Water soluble drug releasing soft contact lens in response to pH of tears

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Abstract. Human tear characteristics including pH and compositions can vary significantly depending on physical and environmental factors. Contact lenses directly contact with human tears can be swelled or de-swelled depending on the pH of the solution due to the nature of the hydrogel. For example, anionic hydrogels, when the solution’s pH is low, is shrunken due to the electric attraction force within the hydrogel network; the opposite phenomenon appears when the solution is basic. The purpose of this study was to evaluate the extent of water soluble drug, hydroxyl propyl methyl cellulose, released from contact lens according to the pH of the artificial tears. Artificial tears are prepared by mixing lysozyme, albumin, sodium chloride, potassium chloride, and calcium chloride following physiological concentrations. Hydrogel contact lens was thermally polymerized using HEMA, EGDMA, and AIBN. The prepared hydrogel lens was immersed in drug for 3 hours and the eluted drug mass was measured as a function of the time. As a result, the drug was released from the lens for 12 hours in all the pH of artificial tears. At the lower pH of artificial tears (pH 5.8), the total amount of dye emitted from the lens was increased than the total amount of dye emitted at the basic tear (pH 8.4). Also, initial burst at acidic tears was increased within 1 hour. Release pattern of water-soluble drug from hydrogel lens turned out to be different depending on the pH of the artificial tears. When designing drug releasing contact lens, physiological pH of tears should be considered.

1. Introduction
Physicochemical and pharmacokinetic properties of drugs should be considered to properly design a drug delivery system using hydrogels.[1-3] For ocular drug delivery, specificity of tears should also be considered. Tears are made up with water (up to 98%), phosphates, fat, tear proteins, sodium chloride and sodium carbonates.[4] The composition and concentration of tears highly depend on the physical human factors and/or environment. Similar to human blood, tears’ pH is typically around 7.5. However, it can vary from 5.8 to 8.3 depending on emotions and/or individual health status.[5] In such, volume of human tears increase or decrease depending on emotional states, such as joy, sadness,
or depression, and also depending on environmental changes, such as wind or cold. The pH of human tears can be decreased or increased by these changes.

Many research articles regarding pH-sensitive hydrogels for drug release uses have been published in recent years.[1,6-8] pH-sensitive hydrogels are composed of polymeric backbones with ionic pendant groups. In solutions, the pendant groups can ionize and develop positive or negative charges on the hydrogel, generating electrostatic repulsive or attractive forces that lead to increase or decrease water contents in the polymer. These behaviors of cationic copolymers based on poly(dimethylaminoethyl methacrylate) [p(DMAEMA)] and poly(diethylaminoethyl methacrylate) [p(DEAEMA)] have been investigated.[9,10] Peppas studied that the pH-modulated swelling and release characteristics of anionic hydrogels of poly(methacrylic acid) [p(MAA)] and poly(hydroxyethyl methacrylate) [p(HEMA)] for releasing drugs such as salicylic acid.[11]

Similar to pH responsive polymers, the contact lens can also be swelled or deswelled depending on the pH of the solution due to the nature of the hydrogel. In general, when the pH is low, it is shrunken due to the electric repulsive forces within the hydrogel network, the opposite phenomenon appears when the solution is basic.[12] The purpose of this study was to evaluate the extent of water soluble drug release from hydroxyl ethyl methacrylate (HEMA) according to the pH of the artificial tears. We have employed our pH-sensitive hydrogels as a matrix system for the ocular delivery of hydroxyl propyl methyl cellulose (HPMC), non-ionic humectants used in artificial tears or eye drops. We selected HPMC as a model drug, since the drug shows good water solubility and its non-ionic property would not disturb the pH of solutions.

2. Experimental

2.1. Hydrogel polymerization

2-hydroxyethyl methacrylate (HEMA) was used as a main polymer backbone. Ethylene glycol dimethacrylate (EGDMA) and ethylene glycol dimethacrylate (AIBN) were used as a crosslinking agent and an initiator. The reagents (HEMA, EGDMA 0.6%, and AIBN 0.4%) were agitated for 30 min. It was molded following thermal polymerization in a cast mold. Polymerized contact lens was rinsed 3 X with deionized water and hydrated in deionized water for 24 hours before drug releasing test to remove unused reagents residues. All chemicals were used as supplied without further purification.

Swelling ratio of hydrogels

Water contents of hydrogels were measured at various pH tear solutions (pH 5.80, 6.45, 7.20, and 8.03). Percentage water (%H₂O) is defined as

\[ \frac{H_w - H_d}{H_w} \times 100 \]  

(1)

Where \( H_w \) and \( H_d \) are the weights of the wet and dry state of hydrogels, respectively.

2.2. Artificial tears

Artificial tear solutions were formulated in deionized water with the composition of lysozyme (1.2 mg/mL, chicken egg white, ≥90%, Aldrich), albumin (3.88 mg/mL, bovine serum, ≥96%, Aldrich), sodium chloride (7 mg/mL), potassium chloride (1.7 mg/mL), calcium chloride (3.88 mg/mL). Final pH of the solution was from 5.80 to 8.04.

