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Assessment of sodium hyaluronate gel as vehicle for intracameral delivery of cefuroxime in endophthalmitis prophylaxis

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ABSTRACT

Sodium cefuroxime is a second-generation cephalosporin widely used at 10 mg/mL for endophthalmitis prophylaxis after cataract surgery. Sodium cefuroxime solution is usually conditioned in pre-filled syringes then frozen for storage. In the present study, 0.2% sodium hyaluronate gel, natural extracellular polymer used in wound healing, was compared to conventional saline solution (0.9% sodium chloride) as drug delivery systems for cefuroxime loading in pre-filled syringes. Therefore, the temperature (4 and 25 °C) and time of storage (up to 21 days) varied in order to appreciate both cefuroxime and vehicle stability. Furthermore, the kinetics of drug release from both hyaluronate gel and saline solution were compared since *in vitro* sets of dialysis experiments.

Results indicated that cefuroxime loaded in either saline solution or hyaluronate hydrogel was found stable in pre-filled syringes stored at 4 °C for 21 days, whereas cefuroxime degradations products appeared from the 2nd day of storage at 25 °C. Both drug delivery systems were found bioequivalent, although statistically slower cefuroxime dialysis was evidenced by using sodium hyaluronate vehicle. Noteworthy, cefuroxime concentration in drug delivery systems during dialysis experiment remained greater than the minimum inhibitory concentrations reported for resistant strains.

In conclusion, the present stability and release study confirmed that sodium hyaluronate hydrogel is a promising vehicle for cefuroxime intracameral delivery in endophthalmitis prophylaxis.

1. Introduction

The surgery of cataract is on the rise in western countries in which the proportion of elderly people is increasing. The endophthalmitis rate consecutive to the surgery of cataract is ranged between 0.05% and 0.36% (Yu-Wai-Man et al., 2008) which, although showing weak incidence, may be responsible for unfavourable visual outcome in 10–30% of cases, and up to 10 days of hospitalization and subsequent costs for patients (Bron and Creuzot-Garcher, 2007). Although being the subject of controversial debates, the intracameral injection of antibiotics (e.g., cefuroxime, moxifloxacine or vancomycin), concomitantly to the surgery of cataract, was advised (O'Brien et al., 2007). The European Society of Cataract and Refractive Surgery (ESCRS) has recently recommended an intracameral injection of cefuroxime as prophylactic treatment of endophthalmitis (ESCRS, 2007; Gore et al., 2009; Yu-Wai-Man et al., 2008). The intracameral administration of antibiotics must congregate non-toxicity for eye cells (Yoeruek et al., 2008) and suitable physicochemical properties (e.g., osmolality and pH ranged between 200 and 400 mOsm kg^{-1} and 6.5–8, respectively). In practical use, 10 mg/mL sodium cefuroxime solution, prepared sterilely in 0.9% sodium chloride, is divided in 100 μL-aliquots filling 1-mL sterile syringes stored at −18 °C. The evaluation of freezing–defrosting practices upon the stability of cefuroxime solution showed the establishment of a gradient of concentration in pre-filled disposable syringes with associated potential detrimental effects for an accurate injection to patient.

Besides, sodium hyaluronate is a natural viscoelastic and mucoadhesive polymer, which is found in the structures of the human eye. Thus, sodium hyaluronate hydrogel is widely used either as eye lubricant (Nepp et al., 2001) increasing pre-corneal residence time and tear film break-up time or as vehicle for ocular drug delivery (Nanjawade et al., 2007). Furthermore, hydrogels

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Table 1
Composition and physicochemical properties of hyaline®.

Composition	
Sodium hyaluronate	0.2 g
Sodium chlorure	0.9 g
Water for injection	*q.s.* 100 mL
Physicochemical properties	
Molecular weight	1.5×10^6 g mol^{-1}
Osmolality	335 mOsm kg^{-1}
pH	7.4
Viscosity	10 mPa s

of sodium hyaluronate have been used for many years in ophthalmic surgery to maintain the shape of the eye, to cover surgical instruments, to protect the corneal endothelium from damage eye (Arshinoff, 1999) and to improve healing and recovery after ocular surgery (Chung et al., 1989).

The general purposes of this study were to assess (i) the stability of cefuroxime in sodium hyaluronate gel used as ocular drug delivery system in pre-filled syringes, and (ii) the release properties of cefuroxime loaded sodium hyaluronate gel.

