GSC Biological and Pharmaceutical Sciences, 2019, 06(03), 001–010

Available online at GSC Online Press Directory

GSC Biological and Pharmaceutical Sciences

e-ISSN: 2581-3250, CODEN (USA): GBPSC2

Journal homepage: https://www.gsconlinepress.com/journals/gscbps

(REVIEW ARTICLE)

Ocular drug delivery system: Approaches to improve ocular bioavailability

Kumari Beena *

School of Medical and Allied Sciences GD Goenka University, Gurugram, India.

Publication history: Received on 25 February 2019; revised on 06 March 2019; accepted on 07 March 2019

Article DOI: https://doi.org/10.30574/gscbps.2019.6.3.0030

Abstract

Ocular drug delivery system (ODDS) is one of the most challenging tasks faced by pharmaceutical researchers. For a prolonged duration the major barriers in ocular medication are the ability to maintain a therapeutic level of the drug at the site of action. The ophthalmic preparations are available as buffered, sterile and isotonic solution. For the ocular delivery of drugs, several types of dosage forms are prepared and marketed. As drops are easier to administer so the most prescribed dosage form is the eye drop solution. For prolonged therapeutic action ointment, suspensions and gelled systems are also used. Frequent dosing in case of eye drop is the main issue for this system. The new drug delivery systems for this type of delivery is ocuserts, which are designed to eliminate the frequent administration of the drug by releasing the drug at predetermined and predictable rates. For this system the bioerodible implantable elements having multiple layers of different materials with different concentrations of materials are used and this generally include controlled, delayed and or sustained released formulation. The elements generally include an inner layer, or core, including a therapeutic agent, and one or more outer layers made of polymeric materials and this system is also able to prolong the residence time.

Keywords: Ocular drug delivery system (ODDS); Soluble ophthalmic drug insert (SODI); Polyvinyl alcohol (PVA); Polyvinyl pyrrolidone (PVP)

1. Introduction

Ophthalmic drug delivery is most interesting and challenging delivery system facing the pharmaceutical scientist [1]. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. These barriers affect the bioavailability of drugs. In ocular drug delivery system, there is a main problem of rapid and extensive elimination of conventional eye drops from eye. This problem results in extensive loss of drug. Only a few amount of drug penetrates the corneal layer and reached to internal tissue of eye. The main region of drug loss includes lachrymal drainage and drug dilution by tears [2]. This indulgence reduces the ocular bioavailability and lead to undesirable side effect and toxicity. To optimize ocular drug delivery systems the following characteristics are required:

- A good corneal penetration
- A continued contact time of drug with corneal tissue
- Easiness in installation and removal.
- A non-irritative form
- Good rheological properties.

* Corresponding author
E-mail address: beenasangwan05111993@gmail.com

On the development of sustained and controlled release drug delivery system the main attention is made from the last two decades. To avoid the dose frequency and improvement in the drug effectiveness the aim of such system based on localization on site of action [3]. The aim of pharmacotherapeutics at the intended site of action is the achievement of an effective drug concentration for a desired period of time. In order to avoid the risk of eye damage from high blood concentrations of drug which are not intended for eye and for the local therapy as against systemic therapy, Eye as a portal for drug delivery is generally used [4]. The conventional ocular dosage forms are eye drops, eye suspensions, eye gels, eye irritation solutions, eye solutions, eye ointments, eye injections, sol to gel systems [5]. Eighty percent of the total ophthalmic preparations are eye drops, eye ointments and gels which are most widely used. The eye drop dosage form is easy to instill but have limitations such as requirement of frequent administration, rapid precorneal elimination, sticking of eye lids, unpredictable doses, loss of drug by drainage, blurred vision, no true sustained effect, eye irritation and poor patient compliance [6-8]. It is usually acceptable that ranging from 5-10% of total administered, the intraocular bioavailability of topically applied drugs is extremely poor [9-11].

1.1. Advantages of ocular drug delivery system [12]

The merits of ODDS are followings:

- Increased accurate dosing, to overcome the side effects of pulsed dosing produced by conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
- To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
- To circumvent the protective barriers like drainage, lacrimation and conjunctive absorption.
- To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
- To provide better housing of delivery system.

1.2. Disadvantages [13, 14]

Various disadvantages of ocular drug delivery system are given below.

- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen.

2. Classification of ophthalmic inserts

The classification of ophthalmic inserts is shown in Figure 1. [15]

Based upon their solubility behaviour

Insoluble

- Diffusion
- Osmotic and
- Contact lens

Soluble

- Based on natural polymers e.g. collagen
- Based on synthetic or semi synthetic polymers e.g. cellulose derivatives like HPMC, HPC, MC etc.

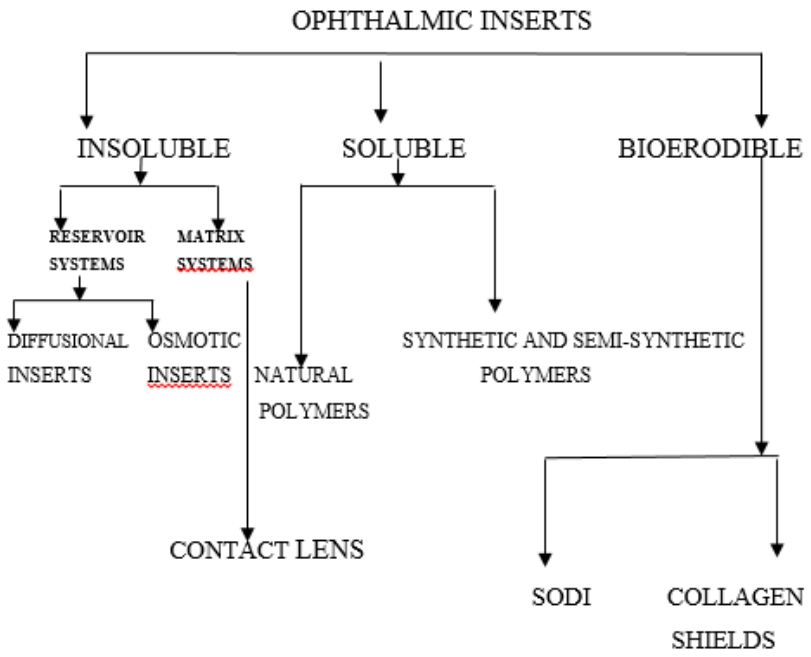

Figure 1 Flowchart showing classification of ocular inserts [15]

2.1. Insoluble ocuserts [16]

Only the insoluble types can usually deliver drugs by a variety of method sat controlled, predetermined rate, but need removal from the eye when empty.

Insoluble ocuserts can be classified into two categories:

2.1.1. Reservoir system

In this system the drug released either by diffusion or by an osmotic process. It contains, respectively, a liquid, a gel, a colloid, a semisolid, a solid matrix, or a carrier containing drug.

Diffusional insert or ocuserts

Based on porous membrane ocuserts system is a novel ocular drug delivery system. From diffusional inserts/Ocusert drug release is based on a diffusional release mechanism.

Osmotic inserts

The osmotic inserts are usually composed of a central part bounded by a peripheral part and are of two types:

Type 1

The central part is composed of a single reservoir of a drug surrounded by the polymer as discrete small deposits, with or without an additional osmotic solute dispersed throughout a polymeric matrix. An insoluble semipermeable polymer film comprised the second peripheral part of these inserts. In the form of apertures, the osmotic pressure against the polymer matrix causes its rupture. Near the surface of the device drug is then released through these apertures from the deposits.

Type 2

The central part is composed of two different compartments. In two separate compartments the drug and osmotic solutes are placed, the drug reservoir being surrounded by an elastic impermeable membrane and by a semi-permeable membrane the osmotic solute reservoir surrounded. The second peripheral part of this type is similar to type 1.

2.1.2. Matrix systems

The second category matrix system is mainly represented by contact lenses and particular group of insoluble ophthalmic devices. It forms a three dimensional network or matrix capable of retaining water, aqueous drug solution or solid components and consist of covalent cross-linked hydrophilic or hydrophobic polymer.

Contact lenses

Contact lenses are initially used for vision correction. The possibility of correcting vision and releasing drug simultaneously the main advantage of this system. Refojo has proposed a subdivision of contact lenses into 5 parts.

