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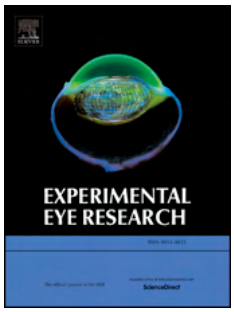

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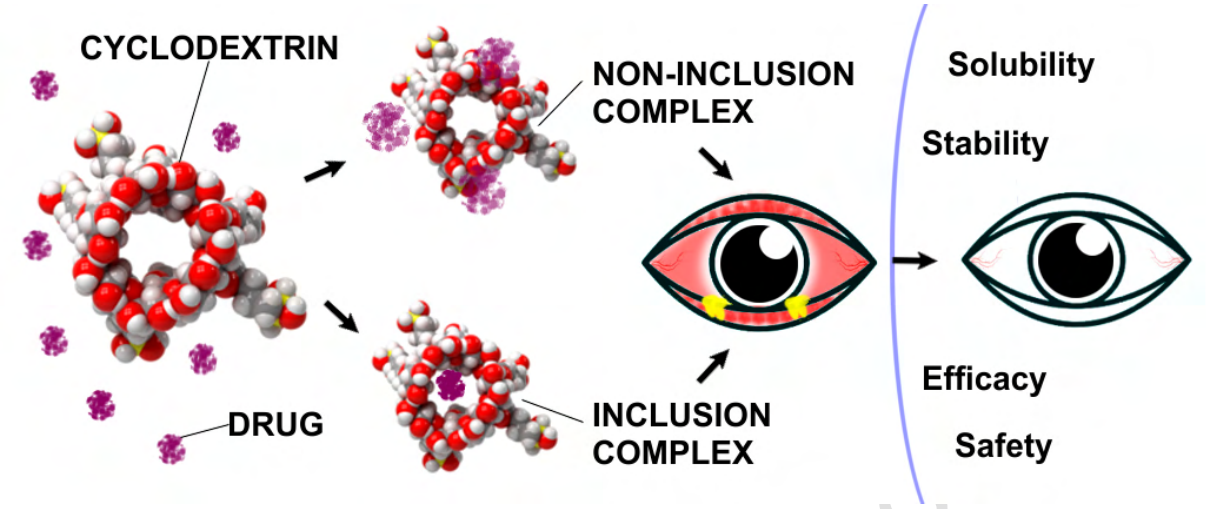

Supramolecular Cyclodextrin Complex:

Diversity, Safety, and Applications in Ocular Therapeutics

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Abstract

Approximately 30 - 70% of the existing and new chemical entities exhibit poor aqueous solubility. For topical ocular delivery, drug molecules need to possess both hydrophilic and lipophilic nature to enable absorption through the aqueous tear layer and permeation through the corneal lipophilic barrier. To overcome the aqueous solubility related issues, various techniques such as solid dispersion, particle size reduction, cyclodextrin complexation, co-solvency, prodrug, derivatization, and salt formation are being explored in the healthcare sector. Cyclodextrin inclusion complexation techniques have been established by several pharmaceutical industries for systemic administration allowing a transition from the lab to the clinics. Though cyclodextrins are exploited in ocular drug delivery, there are prevailing concerns regarding its absorption enhancing capacity and mechanism, retention at the ocular surfaces and, irritation and toxicity profiles. In the present review, the efforts taken by various research groups to address the concerns of using cyclodextrin and its derivatives in ocular therapeutics are summarized. Also, considerations and utility of cyclodextrin systems in fabricating newer formulations such as contact lens, inserts, and implants have been discussed in the review.

Key Words

Cyclodextrin, inclusion complexes, ocular diseases, topical delivery, toxicity, mechanism

1. Introduction

The human eye is a susceptible and a delicate organ which is exposed directly to the environment and, despite significant protective barriers is highly vulnerable to several diseases. Ocular diseases require immediate treatment because of the critical clinical adverse effects that affect the vision and the quality of life to a greater extent. The delivery of ocular drugs is very challenging due to ocular pathophysiology and anatomy. Presence of substantial physiological protective barriers and the delicate nature of the eye require a more sensitive and novel approach maintaining high therapeutic effectiveness (Bilensoy, 2011).

There are various physiological functions of the eye that hinder and challenge the topical delivery of ocular drugs. For instance, the ocular capacity of the conjunctival sac and ocular surface is limited to 25 µL and 8 µL respectively, and large volume instillation causes rapid reflex blinking draining the excess volume (Schoenwald, 2010). Human eye has a blinking rate of about 15-20 times/ min, a crucial mechanism of protection which also plays a vital role in the turnover of tear films, and drainage of tears through the nasolacrimal canal which limits the contact time of the instilled medicine. Tear secretion rate is maintained at 1.2 µL/ min from the contribution of continuous processes within the lacrimal gland, tear film turnover, and drainage from the nasolacrimal duct, which lead to a decrease in residence time and the loss of the instilled drug dose. Instillation of the formulations more than ocular surface capacity, and the inclusion of irritant excipients or microparticles further accelerate the washing out of the instilled drug by stimulating the reflex tearing (Macha *et al.*, 2010).

Apart from physiological barriers, anatomical barriers also restrict the permeation of the drug (***Fig. 1***). Cornea, the first barrier of the human eye, consisting of several distinct layers. The major barriers to topical eye delivery are the tear film, cornea, conjunctiva and retinal blood barrier. A drug that is intended to permeate through the transcorneal membrane requires to be inherent with sufficient hydrophilicity and lipophilicity. The white opaque sclera layer is after conjunctiva, which is permeable only to drugs with a maximum molecular weight in the range of 2000 – 5000 Da (Hosoya *et al*. 2005; Huang *et al,* 1989). The other important barrier of the eye is the retinal barrier, allowing a selective permeation between intercellular retinal space and the vitreous humour (Sharma and Gaur, 2018).

The prevailing diseases (***Table 1***) of the anterior segment are glaucoma, dry eye syndrome (DES), cataract, tumors, injuries, infection and inflammation, and diseases such as age-related macular degeneration (AMD), posterior uveitis, retinitis, and diabetic retinopathy (***Fig. 2***) (Zhang *et al.*, 2015). A major portion of the marketed ophthalmic products is eye drops while posterior segment diseases are treated with repetitive intravitreal injections. Ocular bioavailability of the eye drops is < 5% of the applied dose and the remaining drug either enters into the systemic circulation or drains through the nasolacrimal drainage pathway (Patel *et al.*, 2013). Ocular diseases turn to be a prominent health indicator with age and instillation of eye drops is difficult for old aged patients. Repeated use of intravitreal injections are associated with various drug-related and injection-related adverse effects such as endophthalmitis, intraocular infection and pressure elevation, ocular hemorrhage and rhegmatogenous retinal detachment (Falavarjani and Nguyen, 2013a).

There are various anterior ocular diseases which require topical ocular delivery while research in the direction of topical systems for the posterior ocular diseases has gained a momentum to overcome the ocular barriers along with intravitreal injection-related disadvantages (***Table 2***). Novel formulations include thermosensitive *in situ* gels, implants, inserts, cyclodextrin-drug complexation, drug eluting hydrogel contact lens, vesicular systems, penetration enhancers and mucoadhesive polymers (Yavuz *et.al*., 2016). Cyclodextrin (CD) based topical drug delivery to the anterior and posterior segment is reported to have a potential to overcome the physio-anatomical barriers, and the inadequacy and adverse effects associated with the ocular drug delivery (Loftsson and Stefánsson, 2017).

