INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Review Article

RECENT TRENDS IN OPHTHALMIC DRUG DELIVERY

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Article Received on: 13/05/13 Revised on: 04/06/13 Approved for publication: 16/07/13

DOI: 10.7897/2230-8407.04707

IRJP is an official publication of Moksha Publishing House. Website: www.mokshaph.com

ABSTRACT

The major challenge faced by today's pharmacologist and formulation scientist is ocular drug delivery. Delivery of drugs to the targeted ocular tissues is restricted by various precorneal, dynamic and static ocular barriers. Also, therapeutic drug levels are not maintained for longer duration in target tissues. To overcome the ocular drug delivery barriers and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles and *in situ* thermosensitive gels for the earlier mention ocular diseases.

Keywords: Contact lens, Drug delivery, Emulsions, Formulations, Implants, Liposomes, Nanomicelles, Ointments, Suspensions.

INTRODUCTION

The eye is a complex organ with a unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy is the most prevalent diseases affecting posterior segment of the eye.[1,2]

It is common knowledge that the ocular bioavailability of drugs applied topically as eye-drops is very poor. The absorption of drugs in the eye is severely limited by some protective mechanisms that ensure the proper functioning of the eye and by other concomitant factors. For example: drainage of the instilled solutions; lacrimation and tear turnover; metabolism; tear evaporation; non-productive absorption / adsorption; limited corneal area and poor corneal permeability; and binding by the lacrimal proteins.[3] To overcome the ocular drug delivery barriers and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and *in situ* thermosensitive gels for the earlier mention ocular diseases. This review will provide an overview on various conventional and novel ophthalmic drug delivery systems developed to deliver drug to diseased ocular tissues for the treatment of ocular diseases.

Classification

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:

1. Liquids: Solutions, Suspensions, Sol to gel systems, Sprays
2. Solids: Ocular inserts, Contact lenses, Corneal shield, Artificial tear inserts, Filter paper strips
3. Semi-Solids: Ointments, Gels
4. Miscellaneous: Ocular iontophoresis, Vesicular systems, Mucoadhesive dosage forms, Particulates, Ocular penetration enhancers: Use of Hyaluronic acid, Use of Hydroxy Beta Cyclodextrin.

Conventional Ocular Drug Delivery Systems

Emulsions

An emulsion based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. There are two types of emulsions which are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion system.[4] For ophthalmic drug delivery, o/w emulsion is common and widely preferred over w/o system. The reasons include less irritation and better ocular tolerance of o/w emulsion. Restasise™, Refresh Endura® (a non-medicated emulsion for eye lubrication) and AzaSite® are the examples of currently marketed ocular emulsions in the United States. Several studies have demonstrated applicability of emulsions in improving precorneal residence time, drug corneal permeation, providing sustain drug release and thereby enhancing ocular bioavailability.[5] w/o Micro emulsions offer a promising alternative. They are thermodynamically stable and optically isotropic colloidal systems with excellent wetting and spreading properties. Moreover they are comprised of aqueous and oily components and therefore can accommodate both hydrophilic as well as lipophilic drugs. w/o micro emulsions where administered in the eye; converted into the LC state which releases the drug slowly and produce a sustained release preparation for eye.

Cationic Emulsions

They are developed by the Novagali pharmaceuticals for ophthalmic applications. The topical administration of a cationic emulsion onto the eye has shown to increase the residence time of the drug on the cornea, with a lower contact angle and an increased spreading coefficient in comparison with conventional eye drops and anionic emulsions.

Suspensions

Suspensions are another class of non-invasive ocular topical drop drug carrier systems. Suspension may be defined as dispersion of finely divided insoluble API in an aqueous solvent consisting of a suitable suspending and dispersing agent. In other words, the carrier solvent system is a saturated solution of API. Suspension particles retain in precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution. Duration of drug action for suspension is particle size dependent. Smaller size particle replenishes the drug absorbed into ocular tissues from precorneal pocket. While on the other hand, larger particle size helps retain particles for longer time and slow drug dissolution[6]. Thus, an optimal particle size is expected to result in optimum drug activity. Several suspension formulations are marketed worldwide to treat ocular bacterial infections.

