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Review Article

Hydrogel Contact Lens for Extended Delivery of Ophthalmic Drugs

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Soft contact lenses can improve the bioavailability and prolong the residence time of drugs and, therefore, are ideal drug carriers for ophthalmic drug delivery. Hydrogels are the leading materials of soft contact lenses because of their biocompatibility and transparent characteristic. In order to increase the amount of load drug and to control their release at the expected intervals, many strategies are developed to modify the conventional contact lens as well as the novel hydrogel contact lenses that include (i) polymeric hydrogels with controlled hydrophilic/hydrophobic copolymer ratio; (ii) hydrogels for inclusion of drugs in a colloidal structure dispersed in the contact lenses; (iii) ligand-containing hydrogels; (iv) molecularly imprinted polymeric hydrogels; (v) hydrogel with the surface containing multilayer structure for drugs loading and releasing. The advantages and disadvantages of these strategies in modifying or designing hydrogel contact lenses for extended ophthalmic drug delivery are analyzed in this paper.

1. Introduction

Ocular disorders frequently occur in human body, which are mainly treated by drugs. In therapy uses, the drugs could present some side effects to the human body and even harm the normal tissues when their concentration is too high. On the other side, the drugs will not treat the diseases effectively when their concentration is too low [1]. Moreover, the treatments of ocular disorders are frequently slow processes extending from several days to several weeks. Therefore, the effective therapy must depend on the rational drug concentration and residence time. 90% or more of drugs used in ocular disorder therapy are in the form of eye drops or eye ointments [1]. Only 1–5% of the drugs contained in the eye drops can be effectively used, while a large part of the drugs enters the systemic circulation by either conjunctival uptake or drainage into the nasal cavity. Moreover, the residence time of eye drops is only 2 min or so [2]. These characteristics of eye drops cause inconvenient use, low efficiency, ineffective therapy, severe side effects, and so forth. Although eye ointments may be resident on the eye much longer than eye drops, they may affect the sight and irritate eye tissue [1, 3–5]. In order to overcome the disadvantages of eye drops and eye ointments, numerous strategies have been developed for the treatment of ocular disorders including increasing the viscosity of the eye drops and increasing the corneal permeability. Though these strategies may increase the drugs residence time and the bioactivities, they cannot completely satisfy the need for treatments of ocular disorders, especially for ocular disorders which need long-time therapy [6].

With the development of drug delivery, drug carriers such as particles, hydrogels, insert films, and contact lens have been developed to control the release of ophthalmic drugs [4, 6, 7]. Among these carriers contact lenses are particularly attractive because of their ability to prolong the residence time of drugs and improve their bioavailability, ease of control, and convenient use. Some research reported that in theory the use of efficient ocular drugs delivered by contact lens was 35 times better than that delivered by eye drops [8–11]. Hydrogels are the leading materials of soft contact lenses because of their biocompatibility and transparent characteristic [12, 13]. Therefore, hydrogel contact lenses are widely used in ophthalmic drug delivery.

Most conventional hydrogel contact lenses were used to deliver the ophthalmic drugs by soaking the contact lenses in drug solution to load the drugs, applying eye drops on contact lenses after being inserted into eyes, or incorporating the drugs into the monomer of hydrogel contact lenses. Recently, supercritical fluid- (SCF-) assisted method was used to enhance the drug loading amount in hydrogel contact lenses and to control their release [14, 15]. However, the sustained release time of drugs using the above-mentioned methods is no longer than 24 h, which is not suitable for extended drug delivery [9, 16, 17]. In recent years, many strategies are operated to modify the conventional contact lenses for extended drug delivery with the emergence and development of novel hydrogel contact lens. In this paper, the modifications of conventional contact lenses as well as novel contact lenses based hydrogels for extended ophthalmic drug delivery are introduced.

