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Advances in chemistry and composition of soft materials for drug releasing contact lenses

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Ocular drug delivery has always been a challenging feat to achieve in the field of medical sciences. One of the existing methods of non-invasive ocular drug delivery is the use of eye drops. However, drugs administered through these formulations have low bioavailability in the ocular system. This limitation can be overcome by using contact lenses as drug delivery vehicles. According to USA FDA definitions they can be categorized into two main categories-hard and soft contact lenses. Based on the material properties, hard contact lenses are mostly produced from polymers of acrylate monomers such as MMA (methyl methacrylate). These have the least water retention capacity, thereby, having minimal ability to diffuse oxygen into the corneal layer and are not ideal for long term use. Soft material contact lenses are flexible and are mainly hydrogel based. They have higher water retention capacities as compared to rigid contact lenses, which gives them the ability to transmit oxygen to the corneal layer. These hydrogel based soft materials are mainly produced from polymers of acrylate monomers such as HEMA (hydroxyethyl methacrylate) and found to be better for drug delivery contact lenses. These polymer-based soft materials have been efficiently modified in terms of their chemistry to achieve diverse physicochemical properties to produce efficient ocular drug delivery systems. However, complications such as drug leaching during storage and distribution, sterilisation, preservation of integrity of the lens and the possibility of surface roughness due to the incorporated drug molecules still need to be optimised. This review highlights the chemistries of various polymeric molecules through which physicochemical properties can be modified to achieve optimum drug loading and sustained release of the drug for application in the ocular system.

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1. Introduction

Eyes are one of the most intricate organs of the human body. They have tissues that are found to be arranged in layers.^{1,2} There are many ocular diseases that impede the normal functioning of the eye. Conjunctivitis is one of the most common ocular infections that occur in the conjunctiva of the eye. It is highly contagious and is characterised by excessive tear production. Ocular inflammation and dry eye are some of the most prevalent ocular disorders. Dry eye is caused by inadequate production of tears which in turn causes irritation in the eye. This can also lead to impaired vision. Of the most severe categories of ocular disease, glaucoma, is one of the disorders which causes damage to the optic nerve. This nerve damage can eventually lead to blindness.^{3,4} Age related Macular Degeneration (ADM), Diabetic Macular Edema (DME), Uveitis and CMV retinitis are some of the other ocular diseases affecting a big population across the world.⁵ A variety of therapeutic methods

have been introduced to take care of such ocular problems but drug delivery to the eye has always been one of the most challenging tasks. As eyes have both static and dynamic barriers including static barriers of corneal layers, blood aqueous barrier and dynamic barriers of retinal blood and conjunctival barrier, it causes inhibition to the uptake of drug and thereby reducing the bioavailability.^{6,7} Different routes of administration exist to treat ocular diseases (Fig. 1). Each of the methods is associated with some drawbacks. Topical administration of drugs for ocular therapy is the most commonly used drug delivery method. It is non-invasive and can be self-administered by the patient. It has several disadvantages associated as the corneal barrier is difficult to penetrate and the drug is washed off by the continuous presence of tears. On the other side, oral administration of drug is generally coupled with topical application to increase the efficacy of the treatment whereas systemic route is the parenteral administration of drug and it leads to systemic toxicity. Other routes of administration include intra-vitreous, intracameral, subconjunctival and retro-lobular. All these routes also suffer from the similar obstacles.⁶ There are some transporters present in the eye which are known to efflux drug molecules outside and reduce bioavailability of the drug.^{8,9}

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Due to difference in morphologies and barrier properties of the anterior and posterior segments in eye, different therapeutic measures have to be devised to ensure successful therapy. The anterior ophthalmic disorders are mostly treated with topical eye drops, whereas posterior segment disorders require many of the new methods including dendrimers, microneedles,¹⁰ nanocrystals and lipid based nanosystems.¹¹ Nanotechnology can be used into various drug delivery systems to increase specificity and decrease off target toxicity. Their compatibility and stability of such systems could be increased by coating them with naturally available polymers like chitosan, alginate, hyaluronan, dextran and lecithin.¹² Ocular implants are good options for long term and controlled drug delivery but being an invasive process is generally associated with a lot of complications. Iontophoresis is another method of the delivery of drug using voltage gradient and can be used to deliver a wide variety of drugs to both the anterior and posterior segments of the eye. It is a non-invasive method of delivery and associated with less toxicity. But this process requires frequent administrations while sustained release of drug is not possible using this method.¹³ These mentioned methods have significant therapeutic abilities but many serious drawbacks exist, which can be overcome by using therapeutic contact lenses.

Contact lens can be classified into hard or soft type based on the material used in preparation. Generally hard lenses are made up of rigid gas permeable material whereas soft contact

lenses possess soft and flexible polymer which allows oxygen to pass through to the cornea. FDA further classifies soft material contact lenses into four groups as mentioned in Table 1. To consider the system to be ionic or non-ionic the pH 7.2 is used as the standard pH.

The cornea, an avascular tissue, depends on the atmosphere for oxygen requirement.¹⁴ Insufficient oxygen permeability (Dk) may lead to severities such as ocular and limbal redness neo-vascularization, corneal swelling, and endothelial pH changes.^{15,16,18} Therefore, it is important to ensure sufficient oxygen transmissibility of the contact lens. Holden *et al.*, estimated the critical oxygen transmissibility level of hydrogel contact lens under daily wear conditions to avoid corneal edema. Many studies have reported that the high Dk silicone hydrogel contact lens with its sufficient oxygen flux had resolved the hypoxia-induced complications to a greater extent.^{17–20}

Table 1 Classification of soft material based contact lenses

Group	Water content	Percentage	Ionic/non-ionic
I	Low water content	(<50%)	Nonionic
II	High water content	(>50%)	Nonionic
III	Low water content	(<50%)	Ionic
IV	High water content	(>50%)	Ionic

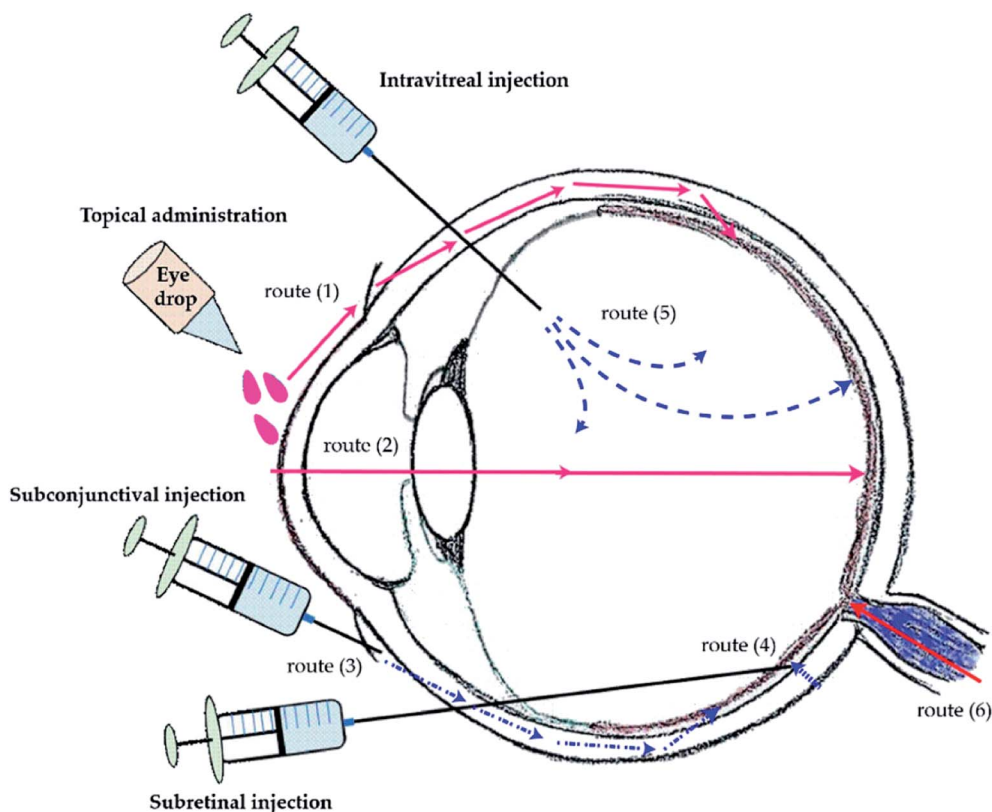


Fig. 1 Methods of ocular drug administration and its delivery routes to the posterior segment. Routes of drug transportation to the back of the eye via topical administration (1) and (2), subconjunctival injection (3), subretinal injection (4), and intravitreal injection (5). The drug transportation from the systemic circulation via oral medication (6). Reprinted from ref. 134.





Table 2 Polymers approved by the US FDA for the fabrication of contact lens^a

Sl no	Group	Polymer used for the fabrication of contact lens	Monomer composition	Water content (%)	Oxygen transmissibility (Dk/t) ^b	Advantages	Disadvantages
1	I	Polymacon	HEMA	38.3	8.5–24.3	The lower water content makes them more rigid and easier to handle. Due to the non ionic nature of the lens material, these are less prone to deposition of proteins.	These are less wettable by the tear film. Due to this, a sense of dryness in the eye is felt by the patient, thus, making it uncomfortable to use
2		Crofilcon	GMA, MMA	38	13	The incorporation of siloxane into the fabrication process enhances the oxygen transmissibility of the lens	
3		Lotrafilcon A	DMA, TRIS, siloxane	24	140		
4		Lotrafilcon B	DMA, TRIS, siloxane	33	110		
5		SenofilconA	HEMA, DMA, mPDMS, siloxane macromer, TEGDMA, PVP	38	103–147		
6		Galyfilcon A	HEMA, DMA, mPDMS, siloxane macromer, EGDMA, PVP	47	86		
7	II	Nelfilcon A	Modified PVA	69	26	The decreased rigidity of the lens increases patient compliance, as it decreases the sensation of irritation in the eye and also reduces chance of corneal abrasion	Due to increased water content, the mechanical property of the lens is altered which often makes the handling of the lens difficult
8		Omafilcon A	HEMA, MPC	58–60	28–36.7		
9		Omafilcon B	HEMA, MPC	62	21.3–52.3		
10		Netrafilcon A	EGDMA, MMA, DMA	65	34.5		
11		Hilafilcon A	HEMA, AMA, NVP	70	35		
12		Hilafilcon B	HEMA, AMA, NVP	59	22		
13		Lidofilcon A	EGDMA, AMA, NVP, MMA	70	31		
14		Lidofilcon B	EGDMA, AMA, NVP, MMA	79	38		
15		Hioxifilcon A	HEMA, EGDMA, GMA	59	28		
16		Hioxifilcon D	HEMA, EGDMA, GMA	54	21		
17		Hilafilcon A	HEMA, EGDMA, AMA, NVP	70	35		
18		Hilafilcon B	HEMA, EGDMA, AMA, NVP	59	22		
19	III	Buflilcon A	HEMA, DAA, TMPT	45	16	Easier to handle due to the increased rigidity caused by the decrease in the water content	The ionic nature renders the surface of the contact lens reactive, thereby causing deposition of proteins present in the tear fluid
20		Deltafilcon A	HEMA, MAA, IBMA, TMPT	43	10		
21		Phemficon	HEMA, β -ethoxyethyl methacrylate	38	9		
22	IV	Ocufilecon B	HEMA, MAA	52–53	16–24		Some of them are difficult to handle due to the decreased rigidity caused by the
23		Ocufilecon C	HEMA, MAA	55	16		



Table 2 (Contd.)

Sl no	Group	Polymer used for the fabrication of contact lens	Monomer composition	Water content (%)	Oxygen transmissibility (Dk/t) ^b	Advantages	Disadvantages
24		Ocufilecon D	HEMA, MAA	55	17.8–28.1	Flexible nature of the lens makes it comfortable to wear thereby curbing the feeling of irritation often felt in the eye	increased water content. Due to ionic nature, they are more susceptible to deposition of proteins from the tear fluid
25		Ocufilecon E	HEMA, MAA	65	22		
26		Ocufilecon F	HEMA, MAA	60	24.3		
27		Etafilecon A	HEMA, MAA, PVP	58	23.8–28		
28		Methafilcon A	HEMA, DEG, MAA, EGDMA	55	14.5–31.3		
29		Methafilcon B	HEMA, DEG, MAA, EGDMA	55	16		
30		Perfilcon A	HEMA, NVP, MAA	71	34		
31		Etafilecon A	HEMA, MAA, PVP	58	23.8–28		

^a HEMA (hydroxy ethylmethacrylate); MAA (methacrylic acid); MMA (methyl methacrylate); NVP (N-vinyl pyrrolidone); GMA (glycerol methacrylate); DMA (N,N-dimethylacrylamide); EGDMA (ethylene glycol dimethacrylate); TEGDMA (tri ethylene glycol dimethacrylate); PDMS (polydimethylsiloxane); TPVC (tris(trimethylsiloxy)silyl)propyl vinyl carbamate); TRIS (3-[tris(trimethylsiloxy)silyl]propyl methacrylate); DAA (diacetone acrylamide); IBMA (isobutyl methacrylate); PVP (poly(vinyl pyrrolidone); DEG (diethylene glycol); AMA (allyl methacrylate); MPC (methacryloyloxyethyl phosphorylcholine). ^b Higher the value of Dk/t, higher is the oxygen transmissibility.