- Rigid
- Semi-rigid
- Elastomeric
- Soft hydrophilic
- Bio-polymeric

2.2. Soluble ocuserts

Soluble (S) inserts normally defined as erodible (E), monolithic polymeric devices that releasing the drug and do not need removal while undergo gradual dissolution. Through polymer swelling true dissolution occurs mainly, while to a chemical or enzymatic hydrolytic process erosion corresponds. In swelling-controlled devices in a glassy polymer, the active agent is homogeneously dispersed. Water from the tear fluid begins to penetrate the matrix when the insert is placed in the eye, then by releasing their drug content, swelling and consequently polymer chain relaxation and drug diffusion take place. They do not need to be removed from their site of application is the main advantage of this system [16, 17]. They can be classified into two parts

2.2.1. Natural polymers

To produce soluble ophthalmic inserts natural polymer used is preferably collagen. The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying, and re-hydrating it before use on the eye. On the concentration of the drug solution into which the composite is soaked as well as the duration of the soaking and the amount of binding agent present the amount of drug loaded will depend. As the collagen dissolves, the drug is gradually released from the interstics between the collagen molecules [16].

2.2.2. Synthetic and semi-synthetic polymer

This is based upon use of polymers i.e. semi-synthetic polymers (e.g., cellulose derivatives) and synthetic polymers i.e. polyvinyl alcohol. By using Eudragit, a polymer usually used for enteric coating or as a coating agent of the insert, a decreased release rate can be obtained [16].

2.3. Bio-erodible ocular inserts

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants. Some important ocular inserts which are available commercially (SODI) or in advanced states of development (collagen shields, Ocufit and Minidisc) [17].

2.3.1. Soluble ophthalmic drug insert

Soluble ophthalmic drug insert (SODI) is a small oval wafer, which was developed by soviet scientists for cosmonauts who could not use eye drops in weightless conditions.

2.3.2. Collagen shields

Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals. This protein has several biomedical applications which is derived from intestinal collagen and the main application of which is probably catgut suture. The ocular inserts devices are given in table 1.

Table 1 Ocular inserts devices [15-18]

Name	Description
Soluble ocular drug insert	Small oval wafer, composed of soluble copolymers consisting of actylamide, ethyl acetate, soften on insertion.
Collagen shields	Erodible disc consist of cross link procine sclera collagen.
Ocuserts	Flat, flexible, elliptical insoluble device consisting of two layers, enclosing a reservoir, use commercially to deliver Pilocarpine for 7 days.
Minidisc or ocular therapeutic	System 4-5 mm diameter contoured either hydrophilic or hydrophobic disc.
Lacrisert	Rose-shaped device made from hydroxyl propyl cellulose use for the eye syndrome as an alternative to tears.
Dry drops	A preservative free of hydrophilic polymer solution that is freeze dried on the tip of soft hydrophobic carrier strip, immediately hydrate in tear strip.
Gelfoam	Slabs of Gelfoam impregnated with a mixture of drug and cetyl ester wax in chloroform.
New ophthalmic drug delivery system	Medicated solid polyvinyl alcohol flag that is attached to a paper- covered with handle. On application, the flag is detaches and gradually dissolves, releasing the drug.
Bioadhesive ophthalmic eye inserts	Adhesive rods based on a mixture of hydroxyl propyl cellulose, ethyl cellulose, poly acrylic acid cellulose phthalate.

3. Barriers to ocular drug delivery systems

The major disadvantage associated with systemic administration ocular therapeutics is its low ocular bioavailability, and only 1%-2% of the administered dose reaches the anterior segment [19].

Therefore, in clinical practices, for ocular diseases related to the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea), topical administration of therapeutics is the preffered route of administration. Even though it seems to be an ideal route of administration, it has to overcome certain physicochemical, metabolic, and biological barriers to reach the intended site of action [20]. Barriers avoiding drug delivery are shown in figure 2.

