ORIGINAL ARTICLE

Pediatric oral solutions with propranolol hydrochloride for extemporaneous compounding: the formulation and stability study

Pediatrické perorální roztoky s propranolol-hydrochloridem pro magistraliter přípravu: formulace a hodnocení stability

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Summary

The aim of this study is to formulate an extemporaneous pediatric oral solution of propranolol hydrochloride (PRO) 2 mg/ml for the therapy of infantile haemangioma or hypertension in a target age group of 1 month to school children and to evaluate its stability. A citric acid solution and/or a citrate-phosphate buffer solution, respectively, were used as the vehicles to achieve pH value of about 3, optimal for the stability of PRO. In order to mask the bitter taste of PRO, simple syrup was used as the sweetener. All solutions were stored in tightly closed brown glass bottles at 5 ± 3 °C and/or 25 ± 3 °C, respectively. The validated HPLC method was used to evaluate the concentration of PRO and a preservative, sodium benzoate, at time intervals of 0–180 days. All preparations were stable at both storage temperatures with pH values in the range of 2.8–3.2. According to pharmacopoeial requirements, the efficacy of sodium benzoate 0.05 % w/v was proved (Ph.Eur., 5.1.3). The preparation formulated with the citrate-phosphate buffer, in our experience, had better palatability than that formulated with the citric acid solution.

Keywords: propranolol hydrochloride • pediatric preparation • extemporaneous preparation • solution • stability testing • HPLC

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Souhrn

Cílem práce je formulace pediatrického perorálního přípravku s propranolol-hydrochloridem (PRO) 2 mg/ml pro magistraliter přípravu, určeného k terapii infantilního hemangiomu nebo hypertenze u cílové skupiny dětí od 1 měsíce do školního věku, a hodnocení jeho stability. K dosažení pH okolo 3, optimálnímu pro PRO, byl jako vehikulum využit roztok kyseliny citronové nebo citráto-fosfátový pufr. K maskování hořké chuti PRO byl použit prostý sirup. Všechny roztoky byly uchovávány v dobře uzavřené hnědé lékovce při 5 ± 3 °C a/nebo 25 ± 3 °C. V časových intervalech 0–180 dní byla hodnocena koncentrace PRO a protimikrobní látky, benzoanu sodného, validovanou HPLC metodou. Všechny přípravky byly stabilní při obou teplotách s hodnotou pH v rozmezí 2,8–3,2. V souladu s požadavky lékopisu byla prokázána účinnost protimikrobní látky, benzoanu sodného (Ph. Eur., 5.1.3). Podle našich zkušeností má přípravek s citráto-fosfátovým pufrem lepší chuť než přípravek s kyselinou citronovou.

Klíčová slova: propranolol-hydrochlorid • pediatrický přípravek • magistraliter přípravek • roztok • testování stability • HPLC

Introduction

Propranolol hydrochloride (PRO) is a non-cardio selective beta blocker. It is usually administered in the form of tablets or capsules in therapy of cardiovascular diseases, to control symptoms of hyperthyroidism, the prophylaxis of migraine, and many other indications[1]. A successful treatment of infantile hemangioma has been observed recently; PRO is orally administered from newborns to school children at an initial dose of 2 to 3 mg/kg daily in two or three divided doses[1–3].

A liquid preparation is the best dosage form for paediatric patients as young children are simply unable to swallow conventionally sized tablets or capsules. Unfortunately, no pediatric oral liquid dosage form is on the market until now.

Under these circumstances, the pharmacist needs to compound such a preparation extemporaneously. When formulating a pediatric preparation in a hospital pharmacy, the pharmacist should attend to the stability of the active pharmaceutical substance for a labelled time period, the suitability and safety of excipients for children in the indicated target age groups, and expected duration of treatment[4, 5]. A simple way of preparing an oral liquid preparation is to crush commercial tablets to make a fine powder and mix it with a suitable vehicle.

Many empirical formulations prepared that way have been published for PRO[6–8]. Unfortunately, some authors of the earlier publications have used excipients which are not suitable for paediatric patients; a commercial suspending vehicle consisting of ethanol 1%, saccharin 0.05%, and cherry-flavoured 33% polyethylene glycol 8000 base, is an example[7]. The lack of valid stability data is the second common disadvantage of earlier publications.

This study was focused on the formulation of an extemporaneous solution containing PRO 2 mg/ml, suitable for therapy of infantile hemangioma in a target group of children from 1 month to approximately 6 years for hospital and/or home care. The stability of PRO was evaluated under two different conditions of storage within a shelf life of 180 days using high performance liquid chromatography (HPLC).

