

Drug delivery to eye: Special reference to nanoparticles

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Abstract

Controlled and sustained delivery of ophthalmic drugs continues to remain a major focus area in the field of pharmaceutical drug delivery with the emergence of new, more potent drugs and biological response modifiers that may also have very short biological half-lives. The major objective of clinical therapeutics is to provide and maintain adequate concentration of drugs at the site of action. In ocular drug delivery, the physiological constraints imposed by the protective mechanisms of the eye lead to poor absorption of drugs with very small fractions of the instilled dose penetrating the cornea and reaching the intraocular tissues. 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. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic solution, suspension, and ointment dosage forms no longer constitute optimal therapy for these indications. Nanoparticles and nanosuspensions are showing a better application as compare to conventional delivery systems. Polymer nanoparticles proposed are reported to be devoid of any irritant effect on cornea, iris, and conjunctiva and thus appear to be a suitable inert carrier for ophthalmic drug delivery. The benefits of having the drug in the form of a nanoparticulate suspension are: reduction in the amount of dose, drug release for a prolonged period of time, higher drug concentrations in the infected tissue, longer residence time of nanoparticles on the cornea surface, reduction systemic toxicity of drug.

Keywords: Nanoparticle; polymer; ocular; bioavailability

Introduction

Anatomical and Physiological Features of the Eye

The eye is a unique organ for drug delivery. Many of its anatomical and physiological features interfere with the fate of the administered drug. First and foremost are blinking; tear secretion, and nasolacrimal drainage. Lid closure upon reflex blinking protects the eye from external aggression. Tears permanently wash the

surface of the eye and exert an anti-infectious activity by the lysozyme and immunoglobulins they contain. Eventually the lacrimal fluid is drained down the nasolacrimal pathways, then the pharynx and esophagus. This means that a portion of the drug is systematically delivered as if by the oral route. In addition, drug binding to tear proteins and to

conjunctival mucin also inactivates a portion of the administered dose. Further loss can arise through physical means. During administration, a part of an aqueous drop instilled in the patient's cul-de-sac is inevitably lost by over flow/drainage, since the conjunctival pouch can accommodate only approximately 20 μ L of added fluid [1-3].

Precorneal losses are the Achilles heel of traditional aqueous formulations and the largest part of drug loss following ophthalmic administration occurs in front of the eye. It is no wonder that many researchers were attracted by the challenge to improve topical ophthalmic formulations. Many attempts were made, but very few products actually completed a full development cycle and were made available for prescription.

Drug Delivery to the Internal Regions of the Eye

The goal of pharmaco-therapeutics is to treat a disease in a consistent and predictable fashion. An assumption is made that a correlation exists between the concentration of a drug at its intended site of action and the resulting pharmacological effect. Three main factors have to be considered when drug delivery is attempted to the intraocular tissues (4): (a) how to cross the blood-eye barrier (systemic to ocular) or cornea (external to ocular) to reach the site of action, (b) how to localize the pharmacodynamic action at the eye and minimize drug action on other tissues, and (c) how to prolong the duration of drug action such that the frequency of drug administration can be reduced.

Eye Penetration of Drugs Administered Locally

It is important if the drug is not intended to act on the external surface of the eye, then the active ingredient has to enter the eye. There is consensus that the most important route is transcorneal; however, a noncorneal route has been proposed and may contribute significantly to ocular bioavailability of some ingredients, e.g., Timolol and inulin [4]. In addition, the sclera has also been shown to have a high permeability for a series of β -blocking drugs [5].

Schematically, the cornea is a sandwich comprising a hydrophilic layer, the stroma, between two lipophilic layers, the epithelium and the endothelium. The epithelium is composed of five to six layers of cells, whereas the endothelium is single-layered on the inner side of the cornea. In humans, the corneal thickness measures slightly more than 0.5 mm at the center and

thickens a little at the periphery. The hydrophilic-lipophilic nature of the cornea clearly indicates that to be well absorbed, active ingredients have to exhibit to some extent both lipophilic and hydrophilic properties. Precorneal tear film produced by tear secretion keeps the cornea moist, clear, and healthy and is spread by the motion of eyelids during blinking. Drugs acting on tear secretion, physicochemical status of the tear film, and blinking can modify transcorneal drug permeation. Indeed, a major issue is the ratio of precorneal disappearance/ transcorneal penetration.

