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Pharmacokinetics of Molecular Imprinted Hydrogels as Drug Delivery Vehicles

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Abstract

Molecular imprinted hydrogels can be made to have a high affinity for a certain compound or drug. A hydrogel can be loaded with a drug and upon a swelling action induced by a pH change or hydration process, the matrix can swell and release the drug. Our hydrogels mimic contact lenses for the purposes of ocular drug delivery. Our hydrogels were imprinted and tested with a prostaglandin derivative, bimatoprost used in the treatment for glaucoma. Major problems preventing entrance to clinical use are bioavailability and drug release kinetics. Our lenses were made to overcome these issues, and were tested for efficacy. The gels were synthesized and were tested to establish a clinically relevant drug delivery profile. Using UV-Vis Spectrophotometry we analyzed the drug released from the gels before, and after cycling. They show a desired and consistent dose release, and a kinetic profile that would indicate a large bioavailability. The testing would also indicate a strong reusability potential, as the hydrogels can release the same amount of drug for over 10,000 cycles (to simulate a daily use). Our samples were tested to show a 10 hour dose release time and they were able to withstand over 10,000 cycles of a swelling mechanical force without degradation or drug release alteration. We imaged the hydrogel lenses with an SEM to visualize if the matrix encountered deterioration over time due to the drug release mechanism. This is due to a need to understand long term use stability. The test results indicate a strong potential to be able to enter the market and be approved for clinical use.

Keyword: Combat disease; Bioavailability; Reusable drug delivery system

Introduction

Pharmacotherapy has become a very broad field and with progressive drugs to combat disease, and there has developed a need for superior drug delivery systems to accompany them. Polymers have been a popular delivery means of chemicals due to high biocompatibility and stability in varying harsh physiological conditions [1]. Many drugs have been developed to mimic naturally occurring processes such as an enzyme-substrate paradigm [2]. Polymer networks have become a means to carry a vast amount of drug per unit of volume and have been shown to be able to have specific molecular recognition capabilities [3]. These molecular imprinted polymers create a delivery system that is capable of releasing a drug to a specific site, and in the proper dose. The nature of these imprinted cavities allows the bulk matrix to also reabsorb the desired drug and become a reusable drug delivery system [4]. Recent studies have shown that hydrogels may be imprinted with selected pharmaceutics to create specific binding sites [5]. Molecular imprinted polymers have been engineered to recognize specific target molecules by increasing the affinity for a specific target molecule by utilizing weak force bonding [6]. The type of binding used in molecular imprinting is important because it will influence the binding specificity for target molecule recognition as well as the kinetics of binding and release of the imprinted molecule [7]. Therefore, it is important to consider non-covalent binding interactions including van der Waals forces, ionic bonding, and hydrogen bonding when selecting binding sites and target molecules [8].

The creation of these systems uses multiple monomers that polymerize and crosslink to form a hydrogel polymer network, where the hydrogel has a high affinity for absorbing water [9]. During this polymerization process the drug will interact with the forming matrix and will have many van der Waals interactions, but no covalent bonds form. This interesting phenomenon allows the bulk material to form around the drug without binding directly to it. This process mimics a two component lock and key system [10]. Once the matrix experiences an external stimulus the matrix will undergo a conformational change, and the drug can diffuse out [11]. The driving force for the diffusion out is due to a concertation gradient [12]. The re-doping is driven by the energy associated with each cavity vacancy. The specific drug molecule finds a lower energy state by entering the imprinted vacancy as each functional group has created a complementary functional group from the matrix [13]. By tuning the responsive monomer ratios you can control the amount of swelling, and thus the drug delivery [14].

In this work, we demonstrate the capabilities of molecular imprinted hydrogels, specifically for ocular drug delivery purposes. Determining the kinetic release will allow a more quantitative analysis and provide a preclinical basis for drug delivery using contact lenses [15]. Also, an accurate and precise dosage delivery is paramount to becoming clinically relevant. We illustrate that a consistent dose can be delivered over a desired time release profile. The goal is to develop a reusable contact lens drug delivery system that will aid patient care in eye diseases, and potentially improve multiple drug delivery options by opening the eye as a possible route for delivery to use more often [16]. The drug release follows general theories for mass transport [17]. The concentration profile and mass transfer for this application will be investigated by determining the diffusion of small molecules through the polymer matrix. The polymer network designed in this study is responsive to changes in pH, which becomes one of the driving interactions responsible for the extraction of the drug from the matrix [18]. The research goal of this project is to determine how the mass transfer varies as a function of time and amount of cycling, investigate the time-release kinetics of the drug delivery material, and explore the reversibility of binding interactions between the drug and the polymer matrix.

