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Recent biopharmaceutical studies on the evolution of ophthalmic drugs

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Abstract. Ophthalmic pharmaceuticals have been one of the most important and widely developed fields of pharmaceutical technology for decades. The main reason for the continued interest of scientists in these forms of medicine is the issue of low bioavailability of the drug after application to the eyeball. The broad classification of ocular drug administration results in two categories: drugs concerned with anterior segment of the eye and drugs concerned with posterior segments of the eye. About 90% of ophthalmic formulations on the market are available in the form of eye drops and the sites of action are for diseases that occur in the anterior segment of the eye. For the release of ophthalmic drugs, the posterior segment of the eye is often a choice of interest to locate the drug, using new approaches. In this regard, this article highlights new developments in ophthalmic pharmaceutical formulations, such as in situ gel formulation, nanoparticles, liposomes, nanosuspension, microemulsion, eye inserts and so on and their progress to overcome problems associated with conventional dosage forms and also to improve bioavailability as well as support the release of the drug at the target site.

Keywords. ocular bioavailability, anterior and posterior segments, topical administration, nanotechnologies, viscosity enhancers, penetration enhancer

1. Introduction

The human eye has a complex structure, both anatomically and physiologically, and this makes it a unique organ made up of physiologically independent functions. Its wide range of varied structures also challenges the development of drug delivery systems for it. The major problem in the conventional eye drop drug delivery system is rapid removal from the eye, causing considerable loss of the drug [1, 2]. In eye drops, only a small portion of a drug penetrates through the corneal layer and reaches the internal tissues present in the eye [3, 4]. The broad classification of ocular administration leads to two main categories: anterior and posterior segment of eyeball. For vision-threatening eye diseases, routine drug delivery systems such as eye drops and ointments cannot be used for optimal treatment [5]. Approximately 90% of ophthalmic preparations on the market are available as eye drops with the site of action located in the anterior part of the eye [6]. Topical delivery of drugs through conventional approaches fails to get it to the posterior segment of the eye. Formulations such as eye drops

and ophthalmic ointments, when instilled into the conjunctival sac, are rapidly cleared from the eye region due to tear flow. Most of the drug is drained away and only a small portion reaches the site of action; therefore, it needs frequent dosing to achieve a beneficial pharmacological effect. For ophthalmic drug delivery, the posterior part of the eye is frequently a choice of interest to localize the drug using novel approaches [7]. All the mentioned should highlight new developments in ophthalmic pharmaceutical formulations, such as formulations of in situ gels, nanoparticles, liposomes, nanosuspensions, microemulsions, ocular inserts, etc., and their Advances in overcoming problems associated with existing conventional dosage forms can also improve bioavailability and support drug delivery at the target site [8].

2. Features required for dose optimization of ophthalmic medicines

The properties required to optimize the ophthalmic dose are as follows:

- Prolonged contact with eye tissue;
- Good corneal penetration of the drug;
- Non-irritating and comfortable shape for eye tissue;
- Ease of administration of ophthalmic pharmaceutical forms for patients.

The penetration of ophthalmic drugs can be achieved by two main routes:

- the general route (oral or parenteral) when there is a diffusion of the drug substance from the blood into the ocular fluids (aqueous humor) through the capillaries of the ocular conjunctiva, also called the conjunctival route;
- local application by instillation, also called the transcorneal route, which is much more effective than the former; many substances used in ophthalmic therapy (antibiotics, local anesthetics, anti-inflammatory, etc.) pass through the corneal barrier.

Recent studies have shown that a third minor pathway, also known as the non-corneal pathway, involving the conjunctiva and sclera (tissue adjacent to the cornea), is the preferred and less well-studied route for drugs with low corneal absorption.

Nearly all ophthalmic drugs in therapeutics pass through the cornea by simple diffusion. A number of physiological factors can influence drug penetration to the eye, namely:

- condition and function of the eye, with limitation of the ability to accept the pharmaceutical form administered;
- tear fluid dynamics (secretion and drainage rate);
- absorption through conjunctival tissue;
- corneal and scleral penetration;
- blink rate;
- tear reflex caused by the administration of ophthalmic eye drops etc.

3. Factors limiting the ocular bioavailability of medicines

Ophthalmic administration has the following barrier effects:

- *Loss of the drug from the ocular surface:* After using the drug dosage form in the ocular system, the tears wiped a part of the drug from its surface, the drug participation rate was only about 1 μl/min and most of the drug was eliminated through the nasolacrimal duct rapidly within minutes. Other sources of drug elimination include systemic absorption of the drug rather than absorption through the eye. Systemic absorption occurs primarily through the conjunctival sac directly to local capillaries or after the solution has passed into the nasal cavity [9].