In order to overcome the barriers novel drug delivery strategies such as liposomes, micelles, dendrimers, nanoparticles, nanocapsules, nanoemulsions, eye inserts, and nanowafers are being perused at the laboratory and industrial setup (Sultana *et al.*, 2006). However, a major challenge in the development of ocular formulation that still remains is the poor aqueous solubility of the drug molecule (Poovi and Damodharan, 2018), which needs to be improved to increase the residence time of the instilled formulations and to increase the permeation across the transcorneal membrane. Solid dispersions, cyclodextrin inclusion complex, reduction of particle size, the formation of salt, cosolvency and prodrug approaches usually intended for other routes of administration are being translated to

address the solubility issues for ocular applications (Kawabata *et al.*, 2011). The approach of using cyclodextrin inclusion complex to increase the drug molecule's aqueous solubility is widely scrutinized, resulting in an increasing number of formulations on the market containing CD as an excipient. There are currently more than 30 pharmaceutical products in the market that contain CD, three of which are approved for the delivery of ocular drugs (Acad, 2007; Palem *et al.*, 2012; Yclodextrins, 2013). A comprehensive list of marketed products containing CD along with the route of administration has been provided in Table 2.

2. Cyclodextrins

2.1 Properties and Applications

Cyclodextrins (CDs) are cyclic oligosaccharides that occur naturally from bacterial digestion of starch. The cyclic structure of α-1,4-glyosidic connections of the structure of α-D glucopyranose units makes them more resistant to non-enzymatic degradation than linear dextrin (Palem *et al.*, 2012). CDs orient in a shape of a truncated cone with hydrophilic exterior surface due to the presence of primary and secondary hydroxyl groups, and a lipophilic cavity due to the presence of carbon skeleton and ethereal oxygens of glucose residues (Loftsson, 2002). Out of the naturally occurring CDs, namely α-CD, β-CD and γ-CD (***Fig.3***), β-CD has limited aqueous solubility compared to the other CDs due to the presence of strong intramolecular hydrogen bonding between C2 – C3 hydroxyl group of the adjacent α-D-glucosepyranosyl units making it less available for hydration (Hedges 2019). The limited aqueous solubility of parent CDs imparts toxicity by absorbing through a lipophilic biological membrane (EMA report, 2013). The significant increase in water solubility is achieved in modified CDs by replacing hydrogen atom from the hydroxyl group in natural CDs. This increased aqueous solubility retains them extracellularly and prevent their absorption through lipophilic biological membrane thus making them non-toxic.

Along with the parent CDs (α-CD, β-CD and γ-CD) modified CDs namely hydroxypropyl β-CD (HP-β-CD), sulfobutylether β-CD (SBE-β-CD), randomly methylated β-CD (RM-β-CD) and hydroxypropyl γ-CD (HP-γ-CD) are most frequently utilized in the marketed pharmaceutical formulations as represented in ***Table 3*** (Eastburn and Tao, 1994). In the USA, CDs are given generally-recognized-as-safe (GRAS) status whereas HP-β-CD and SBE-β-CD are listed as

inactive pharmaceutical ingredients by the Food and Drug Administration (FDA) allowing a higher exploration of the system for drug delivery. However, the regulatory status of γ-CD is also continuously evolving in both the pharmaceutical and food industry (Bilensoy, 2011). The current regulatory status of the parent and modified CDs in different countries have been listed in Table 3 along with the general properties of CDs. In Europe, European Medicine Agency (EMA) published a report on the use of CDs as an excipient along with the per day exposure (PDE) limits for different routes of administration. Additionally, the report also documents the various toxicological considerations and the data presenting the clinical safety (EMA Report, 2013).

2.2 Cyclodextrin supramolecular complexes: Solubility and Stability enhancer

Supramolecular polymer chemistry of CDs as a host is based on the non-covalent interactions and geometric fitting of the guest molecule into the lipophilic cavity (Brewster and Loftsson, 2007). CDs form an integration complex with lipophilic drug molecules by incorporating the drug into the lipophilic interior cavity by forming non-covalent bonds such as Van der Waals interactions, hydrogen bonding and hydrophobic interactions, and CDs also remain in dynamic equilibrium with free drug molecules in the solution (Jambhekar and Breen, 2016). CDs play a diverse role by formation of complexation and increasing the solubility, in addition enhances the transcorneal permeation, improves aqueous stability and minimizes ocular irritation (Arima *et al.*, 2011).

Interesting findings were reported about solubilising effect of CDs based on the physicochemical properties. It was observed that modified CDs with lower molar substitution had a better solubilizing capability compared to derivatives with a high molar substitution which is why randomly methylated α-CD and β-CD with molar substitution 0.6 was seen to be a better solubiliser when compared to randomly methylated CDs with 1.8 molar substitution (Rewster, 1996). Charged CDs have high solubilising efficiency compared to neutral CDs and this solubilising efficiency is dependent on the relative proximity between charges and the cavity of CDs. The larger the distance between the charges the better is the solubilizing capacity of CDs. The sulfobutyl anion charged distanced by sulfobutyl ether chain enhances the solubilising efficiency of SBE-β-CD (Barbara *et al.,* 1995).

Unionised drug has a better complexation efficiency compared to ionized drug molecule with very high stability constant (Boudeville and Burgot, 1995). The other key advantage of CD complexation is chemical stability of labile drug molecules imparted by CD. The CD can slow down the degradation, suppress the reactivity or it can prevent the drug from hostile environment by partial inclusion or complete inclusion. (Rewster, 1996).

2.3 Mechanism of Drug release of CD complexes

The complexation process involving a drug and CD is a dynamic process wherein a non-covalent interaction is established between the host and the guest molecule. The association and dissociation of CD complexes in the medium continually remains in a state of equilibrium. It is also reported that the CD inclusion complex and non-inclusion complex co-exist in the system (Jóhannsdóttir *et al.*, 2015). The reported drug-releasing mechanism from inclusion complexes are dilution, replacement by molecules which have more affinity towards CDs, and transfer of the drug to the lipophilic biological membrane in close proximity for which it has higher affinity (Stella *et al.*, 1999).

Simple dissolution of solid drug/ CD complexes and dilution of aqueous complexation media are the major driving forces for drug release from the CD complex. However, the proposed mechanism kinetics for drug release from CD complexes are drug–protein binding, direct drug partitioning and competitive binding which contributes in rapid drug release from the complexes. A strong competition was observed for drug binding between protein and CD *in vivo* that was shown to facilitate the drug release from the complex (Loftsson, 2005).

Apart from several advantages, CDs exert few negative effects on ocular delivery. Incorporation of competitive moiety such as preservatives in ophthalmic preparation may have a negative impact on stability of the formulation. The stability and drug release from the drug-CD complexes are greatly affected by the high stability constant (Frömming and Szejtli, 1994). In other words, the fraction of drug bound to CDs at any given time point is directly proportional to the stability constant of the drug. Dilution also plays a key role in drug release from both strong and weak drug-CD complexes, whereas protein binding and competitive displacement majorly influences the release of the drug from the complexes representing a strong interaction with the host and the guest molecules (Tella, 1996).

Upon ocular delivery of drug-CD complexes formulation, it gets exposed to minimal dilution as the total tear volume in human eye (~7µL) and the average volume of the instilled eye drops is around 25-35 µL which can be considered as an insignificant dilution. The situation is further worsened by poor contact time and rapid nasolacrimal drainage. In ocular drug delivery, prevalent drug release mechanisms such as dilution, competitive displacement and protein binding have a limited role to play instead the drug uptake by tissue plays a preferential role in dissociation of drug-CD complexes and the absorption of the drug into the ocular tissues (Stella *et al.*, 1999). Based on principle of mass action, biological tissues act as a sink leading to the dissociation of drug-CD complex and the subsequent absorption of free drug molecule. A lipophilic drug has more affinity towards biological membrane compared to the highly hydrophilic CD molecule (Loftsson et.al., 2002).