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Materials and Methods

The following monomers were used as received from Sigma Aldrich: 2-hydroxyethyl methacrylate (HEMA), dimethylaminoethyl methacrylate (DMA), and tetraethylene glycol dimethacrylate (TEGDMA). In addition, 2,2-Dimethoxy-2-phenylacetophenone (DMPAP), a photo initiator complex, and ethylene glycol acting as a solvent for the pregel solution, were also obtained from Sigma Aldrich. The molecular imprinted hydrogel material was synthesized by preparing a pregel solution containing the following monomers and reagents and in a molar ratio of 95 HEMA, 5 DMA, 1.5 TEGDMA for crosslinking, 5 Xalatan (Latanoprost). The pregel solution was stored at 4°C for one hour to encourage hydrogen bonding interactions prior to free radical polymerization. The hydrogels were synthesized with UV curing by adding the ethylene glycol/drug solution to the pregel solution and polymerizing at 4°C for 2 minutes. Upon synthesis, the resulting material was placed in distilled water, where extraction of the target molecules occurred.

The distilled water and drug solution was characterized using UV-Visible spectroscopy to characterize the concentration of drug released after twelve hours. The Beer-Lambert Law was used to calculate the concentration of the drug released into distilled water [19]. The equation for this law is given here:

$$A=\varepsilon cl$$

Where A represents the absorbance, ε represents the molar attenuation coefficient, c represents the molar concentration of the target molecules in solution, and l represents the path length.

To test the reversibility of the binding interaction, drug-extracted hydrogels were placed in a high concentration solution containing the drug for five minutes, then left to absorb until the surface of each gel appeared to be drying. The hydrogels were then placed into distilled water, and the water/drug solution was tested with UV-Vis spectroscopy to determine the concentration of drug absorbed and released. This result determined the maximum dose delivery, and we then had to measure the kinetics of these diffusion mechanisms. The second method of testing was also performed using the UV-Vis spectrophotometer, and the gels were placed into the water after the five minutes, and the solution was placed immediately into the spectroscopy machine to begin measuring drug release. The machine was set up to run scans over the course of 12 hours.

All gels were put through a mechanical cycle to simulate the swelling reaction normal gels encounter on a daily basis. A cycle consisted of putting samples in an automated water shower that will pour water to fully hydrate each gel, then it will turn off after 15 minutes and be left to dry [20]. This cycle is an extreme as a normal use lens becomes dry during wear, but will not reach the level of dehydration of these in the shower. All testing was performed on pre and post cycled gels. Hydrogels that were both uncycled and cycled for 10,000 times were sputter coated with gold nanoparticles. SEM Images were obtained to view on a microscale if there was a difference caused by mechanical cycling. Samples were prepared using an air dry process and then sputter coating for the same amount of time. Both gels were impregnated with the drug to image the drug loading capabilities, and determine if there was a change due to the swelling process. Gels were examined with the SEM using a voltage of 10 kV [21].

Results

Samples were run sequentially in order to determine if the dose delivered changed over time as shown in Figure 1.

There is a consistent release dose for the first six releases, then there is a slight decrease in the total release. Following this there are a few releases that remain steady, and then after the eleventh release there is another drop in the total release. After this decrease there is a consistent dose release for the remainder of the measured hydrogels. The initial measured absorbance is 1.2 and the final absorbance was measured to be 1.13. This overall decrease is less than 6 percent.

We also wanted to know if the mechanical cycling altered the kinetics of the drug release. As shown in Figure 2 we ran a sample before and after cycling to determine any kinetic variations. The initial sample ran before cycling as shown by the blue curve shows a continuous smooth release profile. The dose is delivered consistently over the course of 10 hours, which is perfect for a day wear lens. The question of swell cycle disruption was answered with the red curve, and while there was a less smooth delivery, the diffusion kinetics was the same.

Additionally, we tested the full dose capabilities of the gels that were cycled more than the 20 previously done samples. After the series of cycles reached 10,000 repetitions we tested to validate long term capabilities. The comparison shown in Figure 3 portrays the long term capabilities of this molecular imprinting system. The drug release level after intense cycling shows a reusable lens capability. These gels showed an initial mean absorbance of 1.055, and a final absorbance of 0.99. This difference shows a total decrease of just over 6 percent.

Using an SEM help to visualize the microstructure of the imprinted hydrogels. Figure 4 allows us to see the doped hydrogels before and after cycling. It is clear that the matrix itself has no damage from the mechanical cycling process. Each gel has very comparable drug loading and therefore the loading capacity is not altered from the swelling process. The amount of drug uptake is visible where the bright dots are indicative of the drug loaded into the gel matrix.

The resolution is proportional to the applied voltage and we used a relatively low voltage so we did not melt the gels. The different images collected showed varying degrees of drug concentration, and the figures represent an average number of imprinted sites.

