TCH-023

LIQUID ORAL FORMULATIONS OF PROPRANOLOL HYDROCHLORIDE FOR TREATMENT OF INFANTILE HEMANGIOMAS

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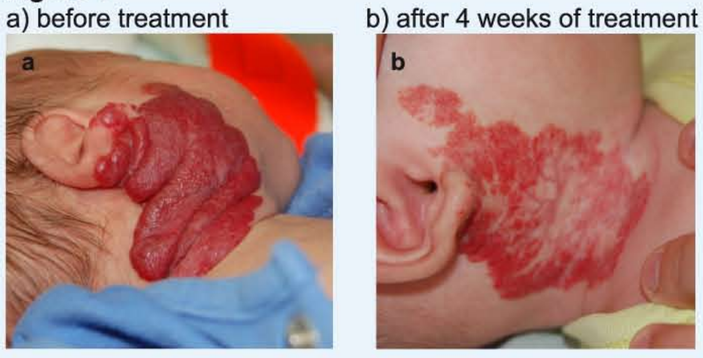
Introduction

Propranolol HCl is a non-cardioselective beta blocker used in the cardiologic indications and recently in the treatment of infantile hemangiomas *(Figure 1)*. No dosage form with propranolol is commercially available in the Czech Republic.

Figure 1

a) before treatment b) after 4 weeks of treatment



Objectives

- To formulate the extemporaneous oral dosage form of propranolol for children in the hospital and home care
- Requirements:
  - Target group: children aged from 30 days to 24 months, minimum amount of safe excipients, suitable palatability
  - Therapeutic dose: 2-3 mg/kg daily in two or three divided doses
  - To ensure and determine physical, chemical and microbiological stability of the formulation (min. 3 months of expiration)
- Design of the preparation process in the hospital pharmacy including quality control of the product and an appropriate container with an applicator (oral dispenser)

Study Design

Solution of propranolol hydrochloride 2 mg/ml was prepared from the substance of pharmaceutical quality. Citrate-phosphate buffer pH 3 was used for achieving the optimum stability of propranolol, we used sugar syrup to mask the bitter taste of the active ingredients.

The stability of preserved solution was evaluated for 180 days (at time intervals of 1, 3, 7, 14, 30, 60, 90, 180 days) at room temperature (20-25 °C) and in a refrigerator (2-8 °C) using validated HPLC method and measuring of pH.

The content of propranolol hydrochloride and sodium benzoate within ± 5% of the initial concentration at the time of compounding (t_0) were the main criteria.

The quality criteria were defined for the stock preparation of the product.

Results

Design of the preparation process of Propranolol solution 2 mg/ml
The quality active substance and excipients used in this formulation complies with the requirements monographs PhEur.

Composition of propanolol solution 2mg/ml	
Propranolol hydrochloride	*0.20 g*
Sodium benzoate	*0.05 g*
Citrate-phosphate buffer	*50.0 mL*
Sucrose syrup (64% w/w)	*ad 100.0 mL*

Preparation process: 0,2 g propranolol hydrochloride and 0.05 g of sodium benzoate were dissolved in 50.0 mL of CP buffer solution and made up the total volume of 100.0 mL with sucrose syrup. Citrate-phophate buffer solution has value of pH= 3 and contains 1.67 g of citric acid and 1.47 g of dibasic sodium phosphate in 100 ml water for injection.

Container:
Glass brown bottle with a bottle adaptor and a syringe for oral use *(Figure 2)*.

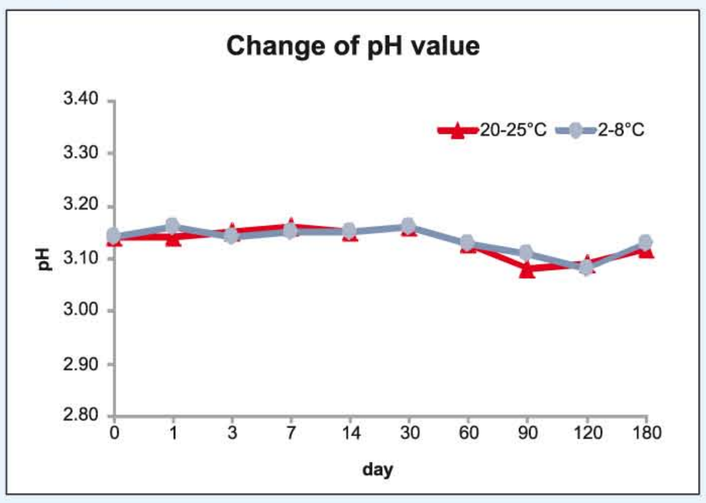
Figure 2

Quality control of the finished product in the pharmacy:
Identification test: Thin-layer chromatography (Propranolol hydrochloride)
Assay: Determination of content of propranolol using titration with silver nitrate and potentiometric indication (0.166 - 0.184% w/w)
pH value: 2.8 - 3.5
Refractive index: 1.392 - 1.396