The specific purpose was to evaluate the stability of cefuroxime in 0.2% sodium hyaluronate gel (i.e., concentration that not significantly increases the intraocular pressure) and 0.9% sodium chloride stored at 4 and 25 °C in pre-filled syringes. Additionally, the transport of cefuroxime through an *in vitro* model of trabeculum (i.e., biological meshwork involved in aqueous outflow resistance in the anterior ocular chamber) was characterised in order to appreciate the potential of 0.2% sodium hyaluronate as vehicle for ocular antibiotic delivery.

2. Materials and methods

2.1. Materials

Sodium hyaluronate solution at 0.2% (Hyaline®, molecular weight: 1.5×10^6 g/mol, viscosity: 10 mPa s, batch #90502) was gratefully provided by LCA pharmaceuticals (Chartres, France). Composition and physicochemical properties of Hyaline® are reported in Table 1. Sodium cefuroxime (molecular weight: 446.4 g/mol was supplied from GlaxoSmithKline (1.5 g per vial; batches #7403 and 8307, Marly-le Roi, France). Analytical reagent grade acetonitrile, sodium acetate and glacial acetic acid were obtained from Sigma–Aldrich (Saint-Quentin Fallavier, France).

2.2. Preparation of cefuroxime in either sodium hyaluronate gel or sodium chloride solution

Fifty milliliters of either 0.2% sodium hyaluronate or 0.9% sodium chloride were introduced, under a horizontal laminar airflow hood, into a vial containing 1.5 g of cefuroxime in order to obtain 30 mg/mL stock solution and hydrogel. Cefuroxime was readily dissolved in hyaluronate gel, then conditioned in 5-mL vials. Cefuroxime preparation was checked for clarity by submitting the filled vials to high speed rotation and high concentrated light beam (Seidenader V90-T, Seidenader Maschinenbau GmbH, Markt Schwaben, Germany), which caused reflection of light onto particles (Tyndall effect). The limit of detection of such visual quality control was about 100-μm particles. Subsequent further dilutions were realized sterilely using filters (Millex®-OR 0.22 μm, Millipore, Carrightwohill, Ireland) with either 0.2% sodium hyaluronate (1 μM) or 0.9% sodium chloride (150 mM) to achieve 10 mg/mL (22 mM) cefuroxime concentration in 1-mL pre-filled polypropylene sterile syringes (PentaFerte, Villeparisis, France) capped with sterile needles (Yu-Wai-Man et al., 2008). Taking account the photo-degradability of cefuroxime, 124 pre-filled syringes containing either cefuroxime loaded 0.2% sodium hyaluronate gel or 0.9% sodium chloride were carefully protected from light into dark bags.

2.3. Stability of cefuroxime preparations in pre-filled syringes

The combined effects of temperature (i.e., 4 ± 0.5 °C and 25 ± 2 °C) and time of storage (up to 21 days) were assessed to study the cefuroxime stability in either sodium hyaluronate gel or sodium chloride solution. Concentration, osmolality, turbidity, and colour were determined at day 0, day 2, day 4, day 8, day 10, day 14, and day 21 whereas pH was measured at day 0 and day 21. Each cefuroxime assay was done in triplicate. Colour and turbidity were assessed visually against white sheet in standardized conditions of lightning (2000–3500 lux). Osmolality measurements were assessed by the determination of freezing point using Fiske Mark 3 Osmometer apparatus (Hach Lange, Noisy-le-Grand, France).

2.4. Cefuroxime assay by high-performance liquid chromatography

Cefuroxime concentration in pre-filled syringes was assayed by reversed phase adsorption chromatography using Lichrospher® 100RP-18 cartridge, (5 μm, 125 mm × 4 mm, Merck, Darmstadt, Germany) installed in Agilent® 1200 chromatographic system. The mobile phase was a mixture of acetonitrile, and 0.1 M acetate buffer (10:90, v/v) adjusted to pH 3.4 with glacial acetic acid (Pharmacopeia, 2008). The sample volume injected was 20 μL. Detection was performed at 275 nm. In these experimental conditions, the retention time of cefuroxime was 5.0 min. For concentrations ranged between 0 and 14 mg/mL, linearity of peak area-concentration response was shown ($R = 0.998$).