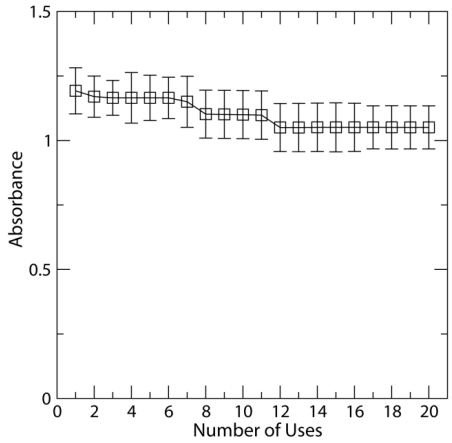

Figure 1: Absorbance measurements of the total drug release for the hydrogels for the first 20 diffusion cycles. Samples were first imprinted during synthesis with the drug lumigan (a bimatoprost derivative) and then allowed to diffuse into water releasing the drug into solution. Each gel was re-doped with the drug dose initially imprinted and allowed to disperse the drug from the matrix again. The drug was detected using spectrophotometry at 205 nm, as this is the characteristic absorbance for this compound. The absorbance was measured for every time the drug was released from each gel providing a trend of total drug delivery per gel for each subsequent use up to 20 uses.

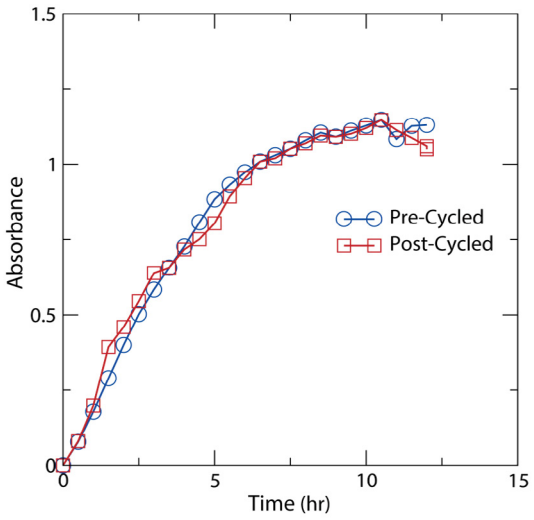

Figure 2: Pharmacokinetic profile before and after many cycles. A sample was tested after synthesis to provide an initial reading on the drug release kinetics. The desired use for these hydrogels is a daytime wear contact lens, so the release was tested for 12 hours. The initial sample was tested using spectrophotometry at 205 nm, and is shown in blue. The same sample was tested after 10,000 swelling and shrinking cycles also at 205 nm, and the drug release profile is shown in red. There is little difference in the kinetics of the release profile before and after cycling.

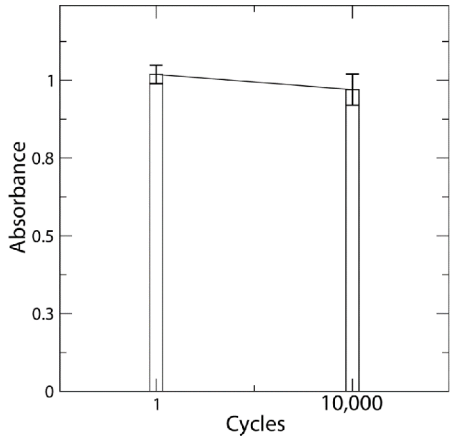

Figure 3: A side by side comparison showing the total drug delivery capabilities before and after mechanical swelling cycles. Samples were tested using the UV-Vis spectrophotometer at 205 nm to determine the total drug release. Samples were tested after synthesis to give a starting dose release. They were put through a cycling process that swelled each gel then de-swelled to simulate a normal day's wear. The samples were cycled for 10,000 times and then tested to again determine the total drug release. The comparison shows that there is a slight drop in drug release capabilities, but with some manufacturing preparation this can be compensated for. The initial imprinting could exceed the needed dose, and then the gels can be cycled to ensure the long term consistency of each dose.

