OBJECTIVES

The commercially available medicinal products do not completely cover the wide spectra of preparations particularly when targeted to the pediatric patients. Under such circumstance, the pharmacist needs to prepare the preparation extemporaneously. In the case of necessity, an oral solution is the best dosage form from both the application and the correct dose points of view.

This study deals with the formulation and stability testing of the extemporaneous oral solutions of three cardiologic drugs: propranolol, sotalol and furosemide, directed to newborns.

Propranolol hydrochloride (PCL) is a non-selective beta blocker administered in therapy of cardiovascular diseases, particularly Familial hypercholesterolemia and hypertension; these relatively new indications include Congenital Heart Defects (Zahálka-Lubná 2003). PCL is orally administered from newborns to school children at an initial dose of 0.3 to 1 mg/kg daily in two or three divided doses.

Sotalol hydrochloride (SCL) is an antiarrhythmic beta-blocker highly effective and well tolerated in the treatment of ventricular and supraventricular tachycardia. In children, its recommended minimum is to administer asthol to children in initial oral dose 1 mg/kg twice daily increased as necessary every 3–4 days to max 4 mg/kg twice daily (Zahálka 2005).

Furosemide (FSM) represents a traditional diuretic widely used in pediatric patients intravenous treatment of hypernatremia and sodiuresis associated with heart failure. Maximal dose for hypernatremia is 0.5 to 2 mg per kilogram of body weight in 3 to 4 hours, from 0.5 to three divided doses from 1 month, increasing the dose in older children.

Stability study

Two batches of the preparation were prepared, each batch was divided into two separate samples which were filled into the closed bottles (Sample BF) or into an autoclave bottle (Sample A). Number of containers was chosen considering to open new container at each stability time point in order to avoid the contamination of samples.

The preparations were stored at room temperature (25 ± 3°C), protected from the light.

The concentration of drugs (PCL, SCL, FSM) was evaluated at the beginning of the stability assay (at time of compounding t₀, a content of 100%) after the sterilization at an autoclave (t₁) and thereafter at time intervals of 7 – 14 – 30 days. The value of pH was estimated (pH 212 Microprocessor pH Meter, Hanna instruments, Germany), as well.

Each sample was measured in triplicate, the average values of the remaining percentage content (% RSD) in brackets are summarized.

RESULTS AND DISCUSSION

The average content of drug in mg/mL in the samples sterilised using bacterial filtration (BF) and/or (autoclave (A)), are respectively summarised in Tables 2 – 4 (relative standard deviations RSD in % in brackets). The limit ±5% of the initial drug concentration is shown in Figures. In Table 5, pH values of drug solutions are listed.

METHODS

Preparation of solutions (Hospital Pharmacy of University Hospital Motol)

The solutions of propranolol hydrochloride (PCL) 2 mg/mL and sotalol hydrochloride (SCL) 5 mg/mL were prepared by dissolving of the substance in water for injection (WFI).

The solution of furosemide (FSM) 2 mg/mL was prepared as fast as possible (protection from the light degradation) by dissolution of FSM in approximately 20 mL of freshly prepared 7.5% (w/v) of disodium hydrogen phosphate dodecahydrate (DNaHP) was used.

The proposed solutions are targeted to neonates (NED), therefore, they should be preservative free. The microbiological stability is provided due to aseptic technique and final sterilization of the product. The influence of the sterilisation method on the stability of a drug was investigated; stability limit of maximum 5% degradation of the drug content was the basic criterion.

HPLC method

Analytical reagents (PCL)

The following reagents of analytical grade were used in HPLC methods: acetonitrile, methanol, tetrahydrofuran, sulphuric acid (≥ 95 - 97%), and sodium dodecyl sulphate (≥ 98.5%) (all obtained from Sigma-Aldrich, Germany), as well.

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HPLC method

Analysis of samples. The preparations were filtered through a 0.45 μm filter (Glass Microfilter Filters, Whatman, UK) and then sonicated for the few minutes (Sonorex Digital, Bandelin, Germany) before HPLC analysis.

The HPLC methods were successfully and completely validated by following 20(R) ICH guidance (1997). System suitability parameters (n = 6) and validation data are summarized in Table 1. Details of the methods are referred to in the articles: Zahálka et al 2013, Matysová et al 2019, Zahařáková et al 2019, and Zahálka et al 2017.

CONCLUSIONS

The preparation of FSU solution using disodium hydrogen phosphate is easy and fast as DNaHP is easier to manipulate and weigh than sodium hydroxide. Moreover, faster preparation serves better light protection of a drug.

The conversion of the aqueous solutions of SOT and FSM was unchanged after autoclaving; the pH value remained in the range of 5.42 - 5.51 for SCL and 7.65 – 7.88 for FSM, respectively, within the time period of 30 days of storage at room temperature.

Although the PCL solution sterilised using BF was stable at room temperature having pH value in a range of 5.84 - 6.36, the preparation complied to the main criterion of maximum drug concentration decay only for less than two weeks. The decrease in PCL concentration was associated with the decrease in pH value. In order to increase stability during autoclaving, the buffering with citric acid before sterilisation is probably necessary. This would be verified in the following study.

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LITERATURE