2.5. Transport of cefuroxime through an in vitro model of trabecular meshwork

The transport of cefuroxime from 0.2% sodium hyaluronate gel and 0.9% sodium chloride solution through an *in vitro* model of trabecular meshwork was characterized in dialysis experiment by using polyvinylidene difluoride membrane (Spectra/Por® Biotech, Fisher scientific, Illkirch, France). The width and molecular weight cut-off of dialysis membrane were, respectively, 16 mm and 250,000 Da corresponding to average 1–10 μm pores similar in size to trabecular meshwork pores. The dialysis bags were filled by 6 mL of either 0.2% sodium hyaluronate gel or 0.9% sodium chloride solution containing 10 mg/mL sodium cefuroxime. Finally, the dialysis bags were immerged into 200 mL of 0.9% sodium chloride solution stirred magnetically and maintained by thermostated water bathing at 32 ± 0.5 °C (i.e., intraocular temperature). Samples of dialysate were withdrawn for cefuroxime content assay ($n = 5$) and replaced by an equal volume of 0.9% sodium chloride solution at regular intervals of time over 290 min.

2.6. Calculations and statistical analysis

The variations of cefuroxime content Q determined *in vitro* within the dialysate as function of time t were fitted, by using KaleidaGraph® software (Synergy Software, Reading, PA), to the general equation of dialysis:

$$Q(t) = Q_{max} \cdot [1 - \exp(-k \cdot t)] \quad (1)$$

where Q_{max} was the maximal cefuroxime amount reached into the dialysate and, k was the dialysis constant. Half-life time was calculated as $T_{1/2} = \frac{\ln(2)}{k}$, whereas T_{max} was approximated considering $T_{max} = 7 \cdot T_{1/2}$. The area under the concentration–time curve (AUC)

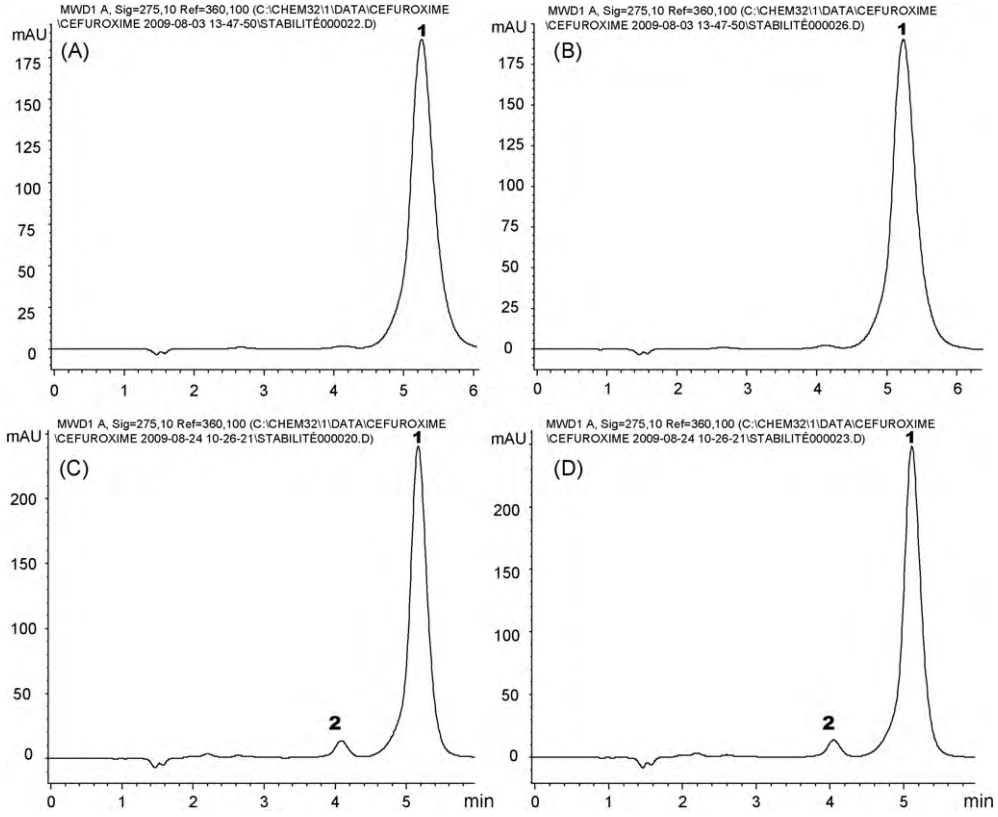

Fig. 1. Typical chromatogram of cefuroxime (1) and its degradation products (2) at day 0 and day 21 in function of vehicles at 4 ± 0.5 °C (hyaluronate 0.2% at day 0 (A); NaCl 0.9% at day 0 (B); hyaluronate 0.2% at day 21 (C); NaCl 0.9% at day 21 (D)).

