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Review

Contact lens as an emerging platform for ophthalmic drug delivery: A systematic review

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ABSTRACT

The number of people with eye diseases has increased with the use of electronics. However, the bioavailability of eye drops remains low owing to the presence of the ocular barrier and other reasons. Although many drug delivery systems have been developed to overcome these problems, they have certain limitations. In recent years, the development of contact lenses that can deliver drugs for long periods with high bioavailability and without affecting vision has increased the interest in using contact lenses for drug delivery. Hence, a review of the current state of research on drug delivery contact lenses has become crucial. This article reviews the key physical and chemical properties of drug-laden contact lenses, development and classification of contact lenses, and features of the commonly used materials. A review of the methods commonly used in current research to create contact lenses has also been presented. An overview on how drug-laden contact lenses can overcome the problems of high burst and short release duration has been discussed. Overall, the review focuses on drug delivery methods using smart contact lenses, and predicts the future direction of research on contact lenses.

1. Introduction

The eyes are windows to the soul and tools for communicating with the outside world; however, they are vulnerable to external diseases. The complex eye can be classified into two parts: the anterior segment, which extends from the cornea to the lens and includes the aqueous humor as well as ocular tissues such as the cornea, conjunctiva, iris, lens, and pupil, and the posterior vascular segment, which extends from the posterior aspect of the lens to the retina and encompasses the vitreous humor (Fig. 1). Both the anterior and posterior segments of the eye are vulnerable to various physical and pathological conditions [1]. Common anterior eye diseases include glaucoma, dry eye, cataracts, ocular infection, inflammation, ocular tumors, and ocular physical

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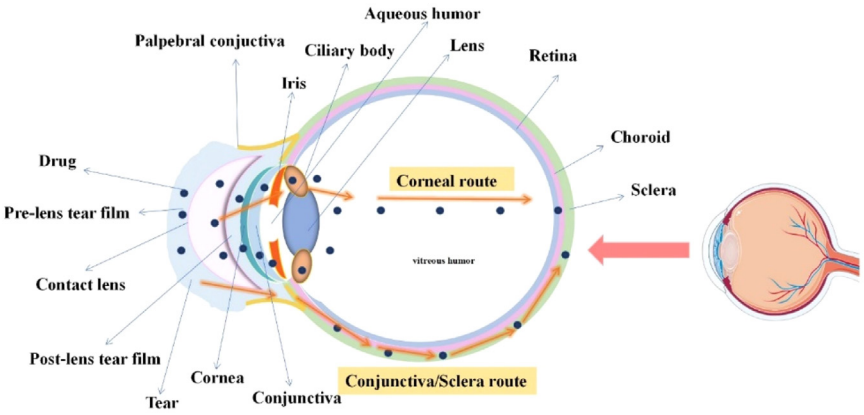

Fig. 1 – Structure of the eye and drug absorption pathways of drug-carrying contact lenses.

damage, while age-related macular degeneration, posterior uveitis retinitis, and diabetic retinopathy affect the posterior segment.

More than 2.2 billion people are affected by visual impairment and blindness; furthermore, more than one billion people with vision impairment can be treated and blindness can be avoided through medication and adoption of preventive measures. Owing to the increase in the use of electronic products and smartphones, as well as the increase in the proportion of the aged population, the global population affected by eye diseases is expected to increase significantly in the next few years. Certain eye diseases do not usually lead to direct visual impairment, but can cause trouble and pain because of the vulnerable nature of the eye. Importantly, these ocular conditions can lead to visual impairment if left untreated [2]. Currently, eye drops are the most commonly used form of ophthalmic drugs, which account for approximately 90% of therapy for common anterior segment diseases, such as bacterial and fungal infections, conjunctivitis, dry eye, and glaucoma. More than 3 million people in the USA are affected by glaucoma. Because of the low bioavailability of eye drops (1%–5%), users may require multiple daily instillations. For patients with glaucoma, long-term treatment reduces patient compliance, which is a key problem associated with the use of eye drops. In other words, most people do not use eye drops correctly, with incorrect instillations or missing of doses being common. A survey assessing patients with glaucoma found that nearly 90% patients failed to properly fill in the prescribed eye drops. This is a serious problem that can lead to suboptimal treatment in the first place, sometimes with serious side effects and even eye damage. In addition, while using eye drops, patients might find the application of the same dosage of each infusion, with similar force of each squeeze and angle of infusion, difficult, which affects the treatment efficacy. Furthermore, preservatives in eye drops can affect the eyes [3–6]. Occasionally, researchers use high biological concentrations of drugs to solve the problem of low bioavailability and insufficient drug content in the lesion tissue, which may damage the eyes. Therefore, improving the bioavailability of eye drops for the treatment of eye diseases is critical. However, owing to the special structure of the eye, drugs cannot reach the lesion site easily. To solve this problem, researchers have developed gel eye drops, prodrugs, ocular micelles, implants, punctual plugs, and penetration enhancer iontophoresis microneedles, although all have certain limitations. For example, 22%–25% patients who receive intravitreal injections do not revisit on time because of the fear and side effects of vitreous implants. The vitreous implants cannot be removed from the eye in a timely manner when drug-related side effects occur, which is a major drawback. Therefore, an ideal ocular delivery system is required. Recently, contact lenses have attracted the attention of researchers as ocular drug delivery systems because they can significantly improve the bioavailability of ocular drugs without affecting vision [7]. The number of people wearing contact lenses is more than 39 million in the USA and 15 million in Japan, indicating that the global market for contact lenses is large and will continue to expand in future. Many types of contact lenses will be available in the market in future, different aspects of which are worth studying.

2. Eye barriers

The eyes have barriers that protect them from external factors; however, they also pose a challenge to drug delivery. The ocular surface barriers mainly include the tear barrier, corneal barrier, conjunctiva, and sclera. The main ocular barriers that affect drug absorption are described below.

2.1. *Corneal surface area and tear film barrier*

The ocular surface can only hold a volume of 30 μl, which is the first barrier to drug delivery. Because of the restricted precorneal surface area, when eye drops enter the ocular surface, the eye will be stimulated to blink, and most eye drops will be eliminated via tears. The tear film is a thin, transparent fluid layer consisting of three phases: an oil phase, an intermediate aqueous phase, and an inner mucin layer. The oil and aqueous phases represent barriers to hydrophilic and hydrophobic drugs, respectively, indicating that improvement of drug absorption and bioavailability by merely altering the hydrophilic and hydrophobic properties of the drug is

difficult. The aqueous phase consists of proteins and enzymes that can immobilize and degrade drugs. The inner layer of tears is composed of mucins, which protect the eye surface from harmful external stimuli and pathogen invasions. They are negatively charged highly glycosylated macromolecules secreted by corneal epithelial cells that attract or repel drugs via electrostatic interactions depending on the charge of the drug molecule or carrier system [8]. When eye drops enter the ocular surface, the secretion of tears and rapid turnover of the eyeball dilute the drug and drain the drug into the nasolacrimal duct, which reduces the retention time of the drug in the eye. In addition, the tear film is a significant barrier to ocular drug delivery because the proteins and mucins in tears bind to drug molecules and reduce free drug concentrations. A drug or dosage form that is retained on or penetrates the surface of the eye first passes through the tear film, which requires it to be isotonic, non-irritating, nontoxic, of normal pH, and capable of spreading properly throughout the tear film.

2.2. *Corneal barrier*

The cornea is an essential barrier limiting the entry of topical medications into the eye. It is a clear crystal-like tissue responsible for two-thirds of the eye's refractive power and is located in front of the iris and pupil. Physiologically, the cornea can be classified into five layers: epithelium, Bowman's layer, stroma, Dermany's membrane, and endothelial cells. The epithelial surface cells, wing, 5–6 cladding layer tightly coupled with columnar cells, half desmosomes, and desmosomes provide most of the hydrophilic drug barrier, and the microvilli on the surface provide surface area for drug absorption [9]. The corneal epithelium impedes the penetration of hydrophilic drug molecules. However, the hydrophilic matrix layer hinders the diffusion of lipophilic molecules. Hydrophobic drug molecules are mainly absorbed via transcellular pathways. The presence of intraepithelial drug efflux pumps and cytochrome P450 is another reason for poor drug bioavailability. Nevertheless, unlike epithelial cells, stromal cells are highly hydrophilic because of their high water content, which can exceed 80%, limiting the penetration of hydrophobic drugs. Finally, the endothelium is also known to act as a hydrophobic barrier owing to the presence of tight junctions; nevertheless, owing to its lower cell thickness, the endothelium represents a weak permeability barrier for epithelial cells. Molecules weighing ≥500 Da can pass through the cornea [10].

2.3. *Conjunctiva and sclera*

The conjunctiva is a fibrous, vascular, and transparent part that accounts for almost one-third of the eyeball. The bulbar region covers the inner layer of the eyelid, which, in turn, covers the exposed part of the eyeball. Its surface area is 16 times that of the cornea, and it has a relatively leaky epithelium owing to the lack of tight junctions [10]. The conjunctiva contributes to the absorption of larger hydrophilic drugs such as siRNAs and peptides. However, its vascular nature may hinder drug clearance. The conjunctiva and sclera surrounding the cornea are low-permeability barriers that limit drug entry into the anterior chamber, but are less resistant than the corneal tissue. The conjunctiva is permeable to molecules in the size range of 5,000−10,000 Da, while the sclera allows the passage of molecules with minimum molecular weight of 500 Da.

Because of these barriers, enhancement of drug permeability simply by changing the nature of the drug is difficult. It is now generally accepted that enhancement of the retention time of drugs on the ocular surface can circumvent the low bioavailability of drugs in the eye, and that contact lenses have better compliance than other agents in enhancing retention time in the eye without affecting vision. The release time of a drug-loaded contact lens is long and can be controlled to be less than a day to a few days. The use of therapeutic contact lenses allows reduction in the total drug dose, frequency of administration, and systemic drug absorption; furthermore, corneal contact lenses can be removed when treatment has to be discontinued and the lenses are well tolerated. These features have attracted the attention of scientists.

3. Contact lens ocular drug delivery system

3.1. *Topical administration*

Similar to that observed in other diseases, treatment of eye diseases by systemic administration of drugs is challenging, because the blood-eye barrier prevents drugs from entering the blood. The blood-eye barrier, which plays an important role in protecting the eyes, is composed of blood-water and blood-retinal barriers. Therefore, systemic administration is not observed in all patients. Topical administration is convenient, noninvasive, and can be administered by self, because of which it is attracting attention. The topically administered drug can be transported by the corneal route (cornea → aqueous humor→ iris and ciliary body→ lens→ posterior segment) or the conjunctiva-scleral route (conjunctiva→ sclera→ choroid or retinal pigment epithelium) or via the conjunctival systemic circulation [11]. Generally, most eye drops are used to treat anterior eye diseases via the corneal route, whereas only few are used to treat posterior segment eye diseases via the conjunctivoscleral route. However, owing to the presence of the ocular barrier, the bioavailability of topical drugs is less than 5%, which considerably limits their application.

3.2. *Mechanism underlying contact lens delivery and its key requirements*

Many studies have shown that drug-laden contact lenses improve bioavailability, mainly because they improve the retention time of drugs in the eye. The tear film is divided by the contact lens into two parts: a part near the air, called the pre-lens tear film (PLTF), and a part near the cornea, called the post-lens tear film (POLTF) [12]. When the drug-carrying contact lens releases the drug, the latter diffuses into the PLTF and POLTF (Fig. 1). The drug diffusing into the PLTF is mainly absorbed via the conjunctival route, whereas the drug diffusing into the POLTF is mainly absorbed via the

corneal route. The difficulty in predicting bioavailability is primarily due to the inability to determine the amount of drug diffusing into each of the two tear membranes. Researchers have predicted the bioavailability of contact lenses under ideal conditions, and predictions have shown that corneal bioavailability can exceed 50%. Currently, drug absorption via the corneal pathway alone is achieved by fixing the drug to the inner surface of the contact lens using electrohydrodynamic atomization technology. The idea is to fix the drug on the outer surface of the contact lens such that the drug is absorbed only via the conjunctival route, thereby enabling the treatment of posterior eye diseases, although the PLTF is disrupted by behaviors such as blinking. Further research in this area is warranted. Thus, contact lenses are mainly used to treat diseases in the front of the eye [13].

As a delivery carrier, contact lenses must meet certain conditions, such as biocompatibility, and comfort and safety of the user. The drug release time of the loaded contact lenses should not be few hours, as it will result in multiple contact lens changes per day and increase the treatment cost. As the use of eye drops is associated with a rapid rise in drug concentration after treatment, followed by a rapid fall in concentration, contact lenses should allow for zero-order release or controlled release of the drug. Contact lenses should also be specific for different diseases, and the release time should vary from one day to several weeks. Achieving this is extremely difficult and needs to be investigated extensively. Currently, drug-containing contact lenses are used by patients for treating eye diseases. Researchers have surveyed the perception of healthcare professionals regarding the use of contact lenses as drug delivery tools and whether they can be prescribed to treat ocular conditions. The results indicated that more than 60% of the individuals accepted contact lenses as a delivery modality. They were attracted to the fact that contact lenses can reduce the frequency of drug administration, and acceptance of their use was higher among those aged 30–49 years. The spatial structure of the contact lens surface affects drug loading and release processes. In particular, contact lenses formed by different polymers may or may not contain pores on their surfaces. In addition, a study found that pores of different lengths, widths, and depths affect the saturation drug concentration in traditional immersion loading; the difference in drug concentration is the driving force behind drug release in immersion contact lenses; hence, the spatial structure of the contact lens surface will also affect the drug loading and release processes. This indicates that the spatial structure of the contact lens surface is a major area of future research on drug-loaded contact lenses and is worth investigating [14].