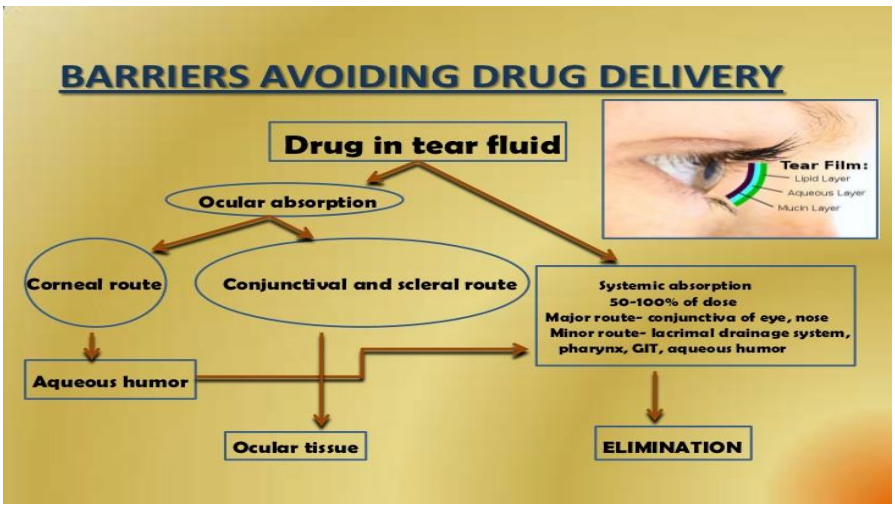

Figure 2 Barriers avoiding drug delivery [21]

The physicochemical barriers include properties of drug such as lipophilicity, solubility, molecular size and shape. The metabolic barriers include the activity of cytochrome P450 enzyme in the ocular tissue [22-23].

3.1. Physiologial barriers of ODDS

Physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constraints such as tear dilution, solution drainage, lacrimation, tear turnover and conjunctival absorption are responsible for poor ocular bioavailability of conventional ophthalmic dosage forms. Drug solution drainage away from the precorneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently ocular bioavailability of topical dosage forms [24]. The instilled dose leaves the precorneal area within two minutes of installation in humans. The ophthalmic dropper delivers 50- 75 µl, of the eye drops. If the patient does not blink, the eye can hold about 30 µl, without spilling on to the cheek [25].

4. Physical approaches to improve ocular bioavailability: formulation approaches (industrial perspective) [26]

4.1. Conventional ophthalmic dosage forms

Solutions are widely used dosage forms for topical delivery of therapeutics to the eye. Factors to be considered in formulating ophthalmic solutions are solubility, ocular toxicity, pka, effect of ph, tonicity, buffer capacity, viscosity, compatibility with other ingredients in the formulation, preservatives to be used, comfort when instilled into the eye, and the ease of manufacturing.

4.1.1. Viscosity enhancers

Polymers are usually added to ophthalmic drug solutions which increases the viscosity on the premise and correspond to a slower elimination from the preocular area, which lead to improved precorneal residence time and hence a greater transcorneal penetration of the drug into the anterior chamber. In terms of improvement in bioavailability it has minimal effects in humans. The polymers used are methylcellulose, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxyethylcellulose, hydroxypropyl methylcellulose (HPMC), and hydroxypropylcellulose. Natural polymers such as HA, veegum, alginates, xanthan gum, gelatin, acacia, and tragacanth can also be used as viscosity enhancers. However, these suffer the drawback of harboring bacteria and fungi [27].

4.1.2. Eye ointments

Ointments are usually formulated using mixtures of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to body temperature and are nonirritating to the eye. Ointments may be simple bases, where the ointment forms one continuous phase, or compound bases where a two-phased system (e.g., an emulsion) is employed. As a solution or as a finely micronized powder the medicinal agent is added to the base either. Upon instillation in the eye, ointments break up into small droplets and remain as a depot of drug in the cul-de-sac for extended periods. Therefore, in improving drug bioavailability and in sustaining drug release ointments are useful. Although safe and well-tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation [28].

4.1.3. Penetration enhancers

By increasing the permeability of the corneal epithelial membrane the transport characteristics across the cornea can be maximized [36-37], so to improve ophthalmic drug bioavailability, one of the approach used which lies in increasing transiently the permeability characteristics of the cornea with suitable substances called penetration enhancers or absorption promoters. Like ocular irritation and toxicity are some disadvantages of it. The transport process from the cornea to the receptor site is a rate-limiting step, and permeation enhancers increase corneal uptake by modifying the integrity of the corneal epithelium [29].

4.1.4. Prodrug

The principle of prodrug is to enhance corneal drug permeability through modification of the hydrophilicity (or lipophilicity) of the drug. Within the cornea or after corneal penetration, the prodrug is either chemically or enzymatically metabolized to the active parent compound. Thus, the ideal prodrug should not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility.

