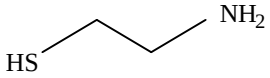
Formulation and Evaluation of Cysteamine for Ophthalmic Delivery

B E Buchan, G Kay, K H Matthews, D Cairns

School of Pharmacy & Life Sciences, The Robert Gordon University, Schoolhill, Aberdeen AB10 1FR

OBJECTIVES

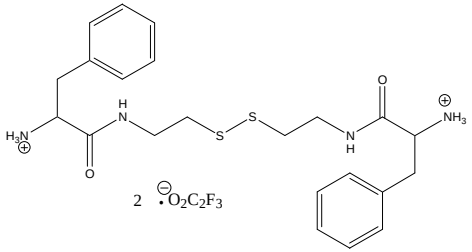
Nephropathic cystinosis is a rare genetic disease characterised by raised intracellular levels of cystine. If untreated, cystinosis results in death from renal failure by the second decade of life[1]. The main treatment for cystinosis is the administration of cysteamine (**1**), an aminothiol with an offensive taste and smell[2]. Furthermore, the ocular symptoms of cystinosis can be debilitating and are treated by delivering a water-soluble cysteamine salt every waking hour via eye-drops. Despite excellent patient compliance, eye drops are rapidly drained from the ocular surface[3]. Ophthalmic gels may provide a viable alternative to the current eye drop formulation.



Cysteamine (**1**)

METHODS

Initially an experimental cystamine conjugate (**2**) was synthesised to enable rapid and quantitative evaluation of release from the eye gels. Carbomer 934 gels were formulated to include either the phenylalanine-cystamine conjugate (chromophore present) or cysteamine hydrochloride. The rheological properties of each gel were evaluated using an Advanced Rheometer from TA Instruments AR1000. Dissolution studies were undertaken in 50ml of Simulated Lachrymal Fluid, SLF (Fig 1). The gel aliquots were secured inside 12-14,000kDa dialysis membrane rods. Testing was performed at 34°C, the temperature of the corneal surface[4]. Results were analysed using the Higuchi method. Mucoadhesivity testing was performed on a Texture Analyser using freshly excised bovine corneas as the mucosa model. Mann-Whitney statistical analysis was performed on the results.



UV-active cystamine-phenylalanine conjugate (**2**)

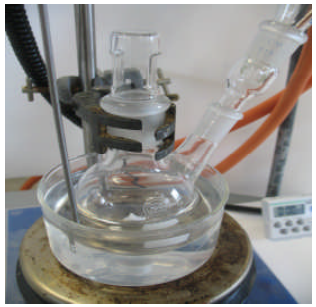


Fig 1. Dissolution apparatus.

RESULTS

To minimize discomfort, the gels were formulated at pH 7.4. All gels demonstrated pseudoplastic behaviour, as exemplified in Fig 2. This property allows the gel to be retained in the eye when the eyelids are at rest, and to flow during periods of blinking. The phenylalanine-cystamine conjugate was released from the gel over 8 hours with a T_{75} = 180mins (Fig 3). First order release was demonstrated (Fig 4). The mucoadhesivity results indicated that there was significant adhesion; e.g. peak adhesive force (N): No Gel 0.025, Gel (no active) 0.096, Cysteamine Gel 0.109.

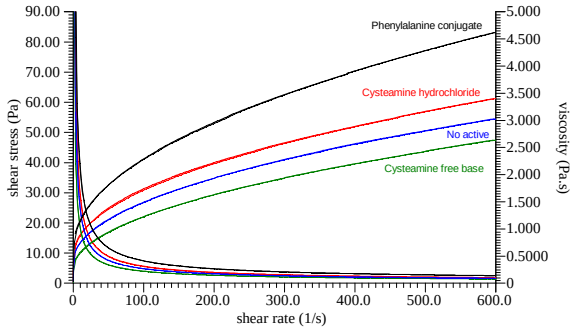


Fig 2. Continuous flow curves for Carbomer 934 gels containing different cysteamine compounds at 34°C.

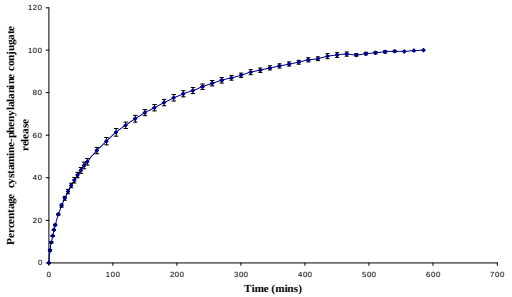


Fig 3. Percentage cystamine phenylalanine conjugate released from Carbomer 934, n = 3.

Carbomer 934 Cysteamine-phenylalanine conjugate Sample time (minutes)	Higuchi model K_H
2	0.05
35	0.08
75	0.08
240	0.07
420	0.06
540	0.04

Fig 4. Results of the Higuchi model analysis on the Carbomer 934 gels., n = 9.

CONCLUSIONS

All the gels tested formed weak gel networks at zero to low shear stresses, desirable properties for increased residence time on the ocular surface. A net bioadhesion and first order release of the active from the sample matrix was also apparent. These results offer the possibility of a gel formulation of cysteamine, which would considerably enhance the quality of life for Cystinosis patients with ocular complications.

1. Gahl, W.A; Thoene, J.G.; Schneider, J.A.; *N. Engl. J. Med.* **2002**, *347*, 111.
2. Cairns, D.; Anderson, R.J.; Coulthard, M.; Terry, J.; *Pharm. J.* **2002**, *269*, 615.
3. Khan, A.O; Latimer, B.; *Am. J. Ophth.* **2004**, *138*, 674.
4. Ooi, E.H; Ng, E.Y.K; Purslow, C; Acharaya, R.; *J. Eng. Med*. **2007**, *3*, 94.

The authors gratefully acknowledge support from TENOVUS Scotland, Cystinosis Foundation UK and UKRC.