3.3. *Evaluating drug release from drug-loaded contact lenses*

The release mechanism of drug-loaded contact lenses is described in Section 3.2. Owing to the special structure and unique clearance mechanism of the eye, a drug that is released rapidly will exert toxic side effects, while that which is released too slowly will not play any therapeutic role, both of which will hinder its therapeutic efficacy. Therefore, evaluation of drug release from drug-loaded contact lenses is important and a correct model of release kinetics should be established. For the *in vitro* release of the drug-loaded contact lenses, we simulated the *in vivo* conditions as much as possible. The most commonly used method is the traditional sink method, in which the drug-loaded contact lens is immersed in the dissolution medium and sampling is performed at a specific time. The commonly used dissolution media include artificial tears, phosphate buffered saline (PBS), and 0.9% NaCl solution. Considering their similarity to tears, artificial tears are the most suitable dissolution media. The volume of the dissolution medium, drug solubility, and mixing rate affect drug release from drug-loaded contact lenses. The classical modeling methods commonly used in research include the following. In the first method, the supplying and receiving cells of the vertical diffusion cell are separated by a dialysis membrane; the drug-carrying contact lens is placed on the dialysis membrane near one end of the supplying cell, and a certain amount of artificial tears is placed on the supplying and receiving cell and stirred at a certain rate. A specific volume of the dissolution medium is removed from the receiving cells at regular intervals for analysis. In the second, more classical method, glass bottles containing 2 ml artificial tears are placed in an incubator at 34 °C and 100 rpm for periodic sampling, while artificial tears are replaced with the same volume of fresh artificial tears to prevent drug saturation. The previous section describes the modeling and analysis of drug-loaded contact lenses *in vitro*. However, owing to the differences in the results of *in vivo* and *in vitro* experiments, the good results of *in vitro* experiments cannot be reproduced *in vivo*. Therefore, modeling and analysis should be conducted *in vivo*. The tears were analyzed and pharmacokinetic parameters, including peak concentration, mean residence time, and area under the concentration-time curve (AUC), were calculated. The release properties of the drug-loaded contact lenses were evaluated based on the above parameters.

4. Contact lens characterization

Owing to their importance in determining drug loading and release, the key properties of contact lenses have to be characterized in detail. The physical and chemical characteristics of the contact lens are illustrated below (Fig. 4).

4.1. *Chemical characterization*

4.1.1. *Optical transparency*

Optical transparency is one of the most important factors that affect contact lenses. This spectral transmission characteristic is particularly important for optical performance and is usually represented as the transmittance of the visible electromagnetic spectrum. Studies have shown that hydrogel as a contact lens material must allow passage of >90% of the visible light spectrum. Owing to the importance of this property, nearly all research on drug delivery by contact lenses includes this parameter. At present, an ultraviolet spectrophotometer is typically used to measure optical transmittance. The main method involved soaking of the prepared contact lens in artificial tears for complete

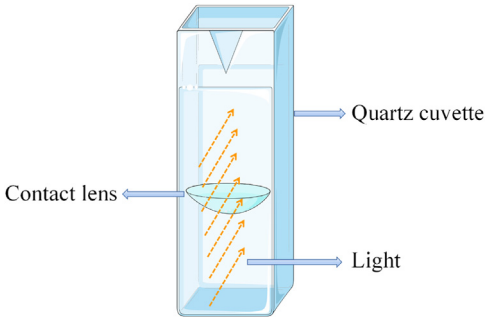

Fig. 2 – Schematic diagram of measuring optical transmittance of the contact lens by ultraviolet spectrophotometer.

hydration, followed by removal of the lens, pasting it on the inner surface of the quartz colorimetric dish, and placing in an ultraviolet spectrophotometer at 400–800 nm to calculate the optical transmittance (Fig. 2).

As the addition of drugs cannot significantly affect the optical permeability of contact lenses, many technologies have been utilized for drug delivery using contact lenses, such as molecular imprinting, and the use of nanoparticles, micelles, and liposomes, and the results have been satisfactory. During the process of adding nanoparticles to contact lenses, the influence of micelles on the optical transparency of contact lenses is lesser than those of other nanoparticle systems owing to their smaller particle size [13]. However, the presence of micelles affects the optical transmittance of contact lenses [15]. Compared to other methods, molecular imprinting technology affects optical transmittance negligibly [16,17]; therefore, it is a desirable ocular drug delivery system. Special attention should be paid to the obvious drug delivery effect of multi-layer contact lenses; however, their influence on the optical transparency of contact lenses is large. To resolve this problem, the drug-loaded film is changed into a ring, which improves optical transparency [18,19]; this will be explained in detail in subsequent sections. Surprisingly, a contact lens designed by Seggio for the treatment of microbial infections achieved 100 an optical transparency, which may provide new options for addressing ocular infections [20]. Drug inclusion delivery has lesser impact on the optical transparency of the contact lens than single soaking in the composite delivery system, as the drug is in the form of molecules in the former method compared to that in nanoparticle drug soaking method. The optical transparency of the contact lens is reduced to less than 90% only under very special circumstances; for example, patients with cystinosis are extremely afraid of light and usually wear sunglasses. Dixon et al. [21] designed a carbon black contact lens with an optical transparency of only 50%. This situation is uncommon, and conventional contact lenses require higher optical transparency.

4.1.2. *Equilibrium water content (EWC)*

The capacity of hydrogels or silicone hydrogels to bind water at equilibrium is called EWC. The ISO 18,369–4:2017 standard defines it as the mass fraction present in a hydrated material that is perfectly equilibrated at room temperature [22]. This figure represents the comfort level of the contact lens and correlates highly with its degree of dehydration. Dehydration of the contact lens affects lens parameters such as diameter, sagittal depth, basal curve, and oxygen and ion permeabilities. Dehydration and dehydration equilibration time are affected by many factors, including the maximum water content of the polymer, lens thickness, temperature, relative humidity, and the volume and tension of the tears of the wearer. Conventional nonsilicone polymers require approximately 38% EWC to maintain eye movement. Reports show that only silicone hydrogel lenses produced under specific conditions exhibit satisfactory oculomotor and ocular surface performance when worn at night, although their EWC is low (from 24% to 38%) [23].

The weight measurement method is the standard method used for measuring the moisture content of test samples, and it involves the use of an oven for determining drying losses. The weight loss was determined from the difference in the weight of the dry lens after removal from the mold and that of the lens after hydration in the required aqueous solution for a specified duration. This is the most popular method for determining the EWC when contact lenses are used for ocular administration. Another way of measuring this property involves the use of a refractometer. The refractive index (RI) and EWC of the polymer show negative correlation. This relationship has also been used in some studies [24]. However, the EWC value obtained using the manual refractive method was relatively high, and that obtained using the automatic photometric method was relatively accurate. This deviation was associated with the percentage of the silicone fraction in the material [24]. The EWC of contact lenses is essential for the comfort of the wearer. Studies have shown that hydrogels with high EWC and low dehydration rates may be used for treating dry eye. At present, silicone hydrogels show excellent water-locking and anti-dehydration abilities, and the addition of 1,2-dimyristoyl-sn–glycero-3-phosphocholine (DMPC) may help maintain the water content in lenses. However, studies assessing the effect of change in the water content of silicone hydrogel lenses alone on comfort level are lacking. This is because changes in water content alone may be difficult to achieve, as variations in water content during the lens manufacturing process may influence the expansion coefficient and change the lens thickness distribution. Therefore, the modulus of the lens might change inadvertently. This aspect may be investigated in the future.

4.1.3. *RI*

In addition to optical transparency, the hydrogel material used for manufacturing contact lenses must provide an RI of approximately 1.37, which is similar to that of the cornea. ISO 18369–1:2017 [25] states that RI is “the ratio of the speed of light in vacuum to the speed of the same light in a material”. The relationship between RI and EWC was illustrated in the previous section, and materials with high RI can reduce the lens thickness to improve wearing comfort [26]. Varikooty et al. [26] determined RI reference values for commercial and silicone hydrogels, which were found to be between 1.40 to 1.43. According to ISO 18369–4:2017 [27], the RI of a contact lens material should be evaluated at 589 nm (sodium D line) or 546.1 nm (mercury E line). The Abbe refractometer is a

comparatively common tool used for measuring the phase RI of materials, including contact lenses. The principle of operating this refractometer is as follows: the lens is trapped between two prisms and illuminated with a monochromatic light source. The incident light is refracted at the lens material or prism interface to determine the critical divergence angle. Based on the RI of the prism and measured angle, the RI of the lens is calculated using Snell's law [28]. Presently, R-1270 is widely used in the measurement of RI; however, the measurement of RI is related to the measurement of the refractive power of a lens soaked in a solution using a wavefront sensor. Even small errors in the solution or material RI can result in significant errors in the converted air power.

4.1.4. *Oxygen transmittance*

The oxygen transmittance of the contact lens significantly impacts the health of the human eye. Oxygen is supplied primarily through contact with air; therefore, oxygen delivery and active carbon dioxide removal must occur through the contact lens to ensure gas circulation [29]. In addition, to maintain the integrity of the cornea and provide adequate anti-infection ability, contact lens materials usually have a certain degree of Dk owing to their high-water content, which is a critical factor in controlling the clinical success of such materials. As described in ISO 18369–1:2017, Dk is defined as "oxygen flux", which is unit pressure diffusion through a unit thickness of contact lens material under specified conditions [25]. "D" is the diffusion coefficient of the material and "k" is the solubility coefficient. As defined by Lebow and Campbell-Burns, Dk is an inherent physical feature of a material that indicates the rate at which oxygen passes through the material. The Dk value of a material depends directly on its water content [30]. Although the oxygen content of contact lenses correlates with their water content, it cannot be increased simply by increasing the water content, as it may interfere with the mechanical hardness and formability of the contact lens.

According to ISO 18369–4:2017 [27], the polarimetric and Coulomb methods are the two primary methods used for estimating Dk values. The acceptable values for the oxygen transmittance of the contact lens are approximately 25 Dk units with the eyes open and 75–200 Dk units with the eyes closed, although the results may differ slightly with the measurement method. However, these are the general criteria to be followed for preventing corneal edema while providing adequate oxygen to the cornea. According to Holden and Mertz, daily contact lens wear should not cause corneal swelling or lens discomfort. Therefore, to diminish the influence of the contact lens on the cornea, the oxygen transport rate of the contact lens should be $(24.1 \pm 2.7) \times 10^{-9}$ units [30]. However, to avoid corneal hypoxia, the oxygen permeability should not be lower than the 87 barriers for long-term contact lenses. Achieving Dk at this level using traditional hydrophilic contact lenses is difficult [29]. Currently, significant efforts have been made to ensure oxygen permeability, and the use of silicone hydrogels is a relatively advanced method. Tran et al. [31] proposed a new method for increasing the oxygen permeability of hydrogels. By adding silica sol, this method has been proven to enhance the oxygen permeability of contact lenses without affecting hydropathy.

4.1.5. *Ionic permeability*

Adequate lens motion can be maintained only when the ionic permeability is minimum. Ion permeation in polymeric membranes involves the dissociation of ions from salts. It involves the movement of anions and cations into the aqueous medium and the diffusion of ions in the enclosed water within the polymer matrix [32]. This property is critical, because it permits the tear film of the posterior lens to change between blinks and removes metabolic waste, thereby reducing the possibility of binding of the elastic contact lenses to the cornea. Ionic permeability is an important parameter of contact lenses that is directly related to comfort and has been cited in some studies on drug-loaded contact lenses; however, currently, ISO standards for measuring the ionic permeability of contact lenses and tolerance for this property are lacking. The transport of oxygen, NaCl, and water by conventional hydrogel and silicone contact lenses was investigated, and the effects of the water content and chemical structure of the polymers on the apparent permeability and water flux of the salts were analyzed. The results showed that ionic permeability increases with water content. Significant changes in ionic permeability were not observed with increasing water content, suggesting that this may be related to the chemical structure of the polymer. The ionic properties of the lens materials improve the permeability, diffusivity, and flux of soft contact lenses to salts and water [23]. Low ionic permeability is also a major problem of Vitamin E (VE)-modified contact lenses, which limits the use of VE for prolonging drug release, as explained in detail in the following sections.

4.1.6. *Glass transition temperature (Tg)*

Glass transition, an inherent property of amorphous polymer materials, is the macroscopic embodiment of the transformation in polymer motion, which directly affects the performance of materials. It is a phenomenon related to molecular motion, which is closely related to molecular structure; therefore, the flexibility of the molecular chain, intermolecular force, copolymerization, blending, and plasticization are important internal factors affecting the Tg of high molecular weight polymers. We believe that the addition of drugs or other substances will not alter the above parameters [29]. Indeed, numerous studies have shown that drug delivery materials and methods do not influence Tg. For instance, the variation in Tg after the addition of β-cyclodextrin (CD) was not obvious, indicating that the addition of β-CD negligibly affected the cross-linking degree of the hydrogel or the stiffness of the network [33]. Xiang et al. [34] did not observe any changes in Tg due to the introduction of drugs when contact lenses were used to deliver indomethacin. However, the Tg of the hydrogel increased with the dosage and concentration of the cross-linker.