Hydrogel based contact lenses are gaining popularity because of their capacity to hold water and allow oxygen diffusion. Hydrogels can be improved by adding silicone monomers to improve durability and other physical properties.^{21,22} FDA also categorises contact lens into two categories based on their chemical properties as hydrophilic and hydrophobic contact lenses. Hydrophilic lens can be used for a longer time and can absorb water. Oxygen present in water can diffuse into the desired location. Hydrophobic contact lenses are often combined with hydrophilic substances to increase biocompatibility.²³ Few disadvantages associated with contact lens include discomfort, irritation, dry eye and red eye. These also contribute to the discontinuation of lens by people. If these properties can be improved in a lens, usage of contact lens can be increased.^{24,25} Lenses made up of hydrogel have become popular due to the numerous advantages like easy preparation, flexibility, transparency, high water content, drug loading possibilities and high biocompatibility.^{26,27} Silicone based contact lenses are the most recent addition to the market of soft material contact lens. FDA approved polymers which can be used in the manufacturing of contact lens is mentioned in Table 2 whereas the IUPAC name of the monomers used is mentioned in the Table 3.

To develop an efficient ophthalmic drug delivery system one of the most important step is the proper use of the chemical compounds for the fabrication of the contact lens and the drug molecule to be used. The drug loading and delivery depends mainly on the interactions between the drug molecule and polymeric network of the contact lens. Other factors such as pH of the drug loading solution and temperature during the drug loading process also play significant roles. One of the most important characteristics of a formulation is the patient compliance. The prolonged use of contact lens have been reported to cause some adverse effects in the ocular system. Some of the most widely reported adverse effects of contact lens are:

- Corneal abrasion: scratches on the surface of the cornea, caused by the edges of the contact lens. This is mostly caused due to the prolonged use of rigid contact lens.

- Hypoxia: use of contact lenses having lower oxygen transmissibility deprives the corneal surface of oxygen supply, thereby causing hypoxia. The cornea needs 3–10 μl of oxygen per cm^2 per h. Due to hypoxic condition, the corneal cells shift to anaerobic respiration leading to formation of lactic acid. The accumulation of lactic acid causes osmotic load, thereby, leading to accumulation of water which eventually causes edema.

- Neovascularization: the extended wear contact lens has been reported to induce corneal neovascularization, which is the pathological development of vascular capillaries from limbus to the corneal apex by 1 mm or less.^{29–31} Several factors like lack of oxygen, lactic acid, stromal softening, and vasogenic stimulations are known to induce corneal neovascularization.²⁸ Kymionis *et al.*, by slit-lamp inspection demonstrated that corneal neovascularization is the side effect of Intacs implantation and RGP contact lens fitting in patients ten years after implantation. Dumbleton *et al.*, using randomized prospective clinical trials observed the development of moderate

- **Reduced corneal reflex:** corneal reflex or blink reflex is an involuntary activity of the eyelids. It is caused by the stimulation of the cornea due to exposure to trauma. Prolonged use of contact lens often leads to reduced corneal reflex.

- **Meibomitis:** meibomium glands are present in the upper and lower eyelids. Oil excreted by these glands is an important constituent of the tear film, which remains on the corneal surface after each blink. It helps in hindering the evaporation of tear film, thereby curbing dryness of the eye. Lens care solutions contain preservatives, which may plug the meibomium glands, thereby disrupting their functionality. This condition is known as meibomitis and it leads to dryness of the eye and raises a feeling of discomfort in the patient.

- Contact lens-induced papillary conjunctivitis (CLPC): a chronic inflammatory process that includes the development of giant papillae in the upper tarsal conjunctiva.³⁴⁻³⁹ The symptoms include excessive mucus production, reduction in lens tolerance, increased lens awareness, excessive lens movement, ocular redness, itching burning sensation, and irritation. Allansmith *et al.*, reported the development of this syndrome in both soft and hard contact lens wearers.³⁸ Chang *et al.*, 2001

- **Dryness and irritation:** use of contact lenses fabricated from non ionic monomers often causes dryness and sensation of irritation in the eye. Contact lenses having lower wettability hinder the spreading of the tear film over the lens surface, thereby causing a sensation of dryness and irritation in the eye. Due to this condition, often redness of the eye is observed.

- **Biofouling:** biomolecular interaction between the contact lens surface and the proteins present in the tear fluid leads to undesired deposition of protein molecules on the lens surface. This affects the visual clarity of the lens.

Utmost care must be taken while handling the contact lens. The patients must follow the instructions given by the manufacturers regarding the handling of the lens. Lens cases and lens storage solutions are often the cause of microbial contamination. Proper lens disinfection techniques must be followed. However, certain modifications during in the fabrication of the lens can also mitigate the adverse effects caused by the use of contact lens. Proper choice of monomers in the fabrication of the contact lens is a major step towards enhancing the patient compliance of the formulation. Various groups have tried to incorporate antibiotics into the polymeric matrix of the contact lens, to curb the microbial contamination in the ocular system. Incorporation of anti-inflammatory drugs such as dexamethasone into the polymeric matrix can be a potential solution to the occurrence of persistent inflammation caused by the prolonged use of contact lens. The thickness and mechanical property of the contact lens shall not interfere with the oxygen transmissibility and optical activity of the lens. The thickness of a contact lens is mainly governed by the purpose of its use. Lenses differ in their central and peripheral

Table 3 IUPAC name of monomers used in the fabrication soft material contact lens

Monomer used	IUPAC name
HEMA (hydroxy ethylmethacrylate)	2-Hydroxyethyl-2-methylprop-2-enoate
MAA (methacrylic acid)	2-Methylprop-2-enoic acid
MMA (methyl methacrylate)	2-Methylprop-2-enoate
NVP (<i>N</i> -vinyl pyrrolidone)	1-Ethenylpyrrolidin-2-one
GMA (glycerol methacrylate)	2,3-Dihydroxypropyl-2-methylprop-2-enoate
DMA (<i>N,N</i> -dimethylacryamide)	<i>N,N</i> -Dimethylprop-2-enamide
EGDMA (ethylene glycol dimethacrylate)	2-(2-Methylprop-2-enoyloxy)ethyl-2-methylprop-2-enoate
TEGDMA (triethylene glycol dimethacrylate)	2-[2-[2-(2-Methylprop-2-enoyloxy)ethoxy]ethoxy]ethyl-2-methylprop-2-enoate
PDMS (polydimethylsiloxane)	Poly(dimethylsiloxane)
TPVC ((tris(trimethylsiloxy)silyl)propyl vinyl carbamate)	Ethenyl- <i>N</i> -[3-tris(trimethylsilyloxy)silylpropyl]carbamate
TRIS (3-[tris(trimethylsiloxy)silyl]propyl methacrylate)	3-Tris(trimethylsiloxy)silylpropyl-2-methylprop-2-enoate
DAA (diacetone acrylamide)	<i>N</i> -(2-Methyl-4-oxopentan-2-yl)prop-2-enamide
IBMA (isobutyl methacrylate)	2-Methylpropyl-2-methylprop-2-enoate
TMPT (trimethylolpropane trimethacrylate)	2,2-Bis(2-methylprop-2-enoyloxymethyl)butyl-2-methylprop-2-enoate
PVP (poly(vinyl pyrrolidone))	1-Ethenylpyrrolidin-2-one
DEG (diethylene glycol)	2,2'-Oxydi(ethan-1-ol)
DAA (diacetone acrylamide)	<i>N</i> -((2-Methyl-4-oxopentan-2-yl)prop-2-enamide)



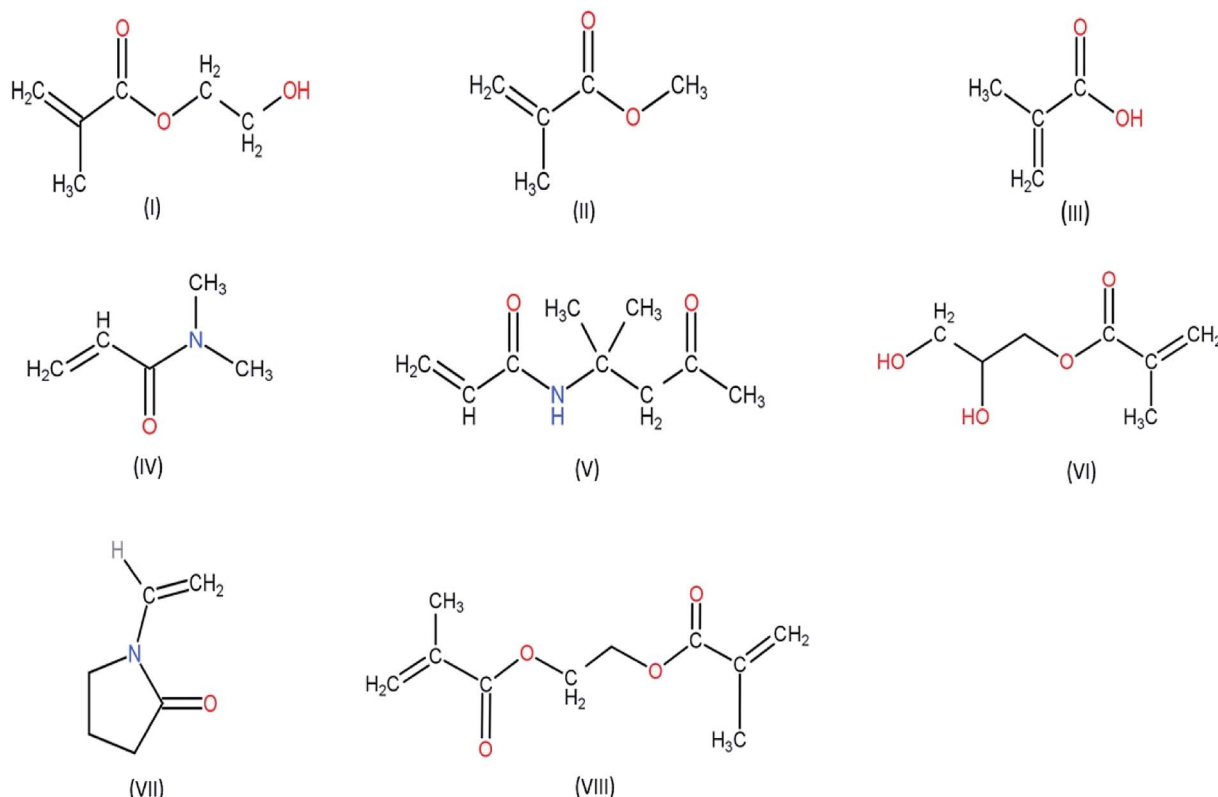


Fig. 2 Chemical structure of monomers used for various hydrogel based contact lens (I) HEMA (hydroxy ethylmethacrylate) (II) MMA (methyl methacrylate) (III) MAA (methacrylic acid) (IV) DMA (*N,N*-dimethylacrylamide) (V) DAA (diacetone acrylamide) (VI) GMA (glycerol methacrylate) (VII) NVP (*N*-vinyl pyrrolidone) (VIII) EGDMA (ethylene glycol dimethacrylate).

thickness according to the purpose of use. The power of the lens often influences the central and peripheral thickness of the lens. Lens used to treat myopia (lens having negative power) have higher peripheral thickness whereas those which are used to treat hypermetropia (lens having positive power) have higher central thickness. The thickness of the lens often influences the mechanical property and oxygen transmissibility of the lens. Lens having higher thickness have lower oxygen transmissibility. However, as the physicochemical property of the polymer influences the oxygen transmissibility, the choice of monomers used during fabrication has varying effect on the swelling capacity and other parameters such as oxygen

transmissibility and mechanical property of the lens. The nature of crosslinking agent used during polymerisation plays a crucial role as well. Higher concentration of crosslinking agent inhibits the swelling capacity. Thus, the parameters – oxygen transmissibility, mechanical properties and swelling capacity of the lens has cumulative effect on the efficacy of the contact lens drug delivery system. Chemical structures of the monomers used in the fabrication of soft material contact lens are given in (Fig. 2 and 3).

