International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 12, Issue 5, 2020

Review Article

OCULAR DRUG DELIVERY SYSTEM: CHALLENGES AND APPROACHES

VISHAL KUMAR RAJ*, RUPA MAZUMDER, MONIKA MADHRA

Noida Institute of Engineering and Technology (Pharmacy Institute), 19 Knowledge Park-II, Institutional Area, Greater Noida 201306, Uttar Pradesh, India
Email: vishalkumarraj089@gmail.com

Received: 15 Jun 2020, Revised and Accepted: 06 Aug 2020

ABSTRACT

The ocular drug delivery deviates through a number of anatomical and physiological barriers, which have been a bottleneck for the ophthalmologists. The ocular barriers, static and dynamic, decrease the absorption of the therapeutic agents and the entry of the xenobiotics. Thus, a conventional ocular dosage form has various disadvantages of its use in ocular diseases. Hence, an ideal ocular delivery system has always been aimed, where the bioavailability of a drug is maintained for a longer period of time. The present review aims to focus on the drawbacks of the conventional ocular therapy and the advantages of designing novel delivery systems, with their certain specific advantages in ocular pharmacokinetics and the enhancement of bioavailability. These novel approaches emphasize on the benefits of various ocular drug delivery systems, like eye ointments, gels and use of viscosity enhancers, prodrugs, penetration enhancers, microparticles, liposomes, niosomes, ocular inserts, implants, intravitreal injections, nanoparticles, nanosuspension, microemulsion, dendrimers, *in situ* gels, iontophoresis and periocular injections. The compiled data presented in this review will act as a good information resource and reference point for further researches in the field of ocular drug delivery aiming non-invasive sustained release of drugs in the anterior and posterior segments of the eye.

Keywords: Barriers, Anterior and posterior segments, Ocular bioavailability, Ocular drug delivery, Convectional delivery, Novel drug delivery

DOI: http://dx.doi.org/10.22159/ijap.2020v12i5.38762. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Human eye is a complex structure, both anatomically and physiologically, that makes it a unique organ consisting of its physiologically independent functions. Its wide range of varied structures also challenges to develop drug delivery systems for it. The major problem in the conventional ocular drug delivery system with eye drops is their fast and extensive elimination from the eye, causing extensive loss of the drug [1, 2]. In eye drops, only a small portion of a drug penetrates through the corneal layer and arrives in the internal tissues present in the eye [3, 4]. Broad classification of ocular drug delivery results in two types, those concerned with the anterior and posterior segments. For vision-threatening ocular diseases, conventional drug delivery systems, such as eye drops, suspensions and ointments, cannot be used for optimal treatment [5]. About 90% of the ophthalmic formulations in the market are available in the form of eye drops and the sites of action are diseases occurring in the anterior segment of the eye [6]. Topical delivery of drugs through conventional approaches is unable to make it reach the posterior segment of the eye. Formulations like eye drops and ointments, when instilled into the cul-de-sac, are wiped away from eye region quickly because of the flow of tear and lachrymal nasal drainage. Most of the drug is drained away and only a small portion reaches the site of action; so, it needs frequent dosing to achieve a therapeutic effect. The eye's posterior segment includes the retina, vitreous humour and choroid; the diseases occurring in these regions can be cured by using intravenous and intravitreal drug delivery systems, implants or by administering drug through periocular route and needs high concentration of the drug as well. For ophthalmic drug delivery, the posterior segment of eye is frequently a choice of interest to locate drugs using novel approaches [7]. The rationale behind this review and novelty of this study are to highlight the newer developments in the pharmaceutical ophthalmic formulations, such as formulation of *in situ* gels, nanoparticles, liposomes, nanosuspension, microemulsion, ocular inserts and so on, and their progress to overcome the problems associated with the existing conventional dosage forms and also to improve the bioavailability as well as the sustained release of the drug at the target location [8].

Barriers for ocular drug delivery

Ocular drug delivery suffers from the following barrier effects:

Drug loss from the ocular surface

After using the dosage form of the drug in the ocular system, flow of lacrimal fluid wipes out a portion of the drug from its surface and its turnout rate is only about 1 µl/min, whereas, a major portion of the drug is wiped out through the nasolacrimal duct quickly within minutes. Other sources of drug removal include the systemic absorption of the drug, instead of being absorbed through the ocular route. Systemic absorption is mostly directed through the conjunctival sac to the local blood capillaries or takes place after the solution flows to the nasal cavity [9].

Lacrimal fluid-eye barriers

Absorption of the drug from the lacrimal fluid can be limited by the corneal epithelium present in the eye. Tight junctions formed from corneal epithelial cells limit the permeation of the drug paracellularly. Lipophilic drugs show higher permeability in the cornea as compared to hydrophilic drugs. In other terms, we can say that conjunctiva has leaky epithelium compared to that of the cornea and also has twenty times greater surface area than the cornea that supports rapid systemic absorption.