2. Hydrophilic/Hydrophobic Copolymer Hydrogel

Hydrogels are water-swollen polymeric materials that can absorb a large amount of water but not be dissolved in water [18]. After poly-hydroxyethyl methacrylate (pHEMA) hydrogels were first prepared as soft contact lenses in the 1960s, the hydrogel contact lenses have been used to deliver ophthalmic drugs. However, the conventional contact lenses have some limitations in the application of long-time therapy due to fast release rate of drugs and low loaded drug amount [11, 16, 17]. In order to enhance the potential capacity of hydrogel to load drugs and prolong the sustained release time of drugs, hydrophobic monomer such as 4-vinylpyridine (VP) or ionic monomer such as N-(3-aminopropyl)methacrylamide (APMA) was incorporated to pHEMA hydrogels [19]. The incorporation of ionic/hydrophobic monomer would increase the interaction between hydrogel and drugs so that the drugs had more difficulties diffusing from the hydrogel. Andrade-Vivero et al. also reported that the incorporated monomers remarkably increased the amount of loaded drugs (ibuprofen up to 10-fold or diclofenac up to 20-fold) without changing the viscoelastic properties and the state of water of hydrogel. The drug release profile of pHEMA-APMA could be controlled by ions in the media, the sustaining release process of pHEMA-VP lasted for at least 24 h for the ibuprofen and almost 1 week for the diclofenac [19].

In order to increase the oxygen permeability, silicone polymers replace the conventional contact lenses monomers [20–22]. Kim et al. used silicone macromer (bis-alpha, omega-(methacryloxypropyl) polydimethylsiloxane), hydrophobic monomer containing silicon (3-methacryloxypropyltris (trimethylsiloxy) silane, TRIS) and hydrophilic monomer (N,N-dimethylacrylamide, DMA) to synthesize extended wear of silicone hydrogel contact lenses and transport ophthalmic drugs (timolol, dexamethasone, and dexamethasone 21-acetate). It was found that the sustained drug release process of silicone hydrogels varied from 20 days up to more than three months depending on the compositions of hydrophobic and hydrophilic components of silicone hydrogels. The result also showed that the properties of silicone hydrogels such as mechanical properties, ion permeability, equilibrium water content, transparency, and surface contact angles were suitable for contact lens application [22]. However, if hydrophilic/hydrophobic ratio was improper, hydrophilic/hydrophobic copolymer hydrogel would became opaque because of phase separation. Although silicone hydrogel contact lenses possess high oxygen permeability, their stiffness also increases with the decrease of water content, which will be uncomfortable to patients because the cornea is soft.

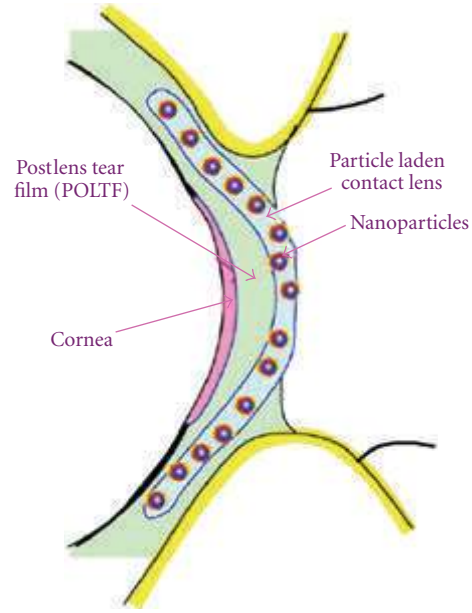

Figure 1: Schematic illustration of the particle-laden lens inserted in the eye [27, 28].

3. Colloid-Laden Hydrogel

Colloidal carriers have been exploited to achieve ophthalmic drug delivery [7]. These colloidal systems consist of micro-/nanoparticles, micro-/nanoemulsions, nanosuspensions, and liposomes [7]. It is reported that drug carriers via nanotechnology are favourable in enhancing drug permeation, controlling the release of drug and targeting drug [24]. Encapsulation of drugs in these colloidal carriers can also significantly prevent degradation from the ocular enzymes [25, 26]. Moreover, the size of these nanocarriers is small enough so as not to affect the vision of patient. Therefore, colloid carriers can be incorporated into hydrogels contact lens in order to prolong sustained release time of drugs and increase their bioavailability further [23, 27–29].

