Recent Trends in Ocular Drug Delivery: A Short Review

Ankit Kumar, Rishabha Malviya and Pramod Kumar Sharma

Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Delhi-Roorkee Highway, NH-58, Baghpat Crossing, Meerut-250005, U.P. India

Abstract: Ocular drug delivery has been a major challenge for scientists due to its unique anatomy and physiology which contains various types of barriers such as different layers of cornea, sclera and retina including blood aqueous and blood–retinal barriers, choroidal and conjunctival blood flow etc. These barriers cause a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment of the eye. To overcome these problems various types of dosage forms such as nanoparticles, nanomicelles, liposomes and microemulsions have been developed. Novel drug delivery strategies such as in situ gels were developed to sustain drug levels at the target site for a sufficient time. Drug delivery via ophthalmic route has proved significant advancement for future perspectives.

Key words: Ophthalmic drug delivery • Novel drug delivery • Occusert • Eye

INTRODUCTION

Eye is the most simply reachable site for topical administration of a medication. Drugs are commonly applied to the ocular system for a localized action on the surface or in the interior of the eye. The ocular system is most interesting organ due to its drug disposition characteristics. For illness of the eye, topical administration is usually ideal over systemic administration, before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route firstly crosses the precorneal barriers. These are the first barriers that slow the penetration of drug into the eye and consist of the tear film and the conjunctiva. The drug in suitable type of dosage form, upon instillation, stimulates the protective physiological mechanisms, i.e., tear production, which exert a difficult defence against ophthalmic drug delivery. Another serious problem of the elimination of topically administered drugs from the precorneal area is the nasal cavity, as the nasal mucosal membrane has greater surface area and higher permeability compared to that of the cornea. With conventional ophthalmic solution normal dropper used which delivers about 50-75µl per drop and portion of these drops rapidly drain until the eye is back to normal resident volume of 7µl. Due to this drug loss in front of the eye, very small drug is available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is relatively low and very small corneal contact time (about 1-2 min) in humans for instilled solution usually less than 10% [1-3]. Therefore only small amount of drug actually penetrates the cornea and reaches intraocular tissue [4-5]. Due to these limitations, Controlled drug delivery to the eye is restricted imposed by the efficient protective mechanism.

An ideal ophthalmic drug delivery must be able to release the drug in sustained manner and to remain in the area of front of the eye for prolong period of time. As a result it is necessary to optimize ophthalmic drug delivery; the best way to do so is by adding of polymers of various grades, development of colloidal suspension or using erodible or non erodible insert, development of viscous gel to prolong the precorneal drug retention [6-7]. Microparticle suspension [8] or polymeric solution [9] can be bioadhesive systems. For small and medium sized peptides major resistance is not size of the compounds (present in formulation) but charge, it is found that resistance to negatively charged compounds is more as compared to positively charged compounds to the cornea [10].

As in situ activated gel forming systems can be administered in drop form and create considerably fewer problems with vision so that it is most preferable type of delivery system. Furthermore, In situ activated gel forming
systems provide better sustained release properties than drops. This type of dosage forms are used now a day in various type of eye disease like combat glaucoma, dry eye syndrome, eye infection etc [11].

The Anatomy and Physiology of the Eye: The human eye is the essential sense organ of the body and its anatomy is quite complex. Eye is able to refract light and produce a focused image that can stimulate nervous system and enable the ability to see.[12].

The Structure of the eye and different Parts of the eye:

**Aqueous Humour:** It is a jelly-like substance located in the anterior chamber of the eye.

**Choroid:** The choroid layer is located behind the retina and absorbs unused radiation.

**Ciliary Muscle:** The ciliary muscle is a ring-shaped muscle attached to the iris. It is important because contraction and relaxation of the ciliary muscle controls the shape of the lens.

**Cornea:** Cornea is a clear transparent epithelial membrane. Light rays pass through the cornea to reach the retina. The cornea is convex anteriorly and is involved in refracting (bending) light rays to focus them on the retina.

**Fovea:** The fovea is a small depression (approx. 1.5 mm in diameter) in the retina. This is the part of the retina in which high-resolution vision of fine detail is possible.

**Hyaloid:** The hyaloid diaphragm divides the aqueous humour from the vitreous humour.

**Iris:** The iris is the visible coloured part of the eye and extends anteriorly from the ciliary body, lying behind the cornea and in front of the lens. It divides the anterior segment of the eye into anterior and posterior chambers which contain aqueous fluid secreted by the ciliary body. The iris is supplied by parasympathetic and sympathetic nerves. Parasympathetic stimulation constricts the pupil and sympathetic stimulation dilates it.