4.2. *Physical characterization*

4.2.1. *Wettability*

The most common method of measuring the wettability of a solid surface involves the determination of contact angle (CA). Indeed, the performance of the contact lens *in vivo* can

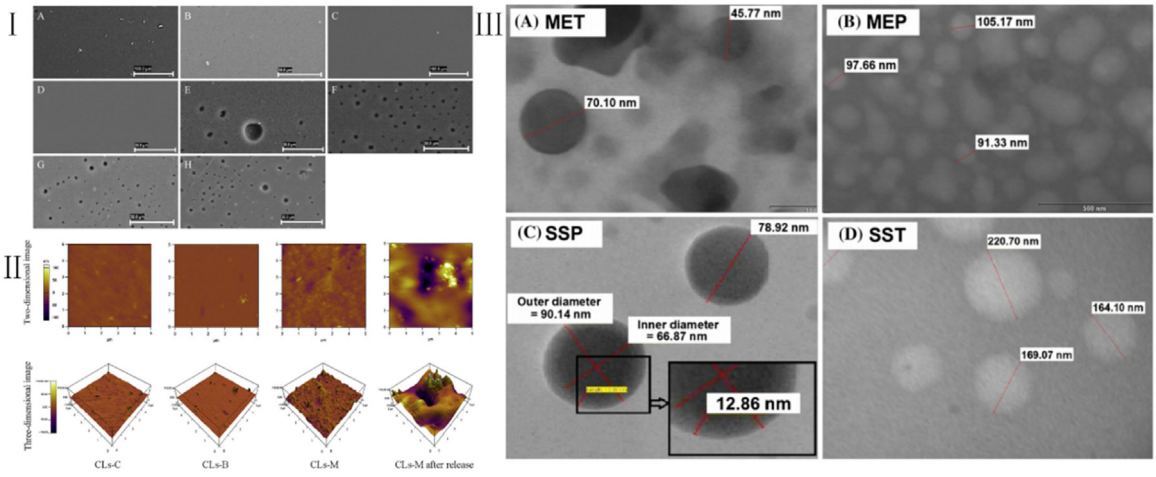

Fig. 3 – (I) SEM was used to observe the surface changes of the monomer mixture when different proportions of water were incorporated [39]. (II) AFM was used to analyze the surface roughness of blank contact lenses, mice-loaded contact lenses, and released contact lenses [13]. (III) TEM is used to measure different nanoparticles to determine their suitability for binding to the contact lens [40].

be predicted by assessing its CA. CA was calculated using Young's formula; the lower the CA, the better the wetting ability of the material to the matrix, and the higher the stability of the tear film covering the lens surface. As stated in ISO 18369–1:2017, CA is created by the intersection of a tangent line at the solid-liquid-air interface formed between the corneal contact lens material and known liquid and air media under certain circumstances. The wettability of contact lenses can be determined using several methods, including those requiring sessile drops, bubble trapping, and Wilhelmy plates. As mentioned by Lin et al. [35], wettability refers to the phenomenon in which adhesive forces are formed between a solid and a liquid when the liquid covers the solid surface. This can also be described as the ability of a solid to diffuse a liquid while maintaining a stable liquid film. Many methods have been proposed to enhance the wetness of contact lenses, which can be achieved by adding surfactants to the blister mask, using an internal wetting agent or a care solution, or performing surface treatment. Among these, the effect of micelles on contact lenses was the most obvious. Polymeric micelles can self-assemble from a hydrophobic core and hydrophilic shell [36] because of the hydrophilic structure on their surfaces and higher hydrogel compatibility of the contact lens material [13]. To overcome this problem, Rickert et al. [37] established a covalent surface coating of mucin macromolecules using pure silicone contact lenses, which showed better wettability.

4.2.2. *Morphology*

Reports show that approximately 50% of the contact lens users worldwide will feel uncomfortable at some point, which correlates with the nature of the contact lens used; however, the main reason is related to the surface morphology of the contact lenses [38]. In other words, comfortable contact lenses must have good surface properties, and the size and smoothness of the surface influence the wearing effect. The morphology and surface roughness of drug-loaded contact lenses have been studied using scanning electron microscopy (SEM), atomic force microscopy (AFM), or transmission electron microscopy (TEM) (Fig. 3). These three approaches have also been used to study the combination of nanoparticles and contact lenses. However, according to the ISO standards, lenses can also be studied using edge contours and comparators. However, reports on this are limited.

4.2.3. *Tensile strength*

Special attention is paid to the tensile strength of contact lenses during lens designing and quality control assessments. Stress can be generated on the lens material for several reasons such as repeated application, lens removal, and eye movement. This may affect clinical manifestations such as eye movement, wettability, and fit, and therefore, client comfort, and may lead to the development of eye lesions. The modulus is a commonly used parameter to represent the mechanical properties of contact lenses, as it reflects the elasticity of the material. Megapascals is the SI unit for this property, also known as the tensile strength. A representative tensile strength test should produce three results: the tensile modulus (Young's modulus), tensile strength, and elongation at break. However, standard lens material and ISO standard are not available; therefore, the validity and accuracy of such measurements are difficult to achieve. Lee et al. [41] added neodymium oxide nanoparticles to a hydrogel lens to improve its tensile strength. Methacrylic acid was used to ensure that the other properties of the lens were optimized and met the standards for contact lenses. Safety assessment is required for improving the tensile strength of lenses using the above method.

4.2.4. *Tribological properties*

Studies have shown that discomfort due to wearing of contact lens is related to various factors, including drying, protein adsorption, physiological factors, and friction generated during blinking. Contact lenses are inserted between the

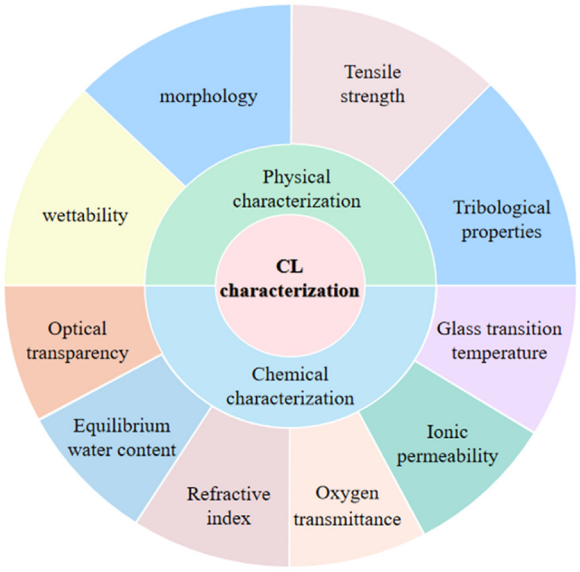

Fig. 4 – Categories of contact lenses and related representations.

cornea and eyelid, resulting in disruption of the natural function of the tear film. This causes changes in tear exchange rates, and the stability and activity of lipids and proteins in the lubricant in contact with the lens surface. To understand the tribological behavior of the material, we determined its CoF, which is the ratio of the frictional and normal forces between two surfaces. The CoF correlates with the *in vivo* comfort of the contact lens; therefore, the comfort of the lens can be predicted based on *in vitro* tribological data. The CoF of the lens is crucial for the development and screening of new lens materials. Su et al. [42] found that normal concentrations of albumin exerted a lubricating effect on silicone hydrogel contact lenses, regardless of concentration. However, ISO standards for measuring the tribological properties of contact lenses are lacking.

5. Contact lens material and preparation methods

5.1. *Contact lens material*

The choice of the material for manufacturing contact lenses depends on the needs of the users, which includes the length of wear, comfort, durability, practical operation, and visual stability. The premise of making custom-made contact lenses has guided material scientists since the 1930s, when glass lenses were in use, and in the 1940s, which saw the use of polymethyl methacrylate (PMMA). Hydrogel lenses were developed in the 1960s and 1970s, and silicone hydrogels have proven to be the most important contact lens material. Contact lenses are mainly divided into two types: rigid and soft. The former is a hard and permeable lens, whereas the latter is made of a soft and high-water-content material.

5.1.1. *Rigid contact lens materials*

Contact lenses were originally made in the shape of glass lenses to address astigmatism and corneal irregularities, including anterior astigmatism, posterior astigmatism, and double astigmatism; however, they were soon replaced by PMMA, which was obtained via MMA polymerization. PMMA is an optically transparent polymer with restricted hydrophilicity. However, the lack of mobility of polymer chains prevents the flow of oxygen or inner water, thereby preventing the movement of oxygen. The oxygen permeability of PMMA is negligible, which may cause eye health problems such as hypoxia, astigmatism, ptosis, and degradation due to radiation [43]. Research has indicated that the long-term use of PMMA contact lenses can lead to increase in the incidence of keratitis in most cases and a significant decrease in corneal function in some cases, because of which its use declined rapidly. Modern rigid gas-permeable lenses rarely use PMMA. The Food and Drug Administration (FDA) approved the use of cellulose acetate butyrate (CAB) in 1978 as an alternative to PMMA. The comfort of CAB contact lenses is intermediate, between those of soft and rigid contact lenses. A clinical study involving 100 patients showed that the success rate of wearing gas-permeable contact lenses was 79%. A good ocular physiological response was observed with minimal corneal edema, corneal staining, and specular blurring, and no increase in follicular hypertrophy. Compared with soft lenses, CAB lenses are highly transparent to O_2 and CO_2 and are less likely to cause edema, and are more versatile and wetter than rigid lenses [44]. Nevertheless, the use of CAB as a contact lens material was discontinued, as the rigidity of the contact lenses was significantly lower than that of PMMA [45]. Researchers combined a methacrylate skeleton with a siloxane group to produce a new generation of contact lenses with high stiffness and air permeability. Surface wetting is a common problem of siloxy methacrylate (SAM) lenses owing to the high lipophilicity of SAM, which leads to surface scratching and subsequent lipid surface deposition. Fluoro-siloxy methacrylates (FSA) was prepared by adding fluorine to SAM to enhance the wettability and comfort of the contact lenses [45]. The proportion of PMMA in the formula of modern rigid contact lenses has been reduced considerably in an attempt to solve the problem of insufficient oxygen transmittance, which affects their use. However, with the development of hydrogel technology, the use of rigid contact lenses has been partially abandoned. In some cases, this has had significant repercussions. For example, modern rigid gas-permeable lenses of large diameter and unknown compositions have been found to enhance the postoperative treatment of patients who have undergone laser-assisted *in situ* keratotomy. The success of modern rigid gas-permeable lenses is attributed to their rigidity, which can reshape the cornea, whereas soft contact lenses cannot be used for such treatments because of their high plasticity.

5.1.2. *Soft contact lens materials*

Owing to the boom in hydrogel technology, the interest in soft contact lenses has increased. Hydrogels are usually defined as extensively swollen polymer networks in water [46]. They can integrate active ingredients into their networks because of their high porosities and surface areas. The soft contact lens was 2 – 3 mm larger than the cornea and had a diameter of 14.5 mm. They were manufactured entirely in the shape of the cornea. Soft lens materials include

hydrogels and silicone hydrogels, both of which have higher oxygen permeability than rigid contact lenses [47]. The drug embedded in a therapeutic hydrogel is released into tears to reach the target tissue. In addition, they are comfortable, have good biocompatibility, and have been proven to be safe and reliable. 2-Hydroxyethyl methacrylate (HEMA) is one of the most important contact lens hydrogel materials in use. Depending on the copolymer, HEMA and correlative hydrogels can act as polymers with high water content and oxygen permeability; the water content of these hydrogels can range from 20% to 80%, with hydrogels consisting of HEMA alone containing approximately 38% water. The oxygen permeability is primarily due to the high water content, and HEMA-derived hydrogels dissolved in water account for approximately 22% of the commercial contact lens market. N-vinyl pyrrolidone (NVP) and methacrylate (MAA) enhance the water content of the hydrogel owing to the strong hydrophilicity produced by the amines, carboxylic acids, and hydroxyl groups. Nevertheless, NVP can also increase the relative evaporation rate of water, which leads to the development of a harsh surface on soft contact lenses. This is not conducive for wearing of soft contact lenses. The copolymerization of the highly negatively charged anionic MAA monomers can enhance the feeding of cationic drugs via the ion-ligand mechanism. Nevertheless, the carboxyl group of MAA attracts positively charged proteins such as lysozyme, resulting in protein stacking on both surfaces of the lens. Polyvinyl alcohol (PVA) is a synthetic polymer with good biocompatibility and oxygen permeability owing to the presence of multiple hydroxyl groups. Furthermore, its properties are better than those of other hydrogels such as HEMA; it has low protein adsorption rate because of the presence of functional groups and can also be cross-linked. PVA hydrogels have even been applied in the field of corneal replacement. The modification techniques and materials for producing PVA hydrogels are increasing. The secondary alcohol groups in the polymer chains can be easily modified by grafting, such as the inclusion of cellulose or β-CD.