Gulsen and Chauhan encapsulated the ophthalmic drug formulations in microemulsion drops, and the drug-laden microemulsion drops were dispersed in the p-HEMA hydrogels, which was further inserted into the eyes as shown in Figure 1. The results of their study showed that the p-HEMA

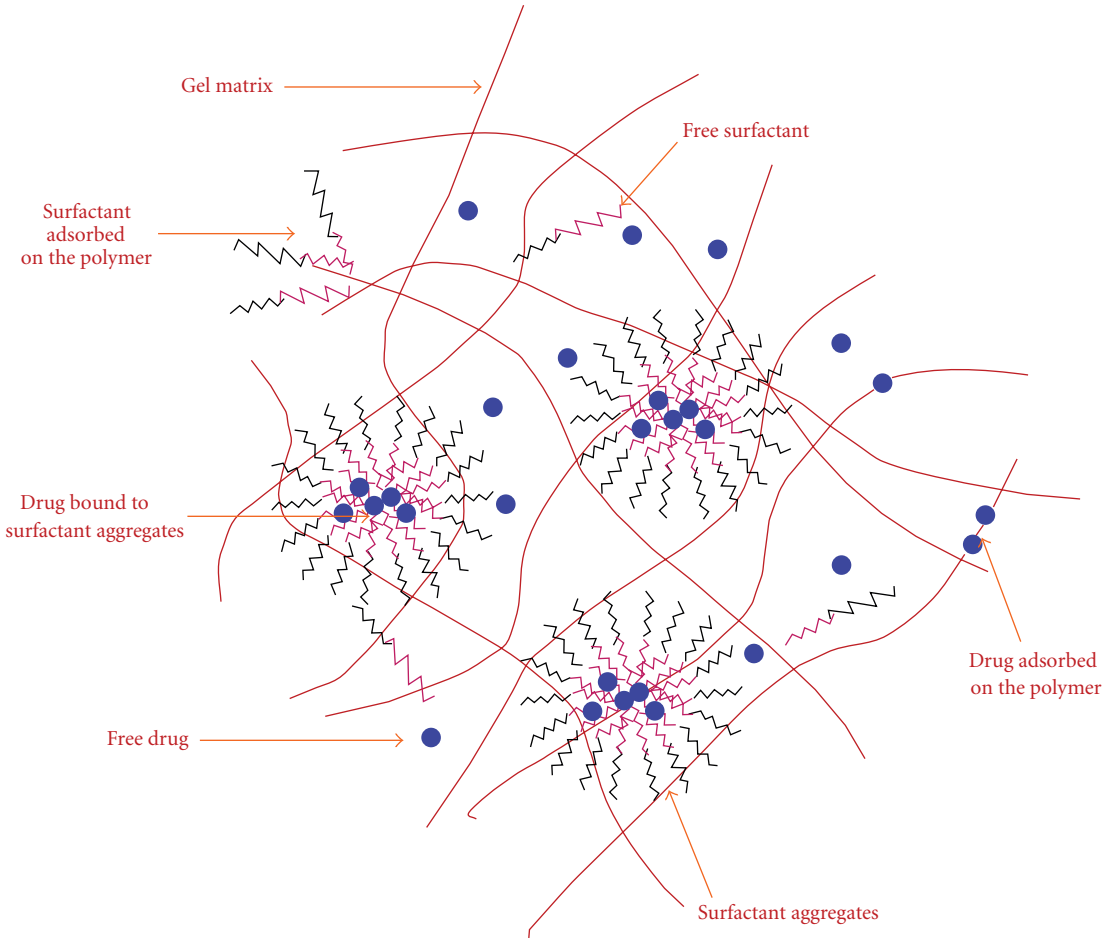

Figure 2: A schematic of the microstructure of the surfactant-laden gels [23].

gels loaded with microemulsions were transparent; these gels released drugs for a period of over 8 days, and the delivery rates could be tailored by controlling the particle and the drug loading. They also found that this system might provide lubricants to alleviate eye problems prevalent in extended lens wear as well as cure the ailments of eyes. However, the fabrication processes of microemulsion-loaded hydrogels require two-step processes: preparation of microemulsion drops, followed by entrapment in the hydrogels [27, 28].

It has also been proposed to create colloid-laden hydrogel *in situ* in one step. Surfactant-laden hydrogels can be prepared by addition of surfactants to the polymerizing mixture. A schematic of the microstructure of the surfactant-laden gels is shown in Figure 2. During the process of fabrication, the surfactants interact with polymer chains and form micelles creating hydrophobic cores, where the hydrophobic drugs will preferentially enter into. The drug transport is inhibited due to the presence of surfactant micelles. Kapoor et al. prepared Brij surfactant-laden p-HEMA hydrogels that can release Cyclosporine A (CyA) at a controlled rate for extended periods of time (20 days). Their results show that Brij surfactant-laden p-HEMA gels provide extended release of CyA and possess suitable mechanical and optical properties for contact lens applications. However, the hydrogels are not as effective for extended release of two other hydrophobic ophthalmic drugs, that is, dexamethasone (DMS) and dexamethasone 21 acetate (DMSA), because of insufficient partitioning inside the surfactant aggregates [23, 29].