**Lens:** The lens of the eye is a flexible unit that consists of layers of tissue enclosed in a tough capsule. It is suspended from the ciliary muscles by the zonule fibers.

**Optic Nerve:** The optic nerve is the second cranial nerve and is responsible for vision. Each nerve contains approximately one million fibres transmitting information from the rod and cone cells of the retina.

**Papilla:** The papilla is also known as the "blind spot" and is located at the position from which the optic nerve leaves the retina.

**Pupil:** The pupil is the aperture through which light - and hence the images we see and "perceive" - enters the eye. This is formed by the iris. As the size of the iris increases (or decreases) the size of the pupil decreases (or increases) correspondingly.

**Retina:** The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, then the hyaloid and finally the vitreous humour before reaching the retina. The retina contains photosensitive elements (called rods and cones) that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

![Fig. 1: Schematic diagram of the human Eye.](image-url)
**Sclera:** The sclera is a tough white sheath around the outside of the eye-ball. It consists of a membrane that maintains the shape of the eye and gives the attachment to the extrinsic muscle of the eye.

**Vitreous Humour:** The vitreous humour (vitreous body) is a jelly-like substance.

**Advantages of Ocular Drug Delivery Systems:** Various advantages of ocular drug delivery system are given below.

- Easy convenience and needle free drug application without the need of trained personnel assistance for the application, self medication, thus improving patient compliances compared to parenteral routes.
- Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
- Rapid absorption and fast onset of action because of large absorption surface area and high vascularisation. Ocular administration of suitable drug would therefore be effective in emergency therapy as an alternative to other administration routes.
- Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

**Disadvantages:** Various disadvantages of ocular drug delivery system are given below.

- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen [13-14].

**Ophthalmic Dosage Forms:** The most common method of ocular drug delivery is the instillation of drops into the lower cul-de-sac. The concentration of drug in the precorneal area provides the driving force for its transport across the cornea via passive diffusion. Thus, efficient ocular drug absorption requires good corneal penetration as well as prolonged contact time with the corneal tissue.

**Liquids:** Eye drops/lotion- Eye drops may be solutions or suspensions and are comparatively convenient, safe, immediately active and acceptable to patients. An eye drop is sterile, contains a preservative (if not singly used only), is isotonic, has a pH of about 7.4 for the patient comfort and has a limited shelf life after opening (if used more than one time). Eye lotions are isotonic, sterile solutions for the irrigation of the eye, usually as a single use first aid treatment [15].

- Polymers are frequently added to ophthalmic solutions and suspensions in order to increase the viscosity of the vehicle, this prolongs contact with the cornea, so that enhancing bioavailability [16].
- Generally, the high molecular weight hydrophilic polymers those are unlikely to cross the biological membrane. They include poly vinyl alcohol, hyaluronic acid, dextran, gellan, methylcellulose, hydroxymethylcellulose [17-18].

**Eye Ointments:** Ointments are the semi solid preparations intended for external application. They are usually formulated using mixture of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to the body temperature and are nonirritating to the eye. Ointments are useful in improving the drug bioavailability and in sustaining drug release. Ointments suffer with relatively poor patient compliance due to blurring of vision. So, they are often used as night time medication [19].

**Aqueous Gel:** Aqueous gel (hydrogels) consists of high molecular weight, cross linked polymers that form a three dimensional network in water. Hydrogels are based on the addition of hydrocolloids to aqueous drug solutions. The most common polymers are used in such formulation are cellulose derivatives, carbomers, polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid. Gels permit longer residence time in the precorneal area then viscous solution. The most important advantage of gel is increase in the contact time of the drug to the tissue. So, that drug can remain for longer period at the desired site [20].

**Microspheres and Nanoparticales:** These are the promising drug carriers for ophthalmic applications; the drug absorption is enhanced significantly in the eye in comparison to eye drop solution owing to the much slower ocular elimination rate of particles. Smaller particles are better tolerated by the patients than longer particles therefore nanoparticles may represent very comfortable
ophthalmic prolonged action delivery systems. However, albumin microspheres reportedly cause adverse reaction in the eye [20].

