RECENT ADVANCES IN DRUG DELIVERY TO POSTERIOR EYE

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Abstract: Posterior eye segment diseases such as diabetic retinopathy, age-related macular degeneration, retinoblastoma, macular edema secondary to retinal vein occlusion, retinitis, etc. cause vision impairment and blindness to millions of people. Treatment and management of such diseases requires availability of therapeutic concentration in the posterior segment. However, anatomy and physiology of ocular barriers prevent efficient drug delivery to the posterior segment. The design of a drug-delivery system targeting the posterior segment is a challenging ophthalmological task. This review describes the recent progress of more efficient drug delivery technologies. Drug delivery systems that provide optimal pharmacokinetics, optimum dose intervals and significantly less invasive routes of administration are being produced. Solid lipid nanoparticles, nanostructured lipid carriers, submicron sized lipid emulsions and other colloidal nanoparticle carriers appear to be useful for enhancing the ocular absorption of drugs and for providing selective and prolonged drug concentration in the eye after topical instillation. In addition to this, Periocular drug delivery devices such as hydrogel contact lenses, implants that can deliver controlled and continuous biologics directly to the back of the eye and microneedles for targeted drug administration are being tested.

Keywords: Posterior eye, Nanotechnology, Hydrogel lens, Implant.

1. Introduction

Diseases which affect the posterior segment of the eye have led to vision impairment and blindness in millions of people. Significant strides in our understanding of the molecular pathways that are involved in ocular diseases of the back of the eye have enabled the discovery of new biomarkers and drugs for managing these diseases[1]. However, treatment and management of these diseases continues to be a challenging task due to the anatomical and physiological ocular barriers that limit entry of therapeutic agents. The conventional routes of administration of drugs have significant limitations. Topical drug applications which are usually formulated as solutions, suspensions or ointments are used to treat ocular diseases. However, anatomical and physiological barriers present in the eye do not allow sufficient amount of drug to reach the posterior segment. The oral and intravenous routes are rarely used in ophthalmology, as satisfactory drug concentration in intraocular tissues is hard to achieve[2].

Also, systemic drug delivery can lead to toxic side effects. Intravitreal delivery allows for high concentrations of a drug to be delivered

directly to the retina, but the necessary surgical procedure often requires repeated injections that can cause cataracts, retinal detachment, infection, and/or vitreous hemorrhage. Therefore, new routes of drug administration are being studied. The transscleral delivery of drug has emerged as a more attractive method for treating retinal disorders because it can deliver a drug locally and is less invasive. Because of its large surface area and high degree of hydration, the sclera is permeable to drugs of different sizes.

The use of nanotechnology is being investigated for several different ophthalmic applications for back of the eye diseases. These applications include improved drug and gene delivery to the target tissue for the treatment of posterior segment disorders (e.g., choroid and retina), improving diagnostics, and retinal prosthesis. Various drug delivery devices in the nanoscale include solid lipid nanoparticles, nanostructured lipid carriers, submicron sized lipid emulsions, colloidal nanoparticle carriers, etc. Certain nanoparticles can gain access to the intracellular environment due to the process ofendocytosis and are being pursued extensively as a safer alternative to viral gene-delivery. Nanodevices are also being pursued in the development of retinal and cortical prostheses and retinal implants. Nanoparticles promise to play an important role in ophthalmology because they show the intrinsic capacity to adhere to the ocular surface and reach out to the epithelial cells depending on their physicochemical characteristics, such as size, shape and surface charge[3].

A hydrogel contact lens for delivering drugs to the eye has been developed. Targeted drug delivery to chorioretinal tissues of the eye can be achieved through the suprachoroidal route of administration using a microneedle device that is minimally invasive. This device is presently being tested on animals.

