# Formulation and Evaluation of Cysteamine for Opthalmic Delivery

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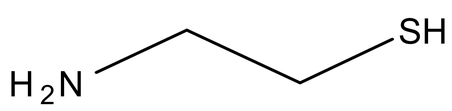
## OBJECTIVES

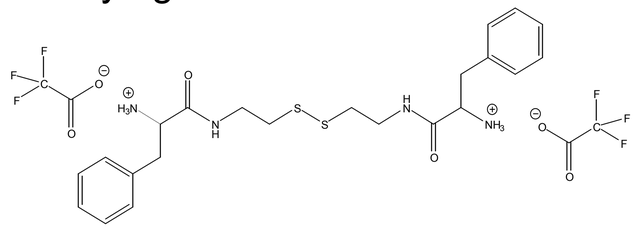
Nephropathic cystinosis is a rare autosomal recessive disease characterised by raised intracellular levels of cystine. If untreated, cystinosis results in death from renal failure by the second decade of life[1]. The main treatment for cystinosis is administration of cysteamine (**1**), an aminothiol with an offensive taste and smell, which is excreted along with its metabolites in breath and sweat causing halitosis and body odour as well as gastric irritation[2]. The ocular symptoms of cystinosis can be debilitating. These symptoms 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]. In order to improve the bioavailability of ophthalmic delivery systems, it is desirable to prolong ocular residence time and encourage site-specific delivery through sustained drug release. 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.



UV-active Cystamine-Phenylalanine Conjugate (**2**)

Carbomer 934, Xanthan gum and Hydroxypropylmethylcellulose (HPMC) gels were formulated to include either the phenylalanine-cystamine conjugate (chromophore present) or cysteamine hydrochloride. Blank gels were used to determine the effect of the actives on the gel structure through rheological testing. The rheological properties of each gel were evaluated using an Advanced Rheometer from TA Instruments AR1000. Dissolution studies [1L of media (Simulated Lachrymal Fluid), stirred at 100rpm, sampled every 15 minutes] were undertaken; the gels were contained within membrane bags of pore size 12-14,000 Da (figure **1**).

Figure **1**. Dissolution apparatus

Mucoadhesivity testing was performed on a Texture Analyser using excised bovine corneas as the mucosal model; parameters of contact force 0.05N, contact time 60s and probe speed 0.5 mm/s were used. Corneal tissue alone was used as a control. The force required to remove the gel samples, as well as the area under the curve (AUC), which correlates as work of adhesion, WAD was measured.

## RESULTS

The mucoadhesivity results indicated that there was significant adhesion for each formulation, particularly the Carbomer 934 and Xanthan gum gels (table **1**).

The dissolution release from respective gels over time are shown in table **2**. Release was quantified using the Higuchi model, and found to be first-order.

The Carbomer formulations demonstrated pseudoplastic rheologies (figure **2**), the Xanthan gum gels were thixotropic with no yield stress, and the HPMC gels were weakly dilatant (data not shown).

| **Carbomer 934**<br><br>**Control: 0.021N, 0.019 AUC** | **Force (N)** | **AUC** |
|---|---|---|
| Tissue vs plain gel | 0.067*** | 0.205*** |
| Tissue vs gel with **1** | 0.107*** | 0.177** |
| Tissue vs gel with **2** | 0.107*** | 0.196*** |
| **HPMC** | | |
| Tissue vs plain gel | 0.076 | 0.051** |
| Tissue vs gel with **1** | 0.081* | 0.048*** |
| Tissue vs gel with **2** | 0.065* | 0.061** |
| **Xanthan gum** | | |
| Tissue vs plain gel | 0.051*** | 0.091*** |
| Tissue vs gel with **1** | 0.108*** | 0.150*** |
| Tissue vs gel with **2** | 0.76*** | 0.145*** |

p<0.05*, p<0.01**, p<0.001***

Table **1.** Significance of control (tissue only) versus tissue and gel formulation.

| Formulation | Time taken to release 95% of active (Hours) |
|---|---|
| Carbomer 934 | 6.75 |
| Xanthan gum | 10.8 |
| HPMC | 5.75 |

Table **2**. Time taken to release 95% of the active from gels.

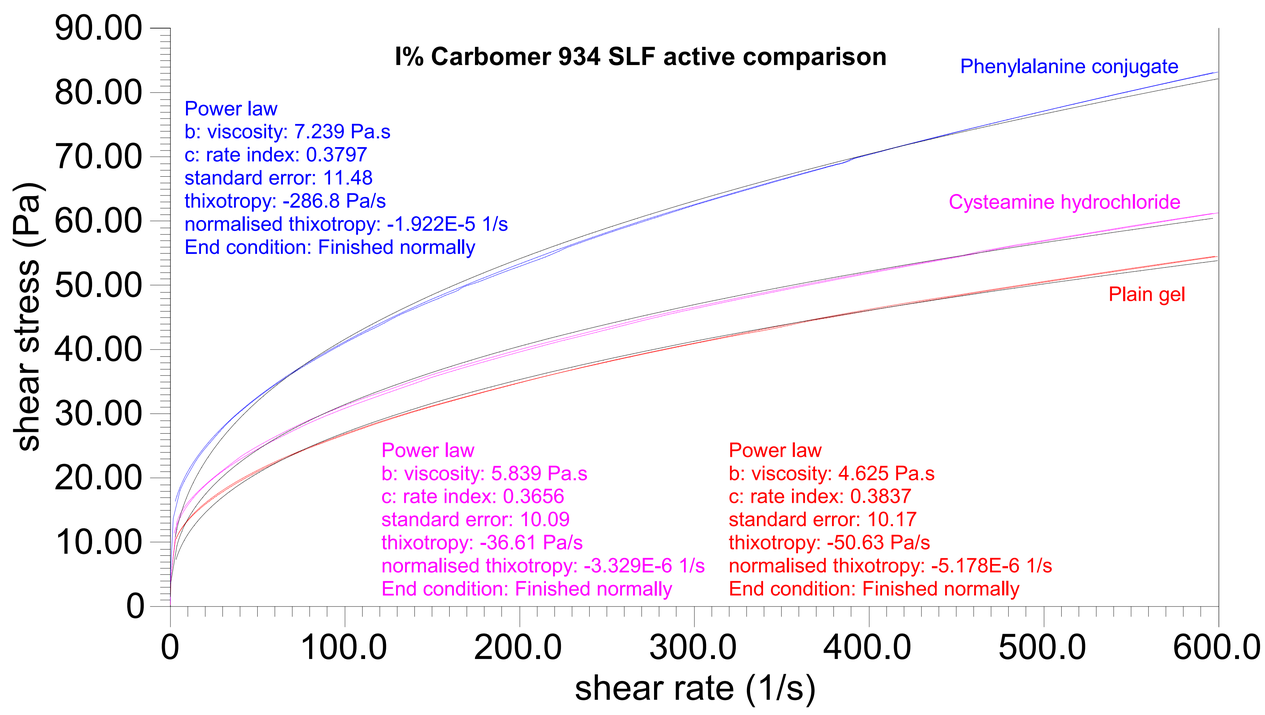



Figure **2**. The effect of active addition on the rheology of Carbomer 934 gels**.**

## CONCLUSIONS

The gels all released the actives over a sustained period of time. The mucoadhesivity results indicated significant adhesion to bovine cornea, thereby prolonging contact time. Rheological findings indicate that Carbomer 934 is the most suitable for use in ophthalmic preparations. All of these characteristics are desirable for ophthalmic gel preparations.

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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.

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