Blood-ocular barriers

Blood-ocular barriers are present in the bloodstream, which protect the eye from xenobiotics. It comprises of two parts, namely blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of endothelial cells in the uvea, *i.e.,* the middle layer of the eye below sclera, iris, ciliary body and choroid. This barrier works to prevent the entry of hydrophilic drugs present in plasma to the aqueous humor and also limits the entrance of plasma albumin in aqueous humor. The posterior barrier which resides in between the eye and stream of plasma consists of retinal pigment epithelium (RPE) and retinal capillaries, resulting in tight wall junction. Choroid vasculature comprises of extensive blood flow and leaky walls, due to which easy access of drugs occurs in the choroidal extravascular space, but again their distribution in the retina is limited due to the presence of RPE and retinal endothelium [10].

Advantages of ocular drug delivery systems

The advantages of ocular drug delivery systems have been summarized below:

- They impart accuracy and uniformity in dosing rate. Pulsed dosing of conventional systems can be avoided.
- Sustained and controlled release of drugs can be achieved.
- By increasing corneal contact time, they cause enhancement in the ocular bioavailability of drugs and it is achieved by effective adherence of the drug to the corneal surface.
- For the prevention of loss of ocular tissues, targeting within the ocular globe is to be done.
- They bypass the protective ophthalmic barriers, such as drainage, lacrimation and conjunctival absorption.
- They also improve patient's compliance, offer comfort and enhance therapeutic drug performance.
- They provide better housing of delivery systems.
- The make self-administration of drugs possible.
- Systemic and visual side effects are lower and absorption is faster [11].

Disadvantages of ophthalmic drug delivery systems

The major drawbacks of ophthalmic drug delivery systems are as follows:

- Short contact time of drug solution and eye surface.
- Poor bioavailability.
- Instability for dissolved drugs.
- Use of preservatives [12].

Limitations of ocular drug delivery

Ocular delivery of drugs suffers from the following limitations:

- Termination of the dosage form is not possible during an emergency.
- Interference with vision.
- Faces difficulty in placement and removal of the dosage form.
- During sleep or while rubbing eyes, there may be an occasional loss of the drug [12].

Routes of ocular drug delivery

The various possible routes for ocular drug delivery are described below:

Intravitreal route

In this route, the medication is delivered through injections in the vitreous humor of the eye. This route of administration is used to cure a number of eye disorders; the delivery through this ocular route is shown in fig. 1.

Intracameral route

Anterior or posterior chambers of the eye are the sites of action for a drug in this route of administration. It can be demonstrated by injecting an anesthetic agent into the anterior chamber of the eye, usually during surgery.

Perilocular route

The drug is administered around the eye in this route of administration. It can be explained by peril ocular steroid injection involving the placement of steroids around the eye to treat intraocular inflammation or swelling [13].

Suprachoroidal route

Supra choroid region of the eye is the target in this route of administration. The space existing between the sclera and the choroid is termed as suprachoroidal space.

Subconjunctival route

In this route, the drug is administered to the mucus membrane, comprising of the open space of the eyeball and the inner surface of the eyelids.

Topical route

Eye drops are the best examples of ophthalmic dosage forms used for topical administration of drugs in the eye as compared to ointments, gels and emulsions, which are used to cure the diseases of the anterior segment of the eye. It is the most convenient method drug delivery to eye, due to ease of administration and lower cost.

Systemic route

Common barriers to the systemic delivery of ophthalmic drugs are blood-aqueous barrier and blood-retinal barrier (BRB) for the anterior segment and posterior segments of eye, respectively [14].

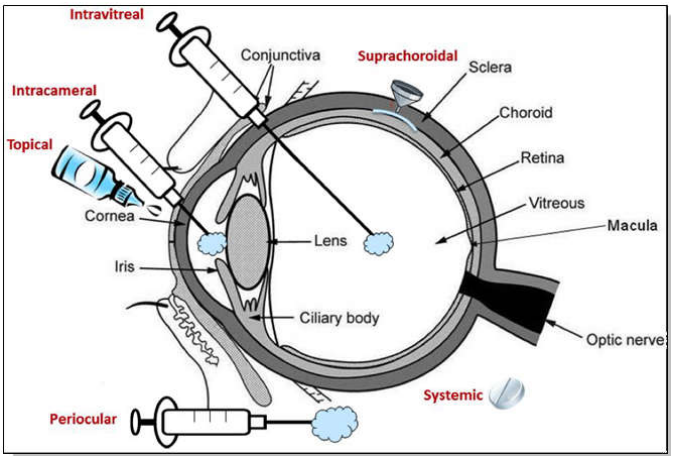

Fig. 1: Routes of ocular drug delivery [14]