Eye Penetration of Systemically Administered Drugs

It is of interest to reflect on the eye penetration of systemically administered drugs, mostly anti-infectious and anti-inflammatory drugs. There are blood-eye barriers. Aqueous humor is produced by the ciliary epithelium in the ciliary processes. It is frequently named an ultra filtrate, since the ciliary epithelium prevents the passage of large molecules, plasma proteins, and many antibiotics. Some molecules can be secreted in aqueous humor during its formation. Inflammation associated with injury, infection, or an ocular disease, e.g., uveitis, disrupts the blood-aqueous humor barrier and drugs enter the aqueous humor and reach the tissues of the anterior segment. There is a blood-retina barrier and there is one between blood and vitreous humor complicated by the high viscosity of the latter, which prevents diffusion of the drugs in the posterior part of the eye. Delivery of drugs to the posterior pole and to the retina is extremely difficult.

Conventional ocular drug delivery constraints

For the ailments of the eye, topical administration is usually preferred over systemic administration so as to avoid systemic toxicity, for rapid onset of action, and for decreasing the required dose.

Though topical administration offers many advantages to treat disorders of anterior structures of the eye, it suffers from a serious disadvantage of poor bioavailability due to several biological factors, which exist to protect the eye and consequently limit the entry of ocular drugs. The constraints in topical delivery of the eye are discussed below.

Pre-ocular retention

It has been estimated that the human eye can hold approximately 30 μ l of an ophthalmic solution without

overflow or spillage at the outer angle [10], while the volume delivered by most commercial ophthalmic eye drop dispensers is approximately 50 μ l.

Thus a large proportion of the drug is wasted due to administration of an excess volume. Following the removal of the excess solution from the front of the eye, a second mechanism of clearance prevails. The eye has an efficient system for tear turnover (1 μ l/min). The two mechanisms of clearance result in a biphasic profile for an instilled solution with a rapid initial clearance phase due to removal of excess fluid followed by a slower second phase due to tear turnover [11].

Corneal absorption

The main route for intraocular absorption is across the cornea [12]. Two features, which render the cornea an effective barrier to drug absorption, are its small surface area and its relative impermeability. In contrast, the area of conjunctiva, which is a vascular thin mucous membrane covering the inside of the eyelids and the anterior sclera, in humans is approximately 17-fold larger than the cornea. Moreover, it is also between 2 and 30 times more permeable to drugs than cornea [8]. Thus, following topical administration to the pre-ocular area, conjunctival drug absorption is an important loss factor that competes with corneal absorption [13].

Secondly in terms of drug delivery, the cornea is considered of three layers, which account for its poor permeability characteristics:

- i. The outer epithelium, which is lipophilic in nature;
- ii. The stroma, which constitutes approximately 90% of the thickness of cornea and is hydrophilic; and
- iii. The inner endothelium consisting of a single layer of flattened epithelium like cells. Since, the cornea has both hydrophilic and lipophilic structures, it presents an effective barrier to the absorption of both hydrophilic and lipophilic compounds.

Another serious route for the elimination of topically applied drugs from the precorneal area is the nasal cavity, with its larger surface area and a high permeability of the nasal mucosal membrane is prone to absorption into systemic circulation through the

nasal mucosal lining, which is continuous with the conjunctival sac.

Formulation approaches to improve ocular bioavailability

Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories. The first is based on use of the drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves, minimizing precorneal drug loss. Some of the requisites of Controlled Ocular Delivery Systems are:

1. To overcome the side effects of pulsed dosing produced by conventional systems.
2. To provide sustained and controlled drug delivery.
3. To increase ocular bioavailability of drug by increasing corneal contact time.
4. To provide targeting within the ocular globes so as to prevent the loss to other ocular sites.
5. To circumvent the protective barriers like drainage, lacrimation and diversion of exogenous chemicals into systemic circulation by conjunctiva.
6. To provide comfort and compliance to the patient and yet improve the therapeutic performance of the drug over conventional systems.
7. To provide better housing of the delivery system in the eye so that the loss to other tissues besides cornea is prevented.