was calculated by using the trapezoidal rule. The bioequivalence of cefuroxime preparations, *F*, was calculated as:

$$F = 100 \times \left[\frac{\mathrm{AUC}_{0.2\%\,\mathrm{sodium\ hyaluronate}}}{\mathrm{AUC}_{0.9\%\,\mathrm{sodium\ chloride}}} \times \frac{\mathrm{Amount}_{0.9\%\,\mathrm{sodium\ chloride}}}{\mathrm{Amount}_{0.2\%\,\mathrm{sodium\ hyaluronate}}} \right] \quad (2)$$

which might be simplified considering that cefuroxime contents were similar in both vehicles as:

$$F = 100 \times \left[\frac{\mathrm{AUC}_{0.2\%\,\mathrm{sodium\ hyaluronate}}}{\mathrm{AUC}_{0.9\%\,\mathrm{sodium\ chloride}}} \right] \quad (3)$$

Therefore, those cefuroxime pharmacokinetics parameters were compared statistically by using non-parametric Wilcoxon test for unpaired data. $p < 0.05$ was chosen as significant threshold.

3. Results and discussion

3.1. Stability of cefuroxime in preparations conditioned in pre-filled syringes

In the present study, cefuroxime content into pre-filled syringes was assayed by high-performance liquid chromatography. Typical chromatograms of cefuroxime assays were presented in Figs. 1 and 2 showing the peaks of cefuroxime and its degradation products as a function of temperature and time of storage. The degradation products of cefuroxime were eluted at 2.2, 2.8 and 4.0 min as reported in Figs. 1c, d, and 2g, h. Notably, taking account that the syringes were protected from light, the magnification of peak areas corresponding to cefuroxime degradation products was shown at 25 °C confirming the minimal drug thermo-stability in both vehicles. The nature of those degradation products was not confirmed in the present study. Consequently, in the defined analytical conditions described in the present study, no major chemical instability of cefuroxime in hyaluronate gel and saline solution was evidenced at 4 °C for 21 days. Hence, as depicted in Fig. 3, no significant difference of cefuroxime concentration in hyaluronate gel and saline solution was shown into pre-filled syringes stored at 4 °C after 21 days of storage (day 0: 10 mg/mL versus day 21: 9.5 mg/mL). However, dramatic decrease of cefuroxime concentration and concomitant increase of degradation products were noticed for cefuroxime preparations stored at 25 °C. Therefore, less than 90% of initial concentration of cefuroxime in preparations were determined after 2 days of storage substantiating a rapid chemical degradation at 25 °C.

The present study demonstrated that the chemical stability of sodium cefuroxime was not affected by hyaluronate hydrogel stored at 4 °C. Nevertheless, the potential chemical interaction between hyaluronate chains and sodium cefuroxime forming, e.g., drug–polymer complex should be considered since a strong drug binding to macromolecules would reduce free drug and its subsequent antimicrobial activity. However, an earlier study showed that hyaluronate hydrogel used as a sponge loaded with gentamicin or vancomycin was effective for the prevention and treatment of orthopaedic infections confirming the weak or reversibility of drug–polymer interactions (Matsuno et al., 2006). In the present study, the minimal role of drug–polymer (molar ratio: 22000:1) interactions on the extended release of cefuroxime was indirectly evidenced by the dialysis experiment showing similar profiles of drug transport through artificial membrane from aqueous solution and hydrogel. Furthermore, the similarity of profile of degradation cefuroxime in both vehicles stored at 25 °C is again an indirect proof of weak interaction of drug with polymer, which presumed significant cefuroxime free content in hydrogel preparation.