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- *Fluid-ocular tear barrier:* Absorption of the drug from the tear fluid may be limited by the corneal epithelium present in the eye. Lipophilic drugs show higher permeability into the cornea compared to hydrophilic drugs. In other words, we can say that the conjunctiva has permeable epithelium compared to that of the cornea and also has a twenty times larger surface area than the cornea which supports rapid systemic absorption.
- *Blood-ocular barrier:* The blood-ocular barrier is present in the bloodstream, and protects the eye from xenobiotics. They are composed of two parts, namely the blood-water barrier and the blood-retina barrier. The anterior blood-eye barrier is consists of endothelial cells in the uvea, in the middle layer of the eye below the sclera: the iris, ciliary body and choroid. This barrier functions exists to prevent the entry of hydrophilic drugs present in the plasma to the aqueous humor and also limits the entry of plasma albumin into the aqueous humor. The posterior barrier that lies between the eye and the plasma stream consists of the retinal pigment epithelium (RPE) and retinal capillaries, resulting in the tight wall. The choroidal vasculature comprises extensive blood flow and permeable 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 the RPE and retinal endothelium [10].

4. Challenges in ophthalmic drug delivery systems

The challenge for ocular drug delivery systems is to design a therapeutic system that ensures optimal drug concentration in the target area with a high therapeutic effect. Rapid drug absorption occurs due to corneal anatomy and physiology and barrier function, requiring rapid instillation of eye drops to balance the tear film or target area for therapeutic levels. A side effect of frequent use of medicated solution doses is that they can be toxic to the surface of the eye and cause cell damage. Most ocular dosage forms have poor bioavailability due to precorneal leakage, including solution drainage, breakthrough, tear dynamics, tear dilution, conjunctival absorption, non-productive absorption, short conjunctival residence time and tear rotation. Other challenges include the relative impermeability of the corneal epithelial membrane, which can lead to problems with drug delivery to the anterior segment after topical administration. Approximately 1% or less of the administered dose reaches the intraocular tissues due to various anatomical and physiological barriers that reduce the absorption of the drug. For better clinical results, topical dosage forms should maintain stability between the hydrophilic phase and the lipophilic phase, and have longer exposure times [11]. The challenges for these ophthalmic drug delivery systems are classified as follows.

4.1. Delivery challenges in the previous segment: In ocular drug delivery systems, topical formulations are generally preferred over systemic formulations because when a drug is administered through the eye, it must face the barrier in front of the cornea, the conjunctiva, and the tear film, along this route, slows the rate at which the active enters the eye area. Precorneal loss factors are responsible for poor drug bioavailability in most ophthalmic drugs. Figure 1 shows the factors that influence the bioavailability of locally applied ophthalmic drugs. In addition, frequent eye drops are required to maintain the tear film or site of action levels of the therapeutic drug, but high concentrations of eye drops are often used, and the drug solution can cause toxic side effects and cell damage on the surface of the eye.

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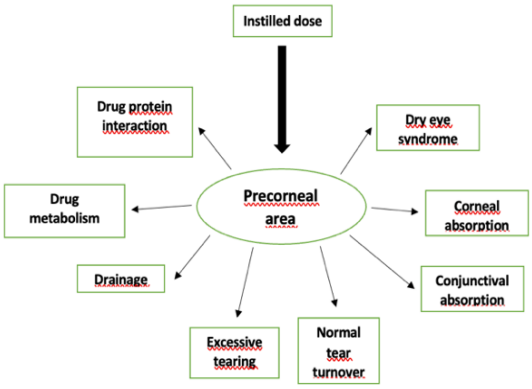

Fig.1. The factors affecting the bioavailability of topical ophthalmic drugs

4.2. Delivery challenges in the posterior segment. The blood-retinal barrier inhibits the entry of ocular drugs applied locally to the posterior part of the eye. Drug transport is inhibited by some factors in the posterior segment of the ocular tissue and this effect is also responsible for poor ocular bioavailability. The blood-retinal barrier is responsible for limiting the effects of the intravenous route on posterior administration and also limits systemically administered drugs enter the retina [12]. In order to cure diseases of the posterior part, high concentrations of drug must be administered intravitreally. The blood-retinal barrier is more permeable to lipophilic molecules and thus allows entry of such drugs into the posterior part of the eye. Frequent administration and high drug concentration routinely cause side effects. A major challenge with posterior drug delivery is maintaining therapeutic concentrations of the drug over an extended period of time and minimizing the number of doses.

