Review Article

OCULAR DRUG DELIVERY: THE CHALLENGES, CURRENT STATUS AND ADVANCEMENTS

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ABSTRACT

Ocular drug delivery is the most fascinating and challenging task faced by pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged periods of time. Major problems encountered by conventional ocular dosage forms include rapid pre-corneal drug loss due to naso-lacrimal drainage; tear turnover and drug dilution resulting in poor bio-availability. Therefore, efforts to improve ocular drug bio-availability led to development of novel drug delivery dosage forms such as nano particles, liposomes, hydrogels, ocuserts and muco-adhesive formulations. Controlled drug delivery systems offer many advantages over conventional dosage forms in terms of improving drug bio-availability, reducing toxicity and decreasing dosage frequency.

Key words: Ocular barriers, intra-ocular penetration, tear film

INTRODUCTION

The eye is a unique organ, both anatomically and physiologically. The tropical drug treatments of ocular diseases face difficulty in achieving sufficient quantity of drug at desired site of action. For ocular drugs to be effective, ideal drug delivery system should provide the drug at the receptor site of the ocular tissue in relatively higher concentration to elicit the desired pharmacological response [1].

Conventional drug delivery systems; which include solutions, suspension gels, and

ointments suffer from problems of poor bioavailability. Ocular absorption of topically applied drugs is limited by protective mechanisms that promote safety and proper functioning of the eye, as well as by a number of factors related to the efficacy of drug application [2].

Firstly the topically applied drug is immediately diluted in ocular tear liquid. Secondly, excess solution spills over the lower eyelid, with some of the remaining drug draining into naso-lacrimal duct. Thirdly, after initial dilution, spilling and drainage of a topically applied agent, any remaining drug can be further diluted due to increased lacrimation and physiological tear turnover induced by the drug application.

The cornea is the main route for the transport of topically applied drugs into the eye. Small lipophilic molecules are normally absorbed through the cornea, while large hydrophilic molecules are absorbed via conjunctiva and sclera [3,4]. However, lacrimal drainage and systemic absorption from conjunctiva act to remove ophthalmic medications from eye. This results in actual absorption of only a small fraction of topically applied drug dose[5,6].

The tight junctions of iris capillaries and retina act as a barrier to the diffusion of drugs from the blood into the aqueous and vitreous. The duration of the drug action in the eye can be extended by improving corneal drug penetration, reducing drainage through the use of viscocity enhancing agents. Factors that affect bioavailability of ocular drugs include pH, salt form of the drug, vehicle composition, osmolarity, toxicity and viscocity [7]. This article provides insight into current status and advances in ocular drug delivery methods.

Medication forms used in Ophthalmology Eye drops: The eye drops may be solutions or suspensions and are comparatively convenient,_safe, immediately active and acceptable. Generally, eye drops are used only for anterior segment disorders as adequate concentration is not usually achieved in posterior segment [8]. Eye drops provide a pulse entry of the drug, followed by a rapid decline in drug concentration. Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye [9].

Ointments: Clinically significant enhancement of drug penetration results from the prolonged contact time with eye. Ointments are especially useful for treating children, who may not cooperate for topically applied solutions. Ointments are especially useful for medicating ocular injuries such as corneal abrasions, where eye needs to be patched. The commonly used ophthalmic ointment bases and liquid oily vehicles are made up of lanolin, petrolatum and peanut oil, which are toxic to the interior of the eye, causing endothelial damage, corneal edema, vascularization, and scarring. For this reason, ophthalmic medication in ointment or oily liquid vehicles should not be instilled into the interior of the eye.

<u>**Gels**</u>: Ophthalmic gels are similar in viscosity and clinical usage as ophthalmic ointments.

Sprays: This form is especially used for pediatric patients and solution is administered using a sterile perfume atomizer or plastic spray bottle.