Challenges in ophthalmic drug delivery systems

Challenges in ocular drug delivery systems are to design a therapeutic system which can provide an optimal concentration of a drug at the target region and with high therapeutic efficacy. Rapid absorption of drugs occurs due to the corneal anatomy, physiology and barrier functions, so quick instillations of eye drops are mandatory to balance the therapeutic level in tear film or at targeted sites. Side effects of using frequent dosing of drug solution are that it can induce toxicity at the ocular surface and cause cellular damage

as well. Most of ocular dosage forms are poor in bioavailability, due to the precorneal loss, including solution drainage, lacrimation, tears dynamics, tear dilution, conjunctival absorption, nonproductive absorption, the transient residence time in the cul-de-sac and tear turnover. Other challenges include relative impermeability of corneal epithelial membrane, causing problems in delivering drugs at the anterior segment following topical administration.

Approximately 1% or even less of the instilled dose of the drug reaches the intraocular tissues due to various anatomical and physiological hurdles, which reduces the absorption of a drug. For better clinical results, topical dosage form needs to maintain a balance between the lipophilicity and hydrophilicity along with higher contact time [15].

The challenges in ocular drug delivery systems are categorized as follows:

Anterior segment delivery challenges

Topical formulations are mostly preferred over systemic formulations in the ocular delivery system because if any drug formulation is administered to eye, before reaching the anatomical barrier of the cornea, the drug molecule has to face the precorneal barriers, the tear film and conjunctiva, which come first in the pathway and slow the penetration of the active moiety in the eye. Precorneal loss factors are responsible for poor bioavailability of the drugs in most of the ocular formulations, as shown in fig. 2.

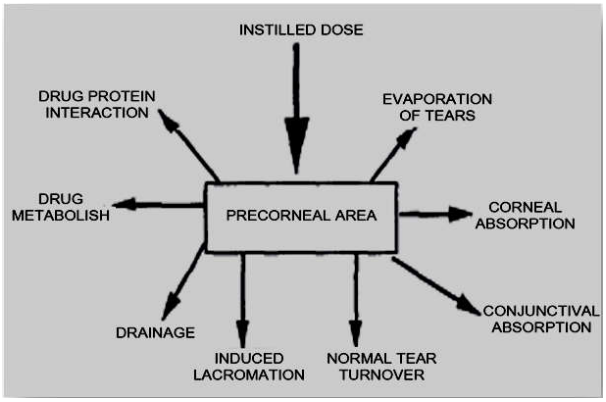

Fig. 2: Precorneal factors influencing bioavailability of topically applied ophthalmic drugs [15]

Moreover, frequent instillations of eye drops are necessary to maintain a therapeutic drug level in the tear film or at the site of action, but the frequent use of highly concentrated drug solutions may induce toxic side effects and cellular damage at the ocular surface.

Posterior segment delivery challenges

BRB inhibits the entry of topically applied ocular drugs at the posterior segment of eye. Delivery of drugs is inhibited by some factors at the posterior segment of ocular tissue and this effect is also responsible for poor ocular bioavailability. The BRB is responsible for limiting the effect of the intravenous route at the posterior site for drug delivery [16] and it also limits the entry of the systemically administered drug in the retina [17]. For curing diseases in the posterior segment of the eye, there is a need for high concentration of vitreal drugs. BRB is permeable to more lipophilic molecules and so allows the entry of such drugs in the posterior segment of the eye. Frequent administration and high concentration of drug cause side effects systematically [18]. A major challenge to deliver drugs to the posterior segment of the eye is to maintain the therapeutic concentration of the drugs, for a longer period of time and minimizing the number of injections as well. Elimination of drug through the anterior route follows to the aqueous humor and, finally, outflows to the humor in the anterior chamber. Many drugs are eliminated through the posterior route, crossing a path of the blood-retinal barrier to the systemic circulation (fig. 3).

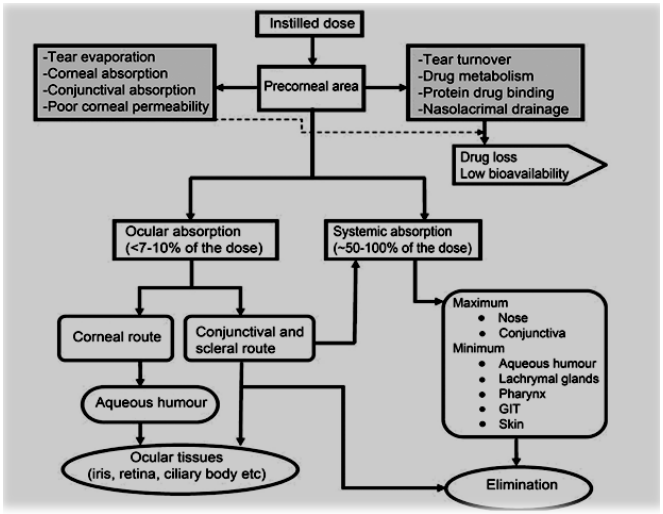

Fig. 3: Fate of ophthalmic drug delivery system [15]