2. Physiology of eye

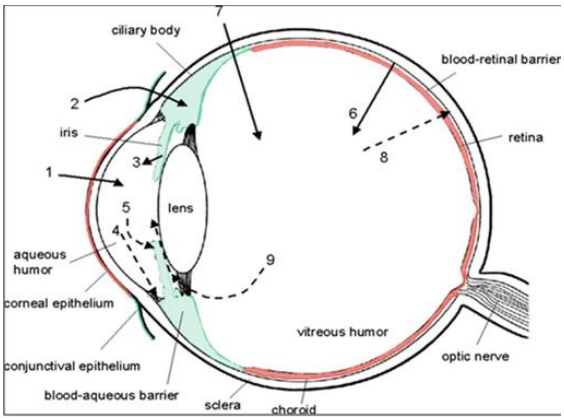

Fig 1[4]: Routes of drug kinetics illustrated in the ocular structure.

1) Transcorneal permeation to the anterior chamber from the lacrimal fluid
2) Drug permeation into the anterior uvea via non corneal route
3) Drug distribution into the anterior chamber through the blood stream via blood-aqueous barrier
4) Drug removal to the Sclemm's canal and the trabecular meshwork by the turnover of aqueous humor from the anterior chamber
5) Elimination of drug from the aqueous humor into the systemic circulation
6) Drug distribution to the posterior eye through the blood-retina barrier from blood

7) Intravitreal drug delivery
8) Elimination of drug from the vitreous via posterior route through the blood-retina barrier
9) Elimination of drug to the posterior chamber via anterior route from the vitreous.

2.1 Ocular surface

The flow of lacrimal fluid extensively removes the compounds deposited on the surface of the eye. The lacrimal turnover rate is only about 1 μl/min but the excess quantity of the instilled fluid flows to the nasolacrimal duct rapidly[4]. Systemic absorption of drug instead of ocular absorption facilitates drug removal. Drug solution present in the conjunctival sac can be absorbed directly into the systemic circulation through the local blood capillaries. Most of drug dose having low molecular weight is absorbed into systemic circulation rapidly in a small amount of time. This explains the low ocular bioavailability of less than 5%. The drug concentration in lacrimal fluid is significantly affected by absorption into the systemic circulation. Ergo, drug release at a constant rate from solid delivery system to the tear fluid can achieve ocular bioavailability of at most 10% as most of the drug is eliminated by the local systemic absorption[5].

2.2 Lacrimal fluid eye barriers

The other barrier to drug absorption into the eye from lacrimal fluid is the one formed by the cells of corneal epithelium. The corneal barrier is formed as the epithelial cells mature. The mature cells are mainly present close to the centre of cornea and in the apical region. The cells present in the apical region form tight junctions and reduce paracellular drug absorption. Still, drugs mainly enter through the transcorneal route to the acqueous humid from the lacrimal fluid[7].

2.3 Blood ocular barriers

Another barrier is the blood ocular barrier. Blood-aqueous barrier and blood-barrier together form this barrier. This barrier does not allow the entry of albumin proteins present in the plasma into the aqueous humor. The hydrophilic drugs present in plasma can enter into the aqueous humor only up to a certain extent. However, the permeability of this barrier is not well defined. Inflammation can affect the integrity of this barrier.

Retinal pigment epithelium (RPE) and walls of retinal capillaries form the barrier between blood stream and the posterior part of the eye. The capillaries present in the choroid have extensive blood flow. Drugs can easily enter into the extravascular space of the choroid, but thereafter the RPE and retinal endothelia limit their access to the retina. Also, blood flow in the choroid is a very minor fraction of the blood flow in the entire body. Ergo, specific targeting systems need to be developed[8].

3. Recent development of novel drug delivery systems targeting the posterior segment

3.1 Nanotechnology

Nanotechnology is a current hot-topic issue because of its potential to significantly impact several fields related to chemistry, engineering, biology and medicine. Some materials at the nanoscale exhibit unique electrical, mechanical, magnetic, optical, and chemical properties. These properties may be put to use in improving the physical, physicochemical or biological aspects of drugs as well as drug delivery systems[1].

