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Recent Advance of Ocular Drug Delivery System

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ABSTRACT

Eye is the most exclusive organ of the body and various drug delivery systems are used to deliver drug into eye. Eye diseases are commonly encountered in day to day life, which are cured or prevented through the conventionally used dosage forms like eye drops, ointments. Delivery to the internal parts of the eye still remains troublesome due to the anatomical and protective structure of the eye. To improve ocular drug contact time, bioavailability and residence time, and to reduce the patient discomfort, frequency of dose, as well as to slow down the elimination of the drug there are significant efforts concentrating towards newer drug delivery systems for ophthalmic administration. This review focuses on the various new drug delivery systems applied in eye like inserts, in-situ gel, the newly developed particulate and vesicular systems like liposomes, pharmacosomes and discomes, niosomes, nanoparticles, iontophorosis, corneal shields, drug embedded contact lenses, ocular wafers etc and the most recent advanced approaches of the ocular delivery systems like the delivery of the genes and proteins to the internal structures which were used in treating the diseases caused due to genetic mutation, along with safety evaluation of ocular drug delivery formulations with some case studies.

Keywords: Advance ocular therapy, control drug delivery systems, corneal permeability, vesicular systems, safety evaluation.

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INTRODUCTION

Topical application of drugs to the eye is the well established route of administration for the treatment of various eye diseases like dryness, conjuctiva, eye flu etc. The protective mechanisms of the eye such as Blinking, baseline and reflex lachrymation, and drainage decrease the bioavailability of drug and also help to remove rapidly foreign substances like the dust particles bacteria, including drugs, from the surface of the eye [1].Conventional eye drops currently account for more than 90% of the marketed ophthalmic formulations. However, after instillation of an eye drop, typically less than 5% of the applied drug penetrates the cornea and reaches the intraocular tissues. This is due to the rapid and extensive precorneal loss caused by drainage and high tear fluid turnover. As a consequence, the typical corneal contact time is limited to 1 – 2 min and the ocular bioavailability is usually less than 10%[2].Various ocular delivery systems, such a ointments, suspensions, micro and nanocarriers, and liposomes, have been investigated during the past two decades pursuing two main strategies: to increase the corneal permeability and to prolong the contact time on the ocular surface[3] . Emerging new controlled drug delivery systems such as dendrimers, microemulsions, muco-adhesive polymers, hydrogels, iontophoresis, collagen shield, prodrug approaches have been developed for this purpose. These novel systems offer manifold advantages over conventional systems as they increase the efficiency of drug delivery by improving the release profile and also reduce drug toxicity. The rapid progress of the biosciences opens new possibilities to meet the needs of the posterior segment treatments. The examples include the antisense and aptamer drugs for the treatment of cytomegalovirus (CMV) retinitis and age-related macular degeneration, respectively, and the monoclonal antibodies for the treatment of the age-related macular degeneration. Other new approaches for the treatment of macular degeneration include intravitreal small interfering RNA (siRNA) and inherited retinal degenerations involve gene therapy. This review article briefly covers general outline with examples of various conventional and recent past time formulations for ophthalmic drug delivery. It also provides the limitations of conventional delivery with a view to find modern approaches like vesicular systems, nanotechnology, stem cell therapy as well as gene therapy, oligonucleotide and aptamer therapy, protein and peptide delivery, ribozyme therapy for treatment of various ocular diseases.[4]

CONVENTIONAL DELIVERY SYSTEMS:

Solutions, Suspensions, Emulsions:

Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and

instilled volume can influence retention of a solution in the eye .5 Less than 5 Percent of the dose is absorbed after

topical administration into the eye. The dose is mostly absorbed to the systemic blood circulation via the conjunctival and nasal blood vessels. Ocular absorption is limited by the corneal epithelium, and it is only moderately increased by prolonged ocular contact. The reported maximal attainable ocular absorption is only about 10 Percent of the dose.[6] When eye drops is administered in the inferior fornix of the conjunctiva, very small amount of the dose reaches to the intraocular tissues and major fraction of the administered drug get washed away with the lachrymal fluid or absorbed systemically in the nasolacrimal duct and pharyngeal sites.[7]

Ointment and Gels:

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. Pilopine HS gel containing pilocarpine was used to provide sustain action over a period of 24 hours. A number of workers reported that ointments and gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs.[8]

Ocular inserts

Solid ocular dosage forms such as films, erodible and non erodible inserts, rods, and shields have been developed to overcome the typical pulse - entry - type drug release associated with conventional ocular dosage forms. A number of ocular inserts using different techniques, namely soluble, erodible, non erodible, and hydrogel inserts with polymers such as cellulose derivates, acrylates, and poly (ethylene oxide), have been investigated over the last few decades. Sasaki et al. prepared non degradable disc - type ophthalmic inserts of β - blockers using different polymers. They found that inserts made from poly (hydroxypropyl methacrylate) were able to control the release of tilisolol hydrochloride[9].