Approaches in ophthalmic drug delivery systems

A number of approaches have been used in the early stages for better results. These approaches, categorized into two types, are:

- Bioavailability improvement and
- Controlled release drug delivery

The first type aims to maximize corneal drug absorption and minimize precorneal drug loss using viscosity and penetration enhancers, prodrugs, gels and liposomes. The second one is for the delivery of active ophthalmic moiety in the form of a sustained delivery system by providing controlled and continuous delivery like implants, inserts, nanoparticles, micro particulates, and colloids. There are a number of traditional approaches, such as viscosity enhancers, gel, penetration enhancer, prodrug and liposomes which enhance the bioavailability, while the newer developments, *i.e.,* ocuserts, nanosuspension, nanoparticles, liposomes, niosomes and implants improve both bioavailability and release of drugs in a controlled manner in the anterior segment of the eye. In the posterior segment of the eye, drug reaches through intravitreal injections, iontophoresis, subconjunctival injection and periocular routes [19, 20].

Approaches to improve ocular bioavailability

Use of viscosity enhancers

Viscosity-increasing polymers are highly preferred additive in the ophthalmic formulations due to their properties of enhancing viscosity and thereby imparting benefit to the penetration of the drug into the anterior chamber of the eye by lowering the elimination rate from the preocular area, resulting in increase in precorneal residence time and transcorneal penetration, but having very fewer effects for enhancing bioavailability in human beings. Examples of polymers are polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxylethylcellulose, hydroxylpropyl methylcellulose (HPMC) and hydroxypropyl cellulose [21]. As per Saettone *et al.* (1984), in their study of tropicamide solution, by using PVA, HPMC, and PVP solution, at concentrations yielding the same viscosity of 20 cst, PVA has been reported to be the most effective among all, probably due to the adhesive property of PVA and its capability to enhance the thickness of the precorneal tear film [21]. Saettone *et al.* (1982) have stated in their study that the retention of drug in the precorneal tear film does not strictly belong to vehicle viscosity, but also with surface spreading properties of the vehicle and to the capability of a polymer to use water as the vehicle spreads over the ocular surface with each eye blinking [22].

Gel formulation

Gels are known to be significantly dilute cross-linked systems, which show rigidity in the steady-state. Gels are generally liquid, but behave like solids due to their three-dimensional cross-linked structure within the liquid [23-25]. On the other side, if the gels have extremely high viscosity, they cannot improve bioavailability; instead, they will control the release, which leads to reduced frequency of dosing to once a day. The highly viscous solution even leads to blurred vision and matted eyelids, which substantially decrease patient's compliance. In aqueous gel, viscosity building agents, such as PVA, polyacrylamide, poloxamer, HPMC, Carbomer, polymethylvinylether, Maleic anhydride, and hydroxylpropylethylcellulose are incorporated, whereas hydrogel or swellable water-insoluble polymers give rise to controlled drug delivery systems [26].

Prodrug formulation

By the development of prodrugs, many properties of the formulation can be improved, which make it suitable for increasing drug permeability through the cornea. It includes modification of the chemical structure that imparts new characteristics to the active moiety *i.e.* site-specificity and selectivity [27]. This can be explained through examples; the formulations which have been developed as prodrugs, are epinephrine, phenylephrine, timolol, and Pilocarpine. Other prodrugs are dipiverine, diester of pivalic acid and epinephrine showing seventeen fold more permeability via cornea as compared to that of epinephrine, which is caused by its six hundred folds more lipophilicity at pH 7.2. So a minor dose of the drug solution (dipiverine), spreads over the entire eyeball and has a therapeutic effect exactly the same as of epinephrine. When compared with conventional eye drops consist of 2% epinephrine, eye drops of dipiverine 0.1% show only mild activity by lowering the intraocular pressure with a significant reduction of side effects [28].

Penetration enhancers

Corneal epithelial membrane plays an important role in terms of permeability. So, by increasing its permeability, the transport property around cornea can be enhanced [29, 30]. Agents showing such properties are chelating agents, preservatives (like benzalkonium chloride), surfactants and bile acid salts, but due to local toxicity, they cannot be used in development ophthalmic formulation [31, 32].