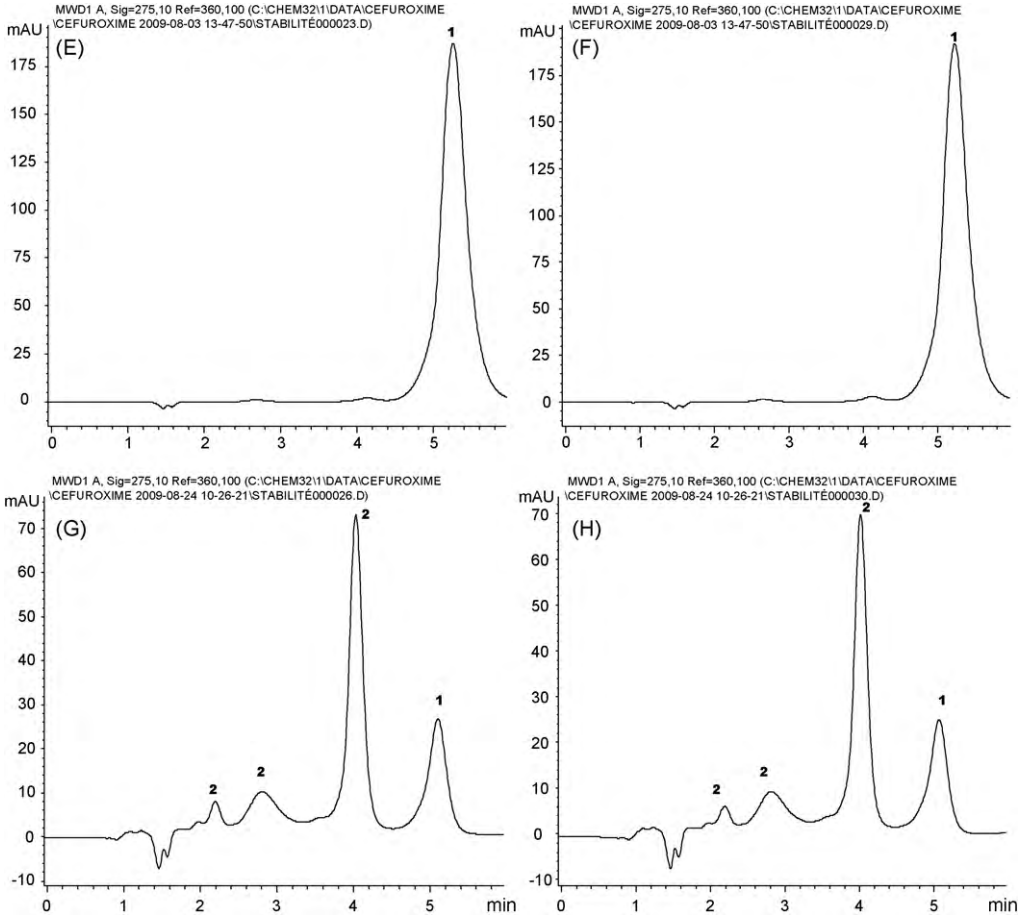

Fig. 2. Typical chromatogram of cefuroxime (1) and its degradation products (2) at day 0 and day 21 in function of vehicles at 25 ± 2 °C (hyaluronate 0.2% at day 0 (E); NaCl 0.9% at day 0 (F); hyaluronate 0.2% at day 21 (G); NaCl 0.9% at Day 21 (H)).

3.2. Stability of sodium hyaluronate gel and saline solution preparations conditioned in pre-filled syringes

The physicochemical stability of cefuroxime loaded hyaluronate gel and saline solution preparations was assessed by measuring the osmolality, pH, visual aspect of colour and turbidity for 21 days of storage at 4 and 25 °C (Table 2). No major variations of osmolality, pH, colour and turbidity were evidenced for 21 days of storage at 4 °C, confirming minimal degradability of both cefuroxime and vehicle at low temperature. At 25 °C, osmolality gradually increased for 21 days, likely due to the degradation of cefuroxime as osmotic products. Moreover, all preparations became yellowish coloured from the 2nd to 21st day, arguing the production of coloured degradation products of cefuroxime in the pre-filled syringes.

Thus, the stability of cefuroxime dosage forms in either hyaluronate or saline vehicles was not affected by 4 °C storage for 21 days as reported previously in sodium chloride solution stored at 4 °C (Das Gupta and Stewart, 1986). Our results countered a technical note edited by French Health Products Safety Agency recommending for cefuroxime pre-filled syringes a storage at −15 °C taking account short-time stability (up to 6 h) after defrosting at either 4 °C or ambient temperature (Afssaps, 2009). Therefore, in spite of these discrepancies, the storage of pre-filled cefuroxime syringes at 4 °C offered obvious advantages upon freezing among whose the absence of gradient of drug concentration during defrosting and the straightforwardness of pharmaceutical production, storage and use in hospital pharmacy and care units.