Numerous studies have also been performed on soluble collagen shields. Collagen shields are fabricated from porcine sclera tissue, which has a similar collagen composition to that of the human cornea. Drug loading is typically achieved by soaking the collagen shield in the drug solution prior to application.[10]

VESICULAR SYSTEM:

Liposomes:

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10000 nm in diameter.[11] 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.[12] The corneal epithelium is thinly coated with negatively charged mucin to which the positive charged surface of the lipsomes may bind.[13]

Niosomes and Discomes:

In order to circumvent some of the limitations encountered with liposomes, such as their chemical instability, the cost and purity of the natural phospholipids, and oxidative degradation of the phospholipids, niosomes have been developed. Niosomes are nonionic surfactant vesicles which exhibit the same bilayered structures as liposomes. Their advantages over liposomes include improved chemical stability and low production costs. Moreover, niosomes are biocompatible, biodegradable, and non-immunogenic[14]. They were also shown to increase the ocular bioavailability of hydrophilic drugs significantly more than liposomes. This is due to the fact that the surfactants in the niosomes act as penetrations enhancers and remove the mucous layer from the ocular surface. Non-ionic surface active agents based discoidal vesicles known as (discomes) loaded with timolol maleate were formulated and characterized for their *in vivo* parameters. *In vivo* studies showed that discomes released the contents in a biphasic profile if the drug was loaded using a pH gradient technique. Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.[15]

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.[16]

Contact lenses:

For prolongation of ocular residence time of the drugs, hydrophilic contact lenses can be used. Greater penetration of fluorescein has been reported by Bionite lens made from hydrophilic polymer (2-hydroxy ethyl methacrylate) in human.[22]

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 hours. Because of its structural stability, good biocompatibility and biological inertness, collagen film proved as a potential carrier for ophthalmic drug delivery system.[23]

Microemulsion:

Microemulsion is dispersion of water and oil stabilized using surfactant and co-surfactant to reduce interfacial tension and usually characterized by small droplet size (100 nm), higher thermodynamic stability and clear appearance. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol for eye diseases.[24]

Nanosuspensions:

Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect. For commercial preparation of nanosuspensions, techniques like media milling and high pressure homogenization have been used.[25]

Microneedle:

Microneedles are developed to deliver drug to posterior segment. Microneedle had shown prominent in vitro penetration into sclera and rapid dissolution of coating solution after insertion while in vivo drug level was found to be significantly higher than the level observed following topical drug administration like pilocarpine.[26]

Prodrugs:

The ideal prodrugs for ocular therapy not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility to such an extent that after corneal penetration or within the cornea they are either chemically or enzymatically metabolized to the active parent compound.[27]

Penetration Enhancers:

Penetration enhancers increases the permeability through corneal epithelial membranes and finally increases transport of drug across the cornea. Examples of enhancers include actin filament inhibitors, surfactants, bile salts, chelators, and organic compounds. But penetration enhancers themselves can penetrate the eye and may lead to unknown toxicological complications e.g., benzalkonium chloride (BAC) was found to accumulate in the cornea for days.[28]

Mucoadhesive Polymers:

They are basically macromolecular hydrocolloids with plentiful hydrophilic functional groups, such as hydroxyl, carboxyl, amide and sulphate having capability for establishing electrostatic interactions.42A mucoadhesive drug formulation for the treatment of glaucoma was developed using a highly potent beta blocker drug, levobetaxolol (LB) hydrochloride and partially neutralized poly acrylic acid (PAA).[29]

In-situ gel system:

Phase transition of the formulation from the liquid form to the gel or solid phase occurs when these systems instilled into the cul-de-sac of eye lead to increase the viscosity of a drug formulation in the precorneal region results in increased bioavailability, due to slower drainage from the cornea. These systems can be influenced by pH, temperature or by ion activation. A sol to gel system with mucoadhesive property to deliver the steroid fluorometholone to the eye was prepared by Middleton and Robinson.[30]

Particulates (nanoparticles and microparticles):

Nanoparticles are prepared using bioadhesive polymers to provide sustained effect to the entrapped drugs. An optimal corneal penetration of the encapsulated drug was reported in presence of bioadhesive polymer chitosan. Similarly Poly butyl cyanoacrylate nanoparticles, containing pilocarpine into collagen shields, showed greater retention and activity characteristics with respect to the controls.

