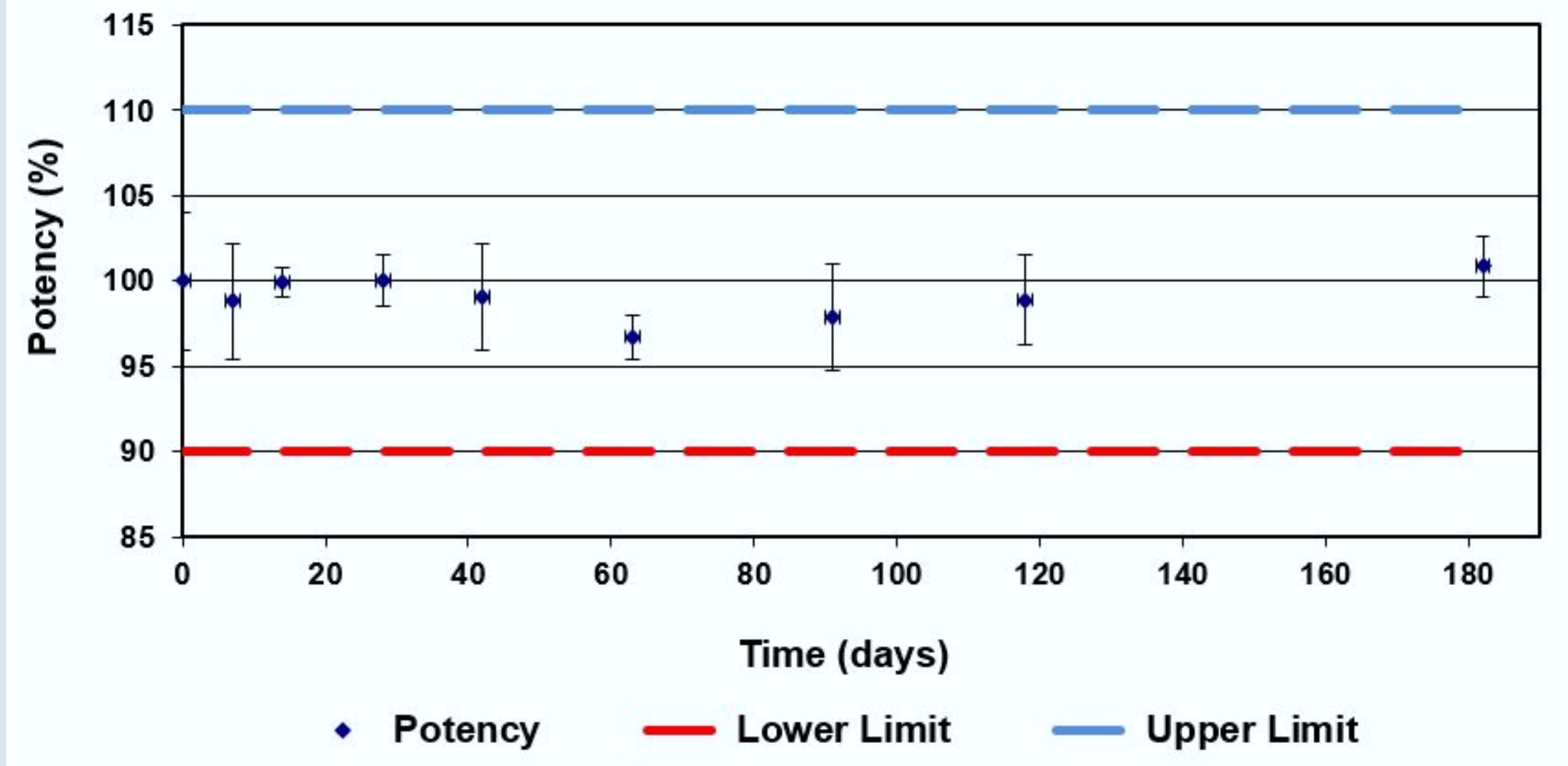


Figure 3. Potency of phenobarbital 50 mg/mL oral suspension stored at room temperature for 182 days.

Conclusions

There is currently a need for a child-appropriate phenobarbital extemporaneous preparation. A formula was developed for phenobarbital 1 mg/mL and 50 mg/mL including a proprietary suspending vehicle (SuspendIt™) and a valid, stability-indicating analytical method was used to determine the BUD of the phenobarbital oral suspensions. As a result, it is concluded that the BUD of the phenobarbital 1 mg/mL - 50 mg/mL oral suspensions, in amber plastic bottles, is 6 months at both room temperature and refrigerated conditions.