Elution of dyes or drugs

Water soluble dyes (Shinhan Co.) or hydroxyl propyl methylcellulose (HPMC, Aldrich) were used for release tests. Water soluble dyes were tested to visually observe dye releasing phenomenon. Freshly made hydrogel contact lenses were immersed for 3 hours in dye or drug solutions. Drug containing
hydrogels were then soaked in artificial tears (pH 5.80, 6.45, 7.20, and 8.03) for designed time periods. At the time intervals, the solution was analyzed for dye or drug and replaced with fresh artificial tears. UV-Vis spectrophotometer (Mega Array, Scinco, Korea) was used to compare optical density of solutions of dyes or drugs in tears.

3. Results and Discussions

3.1. Physical properties of HEMA hydrogels

Figure 1 shows that the water contents of hydrogels in accordance with the artificial tear solutions’ pH. After soaking the lens for 12 hours in artificial tear solutions, the weights of lenses, $H_w$ were measured. Lens was then dried for 24 hours before measured the dried weight, $H_d$. Following eq.1 the water content of each lens was calculated. Water content of control lens (without dipped in artificial lens) was $32.35\pm0.66\%$. Water contents of lenses dipped in artificial tears with different pH (5.8, 6.45, 7.20, and 8.03) were calculated as $41.89\pm0.74\%$, $43.63\pm0.86\%$, $46.40\pm0.59\%$, and $47.12\pm0.33\%$, respectively. When the artificial tear is basic, the water content was increased up to 43% in comparison to control lens.

In general, swelling of a gel is affected by many factors including mechanical forces, pH, temperatures, and electrostatic interactions.[1,6] In acidic solution, the network of polymers bearing acidic groups including HEMA and other methacrylc acid grafted gels tend to expand due to electrostatic repulsion. This leads to relative less water contents in lower pH than those in pH 8.03.

In comparison to control hydrogel soaked in PBS solution, water contents of hydrogels soaked in artificial tears appeared to be higher in overall pH ranges. It is considered that the tear proteins adsorbed to hydrogels contributed to weights of gels in wet states.

Figure 2 displays light transmissions (visible, UV-A, UV-B) through hydrogel lenses with various pH of tear solutions. Light transmittance (visible, UV-A, UV-B) of control gel swelled in PBS was 82, 80, 78\%, respectively. Regardless of pH of artificial tears, the light transmittance of gels dipped in artificial tears were decreased due to haziness caused by proteins adsorbed to the surface of hydrogels. In specific, UV-A transmittance was decreased to $69.35 \pm 3.91\%$, $70.3 \pm 1.75\%$, $72.55 \pm 5.99\%$, $73.45 \pm 2.11\%$ when the gel is soaked in tear solution with pH of 5.80, 6.45, 7.20, 8.03, respectively. As shown in Figure 2, transmittance of UV-B light was also decreased to $65.55 \pm 4.05\%$, $67.9 \pm 1.59\%$, $69.3 \pm 5.08\%$, $69.9 \pm 2.31\%$. In accordance with UV light transmittance, visible light transmittance was reduced to $71.45 \pm 4.14\%$, $72.15 \pm 1.69\%$, $72.9 \pm 5.71\%$, $75.7 \pm 1.89\%$. UV and visible light transmittance of the gels were slightly increased as the artificial tears were basic. This was considered to be due to the majority of protein, albumin in artificial tear solution. Apart from synthetic polymers, albumin, a kind of natural polymer, can also swell and deswell in response to pH of solution.[13] Isoelectric point of Albumin is around 5.4 in deionized water and albumin’s own charge was reported to zero at the isoelectric pH.[13] It became negative with increasing pH of solution and positive with decreasing pH of solution than isoelectric pH. With increasing basicity of solution to 8.03, the charges of albumin were more negative and tend to be swelled due to electrostatic repulsion forces. As a result, overall light transmittance of gels slightly increased as increasing pH.

3.2. Standard curves of dyes and drugs

Figure 3 A and B show standard curves for dyes and hydroxyl propyl methylcellulose. Linear calibration curves were obtained (R2 $\geq$98\%) within the concentration range 0.001 mg/mL < dyes <0.35mg/mL and 0.01 mg/mL < HPMC <3.25 mg/mL. Results reported herein were obtained within the linear-working range for dyes or HPMC. With HPMC, calibration curves exhibited two experimentally-useful, linear-like regions at low (0.01 mg/ml < HPMC <0.06 mg/ml) and high (0.1 mg/ml < HPMC <3.25 mg/ml) concentrations as shown in Figure 3B.
3.3. Dye and drug release with varying pH

Figure 4 A and B compare cumulative mass of dyes and HPMC released from hydrogels with varying pH of artificial tears. Release of dyes and drugs were continued for 12 hours and after that, it did not released regardless of mass remained in the gels. At the lower pH of the artificial tears such as pH 5.8, the initial bursts (up to 20% of total cumulative release) were maximized in both cases. Drug release from hydrogels was supposed to follow simple diffusion, the amount of released mass at a given time was decreased over time in all pH ranges.