Experimental part

Materials

Citric acid monohydrate, sodium phosphate dibasic dodecahydrate, sodium benzoate (SB), and propranolol hydrochloride (PRO) of pharmaceutical quality were used. Simple sucrose syrup (64% w/w) was obtained from Fagron (Czech Republic). Water for injection (WFI) was used throughout the study as the solvent in the preparation of the vehicles and solutions.

Analytical reagents

The following reagents of analytical grade were used: acetonitrile, sulphuric acid (≥ 95–97%), and sodium dodecyl sulphate (≥ 98.5%) (all obtained from Sigma-Aldrich, Germany), butylparaben and tetrabutylammonium dihydrogenphosphate (≥ 97.0%) (both from Fluka, Germany), and sodium hydroxide (Penta, Czech Republic).

Methods

Compounding of buffer solution

To prepare a citrate-phosphate buffer solution of pH 3 (CPB), 1.67 g of citric acid and 1.47 g of dibasic sodium phosphate were dissolved in WFI and made up to 100.0 ml of a solution with WFI. The stock solution was stored in a tightly closed brown glass bottle, protected from light, and refrigerated (5 ± 3 °C).

Compounding of solutions of PRO

The composition of all prepared solutions ***F1–F3*** is shown in Table 1.

The ***F1*** solution of PRO 2 mg/ml was prepared by dissolution of 0.20 g of the substance and 0.05 g of sodium benzoate in an appropriate volume of CPB, then filled with buffer solution up to 50 ml and made up to the total volume of 100.0 ml with Simple Sucrose Syrup.

In the formulation ***F2***, 0.2 g of propranolol hydrochloride, 0.05 g of sodium benzoate, and 0.2 g of citric acid were dissolved in an appropriate volume of WFI, made up to 50 ml with WFI and then filled up to a total volume of 100.0 ml with Simple Sucrose Syrup.

The solution ***F3*** was prepared by dissolution of 0.20 g of propranolol hydrochloride and 0.05 g of citric acid that way as the previous one. This solution was preservative-free.

Measurement of pH

The pH value was measured under stabilized conditions using a pH meter (pH 212 Microprocessor pH Meter, Hanna instruments, Germany) with a combined pH electrode. The pH meter was calibrated at pH 4.01 and 7.00 at 20 °C using standard buffer solutions (WTW, Germany). The results obtained at the time intervals chosen in the stability study are presented in Table 2.

Instrumentation and analytical conditions

A stability indicating HPLC assay was developed for PRO and sodium benzoate, using butylparaben as an internal standard. The HPLC system consisted of a Shimadzu LC-2010C (CLASS-VP Software, Shimadzu, Japan) with a Dual – Absorbance UV Detector. Separation was achieved using a Supelco Discovery® C18 column

Table 1. Composition of the evaluated propranolol hydrochloride solutions

Composition	**F1**	**F2**	**F3**
PRO	0.20 g	0.20 g	0.20 g
Citric acid	–	0.20 g	0.05
CPB	50 ml	–	–
Sodium benzoate	0.05 g	0.05 g	–
Simple syrup	to 100 ml	50 ml	50 ml
WFI	–	to 100 ml	to 100 ml
Taste	sweet&sour	sweet slightly bitter	sweet slightly bitter

Table 2. The results of pH measurement during the stability study at room temperature (room) and/or in a refrigerator (cold)

Time	F1		F2		F3	
(days)	Room	Cold	Room	Cold	Room	Cold
t_0	3.14	3.14	2.89	2.89	2.87	2.88
t_1	3.14	3.16	2.89	2.90	2.86	2.88
t_3	3.15	3.14	2.90	2.88	2.87	2.87
t_7	3.16	3.15	2.90	2.90	2.89	2.89
t_{14}	3.15	3.15	2.90	2.87	2.92	2.89
t_{30}	3.16	3.16	2.91	2.90	2.86	2.87
t_{60}	3.13	3.13	2.88	2.87	–	–
t_{90}	3.08	3.11	2.82	2.84	–	–
t_{120}	3.09	3.08	2.82	2.82	–	–
t_{180}	3.12	3.13	2.89	2.90	–	–

Table 3. System suitability parameters of HPLC method for determination of propranolol hydrochloride (PRO) and sodium benzoate (SB)

System suitability parameters	F1		F2		F3	
	PRO	SB	PRO	SB	PRO	SB
Repeatability t_R RSD (%)	0.16	0.24	0.16	0.24	0.16	–
Repeatability Area	0.09	0.08	0.09	0.08	0.09	–
Theoretical Plates	8441	6408	8441	6408	8441	–
Resolution	8.82	–	8.82	–	8.82	–
Tailing factor	1.19	1.23	1.19	1.23	1.19	–

Table 4. Validation data of HPLC method for determination of propranolol hydrochloride (PRO) and sodium benzoate (SB)

