DEVELOPMENT, STABILITY AND FLAVOUR ACCEPTABILITY OF TWO ORAL LIQUID FORMULATIONS OF PHENOBARBITAL FOR USE IN PAEDIATRICS

C. Simon, W. Griffiths, H. Ing, F. Sadeghipour, P. Bonnabry
Pharmacy, University Hospitals of Geneva, Switzerland

Background and Objectives

Phenobarbital has been a part of the antiepileptic therapeutic arsenal since 1912 and remains the mainstay treatment for neonatal seizures[1]. The pharmaceutical industry supplies oral solid dosage forms that are generally inadequate for paediatric needs. This obliges pharmacies to prepare capsules with doses corresponding to the age and weight of the children. To reduce individualised preparations, oral liquids have been developed. In the case of phenobarbital no such preparations are available on the Swiss market except an elixir containing alcohol which is not recommended for children[2]. The objective of this study was: to formulate oral liquid solutions of phenobarbital covering the usual paediatric and neonatal doses (5 - 45mg), to carry out a flavour acceptability evaluation in adults using a standard questionnaire and to determine the chemical stability of the solutions.

Methods

Two alcohol-free solutions, containing 5mg /ml of phenobarbital as the sodium salt, were prepared with (WS) and without sorbitol (NS), saccharin sodium as artificial sweetener, parabens as preservatives, glycerol and the chosen flavour (cf.Table 1). Twenty five adult volunteers were enrolled to determine flavour acceptability of 6 flavours in 4 combinations, using a standardised questionnaire that included parameters such as bitterness, sweetness, acidity, odour etc…

Flavour acceptability questionnaire .Please taste the sample no……

Please indicate how much you appreciated the flavour

Did you appreciate or not the after-taste ?

Did you find the flavour artificial ?

Very artificial — Very natural

Describe the intensity of the flavour

Very weak — Very strong

Did you find the flavour bitter?

Very bitter — Not bitter at all

Did the flavour seem acid ?

Very acid — Not acid at all

Was the formula sweet ?

Too sweet — Not sweet at all

Did you perceive a metallic after-taste ?

Very metallic — Not metallic at all

Please compare the flavours

Which flavour was your favourite ? Sample no:

Why did you choose this flavour ?

Do you think it could be used for children ? Yes/No

The solutions were stored in amber glass bottles at 25±1 °C and 32±1°C. The stability, for up to 220 days, was investigated using a validated HPLC method (Cf. Table 2).

William Griffiths

Capsules of Phenobarbital at various dosages

Oral liquid and Baxa Exacta-Med® Syringe System

Table 1

Formulas

	WS[3]	NS
Phenobarbital sodium	543mg	543mg
Glycerol	20ml	40ml
Sorbitol 70%	30ml	-
10% Saccharin sodium aqueous sol.	4ml	4ml
Methyl hydroxybenzoate	80mg	80mg
Propyl hydroxybenzoate	20mg	20mg
Raspberry flavour (Givaudan art.N°: 76525-33)	260mg	260mg
Lemon flavour (Givaudan art. no: 87017)	260mg	260mg
Distilled water ($C0_2$ free) to	100ml	100ml

Stock at room temperature and protect from light.

Table 2

HPLC Parameters

MercK LaChrom 7000

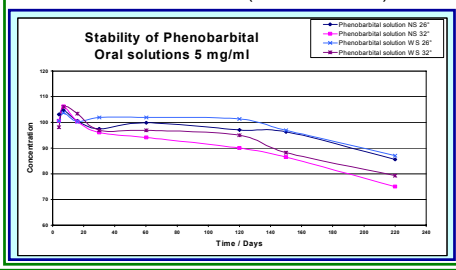
Column:	Lichrospher 100 RP18 5µm, 125 x 4 mm
Detection:	UV 256 nm
Injection Vol.:	20 µl
Mobile phase:	Phosphate buffer 0.03 M pH 7.0 : Méthanol 65 : 35 v:v 1 ml/min.

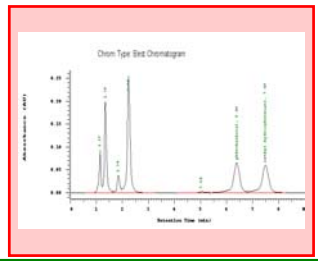
Isocratic HPLC was performed. After the phenobarbital peak, a 100% Methanol gradient is applied in order to elute all the parasite compounds with higher retention time

Results

The flavour combination chosen by the majority of volunteers for the two solutions was a mixture of Raspberry Aroma 76525-33 and Lemon Aroma 87017 (Givaudan®). After 150 days of storage at 25°C the loss in potency was not more than 5% of the initial concentration (3.13% WS and 3.65% NS), but at 220 days the losses were 14.4 % & 12.9 % respectively. In both cases, the losses after 120 days at 32 °C were not greater than 10%, however at 150 days they were 11.64% (WS) and 13,5% (NS) respectively. The pH of the solutions did not change appreciably during the study period.

The Calibration Curve was performed in the range of 200 -300 µg : R^2 [0.9982-0.999] 95% confidence level. RSD : WS (1.55% & 1.98%) and NS (0.97% & 1.63%).





Conclusions

The two oral formulations of phenobarbital were found to be flavour acceptable for adults and chemically stable for 150 days at 25°C. It will be necessary to determine which of them will be used and to test it for paediatric approval. This kind of preparation, as well as reducing the number of individual preparations contributes to security improvement in drug use by avoiding errors due to the large number of dosages, the extemporaneous manufacture and the absence of analytical controls.

References

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Possible conflict of interest : nothing to disclose

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