# A BIOMIMETIC APPROACH OF RECOGNITIVE CONTACT LENSES FOR TAILORED LOADING AND RELEASE OF ANTIHISTAMINES TO TREAT ALLERGIC RHINOCONJUNCTIVITIS

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## Introduction

A biomimetic approach has been exercised using novel biomaterials, to tackle the unmet need for the controlled loading and release of ocular $H_1$-antihistamines, for the treatment of allergic conjunctivitis. Treatment options for allergic conjunctivitis primarily consist of oral antihistamines and topical treatments. Since ocular bioavailability of topical drugs is very poor (typically less than 7% is absorbed by the eye), a high dosage is needed which prohibits contact lens use. Controlling and tailoring the release of anti-histamines via novel recognitive contact lenses with significantly enhanced partitioning can solve these problems with increased bioavailability, less irritation to ocular tissue, and reduced ocular and systemic side effects. Enhanced drug partitioning in hydrogels can be achieved by configurational biomimetic imprinting (CBIP) techniques **[1]** which involve the formation of a pre-polymerization complex between the template molecule and functional monomers by non-covalent chemistry. Inspired by Nature, we have successfully synthesized and characterized recognitive networks for $H_1$ antihistamines by choosing monomers on the basis of the non-covalent interactions found in histamine docking sites.

## Materials and Methods

### *Synthesis of Recognitive networks*

Acrylic acid (AA), acrylamide (AM), 2-hydroxyethylmethacrylate (HEMA), Polyethylene glycol (200) dimethacrylate (PEG200DMA), azobisisobutyronitrile (AIBN), ketotifen fumarate and lysozyme were purchased from Aldrich (Milwaukee, WI) and used as received. Hydrogels of differing compositions were synthesized in a temperature controlled, non-oxidative environment using free-radical UV photopolymerization. Control gels were prepared without the template molecule, following similar steps.

### *Equilibrium Binding and In-vitro Release Studies*

In a typical experiment, the gels were washed with DI water until ketotifen and unreacted monomers could no longer be detected by spectroscopic monitoring. Recognitive and control gels were then dried at room temperature for 24 hours, followed by vacuum drying (T=30 °C, 28 in. Hg vacuum), placed in concentrated solutions of ketotifen fumarate and gently agitated on a Stovall Belly Button Orbital Shaker. After 72 hours, the bound concentration in the gel was determined by mass balances. Kinetic release studies were conducted in DI water, artificial lacrimal fluid (6.78 g/L NaCl, 2.18 g/L $NaHCO_3$, 1.38 g/L KCl, 0.084 g/L $CaCl_2.2\ H_2O$, pH 8), and lysozyme (1 mg/ml) in artificial lacrimal fluid. Gels which had been loaded were placed in 30 ml of DI water, and the solutions were continuously agitated with a Servodyne mixer (Cole Palmer Instrument Co.) at 120 rpm. Release of drug was monitored using a Synergy UV-vis/Fluorescence/Luminescence Spectrophotometer.

## Results and Discussion

We hypothesized that gels composed of multiple functional monomers would outperform those composed of single functional monomers. This would better mimic the docking site of histamine at the molecular level providing all the relevant functionality necessary for non-covalent interactions. We have proved that loading properties of gels are improved with multiple monomer mixtures **(Fig 1)**. Gels of multiple complexation points with varying functionalities outperformed the gels formed with fewer types of functionality and showed the greatest loading potential. Release studies showed that release rates can be tailored via type and amount of functionality. Providing all the relevant functionality to the mimicked docking site affords slower, and hence, controlled release of a therapeutically viable dosage of drug **(Fig 2)**.

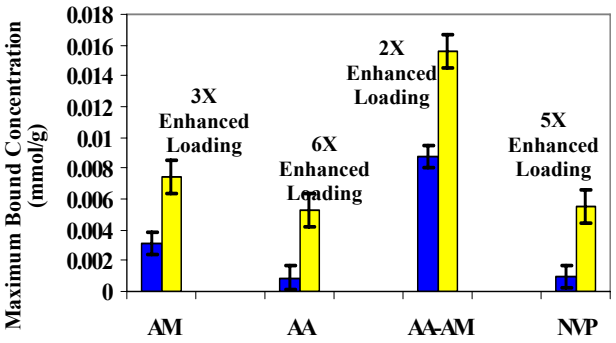


**Figure 1: Enhanced Loading of Multiple Monomer Lenses:** Comparison data of maximum bound ketotifen concentration (mmol/g) for Poly(n-co-HEMA-co-poly(ethylene glycol)200 dimethacrylate), where n is AM, AA, AA-AM, and NVP, networks. Recognitive network (■) and control network (■).

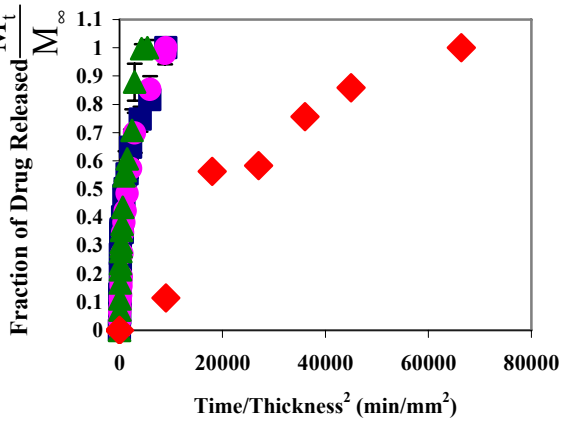


**Figure 2: Tailorable Release Profiles Of Therapeutic Contact Lenses** for Poly(n-co-poly(ethylene glycol)200 dimethacrylate), where n is AM-HEMA (●), AA-HEMA (■), AA-AM-HEMA (▲), and NVP-AA-AM-HEMA (◆) recognitive networks of thicknesses 0.7, 0.7, 0.7, and 0.4 mm respectively. Results demonstrate constant release rate of ketotifen fumurate for 1 to 5 days.

## Conclusions

Recognitive contact lenses with tailorable loading and release properties were designed based on biological receptors, to treat allergic rhinoconjunctivitis. However, the approach is widely applicable for a number of molecules with relevant biological function.

## References

[1] J.Z. Hilt, M.E. Byrne. Advanced Drug Delivery Reviews. 56, 1599-1620, 2004.