Liposomes

Liposomes are defined as microscopic vesicles which consist of one or more concentric lipid bilayers, divided via water or aqueous buffer compartments. Liposomes are widely used in ocular formulations due to their property of having intimate contact with eye surfaces, mainly corneal and conjunctival area, thus drug absorption through ocular route can be increased [33]. Formulation of liposomes can be developed by using phosphatidylcholine, stearylamine and various amounts of cholesterol or lecithin and α-L-dipalmitoyl-phosphatidylcholine [34-37]. Major advantages of this type of delivery system are due to their properties, *i.e.*, biocompatibility, biodegradability, amphiphilic property, relative toxicity [34, 35, 38]. Delivery of drug on targeted site or site-specificity and release of drug in a sustained manner, are also its advantages. Liposomes are generally prepared for the drugs which have poor absorption, lower partition coefficient, poor solubility and having molecular weights in the range of medium to high [39]. Surface charge of liposomes is to be considered during the formulation of ocular delivery system; if liposomes are positively charged, they are observed to be preferably captured by negatively charged corneal surface, while the neutral or negatively charged liposomes are not captured by corneal surface. According to the number of researches reported, the active pharmaceutical ingredients being used in liposomal ophthalmic formulations are acyclovir, pilocarpine, acetazolamide, chloramphenicol and ciprofloxacin [36, 37].

Niosomes and discosomes

Niosomes are chemically stable, bi-layered nanocarriers made up of nonionic surfactants and used as carriers for both hydrophilic and hydrophobic drugs. They do not have drawbacks like liposomes that are chemical instable, susceptible to oxidative degradation and made up of phospholipids that are very much unstable as well as expensive [34, 35, 40, 41]. Thus, niosomes have lots of advantages including that they are biodegradable, biocompatible and nonimmunogenic, which make them increase the contact time between drug and cornea, thereby increasing the bioavailability of drugs. A modified form of niosomes is discosomes that also acts as carrier for ophthalmic drugs. The size of discosomes lies between 12 to 16 ?m. This gives it a benefit of not allowing it to enter in the general circulation and its disc shape provides better fit into the conjunctival sac [35]. The size of discosomes makes it different from niosomes, as the former consists of nonionic surfactants and SolulanC[24], a derivative of lanolin and a mixture of ethoxylated cholesterol (ether of cholesterol and polyethylene glycol) and ethoxylated fatty alcohols (ether of cetyl alcohol and polyethylene glycol). Use of niosomal carrier as a drug delivery system has been reported for genciclovir [42], cyclo-pentolate, or timolol [35].

Nanoparticles/nanospheres

These are polymeric colloidal particles, size varying from 10 nm to 1 nm, where the drug is being dissolved, entrapped, encapsulated, or adsorbed [43]. It consists of a number of biodegradable substances, like natural or synthetic polymers, lipids, phospholipids and metals. To obtain nanoparticles, the drugs can be formulated in many ways as by integrating with the matrix or by attaching to the surface of biodegradable polymers used for the preparation. Nanoparticles used in delivering drug to ocular tissues are polylactides (PLAs), polycyanoacrylate, poly (D, L-lactides) and natural polymers such as chitosan, gelatine, sodium alginate and albumin. Approximately, since

last 10 y, nanoparticles have been used as carriers in delivering drug for ocular disorders and given promising results. A specific type of nanoparticles can be classified as small capsules having a central cavity surrounded by a polymeric membrane and solid matrix spheres, known as nanocapsules and nanospheres, respectively. Marchal *et al.* (1993) have reported that the nanocapsules exhibit better effect as compared to that of the nanospheres, because drug (betaxolol, carteolol) present in unionized form in the oily core, diffuses at a higher rate into the cornea [44]. A number of authors have reported that the nanocapsules are more efficient due to the presence of mucoadhesive property in it that shows a rise in the residence time and biological responses [45]. So, these can enhance the bioavailability of drugs at ocular site and also decrease the frequency of dosing. Alonso *et al.* (1995) have reported in their study that the nanoparticles made from poly-e-caprolactone having cyclosporine exhibit better corneal absorption with respect to the drug's oily solution [46].

Nanosuspension and nanodispersions

Nanosuspensions are generated for poorly water-soluble drugs suspended at nano size range in a suitable dispersion medium. This technology can be utilized in a good way for drug moiety that forms crystals with high energy content, due to which they are insoluble in organic (lipophilic) or hydrophilic media. Polymeric nanoparticle suspensions are being formulated using inert polymeric resins, which can be used as vital drug delivery vehicles, having the capacity to increase drug release as well as improve its bioavailability. The carriers having such type of properties can be used as inert carriers for ophthalmic drugs, because they donot cause any irritation to the cornea, iris or conjunctiva. An example of such carrier is polymeric nanoparticle suspension having flurbiprofen (FLU) as an active ingredient and eudragit RS 1001 and RL 1001 are polymers used. Nanodispersions of alginate chitosan produced for sustained drug delivery and improved transcorneal permeation have been reported by Morsi *et al.* (2015) [47, 48].

