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PREPARATION AND STABILITY OF READY-TO-ADMINISTER DEXAMETHASONE DIHYDROGEN PHOSPHATE 8 MG/ML / 0.02% HYALURONIC ACID INTRATYMPANAL INJECTION SOLUTION

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Background and Importance

Intratympanal injection of glucocorticoids is utilized to treat morbus menière which is characterized by vertigo, acute hearing loss, and tinnitus. As licensed products are not available, pharmaceutical preparations for intratympanal injection are aseptically prepared in hospital pharmacies by using licensed medicinal products as starting material. The re-formulated injection solution contains dexamethasone dihydrogen phosphate (H_2PO_4) 8 mg/mL and 0.02% hyaluronic acid injection solution to increase viscosity and diffusion of dexamethasone into the inner ear. Preparation for stock requires a product dossier and own stability tests (CM/Res(2016)1).

Aim and Objectives

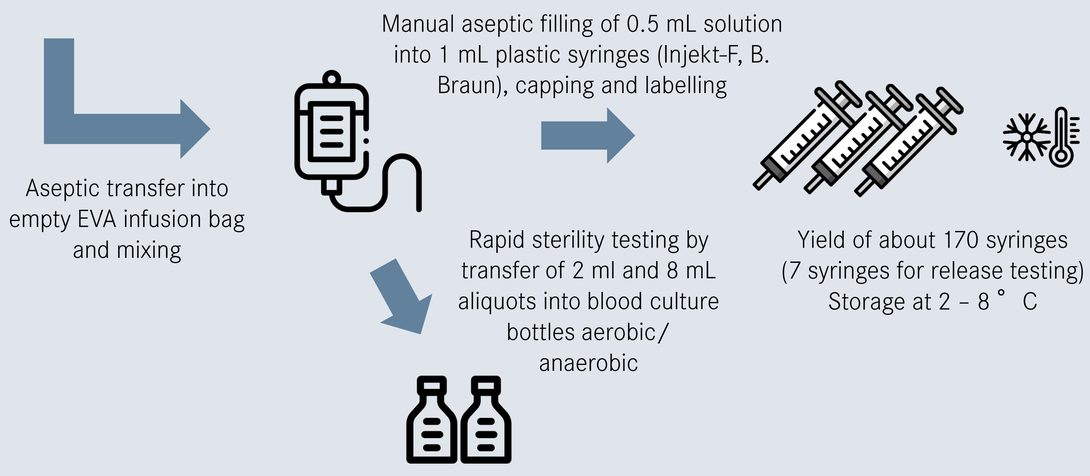
The aim of the project was to validate the preparation process and to determine stability of aseptically prepared ready-to-administer (RTA) dexamethasone 8 mg/mL/0.02% hyaluronic acid intratympanal injection solution.

Materials and Methods

Preparation process

Starting material

Dexa-ratiopharm® 40 mg injection solution (40 mg/5 mL dexamethasone H_2PO_4, water for injection, Na-edetate, NaCl, NaOH)	100 mL (20 ampoules)
Hyalart® (20 mg/2 mL sodium hyaluronate in water for injection, phosphate buffered)	2 mL (1 vial)



Stability testing

- Sampling time points immediately (day 0), day 7, 14, 28, 60, 90

UV-Vis analysis of dexamethasone concentration

- Method based on Ph.Eur. 11.0/0388
- UV-Vis spectral photometer: Evolution 201 (Thermo Fisher)
- Wavelength: 238 nm
- Quartz cuvette 10 mm path length
- Sample measuring concentration: 20 µg/mL dexamethasone
- Sampling: 3 syringes measured in triplicate each (n = 9)
- Blank solution: Ethanol 96%

pH and osmolality measurement (n = 3)

Results

Tab. 1: **Dexamethasone H_2PO_4 concentration in intratympanal injection solution stored at 2-8 ° C over 90 days**

Dexamethasone H_2PO_4 concentration [mg/mL] ± RSD [%] n = 9		Percentage rate of initial dexamethasone H_2PO_4 concentration (T0 = 100%) [%] ± RSD [%] n = 9				
Nominal	day 0	day 7	day 14	day 28	day 60	day 90
8	8.45 ± 0.13	97.83 ± 3.13	99.75 ± 0.38	100.43 ± 0.71	96.14 ± 0.85	99.95 ± 1.16

Tab. 2: **pH value and osmolality of dexamethasone H_2PO_4 8 mg/mL / 0.02% hyaluronic acid intratympanal injection solution stored at 2-8 ° C over 90 days**

	day 0	day 28	day 60	day 90
pH n = 3	7.73	7.81	7.61	7.57
Osmolality [mOsmol/kg] n = 3	286	284	284	n.a.

- No significant changes of dexamethasone concentration, pH and osmolality over a 3-month period of refrigerated storage
- Sterility tests showed no growth of bacteria and yeasts (4 batches tested)
- Starting material and primary packaging is suitable for a 3-month period of refrigerated storage

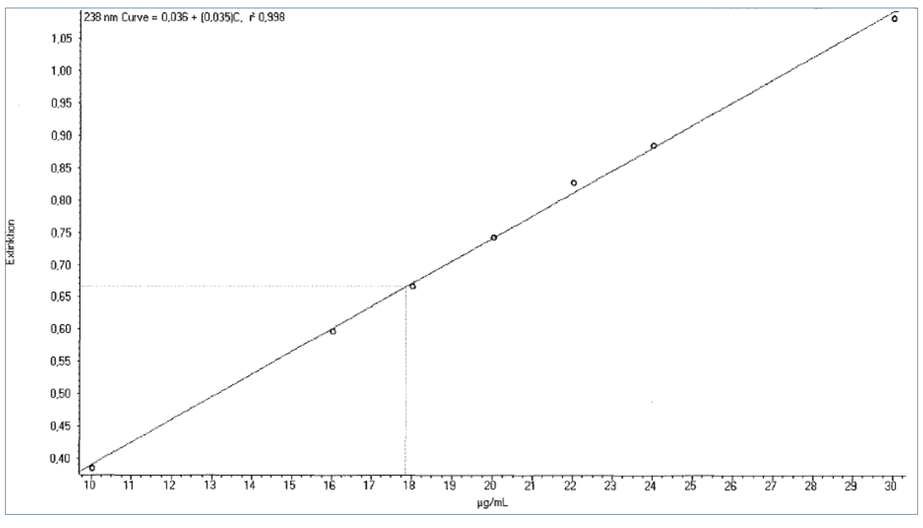


Fig. 1: **UV-Vis calibration curve of dexamethasone analysis (7 dexamethasone standard solutions measured in triplicate)**

Conclusion and Relevance

Preparation of re-formulated RTA dexamethasone H_2PO_4 8 mg/mL/0.02% hyaluronic acid intratympanal injection solution was successfully implemented. Stability was tested via UV-Vis spectroscopy (dexamethasone concentration), osmolality, and pH measurement. Shelf life was proven for at least a 3-month period when syringes are stored refrigerated at 2-8 ° C.