3.1.1 Fundamentals of nanosystems[1]:

Nanosystems exhibit the following properties:

1. Enhanced cell uptake and gene delivery
2. Reduced settling velocity
3. Interactions with large area of cell surface
4. Larger drug particles which results in sustain release for longer periods
5. Enhanced permeation and retention effect increases nanoparticle tissue accumulation
6. Nanomedicines offer a multitude of functions as opposed to being passive carriers

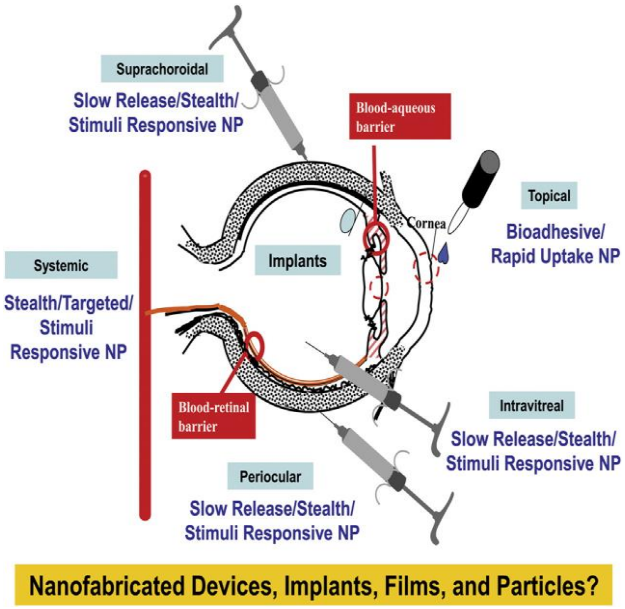

Fig 2[1]Routes of administration (topical, intravitreal, suprachoroidal, periocular and systemic) for delivering different types of nanoparticles (NP)(bioadhesive/rapid uptake, sustained release, stealth, targeted, and stimuli responsive) to the back of the eye.

In addition, future applications of nanotechnology include nanofabricated devices, implants, films, and particles.

In this review, we look at two drug delivery systems that have been developed on nanoscale:

3.1.2 Lipid emulsion drug delivery system:

Submicron-sized lipid emulsion can act as efficient drug carrier for delivery of drug via eye drops to the posterior segment. High pressure homogenization system was used to obtain different formulations of lipid emulsions.

Characterization of liposomes.

	Mean particle size (nm)	Zeta potential (mV)
EPC MLV	5750	−97.5
DSPC MLV	6450	−101.1
EPC ssLip	125.3	−62.9
DSPC ssLip	105.4	−66.2

Fig 3: EPC: egg phosphotidylcholine; ssLip: submicron-sized liposomes; MLV: multilamellar vesicles; DSPC: disteroyl phosphotidylcholine

On administration of lipid emulsion, fluorescence was observed (can be seen in Fig 3) in the retina. Coumarin-6 was used as the model drug and fluorescent marker. The efficiency of the drug delivery was not affected by the inner oil property and the phospholipid emulsifier. Functional polymers chitosan (CS) and poloxamer 407(P407) and a positive charge inducer were employed to modify the surface of the emulsion. Surface modification did increase the fluorescence intensity in the retina. The surface modified emulsions could interact electrostatically with the eye surface. The retention time on the eye surface of the lipid emulsion might have increased due to poloxamer 407 as it is a surface modifier and exhibits adhesive property[9].

It is assumed that the lipid emulsion enters the ocular posterior segment mainly through the non-corneal route in accordance with the study carried out by Hironakaet al[13]. Also, after investigating the properties of various formulations and conducting an in vivo study in mice, it was found that the charge properties of the lipid emulsion had greater impact on intraocular drug delivery than the formulation itself. Furthermore, in accordance with the results of in vivo study of surface modified formulations, CS and P407 could significantly enhance the delivery of coumarin-6 to the retina[9,10].