2.4 Cyclodextrins in Ocular delivery: Inclusion complexes

CDs form complexes by inclusion of lipophilic portion of the drug molecule within its lipophilic cavity (Loftsson and Masson, 2001). The reversible release of enthalpy rich water molecules from the cyclodextrin cavity is a crucial step during formation of inclusion complexes. Various factors which influence formation of inclusion complexes are molecular size of the guest molecule, lipophilicity and steric effects. Inclusion complexation leads to a change in the physico-chemical properties of the guest molecule with respect to free molecules in the solution, a change that can be detected by suitable analytical techniques (Loftsson, 2017). Some indicators used for the detection of the physico-chemical changes that take place upon complexation are a change in solubility, absorbance, fluorescence, chemical reactions, NMR shifts and pKa values (Loftsson, 2005).

3. Applications of cyclodextrin supramolecular complexes

3.1 Eye Drops: Solutions and Suspensions

In terms of patient compliance, ease of preparation and bioavailability, solutions have their own advantages. Achieving significant therapeutic drug concentrations remains a challenge in ocular delivery due to the strong defence mechanisms that protect the eye structure from

foreign substances (Macha *et al.*, 2010). Moreover tear film turnover, continuous tear production, nasolacrimal drainage, and corneal permeation are factors which also limit the ocular bioavailability. The various studies reporting the use of CDs in ocular drops are presented in ***Table 4***.

Serrano *et al.* have reported Amphotericin B (AmB) eye drops using γ-CD for fungal keratitis and showed a 35% increase in the antifungal activity compared to commercially available fungizone and AmBisome. Complexation of AmB with γ-CD improved the solubility, chemical stability and prevented the self-aggregation of AmB, which are paramount hurdles in AmB ocular delivery (Serrano *et al.*, 2012). Cyclosporine A (CsA), a drug of choice for dry eye syndrome, is difficult to formulate due to its high molecular weight and extremely lipophilic nature, which hampers the aqueous solubility. Jóhannsdóttir *et al.* developed CsA eye drops using α-CD/γ-CD inclusion complex. γ-CD showed a positive effect on transcorneal permeation of CsA and the formation of nanoparticles (Jóhannsdóttir *et al.*, 2015). However, the study lacked a report on the toxicity and irritation profiles of the formulation which needs to be considered for ocular safety, while noting that the regulatory status of γ-CD is still in the evolving stage in USA and Europe.

For an ophthalmic solution containing nepafenac and HP-β-CD inclusion complex, Shelley *et al.* reported an 11-fold increase in corneal retention time and an 18-fold increase in transcorneal permeation compared to the Nevanac® a marketed nepafenac suspension. Nepafenac molecular modelling studies showed a strong association with HP-β-CD with constants of stability rate 3665 M^{-1} and 4296 M^{-1} in water and PBS (Shelley *et al.*, 2018a). The developed eye drops appeared to be a better solution for nepafenac delivery but further irritation studies and toxicological evaluation needs to be explored to assure the safety of the developed formulation. A combination of parent CDs and its derivative was reported to have a synergistic effect on drug solubilization during the formation of inclusion complex. This effect was evaluated by Loftsson *et al.* to enhance Dexamethasone solubility, a highly lipophilic drug used during incidences of ocular injury and inflammation. The γ-CD/HP-γ-CD parent derivative combination was used for the preparation of inclusion complexes with dexamethasone resulting in an increased permeation evaluated by performing *in vitro* and *ex vivo* studies which were attributed to the increased solubility of drug with CDs (Jansook *et al.*, 2010). Loftsson *et al.* also reported increased solubility and

thus permeation of dexamethasone by forming an inclusion complex with randomly methylated β-CD (RM-β-CD) (Loftsson and Stefánsson, 2007). The reported formulation showed satisfactory results in terms of solubility, dissolution and permeation but the safety aspects of these formulations are to be evaluated before proceeding further.

It was also reported that drug-CD complexation apart from preventing the drug from exerting its irritation also increases the stability of the formulation. Latanoprost, a prostaglandin and first-line agent for glaucoma treatment, poses challenges of stability, solubility and irritation on topical ocular delivery. Rodriguez-Aller *et al.* reported Latanoprost eye drops for glaucoma treatment with increased solubility, stability as well as preventing degradation and irritation after ocular instillation (Rodriguez-Aller *et al.*, 2015). The CD shielded the ester group of Latanoprost inside the cavity and inhibited the *in vitro* degradation and biotransformation *in vivo* without affecting the ocular efficacy of latanoprost.

Ocular drug delivery to posterior region is quite challenging due to the anatomical and physiological barriers. For posterior delivery, intravitreal injection, periocular injection and implants that requires repetitive injection application, leading to complications such as retinal detachment, retinal haemorrhage and endophthalmitis (Falavarjani and Nguyen, 2013b). To overcome this complication, Johannsdottir *et al.* formulated dexamethasone nanosuspension using α-CD for the delivery to the posterior segment of the eye (Johannsdottir *et al.*, 2018). They reported a higher dexamethasone concentration in the posterior segment compared to the anterior chamber of the rabbit's eye. The most sought-after and patience-friendly formulations are the eye drops, but they have their own strengths and limitations (Patel *et al.*, 2013). Eye drops are reported to be insufficient in delivering the required therapeutic concentration of drugs across the transcorneal membrane and are easily washed out. To circumvent these drawbacks of conventional formulations novel topical ocular drug systems are being explored (Kompella *et.al*., 2011).

3.2 Ocular Inserts

The ocular inserts or conjunctival inserts for treating different ocular conditions have been in use since last four decades, with PVA soaked in pilocarpine being the first ocular insert for

glaucoma treatment in the 80s (Land and Benjamin, 1994). They are a flexible and biologically inert mucoadhesive polymeric device that are to be placed in the cul-de-sac or conjunctival sac without the anterior chamber being involved. Ocular inserts can be a reservoir system or matrix system and release the drug through various mechanisms such as diffusion or osmosis. The fundamental idea behind the use of ocular inserts is to achieve extended release of medication or lubricant. It can also prevent high washing out of the drug molecules in tear fluid and therefore decreasing the frequency of instillation (Kumari *et al.*, 2010). Ocular inserts have potential advantages over the use of conventional eye drops or ointments like effective therapy, efficient delivery, sustained drug release, self-administration, and are preservative free, reduced adverse effects and increased patient compliance.

According to literature, the size and shape of the inserts are reported to have pivotal role in retaining them in cul-de-sac or conjunctiva, and possibly a reason that small rod shaped ocular inserts have superiority over large and oval shape inserts (Land and Benjamin, 1994). Hyaluronan was reported to have a potential role in tear film stabilization, ocular surface lubrication for smooth blinking and corneal wound healing and is commonly found in dry eye treatment solutions as an active or inactive ingredient (Carlson *et al.*, 2018). Despite hyaluronan's biocompatibility and mucoadhesive properties, its use is restricted by poor biomechanical properties and rapid water dissolution. To address the issue, Grimaudo *et al.* designed ocular CsA inserts by tuning the sodium hyaluronate and HP-β-CD to inflect the biomechanical properties and drug release kinetics. They concluded that further preclinical studies were needed to ensure safety and development of ocular inserts as a possible alternative for peptide delivery in the posterior and anterior segments of the eye (Grimaudo *et al.*, 2018).