The soft contact lenses are basically prepared from copolymers. Acrylic polymers such as HEMA (2-hydroxyethyl methacrylate) are used for the fabrication of the lens. The chemical

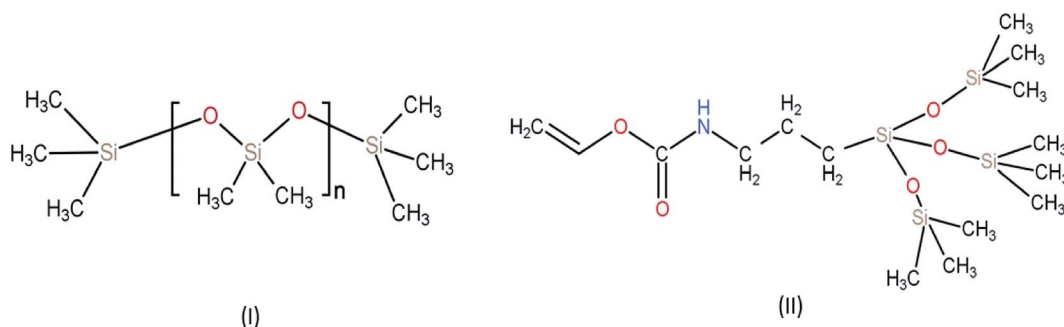


Fig. 3 Chemical structure of monomers used for silicone-based hydrogel contact lens (I) PDMS (polydimethylsiloxane) (II) TPVC (tris(trimethylsiloxy)silylpropyl vinyl carbamate).



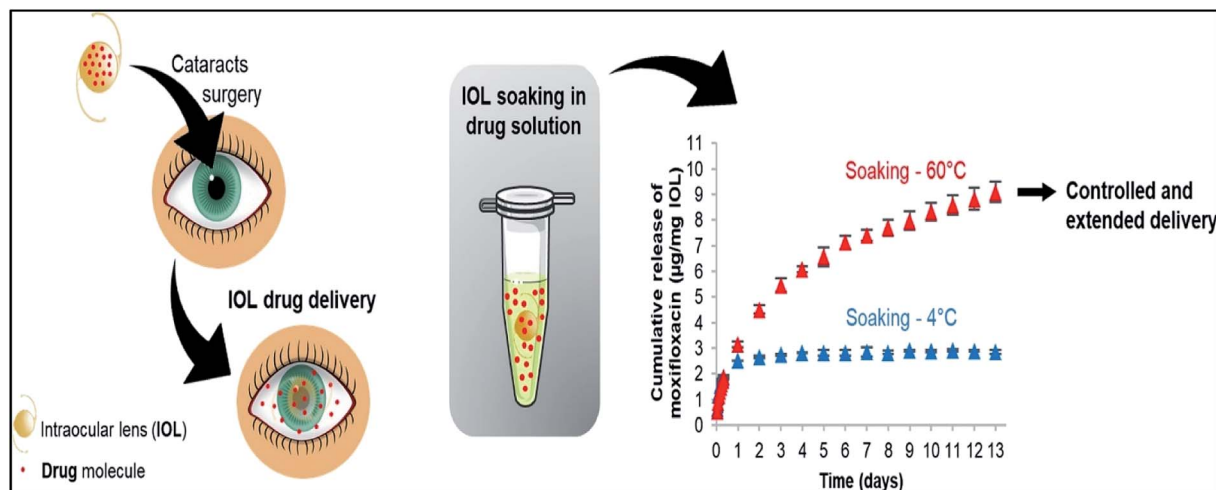


Fig. 4 Effect of loading temperature on the release of drug. Reprinted with permission from ref. 49 copyright (2018), Elsevier.

2. Platforms of ocular drug delivery

2.1. Conventional hydrogel-based contact lens

Hydrogels have been extensively used for the past few decades as a mode of drug delivery due to their unique physicochemical properties. It enables them to be superabsorbent in nature allowing them to absorb and retain a significant amount of water. The water retention capacity depends on the cross linking of the polymer. A vital aspect is the nature in which the water interacts within the hydrogel. The water in the hydrogel can be of three types: bound water; intermediate water and free water.⁴⁶ Free water has the ability to move within the polymeric network without getting hindered by any attractive or repulsive interaction. Bound water remains attached to the hydrophilic groups in the polymeric network *via* hydrogen bonding. Intermediate water is considered to be exchanged with free and bound water. Thus, the hydrophilicity and the polymer cross linking plays a critical role in transport of water within the hydrogel and also the swelling up of hydrogel. They are recently being used to produce soft material contact lenses. Ocular delivery of some drugs has been achieved with the help of soft material contact lenses made from hydrogels which are polymer of hydroxymethyl acrylate (pHEMA).^{47,48} To optimize the performance of the contact lens, hydrophobic monomer 4-vinylpyridine (VP) and ionic monomer, *N*-(3-aminopropyl) methacrylamide (APMA) was incorporated into the polymeric network of pHEMA.⁴⁴ This strategy of polymerization was used successfully for the delivery of NSAIDs (nonsteroidal anti-inflammatory drugs) – diclofenac and ibuprofen. The incorporated monomers kept the viscoelastic properties and the water retention ability of pHEMA hydrogels unaltered. It was observed that the drug uptake capacity of the lenses was enhanced for ibuprofen (upto 10-fold) and diclofenac (upto 20-fold). However, for drug release the pH of the environment plays a vital role. Studies showed that dried loaded pHEMA – APA and pHEMA – VP effectively swelled up on exposure to water but due to the presence of ionic and hydrophobic interactions in the

polymeric system the drug release was less than 10%. When the contact lens was kept in a solution of pH range of 5–8 they showed significant amount of drug release. The high polymeric density of the pHEMA hydrogel helped to achieve sustained release of the drugs. Ibuprofen was released for a period of 24 hours and diclofenac showed a prolonged release of about 1 week.

These conventional contact lenses can be produced by soaking them in the drug solution. The drug uptake and release depend on the affinity with the drug. However, this can be manipulated by altering the loading temperature and the loading time of the drug Fig. 4.⁴⁹ Silicone based hydrogel contact lenses have been fabricated and have been found to be feasible for ocular drug delivery.⁴⁵ These soft material contact lenses have higher ability of oxygen transmission on the corneal surface as compared to conventional hydrogel-based contact lens. These were usually made of polysiloxanes. The flexibility of these lenses along with the ability of oxygen transmission paved the way for a new material for the fabrication of soft material contact lens. The first US FDA approved silicone based contact lens was under the brand name Silsoft manufactured by Bausch and Lomb in 1984. It was patented as 30 day wearable contact lens for aphakia.

García-Millán E. *et al.* studied the effect of chemical and structural modifications of pHEMA (contact lens on the loading and release of corticosteroidal drug, triamcinolone acetonide).⁵⁰ Two different types of contact lens was studied – (a) pHEMA with NVP (*N*-vinyl pyrrolidone) as comonomer; (b) pHEMA with MAA (methacrylic acid) as comonomer. EGDMA was used as a cross linker to fabricate the lens. Varying concentrations of the comonomers were used to check for optimized loading conditions and release kinetics of the drug. Saline solution (0.9% NaCl solution) and PBS buffer solution of pH = 7.4 were used for drug loading. It was observed that the lenses show similar swelling property in saline solution but in case of contact lens with MAA as comonomer, swelling was enhanced in PBS buffer as compared to the swelling in saline solution. MAA, due to the



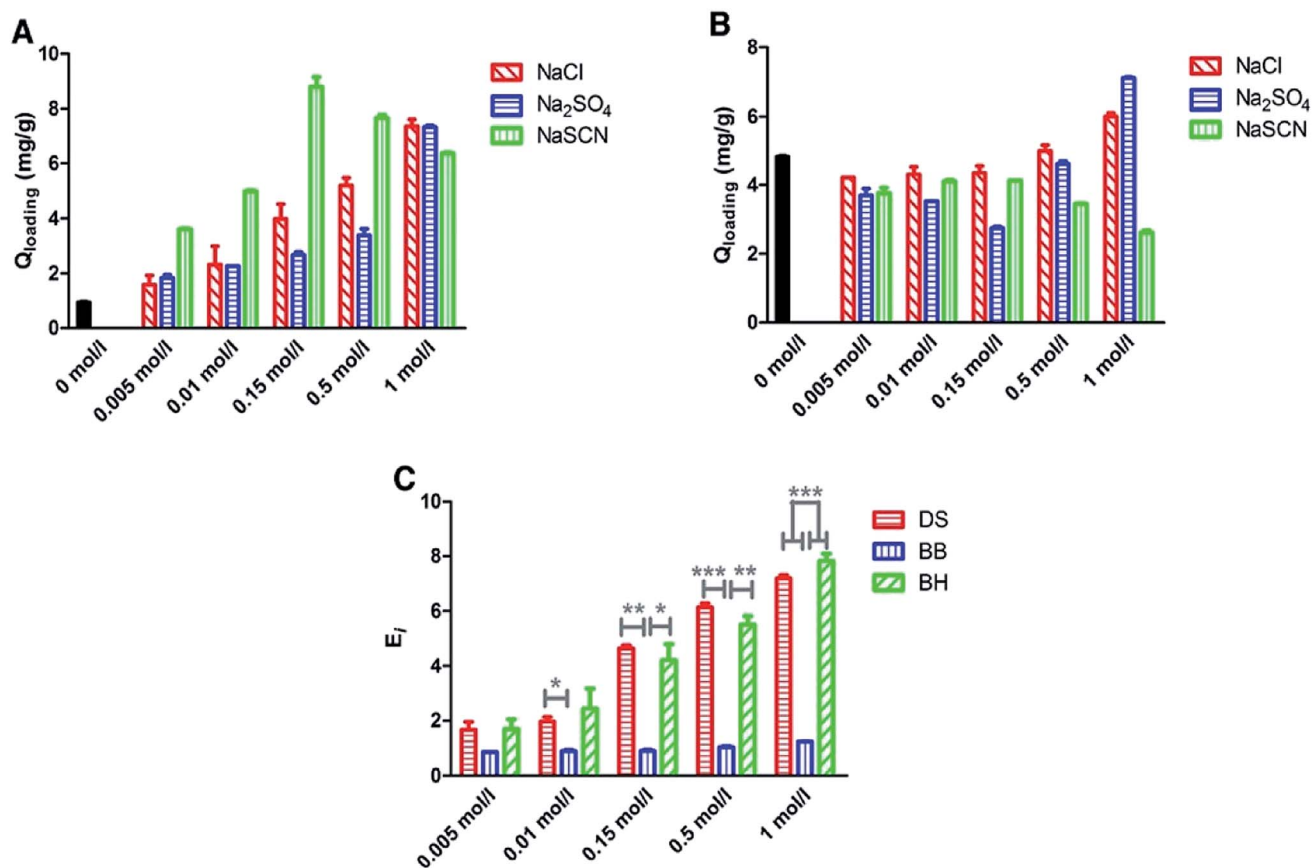


Fig. 5 Loading results of betaxolol hydrochloride (BH) (A) and betaxolol base (BB) (B) in NaCl, Na₂SO₄ and NaSCN solutions with the ionic strength ranging from 0 to 1 mol l⁻¹ and comparison of enhancement factor for diclofenac sodium (DS), betaxolol base and betaxolol hydrochloride in NaCl solutions (C). Each point represents the average of three measurements. (* P < 0.05, ** P < 0.01, *** P < 0.001). Reprinted with permission from ref. 51 copyright (2019) Elsevier.

presence of carboxylic groups has $pK_a = 4.661$. The pH of 7.4 ionises the carboxyl groups in the polymeric structure, thereby increasing the electrostatic repulsion between the carboxyl groups, which causes the hydrogel to swell. The use of comonomers increased the amount of loaded drug in the polymeric network of the lens. The swelling property also influenced the phenomenon of drug loading in PBS buffer. Contact lens having 40% MAA (200 mM) showed the most efficient drug loading in when PBS buffer was used as the drug loading solution. Drug release profiles revealed that all the contact lenses fabricated with varying concentrations of comonomers – NVP and MAA showed similar release kinetics, when they were placed in artificial lachrymal fluid. No lag phase in the release of drug was observed and after 5 hours the release profile showed significant increase in drug release. More than 80% of drug release was achieved in the first 24 hours. So, this specific study showed that 40% MAA (200 mM) when used as a comonomer with pHEMA could be a potential formulation for the anti-inflammatory drug, triamcinolone acetonide. PBS buffer at pH = 7.4 would be the ideal drug loading solution.