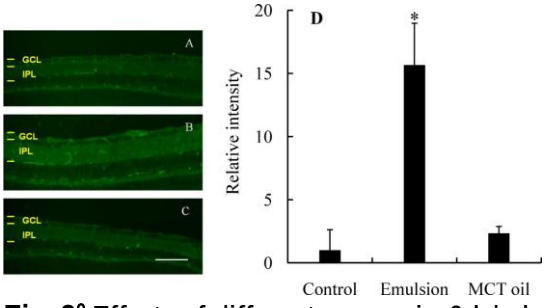

Fig. 3[9] Effects of different coumarin-6-labeled formulations on delivery efficiency in mice retina. Representative epifluorescence microscopic images of the retina30 min after eye drop administration. (A) Untreated (control) (B) coumarin-6-loaded lipid emulsion (formulation A)(C) coumarin-6 dissolved in MCT (D) the accumulated fluorescence intensity in the IPL after eye drop administration in mice

Changes in the viability of conjunctival and corneal cells in the presence of liposomes are shown in Fig. 5. The viability of conjunctival and corneal cells remained unchanged when the cells came into contact with these liposomal suspensions. This confirms very low cytotoxicity of these liposomes. Benzalkonium chloride solution (0.01%) significantly decreased viability, although this concentration of benzalkonium chloride is most commonly used in eye drops.

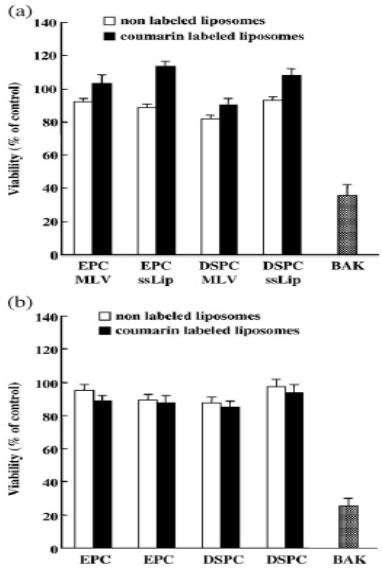

Fig 5: Viability of conjunctival cells and corneal cells after exposure to liposomes as measured by MTS test (mean±SEM,n=8) (a) Conjunctivalcells and (b) Corneal cells. BAK: 0.01% benzalkonium chloride in HBSS:HPP buffer .

The negatively charged liposomes used in this study are found to be highly biocompatible with low toxicity in ocular cells.

In conclusion, delivery of hydrophobic drugs to the posterior segment of the eye via eye drops using submicron-sized lipid emulsion has great potential. Also, the efficacy of lipid emulsions can be enhanced by changing their surface properties. Further research to enhance the ophthalmic bioavailability of drugs should build upon these observations.

3.1.3 Nanostructured lipid carriers: Joana Araújo et al studied the usefulness of nanostructured lipid carriers (NLC) for ocular absorption enhancement of the drug Triamcinolone acetonide (TA). NLC was used to encapsulate TA so as to increase its bioavailability. This was optimized by using a factorial design approach. High pressure homogenization system was again used to obtain nanometric, unimodel and negatively charged NLC. NLC was loaded with fluorescent Nile red lipid marker (NR-NLC) and drug TA (TA-NLC). Also, a combination of lipophilic and hydrophilic surfactants was chosen.

Solid lipid	6.300 %
Liquid lipid	2.700 %
Hydrophilic surfactant	1.800 %
Lipophilic surfactant	0.200 %
TA	0.025 %
Water	Up to 100

Table 1: Composition of the previously optimized TA-NLC formulation

In addition, the encapsulation efficiency (EE) and loading capacity (LC) of TA in NLC were assessed indirectly, determining the free TA (non-encapsulated) by reverse-phase high performance liquid chromatography (RP-HPLC), using a modification of the USP method, and applying the following equations:

$$EE(\%) = \frac{\text{Total amount of TA} - \text{Free TA}}{\text{Total amount of TA}} \times 100 \quad (1)$$

$$LC(\%) = \frac{\text{Total amount of TA} - \text{Free TA}}{\text{Total amount of lipid}} \times 100 \quad (2)$$

After instillation of NR-NLC via eye drops in mice, in vivo tests were done so as to study the behavior of NLC after they were dropped into the eye, sections of sliced eye tissue were obtained and time-course observation was carried out[11].