The preceding summary demonstrated that the formulator faces many constraints and prerequisites when developing a modified-release topical ophthalmic drug. In addition to the traditional requirements of oral drugs for safety, efficacy, and stability, ophthalmic products must exhibit additional properties. The regulatory demands for new ophthalmic chemical entities are, most of the time, outweighed by the development efforts and costs compared to the size of the ophthalmic market. Indeed, because of the small size of the ophthalmic market, it is rather unrealistic to think that manufacturers would develop a totally new chemical entity specifically for ophthalmic use since the return on investment—if any—would be very slow.

However, some derivatives have appeared in recent times, e.g., timolol base hemihydrate instead of timolol maleate [14]. Therefore, in terms of developing a modified-release ophthalmic drug delivery system, the formulator usually attempts to modify the formulation to optimize the release and delivery of an existing drug. Primary approaches attempt to slow down the elimination of the active ingredient drained by the tear flow.

Viscous Solutions and Hydrogels

Viscous solutions and hydrogels, based upon the addition of hydrocolloids to simpler aqueous solutions, are the most common formulations. There is no clear-cut frontier between very viscous solutions and gels in terms of biopharmaceutical results. However, preformed gels are administered in the same way as an ointment, which is less convenient for the patient than the instillation of a viscous drop. The most common polymers used in viscous solutions are cellulose derivatives, carbomers, polysaccharides, and, recently, hyaluronic acid. The advantage offered by this last product could be dependent upon the active ingredient and the formulation environment [15]. Polyvinyl alcohol and polyvinyl pyrrolidone are also used in ophthalmic drugs. Gels permit longer residence time in the precorneal area than viscous solutions. This has encouraged researchers to work on formulations that would be (viscous) solutions in the drug vials but would gel in the conjunctival cul-de-sac.

Three main mechanisms have been explored to induce the sol/gel transition in the conjunctival pouch, namely a change in pH, a change in temperature, or a change in ionic environment [16]. Eventually one formulation of timolol, which was based on gellan gum that underwent a sol/gel transition due to the ionic content of the tears, reached the market in 1994 (Timoptic XE) [17,18].

Phase transition systems are liquid dosage forms which shift to gel or solid phase when instilled in the cul-de-sac. Polymers like Lutrol FC-127, Poloxamer-407 [19] whose viscosity increases when its temperature is raised to 37 °C. In situ forming gels have been actively pursued. Product(s) using the gellan gum technology [20], and with polymer associations like those reported by Kumar *et al.*, 1994 [21], and Smart Gel technology [22] are examples of technologies that use this approach. This field of intricately entangled polymers seems promising since new “patentable” entities might

be obtained through in-depth studies of associations of well-established products. The aqueous formulations of such mixtures exhibit changes in physical properties, i.e., sol-gel transformation, with changes in the environment, e.g., temperature, pH, or ionic strength.

Bioadhesives

It offers several advantages like localizing a dosage form within a particular region, increasing drug bioavailability, promoting contact with surface for longer time, reduce dosage frequency. Several synthetic and natural polymers are used for this purpose like sodium hyaluronate, chondroitin sulphate (natural polymers) and various polyacrylate, carbopols (synthetic polymers). A good bioadhesive should exhibit a near zero contact angle to allow maximum contact with the mucin coat [23].

Soft contact lenses

The rationale for corneal contact devices has not been fully explored in therapy. It is generally accepted that soft contact lenses can act as a reservoir for drugs, providing improved release of the therapeutic agent. Presoaked lenses are considered a more efficient and reliable delivery system. Imprinted soft contact lenses are promising drug devices able to provide greater and more sustained drug concentrations in tear fluid with lower doses than conventional eye drops [24].

Ocular iontophoresis

Iontophoresis is a process by which the direct current drives ions into cell or tissues. Antibiotics, antifungals have been tried by this method [25]. Recent progress in the technology of the associated hardware has stimulated interest in a renewal of its use in ophthalmology.

