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Ophthalmic Drug Delivery System-A Concise Review on its Conventional and Novel Approaches

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ABSTRACT

The main aim of this review is to focus on the various kinds of approaches which are used in ophthalmic drug delivery. Ophthalmic drug delivery system is used to treat various conditions associated with eye. The main purpose of a formulation designer is to formulate an eye formulation which could reside in the eye in an optimum concentration and for a proper duration for its proper effect. The main problem seen in the conventional dosage forms is their poor bioavailability due to fast precorneal drug loss primarily due to nasolacrimal drainage. The residence time of conventional formulations is also very less in the eye resulting into minimal advantages. In order to combat all these problems, now days the pharmaceutical scientists are very much involved in the research towards the novel approaches of ophthalmic drug delivery. The present paper enlists the important novel formulations which have been developed recently and explore their various advantages over conventional forms.

Key words: Ophthalmic drug delivery, Conventional dosage forms, Novel approaches to enhance ocular bioavailability.

1. INTRODUCTION

Ophthalmic drug delivery systems are basically used in the treatment of different forms of diseases which are primarily related to eye. The anatomical structure & physiological aspects of the eye helps this organ in preventing the entry of foreign particles into it. The eye has a complex structure comprising of the anterior as well as posterior segments. The anterior segment consists of cornea, conjunctiva, the ocular tissues comprising of the iris, pupil, lens. The posterior segment bears the retina, vitreous, fovea, choroid and the optic nerve.

Generally, topical application of drugs is the method of choice under most situations because of its ease and safety for ophthalmic therapy.¹ The ophthalmic drug system poses a serious challenge to the formulation designer in bypassing the protective barriers of the eye so that the drug may be sufficiently absorbed at the particular site of infection.² The main problem observed in the conventional dosage forms is, whenever they are instilled into the eye, only 1.2% of the dose gets available in the eye and significant drug loss is seen. Moreover some significant problems are also encountered like nasolacrimal drainage resulting into poor bioavailability.³ Thus in the present era, research on novel approaches towards ophthalmic drug delivery is being done tremendously with an objective to combat all these disadvantages. In designing an ocular therapeutic system, the main aim of the designer is to achieve an optimal concentration of drug at the active site for a significant duration.⁴ Whenever an ophthalmic drug is instilled into the eye for treating any disease, firstly the drug enters into the pre-corneal space before entering further into the cornea. This pre-corneal area consists of the main barriers which results into a very slow penetration of drug into the eye. The pre-corneal factors that lead to poor bioavailability of drugs can be appreciated in figure 1.⁵

1.1 Ideal characteristics of ophthalmic drug delivery system⁶

- Should be simple and easy to instill into the eye
- Must have good corneal penetration
- The residence time of drug in the cornea must be sufficient to show maximum effect
- Must have minimal side effects and toxicity
- Must not cause irritation in the eye
- The dose of drug incorporated must be low
- Frequency of administration must be fewer
- Vision of the patient must be maintained normal
- Concentration and rheological considerations must be fulfilled accordingly

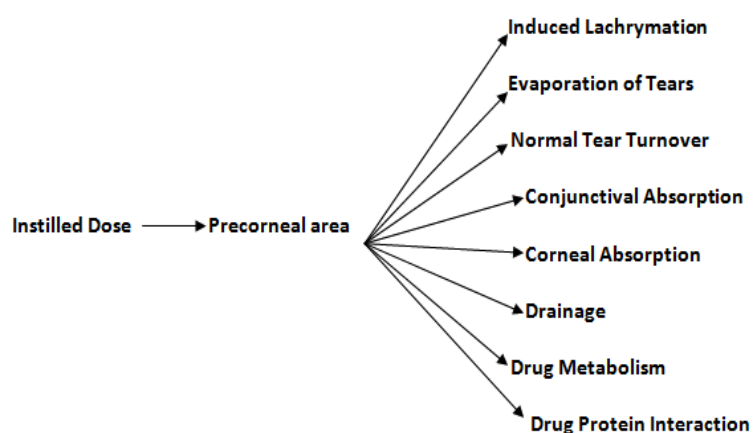


Fig. 1: Precorneal factors that influence bioavailability of topically applied ophthalmic drugs

2. DISORDERS OF EYE

2.1 Cataract

Cataract is one of the major eye problems which affect millions globally. If it is not treated accordingly, then this disease can even result into permanent blindness in individuals. Cataract is a pathological condition in which the lens becomes opaque, thus reducing the amount of light which reaches the retina. The causes for cataract formation are many, which include some heredity factors as well as gene mutation also.⁷ The post-operative treatment of cataract include three topical pharmaceutical agents: an antimicrobial, a potent corticosteroid and a non-steroidal anti-inflammatory drug (NSAID).⁸