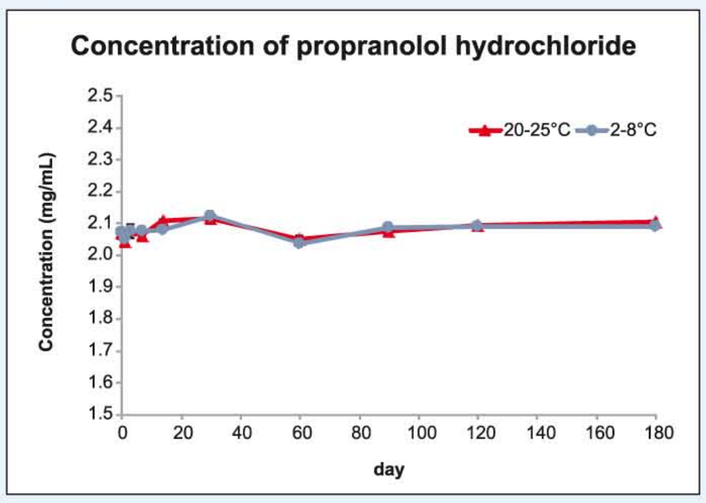
Chemical stability of the product:
The new simple HPLC method for the determination of propranolol and sodium benzoate in this solution was developed and validated in cooperation with the Faculty of Pharmacy .
Preserved formulation was stable at both used temperatures 180 days. The concentration of propranolol varied between 98.2 - 102.5%, sodium benzoate varied between 98.1 - 103.3%, value of pH did not significantly change *(Graph 1-3)*.

Microbiological quality:
The efficacy of antimicrobial preservation (Ph.Eur.,5.1.3) was proven for sodium benzoate 0.05% in this formulation by accredited laboratory.
Based on validated stability studies and microbiological data, we recommend a shelf life of 3 months at 2-8 °C for outpatients.

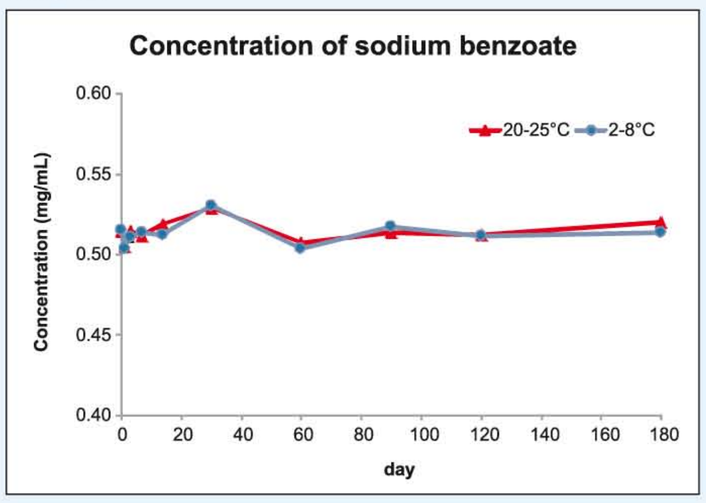
Graph 1



Graph 2



Graph 3



Discussion

The capsules are the most frequently prepared dosage form for pediatric patients in our pharmacy. Preparation of gelatine capsules is expensive, time-consuming and handling of capsules in the compounding and administration (emptying the content) increases the risk of incorrect dose. We used to prepare about 3000 capsules of different doses of propranolol (in range 2 - 8 mg of active substance) monthly. The preparation of capsules was replaced by the preparation of the solution of propranolol 2 mg/ml after finishing the stabilities studies in April 2012. 108 children altogether were treated successfully at the Department of Paediatric Haematology and Oncology using propranolol products from our hospital pharmacy from 2009 to the end of 2012. Thirty-seven children aged 1 month to 21month received a solution, the other capsules. The median period of treatment to regression was 10.3 months.

Conclucions

The oral liquid is cheaper than capsules, easier to prepare, more convenient to administer to children and it enables flexible dosing for different patients. The overall risk of preparation is reduced because the solution provides better control.

Aknowledgements:
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