However, there are some drawbacks of using colloid-laden hydrogel contact lenses. One is the instability of the colloid-laden hydrogel during preservation and transportation because the loaded drugs diffused into the hydrogel matrix. Another is the decaying release rate of colloid-laden hydrogel in ophthalmic drug delivery [11, 28].

4. Ligand-Containing Hydrogels

Weak interactions between drugs and ligands in polymer matrix including hydrogen bond, electrostatic interactions, and host-guest interactions can induce the drug loading and control its release by ions in solution [15, 30, 34–39].

Sato et al. synthesized hydrogels containing cationic functional groups for delivery of anionic drugs and hydrogels containing anionic functional groups for delivery of cationic drugs. The resulting hydrogels are capable of storing the anionic drugs or cationic drugs depending on the charge of functional groups based on ion-exchange reaction. The

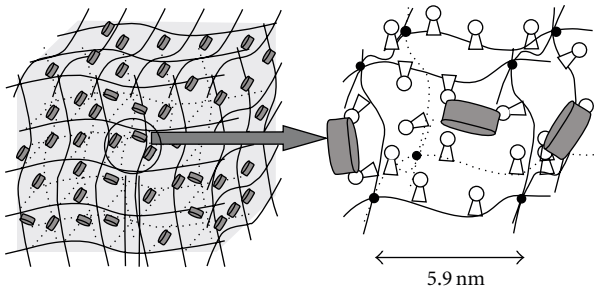

Figure 3: Scheme of a pHEMA-co-GMA hydrogel with pendant β-CDs [30].

incorporated drugs would be released into tear fluid by ion exchange. Their results also show that these hydrogels are suitable for soft contact lenses as ophthalmic drug delivery. However, the sustained release time of these ions ligand-containing hydrogels is only several hours, which made these hydrogels unsuitable for extended delivery of ophthalmic drugs [36, 37].

Cyclodextrins (CDs) are known as "host" molecules having hydrophobic internal cavities that can include "guest" drug molecules. These inclusion complexes are actually dynamic processes that result from noncovalent bonds between the CDs and their guests just as other weak interactions, and this means that CDs have found widespread applications in the fields of drug delivery [15, 34, 35]. Some efforts have been made to incorporate CDs into various polymer matrices in order to increase aqueous solubility and the stability in ophthalmic formulations, increase loaded drugs, and sustain the drug release for several days. dos Santos et al. developed acrylic hydrogels containing β-cyclodextrin (β-CD) by grafting reaction under mild conditions. The structure of hydrogel is shown in Figure 3 [30]. The hydrogels containing β-CD present similar light transmittance, glass transition temperature, swelling degree, viscoelasticity, oxygen permeability, surface contact angle, mechanical properties, and biocompatibility with acrylic hydrogels without β-CD but notably improving their ability to load drugs and sustaining drug delivery in lacrimal fluid for two weeks [30]. Jinku et al. synthesized pHEMA/β-CD hydrogel platform by photopolymerization of HEMA, monomethacrylated β-CD (mono-MA-β-CD), and trimethylolpropane trimethacrylate for sustained release of ophthalmic drugs. Their results showed that the incorporation of β-CD in the hydrogels increased the equilibrium swelling ratio and tensile strength. The drug (puerarin) loading and *in vitro* release rate were dependent on β-CD content in the pHEMA/β-CD hydrogels. The puerarin-loaded pHEMA/β-CD hydrogel contact lenses provided sustained drug release in the precorneal area of rabbits with longer retention time and higher bioavailability [39].