With the development of materials technology, significant breakthroughs in contact lens research may occur in the future. The development of silicone technology has significantly promoted the development of contact lenses that are comfortable to wear owing to the presence of silicone oxygen bonds and higher oxygen permeability. Silicone hydrogel contact lenses are primarily composed of silica-based materials, including PDMS, TPVC, TRIS, and other siloxane macromolecules, and hydrophilic monomers, such as HEMA, DMA, and NVP [48], which have become the first choice in the contact lens industry because of their good wearability. Grafting technology has been developed to prevent biological contamination [49]. In the future, the development of various grafting technologies will consolidate the dominant position of silicone hydrogels in the contact lens industry [50]. The materials used in modern contact lenses are combinations of the above-mentioned materials, which combine the advantages of different materials to produce contact mirrors with better performance. However, the amount of cross-linking agent used should be controlled; this is because when the amount of the cross-linking agent, EGDMA, exceeded 2% (v/v), the light transmission of the contact lens obtained after photopolymerization decreased due to the high cross-linking density (Fig. 5).

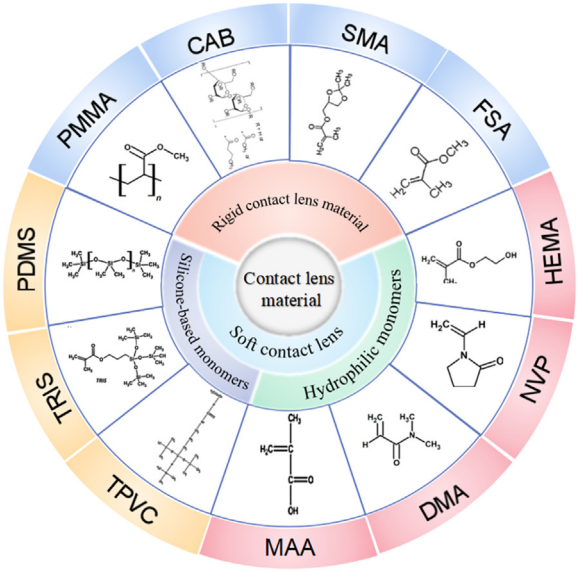

Fig. 5 – Contact lens classification and corresponding contact lens materials.

5.2. *Preparation methods and mechanism of action of contact lenses*

5.2.1. *Laboratory preparation of contact lenses*

Currently, the manufacturing methods for contact lenses in the industry are mainly divided into lathe turning, spin coating, and injection molding. However, this article mainly discusses the fabrication methods used in the laboratory. In laboratory research, owing to the lack of manufacturing facilities and tools, simple methods have been developed to accomplish the experimental purpose of generating drug-loaded contact lenses. Injection molding is widely used in the laboratory preparation of drug-loaded lenticules because of its simplicity of requirements. The mold consisted of two glass plates, and a silicone frame was used to control the contact lens thickness. A dichloromethylsilane layer was applied to the inside of the two glass plates to avoid adhesion of the polymer to the glass after polymerization [51]. Nevertheless, this type of contact lens has negligible curvature, and the laboratory preparation method mainly involves injection of the mirror material into the mold to make the contact lens, followed by its removal for polishing and other operations to form the final molded contact mirror (Fig. 6) [52]. UV and thermal polymerization can be conducted using injection molding methods to form drug-bearing lenses. Notably, the quality of the contact lenses prepared using the two different polymerization methods differed considerably. Contact lenses obtained via thermal polymerization are hard and brittle, whereas hydrogels prepared via UV polymerization are more elastic because of their high water content [53]. At present, the method of making contact lenses in the laboratory mainly involves injecting the required material monomer into the

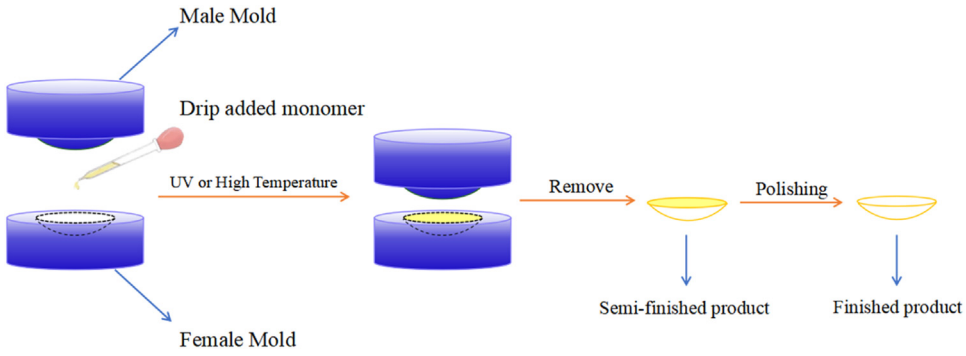

Fig. 6 – Schematic diagram of contact lens made by injection molding.

contact lens mold and aggregating it to obtain the required contact lens. The template can be altered to adjust the size of the contact lens. In addition, the mirror material can be colored to produce colored lenses. It is noteworthy that the reaction between the mold surface and polymer solution affects the surface finish of the contact lens. Therefore, the nature of the mold and polymer solution should be considered while manufacturing contact mirrors using the injection molding method. The 3D printing technology has been used for the production of contact lenses because of its time- and cost-effectiveness, as well as minimal post-processing of finished products. Compared with those of other traditional manufacturing methods, the precision of 3D printing is high and multiple objects can be made simultaneously. The process first designs the parameters required by the contact lens and then uses a 3D printer to print. However, studies on 3D printing of contact lenses are few at present, and the feasibility of using this technology warrants further investigation [54].

5.2.2. *Polymerization of contact lens*

Contact lens materials are mainly polymers composed of hundreds or thousands of repeated molecules called monomers linked via covalent bonds. Common monomers and polymers are used to produce contact lenses. The process of forming this polymer is called polymerization. Polymerization initiation agents are usually chosen based on their interactions with the reactive functional groups within the monomer. The initiator decomposes to form a free radical that reacts with the monomer's functional group to generate another radical, thereby inducing a polymerization reaction. The inceptive monomer forms a new bond with another monomer unit, leading to the generation of a new group to continue the polymerization. This propagation step is repeated to form polymers over time, and the polymerization process ends when no more monomers are consumed. Initiators, such as ultraviolet (UV) or thermal initiators, can be selected according to their utility, which is a significant point to consider in developing contact lens manufacturing methods [55]. Currently, most contact lenses are fabricated by polymerizing two or more monomers. The copolymer is a single polymer. Thus, copolymerization is often the first approach to overcome the problems associated with single polymers. This principle has guided the evolution of contact lenses in the years. For example, silicone polymers are highly hydrophobic despite their high oxygen permeability. Therefore, monomeric materials are not ideal for this purpose. However, silicone copolymers containing hydrophilic monomers can overcome these limitations. Copolymerization may also be selected to improve physical properties by cross-linking polymer chains and increasing the molecular weight of the chain [56].

6. Integrating drugs into contact lens

Drug-loaded contact lenses have been extensively studied since their introduction in 1965. On February 25, 2022, Johnson announced that the FDA had approved its new therapeutic contact lens as the first drug-loading contact lens in the world, which created a precedent for the clinical application of curative contact lenses. More than 50 years have passed since the concept of drug-loaded contact lenses was introduced. Contact lenses have gradually developed into biological products with considerable potential to change human life. Molecular diffusion is the primary drug-release mechanism used in the contact-lens polymer matrix. The drug release duration of the contact lens is expressed as $h2/Deff$, where h is half the thickness of the lens, and Deff is the effective difference. Therefore, the release duration can be increased by increasing h; however, increasing the thickness reduces the oxygen permeability of the contact lens and affects its air permeability and wearing comfort [57]. Certain techniques and methods have been applied to enhance the drug loading capacity and controlled release of contact lenses. A detailed review of the recent research in this direction is presented below.

6.1. *Soaking method*

The soaking method is the easiest method for delivering drugs via contact lenses and is favored by researchers because of its simplicity and industrialization [58]. However, this method has some limitations. Loading of some drugs, especially poorly soluble drugs, using the soaking method is difficult and the lenses burst easily. Therefore, ensuring drug loading and release in the soaking method is one of our research goals. Studies have shown that all drugs

cannot be loaded via soaking. Three main factors affect drug loading into the contact lens via immersion. The first aspect includes the physicochemical properties of the drug, such as molecular weight and solubility. The second aspect includes the physicochemical properties of the contact lens, such as the contact lens material and degree of cross-linking. The third aspect includes the loading conditions such as loading temperature, drug concentration, and loading time. Drug loading into contact lenses relies mainly on the osmotic pressure generated by the concentration, which is the main driver of drug release. Within a certain range, the higher the concentration of the drug in the immersion solution, the higher the concentration of the drug loaded onto the contact lens, and the faster the release speed. However, even if the drug concentration exceeds the maximum drug loading capacity of the contact lens, the release speed of the drug does not increase with drug concentration [59]. The loading ability of traditional hydrogels for hydrophilic drugs is stronger than that of silicone hydrogels, whereas the loading ability of silicone hydrogels for non-hydrophilic drugs is stronger. In general, higher water content is indicative of the presence of large pores between the polymer molecules, resulting in higher drug absorption, and more water solvating the drug molecules, which may increase the drug delivery time [60]. However, it should be noted that the loading and release of drugs are mainly dependent on osmotic pressure, which may prevent the release of high-affinity molecules, whereas low-affinity molecules may be released rapidly, which is not conducive for drug delivery. For example, hyaluronic acid (HA) does not penetrate the aqueous humor channel of contact lenses and remains only on the corneal surface, which may preclude contact lens delivery for dry eye treatment [61].

Chung et al. immersed timolol in a contact lens and found that it enhanced the retention time of the drug. However, such lenses only provide timolol for a few hours and cannot be used for continuous ocular administration [62]. Therefore, it is important to improve the release time during soaking. Desai [63] combined graphene oxide with contact lenses. These lenses have significant chemical, physical, optical, and thermoelectric properties, are widely used as nanocarriers for drug delivery, and show negligible effect on the swelling and light transmission in contact lenses. The authors found that the use of increasing amounts of PVP and graphene oxide to ophthalmic lenses increased the wettability of the lens. The results indicated that the incorporation of graphene oxide into contact lenses may solve the problem of drug encapsulation and release, which may be a very promising application method for contact lenses. Wang [64] designed an intelligent contact lens delivery system by building an antibacterial coating on the contact lens by invertible grafting of antibiotics via a Schiff base reaction. Interestingly, this lens can adjust its pH according to the changes in the microenvironment to achieve pH-responsive drug release [65]. Embedding drugs in nanoparticles and immersing the contact lens in nanoparticles are other ways of overcoming the burst release of drugs. Researchers have immersed Epalystat PEGylated Pluronic solid lipid nanoparticles into contact lenses. Compared with soaking in the free compound, the use of nanoparticles enhanced the absorption rate of Epallistat into the contact lens. *In vitro* and *in vivo* data indicated a lower burst release and persistent administration of the crystals compared with that of conventional immersion [66]. However, changes in swelling, light transmittance, ion and oxygen permeability, protein adherence, surface roughness, mechanical properties, and drug leaching during extraction, sterilization, and storage must be tested before this technique can be translated into clinical trials. Thus, nanotechnology and contact lens manufacture can be combined to deliver drugs, which is discussed in more detail in the following sections.

6.2. *CD-based contact lenses*

CD comprises a series of cyclic oligosaccharides produced from amylose under the action of the CD glucosyltransferase produced by *Bacillus*. CD usually contains 6–12 D-glucopyranose units and are commonly used for the delivery of poorly soluble drugs and for contact lens drug delivery. Three main methods are used for combining CD with contact lenses. First, the acrylic acid and vinyl derivatives of CDs can be copolymerized to load the drug-loaded CDs into the contact lens. Alternatively, propylene methacrylate can be copolymerized with commonly used monomers of contact lenses to form a polymer network with binding points for contact lenses. Finally, guided CDs can cross-link to form hydrogel contact lenses (Fig. 7) [67].

Rui Cong Li [68] has prepared a series of poly HEMA (pHEMA) hydrogels containing cross-linked β-CD-HA, which possess the properties of anti-tear protein adsorption and continuous drug administration and can be used as contact lens materials for ophthalmic diseases. The results showed that the incorporation of β-CD-HA significantly improved the surface hydrophilicity, water absorption, oxygen permeability, and flexibility of pHEMA hydrogel, but did not affect light transmission. This reduced the adhesion of the aureus to the hydrogel surface and enhanced the encapsulation ability and sustainable delivery of diclofenac, owing to the formation of inclusion complexes between β-CD and the drug. Subsequently, some problems have emerged. In a set of control experiments conducted by eye scientist, β-CD significantly enhanced the delivery of chlorhexidine eye drops to the cornea; however, contact lenses loaded with chlorhexidine β-CD failed to enhance the delivery of chlorhexidine to the cornea, probably because β-CD in the hydrogel matrix hindered drug release. A substantial increase in econazole solubility and a further increase in corneal drug concentration were observed when CD-based contact lenses were used to deliver econazole, further demonstrating that CD-based contact lenses are promising drug delivery systems [69]. Li et al. developed a range of pHEMA hydrogels containing cross-linked β-CD-crHA, with characteristics of anti-tear protein adsorption and continuous drug delivery, as a contact lens material for delivering sodium diclofenac and found almost complete disappearance of symptoms at 72 h [39].