Collagen shields

Friedburg *et al.* (1991) [26] developed collagen shields to promote wound healing and perhaps more importantly to deliver a variety of medications to the cornea and other ocular tissues. For drug delivery, the shields are rehydrated in aqueous solution of the drug whereby the drug is absorbed by the protein matrix and is released once the shield dissolves in the eye. However, their size and the constraints they impose on vision render them impractical for a new drug delivery system. Suspensions of collagen microparticulates

(e.g., Collasomes or Lacrisomes) might be better accepted [27].

Pseudolatices

These are a new class of polymeric colloidal dispersion and film forming agents used for topical applications into the animals and human beings for sustaining the drug activity *in vivo* [28].

Ocular penetration enhancer

Penetration enhancers like actin filament inhibitors; surfactants, bile salts, etc. have been used to increase the bioavailability of topically applied proteins and peptides [29].

Ocular inserts and implants

Various erodible implants marketed to date like Lacrisert, Soluble ocular drug insert are made of mainly collagen, fibrin, HPMC, etc. Two products Alza Ocusert [30] and Merck Lacrisert [20], have been marketed, although Ocusert is no longer sold. Ocusert was an insoluble delicate sandwich technology. Filled with sufficient pilocarpine for 1 week's use, whereas Lacrisert is a soluble minirod of hydroxypropyl cellulose, nonmedicated and dissolving within 24 h to treat dry-eye syndromes [20]. Other inserts are more like implants to be placed in the eye tissues by surgery.

Dispersed Systems

Dispersed systems based on liposomes, nanoparticles, or nanocapsules have been extensively studied for potential ophthalmic use [31, 32]. The development of marketable products based on these nano products has been very challenging and a definitive technology has not yet been established. The major issues for this type of delivery system include: percentage of dispersed phase/entrapment coefficient problem (i.e., how much of the active ingredient will be present in a drop of the final product), stability and shelf life, antimicrobial preservation, tolerance of the used surfactants, and, last but not least, large-scale manufacture of sterile preparations. Nanosized systems based on liposomes, nanoparticles, and nanocapsules have been extensively studied and published and call the ophthalmic formulator's attention. Beyond the problem of the entrapment percentage of the active pharmaceutical ingredient, the retention of these particles in the conjunctival pouch is a key consideration. This

retention must be effective in providing an extended source of active and to allow the drug to leak out from the dispersed phase before the instilled formulation is drained away from the precorneal area. Positively charged liposomes were described to have a greater affinity for ocular tissues [33]. A possible vehicle to administer these delicate nanosystems could be a gel, as was described for liposomes [34]. Microemulsions might be systems of future interest, with the basic caveats concerning sterile manufacturing, long-term stability, patient tolerance vis-a-vis any surfactant, and the difficulty to adequately preserve a biphasic system. Pilocarpine was described to largely benefit from such a formulation, and cyclosporine is a potential candidate for it [35].

Nanoparticles for ocular drug delivery

Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10 nm to 1000 nm. The drug of interest is dissolved, entrapped, adsorbed, attached or encapsulated into the nanoparticle matrix. Depending on the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained with different properties and release characteristics for the encapsulated therapeutic agent [36, 37]. Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a polymer membrane, whereas nanospheres are matrix systems in which the drug is physically and uniformly dispersed.

The utility of nanoparticles as an ocular drug delivery system may depend on [38] (a) optimizing lipophilic-hydrophilic properties of the polymer-drug system, (b) optimizing rates of biodegradation in the precorneal pocket, and (c) increasing retention efficiency in the precorneal pocket. It is highly desirable to formulate the particles with bioadhesive materials in order to enhance the retention time of the particles in the ocular cul-de-sac. Without bioadhesion, nanoparticles could be eliminated as quickly as aqueous solutions from the precorneal site. Bioadhesive systems can be either polymeric solutions [39] or particulate systems [40]. Nanoparticles represent promising drug carriers for ophthalmic applications. After optimal binding to these particles, the drug absorption in the eye is enhanced significantly in comparison to eye drop solutions owing to the much slower ocular elimination rate of particles. Smaller particles are better tolerated by the patients

than larger particles therefore nanoparticles may represent very comfortable ophthalmic prolonged action delivery systems.