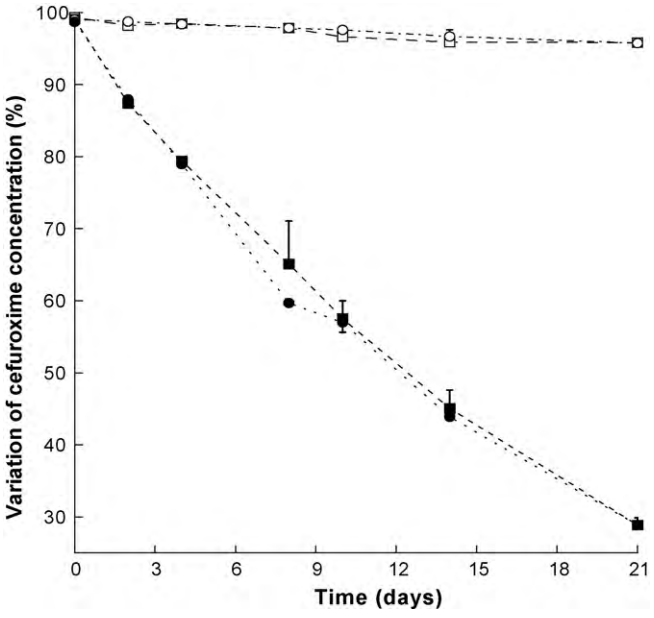

Fig. 3. Assessment of cefuroxime stability in sodium hyaluronate 0.2% at (□) 4 °C, at (■) 25 °C, and saline solution 0.9% at (○) 4 °C, at (●) 25 °C. Each data is the mean ± standard deviation of three experimental determinations.

Table 2
Variations of physicochemical properties of cefuroxime preparations in 1-mL syringes during storage at 4 ± 0.5 °C and 25 ± 2 °C for 21 days.

Cefuroxime vehicles	Time of storage (days)											
	Day 0		Day 2		Day 4		Day 8		Day 10		Day 14		Day 21	
	4 °C	25 °C	4 °C	25 °C	4 °C	25 °C	4 °C	25 °C	4 °C	25 °C	4 °C	25 °C	4 °C	25 °C
0.2% sodium hyaluronate														
Osmolality	387 ± 2	388 ± 4	385 ± 1	395 ± 5	395 ± 5	402 ± 3	368 ± 33	427 ± 18	403 ± 6	402 ± 8	404 ± 8	428 ± 2	387 ± 4	408 ± 2
pH	7.5	7.5	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	7.7	8.3
Colour	None	None	None	Yellowish	None	Yellowish	None	Yellowish	None	Yellowish	None	Yellowish	None	Yellowish
Turbidity	None	None	None	None	None	None	None	None	None	None	None	None	None	None
Number of syringes	8	8	3	3	3	3	3	3	3	3	3	3	8	8
0.9% sodium chloride														
Osmolality	340 ± 2	338 ± 2	339 ± 2	346 ± 1	340 ± 2	354 ± 1	348 ± 14	394 ± 8	390 ± 10	390 ± 5	352 ±	385 ± 6	336 ± 1	368 ± 2
pH	6.8	6.8	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	n.d	7.7	8.3
Colour	None	None	None	Yellowish	None	Yellowish	None	Yellowish	None	Yellowish	None	Yellowish	None	Yellowish
Turbidity	None	None	None	None	None	None	None	None	None	None	None	None	None	None
Number of syringes	8	8	3	3	3	3	3	3	3	3	3	3	8	8

n.d: not determined.