Deshpande *et al.* explored acyclovir ocular inserts of the controlled release reservoir type by sandwiching the hydroxypropylmethyl cellulose (HPMC) matrix with acyclovir-β-CD between the controlled release membranes (cellulose acetate phthalate). Acyclovir ocuserts showed improved water solubility and precorneal residence time, transcorneal permeation and reduced frequency of administration (Deshpande *et al.*, 2010). Rao *et al.* reported smooth, transparent and flexible ocular inserts of norfloxacin for the treatment of ocular infections. The norfloxacin-β-CD inclusion complex was incorporated into the HPMC matrix and

covered with an ethyl cellulose/ polyvinyl pyrrolidine (PVP) K30 rate-limiting membrane. They have optimized the ration of polymers to achieve the zero-order release kinetics with controlled drug release and reduced frequency of administration (Rao and Shyale, 2004). There have been no reports of *ex vivo* or *in vivo* toxicity studies to support the potential of developed eye inserts. Recently, ocular inserts use have become more prominent due to their potential role in the non-invasive and efficacious delivery in the subconjunctival and intra-vitreal drug delivery devices (Kumari *et al.*, 2010).

3.3 Ocular *In situ gel*

The bioavailability of ocular solutions and suspensions is minimal due to protective defence mechanisms and ocular barriers that minimize retention time between drug and ocular surfaces. Only 5 - 10% of the drug is reported to be absorbed from ocular eye solution and suspension, leading to the sub-therapeutic levels of drug and generating the need for frequent instillation (Wu *et al.*, 2019). The use of gel system in ocular delivery is extensively investigated (***Table 5***) to improve the residence time of the drug molecule on the corneal surface, which will increase the permeation at the ocular surface and hence the improvement of bioavailability (Dabir et al., 2016; Majeed and Khan, 2019).

The use of natural or synthetic water-soluble polymers that interact with eye tissue mucin was investigated and reported to increase residence time of the formulation. These mucoadhesive polymers were also reported to increase bioavailability, protect and heal the epithelial cells. Cellulose derivatives, hyaluronan, acrylates, chitosan, polysaccharides, and thiomers were various polymers that are useful for ocular mucoadhesive delivery. Research on the mucoadhesive polymer in the direction of both hydrogels and *in situ* gel is gaining momentum (Salamat-Miller *et al.*, 2005). In topical eye drug delivery research, *in situ* gelling systems have gained special attention to overcome the challenges of shorter residence time, poor permeation and poor bioavailability. Different mucoadhesive water-soluble polymers or combinations of polymers or modified polymers are examined for the development of *in situ* gelling systems by exploiting sol-gel conversion characteristics that are dependent on different stimuli such as temperature, pH or ions.

Sulaiman and Kassab developed ion sensitive hydrogel (ISH) and mucoadhesive hyaluronic acid gel (HAH) for ophthalmic delivery of econazole nitrate for fungal keratitis treatment. Based on permeation studies and irritation studies, ISH and HAH appeared to be promising vehicles for the sustained and safer eye delivery of econazole nitrate hydrogel by solubilizing it with α-CD and incorporating the integration complex into an ion-sensitive gel (Sulaiman and Kassab, 2018). Daily exposure to environmental factors such as radiation, foreign bodies and pathogens affect the eyes, leading to oxidative stress, and generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). By taking advantage of this aspect, Budai-Szucs *et al.* synthesized thiolated poly aspartic acid (PASP) polymer which exhibited sol-gel conversion in the presence of an oxidizing agent. They combined the advantages of PASP and prednisolone-CD complexes for formulating mucoadhesive *in situ* gelling system as an anti-inflammatory treatment modality. However, the irritation profiles and regulatory status of 6-monodeoxy-6-monoamino-beta-cyclodextrin hydrochloride (MA-β-CD) used in the study has not been reported, which effectively limits the advantages of MA-β-CD in ocular delivery (Budai-Szucs *et al.*, 2018).

Nanotechnology is reported to be useful in overcoming eye barriers and poor residence time. Ocular surface carries a negative charge, and taking the lead from this Mahmoud *et al.* developed *in situ* gelling systems for econazole nitrate through the combination of natural, non-toxic cationic chitosan and anionic SBE-β-CD for sustained delivery. Ionically crosslinked nanoparticles of SBE-β-CD-chitosan gave the benefit of overcoming the eye barriers, increased residence time and controlled drug release (Maged *et al.*, 2016).

3.4 Novel ocular delivery systems

Research pertaining to the CDs is flourishing, and its use in various industries and mainly in the pharmaceutical drug delivery system is ever increasing. There have been reports of several novel ocular drug systems using CDs claiming to be superior to conventional formulations. Itraconazole, a first-generation triazole antifungal drug, has broad-spectrum activity, but poor transcorneal permeability associated with its highly lipophilic nature and high drug molecule pKa. Sayed *et al., 2018* reported solvent-free β-CD consisting of micellar dispersion of itraconazole. They have reported the synergistic effects of superonics and β-

CD on enhanced transcorneal permeation of itraconazole. Their findings suggests that dispersion of drug-β-CD complex has increased itraconazole dissolution and permeation. They also report that the micellar dispersion was mucoadhesive, and showed increased stability and transcorneal permeation. Miceller dispersion might be a potential platform technology for the delivery of lipophilic drug molecules in the topical eye segments. Nanda *et al.* reported the amlodipine mucoadhesive ocular film using β-CD and HPMC by exploring the mucoadhesive property of β-CD. They observed the lowest binding energy between amlodipine and β-CD from molecular docking studies. The optimized formulation showed *in vivo* drug release controlled diffusion and permeation due to improved amlodipine dissolution (Nanda *et al.*, 2018). Differential scanning calorimetry (DSC) and X-ray diffraction (XRD) studies confirm the conversion of crystalline amlodipine into amorphous nature. Level A correlation was observed *in vitro* and *ex vivo*, but further irritation and toxicity studies must be conducted to ensure safety.

CsA, a highly lipophilic peptide, is a drug of choice for dry eye disease, but it is highly challenging to formulate. The existing marketed formulation achieves sub-therapeutic drug concentration in the targeted ocular tissue. Several CsA formulations have been reported maninly focused on overcoming the challenges of CsA solubility and permeability, but poor residence time and rapid washing out of the instilled ophthalmic dosage have resulted in poor ocular bioavailability (Agarwal and Rupenthal, 2016; Lallemand *et al.*, 2017). It was reported that the eye inserts increase the residence time and the bioavailability of a drug. Translucent CsA inserts were reported to have been formulated by Maria Aurora *et al.* consisting of cross-linked sodium hyaluronan and HP-β-CD. They reported CsA accumulation in sclera that is approximately 5.6 - 32.7 µg drug / g sclera. No studies have been reported on *in vitro* or *ex vivo* irritation and as such translucent inserts may result in visual disturbance (Grimaudo *et al.*, 2018).

Drug-eluting hydrogel contact lenses are newer introductions into the field of ocular drug delivery. It is reported that hydrogel contact lens increases ocular bioavailability up to 50% compared to < 5% ocular bioavailability of eye drops and it also provides mechanical protection and prevents corneal desiccation (Jones *et al.*, 2017; Li *et al.*, 2006). The drug-eluting hydrogel contact lens for various ocular diseases have been reported such as dry eye syndrome, glaucoma and epithelial defects. The fabrication of hydrogel contact lens by

incorporating CDs will not only increase the aqueous solubility of drug but also have a beneficial effect on swelling ratio and tensile strength of the contact lens (Hu *et al.*, 2016; Xu *et al.*, 2010).