5. Molecularly Imprinted Polymeric Hydrogels

Molecularly imprinted polymers (MIPs) are investigated for the field of drug delivery due to their active sites of specific recognition [31, 40–42]. The general imprinting process includes five steps, as shown in Figure 4. First, template, functional monomer, crosslinking monomer, and initiator (Figure 4(a)) in solution are self-assembled into the prepolymerization complex (Figure 4(b)) via covalent or noncovalent chemistry. Second, the complex is initiated via UV light or heat to form crosslinked network (Figure 4(c)). Third, original template is removed via wash step, the crosslinked polymer network with cavities (Figure 4(d)) is formed. Fourth, new template (potential drug) is rebinding into the crosslinked polymer (Figure 4(e)). Fifth, the new template diffuses into solution via stimulation such as swelling (Figure 4(f)). During this imprinting process, the bioactivity of drugs can also be preserved [31].

In recent years, researchers incorporate MIPs into hydrogel contact lenses for increasing drugs loading and prolonging their sustained release time, considering advantages of MIPs and soft contact lenses in delivering ophthalmic drugs. Imprinted hydrogels with single functional monomer as well as multiple functional monomers are synthesized as soft contact lenses to deliver ophthalmic drugs [43–54]. More recently, some reviews presented comprehensive introduction of molecularly imprinted therapeutic contact lenses [51, 54]. Some representative drug-imprinted soft contact lenses as well as potential technology in drug-imprinted hydrogel are introduced as follows.

Hiratani and Alvarez-Lorenzo prepared imprinted contact lenses made of HEMA or N,N-diethylacrylamide (DEAA), low cross-linker proportions, and a small proportion of functional monomer (methacrylic acid, MAA), which was able to interact with drug (timolol maleate) via ionic and hydrogen bonds. It was found that imprinted HEMA-based and DEAA-based contact lenses uptook more timolol than the corresponding nonimprinted systems, the loaded lenses could sustain drug release in lacrimal fluid for more than 12 h, and the empty lenses could reload drug overnight for the next day use [45, 50]. The effects of four kinds of backbone monomers and the template/functional monomer proportion on the drug loading capacity, released behaviours, and properties such as the hydrophilic character, swelling degree, and mechanical properties were further researched [46, 48]. *In vivo* experiments, it was found that the imprinted contact lenses could be capable of prolonging the retention time of timolol in the precorneal area, compared to conventional contact lenses and eye drops [47]. Later, they designed imprinted HEMA-based hydrogel contact lens using acrylic acid (AA) as functional monomer to load and to release norfloxacin for several hours or even days in a sustained way [44]. However, the duration of drug release in these imprinted hydrogel contact lenses using one functional monomer was limited to less than 1 day *in vitro* and *in vivo* experiments.

Venkatesh et al. synthesized imprinted HEMA-co-polyethylene glycol (200) dimethacrylate- (PEG200DMA-) based contact lenses containing multiple functional monomers of AA, acrylamide (AM), and N-vinyl 2-pyrrolidinone (NVP) for the delivery of ocular medication such as H1-antihistamines. Their results showed that these contact lenses had the potential to load significant amounts of drug, as