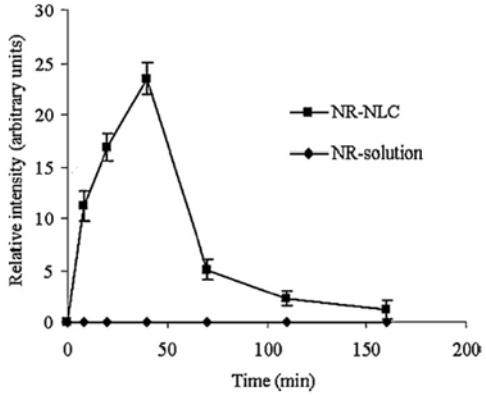

Fig.6 Accumulated fluorescence intensity variation observed after eye-drop administration of NRNLC and NR-solution in the inner plexiform layer. The results are expressed as mean ± S.D (n=3)

Among the desired product characteristics of these nanoparticles is their physical stability. During storage, lipid nanoparticles have shown to lose their physical stability as they form a heterogeneous system and are thermodynamically unstable. However, on optimizing the stabilizer composition, these particles can remain stable for several years[12]. High performance stability analysis was done using Turbiscan®. This was done so as to assess the short and long-term stability of TA-NLC. Backscattering of less than 1.5% was observed. Also, for a period of 6 months, it can be anticipated that these particles would not aggregate to a great extent if stored at room temperature. The data provided by the stability studies show that higher temperature has an important role to play. NLC kept at RT revealed higher stability and lower rates of loss of encapsulated corticoid in comparison with those stored at 4 ◦C. In both cases, the size was kept in the nanometric range, while in the case of storage at 40 ◦C, NLC completely lost their crystalline structure and creamed after 2 months.

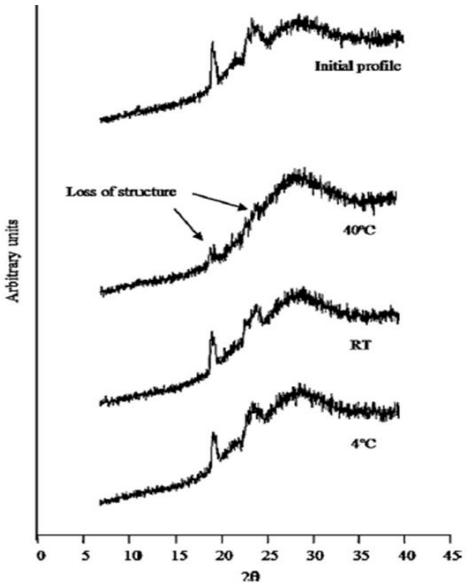

Fig.7: X-ray diffraction patterns of nanostructured lipid carrier within the day of production (initial profile) and after 6 months of storage at 40°C, room temperature(RT) and 4°C.

The crystalline structure of the lipid particles, which is related to the chemical nature of the used lipids, is a key factor to decide in determining whether a drug will be expelled or firmly incorporated for longer time. The above figure shows the Wide angle X-ray scattering (WAXS) profiles for nanostructured lipid carriers stored at different temperatures. The regular crystalline structure is clearly preserved during the storage time for NLC stored at 4°C and RT while NLCs stored at 40°C lost their regular crystalline structure.

Results from the study in mice, evidence the possibility of drug delivery to posterior segment by NLC carriers, making these nanoparticles a promising approach to provide selective and prolonged drug concentration in the eye. Of the various new

drug delivery systems, colloidal nanoparticle carriers studied in this work appear to be useful for ocular absorption enhancement of drugs possibly acting via multidimensional mechanisms, namely, by prolonged drug residence time in the ocular surface and conjunctival sac, by sustained drug release from the delivery system, and/or by reduced precorneal drug loss[11,13].

An extrapolation from animal data to human data should be carefully carried out because of species differences. However, a better understanding about the behaviour of instilled drugs and a thorough knowledge of the physiology of the eye will result in development of useful drug delivery systems.