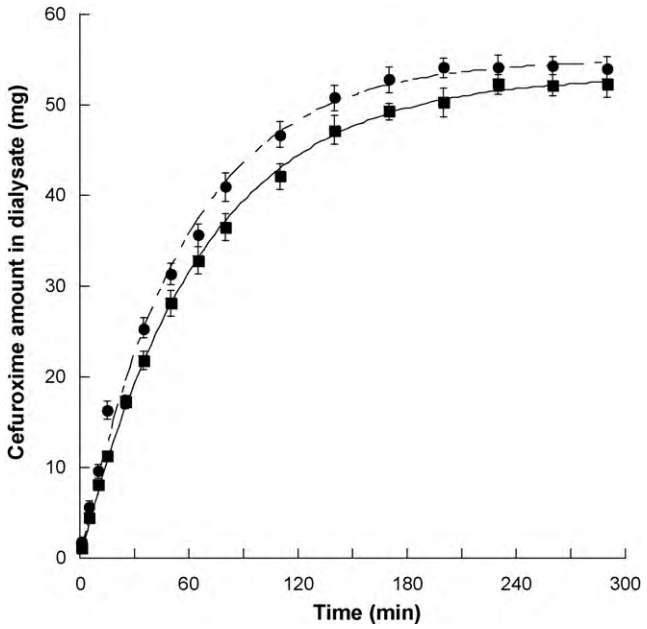

Fig. 4. Cefuroxime amounts dialysed through 1–10 μm porous dialysis bag initially filled with 60-mg cefuroxime either loaded in 0.2% sodium hyaluronate gel (■) or dissolved in 0.9% sodium chloride solution (●) as function of time. Each data is the mean ± standard deviation of five experimental determinations.

3.3. Transport of cefuroxime through an in vitro model of trabecular meshwork

The effects of vehicles upon the kinetic of cefuroxime release were been assessed by conventional dialysis experiment. Fig. 4 showed the release of cefuroxime from both dosage form systems. Burst effect of cefuroxime from formulations was evidenced between 0 and 30 min (zero-order kinetic) followed by a plateau phase (i.e., no subsequent drug diffusion through dialysis bag) after 180 min of dialysis. The curves of drug release were fitted to dialysis mathematical model enabling the determination of pharmacokinetic parameters reported in Table 3. Despite statistical difference between the pharmacokinetics parameters studied, 0.2% sodium hyaluronate gel and 0.9% sodium chloride solution were bioequivalent ($F \sim 93\%$). The use of hyaluronate gel instead of conventional saline solution did not improve significantly *in vitro* release of cefuroxime, although the higher half-time of dialysis was shown by using hydrogel vehicle. Therefore, the use of sodium hyaluronate allowed extended rather than sustained release. Besides, after 5 h of dialysis, final concentration of cefuroxime in dialysis bag (0.83 mg/mL in 0.9% sodium chloride solution and 1.16 mg/mL in 0.2% sodium hyaluronate gel) remained much greater than cefuroxime minimum inhibitory concentration, MIC (about 32 μg/mL or less for main resistant strains) (O'Callaghan et al., 1976).

From cefuroxime concentrations in dialysate, the exponential profile of cefuroxime concentration remaining into the dialysis bag was plotted and AUC was calculated by using trapezoidal rule. Finally, cefuroxime clearance (Cl) was calculated as:

$$\mathrm{Cl} = \frac{\text{Initial cefuroxime amount in dialysis bag}}{\mathrm{AUC}_{0-5\,\mathrm{h}}} \quad (4)$$

Cefuroxime clearance in 0.2% sodium hyaluronate gel (2.5 ± 0.2 μL/min) was significantly lower than determined from saline solution (3.0 ± 0.2 μL/min) ($p < 0.05$ Wilcoxon test). These values were in accordance with drug clearance (i.e. 1–30 μL/min) in the anterior chamber reported in earlier study

Table 3
In vitro cefuroxime pharmacokinetics parameters determined from fitted experimental data of amounts in dialysate (Q)–time (t) curve to the general equation of dialysis: $Q(t) = Q_{max} \cdot [1 - \exp(-k \cdot t)]$. Dialysis bags were filled initially with 60-mg cefuroxime either loaded in 0.2% sodium hyaluronate gel or dissolved in 0.9% sodium chloride solution. Each data is the mean ± standard deviation of five experimental determinations.

