A BIOMIMETIC APPROACH TOWARDS THE FORMATION OF THERAPEUTIC CONTACT LENSES

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Introduction

A biomimetic approach has been exercised to design novel contact lenses, to tackle the unmet need for the controlled loading and release of ocular H_1-antihistamines, for the treatment of allergic conjunctivitis. 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.

Materials and Methods

Synthesis and Equilibrium Binding 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. The gels were washed with DI water until ketotifen and unreacted monomers could no longer be detected. Recognitive and control gels were then dried at room temperature for 24 hours, followed by vacuum drying, 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.

Polymerization Reaction Kinetics

Kinetic studies were carried out in a Q-100 modulated differential photocalorimeter (DPC) (TA Instruments, New Castle, DE) at a constant light intensity of 40 mW/cm^2. Pre-polymerization solutions (10 µL) were weighed in aluminum hermetic pans and purged with nitrogen at a flow rate of 40 ml/min, in order to prevent oxidative inhibition. They were then allowed to equilibrate at 35°C for 15 minutes, before opening the shutter of the UV light source (Novecure 2100, Exfo, Mississaugu, Canada) for 12 minutes. Isothermal conditions were maintained throughout the experiment. The DPC records the heat of reaction, from which the rates of polymerization and conversions were calculated using average molecular weight and theoretical enthalpy of acrylate and methacrylate double bonds.

Results and Discussion

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. The rate of polymerization for a given conversion decreased for increasing mole percentage of template molecule in pre-polymerization monomer solution **(Fig 2)**. Thus, the formation of polymer chains and the enhanced partitioning due to the configurational biomimetic effect may be related to the propagation of polymer chains. The template molecule poses physical constraints to free radical and propagating chain motion and hence effectively lowers the rate of polymerization in the creation of ligand binding pockets. These results show that CBIP is reflected at the molecular level. For a given conversion, the rate of polymerization was lower for the multiple functional monomer pre-polymerization mixtures than the single monomer mixtures (**Fig 3**). We propose that CBIP with multiple monomers results in the formation of better ligand-binding pockets due to slower rates of polymerization, and hence enhanced loading properties.

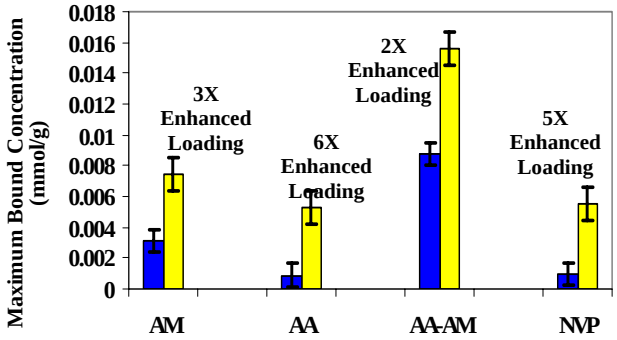

Figure 1: Enhanced Loading of Multiple Monomer Lenses: Comparison data of maximum bound ketotifen concentration (mmol/g) for Poly(n-co-HEMA-co-PEG200DMA), (where n is AM, AA, AA-AM, and NVP) networks. Recognitive network (■) and Control network (■).

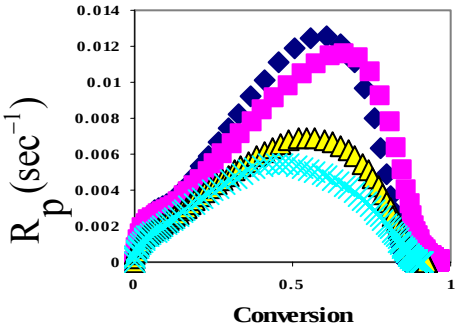

Figure 2: Polymerization Reaction Rate versus Conversion for Poly(AM-co-HEMA-co-PEG200DMA) Networks with a Crosslinking Percentage of 5%. N=3, and T=35˚C. Recognitive networks of varying ketotifen concentration in the initial polymer solutions (■) represents 0.1 mole %; (▲) represents 0.5 mole ; (X) represents 1.0 mole %. The control network (no ketotifen) is represented by the symbol (♦).

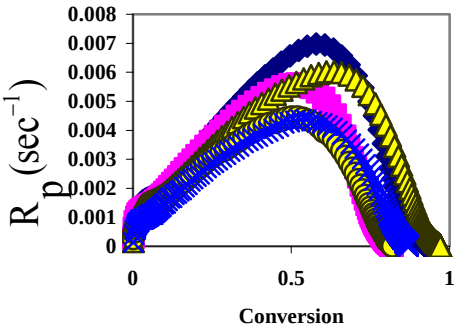

Figure 3: Polymerization Reaction Rate versus Conversion for Varying Comonomer Percentage in Poly(AM-co-AA-NVP-HEMA-co-PEG200DMA) Networks with a Crosslinking Percentage of 5%. N=3, and T=35˚C. Recognitive networks of constant ketotifen concentration and monomer/template ratio in the initial polymer solutions (♦) 3 mole % AM; (■) 3 mole % AA, (△) 3 mole % NVP ; (○) 1.5 mole % each AA and AM, and (X) represents 1.0 mole % each of AM, AA, and NVP.

Conclusions

Mechanisms of non-covalent complexation between template molecule and functional monomers of recognitive contact lenses were characterized using polymerization reaction kinetics. 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.