**Various ophthalmic marketed products in different dosage form [21-23]:** Different ophthalmic marketed products are shown in given Table 1:

**Recent Studies on Ophthalmic Drug Delivery System:**
Gauhar et al. [24] developed ophthalmic suspension of prednisolone acetate (1%). This formulation is useful to obtain a better contactibility of the drug at the desired site of action. During the formulation of prednisolone ophthalmic suspension its physicochemical, physiological and pharmaceutical parameters were evaluated. While viscosity enhancer, preservative, chelating agent were also included in the formulation to increase the transient residence time, antimicrobial preservation respectively and isotonicity of the formulation was also maintained by the addition of tonicity modifiers. Buffering agents used were having buffering capacity NMT 0.05% and pH was adjusted at which prednisolone acetate was stable. The finished product subjected to keep stress conditions to ensure the physical stability of the formulation. The formulation was packed in LDPE plastic vials and then carried out the accelerated stability studies at 40°C and the kinetic and the degradation rate constant and shelf life determined according to the predictive method. The results showed that the development of a new ophthalmic formulation having considerably better contact time by the selection and optimization of viscosity (HPMC) that obtained (21 cps) with better stability studies. Finally, the results concluded that prednisolone acetate 1.0 per cent ophthalmic suspension is much effective than prednisolone phosphate 1.0 per cent ophthalmic solution in suppressing corneal inflammation [24].

Rathod et al. [25] prepared egg albumin microspheres of pilocarpine nitrate by using the heat stabilization method. Factors that affect the size and encapsulation efficiency were optimized to obtain microspheres in the size range 1 to 12 μm to make them undetectable by eyes and sufficient to entrap drug efficiently. Encapsulation efficiency of egg albumin microspheres was found to be that was to be 63.4%. By using spherical matrix in vitro release of drug was evaluated. In the preparation of microsphere gel Carbopol–940 polymer was used. Comparative evaluations were made by preparing simple gels of same drug concentration. Bioavailability parameters of all the formulations were evaluated and comparisons were made [25].

Parmar et al. [26] reported that mucoadhesive microspheres can be prepared by different methods and was evaluated for their mucoadhesive properties. The microsphere prepared by glutaraldehyde (as a crosslinking agent) and thermal cross linking showed good stability in HCl as compared with microsphere prepared by tripolyphosphate and emulsification ionotropic gelation method. In controlled and targeted drug delivery system, microspheres can be used because it overcomes the problems associated with conventional drug delivery like poor absorption, less contact time and poor bioavailability [26].

Prabhu et al. [27] prepared and evaluated the liposomes of brimonidine tartrate and they were found that liposomes are the efficient vesicular carrier system for therapeutic effectiveness in terms of duration of action and decrease in dose frequency. The in vitro and ex- in vitro drug release studies profile showed that, there was

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<th>Table 1: Marketed ophthalmic products</th>
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<tr>
<td><strong>Brand name</strong></td>
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<td>Dichol</td>
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<td>Refresh tears</td>
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<td>Refresh Classic</td>
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<td>Geltar</td>
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<td>Timolol x Eye</td>
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slow and prolonged release of drug from all the formulations with zero order kinetics. The activity of liposome formulation was found to be significantly lowered by the in vivo intraocular pressure and sustained for longer period of time which improves its physiological effectiveness. Thus, liposome offer a promising way to fulfill the need for an ophthalmic drug delivery system that not only has the convenience of a drop, but that can be helpful to provide the localize drug action and maintain drug activity at its site of action for a longer period of time and minimizing frequency of drug administration with patient compliance.

Patel et al. [28] prepared an ocular insert of moxifloxacin HCl by using various polymers for controlled drug delivery. The objective of this preparation was to increase contact time, prolong drug release and minimise precorneal loss of drug. The ocular inserts were prepared by using gelatine (18% and 20%), a natural biodegradable polymer and glycerine (70% w/w of dry polymer) as a plasticizer. The cross linking was achieved by dipping cut inserts (8 mm diameter) in 10% w/v solution of glutaraldehyde (as a cross linking agent) in isopropyl alcohol (5 ml) for four different time period of 15, 30, 45 and 60 minutes to delay the release of drug from the formulation. Physicochemical properties of the inserts were evaluated like uniformity of thickness, drug content, weight, swelling index and surface pH.

Babizhayev et al. [29] studied the functional activity and development aspects of N-acetylcarnosine for the ocular system as revealed by the use of a variety of physiological, biophysical and therapeutic ophthalmic methods. It has been designed for pharmacists and more advanced ophthalmology, optometry and pharmacology researchers who wish to gain a basic understanding of the biological effects of N-acetylcarnosine for vision and to share in the excitement of the latest developments in this field. Topics under the consideration include: ophthalmic drug delivery of N-acetylcarnosine eye drops; clinical and functional types of activity of the developed and patented N-acetylcarnosine lubricant eye drops designed as 1% N-acetylcarnosine prodrug of L-carnosine containing a mucoadhesive cellulose-based compound with corneal absorption promoters in a drug delivery system; management of age-related serious or disabling eye diseases in humans with N-acetylcarnosine eye drop therapeutic platform (ocular inflammation, age-related macular degeneration, macular dystrophies, ocular manifestations of diabetes, hypertonic retinopathy, primary open angle glaucoma, vitreous lesions); development and molecular mechanisms of ocular therapeutic activities of carnosine derivatives in the visual system [29].