3.2 Hydrogel contact lens

Ophthalmic drug delivery via contact lenses is more effective as it leads to a larger fractional intake of drug by the cornea. It also increases the drug residence time. Hydrogel contact lens has the potential to develop into an ideal drug delivery system as:

1. In the present-day, people can wear the soft contact lenses for a long period of time (1-15 days).
2. The lens and the cornea enclose the post lens tear film (POLTF). The drug diffuses into this layer. The residence time of the drug would increase as the POLTF and the outside tear film mix to a very small extent.
3. The contact lenses are made up of cross-linked gels, and thus, it is easy to entrap the drug in the gel matrix. This can be done either by adding the drug during the polymerization process or by soaking the lens in the drug solution[14].

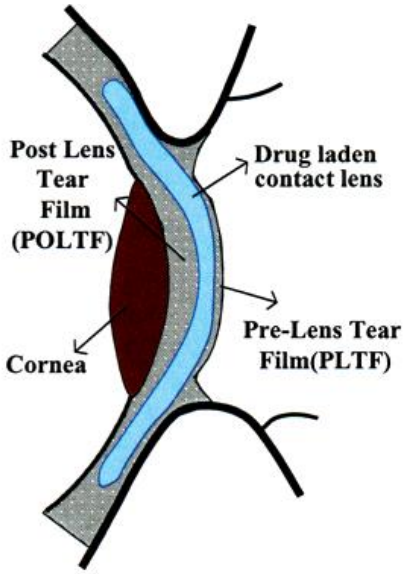

Fig. 8

While a number of in vitro studies have been done to study drug delivery by contact lenses, relatively few in vivo studies on ophthalmic drug delivery by contact lenses have been done. Chi-Chung Li and Anuj Chauhan have developed a model to study the drug release from a contact lens and the subsequent uptake by the cornea. The model assumes Fickian diffusion in the contact lens and takes into account the convective enhancement in mass transfer in the postlens tear film due to the flow driven by the oscillation of the contact lens during the blink. The amount of drug that enters the cornea has been determined for two extreme cases. The first case corresponds to a rapid breakup of the prelens tear film, which prevents drug loss from the anterior lens surface. The second case corresponds to a situation in which the prelens tear film exists at all times and, furthermore, the mixing and the tear drainage in the blink ensure that the concentration in this film is zero at all times. These two cases correspond to the minimum

and the maximum loss to the prelens tear film and thus represent the highest and the lowest estimations for the fraction of the entrapped drug that diffuses into the cornea. The amount of drug that enters the cornea varies from 70 to 95% for the first case and from 20 to 35% for the second case[15].

The results of this study show that a soaked contact lens can significantly reduce the drug wastage and the side effects associated with the entry of the drug into the systemic circulation. However, a soaked lens can supply only a limited amount of drug. This technique is especially inefficient in delivering hydrophobic drugs by HEMA (hydroxyl ethyl methacrylate)-based contact lenses. Second, even for drugs that can absorb in the lens matrix, the drug-release time scale is only a few hours. Thus, a soaked contact lens cannot deliver drugs for extended period of time[15]. However, despite these deficiencies, it is clear that a soaked contact lens is a much more efficient vehicle for ophthalmic drug delivery than the conventional eye drops.

3.3 Scalable controlled-release device

Takeaki Kawashima et al have developed a transscleral drug-delivery device which is designed for the administration of protein-type drugs and consists of a drug reservoir covered with a controlled-release membrane.

A membrane-based capsule that can be implanted on the sclera almost noninvasively by minor surgery and prolongs the controlled delivery of BDNF (brain-derived neurotrophic factor) and other protein-type drugs to the retina with zero-order kinetics has been developed and tested. The designed capsule consists of two parts, a molded triethylene glycol dimethacrylate (TEGDM) reservoir to contain the drug and a new type of controlled-release membrane sealed around the top of the reservoir. The controlled-release membrane is produced by photopolymerizing a mixture of polyethylene glycol dimethacrylate (PEGDM) and collagen microparticles (COLs) (PEGDM/COL membrane). The COLs are hydrogels containing a chemically crosslinked 0.8% (w/v) collagen network, which is permeable to molecules with molecular weights of <200 kDa. Therefore, drugs diffuse through the interconnected COLs embedded in the membrane.