3.5 Non-inclusion complexes in ocular delivery

It is generally assumed that by taking up small part or whole molecule in lipophilic cavity, CDs forms inclusion with the guest molecule. However, it has been reported that CDs and CD complexes tend to congregate to form aggregates, and complexes other than inclusion complexes in an aqueous solution imparting their effect on increasing the aqueous solubility of poorly water-soluble drugs. The micelles like formed structures of self-assembled CDs are present in nanosized aggregates and acts as a potential solubilizer of a poorly water-soluble drug that has low affinity to form inclusion complex (Brewster and Loftsson, 2007; Loftsson, 2004; Messner *et al.*, 2010). The physiochemical properties of free CDs tends to differ from self-aggregated CDs. Different analytical evaluation methods were developed for identification and quantification of CD aggregates including osmometry, viscosity, surface tension, dynamic light scattering and permeability studies (Rodrigues *et al.*, 2018).

Messner *et al.* studied the formation of complex aggregates of hydrocortisone-CD and the influence of various CDs and their concentration on aggregate formation. Their research suggests that micro-aggregate formation leads to non-linear phase solubility as opposed to linear phase solubility of the nano-aggregates. It was suggested that a 4 nm diameter aggregate consisting of six complexes will be formed based on permeability studies and transmission electron microscopy (TEM) analysis. The suggested potential aggregation mechanisms were step-by-step aggregation or spontaneous aggregation, which either co-exists or is concentration-dependent. These findings can be very useful in the development of CD-aggregate complexation models (Messner *et al.*, 2011).

Loftsson *et al.* and Magnusdottir *et al.* reported the drug-CD aggregation phenomenon by investigating the phase solubility studies of various non-steroidal anti-inflammatory class of drugs. In contrast to molecular modelling, nuclear magnetic resonance (NMR) and ultraviolet-visible spectroscopy studies showed the formation of 1:1 stoichiometry complex, whereas the phase solubility results suggested the formation of higher order complexes. This unusual phenomenon was explained by the formation of non-inclusion complexes

between drug-CD complexes, free drug complexation with drug-CD complex or CD-CD self-aggregation, and the coexistence of both inclusion complexes and non-inclusion complexes, capable of solubilizing poorly water-soluble medicines (Loftsson *et. al*., 2003; Magnusdottir *et.al*, 2002).

Different strategies to enhance the complexation between the guest molecule and CDs were explored. It included drug ionization at the appropriate pH, mechanical grinding to increase drug wettability, and ternary complex formation by adding water-soluble polymer viz. PVP, carboxymethyl cellulose (CMC) and HPMC (Loftsson *et.al*., 2012). The concentration of CDs in complexation directly affects the volume of formulation a vital part influencing the development of a solid dosage form. The use of CDs is limited to the drug molecule with a high affinity in order to reduce the concentration of CDs in the dosage form. Ternary complexation strategy helps with lower concentration of CDs improving the complexation efficiency. This phenomenon was attributed to both polymer and CDs synergistic effect on drug molecule solubilisation. Polymers are reported to interact and suppress mobility and enhance the complexation efficiency of CDs by 80 fold (Kurkov and Loftsson, 2012).

It was also reported that the ternary complex is thermodynamically more stable than binary complexes (de Miranda *et al.*, 2011). Chutimon *et al.* reported telmisartan ophthalmic eye drops for the treatment of corneal neovascularization. They used HPMC polymer effectively to form a ternary complex with a drug molecule and γ-CD. The developed eye drops with drug-γ-CD-HPMC ternary complex showed improved dissolution, mucoadhesion with negligible hemolysis (Muankaew *et al.*, 2016). Eye irritation studies are however needed as the reported particle size of ocular suspension ranges from 1.16 µm-2.5 µm in the developed formulation, which could possibly lead to irritation.

In addition to water-soluble polymers, organic salt addition also has the potential to enhance drug aqueous solubility through non-inclusion complex formation (Loftsson and Masson, 2015). Loftsson *et al.* investigated the effect of sodium acetate, sodium salicylate and benzalkonium on drug solubility by adding the salts to the complexation medium. Addition of 1% sodium acetate in aqueous β-CD led to a 220 fold increase in hydrocortisone solubility (7.1 mg/mL). Non-inclusion complexation formation had a significant contribution towards stabilizing and enhancing the overall solubility of dug molecule (Loftssonand and

Matth´ıasson, 2003). Similarly, it was also reported that playing around pH to generate ionisable drug molecule groups will improve drug solubility by enhancing CD complexation. This is because the CDs carry an anionic charge. It is possible to increase the attraction and retain the cationic molecules by ionic interactions into the CD cavity, as well as by nullifying the negative charge or creating a positive charge on the drug anionic molecule, to prevent the electrostatic repulsion between the drug molecule and the CD.

4. Safety and Toxicity

Native CDs and their hydrophilic derivatives are not favoured to be absorbed in their intact form and via any cellular absorption, and are absorbed only through passive transport through transporter proteins. In contrast, lipophilic derivatives (e.g. RM-β-CD) interact with membranes more readily than hydrophilic derivatives, however cannot easily permeate cell membranes (Leclercq, 2016). In addition, oral administration of alkylated CD derivatives such as RM-β-CD is restricted by their prospective toxicity (Marttin et al., 1998). Indeed, α-CD and β-CD tend to solubilize phospholipids and cholesterol, respectively, whereas γ-CD is generally less lipid extracting. β-CD has the greatest affinity for cholesterol incorporation and are the most effective in extracting cholesterol and model membranes (Kilsdonk et al., 1995). On the other hand, α-CDs are the most effective in phospholipid extraction. These variations were ascribed to the internal cavities of the CD's size and lipophilicity. In particular, the α-CD cavity appears to be too narrow to accommodate the molecule of cholesterol and the cavity of α-CDs is not as lipophilic as that of β-CD (Ohvo and Slotte, 1996).

The toxicity of CDs have been evaluated in detail for different route of administration in mice, rabbits, dogs and human. CDs are safe when administered orally and impart toxic effect at higher concentration such as > 1000 mg/kg (Stella Valentino et.al, 2008). The CD toxicity is structure based and concentration dependent. It is also reported that magnitude of CD toxicity is also dependent on type of cells, contact time and experimental conditions. 10% RM-β-CD induces cytotoxic and inflammatory effects on buccal mucosa whereas 2-5% has no toxic effects on repetitive exposure (Arima *et al.*, 2011). Upon dermal delivery in HaCaT keratinocytes at 0.5 - 1% potential cytotoxicity observed in order of RAMEB > βCD >

HPβCD > αCD > γCD (Teixeira *et al.*, 2006). Upon intravenous administration, CDs has short half-life and rapidly excreted intact via renal excretion. Pulmonary administration of β-CD and HP-β-CD are safe at 1.5% and 20% respectively, whereas RM-β-CD causes severe nasal mucosa damage (Asai *et al.*, 2002). The significant bioavailability is observed for β-CD and HP-β-CD upon pulmonary administration with bioavailability up to 80% (Irie and Uekama, 1997). HP-β-CD and SBE-β-CD are relatively safe compared to other CD derivatives with SBE-β-CD being the safest CD derivative with administration of high dose up to 250 mg/kg/day for 6 months without significant toxicity (Loftsson and Brewster, 2010).

It is observed that parent CDs with limited water aqueous solubility i.e. α-CD, β-CD and γ-CD have significant toxic effect upon ocular delivery (***Table 6***). The observed toxicity is attributed to the potential role in extracting phospholipids from the biological membrane. Also the permeation enhancing property of the CDs is reported to be expedited by damaging the corneal epithelium. Ocular irritation and toxicity studies on rabbits showed that solutions of 10% SBE-β-CD and 12.5% HP-β-CD are safe and have no ocular irritation or toxicity (Siefert and Keipert, 1997).