Bhowmik et al. [30] developed Methyl Cellulose (MC) based thermo-triggered in-situ gelling formulations of Ketorolac tromethamine (KT) to enhance its ocular bioavailability. The gelation temperature of 1% w/v MC solution was 60°C. Sodium bicarbonate (NaHCO₃) was added to reduce the gelation temperature of MC solution below physiological temperature, i.e., 370°C. The effect of NaHCO₃ concentration on the gelation temperature, rheological property and drug release profile of prepared formulations were also evaluated. It was observed that 5% w/v NaHCO₃ lowered the gelation temperature below 370°C and the solution was free flowing liquid at 250°C for proper instillation to the eye as drop and provides the sustained drug release profile.

Prabhu et al. [31] prepared and evaluated the Niosomes of brimonidine tartrate and certified that niosomes is a significant vesicular carrier system for therapeutic effectiveness as helpful to increase the duration of action and decrease in dose frequency. During evaluation of drug preparation it follows zero order kinetics and show prolong release of drug. The activity of niosome formulation was found to be lowered significantly by the in vivo intraocular pressure and sustained for long period of time which encourages its physiological effectiveness. Thus, niosomes offer a promising way to fulfill the need for an ophthalmic drug delivery system that not only has the convenience of a drop, but that can localize and maintain drug activity at its site of action for a longer period of time thus allowing for a sustained action; minimizing frequency of drug administration with patient compliance.

Giunchedi et al. [32] studied that the poly (lactide-co-glycolide) (PLGA) microspheres serve as carriers for the topical ocular delivery of a peptide drug vancomycin. In this experiment microspheres were prepared by an emulsification/spray-drying technique that can be proposed as an alternative to the double emulsion method for preparation of peptide-loaded microparticles. The drug encapsulation efficiencies were evaluated that was close to the theoretical values (84.2–99.5%); the average particle size was about 11 mm. The microspheres were able to modulate the in vitro drug release of vancomycin with behavior dependent on their composition: the highest drug content corresponded to the highest release rate. In vivo studies were carried out by determining the pharmacokinetic profile of VA in the aqueous humor of rabbits after topical administration of aqueous suspensions of microspheres. High and
prolonged VA concentrations and increased AUC values (2-fold) with respect to an aqueous solution of the drug were observed. Increasing the viscosity of the microsphere suspension by addition of a suspending-viscosizing agent (hydroxypropylcellulose) did not produce an increase of the ocular bioavailability. PLGA microspheres can be proposed as a system for ocular delivery of peptide drugs.

Giunchedi et al. [33] evaluated the Pectin microspheres as ophthalmic carriers for piroxicam. In this they were prepared the microspheres by a spray-drying technique; their morphological characteristics were investigated by scanning electron microscopy (SEM) and their in vitro release behaviour was determined at pH 7.0 USP buffer using a flow-through apparatus. Px loaded in the pectin microspheres showed a faster in vitro dissolution rate with respect to solid micronized drug. The precorneal retention of fluorescein-loaded microspheres was evaluated in vivo in albino rabbits: an aqueous dispersion of fluorescent microspheres showed a significantly increased residence time in the eye (2.5 vs. 0.5 h) then fluorescein solution. Hence, concluded that increased bioavailability. In vivo tests in rabbits of dispersions of Px-loaded microspheres also indicated a significant improvement of Px bioavailability in the aqueous humour (2.5-fold) when compared with commercial Px eye drops.

Kreuter et al. [34] reported that nanoparticles and microspheres provide the promising drug carriers for ophthalmic applications. The binding of drugs depends on the physicochemical properties of the drugs and polymer used, as well as of the nano and microparticle material and also on the manufacturing process for these particles. After optimal drug binding to these particles, the ocular bioavailability of a number of drugs is significantly enhanced in comparison to normal aqueous eye drop solutions as increased solubility. Generally, smaller particles are better tolerated by the patients than larger particles (no irritation). For this reason especially nanoparticles may be preferred for long-acting ocular drug delivery systems, although larger microparticles showed slower elimination kinetics from the precorneal compartment.

CONCLUSION

It can be concluded from whole study that ocular drug delivery offers the unique carrier system for many pharmaceuticals. Ocular delivery based formulations could be making more acceptable and excellent drug delivery systems by using the biodegradable and water soluble polymers. It has been found from literature survey that ocular delivery based formulations have great applications for local treatment of eye disease with relatively lesser side effects as compared to other route of drug delivery.

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REFERENCES