Ointments

Ophthalmic ointments are another class of carrier systems developed for topical application. Ocular ointment comprises of mixture of semisolid and a solid hydrocarbon (paraffin) that has a melting point at physiological ocular temperature (34°C). The choice of hydrocarbon is dependent on biocompatibility. Ointments help to improve ocular bioavailability and sustain the drug release.[7] Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use.

Novel Ocular Drug Delivery Systems

Nanotechnology Based Vesicular Ocular Drug Delivery

In a last few decades, many approaches have been utilized for the treatment of ocular diseases. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery. Some of them have shown promising results for improving ocular bioavailability.

Nanomicelles

Nanomicelles are the most commonly used carrier systems to formulate therapeutic agents in to clear aqueous solutions. In general, these nanomicelles are made with amphiphilic molecules. These molecules may be surfactant or polymeric in nature. Currently, tremendous interest is being shown towards development of nanomicellar formulation based technology for ocular drug delivery. The reasons may be attributed due to their high drug encapsulation capability, ease of preparation, small size and hydrophilic nanomicellar corona generating aqueous solution. In addition, micellar formulation can enhance the bioavailability of the therapeutic drugs in ocular tissues, suggesting better therapeutic outcomes. Due to their extremely small size and hydrophilic corona, nanomicelles may be retained in systemic circulation for longer time and accumulate at the diseased tissue. Thereby, non-specific drug accumulation in to normal tissues may be minimized. Proper selection of surfactant/polymer and engineering technique may aid in delivery of drugs to both anterior and posterior eye segments.

Nanoparticles

Nanoparticles are colloidal carriers with a size range of 10 to 1000 nm. For ophthalmic delivery, nanoparticles are generally composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. Drug loaded nanoparticles can be nanocapsules or nanospheres. In nanocapsules, drug is enclosed inside the polymeric shell while in nanospheres; drug is uniformly distributed throughout polymeric matrix. From past few decades, nanoparticles have gained attention for ocular drug delivery and several researchers have made attempts to develop drug loaded nanoparticles for delivery to both anterior and posterior ocular tissues. Nanoparticles represents a promising candidate for ocular drug delivery because of small size leading to low irritation and sustained release property avoiding frequent administration. However, like aqueous solutions, nanoparticles may be eliminated rapidly from precorneal pocket. Hence, for topical administration nanoparticles with mucoadhesive properties have been developed to improve precorneal residence time.[8] Polyethylene glycol (PEG), chitosan and hyaluronic acid are commonly employed to improve precorneal residence time of nanoparticles. Chitosan coating is most widely explored for improving precorneal residence of nanoparticles.

Nanosuspensions

Nanosuspensions are colloidal dispersion of submicron drug particles stabilized by polymer(s) or surfactant(s). It is emerged as promising strategy for delivery of hydrophobic drugs. For ocular delivery, it provides several advantages such as sterilization, ease of eye drop formulation, less irritation, increase precorneal residence time and enhancement in ocular bioavailability of drugs which are insoluble in tear fluid[9]. The efficacy of nanosuspensions in improving ocular bioavailability of glucocorticoids has been demonstrated in several research studies. Glucocorticoids such as prednisolone, dexamethasone and hydrocortisone are widely recommended for the treatment of inflammatory conditions affecting anterior segment ocular tissues. The current therapy with these drugs requires frequent administration at higher doses which induce cataract formation, glaucoma and damage optic nerve. Efforts have been made toward improving ocular bioavailability of glucocorticoids by formulating as nanosuspensions.