5. Approaches in ophthalmic drug delivery systems

A number of approaches have been used in the early stages for better results. These approaches can be classified into two types:

- Improved bioavailability and;
- Controlled release of medicines.

The first approach aims to maximise corneal drug absorption and minimise pre-corneal drug loss by using viscosity and penetration enhancers, prodrugs, gels and liposomes. The second approach is for delivery of the active substance in the form of a delivery system supported by controlled and continuous delivery such as implants, inserts, nanoparticles, microparticles and colloids. There are many traditional methods, such as viscosity enhancers, gels, penetration enhancers, prodrugs, and liposomes, to improve bioavailability, while a new development, namely ocuserts, nanosuspensions, nanoparticles, liposomes, niosomes and implants that improved anterior segment bioavailability and drug delivery in a controlled manner. In the posterior part of the eye, the drug reaches through intravitreal injections, iontophoresis, subconjunctival injections and periocular routes [13].

5.1. Ways to improve ocular bioavailability

Use of viscosity enhancers: Viscosity-enhancing polymers are highly preferred additives in ophthalmic formulations due to their viscosity-enhancing properties and confer benefits to drug penetration into the anterior chamber of the eye by decreasing the rate of elimination from the preocular area, resulting in increased precorneal residence time and

transcorneal penetration, but having very little effect in improving bioavailability in humans. Examples of polymers are polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose.

Gels: Gels are known to be significantly dilute cross-linked systems that exhibit stiffness in the steady state. Gels are generally liquids, but behave like solids due to their three-dimensional cross-linked structure within the liquid [14]. On the other hand, if gels had extremely high viscosity, they would not be able to improve bioavailability; instead, they would control drug release, leading to reduced dosing frequency to once daily. The highly viscous solution even leads to blurred vision and dull eyelids effect, which substantially decrease patient compliance. In the aqueous gel, viscosity builders such as PVA, polyacrylamide, poloxamer, HPMC, carbomer, polymethylvinylether, maleic anhydride, and hydroxypropylethylcellulose are incorporated, while water-insoluble, super-absorbent hydrogels or polymers result in a drug with controlled delivery systems [15].

Promedicament forms: Through the development of prodrugs, many properties of the formulations can be improved, making it suitable for increasing the permeability through the cornea of the drug. Prodrug strategies can be used for a variety of purposes, including increasing solubility, extending the shelf life of the drug or chemical and metabolic stabilisation of the drug.

Penetration enhancers: The corneal epithelial membrane plays an important role in permeability. Therefore, by increasing its permeability, the transport properties around the cornea can be improved. Agents exhibiting this property are chelating agents, preservatives (e.g. benzalkonium chloride), surfactants and bile salts, but cannot be used in the development of ophthalmic formulations due to local toxicity [16].

Liposomes: Liposomes are widely used in ocular formulations due to their close contact with the ocular surface (mainly the corneal and conjunctival regions), thereby increasing ocular absorption of drugs. Liposome formulations can be developed using phosphatidylcholine, stearylamine and varying amounts of cholesterol or lecithin and α-L-dipalmitoyl-phosphatidylcholine. The main advantages of this type of delivery system are due to their properties, namely biocompatibility, biodegradability, hydrophilicity, relative toxicity. Liposomes are generally prepared for drugs with poor absorption, low partition coefficient, poor solubility and medium to high molecular weight. According to the number of reported studies, the active pharmaceutical ingredients used in liposomal ophthalmic formulations are acyclovir, pilocarpine, acetazolamide, chloramphenicol and ciprofloxacin [17].

Nanoparticles and nanospheres: To obtain nanoparticles, drugs can be formulated in a variety of ways, either by binding to a matrix or by attaching to the surface of the biodegradable polymers used for preparation. Nanoparticles used in drug delivery to ocular tissues are polylactide (PLA), polycyanoacrylate, poly(D, L-lactide) and natural polymers such as chitosan, gelatin, sodium alginate and albumin. In the last 10 years, nanoparticles have been used as carriers for drugs to treat eye diseases with promising results. A specific type of nanoparticles can be classified as small capsules having a central cavity surrounded by a polymer membrane and spheres with a solid matrix, known as nanocapsules and nanospheres respectively. Many authors reported that nanocapsules were more effective due to the presence of mucoadhesive properties, which indicated an increase in residence time and biological response [18]. So, they may improve the bioavailability of drugs at ocular level and also decrease the frequency of dosing.