Biodegradable polymer nanoparticles have great potential as drug delivery devices for the eye. The formulation of biodegradable polymers as colloidal systems holds significant promise for ophthalmic drug delivery [41]. A colloidal system is suitable for poorly water-soluble drugs, and would allow drop-wise administration while maintaining the drug activity at the site of action. Additionally, surface-modified nanoparticulate carriers may be used to accommodate a wide variety of actives. Although several synthetic methods and drug loading techniques are reported to be safe and reproducible, no procedure for the formulation of drug-loaded nanoparticles has yet been standardized. The major developmental issues in the case of nanoparticles include formulation stability, particle size uniformity, control of drug release rate, and large-scale manufacture of sterile preparations [42]. Nanosystems having surface-segregated chitosan or polyethyleneglycol have been found to be relatively stable and also efficient at overcoming mucosal barriers [43].

Polymers used in the preparation of nanoparticles

Nanoparticles made of non biodegradable polymers are neither digested by enzymes nor degraded in vivo through a chemical pathway [44]. The risk of chronic toxicity due to the intracellular overloading of nondegradable polymers would be a limitation of their systemic administration to human beings, making these materials more suitable for removable inserts or implants. Erodible systems have an inherent advantage over other systems in that the self-eroding process of the hydrolyzable polymer obviates the need for their removal or retrieval after the drug is delivered. Upon the administration of particle suspension in the eyes, particles reside at the delivery site and the drug is released from the polymer matrix through diffusion, erosion, ion exchange, or combinations thereof [38]. Few examples of reported polymers for successful preparation of nanoparticle are described below:

1. Polymethylmethacrylate (PMMA) nanoparticles, which are excellent adjuvants for vaccines, can be produced by the emulsion polymerization technique. In this process, monomeric methylmethacrylate is

dissolved in a concentration range of 0.1–1.5% in water or phosphate-buffered saline or a solution or suspension of drugs or antigens [45]. But nanoparticles made of polyacrylamide or PMMA do not degrade either biologically or enzymatically, which makes them less attractive for ophthalmic use.

2. Cellulose acetate phthalate has been used for in situ gelling of latex nanoparticles [46] [42]. The preparation of these latex particles involves emulsification of polymer in organic solvent followed by solvent evaporation. This latex suspension, upon coming in contact with the lacrimal fluid at pH 7.2–7.4, gels in situ, thus averting rapid washout of the instilled solution from the eye. But the disadvantage of these preparations is vision blurring.

3. PACA (polyacryl-cyanoacrylate) particles possess properties of biodegradation and bioadhesion, making them of considerable interest as possible drug carriers for controlled ocular drug delivery and drug targeting. Wood *et al* [47] showed that PACA nanoparticles were able to adhere to the corneal and conjunctival surfaces, which represent their mucoadhesion property. This polymer has the ability to entangle in the mucin matrix and form a noncovalent or ionic bond with the mucin layer of the conjunctiva. Betaxolol [48] and amikacin sulfate [49] loaded polyalkylcyanoacrylate has shown good result. Polyalkylcyanoacrylate (PACA) nanoparticles and nanocapsules have been shown to improve and prolong the corneal penetration of hydrophilic and lipophilic drugs. Despite these positive results, the potential of the PACA nanoparticles is limited because they cause disruption to the corneal epithelium cell membrane [50].