Microspheres of poly lacto gylcolic acid (PLGA) for topical ocular delivery of a peptide drug vancomycin were prepared by an emulsification/ spray-drying technique.[31]

EVALUATION OF OCULAR DRUG DELIVERY SYSTEM[32]

IN-VITRO EVALUATION METHODS

Bottle method

In this method, dosage forms are placed in the culture bottles containing phosphate buffer at pH 7.4. The culture bottles are shaken in a thermostatic water bath at 37°C. A sample of medium is taken out at appropriate intervals and analyzed for drug contents.

Diffusion method

An appropriate simulator apparatus is used in this method. Drug solution is placed in the donor compartment and buffer medium is placed in the receptor compartment. An artificial membrane or goat cornea is placed in between donor and receptor compartment. Drug diffused in receptor compartment is measured at various time intervals.

Modified rotating basket method

In this method, dosage form is placed in a basket assembly connected to a stirrer. The assembly is lowered into a jacketed beaker containing buffer medium. The temperature of system is maintained at 37°C. A sample of medium is taken out at appropriate time intervals and analyzed for drug content.

Modified rotating paddle apparatus

In this method, diffusion cells (those that are used for analysis of semi-solid formulations) are placed in the flask of rotating paddle apparatus. The buffer medium is placed in the flask and paddle is rotated at 50 rpm. The entire unit is maintained at 37+0.5° C. Aliquots of samples are removed at appropriate time intervals and analyzed for drug content.

Flow through devices

There are obvious and insurmountable limitations to the official dissolution testing apparatus concerning maintenance of sink condition for drugs that saturate rapidly in large volumes of medium. The in- homo genicity of the solution in the rotating basket and poor reproducibility led to enhanced use of flow through devices. A constant fluid circulation apparatus is used as a flow through device. The apparatus consist of a glass dissolution cell, a continuous duty oscillating pump, a water bath and a reservoir. The dosage form is placed in the reservoir of the dissolution medium. The whole assembly is maintained at the temperature of 37°C. The dissolution medium is circulated through the apparatus. Sampling of medium is done at various time intervals and analyzed for drug content.

***In-vivo* methods**

•The drug delivery systems can be evaluated for its pharmacokinetic and pharmacodynamic profiles.

• The main objective of the pharmacokinetic studies is to determine the drug release from the dosage form to the eye.

• Rabbit is used as an experimental animal because of a number of anatomical and physiological ocular similarities and also due to larger size of the eye.

• Pharmacokinetic studies are performed by measuring drug concentration in various eye tissues eg. lens, cornea, iris, ciliary body, retina, sclera, aqueous and vitreous humour in rabbits.

The intraocular pressure of the eye is measured with a tonometer

• Ocular pharmacokinetic studies can also be carried out by tear fluid sampling, which is a non-invasive technique.

• Usually, disposable glass capillaries of 1ml capacity are used for sampling. The samples are collected from the marginal tear strip of the rabbits.

• Extreme care must be taken to avoid any corneal contact and possible induced lacrimation.

• To withdraw aqueous humour, rabbits are anaesthetized with ketamine and aqueous humour about 200ml is withdrawn from the anterior chamber using 1ml syringe with 26 gauge needle.

• Vitreous samples are also obtained with 20 gauge needle. The entire cornea, lens, and iris-ciliary body are also removed and analyzed for the drug content.

Sterility Testing

Sterility testing is performed for aerobic and anaerobic bacteria and fungi by using fluid thioglycolate and soybean casein digest medium respectively as per the Indian Pharmacopoeia. The method used for sterility testing is direct inoculation method.10 ml culture is added to 100 ml of culture medium. Both media are kept for incubation at 320C for 7 days and observed for any microbial growth. The sterility test results are compared with positive and negative controls.[33]

Safety Evaluation of Ocular Drug Delivery Formulations: Case Studies11

Injectable Therapies

Most injectable therapies are used intra vitreally, and there is a plethora of literature on the safety and pharmacokinetics of these formulations by this route, mostly conducted in rabbits. These intravitreal biologics produce ocular inflammation in animals at high doses, as detected by ophthalmoscopic and/or microscopic examination. There is often no prediction of which species Satya *et al.*, American Journal of PharmTech Research. 2011; 1(4): 72-92. ISSN: 2249-3387 87 www.ajptr.com are more sensitive to ocular inflammation induced by high doses of intravitreal biologics; rabbits are usually more sensitive to oligonucleotides than other species (Doug Kornbrust, personal communication, Preclinsight, Reno, NV). Both intravitreal fomiversen and pegaptanib cause ocular inflammation at lower doses in rabbits compared to monkeys and/or dogs. This may be because of the smaller vitreal volume, decreased retinal vascularity, and/or decreased aqueous humor outflow from the uveoscleral pathway in rabbits compared to larger species, which increase drug half-life. Toll-like receptors (TLRs) play a crucial role by recognizing proteins or DNA/RNA sequences belonging to infectious agents, and activation of TLRs results in the production of proinflammatory mediators and cytokines and links innate adaptive responses under pathological conditions, including the various regions and diseases of the eye. Therefore, it is possible that TLRs play a role in inflammation induced by biologicals injected in the eye. In addition, the influence of biologicals—for example, small interfering RNAs—on inflammatory responses depends on the contemporaneous administration of vehicles and the mode of delivery. Monkeys were more sensitive to ocular inflammation than rabbits at