6.3. *VE-based contact lenses*

VE acts as a fat-soluble antioxidant in the human body and blocks ultraviolet rays when added to contact lenses.

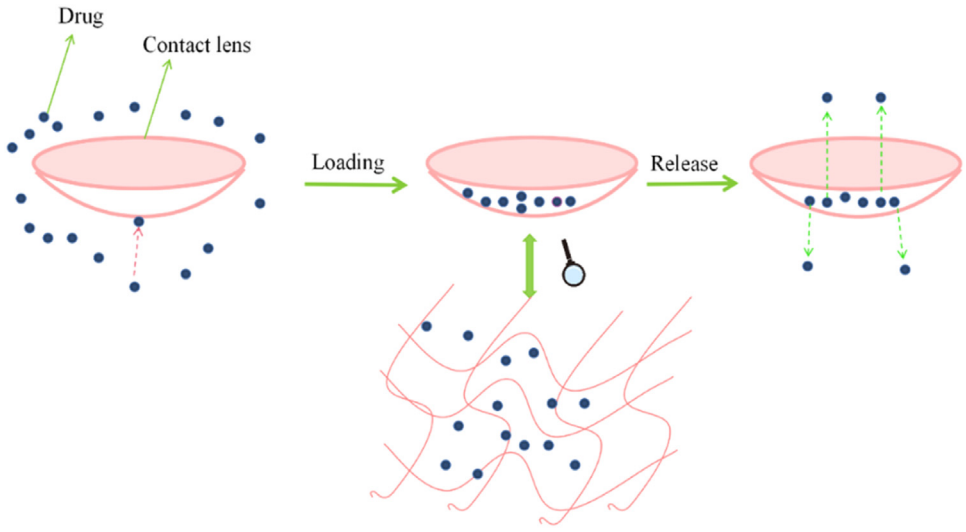

Fig. 7 – Loading and release processes of contact lens drugs loaded by soaking method.

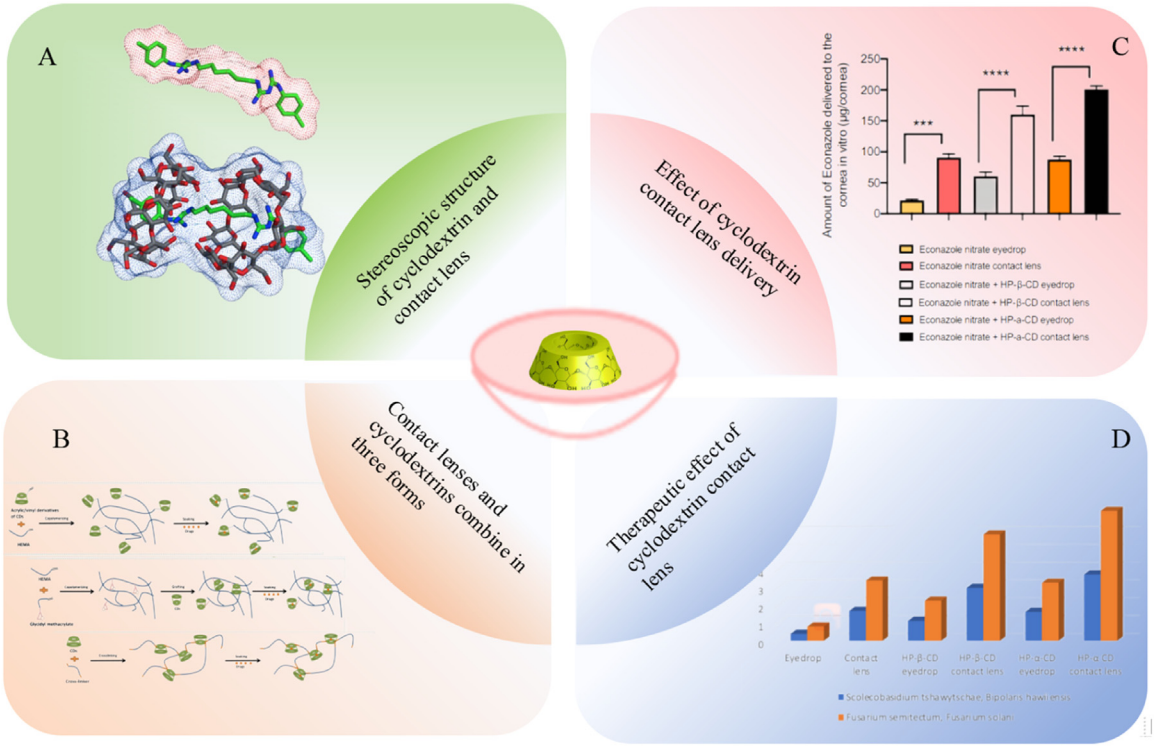

Fig. 8 – (A)Spatial diagram of drug molecules and cyclodextrin binding reprinted and adapted from [70]. (B)Illustration of three methods of cyclodextrin and contact lens binding reprinted and adapted from [43]. (C)Cyclodextrin-type contact lenses further increase the concentration of drugs on the cornea reprinted and adapted from [69]. (D) Symptoms disappear almost completely in 72 h reprinted and adapted from [39].

Moreover, *in vivo* studies confirmed its possible role in inhibiting postoperative corneal stromal cell apoptosis, delaying cataract development, and preventing glaucoma. Unlike normal soaking contact lenses, VE can be used as a diffusion barrier for hydrophilic drugs. This can increase the diffusion path of hydrophilic drugs, enhance the release time of drugs, and solve the problem of drug burst release (Fig. 8). The transport of hydrophobic drugs through VE can occur via three pathways (Fig. 9): diffusion of hydrophobic drugs through VE molecules into the human eye, into VE and formation of agglomerates, and formation of agglomerates, some of which dissolve and diffuse. Several research teams have conducted series of studies on VE as a diffusion barrier to improve drug release time.

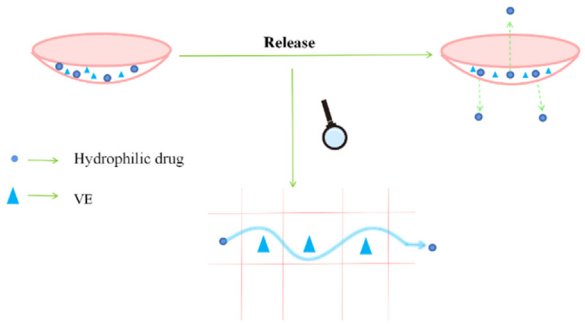

Fig. 9 – Illustration of the principle of VE to prolong the release time of hydrophilic drugs.

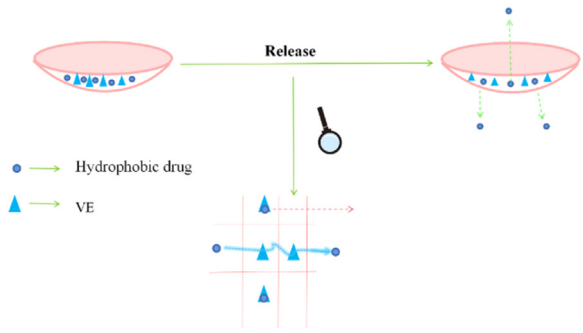

Fig. 10 – Drug delivery mechanisms in VE-laden contact lenses hydrophobic drug delivery mechanism with vitamin E.

Paradison et al. [71] demonstrated that hydrophilic antibiotics can be released from silicone hydrogel contact lenses within days rather than in hours, and VE was examined as a diffusion barrier in pHEMA hydrogel contact lenses. VE allows the contact lens to swell and does not enhance the drug-carrying capacity of the contact lens, but merely increases the release time of the drug. Peng et al. showed that addition of VE to the lens considerably increased the release time of hydrophilic drugs from commercial silicone hydrogel contact lenses. In particular, for commercial contact lenses, approximately 20% VE content increased the release time by approximately 40-fold, while ion and oxygen permeabilities decreased by 90% and 20%, respectively [72]. Studies have shown that when the contact lens contains about 30% VE, the release time of dexamethasone can be prolonged to 7–9 d, which is 9–16 times longer than the dexamethasone release time of the simple contact lens. In the past, VE has been loaded into contact lenses by soaking the latter in a VE ethanol solution, which causes swelling of the contact lens. To solve this problem, Liu et al. investigated the feasibility of creating a VE barrier by soaking contact lenses in VE dissolved in an aqueous ethanol solution to reduce swelling. They found that when the moisture content of the loading solution reached 15% and 25% (v/v), the distribution coefficient of VE was enhanced by more than 5 and 10 times, respectively. This may address the shortcomings of VE-loaded contact lens [73].

The above results also suggest that the large reduction in ion transmittance may be a limitation of VE as a barrier to prolongation of the drug action time. An additional limitation of VE-modified contact lenses is that they showed first-order "burst" kinetics, which has to be assessed and controlled to prevent toxicity and maintain clinically relevant therapeutic doses over time, as well as shelf life, if they are to be commercially viable.

6.4. *Molecularly imprinted contact lens*

The molecular imprinting technology can be used to build an imprint of the drug to be delivered to the contact lens hydrogel network (Fig. 10), which can increase the drug-carrying capacity of the target drugs. This method is now widely used in various ocular drug delivery systems. Compared with traditional contact lenses, molecular imprinting technology improves the kinetics of drug absorption and release from contact lenses, which is related to the physical properties of contact lenses. DiPasquale [74] developed a molecularly imprinted contact lens to achieve controlled release of two groups of drugs. These monomeric drug complexes are retained during polymerization, leading to templating of the drug within the lens and the formation of macromolecular memory sites. These sites provide tight loading control and release without negatively affecting the physical properties of the lens, such as oxygen transmission, optical clarity, elastic modulus, and water content. Studies have shown that drug release can be achieved for more than 7 d, and that the release time can be adjusted according to the ratio of the functional monomer to the template, which is an advantage of molecular imprinting. Owing to the difficulties associated with the administration of poorly soluble pravastatin, researchers have prepared contact lens membrane material as a biomimetic monomer of pravastatin's target, which has increased the drug-loading capacity of pravastatin considerably. *In vivo* experiments have shown that the contact lens can effectively control the release of pravastatin from the eye surface, significantly prolong the duration of pravastatin in tears, and promote drug entry into the aqueous and vitreous humors. Moreover, the contact lens did not show less progress in the previous *in vitro* and *in vivo* correlation experiments; however, the correlation was evaluated in this study [75]. With the development of materials science, researchers have prepared nontoxic photonic crystal-embedded hydrogel contact lenses based on CS and PVA hydrogels [76]. The color of the lens changed from green to cyan after 6 h of controlled release of the imprinted dexamethasone sodium phosphate molecules, and the 150 mg/l drug solution reached saturation within 8 h. Furthermore, the lenses can be stockpiled in water to prevent drug loss. Reversible feeding and release measurements ensure that the lens can be reused eight times, which is in agreement with the usage habits and demands of ordinary contact lenses, and is an area open for future development.

The ability of the polymer to control the release rate of the drugs is an advantage of using molecular imprinting; indeed, control of the molecular imprinting process has been shown to be better than those of other methods, which is one of the attractive features of this technology; however, the success of this technology depends on the conditions of the functional

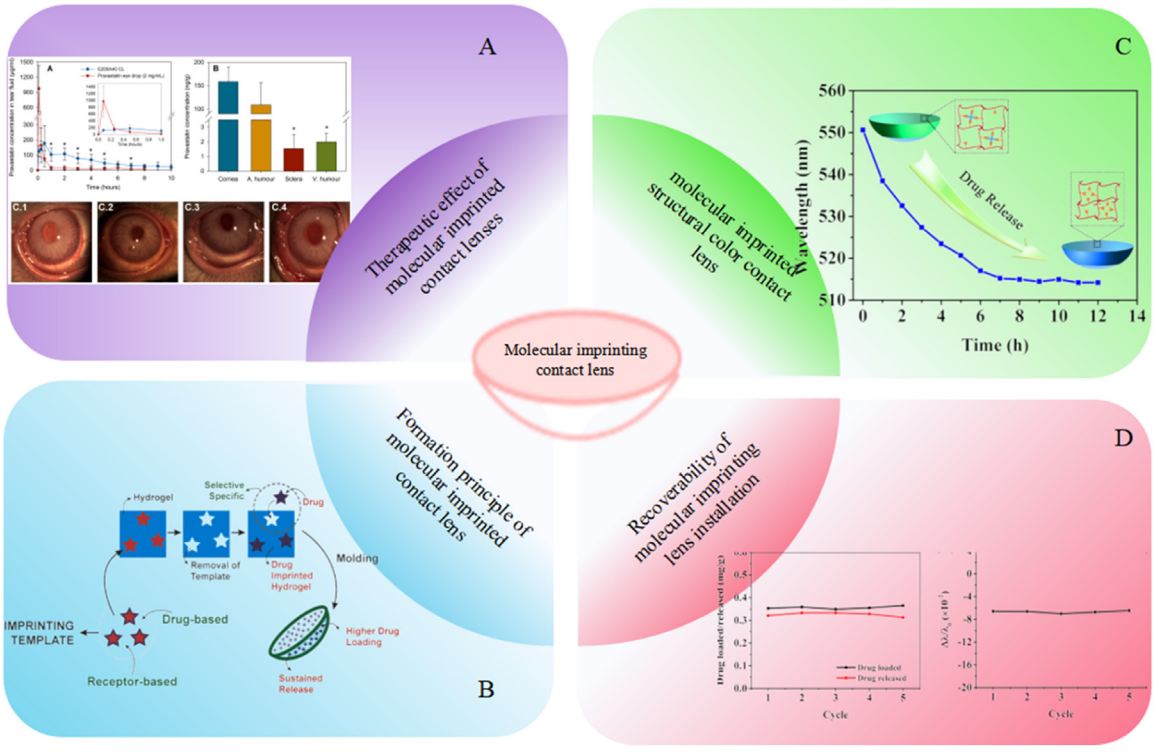

Fig. 11 – (A) The molecular imprinting contact lens prolongs the release time, improves the tissue distribution of the drug in the eye, and a good therapeutic effect is observed under the slit lamp [75]. (B) Schematic diagram of the molecular imprinting technique applied to contact lens [77]. (C) Molecular imprinting structure color long-acting drug-release contact lens release time and color change with drug concentration. (D) Drug release and repeated loading ability of molecularly imprinted contact lenses [76].

monomers and the extent of cross-linking, which may limit the maximum amount of the drug loaded. Excessive cross-links may affect drug release and the nature of the contact lens during the design process. Whether the labeling will change after the release of the drug should also be considered, as it might limit its application (Fig. 11).