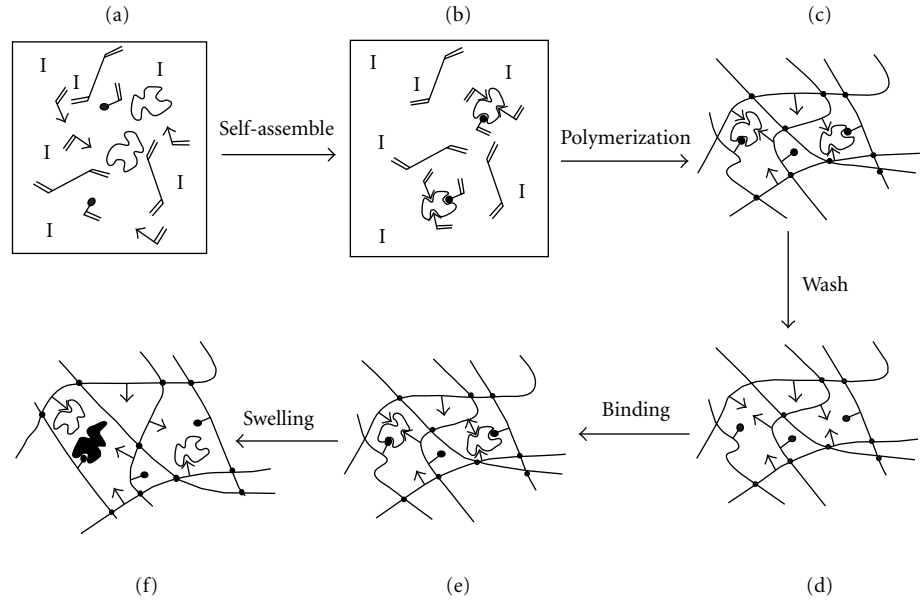

Figure 4: Imprinting process. (a) Solution mixture of template, functional monomer(s) (triangles and circles), crosslinking monomer, solvent, and initiator (I). (b) The prepolymerization complex is formed via covalent or noncovalent chemistry. (c) The formation of the network. (d) Wash step where original template is removed. (e) Rebinding of template. (f) In less crosslinked systems, movement of the macromolecular chains will produce areas of differing affinity and specificity (filled molecule is isomer of template) [31].

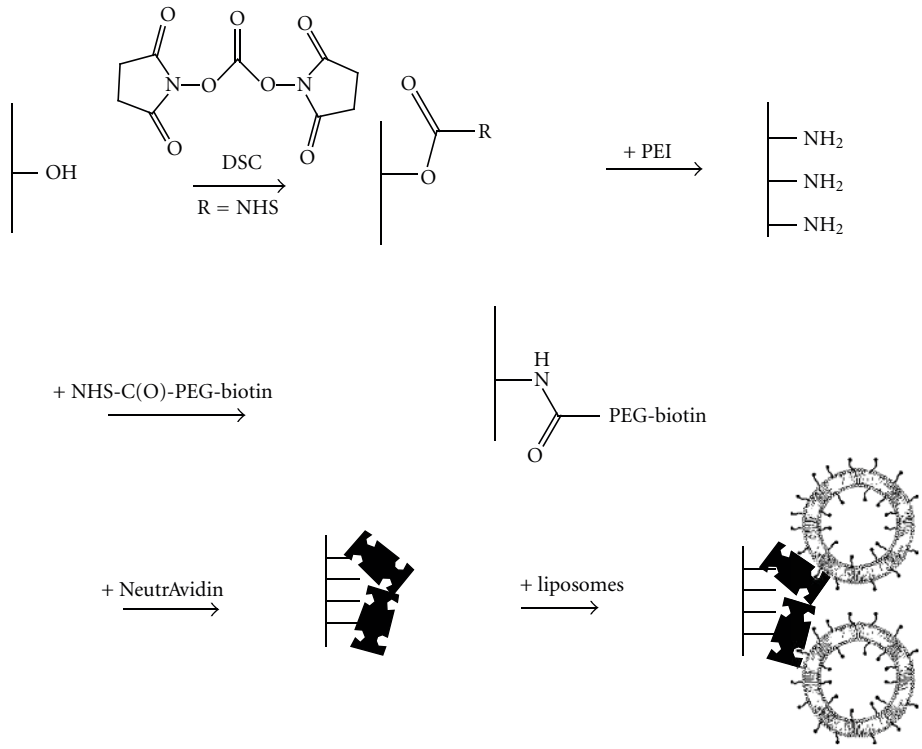

Figure 5: Chemical reactions leading to the attachment of liposomes onto the surfaces of soft contact lenses [32].

well as to release a therapeutic dosage of drug *in vitro* in a controlled fashion for 5 days with an even further extension in the presence of protein. It was also found that hydrogels of multiple complexation points with varying functionalities outperformed hydrogels formed with less diverse functional monomers, mechanical and optical properties of these hydrogels agreed with conventional lenses, and increased loading was reflected in a reduced propagation of polymer chains [49]. Ali and Byrne designed imprinted poly(vinyl alcohol)- (PVA-) based contact lenses containing multiple