The effect of salt induced modulation on the process of drug loading was studied by Zhu *et al.*⁵¹ The loading of three drugs – betaxolol hydrochloride, betaxolol base and diclofenac sodium

into the polymeric matrix of pHEMA contact lens was studied. It was found that use of different types of salts influenced the ionic strength of the drug loading solution and also the solubility of drug, eventually, influencing the process of drug loading. The effect of three salts – NaCl, Na₂SO₄, NaSCN was studied. Drug loading was performed by immersing the dry contact lens in 1 mL aqueous drug solutions. In case of diclofenac sodium, use of NaCl and Na₂SO₄ increased the ionic strength of the drug loading solution leading to enhanced drug loading into the contact lens. However, use of NaSCN significantly reduced the loading of diclofenac sodium. In case of betaxolol hydrochloride, highest drug loading was achieved when NaSCN was used. At physiological ionic strength of 0.15 mol l⁻¹ the amount of drug loading achieved is in the order of NaSCN > NaCl > Na₂SO₄. However, beyond the physiological ionic strength, increasing ionic strength of NaSCN lead to reduced drug loading. In case of betaxolol base, no significant change in drug loading was observed below ionic strength of 0.15 mol l⁻¹. However, on increasing the ionic strength beyond 1.0 mol l⁻¹, an increase in amount of drug loaded was observed during the usage of NaCl and Na₂SO₄. However, use of NaSCN decreased the amount of drug loading. Thus, both the nature of

the drug and the salt system used, has an influence in the drug loading (Fig. 5).

Paradiso *et al.* studied the drug release in two different types of contact lenses – (a) pHEMA based hydrogel (HEMA and PVP-polyvinylpyrrolidone); (b) silicone hydrogel produced by using a hydrophobic comonomer, TRIS (3-[tris(trimethylsiloxy)silyl] propyl methacrylate) and NVP (*N*-vinyl pyrrolidone).⁵² An antibiotic, levofloxacin and an antiseptic, chlorhexidine were used as a model drug in which the contact lenses were soaked for drug loading. The swelling capacity of the hydrogel was dependent on temperature. Both the hydrogels showed decreased swelling on increasing the temperature. However, the pHEMA based hydrogel showed significant changes as compared to the silicone-based hydrogel. The silicone-based hydrogel had lower cross linking than the pHEMA hydrogel due to which the silicone based hydrogel had higher swelling capacity. The swelling capacity was highest at 4 °C, thus, drug loading was performed at this temperature for both the contact lenses. The drug release profile was studied after the contact lenses were soaked for 14 and 36 hours, respectively. The loading time of levofloxacin did not affect its release profile for the silicone based contact lens and the release kinetics shows

that there was an initial burst release. In case of the pHEMA based contact lens, higher loading time increased the duration of release of levofloxacin. The release kinetics also showed that the pHEMA based contact lens shows a controlled release of the drug. Release profiles of chlorhexidine showed that the loading time did not affect the pHEMA based contact lens. The release kinetics also showed that both the pHEMA and silicone based contact lens showed controlled release of the drug, though the silicone based contact lens showed an initial burst.

Minami *et al.* studied the loading and release of the selective histamine H1 receptor antagonist, epinastine hydrochloride (EH) from soft material contact lens having anionic, cationic and non-ionic co-monomers incorporated during the fabrication of the contact lens.⁵³ The ionic nature of the comonomer used, influenced the drug release kinetics. HPMA (*N*-(2-hydroxypropyl)methacrylamide), a non-ionic monomer was used of the fabrication of all the contact lenses. The other non-ionic monomers used were CHDMMA (1,4-cyclohexanedimethanol monoacrylate) and NVP (*N*-vinyl pyrrolidone). HO-MS (mono-2-(methacryloyloxy)ethyl succinate) was used as anionic comonomer. MAPTAC ([3-(methacrylamido) propyl]trimethylammonium chloride) was used as the cationic

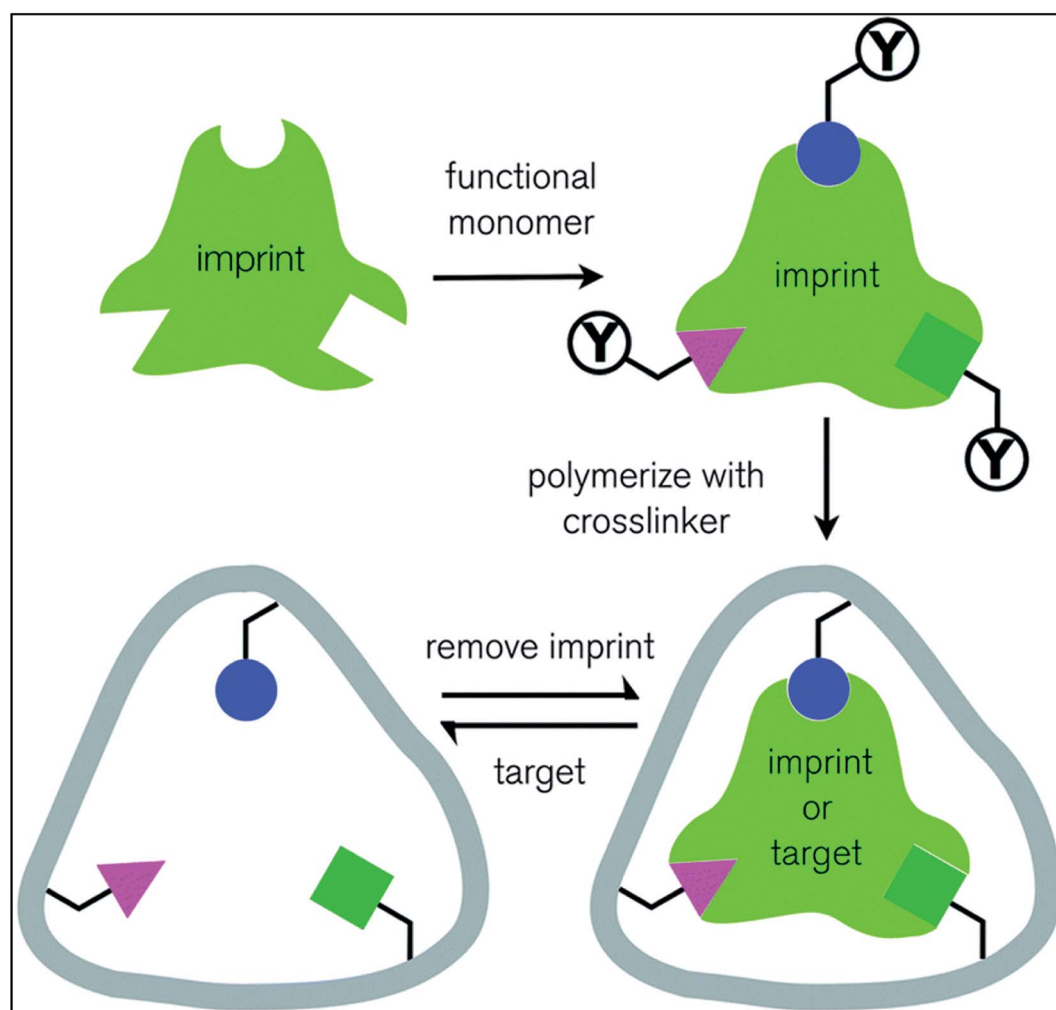


Fig. 6 Schematic representation of molecular imprinting technique. Reprinted from ref. 63 with permission from the Royal Society of Chemistry.



In another important study, Yang *et al.* studied the drug loading and release profile by using eleven types of soft material contact lenses, which are commercially available and are produced from polymers approved by the US FDA.⁵⁴ Pirfenidone (PFD), a drug used for treating scarring in the eyes was used as the model drug. The polymers used in the contact lenses were – Polymacon, Nelfilcon A, Omafilcon A, Hilaflcon B, Ocuflcon D, Etafilcon A, Balafilcon A, Lotrafilcon A, Lotrafilcon B, Senofilcon A, Galyfilcon A. *In vitro* studies showed that polymacon and etafilcon lenses showed highest drug uptake. However, the amount of drug released was higher for polymacon and thus polymacon lens was chosen for the *in vivo* studies. *In vivo* studies showed that as compared to eye drops, the drug loaded contact lens showed higher drug release in different anatomical parts of the ocular system – cornea, sclera and aqueous humour. The *in vivo* release kinetics revealed that there was initial burst release and the drug was released for a period of 150 minutes. The retention time of the drug was 240 minutes in the ocular system, which was higher as compared to pirfenidone eye drops.

In some of the cases an innovative approach to extend duration for drug release was achieved by using Vitamin E as the diffusion barrier over the lens.⁵⁵ Vitamin E is hydrophobic and a potent antioxidant and has low water solubility. It has been found useful in treatment of various eye diseases such as cataract and apoptosis of corneal epithelium. Additionally, Vitamin E serves as protective agent against UV radiation and

prevent corneal damage. Considering the biocompatible nature and therapeutic properties, Vitamin E can be utilised in creating diffusion barriers for various hydrophilic drugs, which diffuse faster in the aqueous environment of tear film. Most of the hydrophilic drugs are charged at physiological pH, hence, a hydrophobic environment created by Vitamin E will serve as an effective drug barrier. Three hydrophilic ophthalmic drugs, timolol (a beta blocker, used for treatment of glaucoma), fluconazole and dexamethasone 21-disodium phosphate (an anti-inflammatory corticosteroid) have been tested for extended release using Vitamin E as a diffusion barrier. Increased lens thickness, reduced ion permeability and slight reduction in oxygen permeability have been observed with negligible toxicity. Although transparency of the Vitamin E coated lenses was maintained, the drugs were observed to have an extended release profile.

Molecular imprinting is an efficient technique to ensure high amount of drug loading into the contact lenses Fig. 6. During polymerization reactions, high affinity cavities are created using the same drug molecules. These drug molecules then serve as memory sites for the drugs. Initially, monomers undergo polymerization whereas drug molecules are mixed during polymerization and released after a network is formed. This creates drug sized pockets of very high affinity for the drug molecules. The properties of the functional monomer, its functionality, composition of the lens, drug release kinetics together comprehend for loading and release of the drug template into the contact lens. However, backbone monomers and other functional monomers decides the layout of structure of the polymeric network and size and shape of high affinity cavities.⁵⁶ Adequate amounts of functional monomers and cross-linking agent should be provided as excessive quantity of them binds the drug molecules so tightly that they are retained in the polymeric matrix for a very long duration, which renders them ineffective.^{57,58}

In 2011, White *et al.*, reported that the concentration of cross-linking agent should be less than 5% to get better contact lenses.⁵⁹ Higher concentrations were reported to increase the network stiffness and reduces drug release rate. However, Hiratani *et al.*, showed that when using DMA (*N,N*-diethyl acrylamide) and EGDMA (ethylene glycol dimethacrylate) as cross-linking agent, the effective concentration was found to be 80 mM. In their study, the authors demonstrated the use of weakly cross-linked hydrogels for the loading of timolol using MAA (methacrylic acid) as functional monomer. The study demonstrates that timolol loading increased effectively. The imprinted adsorption sites enhance the drug loading efficiency of the contact lens.⁶⁰ Different drugs have different capability of release with a range of concentration of MAA monomers. Contact lenses imprinted with dorzolamide show greatest capability to release at MAA with 1 : 4 molar ratio.⁶¹ However, low molecular weight drugs were usually exploited for these studies, another approach using high molecular weight drugs came up in 2009, when Ali *et al.*, demonstrated control of drug release from contact lenses using hyaluronic acid. In their study, the authors observed that hyaluronic acid can be delivered with the release rate of $6 \mu\text{g h}^{-1}$ for 24 hours.⁶²

2.2. Use of nanoparticles for ocular drug delivery by contact lens

Researchers have been trying to use drug loaded nanoparticles conjugated on the surface of the contact lens for improved drug delivery.⁶⁴ The nanoparticle-laden contact lens can be produced mainly by four methods – (a) dispersion of drug encapsulated nanoparticles in the hydrogel monomer (b) formation of micelles by addition of surfactant and drugs to the pre monomer of the mixture.^{65,66} (c) Soaking the contact lens in suspension of the nanoparticles⁴² and (d) attachment of nanoparticles on the surface of the contact lenses by chemical modifications.^{67,68}

In some of the cases, drugs are encapsulated in nanoparticles and loaded in therapeutic contact lenses by dispersing them in HEMA monomers followed by polymerisation of the monomer by using ethylene glycol-dimethacrylate (EGDMA) as a cross linking agent. Process was performed in presence of photo initiator Darocur. Colloidal nanoparticles used for the purpose of ocular drug delivery encapsulate the drug to prevent them from getting degraded by the enzymes such as lysozymes which are present in tear fluid. This increases the residence time in the ocular system. Further studies also showed that a drug delivery system comprising of both the nanoparticles and the contact lens shows a better sustained drug release

profile as compared to either of them when used alone. The drug is released from the nanoparticle into the hydrogel matrix of the contact lens and then it diffuses into the tissues. The use of nanoparticles laden contact lens curbs the leaching of drugs during the process of storage and sterilization. However, a major concern of using nanoparticle-laden contact lens is the aggregation of nanoparticles which would eventually hamper the transparency of the contact lens thus leading to improper vision.