Microemulsion

A stable dispersion of water in oil, facilitated by adding surfactant and co-surfactant in combination in a way to decrease interfacial tension, is termed as a microemulsion. Microemulsion leads to decrease in administration frequency and enhancing ocular drug bioavailability. Major advantages of this dosage form are its high thermodynamic stability, smaller droplet size, *i.e.*, 100 nm (approx.) and clear appearance. Ansari *et al.* (2008) have reported a microemulsion formulation, which is an oil in water system consisting of pilocarpine as a drug, lecithin, propylene glycol, PEG 200 as surfactant/co-surfactants and isopropyl myristate forming the oil phase [49].

Dendrimers

Dendrimers are symmetric structures made from repetitive branched molecules surrounding a central core, proposed recently as topical ocular drug delivery systems [50]. Frequently used dendrimers for delivery in ocular system are poly-(amidoamine) (PAMAM), PLL, polypropylenimines (PPI) and phosphorus dendrimers. These are used as carriers to deliver nucleic acid-based drugs, mostly in ocular delivery system [51], but sometimes used for drugs with low molecular weight that can be hydrophilic (antibiotics) or lipophilic (anti-glaucoma) drugs as well [52–58]. According to the reported methods, it has been found that the carrier's performance can be increased by making a change on their surface using methods like PEGylation or acetylation, which also help in reducing their toxicity factors [53, 54, 59]. So, the advantages of using dendimers as carrier of drugs for topical applications are enhancement of the drug residence time in the pre-corneal area, increase in bioavailability of drugs and prolonged therapeutic effect [52, 55, 57, 58].

***In situ* forming gel**

Researchers have found the new concept of *in situ* gel in the early1980s. Delivery of drug to ocular system through *in situ* gel is mainly for enhancing viscosity to decrease drug drainage from the cornea. The pourable gels are in liquid form when applied, after which they undergo a phase transition, when reaches to cul-de-sac of eye and converted into a visco-elastic gel giving rise to a response to changes environmentally, thereby increasing the bioavailability of the drug automatically. The major disadvantages of the *in situ* gels are that they get affected by temperature, pH or ions. Bazzaz *et al.* (2018) reported that *in situ* gelling system provides better and prolonged effect of a drug rather than conventional eye drops [60].

Approaches for controlled and continuous ocular drug delivery

The following ocular drug delivery systems have been reported for controlled as well as continuous release of drugs:

Microparticles

Microparticles are isotropic, transparent, translucent, thermodynamically stable system of oil, surfactant and water droplets the size of which ranges between 20 to 200 nm [61]. Microparticles are defined as micron-sized polymeric particles in which drugs in the polymeric matrices are suspended in liquid medium. Drugs are uniformly dispersed in the polymeric matrix or covalently bound to the backbone of the polymer [62]. During topical application in the eye these particles go into the ocular cul-de-sac and the drug releases from it through a number of processes like diffusion, chemical reaction or polymer degradation. Microparticles increase precorneal residence time, which allow continuous and sustained release of the drug. Ultimately this leads to increased ocular bioavailability of the drug and minimizes frequency of dosing, but microparticulate preparations are generally not administered to the eye as they cause irritation due to their large particle size. Microparticles have properties like biodegradation, bio-adhesion, and biocompatibility, which make it suitable for fabrication with polymers.

Ocular inserts

Ophthalmic inserts are solid patches, which, when placed in the conjunctival sac of the eye, slow down the rate of drug release. Ocular inserts also overcome the problem of frequent dosing by maintaining drug concentration in an effective manner and give rise to controlled, sustained and continuous drug delivery. Ocular Inserts also have various advantages like enhanced drug absorption due to increased contact time and minimized dose and application frequency. The major disadvantages of these inserts are patient noncompliance with frequent feeling like the entry of foreign body in the eye, difficulty in self-insertion feels and feeling of loss of the insert from eye. Ocular inserts are made by various techniques that make them soluble, erodible and in hydrogel form [table 1] [63].

Table 1: Various types of ophthalmic inserts

Types	Description	Reference(s)
Erodible inserts	The fabrication polymer is hydrophobic but biodegradable. The drug is released through the erosion of the surface of the insert.	[64]
Soluble inserts	The fabrication polymer is hydrophilic and water-soluble. Drug is released by diffusion control for soluble drugs and dissolution for less soluble drugs.	[65]
Hydrophilic but water-insoluble inserts	The fabrication polymer is hydrophilic but water-insoluble. Drug is released by diffusion control for soluble drugs and dissolution for less soluble drugs.	[64]
Inserts using osmotic system	A polymeric matrix in which the drug is dispersed as discrete small domains. Upon placement in the cul-de-sac, tears are imbibed into the matrix because of an osmotic pressure gradient created by the drug, whereupon the drug is dissolved and released.	[64]
Membrane controlled diffusion inserts	The drug core is surrounded by a hydrophobic polymer membrane; this controls the diffusion of the drug from the core to the outside.	[66]