Example; antiviral medications ganciclovir and acyclovir are the suitable prodrug [30].

4.2. Novel ophthalmic dosage forms

4.2.1. Microemulsions

Microemulsions are novel ocular delivery systems that are mainly dispersions of water and oil along with a surfactant. Microemulsions confer advantages such as higher thermodynamic stability, improved solubility, and improved corneal permeation. The critical parameters that affect the stability of the microemulsion system are selection of aqueous phase, organic phase, and surfactant/cosurfactant systems. Cyclosporine A was formulated with microemulsions made of Brij 97 and loaded into 2-hydroxyethyl methacrylate (p-HEMA) hydrogels. Release of cyclosporine from these formulations was observed for a period of 20 days in an in-vitro release study. A microemulsion-based phase transition system was developed and evaluated for ocular delivery of pilocarpine hydrochloride. This system used sorbitanmonolaurate and polyoxyethylenesorbitan mono-oleate, which are nonionic surfactants with ethyl oleate, theoil component, and water. The system undergoes various phase transitions with change in viscosity depending on water content [30-32].

Both microemulsion and liquid crystalline formulations showed the greatest miotic response and duration of action, indicating high ocular bioavailability. Therefore, the microemulsions undergoing phase transition upon encountering aqueous medium such as tears can be very attractive ocular delivery systems as they provide the fluidity with increased viscosity after application, which increases ocular retention while retaining therapeutic efficiency.

Various drugs for ophthalmic use such as timolol, sirolimus, and chloramphenicol were formulated in various microemulsions with improved stability, solubility, and bioavailability [33, 34].

4.2.2. Nanosuspensions

Nanosuspensions are submicron colloidal systems made with inert polymeric resins and usually have a poorly water-soluble drug suspended in an appropriate dispersion medium. Advantages of nanosuspension include improved solubility of the drug, enhanced bioavailability, and reduced irritation to the eye. Results indicated that the nanosuspension has shown greater anti-inflammatory activity when compared with microsuspensions [33].

4.2.3. Iontophoresis and sonophoresis

Iontophoresis involves application of a low-density electrical current to enhance drug transport across various epithelia such as the skin, nail, and eye structures [47-49]. Iontophoresis for ocular delivery was first studied in 1908 by Wirtz, who studied topical ocular delivery of zinc salts for the treatment of corneal ulcers.

Iontophoresis is a noninvasive method of transferring ionized drugs through membranes with low electrical current. The drugs are moved across the membranes by two mechanisms: migration and electro-osmosis.

Ocular iontophoresis is classified into transcorneal, corneoscleral, or trans-scleral iontophoresis, the latter being the most interesting option. It is noninvasive method and easy to use. It has ability of modulate dosage (less risk of toxicity), a broad applicability to deliver a broad range of drugs or genes to treat several ophthalmic diseases in the posterior section of the eye. It has some drawbacks such as requirement of repeated administrations, no sustained half-life and side effects i.e. mild pain in some cases.

The merits of this system is fast, painless and safe system, and to a specific site delivery of high concentrations of drug [33-35].

Sonophoresis or ultrasound, involves application of ultrasound at frequencies higher than 20 khz to enhance transdermal and ocular permeation. An ultrasound is usually applied over the epithelium through a coupling medium such as emulsion suspension of any formulation that allows the propagation of acoustic field. In a recent report, sonophoresis was used to enhance intra scleral delivery of fluorescein isothiocyanate conjugated to serum albumin in an ex- vivo rabbit eye model. The frequency used was 1MHz with an intensity of 0.05 W/cm^2 and 30s exposure time. Results have shown that sonophoresis enhanced the transcleral permeation of the protein 1.6-fold without damaging ocular tissues [34].

4.3. Chemical approaches to improve ocular bioavailability

The objective behind improved ocular drug delivery should not only consider enhanced ocular drug absorption but also reduced systemic absorption. Systemic absorption of drugs is not only nonproductive absorption but also leads to undesirable systemic side effects associated with the drugs. Therefore, it is important to optimize the drug delivery systems, which could offer improved biopharmaceutical properties and have the capability to concentrate in ocular

tissues in a predictable manner. Chemical modification of drugs to improve therapeutic efficacy and to enhance various physicochemical properties such as solubility, stability, permeability, and evasion of efflux pump is an established approach in therapeutic drug delivery. The metabolic activity of ocular tissues provides an opportunity of utilization of chemically modified drugs that have a predictable metabolic bioconversion in the eye. The most important strategies in chemical approaches for ocular delivery are

- Designing ocular drugs that are inactive at sites other than the eye (prodrugs)
- Designing drugs that undergo sequential metabolic conversion and finally reach the target (retro metabolic design), and
- Chemical modification of a known inactive metabolite or analog to restore the therapeutic activity that transforms back into the inactive metabolite in a predictable one-step biotransformation (SD) [35].