CDs offer several advantages and are safe when used in range of ocular permitted dose. CDs, apart from increasing solubility and stability of drug conceals the drug related irritation and discomfort (Arima et al., 2011). A decrease in CsA conventional ophthalmic eye drops related ocular irritation toxicity as well as 5-10 fold increase in corneal permeation was observed with 40 mg/mL of α-CD (Kanai *et al.,* 1989). The adverse effects of conventional pilocarpine ophthalmic formulations such as irritation and intense myopia and miosis was diminished by CD inclusion complexation with greater bioavailability. The reported increase in corneal permeability was not attributed to the corneal epithelium damage confirmed by electrophysiology and scanning electron microscopy (SEM) studies (Aktaş *et al.*, 2003; Freedman *et al.*, 1993; Järvinen *et al.*, 1995; Suhonem *et al*., 1995; Siefert *et.al*., 1997).

5. Conclusion

In the development of new formulation, the versatile nature of CDs can be used to overcome the three major constraints of topical ocular delivery. The first is the drug's

aqueous solubility to permeate through the tear film, which in nature is significantly hydrophilic. The second hurdle is poor ocular surface retention time of the drug, which is 2 – 3 min owing to the drainage from the nasolacrimal pathway. The third obstacle is the largely lipophilic corneal and conjunctival membrane. Drug lipophilicity and charge drive the drug's permeation, with an optimal LogP to be 2 – 3 for corneal permeation. CDs present an attractive way to enhance the solubility of the poorly soluble and wettable drugs, increase their retention and permeation at the ocular surfaces. In addition, CDs are increasingly being reported for their drug stabilizing properties and safety profiles. CD has the potential to improve the conventional eye drops to offer better permeation, efficacy, safety and stability in the ophthalmic topical delivery of the anterior and posterior segments. A careful selection of process parameters, and concentrations of CDs and other excipients can enable the development of a suitable ocular delivery platforms in terms of nanotechnology, contact lens, inserts and *in situ* gels.

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Figures

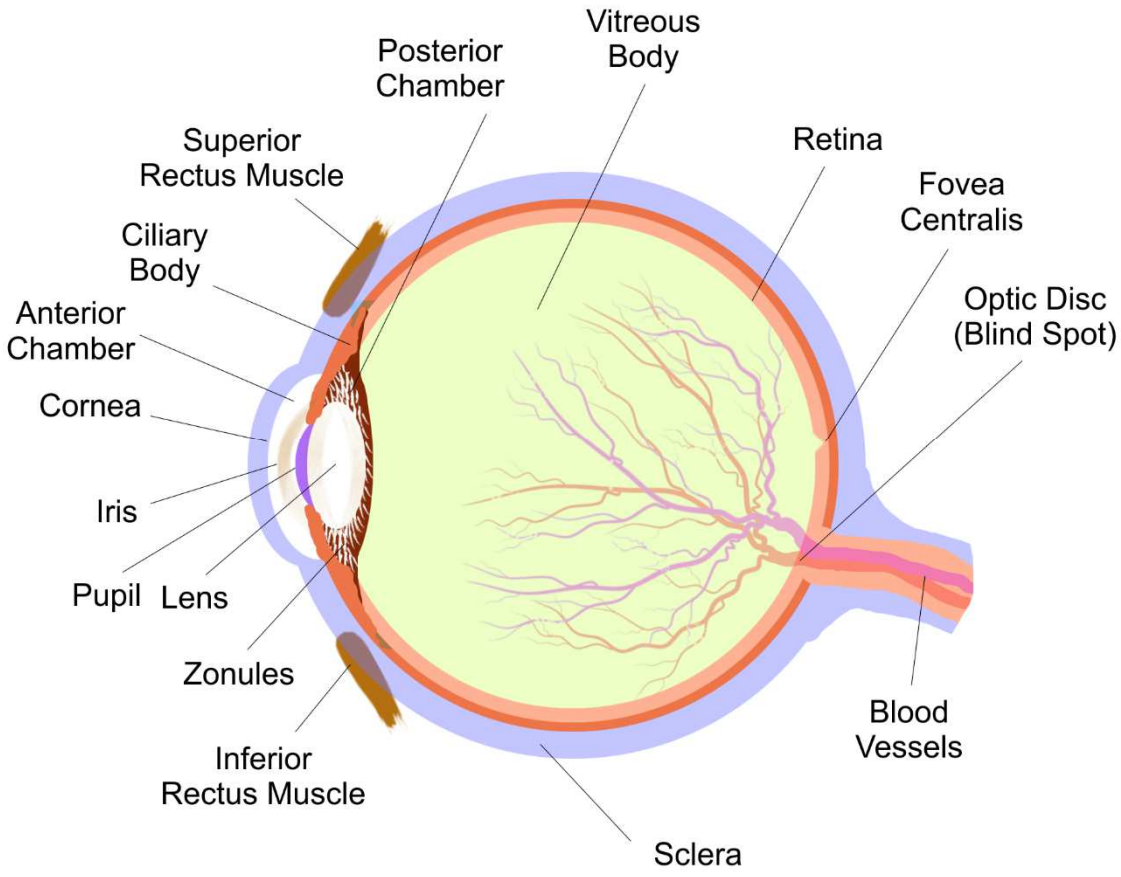

Fig. 1: Cross-section of the human eye

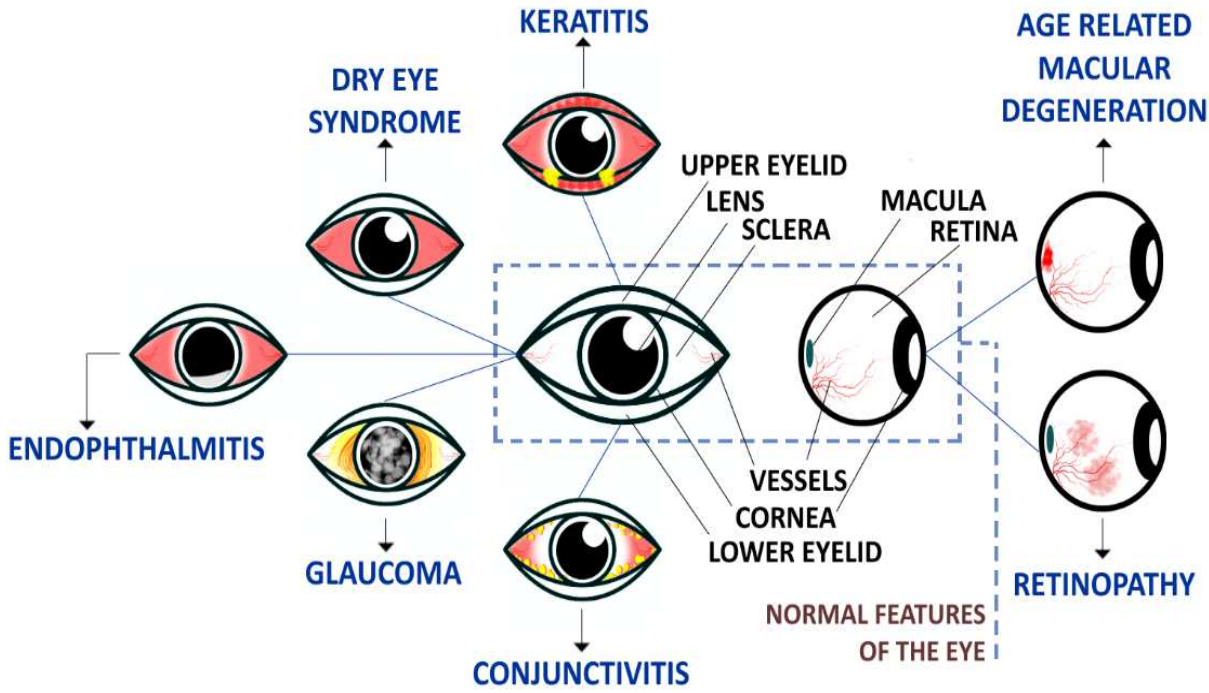

Fig. 2 Graphical representation of the anterior and posterior diseases of the eye