One of the most recent work in this field has been a study of the effect of gold nanoparticles (AuNPs) on the uptake and release of a drug, timolol from contact lens which is a potent non-selective beta blocker.⁶⁹ The release profile of the drug was analyzed under both *in vitro* and *in vivo* conditions. The main objective of this study was to find novel treatment methodologies for glaucoma by the use of therapeutic contact lens. Timolol was used as a model drug as being a beta blocker shows fall in intraocular pressure in the aqueous humour fluid of the eye. The drug loading of the AuNPs was done by two methods – (a) the AuNPs were soaked in a solution of the drug timolol (b) the AuNPs were incorporated into the contact lens during the process of fabrication and then the contact lenses were soaked in two different concentrations of the drug solution. The release kinetics of both the cases were analysed. Both the cases showed

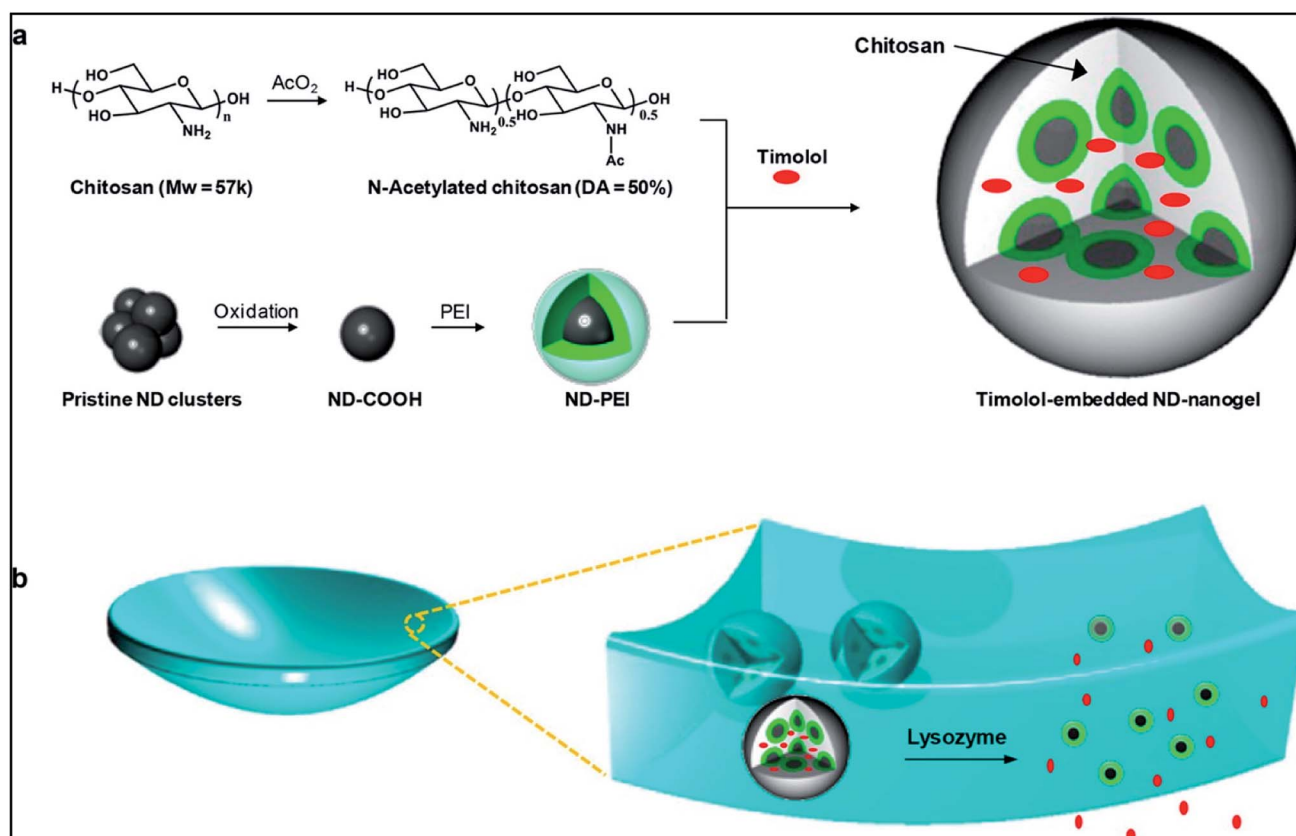


Fig. 7 Schematic illustration of lysozyme-activated drug eluting contact lens. (a) Drug loaded ND-nanogels are synthesized by cross-linking PEI-coated NDs and partially *N*-acetylated chitosan (MW = 57 kDa; degree of *N*-acetylation = 50%) in the presence of timolol maleate. The ND-nanogels are then embedded in a hydrogel and cast into enzyme-responsive contact lenses. (b) Exposure to lacrimal fluid lysozyme cleaves the *N*-acetylated chitosan, degrading the ND-nanogels and releasing the entrapped timolol maleate while leaving the lens intact. Reprinted with permission from ref. 72. Copyright 2014, American Chemical Society.



A major concern of developing therapeutic contact lens loaded with drug is the leaching of drug during storage. The drug should only diffuse out of the contact lens on being placed in the eye. An attempt to curb the drug leaching has been made to develop timolol containing contact lenses which do not show any leaching.⁷⁰ Timolol was encapsulated in crosslinked particles formed by the cross linking of monomers of EGDMA (ethylene glycol dimethacrylate) and PGT (propoxylated glyceryl triacrylate). Then, these crosslinked polymeric nanoparticles were incorporated in the monomers of HEMA before performing polymerization. This work also gave an insight to the drug release mechanism from the polymeric matrix, which could

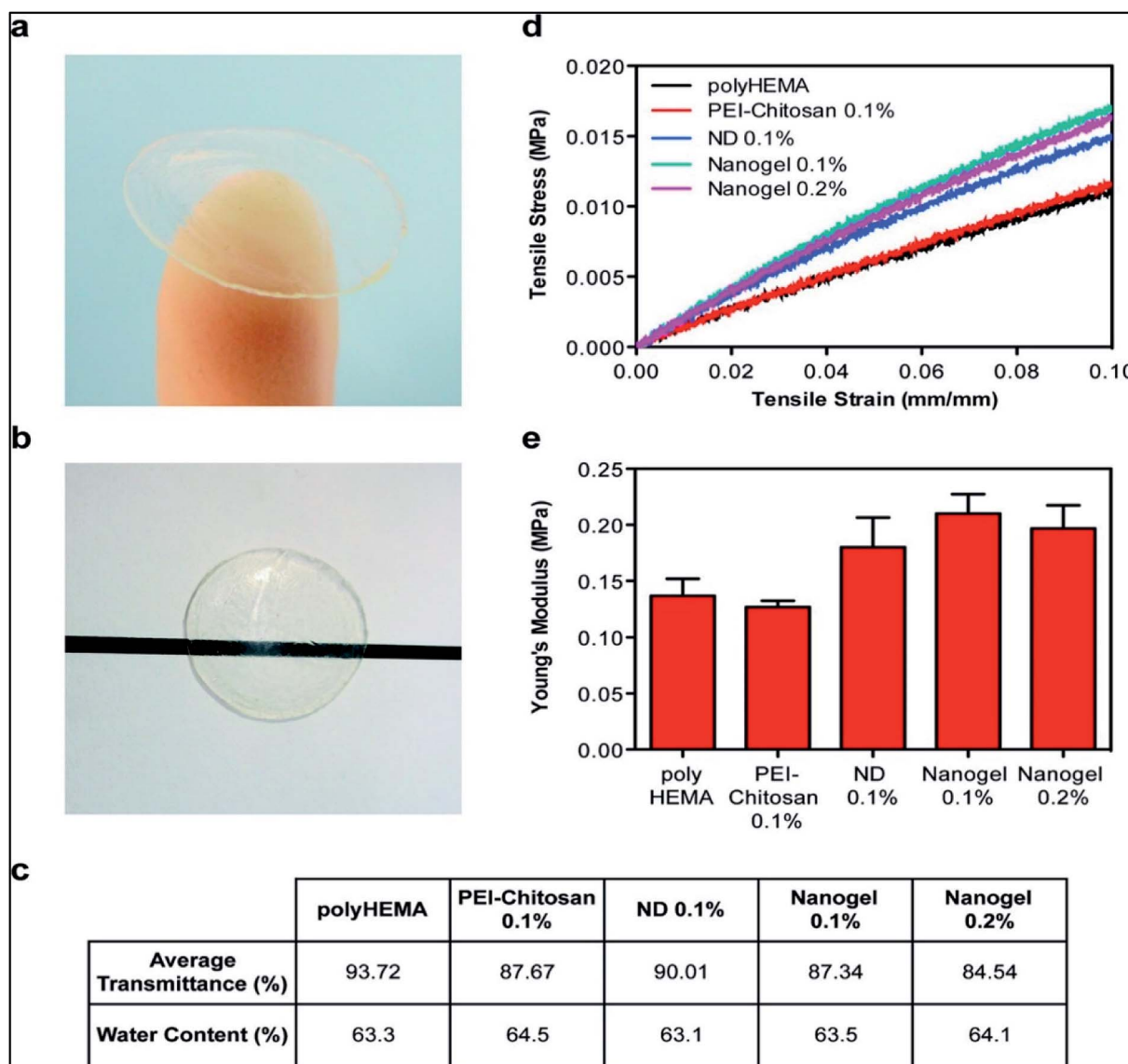


Fig. 8 Characterization of physical properties of contact lenses. (a) ND-nanogels can be embedded into polyHEMA gels and cast into contact lenses. (b) ND-nanogel embedded lenses maintain optical transparency. (c) Comparison of average visible light transmittance (400–700 nm) and water content of polyHEMA lenses without additives, with 0.1% (w/w) PEI-chitosan, with 0.1% (w/w) pristine ND, with 0.1% (w/w) ND-nanogel or 0.2% (w/w) ND-nanogel. (d) Tensile stress–strain curves comparing polyHEMA lenses without additives, with 0.1% (w/w) PEI-chitosan, with 0.1% (w/w) pristine ND, with 0.1% (w/w) ND-nanogel or 0.2% (w/w) ND-nanogel. (e) Young's modulus of the polyHEMA lenses without additives, with 0.1% (w/w) PEI-chitosan, with 0.1% (w/w) pristine ND, with 0.1% (w/w) ND-nanogel or 0.2% (w/w) ND-nanogel, as determined by the first 5% of the stress–strain curve slope. Reprinted with permission from ref. 72. Copyright 2014, American Chemical Society.

Another approach of development of ocular drug delivery system was the use of a pH sensitive drug releasing system.⁷¹ This work helped in developing a system which would also prevent drug leaching when the contact lens would be stored in a specific pH range. Drug release kinetics of two cases was studied – (a) normal contact lenses without nanoparticles in which the drug was loaded directly by the conventional soaking method; (b) nanoparticles of Eudragit S 100, a copolymer of methacrylic acid and methyl methacrylate, was incorporated in the contact lens. Cyclosporine was used as the model drug. This study showed that there was release of drug only above pH of 7.2. So, the therapeutic contact lens could be easily stored at a pH of 6.5 without any drug leaching. The nanoparticle-laden contact lens showed a higher drug release *in vitro* and it also showed a sustained release of the drug cyclosporine. The optical

activity of the lens also remained unaltered. Contact lens loaded with drug by direct soaking showed decrease in the optical activity. Under *in vivo* conditions the nanoparticle-laden contact lens showed higher bioavailability of the drug as compared to *in vitro* conditions and the bioavailability was increased by a significant amount as compared to the conventional eye drops. However, these drug delivery systems show decrease in the oxygen permeability which is a major drawback of this ocular drug delivery system.

