

Controlled Release Society's 37<sup>th</sup> Annual meeting and  
Exposition

Portland, Oregon, USA

Barbara Buchan



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## Overview

The Controlled Release Society's Annual conference 2010 was held in Portland, Oregon, USA. Over 1400 people attended the conference, with over 100 exhibitors. This prestigious conference focussed on pharmaceuticals, and was attended by students, scientists, physicians, healthcare professionals and instrument manufacturers from around the world.

## Main points of the conference

### Events attended

- Young scientist workshop – career development
- Controlled ocular drug delivery systems in posterior disease
- Controlled ocular drug delivery in the anterior of the eye
- Pearls of wisdom – bioactive materials
- Women in science lunch
- Scientific sessions: pulmonary drug delivery

### Conference presentations – points raised

- Ophthalmic preparations should test pKa, Osmolarity, contact angle (spreadability), gamma scintigraphy.
- Carbomer 934 is irritating to mucosal membrane (only if pH unadjusted).
- Accumulation of microspheres in the lung?
- Below 10 micrometers, gravity becomes less of a factor, and static/van der waals rules.
- Rumpf 1967 – characterized dispersity.
- Different morphology gives varying morphology to microspheres.
- Lactose as a carrier fading to zero use in the future.
- Lymph nodes of lungs primary distributor of microspheres, regardless of size.

### Trade stands

- Transmission Electron microscopy (TEM) can show not only the size of a micro particle, but also its 3D structure.
- Lactel ® absorbable polymers can produce a polymer tailored to our specific needs
- Gamma scintigraphy is available for both inhaled and ophthalmic products, and there is no minimum trial size.
- Micro-Sphere Sa, based in Switzerland, can produce GMP-level microspheres for human administration.
- Patheon <sup>TM</sup> can manufacture eye gels and suppositories for clinical trials, but not microspheres for inhalation.
- Sympatec manufacture a particle sizer which breaks up agglomerated clumps of powder before testing, and is useful for microspheres subject to static. It can also analyze down to 0.1micrometer in size.
- Cydex pharmaceuticals can formulate any insoluble drug into almost any form (inquired with the old prodrugs in mind).
- Spraying Systems Co® can supply smaller spray drier nozzles for our equipment to improve our particle size control.

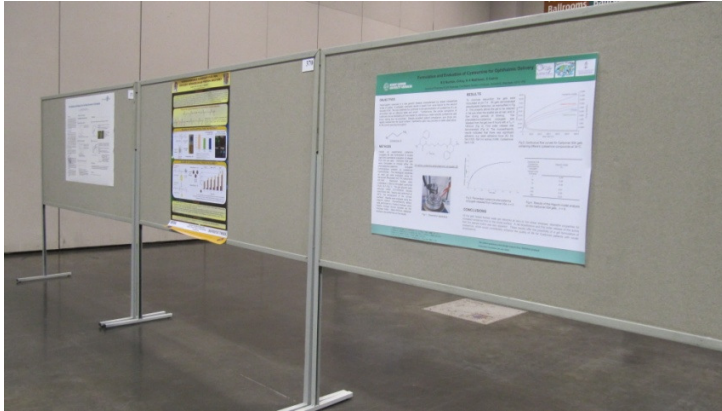
### Scientific focus

Attending the Controlled Release Society's 37<sup>th</sup> Annual Meeting and Exposition in Portland, Oregon highlighted some interesting points relating both to past work, and also possibilities for future work. There were young scientist workshops focusing on career development and ophthalmic delivery, and also scientific sessions on pulmonary drug delivery.

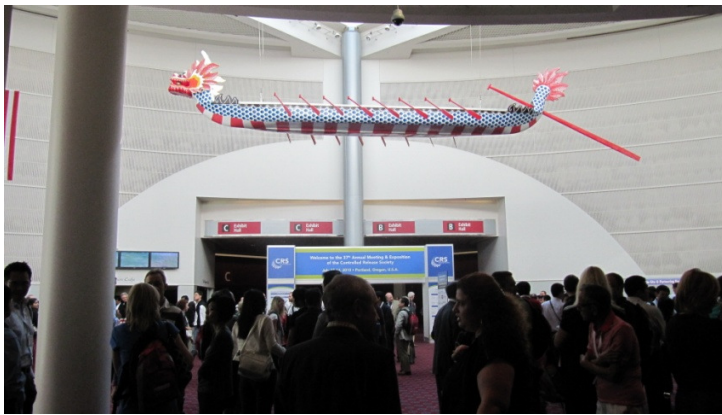
Among many highlights was a technique called gamma scintigraphy, which 'tags' the eye gel or respiratory powder with a dye to make it easier to trace upon installation. This company, based in Glasgow, also runs these clinical trials on human volunteers, and may be the first step in bringing a product to market. Transmission Electron Microscopy (TEM) is another technique for analysis, and can show not only the size of a micro particle, but also its 3D structure. This may be useful for fully characterizing and improving the respiratory powders. Lactel ® absorbable polymers is a company which can produce a polymer tailored to our specific needs, while Spraying Systems Co® can supply smaller spray drier nozzles for our equipment to improve our powders for inhalation. There were also other companies who can manufacture all types of formulations to a high quality and standard required for clinical trials. It is my hope that my work will be continued to the clinical trial stage and beyond, either by myself or others, in order that it might bring benefits to cystinosis patients and their families.