Validation criteria	F1		F2		F3	
	PRO	SB	PRO	SB	PRO	SB
Precision RSD (%)[a]	0.44	0.59	0.21	0.19	0.33	–
Linearity (R)[b]	0.9997	0.9997	0.9997	0.9997	0.9997	–
Accuracy Recovery (%)[a]	101.49	101.11	99.55	99.09	99.51	–
Accuracy RSD (%)[a]	0.80	0.78	0.30	0.29	0.23	–
Selectivity	No interference		No interference		No interference	

[a] six samples, three injections of each sample
[b] at 50, 75, 100, 135, 170, 200 % levels

Table 5. The percentage content of propranolol hydrochloride during the stability study at room temperature (room) and/or in a refrigerator (cold). RSD (%) in brackets

Time	F1		F2		F3	
(days)	Room	Cold	Room	Cold	Room	Cold
t_0	100.00 (*0.34*)	100.00 (*0.68*)	100.00 (*0.11*)	100.00 (*0.49*)	100.00 (*0.40*)	100.00 (*0.40*)
t_1	98.82 (*0.06*)	99.01 (*0.86*)	100.17 (*0.14*)	98.65 (*1.03*)	100.17 (0.27)	100.34 (0.07)
t_3	100.60 (*0.14*)	100.14 (*0.18*)	103.24 (*0.08*)	101.13 (*2.06*)	100.39 (0.30)	100.14 (0.31)
t_7	99.57 (*0.16*)	100.15 (*0.09*)	99.94 (*0.35*)	101.23 (*0.65*)	99.87 (0.23)	100.37 (0.13)
t_{14}	101.99 (*0.16*)	100.25 (*0.45*)	101.89 (*0.46*)	100.83 (*0.77*)	100.97 (0.11)	101.30 (0.15)
t_{30}	102.31 (*0.13*)	102.51 (*0.39*)	102.96 (*0.75*)	102.47 (*0.23*)	99.87 (0.18)	99.80 (0.09)
t_{60}	99.14 (*0.51*)	98.20 (*0.11*)	98.96 (*0.24*)	97.87 (*0.04*)	–	–
t_{90}	100.40 (*0.07*)	100.77 (*0.41*)	100.79 (*0.14*)	100.34 (*0.26*)	–	–
t_{120}	101.18 (*0.34*)	100.91 (*0.04*)	102.32 (*0.62*)	101.09 (*0.50*)	–	–
t_{180}	101.82 (*0.14*)	100.86 (*0.17*)	101.71 (*0.28*)	101.63 (*0.09*)	–	–

(25 cm x 4.6 mm x 5 µm) (Supelco, USA). The isocratic flow rate was 1.8 ml/min and the UV detector was set at a wavelength of 230 nm.

The mobile phase consisted of 1.6 g of sodium dodecyl sulphate, 0.31 g tetrabutylammonium dihydrogenphosphate, 1 ml of sulphuric acid, 450 ml of HPLC grade water, and 550 ml of acetonitrile, and was adjusted to the pH value of 3.3 using sodium hydroxide solution. The mobile phase solution was filtrated through a 0.45 µm filter (Glass Microfiber Filters, Whatman, UK) and then was sonicated for a few minutes (Sonorex Digitec, Bandelin, Germany) before HPLC analysis.

Table 6. The percentage content of sodium benzoate during the stability study at room temperature (room) and/or in a refrigerator (cold). RSD (%) in brackets

Time	F1		F2	
(days)	Room	Cold	Room	Cold
t_0	100.00 (*0.37*)	100.00 (*0.74*)	100.00 (*0.21*)	100.00 (*0.47*)
t_1	98.15 (*0.65*)	97.67 (1.15)	97.52 (*0.26*)	97.40 (*0.30*)
t_3	99.91 (*0.60*)	99.14 (*0.59*)	99.55 (*0.19*)	99.83 (*0.91*)
t_7	99.42 (*0.23*)	99.71 (*0.35*)	99.35 (*0.18*)	99.76 (*0.23*)
t_{14}	100.82 (*0.19*)	99.46 (*0.14*)	100.48 (*0.21*)	99.43 (*0.14*)
t_{30}	102.76 (*0.13*)	102.89 (*0.17*)	102.96 (*0.60*)	102.69 (*0.19*)
t_{60}	98.54 (*0.51*)	97.67 (*0.10*)	98.42 (*0.28*)	97.47 (*0.10*)
t_{90}	99.83 (*0.16*)	100.40 (*0.33*)	100.00 (*0.16*)	99.42 (*0.27*)
t_{120}	99.48 (*0.35*)	99.28 (*0.64*)	99.89 (*0.52*)	99.02 (*0.25*)
t_{180}	101.08 (*0.23*)	99.71 (*0.19*)	100.37 (*0.08*)	100.17 (*0.10*)

The HPLC method for the analysis of the proposed oral solution was successfully and completely validated by following the Q2(R1) ICH guideline (1997). System suitability parameters (n = 6) and validation data are summarized in Tables 3 and/or 4, respectively.