Recently researchers have been working in the field of developing nanodiamonds (NDs) for the purpose of ocular drug delivery.⁷² NDs have huge potential to be used as a vehicle for drug delivery as many *in vivo* studies found them to be biocompatible. The unique structural property of NDs allow them to bind reversibly to the drug, thus, influencing the drug uptake and release kinetics. However, ocular compatibility of NDs have not yet been studied but nanohorns, a structure which shows resemblance to that of NDs have been found to be compatible to the eye. The aim of using nanodiamond was to improve the mechanical property of soft material contact lens. Moreover, studies showed that nanodiamond arrays do not interfere with the optical activity of the lens. NDs coated with polyethyleneimine (PEI) were crosslinked with biodegradable polymer chitosan forming a ND nanogel based ocular drug delivery system. Chitosan, when degraded by the enzyme lysozyme present in the tear fluid, caused the release of the drug timolol. Thus, this ocular drug delivery system is an enzyme sensitive system (Fig. 7).

Drug release kinetics study of this system showed that the sustained release of timolol was under the control of the degradation of the polysaccharide chitosan by the enzyme lysozyme. The optical activity and the oxygen permeability of the lens was also within the desired limits. However, this drug delivery system was studied under *in vitro* conditions (Fig. 8 and 9). Studies under *in vivo* conditions would confirm the possibility of clinical application of this drug delivery system paving

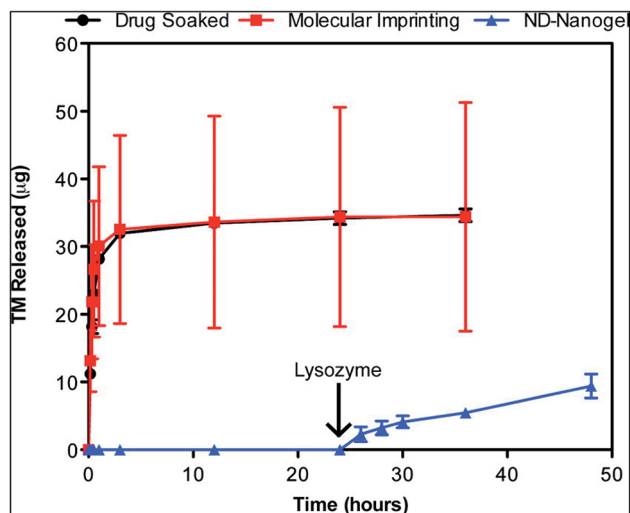


Fig. 9 Enzyme-triggered drug release. Drug-eluting profiles from drug-soaked (black line), molecularly imprinted (red line) and ND nanogel-embedded contact lenses (blue line) in saline solution at 37 °C as determined by HPLC analysis of TM. Lysozyme (2.7 mg mL⁻¹) in PBS was added after 24 h of incubation (*N* = 3 for each type of lens). Reprinted with permission from ref. 72. Copyright 2014, American Chemical Society.

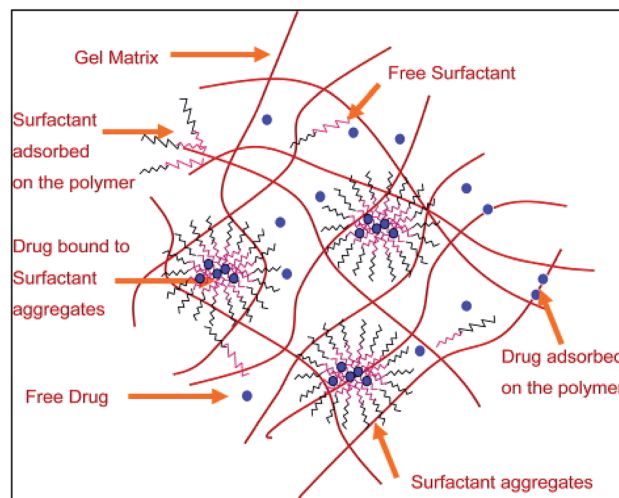


Fig. 10 A schematic representation of the microstructure of the surfactant laden gels. Reprinted with permission from ref. 66. Copyright (2009), Elsevier.

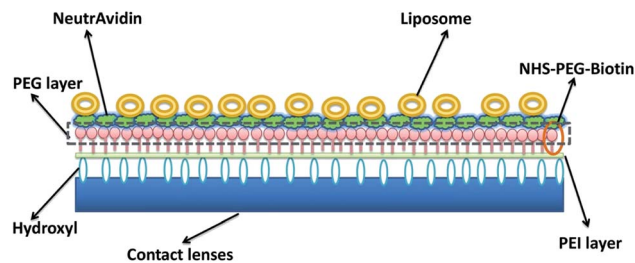


Fig. 11 Schematic diagram of liposomes immobilized on the surface of contact lens. Reprinted with permission from ref. 82. Copyright (2018), Elsevier.

way for a novel therapeutic approach to the treatment of glaucoma.

Chitosan nanoparticles have also been studied for the ocular delivery of anti-inflammatory drug, dexamethasone sodium phosphate (DXP).⁷³ Chitosan nanoparticles were prepared by the crosslinking mediated by sodium tripolyphosphate (TPP). These nanoparticles encapsulated the anti-inflammatory drug DXP. The nanoparticles were incorporated into monomers of

HEMA while fabrication of the polymeric soft material contact lens. *In vitro* studies of this ocular drug delivery system showed enhanced bioavailability as compared to the conventional eye drops. Sustained release of the drug was also achieved. Although there was no significant loss in the optical activity but the oxygen permeability of the lens was affected. So, these contact lenses must only be used for shorter duration of time. Cytotoxicity studies of this drug delivery system under *in vivo* conditions have not yet been done. If this system is found biocompatible then this can be used as therapeutic approach to the treatment of eye injuries. The use of silver nanoparticles incorporated in the contact lens^{74–76} were found biocompatible with the human tissues and had shown antimicrobial effect due to its ability to interrupt the cellular metabolic processes of the microbes. It also interacts with the microbial enzymes, often, causing conformational changes, leading to loss of activity. These silver nanoparticle laden contact lenses can also be used to treat microbial infections in the eyes which are often caused by the prolonged use of contact lens. They were found effective against *P. aeruginosa* and *S. aureus*.⁷⁵

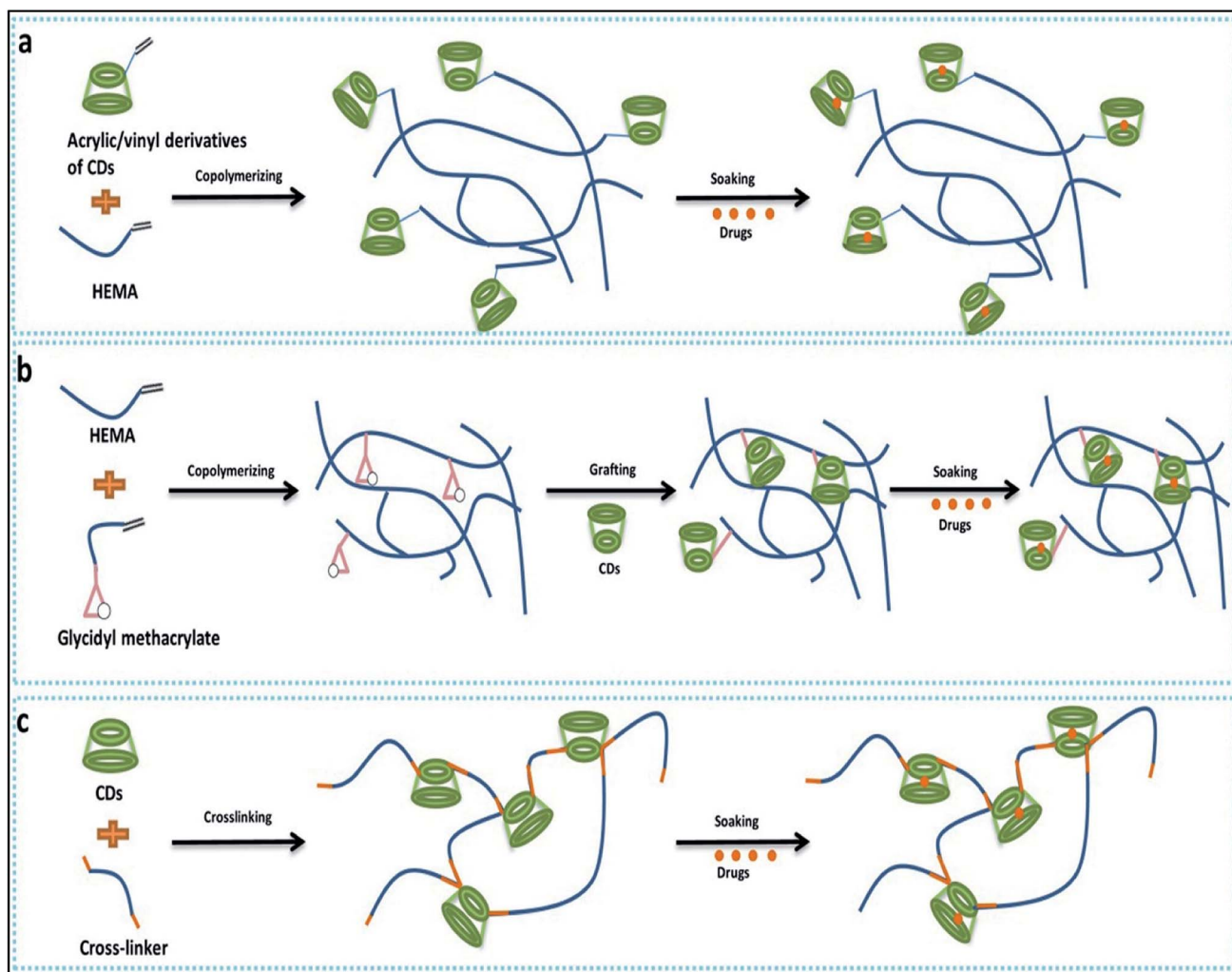


Fig. 12 Cyclodextrin-based contact lens used for drug delivery. (a) Copolymerization of acrylic/vinyl CDs derivatives; (b) grafting of CDs to preformed polymer networks; (c) directing cross-linking of CDs. Reprinted with permission from ref. 82. Copyright (2018), Elsevier.

Polymeric micelles based core-shell nanocarriers are widely used as a vehicle for drug delivery (Fig. 10). Micelles help in achieving sustained release of a drug. Polymeric micelles loaded with drug are incorporated into HEMA hydrogels to develop therapeutic contact lens.^{77,78} The use of surfactant Brij98 along with the drug loaded micelle laden contact lens showed a controlled and extended drug release. There was no initial burst release of the drug. The use of surfactant played a critical role in achieving the controlled release of the drug. Drug release profile showed that the release of the drug was affected significantly by the partitioning of the drug in the surfactant aggregates. Moreover, further analysis showed that pHEMA contact lenses with micelles and surfactant laden in them showed better optical activity than the normal pure pHEMA contact lenses. The oxygen permeability of the lens was also not hampered. Thus, these may be used as an effective ocular drug delivery system.

2.3. Liposomal drug delivery-based contact lens

Ocular drug delivery has also been studied by the incorporation of liposomes in the contact lenses (Fig. 11). In one of the cases, dimyristoyl phosphatidylcholine (DMPC) liposomes were incorporated in poly-2-hydroxyethyl methacrylate (p-HEMA) hydrogels.⁷⁹ DMPC, a lipid was converted to liposomes and loaded with drug, lidocaine. Drug release kinetic studies showed that there was an initial burst in the release of the drug, however, the drug release was decreased significantly after a certain duration of time. This effect was due to the diffusion of drug which slowed down the release process after a certain time. However, this is a major drawback of this drug delivery system. The liposomes on getting aggregated also hampers the

optical activity of the lens, but this can be optimised by manipulating the size of the liposomes to prevent aggregation. The initial burst of the drug can be altered by conjugating the liposomes with polyethylene glycol (PEG).

Therapeutic contact lens can also be produced by surface modification with drug loaded liposomes.⁸⁰ Polyethylene amine was conjugated to the hydroxyl group while surface amine group was conjugated with NHS-PEG-Biotin molecules to prepare contact lenses. Simultaneously, the biotin molecules were bound to neutravidin and further surface immobilized the liposomes containing the PEG-biotin layer possessing neutravidin. The liposomal layer can be of single to multiple layers. Drug release profile of double layer of liposome loaded with levofloxacin showed a release for 30 hours and about ten layers of liposome showed drug release of upto 120 hours.⁸¹ However, multiple layers of liposome affect the oxygen permeability of the contact lens.