2.2 Glaucoma

Glaucoma is recognized as a leading cause of irreversible blindness in the developed world. It is known that a rise in intraocular pressure (IOP) is the primary risk factor for glaucoma patients. Corticosteroid has long been accepted to raise the

intraocular pressure (IOP). IOP rise is related to duration of treatment, the type and class of corticosteroid, its dose as well as individual susceptibility. Steroid has been shown to produce an IOP rise over a period of weeks in both normal and glaucomatous eyes.⁹

2.3 Diabetic Retinopathy

Diabetic retinopathy is a disease which results from diabetic hyperglycaemia characterized by vascular complications in the retina, where neuronal elements responsible for vision are present. The patients associated with this disease have visual loss in one eye or it can affect both the eyes also. Retinal detachment is generally the prime cause of this disease.¹⁰

2.4 Dry Eyes

It is a term characterized by decreased lubrication and secretion of moisture on the surface of eyes. Generally, it is related to irritation as well as inflammation of ocular tissues which are present on the surface of eyes. Decreased quantity as well as quality of tears is associated with this disorder. The conventional treatment of steroids in the form of eye drops is been used as a treatment in this case but these are associated with some side effects also.¹¹ Thus a need of development of novel approach is definitely needed presently.

2.5 Corneal Ulcers

This disorder is also termed as Keratitis and mainly characterized by the inflammation of cornea. Some studies have already proved some of the viruses as well as bacteria as the prime causative agents for corneal ulcers. Cornea is the outermost part of the eye, so the exposure of this part of eye to the atmosphere is much higher as compared to other parts of eye, thus making this part more prone to infections.¹²

2.6 Conjunctivitis

This disease is quite common and is accompanied by redness in the anterior segment of the eye. Inflammation in the conjunctiva occurs generally in both eyes but sometimes the extent of infection in one eye is higher than the other one. An allergic or infective cause is usually present resulting into conjunctivitis. The exact percentage of infections that are bacterial or viral is not clear, and it has been estimated that somewhere between 33% and 78% of infective conjunctivitis cases are bacterial in origin.¹³

2.7 Inflammation of eyelids

This disorder is also accompanied by inflammation of the margin of one eyelid and is resulted due to a small abscess or styne, which is basically an infection of hair follicle gland at base of an

eyelash. The common symptoms are redness, irritation, discomfort and pain. Styes can come back again also if not treated properly. The inflammation will be localised at first but may spread to the rest of eyelid after some duration, which becomes tender and painful.¹³

2.8 Endophthalmitis

It is a severe form of intraocular inflammation which generally involves the ocular cavities & inner coats of eyeball. Causative organisms include Streptococci, E.coli, Pseudomonas, etc. Endophthalmitis is the infection of the intraocular tissues. This disease of eye may spread from the environment which is surrounding the individual. (Exogenous form). But sometimes it may also result by the own bacteria of individual due to some specific reasons. (Endogenous form).¹⁴

3. OPHTHALMIC DRUG DELIVERY SYSTEMS

3.1 Conventional Ophthalmic Systems

Such forms of ophthalmic systems are being used from decades in the treatment of eye disorders. But these have some limitations along with them like poor bioavailability, less residence time of drug in the pre-corneal area and many other evident reasons which have been already discussed above in the present paper. Some of the important types of conventional ophthalmic preparations are:

3.1.1 Solutions and Suspensions

Their main action is on the surface of eye after passing through the cornea or conjunctiva. Such type of preparations are used enormously from past because being liquids, they act quite rapidly on the site of action. To increase the corneal contact time of an ophthalmic drug and to provide a better controlled action, ophthalmic suspensions are also used.¹⁵

3.1.2 Eye drops

It comes under the class which takes an important place in the dosage regimen from decades. The important constituents present in these may be antihistamines, steroids which are commonly used in glaucoma patients, beta receptor blockers, prostaglandins, topical anesthetics and many others.¹⁶ Some eye drops marketed do not contain any active pharmaceutical agent and they are used only for a lubricating and tear replacement purpose.¹⁷

3.1.3 Ointments

These are categorized under semi solid dosage forms and these are also used from the past in the treatment of ocular

diseases. These generally contain paraffin as one of an important constituent which helps this preparation in gaining melting or softening point quite close to the body temperature. These are applied externally on the surface of eye and after instillation into the eye, ointments break into small droplets and remain in the cul-de-sac for appropriate duration showing its effect.¹⁷ Sometimes in some patients, irritation and blurred vision is observed which makes this dosage form less preferred as compared to the emerging dosage ophthalmic forms.