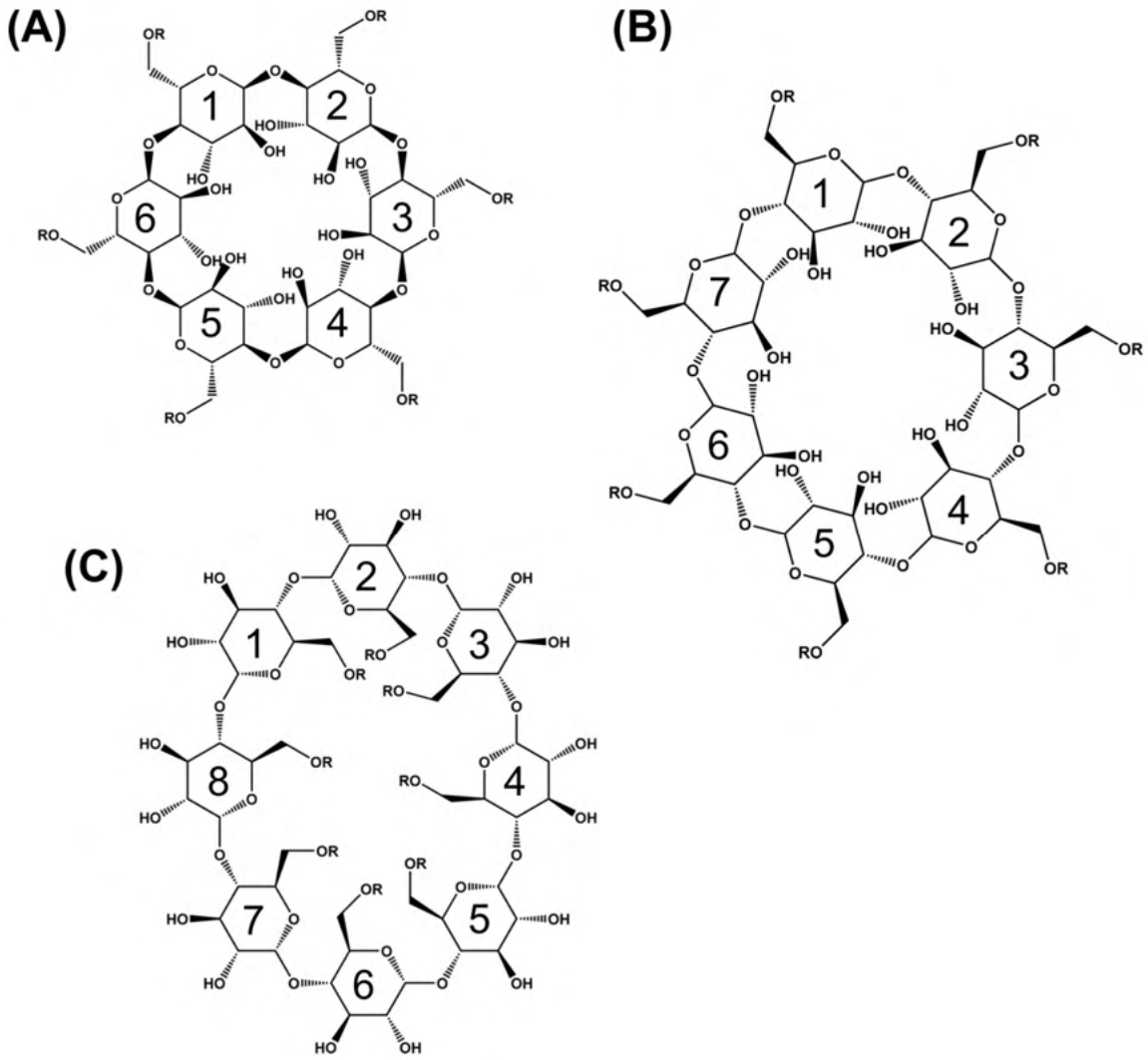

Fig. 3: Molecular structure of α- cyclodextrin (αCD); β-cyclodextrin (βCD) and γ-cyclodextrin (γCD) containing seven glucosepyranose units. R represents the portions where the substitutions can be made to prepare various types of cyclodextrins

Table 1: List of ocular diseases and its characteristics

Ocular Diseases	Characteristics
Dry eye syndrome (DES)	Disease related to tear film and ocular surface leads to a symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface (Arima *et.al*, 2011)
Glaucoma	Total blindness due to optic nerve damage by increased Intraocular pressure (IOP) (Saccà *et al.*, 2014)
Age related macular degeneration (AMD)	Formation of drusen and pigmentary alteration in macula leads to a mild to moderate visual disability (Hernández-Zimbrón *et al.*, 2018)
Diabetic Retinopathy	Retinal microvascular disease and major complication of diabetic mellitus, retinal neurodegeneration, inflammation and microvasculopathy leading to a decrease in visual acuity of vision loss (Wang and Lo, 2018)
Infectious conjunctivitis	Infection leads to dilation of conjunctival blood vessels and results inflammation (Watson and Cabrera-aguas, 2018)
Infectious Keratitis	Infection of the cornea and can lead to a corneal blindness and visual impairment (Watson and Cabrera-aguas, 2018)
Infectious endophthalmitis	Ocular inflammation of inner side of eye caused by infection leading to a redness, pain and hypopyon and chances of permeant vision loss if not treated timely (Watson and Cabrera-aguas, 2018)

Table 2: Marketed pharmaceutical products containing cyclodextrin (CD)

CD	Drug	Trade Name	Dosage form	Company	Country
β-CD	Aceclofenac	Aceclofenac- β-Cyclodextrin	Tablet	Taj Pharma	India
	Betahistine	Betahist	Tablet	Geno Pharm	India
	Cefotiam	Pansporin-T	Tablet	Takeda	Japan
	Cephalosporin	Meiact	Tablet	Meiji	Japan
	Chlordiazepoxide	Transillium	Tablet	Gabor	Austria
	Dextromethorphan	Ryndthisol	Tablet	Synthelabo	Italy
	Flunarizine	Fluner	Tablet	Geno Pharm	India
	Meloxicam	Mobitil	Tablet, suppository	Med. Union Pharm.	Egypt
	Nicotine	Nicorex/ Nicorette	Tablet	Pierre Fabre	Europe
	Nimesulide	Nimedex	Tablet	Novartis	Europe
	Norfloxacin and Tinidazole	Entronor –TZ/ Noroxin	Tablet		India
	Piroxicam	Cycladol/ Brexin/ Flamexin	Tablet	Chiesi	Europe
	Piroxicam	Cycladol/ Pyrodex/ Medicam	Tablet	Ranbaxy/ Sun	India
	Refocoxib	Rofizgel	Tablet	Wockhardt	India
	Tiaprofenic acid	Surgamyl	Tablet	RousselMaestrelli	Italy
	Cetirizine	Zyrtec	Chewing tablet	Losan Pharma/ UCB Pharma	Europe/ US
	Diphenydramine	Stada-Travel	Chewing tablet	Stada	Germany
	Nitroglycerin	Nitropen	Sublingual tablet	Nippon Kayaku	Japan