**Figure 1.** Water contents of hydrogels with varying solution pH

**Figure 2.** Light transmittance of hydrogel lenses according to various solution pH.
Figure 3. Calibration curves for water soluble dyes (A) and HPMC (B).
We analyzed that in acidic tears (pH 5.80 and 6.45) the amount of released drug was more than twice than that in basic tears. In particular, the cumulative released mass in tear of pH 5.80 was 1.04 mg when that in tear of pH 8.03 was 0.42 mg.
pH sensitive hydrogels such as polyacrylamide and methacrylate gels tends to swell in basic medium attracting more water due to ionization and hydrolysis from acrylic acid.[14] According to Peppas, polymer networks dissociate due to ionization of pendent groups such as acrylic acid with increasing pH. Furthermore, the electrostatic repulsion forces cause the hydrogel to swell, and water passes in. [11]

The total released amount of drug, which diffused through the hydrogel is [7]
\[
\text{Total released amount of drug} = \frac{ADC_0}{l} \left( t - \frac{l^2}{6D} \right)
\]
(2)

Where \( A \) is the area of the hydrogel, \( D \) is diffusivity, \( l \) is membrane thickness, \( C_0 \) is the drug concentration within the hydrogel and \( t \) is the time. When released amount is plotted against time, the slope is:
\[
\text{Slope} = \frac{ADC_0}{l}
\]
(3)

The diffusivity can be calculated from the slope and the hydrogel area. Applying lens thickness as 90 \( \mu \)m, the diffusivity of gels in tear pH (5.8, 6.45, 7.20, and 8.03) were derived as 5.60 x 10\(^{-10}\), 4.55 x 10\(^{-10}\), 3.13 x 10\(^{-10}\), and 2.82 x 10\(^{-10}\) m\(^2\)hour\(^{-1}\), respectively. (Table 1) Note that the diffusivity of drugs in hydrogel lens decreased as increasing artificial tears’ pH resulting that less drugs delivered at a given time. We reason that the different release rates of dyes and drugs were due to difference in physical properties of dyes and drugs. Typically, it is understood that drug release from hydrogel depends on drugs molecular weights, solubility, and concentration besides from wettability and thickness of gels.

Drug release in short time can be predicted by the following formula.[15]
\[
\text{Cumulative drug release} = 4\sqrt{\frac{Dt}{\pi h^2}}
\]
(4)

Where \( D \) is the diffusion coefficient, \( h \) is thickness of the gel, \( t \) is time. This formula is supposed to be valid only in short time drug release. Following the eq. 3, cumulative drug release found to be increased in proportion to the square root of the release time.

Figure 5 shows that drug exhibited a linear-like release trend over square root of time. With computing eq. 3, drug release was proportional to square root of time with more than 95% agreement. Figure 6 compiles the maximum release amount of drugs with varying pH of artificial tears. In acidic condition (pH 5.80), 0.45mg of HPMC was released and in basic condition (pH 8.03) less than 0.2mg was released from the hydrogels containing same amount of drugs in preparation. Note that as the pH is increased, the maximum release amount of drugs decreased due to increased ionization of hydrogel pendent group.

| Tear pH | Slope | Thickness (\(\mu\)m) | Diffusion coefficient, \(D\) (x10\(^{-10}\) m\(^2\)hour\(^{-1}\)) |
|---------|-------|----------------------|----------------------------------|
| 5.80    | 0.20  | 90                   | 5.60                             |
| 6.45    | 0.16  | 90                   | 4.55                             |
| 7.20    | 0.11  | 90                   | 3.13                             |
| 8.03    | 0.10  | 90                   | 2.82                             |
Figure 5. Linear fits for the short time drug release in response to artificial tears’ pH.

Figure 6. Maximum amount of HPMC with artificial tears’ pH released for 12 hours.
4. Conclusions
The ability of pH-sensitive hydrogels to respond to its environment makes them suitable candidates for ophthalmic delivery of water soluble drugs. This hydrogel shows excellent biocompatibility and versatile physical properties. We thermally polymerized a hydrogel contact lens with hydroxyl ethyl methacrylate for water soluble drug delivery. The polymerized gels loaded with drugs were then, dipped in various pH of artificial tears. The drug release from the gel in response to pH was evaluated. As a result, drug was released from the lens for 12 hours in all the pH of artificial tears. At the lower the pH of artificial tears (pH 5.8), the total amount of dye emitted from the lens was increased more than the total amount of drug emitted from the basic tear (pH 8.4) due to the ionization of the carboxylic pendent groups (-COOH). Also, initial burst from acidic tears was increased within 1 hour. Release pattern of both water-soluble dye and drug from hydrogel lens turned out to be different depending on the pH of the artificial tears. We demonstrated that hydrogel contact lens is suitable candidate for ophthalmic water soluble drug carrier suggesting physiological pH of tears needs to be considered when designing the drug releasing contact lens.

5. References

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