Table 2: Marketed ophthalmic implants

Registered name	Active substance	Mode of administration	Reference(s)
Vitrasert®	Ganciclovir	Surgical implantation at the pars plana	[69]
Retisert®	Fluocinolone acetonide	Surgical implantation at the pars plana	[70]
Medidur®	Fluocinolone acetonide	Injected in the vitreous cavity	[70]
Posurdex®	Dexamethasone	Injected or through a small incision at the pars plana	[71]
Surodex®	Dexamethasone	Placed underneath the scleral flap	[70]

Implants

The aim of designing an intraocular implant is to prolong the activity of the drug, along with its controlled release by using a polymer or polymer system. An injectable delivery system of drug, like liposomes and nanoparticles, is easy to administer, but having limitation that after insertion, it becomes difficult to retract those particles during any complication, like toxic responses. So it is beneficial to use implants for balancing the rate and duration of drug release. Removal of ocular implants is easy and can be removed by surgical intervention. Implants can be categorized into two types based on the characteristics of the polymer(s) used:

Nonbiodegradable implants

They do not dissolve to any significant extent and are not even eroded *in vivo* [66].

Biodegradable implants

They mostly dissolve *in vivo* with soluble components by processes such as enzymatic or nonenzymatic degradations [67, 68]. Examples of marketed implants used worldwide have been cited in table 2.

Approaches for posterior segment drug delivery

Intravitreal injections

Research reports reveal that intravitreal injections for the posterior segment are gaining worldwide popularity as a drug delivery system, over the past few years. Injections are directly given into the posterior segment via pars plana for delivering drugs to overcome all barriers. A number of studies have been conducted to find out the pharmacokinetic parameters of antiviral agents, like ganciclovir [71], foscarnet [71] and cidofovir [72], antibiotics: Cefazolin [73], amikacin, moxifloxacin [74], ceftizoxime, ceftriaxone ceftazidime [75], clindamycin [76] and gentamicin [77], steroids: dexamethasone [78], triamcinolone acetonide [79] and monoclonal antibodies, such as rituximab [80], bevacizumab [80] following intravitreal injections. If the molecular weight of the drug is very high, vitreal retention times seem to be higher as well. Molecules that are larger, *i.e.*, linear>40 kDa and globular molecules>70 kDa seem to have long retention time due to the presence of tight barriers around the vitreous humor [81, 82]. So, this route is preferable for higher molecular weight drugs (>500 Da) and also having longer half-lives. First-order rate kinetics is mainly responsible for the elimination of residues out of the vitreous humour [83]. Even the drug delivery through intravitreal injections can be gained by increasing concentrations of drugs in neural retina; side effects like retinal detachment due to repeated injections, retinal hemorrhage, endophthalmitis and other toxicities in the retina occurs because of more concentrations upon bolus dose administration that can cause patient's non-compliance [84-87]. Ausayakhun *et al.* (2005), have found in their study, that the cytomegalovirus (CMV) retinitis can be controlled by using intravitreal ganciclovir (2 mg in 0.1 ml per) and the reported data has shown that 60% of the treated eyes have remained stable, 13% have shown improvement and 26% have shown a reduction in visual acuity [88]. However, a retinal detachment has been noticed in 6%, intravitreal hemorrhages observed in 1% and endophthalmitis observed in 1% of treated eyes. So we can observe from the study that the problems associated with intravitreal injections should be taken into consideration [88]. A number of other studies have also been carried out for similar findings, which have stated that the intravitreal injections are useful, but not good for posterior segment diseases [89-91]. Development in designing of drug delivery system and surgical procedures has led to the development of intravitreal implants that can be instilled inside the vitreous chamber for a longer duration. The difference between intravitreal injections and intravitreal implants is their administration time. Injections can be taken 2 or 3 times a week and preferably can be changed every month, respectively.

Iontophoresis

Ocular iontophoresis is one of the growing fields in research due to its noninvasive nature of delivering drugs to both the anterior and posterior segments of eye. Iontophoresis is defined as a noninvasive procedure for the transfer of ionized drugs via membranes with low electrical current [92, 93]. The drugs can move across the membranes by two ways, migration and electro-osmosis. Ocular iontophoresis, categorized as transcorneal, corneoscleral, or trans-scleral [92], is considered as one of the most attractive options. OcuPhor™ system has been designed with the help of an applicator, dispersive electrode and a dose controller for trans scleral iontophoresis [94]. The device works, as it releases the active drug moiety into retina-choroid. Another similar device being made known by name called Visulex™, which allows specific transport of ionized molecules through the sclera. Antibiotics, which are successfully used, are gentamycin, tobramycin, and ciprofloxacin, but not vancomycin, due to its high molecular weight [95]. Fruitful results of delivery have been observed with drugs such as dexamethasone and antisense ODNs [96].