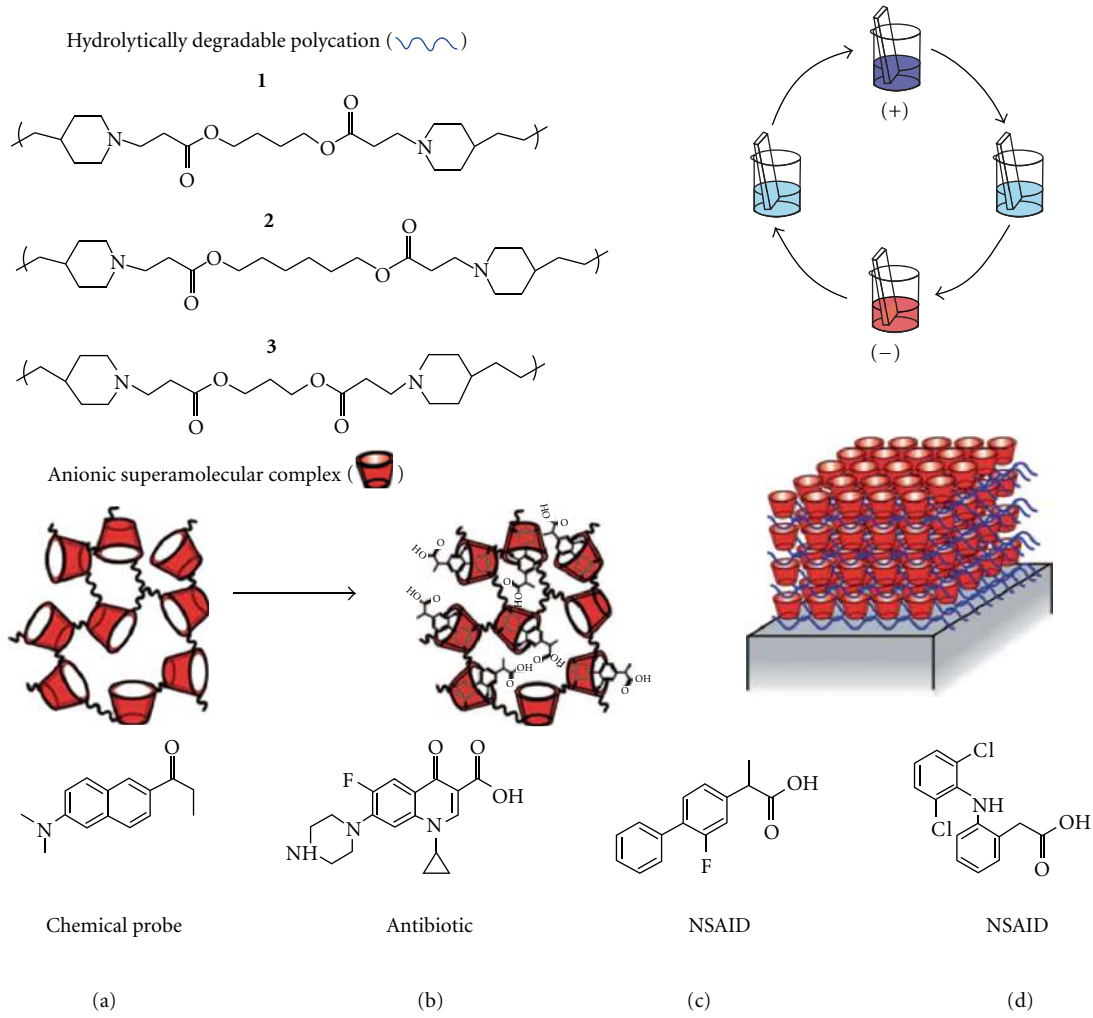

Figure 6: Methodology for LbL films. Left: film components. Three poly(β-amino esters) were investigated as degradable polycations. Poly(carboxymethyl-β-cyclodextrin) was used as the anionic supramolecular complex. Right: electrostatic assembly. Light blue: water. (+) indicates addition of polycation. (−) indicates addition of anionic supramolecular complex. Bottom shows molecules used in experimentation. NSAID: nonsteroidal anti-inflammatory drug [33].

functional monomers of AM, NVP, and 2-(diethylamino) ethyl methacrylate (DEAEM) for the therapeutic delivery of hyaluronic acid (HA) to the eye surface in desired release kinetics, to improve the wettability of lenses and to treat symptoms of dry eye [43].

More recently, Ribeiro et al. designed bioinspired imprinted hydrogels using HEMA as the backbone component. Zinc methacrylate, 1- or 4-vinylimidazole (1VI or 4VI), and N-hydroxyethyl acrylamide (HEAA) were combined to reproduce in the hydrogels the cone-shaped cavity of the CA, which contains a Zn^{2+} ion coordinated to three histidine residues. Consequently, biomimetic networks can load more drug and control better drug release than conventionally synthesized pHEMA hydrogels, being useful for the development of advanced controlled release systems. Nevertheless, aspects such as optical transparency, the effect of thickness on drug release length, and long-term durability of the biomimetic receptors require further studies to elucidate fully the practical potential of enzyme-mimicking networks [52].