3.1.4 Viscous Solutions

These were also formulated in the labs by the efforts of formulation designers in order to enhance the viscosity of ophthalmic preparations so that the residence time could be increased in the precorneal area and with a hope of increasing bioavailability of drugs. These preparations generally consist of some viscosifying agents such as cellulose, polyacrylic acid. Carbomer, Xanthan gum also holds an important place in increasing viscosity of these agents.¹⁸

3.2 Novel approaches towards Ophthalmic Drug Delivery

3.2.1 In Situ Forming Gels

These systems are accepted widely as studies have already proved that they help in increasing the residence time in the precorneal area, thus increasing the bioavailability of drug. These systems are basically in liquid form but they undergo sol to gel phase transition as they are instilled into the eye due to a particular stimulus. After becoming a gel, these remain for a much higher extent in the eye as compared to the conventional dosage forms. These employ certain class of polymers which show their action after getting a response from a stimuli. The stimuli which is responsible for the phase transition is generally temperature, change in pH or a change in ionic environment. These have found to definitely increase the therapeutic response of the particular drug.^{19,20}

Pluronic F-127 is an important polymer used to prepare In-Situ gelling system and it shows its action with a change of temperature. ProLastin, a protein polymer after investigation and research was found that it undergo an irreversible sol to gel transition, when injected as a solution into the body, and the material forms a solid stable gel within minutes. It remains at the site of injection for a long time helping the drug to get absorb slowly from weeks to a month.

Carbopol comes in another important category of such polymers which exerts its action after a change in pH. These

polymers basically consist of some acidic or basic groups which release or accept the protons accordingly. Hydroxy Propyl Methyl Cellulose (HPMC) is also added into this to enhance the viscosity.

Sodium Alginate is a polymer which helps to change liquid into a gel through change in the ionic environment. Its virtue of forming an instantaneous gel when instilled into the eye is due to the formation of calcium alginate after getting interacted with the divalent cation (Ca^{2+}) present in lachrymal fluid (pH 7.4).²¹

3.2.2 Ocular Inserts

These hold an important place in the novel approaches of ophthalmic drug delivery as they show a much higher extent of controlled, sustained drug release as compared to the conventional forms. These are solid dosage forms and are helpful in maintaining a higher concentration of drug at the site for a longer period also. Ocular inserts are also efficient in decreasing the frequency of administration, thus resulting into a better patient compliance.²²

3.2.3 Artificial Tear Inserts

These were developed by researchers Merck, Sharp and Dohme in around year 1981. Such an ophthalmic insert is responsible for giving a sustained effect for higher duration. Commercially Lacrisert is available in the market. It contains hydroxyl propyl cellulose without any inclusion of preservative. This was proved to be a blessing to the patients suffering from dry eyes.²³

3.2.4 Nanoparticles and Microspheres

These act as important drug carriers for carrying the ophthalmic drugs at the infected site in a proper concentration. Basically, the drug gets bind to these carrier molecules and they provide a much higher absorption and penetration rate in the eye as compared to the conventional ones. Bioavailability can also be enhanced by using these carriers. The appropriate size of drug particles in the employment of these is 5-10 micro meter and the drug is micronized before combining it with these carriers.²⁴

3.2.5 Liposomes

Certainly an important class of ophthalmic drug delivery, these are tiny vesicles or bubbles in which the membrane is made up of phospholipids. These act as a carrier and due to its virtue of having structure similar to the cell membrane, these can be loaded with low dose of drug molecule and could be used for site specific drug delivery. They have an inherent property to get stick with the wall of corneal and conjunctival membrane in the eye and thus, the chances of drug absorption in the eye is much higher as compared

to the conventional ones.²⁵ The charge difference between the surface of liposome and the corneal surface is what, makes the liposomes being captured by the corneal layer. Particularly the tendency of positively charged liposomes is much higher to get captured on the negatively charged corneal membrane than other charged liposomes. Studies were carried out on the drugs. Indoxole and Penicillin G by an eminent researcher Schaeffer and it was proved that the positively charged liposomes have the maximum tendency of getting captured as compared to neutral charged liposomes.²⁶

3.2.6 Micro emulsions

These are stable dispersions of water and oil, consisting of a mixture of surfactant and co-surfactant in a manner to reduce interfacial tension. These have been found to increase the ocular bioavailability of drug and the need of frequent administration of the drug is also minimized by employing such novel ophthalmic systems. These systems have high thermodynamic stability, small droplet size (~100 nm), and crystal clear appearance.²⁷ Sustained effect is the biggest advantage of such kind of systems. Much of the emphasis is given these days on research of micro emulsions and a lot of work is being done to explore more benefits of such ocular systems.