2.4. Microemulsion based contact lenses

Microemulsions, integrated with contact lenses, are another set of interesting ocular drug delivery vehicles. They are simple to prepare and sterilise which give them advantage over other drug delivery means. The drug release kinetics depends on microemulsion stability.⁸³ A study shows that oil-in-water microemulsions of the drug timolol were incorporated in the contact lenses that were made up of pHEMA. High drug loading was achieved. However, the drawback in this experiment was a rapid release of the drug. This posed a problem as the drug could not have a long-lasting effect. This drawback was explained by the assumption that pluronic surfactant used in microemulsions doesn't provide with a barrier strong enough to impede drug

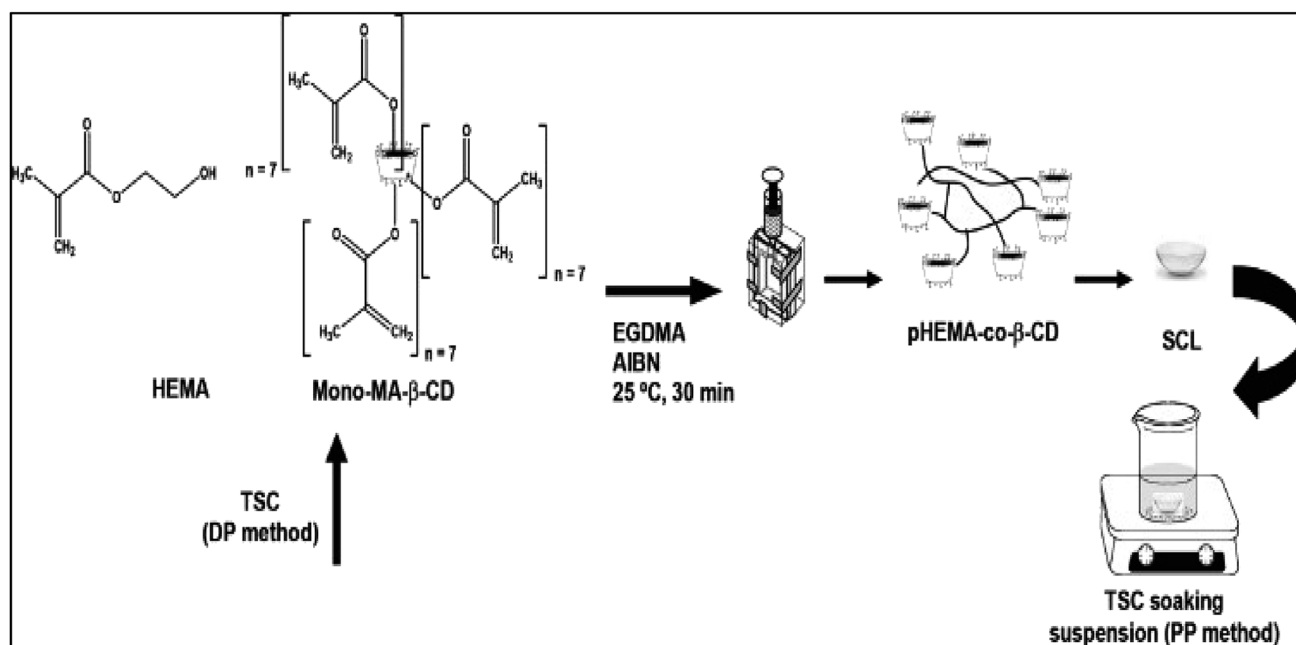


Fig. 13 Schematic representation of the synthesis of TSC (thiosemicarbazone) loaded beta CD conjugated soft contact lenses by DP (during polymerization) method and PP (post polymerization) method. Reprinted with permission from ref. 95. Copyright (2013), Elsevier.



release.⁸⁴ This problem was overcome by using Brij 97 as a surfactant. It was seen that this surfactant enabled slow release of drug, cyclosporine A, from HEMA lenses that were incorporated with microemulsions. It was observed that the release of cyclosporine A from HEMA lenses in *in vitro* conditions was maintained for around 20 days when Brij97 was used.⁸⁵ Another method devised to extend the release of drugs from the lenses was adding a silica shell around microemulsions. Octadecyltrimethoxysilane was used as a silica source. It was noticed that due to the silica shell the release of lidocaine extended upto 8 days, though 50% of the drug got released within the first few hours.⁸⁶ When silica shell reinforced-microemulsions were made using Brij 97 or Tween 20, the HEMA lenses showed lidocaine release over 4–8 days. However, initial burst release was also observed. Moreover, the lenses with microemulsions prepared using Brij 97 showed more transparency than those without use of it.⁸⁷

2.5. Cyclodextrin based contact lenses for ocular drug delivery

Cyclodextrin are cyclic oligosaccharides which contain α -1,4-linkages in α -D-glucopyranose unit. Cyclodextrin's have truncated cone like structure because of glucopyranose having chair conformation. Cyclodextrin are widely used to form inclusion

complexes. While forming inclusion complexes the inner naturally occurring water molecule of cyclodextrin are replaced by appropriate guest moieties (Fig. 12).⁸⁸

Primarily hydrogels were used for designing of drug delivery due to high degree of comfort, significant release of the drug into target and bioavailability. Recent studies have demonstrated that cyclodextrin based hydrogel contact lens that can be a useful addition to ophthalmic drug delivery.^{89,90} Efficient drug loading was reported with CD/Hydrogel based contact lenses as well as the sustained drug release for a prolonged period was also reported.⁹¹ The methods to develop cyclodextrin loaded into contact lenses are classified in three major groups. The co-polymerisation of various monomers used to design soft contact lens with the glycidyl methacrylate provides a polymeric network with binding points for cyclodextrin.⁹² Vivid application of such contact lenses can be envisioned like various hydrophobic drugs used to tackle anti-fungal and antiviral activity in ophthalmology, for example, TSC (thiosemicarbazone), a hydrophobic drug which display a higher tendency to self-aggregate in water, hampers the reproducibility of these drug *in vitro*. This can be improved with cyclodextrin mediated protected delivery of these drugs.⁹³ Contact lens formed after the co-polymerisation of HEMA and GMA, are grafted with the beta-cyclodextrin using the reaction of the

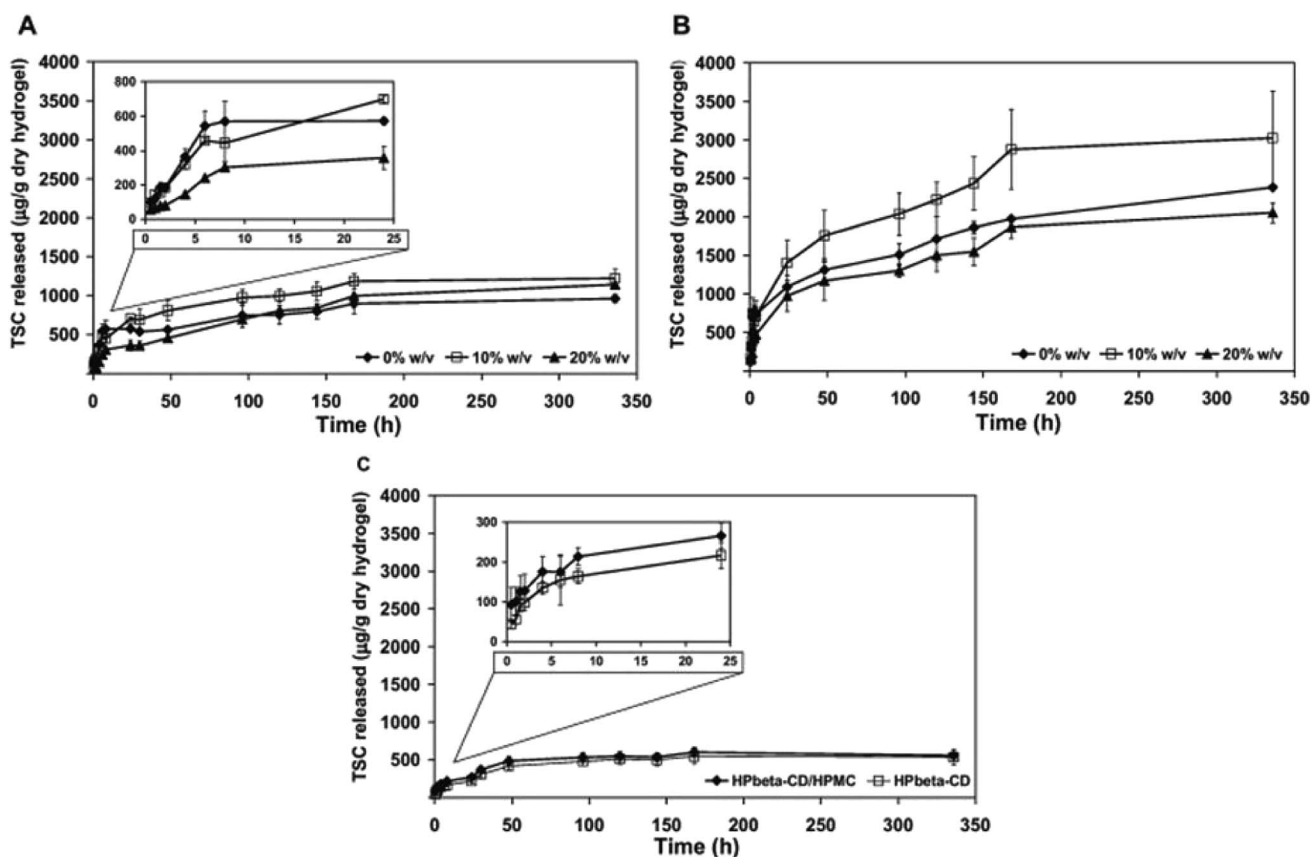


Fig. 14 Thiosemicarbazone release kinetics from different hydrogels over two weeks, at 25 °C. (A) pHEMA-co-β-CD produced by the DP method, (B) pHEMA-co-β-CD produced by the PP method and (C) HPβ-CD and HPβ-CD/HPMC SHHs. The artificial lacrimal fluid medium was replaced to maintain sink conditions every (A) 30 h, (B) 4 h and (C) 8 h. Figure insets show the release during the first 24 h. Reprinted with permission from ref. 95. Copyright (2013), Elsevier.



glycidyl group of contact lens and the hydroxyl group of cyclodextrin under mild condition. By this strategy, soft contact lens with pendent beta-cyclodextrin which is not part of the contact lens structure are made.⁹² As medicated soft contact lenses have various strict requirements like oxygen permeability, device compatibility⁹¹ a CD grafted contact lens can overcome such problems. This soft contact lens with pendent beta-cyclodextrin showed reduction in frictional coefficient by 50% without hampering the useful property of contact lens like optical transparency, swelling degree, glass transition and oxygen permeability. This modified soft contact lens were also checked for their ability like drug loading capacity, drug affinity and sustained drug delivery and reported with approximately 1300% increase in loading capacity, 15 fold in increase in drug affinity and sustained drug delivery for 2 weeks.⁶⁷ Different types of cyclodextrin (alpha, beta, gamma) were also used to check their influence in soft contact lenses, out of which gamma cyclodextrin were noted to have high affinity for contact lens structural network and remarkable decrease in protein deposition.⁹⁴

Contact lens fabricated with crosslinked cyclodextrin use method of hydrogel/CD contact lens preparation, obtained by direct cross-linking of hydroxypropyl- β -CD (HP β -CD) and HP β -CD/hydroxypropylmethyl cellulose (HPMC) (1.0%, w/v) with ethylene glycol diglycidyl ether (EGDE) (Fig. 13).⁹⁵ After preparation, these contact lenses are directly soaked with drug. *In vitro* release assay was performed with 1-indanone thiosemicarbazones drug (TCSS) and sustained release of drugs for 2 weeks was reported (Fig. 14). Finally, antibacterial activity of these drugs was also checked against pathogen associated with eye infection and localized release of therapeutic drug in to the

eye was reported. These contact lenses were 90% transparent as well.⁹⁵ Various entity are essential and should be consider while developing contact lenses based on CD and hydrogel cross-linking like mechanical property, oxygen permeability, and transmittance. Such properties can conquer the suitability of hydrogel/CD based contact lenses. Other novel approaches are also prominent where poly CDs were designed by directly cross-linking CDs with citric acid. Then these poly CDs were loaded with a drug ethoxzolamide and finally incorporated into HEMA. It was reported that sustained drug release occurred for six days and were having extremely high loading capacity.⁹⁶