6. Surface-Modified Hydrogels

Besides the efforts of modification during the hydrogel contact lenses fabrication to load drugs for ocular disorders' therapy, some efforts have been made to modify the surface of commercial contact lenses for the ophthalmic drug delivery. Danion et al. encapsulated drugs into liposomes and then subsequently bound these intact lipid vesicles onto both the anterior and posterior surfaces of commercial contact lenses. The process of immobilizing liposomes included three steps, as shown in Figure 5. In first step, polyethylenimine was grafted onto the surface of a commercial contact lens (Hioxifilcon B) via amidation under the catalyzation of disuccinimidyl carbonate (DSC). NHS-PEG-biotin molecules were following covalently bounded onto the surface by

carbodiimide chemistry. In the second step, NeutrAvidin was immobilized to the PEG-biotin layer via biotin-avidin affinity. Liposomes containing PEG-biotinylated lipids were then docked onto the surface-immobilized NeutrAvidin. In the third step, multilayers of liposomes were fabricated by consecutive addition of further NeutrAvidin and liposome layers or by exposing contact lenses coated with Neutr-Avidin to liposome aggregates produced by the addition of free biotin in solution. The results showed that the surface-immobilized, drug-filled liposome multilayers provide a promising avenue for site-specific delivery. However, no actual drug was investigated in this research [32].

Recently, layer-by-layer (LbL) platforms have been applied for drug delivery due to its simple, mild aqueous manufacturing conditions at room temperature [33, 55, 56]. Yet, LbL platforms cannot deliver small molecule drug with highly controlled release kinetics, and the release time scales delivered by LbL platforms is short. Some efforts have been made to modify the conventional LbL technique for small molecule drug delivery such as incorporating the cyclodextrin into LbL platform. Smith et al. designed layer-by-layer platforms to deliver small-molecule therapeutics from virtually any surface, regardless of geometry or surface chemistry, with programmable zero-order release kinetics through hydrolytic top-down degradation. Methodology for LbL films was shown in Figure 6 [33]. Poly(carboxymethyl-β-cyclodextrin) (polyCD) was complexed with a small molecule (Figures 6(a)–6(d)) as the anionic supramolecular complex. Poly(β-amino esters) (PBAEs) as the degradable polycations and the anionic supramolecular complex were alternately immobilized on the surface of the films via LbL technique. The drug of diclofenac or flurbiprofen in the LbL film could sustain release for 15 days in zero-order release kinetics [33].

7. Conclusions and Perspectives

It is estimated that nearly 100 million people wear contact lenses and the number is still increasing. Although contact lenses are designed to correct ametropia, they also show great perspective as therapeutic devices for delivery of ophthalmic drugs. An ideal contact lens-based ophthalmic drug delivery system would have the capacity of loading large amount of drugs and controlling the release in zero-order release profiles without influencing its own properties such as shape retaining, transparency stability, and oxygen permeability. The modification either during or after the manufacture of hydrogel contact lenses including the controlled hydrophilic/hydrophobic ratio, colloid-laden incorporation, ligand modification, MIPs, and multilayer technique broadens their applications in the field of ophthalmic drug delivery. According to the different properties of ophthalmic drugs, different measures must be made. For hydrophobic ophthalmic drugs, CD-containing hydrogels show potential application in therapeutic contact lenses, because hydrophobic internal cavities of CD can regulate hydrophobic drug release profiles though host-guest interaction. Imprinted hydrogels show great advantages to control hydrophilic drugs release and reload drugs. According to different usage of contact lenses such as daily disposable, monthly disposable, and yearly disposable, different hydrogel design must be made. For extended delivery of ophthalmic drugs, contact lens is often required prolonged use time. However, some ocular disorders are caused by contact lens wearing because of protein absorption or lacking biocompatibility surface. Therefore, some special hydrogel designs must be made to decrease the protein absorbing and increase biocompatibility of hydrogel. Moreover, *in vivo* studies are also needed for ocular therapeutic contact lenses application.

Acknowledgments

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