Liposomes

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter.[10] They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increases the probability of ocular drug absorption.[11] The corneal epithelium is thinly coated with negatively charged mucin to which the positive charged surface of the liposomes may bind.[12]

Dendrimers

Dendrimers are characterized as nanosized, highly branched, star shaped polymeric systems. These branched polymeric systems are available in different molecular weights with

terminal end amine, hydroxyl or carboxyl functional group. The terminal functional group may be utilized to conjugate targeting moieties.[13] Dendrimers are being employed as carrier systems in drug delivery. Selection of molecular weight, size, surface charge, molecular geometry and functional group are critical to deliver drugs. The highly branched structure of dendrimers allows incorporation of wide range of drugs, hydrophobic as well as hydrophilic. In ocular drug delivery, few promising results were reported with these branched polymeric systems[14,15] Poly (amidoamine) (PAMAM) dendrimers are widely employed in ocular drug delivery and their influence of size, molecular weight and number of amine, carboxylate and hydroxyl surface groups in several series of dendrimers was determined. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups.[16]

Niosomes and Discomes

Niosomes are nonionic surfactant vesicles drugs. They are chemically stable as compared to liposomes and can entrap both hydrophobic and hydrophilic drugs. They are non toxic and do not require special handling techniques. Non-ionic surface active agents based discoidal vesicles known as (discomes) loaded with timolol maleate were formulated and characterized for their *in vivo* parameters.

Pharmacosomes

This term is used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. The amphiphilic prodrug is converted to pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea and a controlled release profile.[17]

Control Delivery Systems

Implants

Ocular implants are available as biodegradable and non-biodegradable drug releasing devices. Non-biodegradable implants offer long-lasting release by achieving near zero order release kinetics[18]. Polymers such as polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA), and polysulfone capillary fiber (PCF) are being employed for fabricating non-biodegradable implants[19]. Vitrasert® and Retisert® are the examples of marketed non-biodegradable implants. Another category of ocular implant includes biodegradable implants. Because of biodegradable nature, these implants are not required to be surgically removed which signify a distinctive advantage over the non-biodegradable implants. Polylactic acid (PLA), polyglycolic acid (PGA), PLGA and polycaprolactones are the most commonly used polymers for the fabrication of biodegradable implants[19]. Examples of biodegradable implants for ocular delivery include Surodex™ and Ozurdex® which are designed for the sustained delivery of dexamethasone for the treatment of intraocular inflammation and macular edema (ME), respectively[18].

Iontophoresis

In Iontophoresis direct current drives ions into cells or tissues. For iontophoresis the ions of importance should be charged molecules of the drug.[20] positively charge of drug are driven into the tissues at the anode and vice versa. Ocular iontophoresis delivery is not only fast, painless and safe but it can also deliver high concentration of the drug to a specific site. Iontophoretic application of antibiotics in eye not only increases their bactericidal activity but also reduce the severity of disease. Similarly application of anti-inflammatory agents can reduce vision threatening side effects.[21,22]

Contact Lenses

Contact lenses are thin and curved shape plastic disks which are designed to cover the cornea[23]. After application, contact lens adheres to the film of tears over the cornea due to the surface tension. Drug loaded contact lens have been developed for ocular delivery of numerous drugs such as β-blockers, antihistamines and antimicrobials. It is postulated that in presence of contact lens, drug molecules have longer residence time in the post-lens tear film which ultimately led to higher drug flux through cornea with less drug inflow into the nasolacrimal duct. Usually, drug is loaded into contact lens by soaking them in drug solutions. These soaked contact lenses demonstrated higher efficiency in delivering drug compared to conventional eye drops. In a study, ketotifen fumarate loaded imprinted lenses have revealed higher tear fluid bioavailability compared to drug soaked lenses or ketotifen fumarate marketed eye drops. The relative bioavailability for the imprinted lenses was 3 times greater than that of non-imprinted lenses.

Collagen Shield

Collagen shield basically consist of cross linked collagen, fabricated with foetal calf skin tissue and developed as a corneal bandage to promote wound healing. Topically applied antibiotic conjugated with the shield is used to promote healing of corneal ulcers. Tear fluid makes these devices soft and form a thin pliable film which is having dissolution rate up to 10, 24 or 72 h. Because of its structural stability, good biocompatibility and biological inertness, collagen film proved as a potential carrier for ophthalmic drug delivery system.

Ocular Inserts

Ocular inserts are solid dosage forms and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The ocular inserts maintain an effective drug concentration in the target tissues. A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible and hydrogel inserts.