4. poly-ε-caprolactone (PECL) nanocapsules may serve as superior polymer systems for ocular drug delivery [51, 52]. Marchal-Heussler *et al.* [52] compared nanoparticles prepared by using PACA, PECL, and polylactico-glycolic acid with betaxolol as model drug. It was shown that the PECL nanoparticles yielded the highest pharmacological effect. This was believed to be due to the agglomeration of these nanoparticles in the conjunctival sac. Nanocapsules for topical ocular delivery of cyclosporin A (CyA) comprising an oily core (Miglyol 840) and a poly-ε-caprolactone coating increased the corneal levels of the drug by 5 times compared to the oily solution of the drug when administered to the cul-de-sac of fully awake New

Zealand white rabbits [53]. Poly- ϵ -caprolactone nanocapsules also showed good performance in increasing the ocular availability of drugs such as metipranolol [51] and betaxolol [52] while suppressing their systemic absorption. An alternative colloidal system, poly- ϵ -caprolactone (PECL) nanocapsules have shown the usefulness as ocular drug delivery systems. More specifically these nanocapsules have been shown to increase ocular penetration of lipophilic drugs such as metipranolol, betaxolol, amphotericin-B. Calvo *et al.*, 1996 [53] observed that PECL nanocapsules are specifically taken by the corneal epithelium cells without damaging the cell membrane.

5. Cationic polymer chitosan (CS) has attracted a great deal of attention because of its unique properties, such as acceptable biocompatibility and biodegradability [54, 55]. The bioavailability of nanoparticles coated with poly-L-lysine and chitosan (both have positive charge) were compared to that of noncoated nanoparticles. It was suggested that the specific nature of chitosan was responsible for bioavailability improvement rather than the charge. CS-coated nanocapsules were more efficient at enhancing the intraocular penetration of some specific drugs [56, 57].

6. Eudragit® Retard polymer nanoparticle suspensions have been investigated as a carrier system for the ophthalmic release of nonsteroidal antiinflammatory drugs, such as ibuprofen and flurbiprofen [58, 59]. Polymeric nanoparticle suspensions will be prepared from inert polymer resins (Eudragit® RS100, RS, and RL100, RL). When loaded with drugs, these resins are proposed as delivery systems to prolong the release and improve ocular availability of the drug. Polymer nanoparticles proposed are reported to be devoid of any irritant effect on cornea, iris, and conjunctiva and thus appear to be a suitable inert carrier for ophthalmic drug delivery.

7. Polybutylcyanoacrylate nanoparticle delivery system for pilocarpine nitrate has been evaluated in comparison to the solution of the drug for pharmacokinetic and pharmacodynamic aspects [60]. Diepold *et al.* [61] incorporated pilocarpine into polybutylcyanoacrylate nanoparticles and evaluated the aqueous humor drug levels and the intraocular pressure-lowering effects using three models (the

water-loading model, the alpha-chymotrypsin model, and the betamethasone model) in rabbits. The miotic response was enhanced by about 33% while the miotic time increased from 180 to 240 minutes for nanoparticles compared to the control solution.

8. Acyclovir-loaded PEG-coated polyethyl-2-cyanoacrylate (PECA) nanospheres prepared by emulsion polymerization technique showed increased drug levels in the aqueous humor compared to the free drug suspension in the rabbits [62].

9. Polylactide and polylactide-co-glycolide biopolymers in the molecular weight range of 3000–109,000 have been employed in the preparation of microparticulate systems for intravitreal administration of acyclovir [63]. Spray-drying technique was employed for the preparation and the *in vivo* evaluation was performed by intravitreal administration in rabbits. The poly-D, L-lactide microspheres of acyclovir were more efficient compared to the free drug in providing a sustained release of the drug in the vitreous humor in rabbits. A promising result is reported by Agnihotri *et al.*, 2008 [64] for polymeric nanoparticle suspensions (NS) which was prepared from poly (lactide-co-glycolide) and poly (lactide-co-glycolide-leucine) {poly [Lac (Glc-Leu)]} biodegradable polymers and loaded with diclofenac sodium.

Conclusion

Particulate systems have the potential to become promising systems for ophthalmic drug delivery. The potential for success of nanoparticles in ophthalmic drug delivery has been demonstrated in a number of studies of either hydrophilic or hydrophobic drugs. Though formulation stability, control of particle size, control of the rate of drug release, and large-scale manufacture of sterile preparations are some of the major issues involved in the development of ophthalmic particulate formulations. In spite of that the successful results of various researchers establishing the potential of nanoparticles for ocular drug delivery.

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