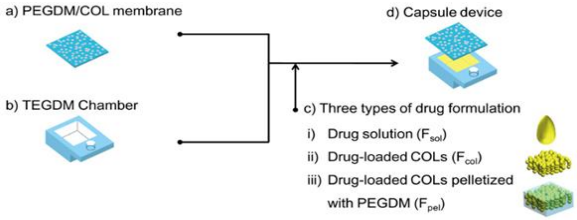

Fig. 9

The drug release kinetics can be controlled by changing the drug formulation and/or the membrane COL density so that the size of the bursts is reduced, which extends the release period.

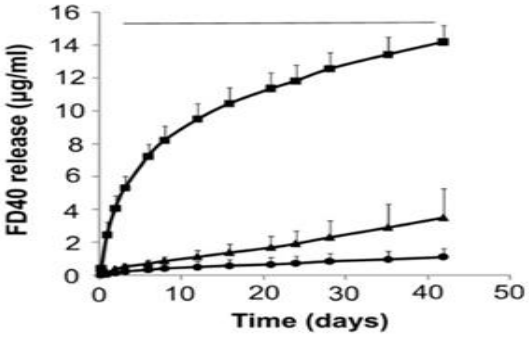

Fig 10: Release of FD40 in vitro. The permeability of FD40 through PEGDM/COL membranes was studied using modified Transwells for which the PEGDM/COL membranes replaced the original Transwell membranes. The concentrations of the COLs were 100 mg/ml (circles), 300 mg/ml (triangles), and 500 mg/ml (squares).

Additionally, the capsule can be designed toload and release low molecular weight drugs, protein type drugs, and even drugs produced by encapsulated cells, allowing for a wide range of biomedical applications. The device thus has great potential as a conduit for continuous, controlled drug release[16].

Summary

Delivery system	Features
Sub-micron sized lipid emulsion	Can deliver hydrophobic drugs to the posterior eye and the efficacy greatly depends on surface properties
Nanostructured Lipid carriers	Heterogeneous systems, physically stable with optimized stabilizer composition, can provide selective and prolonged drug concentration in the eye
Hydrogel contact lens	More efficient vehicle for ophthalmic drug delivery than the conventional eye drops, fraction of drug that enters the cornea varies from 70 to 95%, can supply only a limited amount of drug.
Transscleral drug-delivery device	Has great potential as a conduit for continuous, controlled drug release, the capsule can be designed toload and release low molecular weight drugs, protein type drugs, and even drugs produced by encapsulated cells, drug release kinetics can be controlled by changing the drug formulation and/or the membrane COL density

4. Conclusion and Future prospects:

Innovation is the key when thinking about improving the drug delivery systems to the back of the eye. Nanosystems have been evaluated for various applications in preclinical studies. Although preclinical nanomedicine research for ocular use has witnessed technological advances, few have reached market approval for human clinical use. Also, prior to translation of

nanomedicines and nanosystems for treatment and management of ocular diseases, a number of obstacles need to be overcome. Among therapeutic devices, hydrogel contact lenses have shown great potential for delivery of drugs to the eye. However, some ocular disorders are caused by them because of lack of biocompatibility surface. Ergo, to increase the biocompatibility of hydrogel, other hydrogel designs should be developed. Many biodegradable drug delivery systems are currently in clinical trials or in experimental stages. In addition, several non-biodegradable implants are in late developmental phase and a few are used in clinical practice. For the foreseeable future, bioerodible and nonbio erodible intravitreal drug delivery systems may provide the best methods of disposition into the posterior segment. Further studies need to be carried out so as to validate drug release from different delivery systems. In addition, new technologies need to be developed. This holds the future of clinical importance of different delivery systems in the effective treatment of posterior eye diseases.

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