<u>Ocular drug delivery devices in</u> <u>Ophthalmology</u>

<u>Ocular inserts</u>: Ocular inserts are defined as sterile preparations with a thin, multilayered, drug impregnated, solid or semisolid consistency devices placed into cul-de-sac or sac of conjunctiva and whose size and shape are especially designed for ophthalmic application. The inserts are usually placed in the lower fornix and less frequently in the upper fornix on the cornea. They are usually made of polymeric vehicle containing drug.

Advantages offered by ocular inserts is that by increasing contact time, they improve bioavailability, possibility of providing a prolonged drug release and thus better efficiency, reduction of systemic sideeffects, possibility of incorporation of various novel chemicals and technological approaches such as prodrug, mucoadhesives, permeation enhancers, microparticulate, salts acting as buffers.

Classification of patented Ocular inserts (Based on solubility behaviors):

- 1) Insoluble inserts-
- a- Diffusion based

- b- Osmosis based
- c- Soft contact lenses
- 2) Soluble inserts
- 3) Bio-erodible inserts

Filter paper strips: Sodium fluorescein, rose Bengal and lissamine green are commercially available as drug impregnated filter paper strips. For administration, the drug impregnated paper strip moistened with a drop of normal saline and applicator is gently touched to the superior or the inferior bulbar conjunctiva or to inferior conjunctival sac.

Liposomes: Liposomes are biocompatible and biodegradable lipid vehicles made up of natural lipids. They are having intimate contact with corneal and conjunctival surfaces which are desirable for drugs that are poorly absorbed.

Niosomes and Discomes: The major limitation of liposomes are chemical oxidative degradation instability, of phospholipids. To avoid this, niosomes are developed as they are chemically stable and hydrophobic entrap both can and hydrophilic drugs.

<u>Nanoparticles</u>: The diseases like inflammatory diseases and cancer could be treated more effectively with reduced sideeffects if we can deliver these drugs to a specific location. To overcome this problem, drugs are incorporated into small particles, which can release the drugs they are carrying at the site of interest.

It has been found that the particles need to be very small around 50-150nm in diameter to reach suitable targets. Also, that the particles need to be coated to make them invisible to the body's immune system to avoid them being prematurely removed by organs like the cornea and liver. Following three drugs are under development for nanoparticles delivery applications: Conventional low molecular weight drugs, protein and polypeptide drugs and DNA for oligonucleotide or gene therapy [10].

Lontophoresis: In iontophoresis, direct current drives ions into the cell or cells or tissues. Ocular iontophoresis delivery is not only fast, painless and safe, but it can also deliver high concentrations of the drug to a specific site. Iontophoretic application of antibiotics in eye not only increases their bactericidal activity but also reduces the severity of disease. Similarly, application of anti-inflammatory agents can reduce vision threating side effects [11,12].

<u>**Contact lenses:**</u> Water soluble drugs soaked in drug solutions can be absorbed through contact lenses. The drug saturated contact lenses are placed in the eye which releases the drug in eye for a long period of time.

<u>Collagen shield</u>: Collagen shield basically consists of cross linked collagen, fabricated with foetal cell tissue and is developed as corneal bandage to promote wound healing.

<u>Micro-needle</u>: As an alternative to topical route, researchers have developed micro-needle to deliver drugs to posterior segment.

Advances in Ophthalmic drug delivery

Recent advances in ocular drug delivery have ranged from improvement of primitive eye drops to iontophoretic drug delivery to cell encapsulation, gene therapy, stem cell therapy, protein and peptide therapy, scleral plug therapy, SiRNA, oligonucleotide therapy, Aptamer and Ribozyme therapy.

CONCLUSION:

Ocular drug delivery systems provide local as well as systemic delivery of drugs. A substancial amount of work has been carried out to develop new drug delivery systems which are efficient in delivering accurate and precise doses with minimum toxic effects. The novel advanced delivery systems offer more protective and effective means of the therapy for nearly inaccessible diseases.

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