3.2.7 Implants

Ocular implants are gaining much of importance in the ophthalmic drug delivery and it is proving to be a dynamic area of interest in pharmaceuticals. These can release the drug at pre-determined rate without interference with the normal vision, thus enhancing the patient compliance. Implants could help in absorbing the drug within the anterior or posterior segments in a better and prolonged way, thus enhancing bioavailability. These are implanted in effected patients with a minor surgical procedure and the active drug is being absorbed for a very long duration.²⁸ Ocular implants holds an important place in ophthalmics and are promising ocular delivery systems that have been incorporated recently. An approach towards increasing the trans-corneal penetration is also appreciated in their preparation.²⁹ A pellet implant of ganciclovir was implanted into the vitreous region of rabbit eyes to maintain therapeutic levels of drug for extended periods. These Pellet implant was well tolerated with no toxic effects with respect to the polymers used in the devices for incorporation in the rabbit eyes.³⁰

3.2.8 Mini disc or Ocular therapeutic system (OTS)

This system generally employs the use of a round disc having a convex front and a concave back surface which remains in contact with the eyeball. The drug which has to be reached on

the site of action in eye, is being loaded on to this disc. It is like a minute contact lens with a diameter of approximately 4-5 mm. Both of highly and poorly water soluble drugs can be incorporated to these discs for a sustained effect.³¹

The comparison between the conventional and novel ophthalmic approaches has been illustrated in the table (Table No.1) which surely depicts that the novel approaches overcast the conventional approaches.

4. CONCLUSION

The ophthalmic drug delivery system is an emerging area of interest in the research and development of novel forms of ophthalmic system. The upcoming approaches towards the development of newer ophthalmic systems have been established in overcoming the disadvantages which the conventional

ophthalmic systems use to have. The newer generation of ophthalmic systems like In-Situ gels, Ocular Inserts, Artificial tear inserts, Nanoparticles and Microspheres, Liposomes etc. have proved to increase the ocular bioavailability and the therapeutic response of the drug up to many folds. The targeted drug delivery in the eye could also be achieved by employing such systems. The residence time of drug in the cornea can be increased by using these systems resulting into the reduction in frequency of administration and thus optimizing the ocular therapy. The development of these novel systems have surely revolutionized the whole era of ophthalmics.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

Table No. 1. Comparison of Conventional Approaches with Novel Approaches

S. No.	Conventional Ophthalmic Delivery Systems	Novel Ophthalmic Delivery Systems
1.	Ocular contact time is less	Ocular contact time is much higher
2.	Rate of systemic absorption of drug is high	Rate of systemic absorption of drug is less
3.	Site specificity is much lesser	Site specificity is much higher in this approach
4.	Bioavailability of drug is less	Rate of bioavailability can be increased
5.	Frequency of administration is high, patient compliance is less	Frequency of administration is less, thus increasing the patient compliance
6.	Time of drug remaining above the critical concentration is quite less	Time of drug remaining above the critical concentration is much higher
7.	Conventional Ophthalmic Delivery Systems	Novel Ophthalmic Delivery Systems
8.	Ocular contact time is less	Ocular contact time is much higher
9.	Rate of systemic absorption of drug is high	Rate of systemic absorption of drug is less

Table No. 2. Recent Marketed Ophthalmic Drug Products and Delivery Systems based on Novel Approaches^{32, 33,34,35,36}

S. No.	Product Name	Manufacturer	Type of Novel Approach	Used In/As
1.	EyeSol [®]	Novaliq	Aqueous Free Technology	Dry Eyes
2.	NovaTears [®]	Novaliq	Disruptive Drug Delivery Technology	Dry Eyes
3.	Novelia [®] Delivery System	Nemera	Flow Control Technology	Multidose Eye Dropper
4.	Oculief [®]	Re-Vana Therapeutics Ltd	Sustained Release Implant Technology	Glaucoma, Macular Degeneration
5.	Ozurdex [®]	Allergan	Sustained Release Implant Technology	Uveitis, Macular Edema
6.	Pilopini [®]	Alcon	pH triggered In Situ-Gel	Miotics
7.	Timolol [®]	Transo-Pharm	pH triggered In Situ-Gel	Glaucoma
8.	Visudyne	Novartis	Liposomal Drug Delivery	Choroidal neovascularisation

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