5. Conclusion

In the therapy of eye disease the ocular insert represents a significant advancement. This system of ocuserts provides many advantages such as; improve patient complicance by reducing the frequency of dosing, provide sustained and controlled drug delivery and reduce the dose and thereby reduce the adverse effects of the drug.

Consequently, it seems logical to consider nonconventional approaches such as nanotechnology, microspheres, liposomes, appropriate prodrug *in situ* forming gel, and iontophoresis for effective delivery and to further enhance ocular absorption and reduce side effects.

Compliance with ethical standards

Acknowledgments

The author (Beena Kumari) is very thankful to her family specially to her mother Krishna Devi. Because without her cooperation this review was not possible.

Disclosure of conflict of interest

None

References

[1] Zaki I, Fitzgerald p, Hardy JG and Wilson CG. (1999). Comparison of effect of viscosity on the precorneal residence of solution in rabbit and man. Journal of Pharmacy and Pharmacology, 38, 463–466.

[2] Lee VH and Robinson JF. (2009). Review: Topical ocular drug delivery; recent developments and future challenges. Journal of Ocular Pharmacology and Therapeutics, 2, 67.

[3] Sikandar MK, Sharma PK and Visht Sikandar S. (2011). Ocular drug delivery system: an overview. International Journal of Pharmaceutical Sciences and Research, 2, 1168-75.

[4] Saettone MF and Salminen L. (2001). Ocular inserts for topical delivery. Asian Journal of Pharmaceutics, 16, 95–106.

[5] Schoenwald RD. (2003). Ocular Pharmacokinetics/Pharmacodynamics. In: Mitra AK, editor. Ophthalmic drug delivery systems. New York: Marcel Dekker, 260-65.

[6] Neefe CW. (1974). Contact lens for ocular drug delivery. US Patent. 3: 786–812.

[7] Gibaldi M and Perrier D. (1993). Pharmacokinetics: Drugs and the pharmaceutical sciences 2nd edition. Marcel Dekker, New York. 15: 1000-08.

[8] Robinson JC. (2002). Ocular Anatomy and Physiology Relevant to Ocular Drug Delivery. In: Mitra AK, editor. Ophthalmic drug delivery systems. New York: Marcel Dekker. 573-79.

[9] Chien YW. (2003). Novel drug delivery systems. 2nd edition. Marcel DekkerNew York. 301.

[10] Khar RK and Vyas SP. (2002). Targeted and controlled drug delivery novel carrier systems. 1st edition New Delhi: C.B.S. Publishers and Distributors, Inc, 111.

[11] Mainardes RM, Urban MC, Cinto PO and Chaud MV. (2017). Colloidal carriers for ophthalmic drug delivery. Current Drug Targets, 6, 363–371.

[12] Arul kumaran KSG, Karthika K and Padmapreetha J. (2010). Comparative review on conventional and advanced ocular drug delivery formulations, International Journal of Pharmacy and Pharmaceutical Sciences, 2, 1.

[13] Kumar A, Malviya R and Sharma PK. (2016). Recent Trends in Ocular Drug Delivery: A Short Review, European Journal of Applied Sciences, 3, 86-92.

[14] Boarse Manoj B, Kale Sachin S, Bavisker Dheeraj T and Jain Dinesh K. (2013). Comparative review on conventional advanced ocular drug delivery system. Journal of Drug Delivery & Therapeutics. 3(1), 114-1233.

[15] Sampath K, Bhowmik D, Harish G, Duraivel S and kumar P. (2013). Ocular Inserts: A Novel Controlled Drug Delivery System. The Pharma Innovation Journal, 1(12), 1-16.

[16] Saettone MF, Salminen L. (2015). Ocular inserts for topical delivery. Advanced Drug Delivery, 16, 95–106.