6.5. *Nanoparticle-modified contact lenses*

Nanotechnology has been broadly used for delivering drugs to the eye, as it can improve penetration and small particle sensation in the eye; in fact, some nanoparticles can enhance the retention time in the eye. Different nanoparticles, such as micelles, microemulsions, and liposomes, have been combined with contact lenses using four primary methods. The first method involves loading of nanoparticles into contact lenses using the immersion method; the second method involves mixing of nanoparticles and contact lens material before making contact lenses; the third method involves implanting rings loaded with nanoparticles into contact lenses, while the fourth method involves coating of the surface of contact lenses with nanoparticles [78]. Four different binding methods have been reviewed in this study (Fig. 13), along with the different types of nanoparticle-contact lens combinations. Furthermore, we have analyzed the advantages and disadvantages of these combinations.

6.5.1. *Micelles*

Nanoparticles negligibly affect the properties of contact lenses because of their small particle size. Several studies have revealed that a combination of nanoparticles and contact lenses can solve the problems of drug encapsulation and release. Among these, micelles have attracted considerable attention because of their excellent drug-feeding capacity and controlled drug delivery. Hydrophobic drugs can be wrapped near the hydrophobic end of the micelle. Micelles can be combined with contact lenses using two methods. In the first method, the formed micelles are combined with the contact lens material to form the contact lens under suitable conditions. In the second method, the drug is mixed with contact lens material to form micelles under the action of a surfactant.

Xu et al. used MPEG-PLA as a micelle material to simultaneously pack timolol and latanoprost for glaucoma therapy, and the results showed that timolol and latanoprost could be released separately in simulated tears for 6 and 5 d, respectively. *In vivo* pharmacokinetic studies showed sustained tear release of timolol and latanoprost for 5 and 4 d, respectively. The mean residence time of timolol and latanoprost was 79.6 times and 122.2 times longer than those of the marketed eye drops, respectively. The bioavailabilities of timolol and latanoprost were 2.2 and 7.3 times higher than those of the eye drops, respectively.

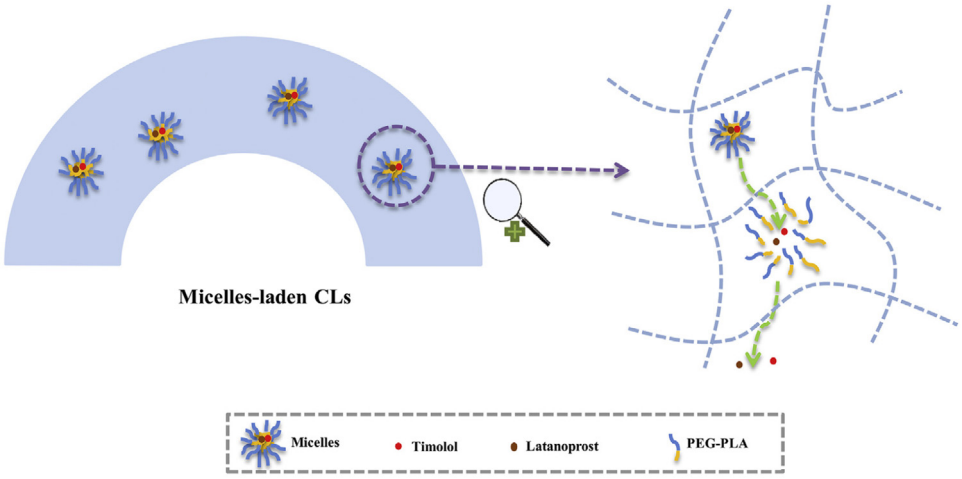

Fig. 12 – Drug release mechanism from micelles-laden contact lenses reprinted and adapted from [13].

In vivo studies in a rabbit model of ocular hypertension revealed a persistent decrease in intraocular pressure (IOP) over 168 h. The drugs are released from the micelles into the contact lens, which are then released into the human eye and lesion site (Fig. 12) [13]. Most importantly, micelles are more compatible with contact lenses than other nanoparticles because of their hydrophilic structure. However, the presence of micelles affects the physical nature of contact lenses [84]. Mun et al. [79] designed a drug-eluded contact lens containing cyclosporine cholesterol-HA micelles for treating dry eye. *In vitro* release tests showed that the contact lens containing cyclosporine C–HA micelles continuously released cyclosporine for more than 240 h, which successfully improved the effectiveness of dry eye treatment. However, the opposite effect of micelles on the visual transmittance of contact lenses has also been observed [15]. Using a Plackett-Burman design, Maulvi et al. showed that the migration of Pluronic® F-68 micelles in the contact lens matrix resulted in the dissolution of the gatifloxacin precipitate, leading to higher optical transmission and better-swelling properties of the contact lens [80]. Therefore, Maulvi et al. optimized a contact lens using a 3^2 design to improve light transmission, swelling, and drug loading of the contact lens, and the designed drug delivery system released drug *in vitro* for up to 72 h [15].

Anionic aggregates formed by pharmaceutical compounds with oppositely charged surfactants have received particular attention for drug delivery applications. Aggregates consisting of ionic drugs and surfactants have been shown to prolong the release time of drugs from hydrogels from hours to days, owing to the presence of vesicles or entangled micelles [81,82]. Some investigators have mixed target drugs such as cyclosporine with contact lens materials to form polymeric micelles in the presence of nonionic surfactants and extend the delivery time of hydrophobic drugs. Micelles made from nonionic surfactants can prolong the release of cyclosporine; however, studies on the delivery of dexamethasone have shown that the release time cannot be prolonged, owing to insufficient distribution of the drug in the surfactant aggregates. Chauhan et al. [83] investigated whether the anionic drug delivery time in contact lenses could be prolonged using long-chain cationic surfactants. Although the release time of dexamethasone sodium was prolonged from 2 to 50 h, this was not due to the formation of ionic surfactant aggregates, but due to the interaction of positive and negative charges. The direct loading of micelles after micelle formation or the formation of micelles using surfactants may prolong drug delivery. However, the presence of nanoparticles still affects the nature of contact lenses. Incomplete drug release and difficulties in clinical transformation are the limitations in using nanoparticles in drug delivery contact lenses.

6.5.2. *Liposome-modified contact lens*

Liposomes have been widely used as biocompatible, biodegradable, and highly loaded nano-drug carriers and have also been applied in ocular drug delivery, especially in combination with contact lenses. Two main methods are used for combining liposomes with contact lenses: (1) polymerization of liposomes and contact lens monomers into contact lenses under specific circumstances after mixing; (2) adsorption of liposomes on the surface of contact lenses. Because of their special phospholipid structure, the liposomes adsorbed on the surface of contact lenses can improve the stability of the tear film while affecting human vision negligibly. The experimental results of these two loading methods were satisfactory. Jain et al. [84] has developed a liposome-coated contact lens surface. The experimental results showed that the retention time of the liposome-encapsulated drugs on the lens was approximately 24 h *in vitro*, whereas the retention time of the same drugs applied as drops was approximately 2–5 min. The drug encapsulation and release curves were influenced by drug content, and the sustained release time of the multi-layer liposomes was longer than that of the monolayer liposomes. Paradisoet al. [85] analyzed the liposome coatings used to control drug release from soft contact lens materials and studied the influence of friction and temperature on drug release. The friction test was designed to simulate the blinking of eyelids

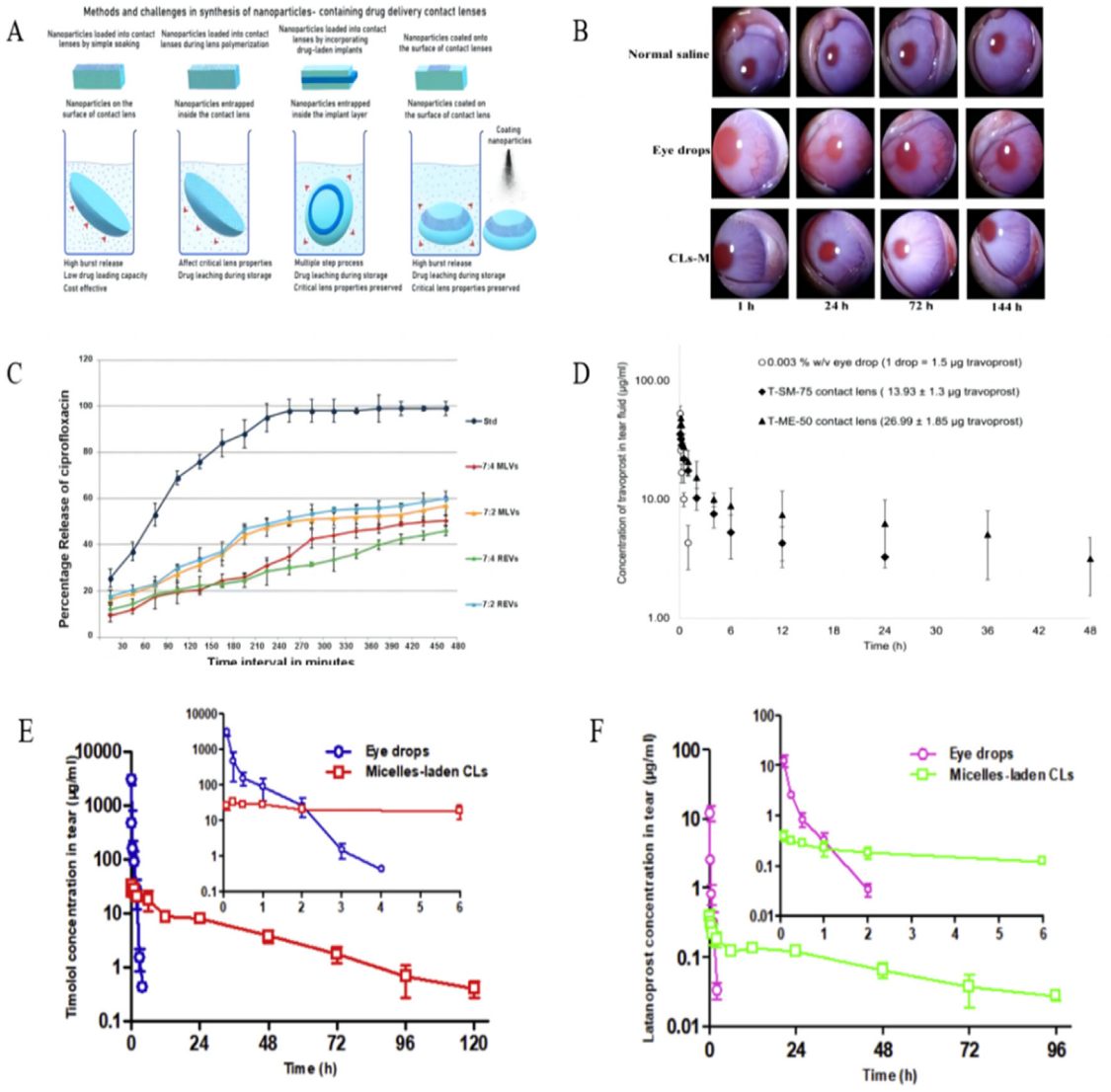

Fig. 13 – (A) Methodologies to load nanoparticles in the contact lenses reprinted and adapted from [78]. (B) security results of micellar contact lenses in the treatment of glaucoma in rabbits [13]. (C) Release curve of lipid body contact lens [84]. (D) Release curve of microemulsion contact lens [90]. (E-F) *In vivo* release curve of micellar contact lens [13].

and determine whether the liposome-encapsulated contact lens material could maintain its properties, especially the drug-release ability. Friction between the eye and contact lenses did not significantly affect drug release from liposome-loaded contact lenses; however, increasing the release temperature increased the diffusion rate of the drug in the hydrogel. Xue studied the liposome-loaded contact lens delivery of latanoprost for treating glaucoma and detected improvements in contact lens swelling, light transmissivity, oxygen permeability, and lysozyme adhesion compared to that observed with lenses made via the immersion method. The liposome-loaded contact lenses did not show higher burst drug release in the *in vitro* drug release study and sustained drug release for up to 96 h than those prepared using the immersion method. In animal studies, liposome-loaded contact lens batches showed higher drug concentrations than immersion and eye drops [86]. Although liposome-loaded corneal contact lenses extend the duration of drug delivery, the presence of multiple layers of liposomes decreases permeability to oxygen and carbon dioxide, which has to be considered in clinical practice.