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Microemulsions : Microemulsion is a liquid dispersion composed of oil phase, aqueous phase, surfactant and co-surfactant, which is uniform, transparent and stable. Microemulsions reduce dosing frequency and increase bioavailability of ophthalmic drugs. The main advantages of this dosage form are high thermodynamic stability, small droplet size, i.e. 100 nm (approximately) and clear appearance. Ansari et al. (2008) reported a microemulsion formulation consisting of an oil-in-water system, pilocarpine as active ingredient, lecithin, propylene glycol, PEG 200 as surfactant/cosurfactant and isopropyl-inosyl composition [19].

5.2. Approaches to the controlled and continuous administration of ophthalmic medicines. The following ocular drug delivery systems have been reported for controlled and continuous drug delivery.

Microparticles: Microparticles are isotropic, transparent, translucent, thermodynamically stable systems of oil, surfactants and water droplet size ranges from 20 to 200 nm [20]. Microparticles are defined as micron-sized polymeric particles in which the drugs in the polymeric matrix are suspended in a liquid medium. During topical ocular application, these particles enter the conjunctival sac from which the drug is liberated through a variety of processes, such as diffusion, chemical reactions, or degradation of polymers. The microparticles enhance the pre-corneal duration of residence, which allows continuous and sustained release of the drug. Ultimately, this leads to increased ophthalmic bioavailability of the medicine and decreased dosing frequency. Microparticles have properties such as biodegradation, bioadhesion and biocompatibility that make them suitable for polymer manufacture.

Ocular inserts: Ophthalmic inserts are solid patches that, when placed in the conjunctival cul-de-sac of the eye, slow down the rate of drug release. Ocular inserts also overcome the problem of frequent dosing, maintain drug concentration in an efficient manner and result in controlled, sustained and continuous drug delivery. Ocular inserts also have various advantages, such as improved drug absorption due to increased contact time and reduced drug dosing and application frequency. The major disadvantage of these inserts is the non-compliance of the patient, having the frequent feeling of a foreign body entering the eye and difficulty in self-insertion. Ocular inserts are manufactured by different techniques that make them soluble, erodible and in the form of hydrogels, their characteristics are shown in Table 1 [21].

Table 1. Different types of ophthalmic inserts

Ocular inserts	Features
Erosion-proof inserts	The manufacturing polymers are hydrophobic but biodegradable. The drug is released by eroding the surface of the insert.
Soluble inserts	The manufacturing polymers are hydrophilic and water soluble. The drug is released by diffusion control for soluble medicines, and by dissolution for less soluble medicines.
Hydrophilic but water-insoluble inserts	The manufacturing polymer is hydrophilic but insoluble in water. The drug is released by diffusion control for

Inserts using the osmotic system	soluble medicines and dissolving for less soluble medicines. A polymer matrix in which the drug is dispersed as small discrete domains. After placement in conjunctival cul-de-sac, tears are absorbed into the matrix due to an osmotic pressure gradient created by the drug, after which the drug is dissolved and released.
Membrane controlled diffusion inserts	The centre of the drug is surrounded by a hydrophobic polymer membrane; this controls the diffusion of the drug from the inside to the outside.

Implants: The purpose of designing an intraocular implant is to prolong the activity of the drug along with its controlled release using a polymer or polymer system. An injectable drug delivery system, such as liposomes, is easy to administer, but having limitation after insertion, it becomes difficult to withdraw their particles during any complication such as toxic responses. So it is beneficial to use implants to balance the rate and duration of drug release. Eye implant removal is easy and removable through surgery. Depending on the nature of the polymer used, implants can be divided into two types:

- *Non-biodegradable implants*: They do not dissolve to a significant extent and are not even eroded in vivo;
- *Biodegradable implants*: They dissolve mostly in vivo with soluble components through processes such as enzymatic or non-enzymatic degradation. Surodex and Ozurdex are biodegradable implant samples that slowly release corticosteroid medication over time (dexamethasone) without the need for monthly injections. It will dissolve naturally and will not need to be removed [22].

