Development of eye drops containing lidocaine hydrochloride

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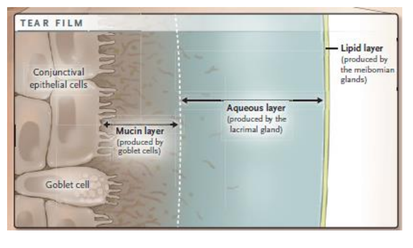
BACKGROUND AND OBJECTIVE

Eye drops are the most commonly used ophtalmic preparations due to the easy production, better homogeneity and dose uniformity. To obtain well tolerated formulations it is necessary to take into account different critical parameters such as the tonicity, pH, surface activity and viscosity. In particular, it is desirable that eye drops present properties as close as possible to the lacrimal fluids (osmolarity 302±6 mOsm/L, pH range 6,9 – 7,5, surface activity range 40-46 mN m^{-1}). Moreover in order to increase the drug residence time a viscosity enhancer can be introduced to obtain a viscosity range of 40-70 mPa*s. Finally it is a regulatory requirement that ophthalmic preparations must be sterile [1]. The purpose of this study was to develop a formulation and preparation method of eye drops containing lidocaine hydrochloride.



FORMULATIONS AND CHARACTERIZATION

Formulations

On the basis of preliminary studies two polymers were selected as viscosity enhancers (HPMC 0,5% m/V, CMC 0,75% m/V). Two different buffer systems (phosphate - PB and borate - BB) were tested for pH adjusting and sodium chloride was used as tonicity adjuster [1,2]. The formulations are reported in table 1.

Preparation methods of eye drops

Method A: All the components were solubilized in the water and the final preparation was steam sterilized (T=121°C, 15 min.).
Method B: Polymer, sodium chloride and the buffer salts were dissolved in 70% of water content and then steam sterilized. LD was soluted in the remaining water and the solution filtered through a 0.20 µm filter. Finally water solution was added to the vehicle.

Eye drops characterization

On the obtained preparations the following tests were performed:

- Rheological characterization using a rotational viscosimeter (Visco Tester 7R, Haake, Germany, rotor R2) at rotor speed of 100 rpm.
- pH measurement.
- Surface activity measurements by a pendent drop method using the drop shape analyzer DSA 30 (Kruss, Germany).
- Lidocaine hydrochloride content by spectrophotometrical evaluation at 263 nm (Cary 50 Scan, Varian, USA).

Formulation	LD (g)	Polymer (g)		Phosphate buffer (mL)		NaCl (g)
		HPMC	CMC	Na_2HPO_4 0,045M	NaH_2PO_4 0,033M	
HPMC_P	2	0,5		95	5	0,07
CMC_P	2		0,75	95	5	0
Formulation	**LD (g)**	**Polymer (g)**		**Borate buffer (mL)**		**NaCl (g)**
		HPMC	CMC	H_3BO_3 0,05M	Borace 0,0125M	
HPMC_B	2	0,5		40	60	0,27
CMC_B	2		0,75	40	60	0,19

Tab. 2
Composition of eye drops containing Lidocaine hydrochloride formulated with HPMC or CMC.

RESULTS

VISCOSITY

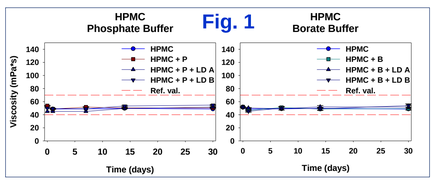


Fig. 1

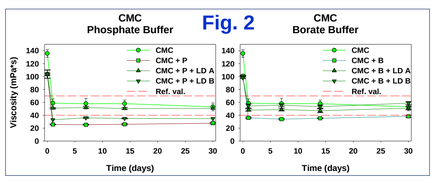


Fig. 2

Fig. 1 and 2
Viscosity (100 rpm) of vehicles and eye drops with HPMC (fig. 1) or CMC (fig. 2) at different time intervals.