Micro Needles

Micro needle based technique is an emerging and minimally invasive mode of drug delivery to posterior ocular tissues. This technique may provide efficient treatment strategy for vision threatening posterior ocular diseases such as age related macular degeneration, diabetic retinopathy and posterior uveitis. This new micro needle based administration strategy may reduce the risk and complications associated with intravitreal injections such as retinal detachment, haemorrhage, cataract, endophthalmitis and pseudoendophthalmitis. Moreover, this strategy may help to circumvent blood retinal barrier and deliver therapeutic drug levels to retina / choroid. Micro needles are custom designed to penetrate only hundreds of microns into sclera, so that damage to deeper ocular tissues may be avoided. These

needles help to deposit drug or carrier system into sclera or into the narrow space present between sclera and choroid called "suprachoroidal space" (SCS). Puncturing of sclera and depositing drug solution or carrier systems in sclera or SCS may facilitate diffusion of drug into deeper ocular tissues, choroid and neural retina.[24]

Advanced Delivery System

Cell Encapsulation

The entrapment of immunologically isolated cells with hollow fibres or microcapsules before their administration into the eye is called Encapsulated Cell Technology (ECT) which enables the controlled, continuous and long-term delivery of therapeutic proteins directly to the posterior regions of the eye.

Stem Cell Therapy

Emerging cell therapies for the restoration of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina.[25] Current strategy for management of ocular conditions consists of eliminating the injurious agent or attempting to minimize its effects. The most successful ocular application has been the use of limbal stem cells, transplanted from a source other than the patient for the renewal of corneal epithelium. The sources of limbal cells include donors, autografts, cadaver eyes and (recently) cells grown in culture. Stem-cell Therapy has demonstrated great success for certain maladies of the anterior segment.[26]

Protein and Peptide Therapy

Delivery of therapeutic proteins / peptides has received a great attention over the last few years.[27] The intravitreous injection of ranibizumab is one such example. Immunoglobulin G has been effectively delivered to retina by transscleral route with insignificant systemic absorption.[27]

Scleral Plug Therapy

Scleral plug can be implanted using a simple procedure at the pars plana region of eye, made of biodegradable polymers and drugs, and it gradually releases effective doses of drugs for several months upon biodegradation.[28]

Oligonucliotide Therapy

Oligonucleotide (ON) therapy is based on the principle of blocking the synthesis of cellular proteins by interfering with either the transcription of DNA to mRNA or the translation of mRNA to proteins. Among several mechanisms by which antisense molecules disrupt gene expression and inhibit protein synthesis, the ribonuclease H mechanisms is the most important.[29]

Aptamer

Aptamers are oligonucleotide ligands that are used for high-affinity binding to molecular targets.[30] They are isolated from complex libraries of synthetic nucleic acid by an iterative process of adsorption, recovery and re amplification. They bind with the target molecules at a very low level with high specificity. One of the earliest aptamers studied structurally was the 15 mer DNA aptamer against thrombin, d(GGTTGGTGTGGTTGG).56 Pegaptanib sodium (Macugen; Eyetech Pharmaceuticals/Pfizer) is an RNA aptamer directed against VEGFb165, where VEGF isoform primarily responsible for pathological ocular neovascularization and vascular permeability.[30]

CONCLUSION

Drug delivery to targeted ocular tissues has been a major challenge to ocular scientist, for decades. Administration of drug solutions as topical drop with conventional formulations was associated with certain drawbacks which initiated the introduction of different carrier systems for ocular delivery. Tremendous efforts are being put into ocular research toward the development of safe and patient compliant novel drug delivery strategies. The latest available targeted drug delivery systems focus on the localised delivery of the drugs as well as certain macromolecular substances like proteins, genes like DNA, siRNA to the internal parts of the eye. A reasonable strategy to circumvent the drawbacks of individual technologies is to combine technologies. Reported examples include liposomes and nanoparticles in droppable gels and liposomes and nanoparticles coated with bio adhesive polymers.

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Cite this article as:
Sharma Reshu, Goswami Laxmi. Recent trends in Ophthalmic drug delivery. Int. Res. J. Pharm. 2013; 4(7):31-35 http://dx.doi.org/10.7897/2230-8407.04707