Copolymerization of acrylic/vinyl CDs derivatives can be performed for preparation of contact lenses. In this method of medicated contact lens preparation, hydroxyethyl methacrylate (HEMA) are copolymerized with methacrylate-derivative of β -cyclodextrin (β -CD) to produce hydrogel having adjustable drug loading and drug release property.^{96,97} With the content of methacrylate β -CD in contact lenses, properties like glass transition temperature and degree of swelling were also affected. Further study were carried out by loading of hydrocortisone and acetazolamide.⁹⁷ It was reported that hydrocortisone loading was decreased while loading of acetazolamide was found to be maximum with decrease in beta-CDs content. The increase in the beta-CDs content increased the cross linking in the polymeric network, thereby, decreasing the pore size. The decreased pore size reduces the water retention capacity of the polymeric network. Drugs such as, hydrocortisone and acetazolamide are loaded into the hydrogel as they had the ability to form complexes with CDs with water molecules of the hydrogel matrix. Thus, increase in the beta-CDs content reduces the drug loading capacity of the

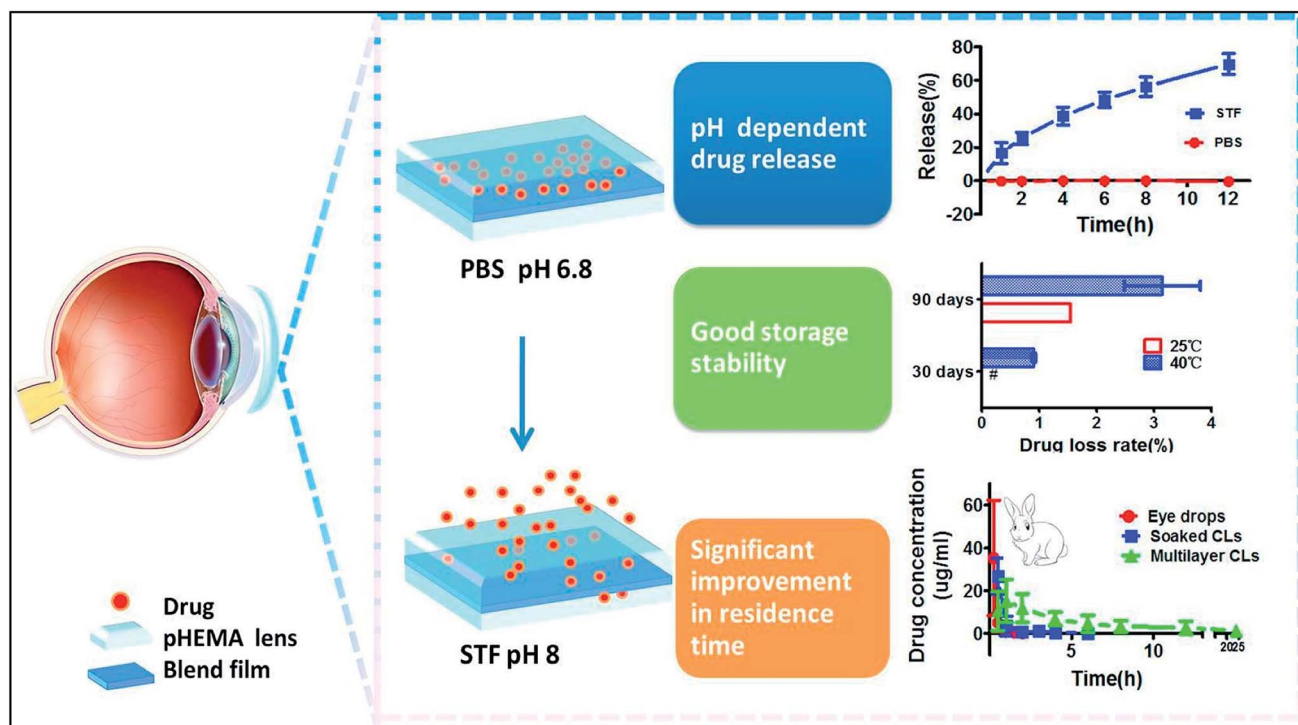


Fig. 15 Schematic representation of the pH dependent release of drug from pHEMA lens embedded with drug. Reprinted with permission from ref. 102. Copyright (2018), Elsevier.



hydrogel. Another study was carried out for investigating sustainable ophthalmic drug release by poly(2-hydroxyethyl methacrylate) hydrogel containing β -cyclodextrin (pHEMA/ β -CD).⁹⁸ Here contact lenses were prepared by photopolymerization of HEMA, mono-methacrylate β -CD (mono-MA- β -CD) and trimethylolpropane trimethacrylate using a cast molding process. It was reported that such mixtures increase in release duration of puerarin, as well as increase in tensile strength and hydrogel swelling.

2.6. Use of drug-polymer film embedding to contact lens

Sustained release of drugs can also be achieved by encapsulation of drug molecules in polymer films. Ciolino *et al.*, developed various types of prototypes that employed this technique. PLGA (poly[lactic-co glycolic acid]) films that were impregnated with an antifungal drug (econazole) in pHEMA were developed as therapeutic contact lenses. These lenses showed antifungal activity against *Candida albicans*.⁹⁹ Ciprofloxacin, a well-known antimicrobial drug for *Staphylococcus aureus*, showed sustained release when encapsulated in PLGA films with pHEMA lenses. Altering the ratio of ciprofloxacin to PLGA can affect the rate of release. pHEMA can also affect the kinetics of drug release.¹⁰⁰ Similar lenses have been developed for treatment of glaucoma. UV polymerisation was used to embed Latanoprost in poly(lactic-co-glycolic acid) films with methafilcon lenses. These lenses showed prolonged release of drug for 30 days and the results were similar to topical application of the same drug. The thickness of the film affects the rate of release for loaded drug.¹⁰¹

Zhu *et al.*, designed two different types of such lenses where drug delivery is controlled by pH or by presence of various ionic species. Diclofenac sodium was embedded in a film made using a blend of ethyl cellulose and Eudragit S100 with pHEMA lenses. When the lenses are stored in a phosphate buffer (pH 6.8), no leaking of drug was observed. When the contact lenses are applied on rabbit eyes, drug release occurs upon contact with tear fluid (pH 8.2) (Fig. 15).¹⁰² A similar prototype that used a mixture of cellulose acetate and Eudragit S100 for the polymer film with a silicone hydrogel base also showed sustained drug release under both *in vivo* and *in vitro* conditions upon pH change in tear fluid.¹⁰³ Ion-triggered drug release was achieved by a silicone-based contact lens with a cellulose acetate film embedded with betaxolol hydrochloride¹⁰⁴ and the drug was conjugated to poly(styrene-divinyl benzene) sulfonic acid resin. The lens could be stored in distilled water with negligible drug loss and allowed controlled release of drug for up to 1 week in rabbit model. The electrolytes present in tear fluid triggers sustained drug release. Carreira *et al.*, developed drug eluting lenses for use after keratoprosthesis as a bandage. Vancomycin chlorhydrate was embedded in a PVA and chitosan blend film that used glyoxal for crosslinking. These lenses showed promising biocompatibility under *in vitro* conditions and sustained drug release for over 8 hours.¹⁰⁵

3. Optimization of contact lenses for clinical application

Infections, allergies, immune reactions, accidental damage to cornea and vascular degeneration are the generally reported

drawbacks of the ophthalmic implants. Thus it can be emphasized that biocompatibility is one of the most important issues which raises concern about the extended wear life of the soft contact lenses (SCLs). Spoilage of contact lenses by the proteins and lipid adsorption is the major factor compromising the biocompatibility of contact lenses.¹⁰⁶ Silicone hydrogels were found to adsorb less amount of protein than the conventional hydrogels. This behavior can be attributed to the hydrophilic properties of the silicone hydrogels which increases the wettability of the surface, and hence less protein adsorption. Protein adsorption are often accompanied by the denaturation and structural changes which accounts for irreversibility of these interactions. Some of the consequences are inflamed cornea, hazy vision, foreign body reactions and disrupted tear film. Protein adsorption from tear fluid to the lens surface can be managed using different measures. Hence, there has been an increasing demand of biocompatible contact lenses, which can provide comfort to the user and can be used as a potential therapeutic drug delivery device. Hydrophobic interactions and static electric field are considered two most important factors which cause protein adsorption.¹⁰⁷ To achieve reduced protein and lipid adsorption, there was a need to increase hydrophilicity of the material used. PEG (polyethylene glycol) is a condensation polymer of ethylene glycol and it possess some unique properties such as strong polarity, high water solubility and hydrophilicity. PEG has been widely used to modify the surfaces of materials. Being long chain polymer and electrically neutral in wide range of pH, it can resist electrostatic interactions between protein and lens surface. Polymerization, grafting and immobilization on the lens surface are some of the common ways to introduce PEG and to decrease the surface roughness.¹⁰⁸

The siloxane based lens are relatively more hydrophobic as compared to that of pHEMA lens. Lipids present in the tear fluid are deposited on the surface of the contact lens, thereby decreasing the wettability of the contact lens. Hydrophilic copolymers carry functional groups which make them soluble in water, thus, they have the potential to increase the wettability of the contact lens on being incorporated into the polymeric network of the contact lens. PVP (polyvinylpyrrolidone),

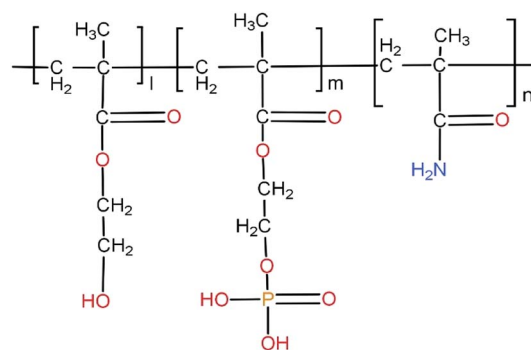


Fig. 16 Chemical structure of poly(HEMA-co-MOEP-co-Mam). The presence of phosphate groups in the side chain of the polymer forming hydrogel is seen.

activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

After manufacturing the lenses, they must be sterilised against contamination and preserved until they are used. Some of the major methods for the sterilisation and packaging of contact lenses are

(iv) Appropriate measures should be taken to keep the packaging intact during sterilisation process.

The properties of the biomaterial must be preserved after sterilisation and the agents used for sterilisation should not alter the composition of the drug. Depending on the material and drug used, suitable sterilisation techniques must be optimised.

The swelling behaviour of the contact lens is a significant study to understand the optimization of drug loading and delivery. It gives the effect of any incorporated material on the structural integrity of the contact lens. Maulvi, F. A. *et al.*, studied the swelling behaviour of gold nanoparticles and timolol incorporated contact lenses. They observed an insignificant increase in % swelling of the drug-laden contact lens compared to the blank contact lens.⁶⁹ This increase may be due to the effect of incorporated nanoparticle and drug on the crosslinking capacity of the fabricated lens. The dry weights of the blank contact lens (lens without soaking) and nanoparticles-drug soaked contact lens were measured and the swelling capacity measured using the formula

$$\% \text{ Swelling} = \frac{W_s - W_d}{W_s} \times 100$$

Water content and optical transparency is an important parameter to compare between a blank contact and drug-laden contact lens. Optical transparency is measured by calculating the transmittance percentage using an UV spectrophotometer in the range of 200–800 nm.^{69,71}

Depending on the chemical nature of the drug, different methods are adapted to measure the amount of drug uptake by the lens. Solvent extraction and colorimetric analysis are two of the important methods to study drug uptake and release. During the solvent extraction method, a solvent in which drug

A major aspect of ocular drug delivery deals with the microbial interactions on the interface of contact lens and surface of the eyes. However, various attempts have been made to provide antimicrobial activity to the soft contact lenses to deal with such issues. Incorporation of selenium,¹¹⁴ silver,¹¹⁵ cationic peptide,¹¹⁶ NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)^{117,118} phosphoryl choline,¹¹⁹ fimbrolide-coated,¹²⁰ PEO coated¹²¹ were the strategies analysed for the effective antimicrobial behaviour of soft contact lenses. These modifications proved to be effective to some extent, however, they were also associated with certain limitations. Surface coatings such as Mel4 peptide coatings,¹²² covalently attached melamine^{123,124} and immobilized nanoparticle coatings like Zn-doped CuO¹²⁵ have been observed to show stable and efficient anti-microbial

The elution assay is an indirect assay that is used to measure the cytotoxicity effect of extract solution from the test material. It does not measure the physical or mechanical impact because the test material is not in direct contact with the cells.¹³⁰ Danion *et al.*, investigated the potential toxicity of the extracted solution from a soft contact lens coat with liposomes on the epithelial cells.¹²⁹ They incubated the lens on the culture media, which was then used for the growth of the cells without involving direct contact of the lens and calculated the cell viability by XTT

6. Future perspective

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properties. However, it must be ensured that properties such as oxygen transmission and optical clarity should never be compromised during the production of drug delivering soft material contact lens.

Conflicts of interest

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