high intravitreal doses of ranibizumab, with no apparent correlation between the degree of ocular inflammation and the appearance of serum antibodies to ranibizumab.

Microparticles:

Localized foreign-body reaction has been observed after intravitreal injection of microspheres loaded with Ganciclovir, PLA, or PLGA particles loaded with inert fluorochromes.

Nanoparticles:

Functionally, however, the intravitreal nanoparticle injections do not affect the ERG.The disadvantages of microparticles and nanoparticles is the risk of injection and that intraocular injections may cause vitreous clouding and periocular injections may cause a foreign-body response in the case of microparticles.

Liposomes: I

ntravitreally injected liposomes of antibiotics, antivirals, antifungals, and antimetabolic agents are less toxic than the free form because there is less free drug in contact with tissues. Liposomes also protect poorly stable drugs from degradation, such as phosphodiester antisense oligonucleotides and peptides.

Ocular Implants

Insertion of implants by incision is slightly more invasive compared to injection, and the normal wound-healing process takes place with both procedures. Pars plana incisions and injections have been studied in monkey eyes from 6 to 13 years following the procedure, and the scars were found to consist of fibrous tissue and blood vessels that extended from the epislera into the vitreous. There were quantitative but no qualitative differences between the two procedures, and there were ultrastructural features of mature scar tissue.

Nonbiodegradable Implants

The ocular safety of non-biodegradable implants of ganciclovir (Vitrasert) was studied in rabbits 80 days following implantation. No evidence of ocular inflammation by indirect ophthalmoscopy was observed, but lens opacification, cataracts, and retinal-detachment ERG changes were observed. There was no evidence of drug-related effects microscopically, although a chronic inflammatory reaction with multinucleated giant cells around the silk suture used to secure the implant to the sclera was observed. Although Vitrasert is an approved, marketed drug in the United States, the pharmacology review is unavailable on the FDA Web site.

Biodegradable Implants

Scleral plugs of biodegradable PLGA to deliver ganciclovir, doxorubicin, and fluconazole to the vitreous have been evaluated for ocular toxicity up to 24 weeks following implantation in

rabbits. Slit-lamp biomicroscopy showed no ocular inflammatory reactions, and no substantial changes were observed by ERG. Histology showed no abnormalities in the rabbit retinal tissue adjacent to the implant site and the posterior pole. Inflammatory cells infiltrated the matrix pore, and fibrous tissue closed the sclerotomy site. An intramscleral PLA implant of betamethasone evaluated for ocular toxicity for up to 16 weeks following implantation in rabbits showed no ERG changes and complete degradation of the implant at 16 weeks, with replacement by loose connective tissue and a few multinucleated giant cells with no histological retinal changes. Similarly, there was no ocular toxicity for up to 3 months following insertion of a PLGA cyclosporine implant into the anterior chamber in rabbits. Clinical safety evaluation of a PLGA rod implant of dexamethasone DDS following intravitreal insertion by sclerotomy in a phase 2 study in patients with persistent macular edema showed a mild increase in incidence of adverse events in the dexamethasone DDS treatment groups compared to the observation groups on day 8 that were expected as a result of the surgical procedure (hyperemia, pruritis, vitreous hemorrhage, and anterior chamber cells and flare. The rate of ocular adverse events after day 8 and up to study termination at day 180 was similar between treatment and observation groups, including no corticosteroid-induced cataract formation or increases in IOP.

CONCLUSION:

Ocular drug delivery systems provide local as well as systemic delivery of the drugs. The novel advanced delivery systems offer more protective and effective means of the therapy for the nearly inaccessible diseases or syndromes of eyes. Species and strain differences in ocular pigmentation and anatomy, retinal vasculature, and vitreal volume are important for designing and interpreting ocular toxicity studies and human risk assessment. Novel ocular drug formulations and sustained delivery are generally well tolerated, and inflammatory effects appear to be more pronounced in animals than humans. Although regulatory guidance is meagre for ocular drugs, review of FDA Pharmacology Reviews and selected literature can provide insights.

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