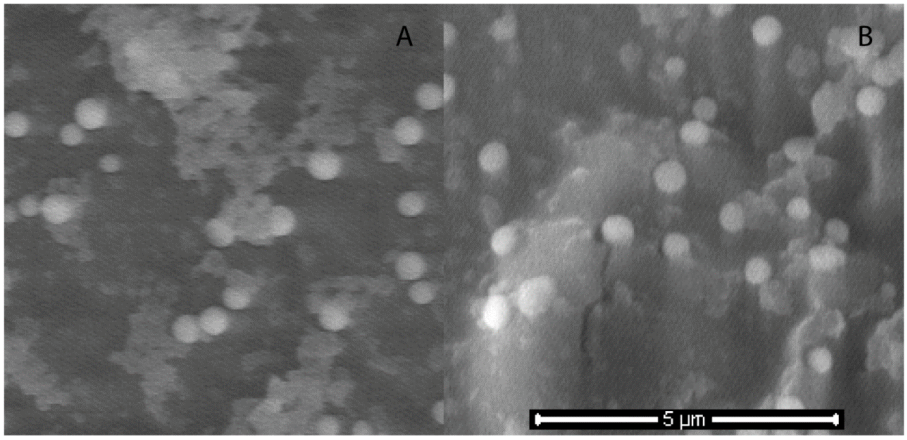

Figure 4: SEM visualization of molecular imprinting before and after cycling. Figure A illustrates a hydrogel that has just been synthesized and gold sputtered, where the bright spots represent the drug. It is shown using a voltage of 10,000 kV. Figure B shows a hydrogel that has been cycled for 10,000 times and then re-doped with the drug. It was sputter coated with gold and also visualized with 10,000 kV. This was to determine any matrix damage after the cycling process or any variation in drug re-doping capabilities.

Discussion

As illustrated in Figure 1, the amount of drug changes over time in a slight decrease, but levels off. This indicates that the polymer matrix also changes over time reaching asymptotic behavior. The slight decrease after the gels were tested for the first time delivery suggests that the drug does not reload the gel as much as the initial imprinted polymer holds. There is a slight decrease after another couple swell and six delivery cycles, which points to a matrix phenomenon. We postulate that this is due to unreacted monomers that were trap in the hydrogel following the polymerization process leaving the hydrogel. The swelling mechanism is providing means for the transport through the bulk material and the concentration gradient from gel to solution is driving the monomers out of the gels. The fact that the drug dose release plateau indicates that the system is overall accurate. The initial changes demonstrate that the system needs to be prepared after synthesis before it can be clinically usable. After approximately eleven cycles the hydrogels reach a very stable delivery profile.

As shown in Figure 2 the small instabilities in the curve could be explained again by the removal of the unreacted monomers. They could potentially be keeping the gel in a slightly swelled state and creating small channels for drug to diffuse through as an alternate pathway regardless of the swollen state of the gel. Also the change in slope of the red curve could be explained by the lack of unreacted monomers. This could allow the system to have a more direct affinity for the drug and make it harder for the release of the drug. These experiments were performed in a test tube and therefore do not

mimic the actual physiological environment and drug metabolism. *In situ* experiments could show different dose releases and different kinetic profiles, but these data are promising. The drug release illustrated here is very desirable for an eye drop replacement. The variations could in part be systematic errors, but the general trend shows consistent data. A 10 hour total release time means that a patient could wear the lenses all day and be able to receive a steady dose throughout the day.

In Figure 3 we find that if you load the lenses during synthesis so that the initial molecular imprints exceed the amount needed by the percent loss, the total delivery will be the precise dose needed. The total amount needed to overcome this loss is approximately 6 percent of the absorbance, which is directly proportional to the amount of drug to be added. Once the lenses are cycled to prepare them for long term steady use, the drug could be collected from solution and reused to make more gels. The gels themselves will be ready to absorb and deliver a desired dose.

Due to the very low voltage used during the imaging, gels shown in Figure 4 were not able to get more resolved images. Very little data is available to compare SEM imaging of drug molecules, so the nature of each drug spot is not entirely clear. However the important fact is that there are a very similar number of drug molecules per unit area on both images, and the hydrogel appears unharmed.

These data provide concrete evidence that this HEMA based hydrogel system is capable of being used in market ready drug delivery contact lenses. There is similar data provided for many different hydrogel systems, however, there are few that provide such a comprehensive picture. These experiments show that this system is very controllable and can withstand over 10,000 daily uses. The average eye doctor will recommend that you discard your lenses after far fewer uses and use a new lens. These hydrogel lenses are intended to capable of being used as contact lenses to be worn in the day, and with the reloading capabilities, the same gels can be reused multiple times as a safe and reliable drug delivery device.

Conclusion

Hydrogels with a HEMA based backbone structure prove to serve as a viable drug delivery system. Accurate doses are delivered consistently where each gels is capable of being used multiple times. This drug delivery system can potentially be integrated into current contact lenses and be reused easily. Each use of a contact lens represents a cycle where the gel will swell and collapse due to the changes in water content and pH environments. These hydrogel lenses are capable of withstanding over 10,000 cycles of this mechanical movement of swelling and it does not affect the drug delivery ability of the lens. The swelling process does not alter the gel microstructure, and allows the kinetics to remain unaltered. Future testing could include the manufacturing of these imprinted hydrogels in combination with current clinical ready lens materials. This could provide a good bridge from lab testing to preclinical testing.

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