Stability study

The batch of the preparation was divided into two separate samples and stored in a tightly closed brown glass bottle at room temperature (25 ± 3 °C) and in a refrigerator (5 ± 3 °C). The concentration of propranolol hydrochloride and the preservative, sodium benzoate, in the preparations ***F1*** and ***F2*** were evaluated at the beginning of the stability assay (t0, a content of 100 %) and thereafter at time intervals of 1 – 3 – 7 – 14 – 30 – 60 – 90 – 120 – 180 days. The concentration of propranolol hydrochloride in solution ***F3*** was evaluated the same way but only at the time interval up to 30 days. Stability limit of maximum 5% degradation of the drug and the preservative contents were the basic criteria.

Each sample was measured in triplicate. The average values of the percentage content (n = 6) of propranolol hydrochloride with relative standard deviations (RSD, %) in brackets are summarized in Table 5. Similarly, the results for sodium benzoate are shown in Table 6.

Results and Discussion

In an aqueous vehicle, PRO has good solubility (50 mg/mL). Solutions are stable at about pH 2.8 – 4 with the best at pH 3[9]. A disadvantage of PRO is a bitter taste leading to the necessity of the addition of a sweetener.

In this study, three formulations of PRO solution were compounded (Table 1). The citric acid and/or the citrate-phosphate buffer solution, respectively, were used as the vehicles to achieve pH value of about 3. Generally, a multi-dose preparation needs an addition of a preservative. Since there are some references indicating possible incompatibility between PRO and parabens resulting in the degradation of the parabens[6], sodium benzoate was used as an alternative[8, 10] assuming the use in a children target group of 1 month and older (the formulations ***F1*** and ***F2***). Simple Sucrose Syrup is added to improve palatability of the solutions. The preparation ***F3*** was formulated preservative-free assuming the use for neonates below 1 month.

According to the analytical procedures validation ICH guidelines (Q2(R1)), the HPLC method was completely validated. In Tables 3 and 4, system suitability parameters (n = 6) and validation data are presented.

All solutions were stored in tightly closed brown glass bottles at 5 ± 3 °C and/or 25 ± 3 °C, respectively. At time intervals mentioned in the experimental section, samples were withdrawn and used to estimate pH value and the content of PRO and SB (preserved preparations ***F1*** and ***F2***). The results in Table 2 show good consistency in pH value during the stability study. This is important particularly in the case of the preserved solutions ***F1*** and ***F2*** as sodium benzoate has an alkaline effect on pH value, which might lead to degradation of PRO[9].

The percentage content of PRO and SB content estimated using HPLC during the stability study at room temperature and/or refrigerator are summarized in Table 5 and/or Table 6, respectively. As ***F3*** did not contain sodium benzoate, only the results for ***F1*** and ***F2*** are shown in Table 6. In all cases, the concentration of drug and/or preservative, respectively, was within recommended limits of ± 5% of the initial concentration at the beginning of the stability assay (t_0)[11]. Based on the results, the estimated shelf-life[12] of 180 days was proved at both temperatures of storage for ***F1*** and ***F2*** formulations when stored in a tightly closed brown glass bottle.

Conclusions

The aim of the study was to find an optimal vehicle for paediatric oral solution of PRO and to verify its stability at two temperatures of storage. The proposed oral aqueous solutions ***F1*** and ***F2*** for extemporaneous compounding

were stable at room temperature and/or refrigerator for 180 days. In accordance with the European Pharmacopoeia (Ph.Eur. 7.0, 5.1.3 Efficacy of antimicrobial preservation), the efficacy of the antimicrobial preservative, sodium benzoate 0.05 % w/v, was demonstrated by an accredited laboratory. A labelled shelf-life of 3 months, storage in a refrigerator at 5 ± 3 °C, and protection from light can be recommended. The formulation ***F1*** consisting of citrate-phosphate buffer mixed with sugar syrup we considered better than ***F2*** for a sweet and sour taste, particularly in the therapy of older children. Formulation ***F3*** represents the composition formulated with a minimal content of excipients and is preservative-free. It must, therefore, be prepared under aseptic conditions. It can be expected for use in the therapy of neonates under supervision of a caregiver. A labelled shelf-life of 7 days can be recommended for extemporaneous compounding in real-life situations if stored in a refrigerator at 5 ± 3 °C. To protect from microbial contamination and to allow easy administration, preparations should be packaged in a glass container with a screw cap suitable for administration using a syringe for oral use.

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