6.5.3. *Microemulsion-modified contact lens*

Microemulsions are transparent or translucent liquids with particle sizes ranging from 5 to 100 nm, and are widely used in drug delivery because of their high drug-carrying capacity and excellent physical properties. Their use in combination with contact lenses is an emerging means of resolving the high outbreak of contact lenses, and has received considerable attention owing to the simplicity of their preparation method. Wei et al. [87] successfully certified the use of microemulsions to enhance the uptake of timolol from the packaging solution (soaking solution) into contact lenses, and improved timolol release kinetics using the soaking method. Maulvi et al. [40] developed curative soft contact lenses utilizing drug-loaded microemulsions and silicon shell nanoparticles to

achieve long-term delivery of ophthalmic drugs without changing the key properties of the lens. The sustained release of ketotifen from hydrogels occurred in the following order: direct loading of less than microemulsion and less than silicon shell nanoparticles. The Si-shell batch exhibited the highest potential for prolonged drug delivery. Direct loading of ketotifen did not affect the optical and swelling properties, or ion permeability of the hydrogel contact lenses significantly, while the microemulsion and hydrogel loaded with silicon-shell nanoparticles did not affect these properties either.

6.5.4. *Contact lenses modified with other nanoparticles*

Au nanoparticles (AuNPs) have been used as efficient carriers in several fields of drug delivery. Owing to their superior biocompatibility and excellent performance in safety experiments, they have been popular among pharmacological researchers. Kim designed a nanodiamond-type contact lens for the controlled delivery of ocular therapeutic drugs. In this study, individual AuNPs were covered with polyethyleneimine and combined with enzyme-cleavable polysaccharides to achieve enzyme-responsive and sustained drug release [88]. He et al. developed a new type of bimatoprost-loaded silicon shell-coated nanoparticle soft contact lens to achieve continuous drug delivery without changing the optical or physical characteristics of the contact lens. The silicon shell nanoparticles were prepared using octyl trimethoxysilane and microemulsion methods. Compared with the lenses obtained using soaking and direct loading methods, silica shell-coated nanoparticle soft contact lenses have better swelling degree, light transmittance, oxygen permeability, and lysozyme adhesion, and the drug can be released steadily in the eye for 72 h [89].

Numerous experiments have shown that the interplay between nanoparticles and contact mirrors is critical for effective drug delivery, and that nanoparticles affect the properties of hydrogels. If commercialization is desired, the impact of nanoparticles on hydrogels must be minimized to meet the regulations related to commercial contact lenses. Second, long-term toxicity tests must be conducted prior to clinical trials. In addition, particle stability experiments have to be performed to determine whether the particles will decompose or aggregate, and to exclude the deleterious effects of decomposition or aggregation. In addition, the problem of incomplete drug release has to be solved. However, research on nanoparticles and contact lenses has progressed considerably, and the feasibility of using nanoparticle contact lenses in ocular drug delivery has been tested in clinical trials. For example, dexamethasone wrapped around contact lenses has been used to treat cystic macular edema. The therapeutic efficacy and the conditions associated with the launch of the latanoprost-eluting contact lens developed at Harvard University are also being evaluated for treating glaucoma. A study at the National Eye Center in Singapore assessed the effectiveness of contact lenses containing alginate in treating dry eyes; however, the consequences have not yet been investigated. Similarly, the University of Florida has evaluated the feasibility and safety aspects of treating glaucoma patients with contact lenses loaded with timolol and doxorubicin; however, the results have not been made public [78].

6.6. *Multi-layer contact lens*

Multi-layer contact lenses are also used to understand drug feeding and drug release from contact lenses. The advantage of using multi-layer contact lenses is that drug release can be controlled according to the membrane material of the lens. Guzman proposed a three-tier system, in which the center tier included the drug and the exterior tier contained the VE diffusion barrier, to maintain a relatively low local concentration at the interface of the lens and the surrounding liquid. Consistent drug delivery speed was obtained without any primary burst, which was consistent with antibiotic release beyond curative levels that may last for several days [91]. Maulvi et al. devised a nanoring contact lens delivery system to deliver timolol to patients with glaucoma. Researchers have encapsulated drugs in ethylcellulose nanoparticles, which were then dispersed in an acrylate hydrogel to form a ring implant and embedded in the contact lens to form a sandwich-like structure. The mechanism underlying drug release from this drug delivery system may involve the delayed diffusion of drugs through the polymer fence of ethylcellulose nanoparticles and the stroma of the ring and implant, which can achieve sustained release and overcome transformation of the key nature of contact lenses. *In vivo* pharmacokinetic studies have demonstrated sustained drug release for more than 8 d in tears with an implantable contact lens, which can enhance the retention time of drugs in tears and drug bioavailability [52]. However, this type of medical system has certain limitations; research shows that the intraocular lenses cannot be stored under hydrated conditions. The system exhibits continuous release kinetics when it gradually loses its integrity. Therefore, artificial contact lenses should be stored under arid conditions following radiation sterilization. The premature washout of drugs during the production and storage of contact lenses has hindered the clinical application of inner-embedded contact lenses [19]. Therefore, the development of environmentally-sensitive and persistent drug release systems that release drugs in response to fictitious or biological stimuli may result in premature drug release. Eudragit S100 nanoparticles showed a particular dissolution behavior at pH $>$ 7.0. Eudragit has been applied in various drug delivery systems, such as enteral coatings and drug carriers. Eudragit also provides controlled drug delivery when applied in combination with other excipients. Results showed that Eudragit S100 nanoparticles blocked the release of the drug for 3 months in the packaging solution. *In vivo* release kinetics showed that the drug remained in tears for up to 336 h, suggesting that the nanoparticle-loaded lenses improved drug retention [92]. Zhu et al. [93] used cellulose acetate and Eudragit S100-embedded layers, and the *in vitro* drug release speed of the membrane was modulated by altering the inner membrane and the ratio of cellulose acetate to Eudragit S100. With higher drug loading and release times than that obtained using the immersion method, the inner embedded contact lens could maintain drug release for 10 d *in vitro*, and the pH-drug elution mode ensures the stability of the inner embedded contact lens in PBS. The average residence time of the inner nested contact lenses in rabbit eyes was 53 times longer than that of immersed contact lenses. However, the physical nature of

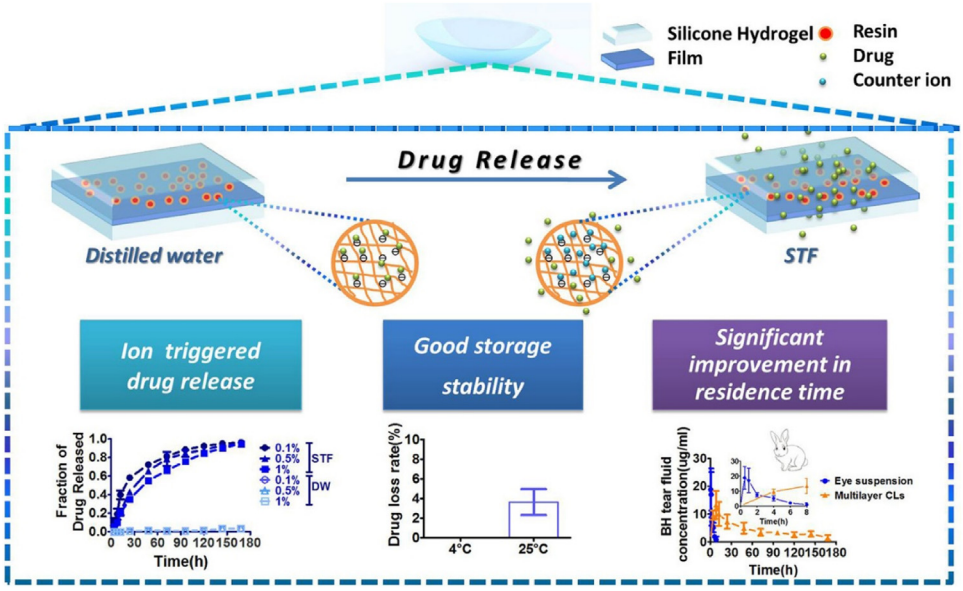

Fig. 14 – Schematic diagram of multilayer drug-loaded contact lens reprinted and adapted from [18].

contact lenses is affected by the sandwich structure of the system.

Zhu et al. developed an ion-triggered drug delivery system for contact lenses (Fig. 14) that exhibited good storage stability while changing the drug-loading membrane into a ring form. As the drug-loading capacity of the ring is low, cellulose acetate membranes and drug-resin complex carriers are used to increase drug loading. Continuous drug release was achieved upon stimulation, and the external layer was used with a silicone hydrogel, which increased the oxygen content and controlled drug delivery for 1 week after exposure to tears. Interestingly, researchers have designed *a* <500 μm-thick magnetic micropump, which can be combined with the contact lens for drug delivery [94]. Such delivery systems overcome the high cost, need for surgical fixation, and procedural complexity, which render their integration into contact lenses difficult. Drug leakage may continue, causing toxicity, device thickening, and other problems. In addition, some researchers have coated the surface of the contact lens with an electrostatic coating; heparin is negatively charged, whereas vancomycin wrapped in chitosan nanoparticles is positively charged. These are adsorbed onto the surface of the contact lens via electrostatic adsorption. In this way, the drug loading of the contact lens increases, while its transmittance and other characteristics are not affected. These systems showed good antibacterial effect *in vitro* and in animal experiments.

Currently, research on drug-loaded multi-layer contact lenses is in the limelight, and it is believed by the scientific fraternity to be the most promising product for clinical use. However, this study had certain limitations. First, the cost of production and difficulties in the production process are more than those of other contact lenses. Second, the multi-layer contact lens may affect the comfort of the wearer, and there may be drug leakage during storage. Currently, whether the three layers of different membrane materials affect the permeability of key factors is not known. Finally, the safety of the multi-layer contact lenses warrant further investigation (Table 1).

7. Smart contact lenses for treating eye diseases

Smart contact lenses were first used for disease monitoring, as the eye contains many physical and chemical markers that reflect the body's condition and are indicators of human diseases. For example, smart contact lenses have been used to monitor glucose levels and intraocular pressure. Compared with traditional blood glucose monitors, smart contact lenses allow for higher patient compliance, less patient distress, and real-time monitoring that can guide patients regarding their medications. The use of IOP monitoring is beneficial for glaucoma patients, as IOP has always been an important indicator of glaucoma; thus, patients can adjust their medication dosage based on changes in IOP. Today, data can be transferred to smartphones, and people can view them easily [104]. Smart contact lenses are also used for visual correction. Smart contact lenses can actively adjust light transmission and effective pupil size, which may be an alternative to surgical vision correction. As mentioned in previous sections, contact lenses have been used for ocular drug delivery to treat ocular diseases, and drug-laden corneal contact lenses have considerably improved the duration of action and bioavailability of drugs. However, drug-laden corneal contact lenses cannot be used to deliver different doses of drugs depending on the severity of the disease; today, smart contact lenses can be used for disease monitoring, and a combination of the two can be used to develop a device that can release different doses of drugs for ocular diseases depending on the severity of the disease, which may be the next generation ocular drug delivery system. In the

Table 1 – Drug-loaded contact lens eye drug delivery system.