When HPMC was used, both the steam sterilization and the presence of the buffers did not produce any relevant change in eye drops viscosity. The viscosity was constant during the observation time and also the preparation method did not show to have any relevant effect in the eye drops viscosity (fig. 1).

When CMC was used, the viscosity of the polymer dispersions was decreased after steam sterilization. This effect was more marked in the presence of the buffer systems, particularly with phosphate buffer. Moreover, when the API solution was added to the autoclaved dispersion (method B), the effect of phosphate buffer on viscosity was even more marked and the viscosity values were under the recommended range (fig. 2).

pH

Although widely used in ophthalmic formulations, phosphate buffers are not recommended due to significant cytotoxic effects concentration-related (2).
As an alternative, a borate buffer was tested as a pH adjuster and the results obtained with HPMC and CMC based formulations are showed in figures 3 and 4.

Both the tested buffers were able to stabilize pH to the physiological levels (7,0-7,6, red dotted lines) during the observation time (30 days) (fig. 3 and fig. 4)

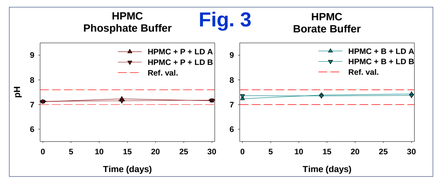


Fig. 3

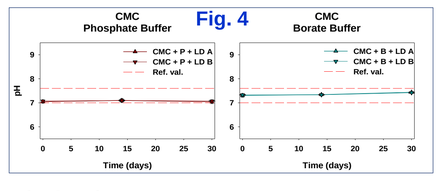


Fig. 4

Fig. 3 and 4
pH values of eye drops containing HPMC (fig. 3) or CMC (fig. 4) at different time intervals.

SURFACE ACTIVITY

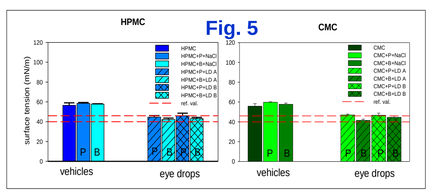


Fig. 5

Fig. 5
Surface activity of vehicles and eye drops containing HPMC or CMC.

Although the surface activity is not required by the current Pharmacopoeias as a specification of eye drops, this property is critical and can influence the standard manufacturing process, the accuracy of drop volume, the tolerance and the stability of the lacrimal film.
The desirable surface activity values of aqueous eye drops range from 40 to 46 mN/M. The surface activity of the formulated vehicles and of the complete formulations were investigated with the pendant drop method and the obtained results were compared to the desirable values.

The surface activities of the aqueous dispersions were higher than physiological levels both for the polymer dispersions and in the presence of the buffer systems. However, the values were decreased to desirable values when LD was added due to its chemical structure (fig. 5) [4].

API CONTENT

The API content was assayed to evaluate whether any loss of drug occurred after steam sterilization (method A) or filtration sterilization (method B).

With both the methods the API content in the final products was within the regulatory limits (±10%) (tab. 2).

Formulation	Method	Lidocaine hychloride (g/100 mL)			
		Not autoclaved	Day 1	Day 14	**Day 30**
HPMC + P + LD	A	1.99	1,95	2,05	2,06
	B		2,05	1,95	2,02
HPMC + B + LD	A	2,05	2,05	2,09	2,05
	B		1,97	2,08	2,06
CMC + P + LD	A	1,91	2,06	2,02	2,07
	B		2,07	2,06	2,08
CMC + B + LD	A	2,02	2,08	2,01	2,08
	B		1,99	1,99	2,03

Tab. 2
API content of eye drops containing HPMC or CMC at different time intervals.

CONCLUSIONS

Eye drops must meet as close as possible the physiological properties of the lacrimal film. The choice of the formulation is critical to guarantee safety and comfort after administration and to meet different requirements including not only isotonicity and physiological pH levels, but also surface activity and viscosity properties. Therefore when developing a formulation the influences of the API, of the buffer system and even of the method of preparation on product characteristics are to be carefully considered.

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