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FORMULATION AND QUALITY CONTROL OF A BISOPROLOL FUMARATE 0.5 MG/ML ORAL SOLUTION FOR PAEDIATRIC USE

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Background and Importance

Bisoprolol is a beta-blocker indicated for the treatment of heart failure in paediatric patients. There are no licensed bisoprolol containing paediatric dosage forms available in the EU. Pharmacy preparation of patient individually dosed bisoprolol capsules is common practice. However, the preparation and use of bisoprolol oral liquids are the gold standard for paediatric patients because they allow body weight oriented dosing for different age groups. So far, there is no published information regarding the formulation, quality control, and stability of pharmacy-prepared bisoprolol oral solutions.

Aim and Objectives

The aim of this project was to formulate a bisoprolol fumarate 0.5 mg/mL oral solution for paediatric use, establish suitable quality-control measures, and to perform stability tests.

Materials and Methods

Formulation development

- Formulations were developed based on national standardised formulations, i.e. propranolol hydrochloride oral solution (*NRF 11.142.*) and metoprolol tartrate oral solution (*NRF 10.3.*)

Efficacy of Antimicrobial preservation

- Efficacy of antimicrobial preservation was tested according to Ph. Eur. 5.1.3 by an external lab

HPLC assay [1]

- Validated according to ICH Q2 (R1) guideline
- RP-HPLC with photodiode array detector at 228 nm
- Column: Inertsil ODS-3 5 µm 4.6 x 250 mm
- Mobile phase: 30% acetonitrile in 0.1 M KH_2PO_4 buffer
- Flow rate: 1 mL/min
- Injection volume: 10 µL in triplicate
- Runtime: 15 Min.

Stability testing

- Quantitative HPLC assay, pH measurement
- Storage at room temperature
- Time points of measurement: day 0, 7, 14; month 1, 3, 6, 12

[1] Joshi SJ et al.: RP-HPLC method for simultaneous estimation of bisoprolol fumarate and hydrochlorothiazide in tablet formulation, J Pharm Biomed Anal. 2010 Jul 8;52(3):362-71

Results

Formulation of bisoprolol oral solutions

Tab. 1: Bisoprolol fumarate 0.5 mg/mL solution with sucrose and flavour; osmolality: 1215 mOsmol/kg

Bisoprolol fumarate	0.05 g
Sucrose	25 g
Potassium sorbate	0.14 g
Anhydrous citric acid	0.07 g
Raspberry flavour	0.1 g
Purified water	84.34 g

Tab. 2: Bisoprolol fumarate 0.5 mg/mL solution without sucrose and flavour; osmolality: 25 mOsmol/kg

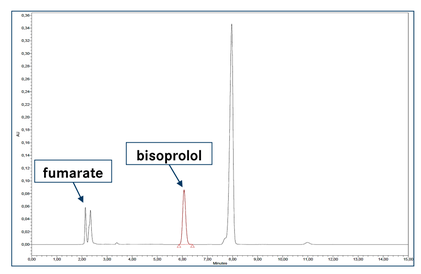
Bisoprolol fumarate	0.05 g
Potassium sorbate	0.14 g
Anhydrous citric acid	0.07 g
Purified water	99.74 g

Efficacy of Antimicrobial preservation

- Proven in accordance with Ph. Eur. 5.1.3

Validation HPLC assay

- Forced Degradation: bisoprolol degradation under acidic and heat conditions confirmed known instability of hydrous bisoprolol solutions at pH < 3.



- Intraday-precision: 0.4 % RSD
- Interday-precision: 3.2 % RSD
- Linearity: correlation coefficient 0.9998

Fig. 1: Exemplary chromatogram of bisoprolol fumarate solution 0.5 mg/mL, peaks not declared are matrix-related

Stability testing

Tab. 3: Stability and pH value of bisoprolol fumarate solution 0.5 mg/mL with sucrose and flavour

Bisoprolol fumarate 0.5 mg/ml with sucrose and flavour	d 0	d 8	d 14	d 37	d 91	d 174
Remaining percentage rate of the initial bisoprolol concentration [%] ± RSD [%] (n=9)	100 ± 1.1	102 ± 0.1	104 ± 0.6	99 ± 2.1	95 ± 1.0	100 ± 1.1
pH-values ± RSD [%] (n=3)	4.58 ± 0.1	4.61 ± 0.1	4.58 ± 0	4.63 ± 0.1	4.56 ± 0.2	4.60 ± 0

Tab. 4: Stability and pH value of bisoprolol fumarate solution 0.5 mg/mL without sucrose and flavour

Bisoprolol fumarate 0.5 mg/ml without sucrose and flavour	d 0	d 83	d 184
Remaining percentage rate of the initial bisoprolol concentration [%] ± RSD [%] (n=9)	100 ± 0.4	106 ± 0.8	105 ± 0.8
pH-values ± RSD [%] (n=3)	4.57 ± 0.1	4.63 ± 0.1	4.57 ± 0.1

Conclusion and Relevance

The therapeutic need for a liquid oral bisoprolol preparation could be addressed with the formulation of a bisoprolol fumarate 0.5 mg/mL oral solution, suitable for preparation in stock. Bisoprolol oral solution formulated without sucrose and flavour can be used when high osmolality is to be avoided. For both formulations adequate in-use preservation is given and stability is proven for at least 6 months.