[17] Sahane NK, Banarjee SK, Gaikwad DD, Jadhav SL and Throat RM. (2010). Ocular Inserts- A Review. Drug Invention, 2, 57–64.

[18] Duvvuri S, Majumdar S and Mitra AK. (2003). Drug delivery to the retina: challenges and opportunities. Expert Opinion and Biological Therapeutics, 3, 45-56.

[19] Keister JC, Cooper ER, Missel PJ, Lang JC and Huger DF. (1991). Limits on optimizing ocular drug delivery. Journal of Pharmacetical Sciences, 80, 50-3.

[20] Lambert G and Guilatt RL. (2005). Current ocular drug delivery challenges. Drug Development Report Industry Overview Details, 33, 1-2.

[21] Souza JG, Dias, Pereira TA, Bernardi DS and Lopez RF. (2014). Topical delivery of ocular therapeutics: carrier systems andphysical methods. Journal of Pharmacy and Pharmacology, 66, 507-30.

[22] Ruponen M and Urtti A. (2015). Undefined role of mucus as a barrier in ocular drug delivery. European Journal of Biopharmaceutics, 96, 442-446.

[23] Nakano M, Lockhart CM, Kelly EJ and Rettie AE. (2014). Ocular cytochrome P450s and transporters: roles in disease and endobiotic and xenobiotic disposition. Drug Metabolism, 46, 247-60.

[24] Saettone MF, Giannaccini B, Ravecca S, LaMarca F and Tota G. (2015). Evaluation of viscous ophthalmic vehicles containing carbomer by slit-lamp fluorophotometry in humans. International Journal of Pharmaceutics, 20, 187-202.

[25] Sasaki H, Yamamura K, Mukai T, Nishida K and Nakamura M. (2016). Enhancement of ocular drug penetration. Drug Carrier System, 16, 85-146.

[26] Lee VH. (2012). Precorneal, corneal and postcorneal factors. In: Mitra AK (Ed.). Ophthalmic Drug Delivery Systems. New York: Marcel Dekker. 59-82.

[27] Sasaki H, Igarashi Y, Nagano T, Yamamura K, Nishida K and Nakamura J. (2009). Improvement of the ocular bioavailability of timolol by sorbic acid. Journal of Pharmacy and Pharmacology, 47, 17-21.

[28] Lee VH. (2011). Evaluation of ocular anti-inflammatory activity of Buteafrondosa. Journal of Pharmacy and Pharmacology, 11, 79-90.

[29] Tirucherai GS, Dias C and Mitra AK. (2012). Effect of hydroxypropyl beta cyclodextrin complexation on aqueous solubility, stability, and corneal permeation of acyl ester prodrugs of ganciclovir. Journal of Ocular Pharmacology and Therapeutics, 18, 535-48.

[30] Vandamme TF. (2015). Microemulsions as ocular drug delivery systems: recent developments and future challenges. Journal of Pharmacy and Pharmacology, 21, 15–34.

[31] Kapoor Y and Chauhan A. (2018). Ophthalmic delivery of Cyclosporine A from Brij-97 microemulsion and surfactant-laden p-HEMA hydrogels. International Journal of Pharmaceutics, 361, 222–229.

[32] Chan J, Maghraby GM, Craig JP and Alany RG. (2017). Phase transition water-in-oil microemulsions as ocular drug delivery systems: in vitro and in vivo evaluation. International Journal of Pharmaceutics, 328, 65–71.

[33] Li CC, Abrahamson M, Kapoor Y and Chauhan A. (2018). Timolol transport from microemulsions trapped in HEMA gels. Journal of Colloidal Interface and Sciences, 315, 297–306.

[34] Buech G, Bertelmann E, Pleyer U, Siebenbrodt I and Borchert HH. (2017). Formulation of sirolimus eye drops and corneal permeation studies. Journal of Ocular Pharmacology and Therapeutics, 23, 292–303.

[35] Kaur IP and Kanwar M. (2018). Ocular preparations: The formulation approach. Drug Development and Industrial Pharmaceutics, 28, 473–93.

How to cite this article

Kumari B. (2019). Ocular drug delivery system: Approaches to improve ocular bioavailability. GSC Biological and Pharmaceutical Sciences, 6(3), 01-10.