Contact lens material	The method of Integrating drugs into contact lens	Drug	Eye disease	Effect of treatment	Ref	Pros and cons	Security
HEMA MAA EGDMA	Multi-layer and Nanotechnology	Timolo	Glaucoma	*In vivo* pharmacokinetic study, the drug released more than 192 h in tear fluid. *In vivo* pharmacodynamic 192 h decrease in IOP.	[52]	Pros: prolonging the action time of the drug. Cons: the effect of the nanoparticles on the key properties of the contact lens, the drug release is incomplete.	It is necessary to pay attention to the influence of nanoparticles on the roughness of the contact lens, which increases protein adsorption. It is also necessary to pay attention to the possibility that multi-layer contact lenses may reduce oxygen transmittance. Attention should be paid to the damage to the human eye caused by the reduction of oxygen transmission caused by the multi-layer contact lens material.
HEMA MAA EGDMA	Multi-layer and Nanotechnology	Moxifloxacin HCl	Bacterial conjunctivitis	The *in vitro* moxifloxacin HCl and hyaluronic acid release for 96 h. The *in vivo* drug release time significant improvement.	[95]		
HEMA EGDMA NVP TRIS	Multi -layer	Timolol and Bimatoprost	Glaucoma	The in-vitro drug release for 72 h, the *in vivo* drug release data showed sustained release with high drug level. The *in vivo* pharmacodynamic: reduction in IOP for 96 h and 120 h respectively	[96]	Pros: extend the duration of the drug's action. Cons: effect of multi-layer materials on light transmittance and oxygen content.	
HEMA NVP TRIS EGDMA	Multi-layer	Betaxolol hydrochloride	Glaucoma	*In vivo* drug release for 168 h in tear fluid and solved the drug leak problem	[18]		
HEMA NVP TRIS EGDMA	Multi-layer	Betaxolol hydrochloride	Glaucoma	The drug action time is prolonged and the problems of drug leakage and low transmittance of multilayer glasses are solved	[97]		
HEMA EGDMA MAA DMA TRIS	Molecular imprinting	Bimatoprost	Glaucoma	The drug release time is 36–60 h without changing the physical properties of the contact lens	[98]	Pros: different molecular blots can be prepared according to different drugs, with little impact on the key attributes of the contact lens. Cons: the imprint may deform after the drug is released.	It has better security.
HEMA MAA EGDMA	Molecular imprinting	Acyclovir	Virus infection	Increased drug penetration and increased drug release time to 10 h	[99]		

(*continued on next page*)

Table 1 (*continued*)

Contact lens material	The method of Integrating drugs into contact lens	Drug	Eye disease	Effect of treatment	Ref	Pros and cons	Security
HEMA EGDMA TRIS AA	Molecular imprinting	moxifloxacin hydrochloride	Fungal infection	The drug was released for 13 d without affecting the physical properties of the contact lens too much	[100]		
HEMA EGPEM APMA EGDMA	Molecular imprinting	Pravastatin	Diabetes	Reduce systemic side effects, the tissue drug concentration is higher Increased retention time.	[75]		It has better security
ACUVUE Oasys® and ACUVUE TruEye®	VE	NSAIDs	Inflammation of the eye	The surfactant increased the drug loading and the drug action time was extended to 150h	[101]	Pros: extend the duration of the drug's action. Cons: VE has a great influence on the ion permeability of the contact lens.	It should be noted that the increase of VE leads to a decrease in ion permeability and damage to the eye.
ACUVUE TRUEYE® ACUVUE OASYS®	VE	Ofloxacin	Bacterial keratitis	Both showed longer release and therapeutic effects	[101]		
HEMA EGDMA	Nanotechnology	Timolol	Glaucoma	Drug release duration from 1 to 2 h to about 2 to 4 weeks	[102]	Pros: solve the problem of poor solubility of drugs in contact lenses, and extend the duration of the drug's action. Cons: the key properties of the contact lens are affected, and the drug release is incomplete.	It is necessary to pay attention to the impact of the introduction of nanoparticles on the surface roughness and the impact on the key properties of the contact lens, thus bringing safety problems.
DMA, MAA, NVP, TRIS, PDMS	Nanotechnology	Timolol	Glaucoma	The lens with 5% particle loading released the drug for about a month at room temperature. Studies in beagle dogs demonstrated the safety and efficacy of timolol in lowering IOP for 4 d	[103]		
PHEMA	Nanotechnology	latanoprost and timolol	Glaucoma	*In vitro* studies, the release reached 144 and 120 h, respectively, and the pharmacokinetics showed that the bioavailability was 2.2 and 7.6 times that of eye drops	[13]		
HEMA NVP DMA EGDMA	Nanotechnology	Bimatoprost	Glaucoma	Can be extended to 96 and 72 h shows a higher drug concentration.	[89]		
PHEMA	β-cyclodextrin	Diclofenac sodium	Conjunctivitis	Increased drug loading capacity, extended drug delivery time, reduced protein adsorption	[39]	Pros: prolong the action time of the drug. Cons: require the drug molecule and the cavity of cyclodextrin to match, cyclodextrin citation has an impact on the key properties of the contact lens.	It is necessary to pay attention to the impact of the introduction of nanoparticles on the surface roughness and the impact on the key properties of the contact lens, thus bringing safety problems.

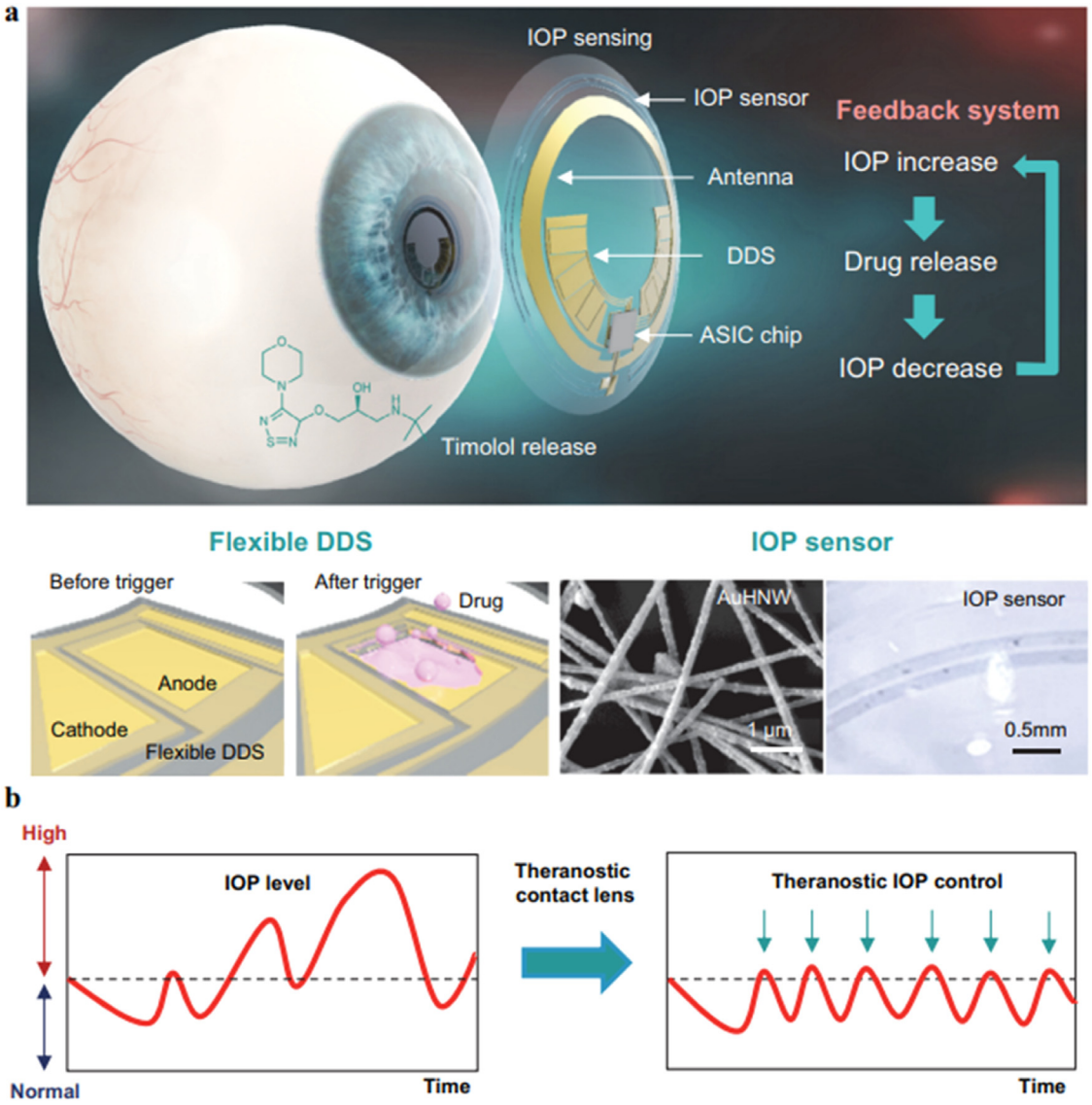

Fig. 15 – Schematic illustration of a theranostic smart contact lens for glaucoma treatment reprinted and adapted from [106].

subsequent section, we have discussed research on smart contact lenses, focusing on ocular disease therapy and ocular drug delivery.

Keumd et al. developed a smart contact lens that combined electronically controlled delivery of metformin with real-time glucose monitoring for the treatment of diabetic retinopathy. The sensor in the smart contact lens enables real-time monitoring of blood glucose, whereas the drug can be released from a self-regulating pulse in the soft contact lens via remote communication. This smart contact lens can be powered wirelessly, and it was found to be biocompatible and less irritating to the eye in safety experiments; furthermore, the temperature of the electronic software worn on the eye surface increased only slightly during operation without causing any damage to the eye, indicating that thermal safety of the device was good.

In a further development, researchers have fixed glucose oxidase in a mixture of PVA and hydrogel, which improved the sensitivity, stability, and reproducibility of monitoring, making it possible to maintain high sensitivity during 63-d experiments. Furthermore, *in vivo* and *in vitro* experiments have shown good therapeutic effects and on-demand drug delivery [105]. At present, although contact lenses for monitoring intraocular pressure are available, treatment of glaucoma by releasing different doses of drugs according to the intraocular pressure has not been realized. Kim et al. has designed a smart contact lens that integrates monitoring and drug release for the treatment of glaucoma (Fig. 15). This smart contact lens uses hollow gold nanowires as the intraocular pressure sensor, which makes it more sensitive than conventional smart contact lenses. This device was found to have good biocompatibility and high chemical stability. *In vivo* experiments have shown that its therapeutic effect is good and that on-demand drug delivery can maximize the therapeutic effect and minimize side effects, providing a new choice for the treatment of glaucoma [106]. Jang et al. designed a smart contact lens in combination with an attached therapeutic device for monitoring and treatment

of chronic ocular surface inflammation. The smart contact lens monitors the concentration of metalloproteinase-9 in real time, and the data can be viewed and stored on a smartphone that controls the attached thermal patch for self-physiotherapy. Graphene field-effect transistors, surfaces of which are functionalized with IgG as biosensors, are used to monitor metalloproteinase-9 level, resulting in more accurate monitoring. In human experiments, the presence of a cell phone within the sensing range of a smart contact lens enabled data transmission, and the level of treatment was good, which may be a suitable direction for future research [107]. Lee et al. designed a new method for the integrated monitoring of intraocular pressure and temperature-triggered drug elution. This contact lens is a combination of smart contact lenses and drug release, and experimental results demonstrate the feasibility of this idea. This provides a new option for developing smart contact lenses [108].

Achieving controlled drug delivery has always been the pursuit of pharmacists, and now the stage is set for real-time monitoring and responsive treatment using smart contact lenses, which will lead to more rational drug delivery. Despite the scarcity of relevant research, this is certainly a promising research direction for the future; however, for clinical applications, the safety and other aspects of these systems have to be evaluated.

8. Summary and future prospect

This article reviews the key characteristics, related materials, and preparation methods of contact lens delivery systems, highlights the types of drugs used in drug-loaded contact lenses, as well as the emerging smart drug-carrying contact lenses, and analyzes their advantages and challenges. It is a good sign that drug-loaded contact lenses are now available on the market. As contact lenses considerably improve bioavailability, contact lens-based drug delivery is believed to be a promising system. Currently, research on drug-loaded contact lenses is focused on clinical translation, molecular imprinting, and development of nanoparticle-contact lens composite delivery systems. A range of delivery systems, such as VE-modified contact lenses, now appear to be off the market owing to the limitations mentioned above. At present, contact lenses are being developed for clinical use mainly via soaking administration because of convenience in production. Second, the round-the clock wearing of contact lenses is still an unrealized dream, with the day wearing of contact lenses being relatively more popular among consumers. Currently, the emphasis should be on the development of contact lens wash solutions and transfer boxes that can solve the storage and transportation problems of contact lenses. Recently, owing to the development in material science, intelligent hydrogels have been used for the treatment of many diseases, although the combination of smart hydrogels and contact lenses for the delivery of ocular drugs has not yet been reported. Perhaps the development of a combination of intelligent hydrogel materials and contact lenses that can achieve drug delivery and halt the elution of drug-containing contact lenses in the care solution and during transportation may be a hot topic of future research.

3D printing has revolutionized the medical and surgical disciplines worldwide. Various studies have used 3D printing technology to manufacture eyewear and medical devices. The future of 3D-printed contact lenses may also be promising. Eye monitoring with smart contact lenses has been around for many years, but the era of eye treatment with smart contact lenses may have just begun. We believe that this direction of research is promising, and studies on-demand dosing, high bioavailability, and minimized side effects are underway. However, the adaptation of contact lenses, electronic components, and eye tissues should be carefully considered to avoid damage to the eyes. Second, smart contact lenses have to be soft and stretchable to adapt to the eyes; however, the contact lens material swells, resulting in damage to the electronic components. Thus, materials with lower water content are generally chosen to reduce the expansion of the material, which, however, will decrease the level of comfort of the wearer. Considering the aforementioned problems, contact lens materials that are more suitable for smart contact lenses should be developed. In addition, the safety and stability of the electronic components in smart contact lenses should be carefully studied under specific physiological conditions, and more animal experiments on release kinetics are required to prove their safety. In the future, interdisciplinary research encompassing ophthalmology, material science, pharmacology, and biomedical engineering should be conducted, and more advanced and smart contact lenses should be developed. In conclusion, contact lenses are promising tools for delivering ocular drugs and treating ocular diseases. Thus, contact lenses are expected to open a new era of ocular drug delivery.

Declaration of Competing Interest

The authors have declared no conflicts of interest.

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