5.3. Approaches for the transport of medicines on the posterior segment

Intravitreal injections: Research reports show that, in the back of the eye, intravitreal injections are gaining popularity worldwide in recent years in terms of drug delivery. The injections are delivered directly into the posterior segment through the ciliary body (pars plana) for drug delivery, overcoming all barriers. If the molecular weight of the drug is very high the vitreous retention times appear to be even higher. So this route is preferable for drugs with higher molecular weight (> 500 u) and also having longer half-lives. Based on studies in the literature, it has been observed that intravitreal injections are useful but not beneficial for posterior segment disease [23]. Developments in drug delivery systems and surgical design have led to the development of intravitreal implants that can be instilled in the vitreous cavity for prolonged periods of time. The difference between intravitreal injections and intravitreal implants is the timing of their administration. Injections can be given 2 or 3 times a week and can be changed monthly.

Iontophoresis: Ocular iontophoresis is one of the growing areas by its non-invasive nature deliver drugs to both parts of eyeball. Iontophoresis is defined as a non-invasive procedure for transferring ionized drugs across membranes with low electric current [24]. Drugs can move across membranes by two routes: migration and electro-osmosis. Ocular iontophoresis, classified as transcorneal, corneo-scleral or trans-scleral, is considered one of the most attractive options.

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Advantages

- It can overcome major side effects caused by intraocular injections and implants.
- Diseases that could be cured by iontophoresis include fungal keratitis, uveitis, retinitis, retinoblastoma, vitreous proliferative retinopathy and various retinal degenerations.

Disadvantages

- Since there are chances of burns and pain due to excess current density, it should be used in such a way that it takes a short period of drug delivery.
- The drug must be in ionic form and have a sufficient concentration because of the high molecular weight.

The periocular route: The periocular region is the region surrounding the eye. Of all the current routes, the periocular route is the least painful and is a promising route for drug administration to the posterior part of eyeball. In periocular route drug delivery, the drug is placed in the closest position to the scleura; as a result, vitreous drug levels can be observed after 20-30 min. Periocular delivery includes retrobulbar, peribulbar, subtenon and subconjunctival pathways.

- *Retrobulbar injection:* retrobulbar injection consists of depositing a drug solution in the retrobulbar space inside the muscle cone. This route is used when the formulation needs to be in direct contact with the macular region.
- *Peribulbar injection:* Peribulbar injections are used to decrease the risk of injury to intraorbital structures related to retrobulbar administration during cataract surgery.
- *Subtenon injection:* The subtenon space is an empty space between the tenon capsule and the sclera. Subtenon injection is used to administer the drug in contact with the sclera for prolonged periods due to its vascular nature.
- *Subconjunctival injection: The* conjunctiva is a membrane that covers the sclera. Injection administered as a drug solution under the conjunctiva follows a minimally invasive technique for administering a drug into the posterior segment of the eye. Subconjunctival injection can be used in critical conditions where the molecule diffuses directly through the sclera [25].

6. Future perspectives

Because the eye is more challenging than the skin, scientists need to pay more attention to the sustained release of non-invasive drugs that target both sides of the eye. The ideal system should be able to deliver effective concentrations of the medication to the target site over longer periods of time, exposure systematically decreased. The result of such systems makes them simple and convenient to use. Relevant strategies are generated to overcome disadvantages of each technology or by combining technologies. According to reported studies, an ocular delivery system includes liposomes and nanoparticles in gels droplets, nanoparticles and liposomes covered with bioadhesive polymers. Challenges facing ocular drug delivery systems in the future are:

- The ocular route improves bioavailability by no more than 15 to 20% of the administered dose.
- The majority of marketed ocular formulations are highly non-specific. So they need to focus on developing new drugs.

- Further studies to explore non-corneal routes, mainly for ionic/water-soluble contents and drug molecules with preferential corneal absorption (and minimal absorption through the nasal mucosa) should be explored.

7. Conclusions

Due to the nature of eye disease, the particular structure of the eye and the barriers that exist in the system, the effective treatment of eye disease is an important task and challenge for scientists, especially the posterior part of eyeball, which makes this system inaccessible. Numerous attempts have been made to improve ocular bioavailability by manipulating product formulations using factors such as viscosity and the use of mucoadhesive polymers. These methods have been found to increase corneal contact time and also increase ocular bioavailability. Therefore, it can be concluded that modern technology seems to be logically explored in various ways and has many advantages over traditional ocular dosage forms. Examples of unconventional approaches include the use of nanotechnology, microspheres, liposomes, appropriate prodrugs, in situ gels, and iontophoresis as effective means of ocular drug delivery, enhancing ocular absorption while reducing side effects.

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