## Details of the event

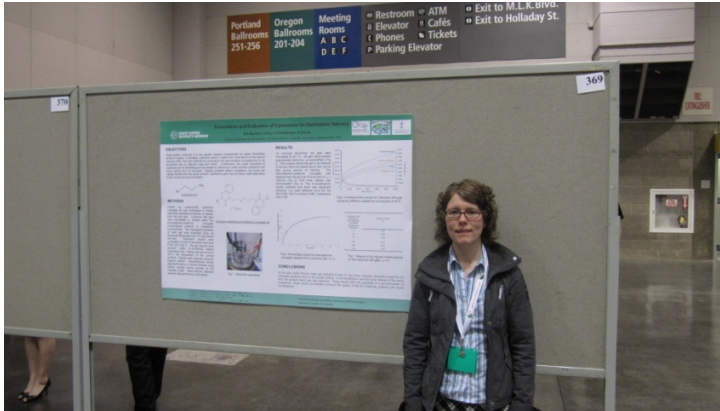
I have recently returned from the 37<sup>th</sup> meeting and exposition of the Controlled Release Society 2010, held in Portland, Oregon, USA, which Cystinosis Foundation UK kindly funded. I was accepted to display a poster on sustained-release eye gels for cystinosis.



The conference was extremely relevant to me, focusing on formulation. There were an expected 1900+ attendees. I have never attended such a large and prestigious conference, and I was spoilt for choice in the program of events. I think attending such a conference in the final few months of my PhD allowed me to get as much out of the trip as I could.



After setting up my poster, I was quickly approached by attendees, and within my one hour of designated attendance I was asked over 20 questions on my work, some of which raised points I hadn't considered. One person came back twice to see the poster, and another praised the quality of my writing. I hope to have introduced a new field of people to cystinosis.



Subsequently I attended a ticket-only event for women, which was inspirational. I watched many lectures on my subject area, and spoke with a large number of company representatives about my work. I got ideas for my PhD write-up, and also for post-doc work. I also attended round-table discussion sessions and debates, and it was exciting to hear experienced scientists talk enthusiastically about something which they believed in. I attended many interesting lectures on my area of interest, and made me aware of potential post doc work. I also learnt about the CRS mentoring scheme, which pairs a young scientist with an experienced mentor, in order to impart some knowledge and experience as they begin their career. Since returning home, I have had numerous emails and requests from people who I met at the event, giving me quotes or asking for more information. I feel more prepared now for my PhD write up, and have grown in confidence after the experience. I have been inspired by the speakers I have seen, and have lots of fresh ideas, both for my PhD write up and future work. The experience has also given me confidence in my own abilities as I move toward new challenges. It was particularly good and encouraging to meet so many enthusiastic scientists, and I hope this helps to launch me into the profession which I enjoy so much.

# Formulation and Evaluation of Cysteamine for Ophthalmic Delivery

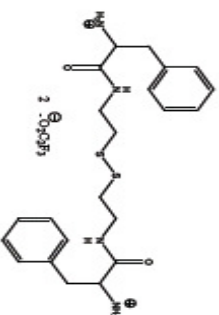
B E Buchan, G Kay, K H Matthews, D Cairns

School of Pharmacy & Life Sciences, The Robert Gordon University, Scotland, 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. The main treatment for cystinosis is the administration of cysteamine (1), an aminothiol with an offensive taste and smell. 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<sup>1</sup>. Ophthalmic gels may provide a viable alternative to the current eye drop formulation.



## METHODS

Initially an experimental cysteamine conjugate (2) was synthesised to enable rapid and quantitative evaluation of release from the eye gels. Carbomer 834 gels were formulated to include either the phenylalanine-cysteamine 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<sup>2</sup>. Results were analysed using the Higuchi method. Mucoadhesively 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.



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-cysteamine conjugate was released from the gel over 6 hours with a  $T_{90}$  = 180mins (Fig 3). First order release was demonstrated (Fig 4). The mucoadhesively results indicated that there was significant adhesion; e.g. peak adhesive force (N): No Gel 0.025, Gel (no active) 0.086, Cysteamine Gel 0.109.

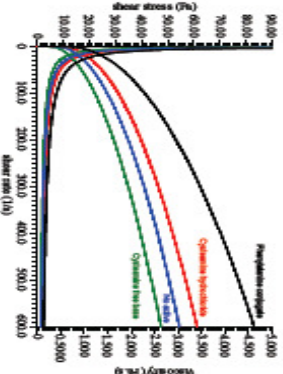


Fig 2. Continuous flow curves for Carbomer 834 gels containing different cysteamine compounds at 34°C.

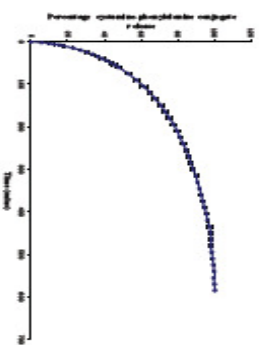


Fig 3. Percentage cysteamine-phenylalanine conjugate released from Carbomer 834, n = 3.

Carbomer 834 Cysteamine-phenylalanine conjugate Sample time (minutes)	Higuchi model $k_1$
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 834 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.

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