Cefuroxime vehicles	Pharmacokinetics parameters				
	$10^3 \times k$ (min^{-1})	Q_{max} (mg)	$10^{-4} \times$ AUC (mg min)	$T_{1/2}$ (min)	F^a
0.2% sodium hyaluronate	$15 \pm 1^*$	$53 \pm 1^*$	$1.19 \pm 0.27^{**}$	$46 \pm 2^*$	92.7%
0.9% sodium chloride	17 ± 1	55 ± 1	1.29 ± 0.29	41 ± 3	

[a] Calculated as: $F = 100 \times \left[\frac{AUC_{0.2\%\ sodium\ hyaluronate}}{AUC_{0.9\%\ sodium\ chloride}} \times \frac{Amount_{0.9\%\ sodium\ chloride}}{Amount_{0.2\%\ sodium\ hyaluronate}}\right]$.

* $p < 0.05$ as compared to 0.9% sodium chloride group (non-parametric Wilcoxon test).

** $p < 0.01$ as compared to 0.9% sodium chloride group (non-parametric Wilcoxon test).

(Avtar and Tandon, 2008) confirming, in the present study, the relevance of trabecular meshwork model chosen for dialysis experiment.

Herein, the reported results showed comparable *in vitro* pharmacokinetics of cefuroxime loaded 0.2% sodium hyaluronate and 0.9% sodium saline vehicles. Consequently, in physiological conditions, hyaluronate gel exhibiting remarkable osmotic and swelling properties might constitute a limiting barrier against aqueous humor flow. In a previous study, the increase of intraocular pressure after intracameral injection of 1% sodium hyaluronate was reported (Passo et al., 1985) suggesting that the efflux through trabecular meshwork might be compromised by high hyaluronate concentration in pre-filled syringes. Therefore, the hyaluronate concentration as ocular delivery vehicle should be chosen properly (<1%) in order to improve the extended drug release and to reduce the colmation effects in the trabeculum's pores responsible of ocular hyperpressure.

At our knowledge, the concomitant use of cefuroxime and hyaluronic acid was not reported in the literature. Therefore, the qualitative and quantitative association of cefuroxime and hyaluronic acid for intracameral injection was clearly new. Lower hyaluronate concentration used in the present study compared to ocular surgery was justified to avoid both increase of intraocular pressure and potential cefuroxime–hyaluronate complex susceptible to delay or to reduce antibiotic activity. Furthermore, although hyaluronate is currently employed in ocular surgery, earlier study reported also the related use of gentamicin and hyaluronate for intraocular drug delivery (Moreira et al., 1991). In another field, previous report showed the usefulness of hyaluronate as antibiotic carrier (e.g., vancomycin and gentamicin) for the treatment of deep infections (Matsuno et al., 2006). Considering that sodium hyaluronate gel was 10-fold more viscous than saline solution, the increase of viscosity would influence the extent of drug release into the anterior chamber which was characterized by the calculation of half-time of cefuroxime removal from dialysis bag (Grove et al., 1990; Moreira et al., 1991). In this field, the release of doxycycline was shown closely dependant on the molecular weight of sodium hyaluronate (Miyazaki et al., 2001). Furthermore, although the relationship between gel viscosity and inhibition of bacterial growth is poorly understood, an earlier study reported discrete antimicrobial effect of sodium hyaluronate against *Staphylococcus* strains (Moreira et al., 1991). Therefore, the use of sodium hyaluronate as vehicle for intracameral drug delivery would reinforce cefuroxime antibiotic activity. The cefuroxime MIC against *Staphylococcus aureus* was reported to be about 4 μg/mL (O'Callaghan et al., 1976). In practical use, after intraocular injection of 1-mg cefuroxime, drug concentration in anterior chamber raises up 250 μg/mL, which is much higher than cefuroxime MIC against *S. aureus*. In our study, after 5-h dialysis experiment, residual cefuroxime concentration in dialysis bag was maintained up to cefuroxime MIC that would favour extended antimicrobial activity into the anterior chamber.

4. Conclusion

In conclusion, the present study showed that the cefuroxime loaded in either 0.9% saline solution or 0.2% sodium hyaluronate hydrogel was stable in pre-filled syringes stored at 4 °C for 21 days. From *in vitro* conventional experiments, both drug delivery systems were found bioequivalent, although statistically slower cefuroxime dialysis was evidenced by using sodium hyaluronate vehicle. In addition, noteworthy healing properties of sodium hyaluronate would constitute a challenging and relevant strategy for cefuroxime intraocular delivery. Further clinical studies will assess the benefits of cefuroxime loaded sodium hyaluronate in pre-filled syringes designed for preventing the emergence of endophthalmitis consecutive to invasive surgery.

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