β-CD	Benexate	Ulgut/ Lonmiel	Capsule	Teikoku/ Shionogi	Japan
	Omeprazol	Omebeta	Enteric capsule	Betafarm	Germany
	Ethinyl estradiol	Safyral/Beyaz/Lorina	Tablet	Bayer Healthcare/ Sandoz	Europe
	Iodine	Mena-Gargle	solution	Kyushin	India
	Dexamethasone	Glymesason	Ointment	Fujinaga	Japan
	Cisapride	Propulsid	Suppository	Janssen	Europe
	Metronidazole	Metrogel/ Flagyl/ Vandazol/ Nidagel	Vaginal gel	Curatek/Fougera /Tolmar	US/Canada
	Piroxicam	Flogene	Paediatric liquid	Ache	UK
	Naphasoline hydrochloride	Clear eyes	Eye drop	Medtech	S. Africa
α-CD	PGE1	Prostavasin	Intra-arterial inf.	Ono/Schwarz	Japan/Germany
	PGE1	Prostandin 500	Infusion	Ono	Japan
γ-CD	Minoxidil	Alopexy	Solution	Pierre Fabre	Europe
	PGE1- OP-1206	Opalmon	Tablet	Ono	Japan
HP-β-CD	Indomethacin	Indocid/Indocyllir	Eye drop	Chauvin/ Bausch & Lomb	Europe
	Cisapride	Prepulsid	Suppository	Janssen	Europe
	Diclofenac	Dyolect	IV and IM Solution	Javelin Pharm	Europe
	Mitomycin	MitoExtra	IV infusion	Novartis	Europe
	Itraconazole	Sporanox	Oral solution IV solution	Janssen	Europe/USA
	Televancin	Vibativ I	IV infusion	Astellas	Europe

				Pharma/ Therevance	
	Voriconazole	Vorzu	Tablet	Rhambaxy	India
HP- γ-CD	Diclofenac	Voltaren/ Voltarol	Eye drop	Novartis	Europe
	Tc-99 Teoboroxime	CardioTec	IV solution	Bracco	USA
SBE-β-CD	Amiodarone	Nexteron	IV. solution	Hikma	
	Aripiprazole	Abilify	IM solution	BMS/Otuska	
	Maropitant	Cerenia	Parenteral solution	Pfizer Animal Health	USA
	Voriconazole	Vfend	IV solution	Pfizer	USA/Europe
	Ziprazidone	Geodon, Zeldox	Capsule/ IM solution	Pfizer	USA/Europe
RAMEB	Ostradiol	Aerodiol	Nasal spray	Servier	Europe
	Chloramphenicol	Clorocil	Eye drop	Oftalder	Poland

Table 3: Various types of cyclodextrin along with the substitutions, key physicochemical parameters and the related regulatory status

Cyclodextrin	Substitution R	Degree of substitution	Molecular weight (g/mol)	Log P	Solubility in water (mg/mL)	Pharmacopeia Monographs Regulatory status		
						US/NF	Ph.Eur	Japan
α CD	H	NA	972.8	-13	130	Yes	Yes	Yes
β CD	H	NA	1135	-14	18.5	Yes	Yes	Yes
γ CD	H	NA	1297	-17	249	In Progress	In progress	Yes
HPβCD	$CH_2CHOHCH_3$	0.65	1400	-11	>600	Yes	Yes	Yes
SBEβCD	$-(CH2)4SO^-_3Na^+$	0.9	2163	<-10	>500	Yes	Yes	Yes
RMβCD	$-CH_3$	1.8	1312	-6	>600	Yes	Yes	Yes
HPγCD	$CH_2CHOHCH_3$	0.6	1576	-13	>500		In progress	Yes

Table 4: Studies pertaining to the use of cyclodextrin in topical eye drops

Type of cyclodextrin	Drug molecule	Ocular condition	Observations	References
γCD	Amphotericin	fungal keratitis	35 fold increase in antifungal activity compared to fungizone®	(Serrano *et al.*, 2012)
αCD/γCD	Cyclosporine A	Dry eye disease	Increased transcorneal permeation	(Jóhannsdóttir *et al.*, 2015)
HPβCD	Nepafenac	Pain and Inflammation	Improved corneal retention and permeation	(Shelley *et al.*, 2018a)
γCD/HPγCD	Dexamethasone	ocular injury or inflammation	Increased dissolution and permeation	(Jansook *et al.*, 2010)
RMβCD	Dexamethasone	ocular injury or inflammation	Increased dissolution and permeation	(Loftsson and Stefánsson, 2007)
βCD/HPβCD	Curcumin	Retinitis pigmentosa	Improvement in water solubility and sustained release	(Maria *et al.*, 2016)
HPβCD	Ilomastat	Ocular scarring	Increased solubility and permeation through ocular tissue at a therapeutic concentration	(Mohamed-Ahmed *et al.*, 2017)
HPβCD	Melatonin	Granular corneal dystrophy type 2	Increased melatonin stability, decrease in irritation and improved therapeutic efficacy	(Ahn *et al.*, 2017)
HPβCD	Loteprednol	Ocular Inflammation and allergy-related disease	Improved anti-inflammatory efficacy and bioavailability	(Soliman *et al.*, 2017)
HPβCD/HPγCD	Prednisolone	Postoperative inflammation	Optimal mucoadhesive and antimicrobial properties	(Budai-Szucs *et al.*, 2018)

Table 5: Studies pertaining to the use of cyclodextrin in ocular *in situ gels*

Type of Cyclodextrin	Gelling Agent	Drug molecule	Ocular Conditions	Observations	References
HPβCD	Sodium alginate	Nepafenac	Pain and Inflammation	10 fold increase in transcorneal permeation and retention compared to marketed formulation	(Shelley *et al.*, 2018b)
αCD	Hyaluronic acid	Econazole	Fungal Keratitis	High residence time, sustained and safer ocular delivery	(Sulaiman and Kassab, 2018)
HPβCD	Pluronics	Voriconazole	Fungal Infection	Prolonged release and enhanced efficacy studies	(Üstünda *et al.*, 2019)
HPβCD	K Carrageenan +HPMC	Acyclovir	Antiviral	Enhanced residence time and permeability	(Li *et al.*, 2018)
αCD	MPEG/PCL	Dexamethasone + Bevacizumab	Corneal neovascularization	Improved precorneal retention and efficacy with no irritation observed over monotherapy	(Huang *et al.*, 2017)
SBEβCD	Chitosan	Honokiol	Corneal neovascularization	Safe, effective and sustained release drug delivery system	(Deng *et al.*, 2017)
αCD	HM-HPMC	Diclofenac	Inflammation	Increased ocular bioavailability	(Iohara *et al.*, 2017)

Table 6: Ocular Permitted daily dose (PDE) of various cyclodextrins and observed toxicity

SN	Cyclodextrin	Ocular Permitted Daily Dose (%)	Observed Toxicity	References
1	αCD	<4	Ocular irritation, renal toxicity	(Siefert and Keipert, 1997)
2	βCD	±1	Renal toxicity	(Stella Valentino et.al, 2008)
3	HPβCD	10	Extra care with neonates and patients with renal impairment, reversible diarrhoea	(EMA, 2014)
4	SBEβCD	10	Extra care with Neonates and patients with renal impairment	(EMA, 2014)
5	RMβCD	<5	Haemolysis (150 mg/kg in mice) Corneal epithelium toxicity	(Marttin *et al.*, 1998)

Highlights

- Overview of ocular diseases and a need of advanced therapeutic interventions.
- Versatality of cyclodexrin supramolecular complexes in ocular therapeutics.
- Drug solubility, stability and activity enhancement by complexation.
- Addressing the safety and toxicity concerns for ocular delivery.