Advantages

- It can overcome the major side effects caused by intraocular injections and implants [97].
- Disease that might be cured using iontophoresis includes fungal keratitis, uveitis, retinitis, retinoblastoma, proliferative vitreal retinopathy and various retinal degenerations [98].

Disadvantages

- As there is a chance of burns and pains because of excessive current density, it should be used in such a manner that it takes a short period for delivering the drug.
- Drug should be in ionic form and have sufficient concentration because of high molecular weight, *i.e.*, 8 000–12 000 [99].

Periocular route

Periocular region is the region surrounding the eye. Among all the present routes, the periocular route is least painful and a promising route for delivery of the drug to the posterior segment of the eye. In drug delivery through periocular route, the drug is placed in the nearest position to sclera; as a result, vitreal drug levels can be noticed after 20-30 min. Periocular delivery includes retrobulbar, peribulbar, subtenon and subconjunctival routes.

Retrobulbar injection

Retrobulbar injection consists of drug solution deposition into retrobulbar space within the muscle cone. This route is used when the formulation needs to be in direct contact with the macular region. These injections are mostly given through specific 23 gauge sharp, 1.5-inch needle with a rounded tip and a 10 bend.

Peribulbar injection

Peribulbar injections are used for lowering the risk of injury to intraorbital structures related to retrobulbar administration during cataract surgery. The injection is given in the quadrant between the inferior and the lateral of the orbit using a 26-gauge half-inch disposable needle [100].

Subtenon injection

The Tenon's capsule is a facial sheath of connective tissue sandwiched between the conjunctiva and episcleral plexus. The episcleral or subtenon's space is a void space between the tenon's capsule and sclera [101]. Subtenon injection is used to administer the drug in contact with sclera for prolonged periods because of its vascular nature.

Subconjunctival injection

The conjunctiva is a membrane that covers the sclera. The injection administered as a drug solution below the conjunctiva follows minimally invasive technique for delivering a drug to the posterior segment of the eye. About 500 µl of a drug solution as dosage form is injected into the subconjunctival area (bulbar conjunctiva) using a 25/30 gauge, 30 mm long needle. Subconjunctival injection can be used in critical conditions in which a molecule diffuses directly through sclera [102].

Future prospects

As challenges are more for eye as compared to the skin, so there is a need to focus more on non-invasive sustained drug release for eye disorders in both segments [103]. An ideal system is a system which should be able to administer an effective drug concentration at the targeted site for a prolonged period of time, while lowering systemic exposure. The output resulted from such systems, makes the system comfortable and easy to use. Patient's compliance is one of the important factors for designing future ophthalmic drug delivery systems. Relevant strategies are being generated to overcome the drawbacks from each technology or by combining technologies. According to the reported studies, an ocular delivery system includes liposomes and nanoparticles in droppable gels and liposomes and nanoparticles coated with bioadhesive polymers. The challenges to be faced by topical ocular drug delivery systems in the future are:

- The ocular route enhances bioavailability not more then 15 to 20% of the administered dose.
- Most of the marketed ocular formulations are highly non-specific. So, it needs to focus on the development of new drug candidates initially intended for ocular use.
- Further studies need to be carried out for exploring the non-corneal routes, mainly for ionic/water-soluble contents and drug molecules with a preferential corneal absorption (and minimum absorption through nasal mucosa) should be explored.
- Further researches are needed for suitable designing and packaging of the delivery systems. Several scientific and technological advancements need to progress in this field. Mainly the advancement in nanotechnology and biomaterials science may provide new technologies to improve the ophthalmic drug delivery systems.

CONCLUSION

Treatment of ocular diseases in an effective manner is a major challenge for scientists working in the field of ocular drug delivery because of nature of the ocular diseases, unique structure of the eye and barriers present in the system; particularly the posterior ocular segments make the system unapproachable. Many attempts have been made to enhance ocular bioavailability by manipulating product formulation using factors, such as viscosity and use of mucoadhesive polymers. These approaches have been found to be capable of increasing the corneal contact time and improving ocular bioavailability also. Therefore, it could be concluded that modern technology seems to be logically explored in various ways over the conventional approaches, examples of non-conventional approaches being the use of nanotechnology, microspheres, liposomes, appropriate prodrug *in situ* forming gel and iontophoresis as effective means of ocular drug delivery enhancing ocular absorption along with reduction in side effects.

ACKNOWLEDGEMENT

Noida Institute of Engineering and Technology (Pharmacy Institute), 19 Knowledge Park-II, Institutional Area, Greater Noida–201 306, Uttar Pradesh, India

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

Declared none

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