ISSN: 2230-7346
Available online http://WWW.JGTPS.COM
Research Article
Journal of Global Trends in Pharmaceutical Sciences

Vol.2, Issue 2, pp -131-148, April-June 2011

CURRENT STATUS AND ADVANCED APPROACHES IN OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT

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. The newly developed particulate and vesicular systems like liposomes, pharmacosomes and discomes are useful in delivering the drug for a longer extent and helpful in reaching the systemic circulation. The most recent advancements of the ocular delivery systems provide the delivery of the genes and proteins to the internal structures which were once inaccessible and thus are of great importance in treating the diseases which are caused due to genetic mutation, failure in normal homeostasis, malignancy but also maintaining the physiological function of eye. The review focuses on the developments achieved in this mode of delivery of the drugs along with the pros and cons associated with greater focus on the advanced delivery systems.

Key words: Advance ocular therapy, control drug delivery systems, corneal permeability, eye, ocular therapy, vesicular systems

INTRODUCTION:

Ocular drug delivery has remained as one of the most taxing task for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action.[1] Innovatory novel therapy for treatment of ocular diseases has emerged due to the recent advances in drug delivery approaches and material sciences. In the earlier period, drug delivery to the eye has been limited to topical application, redistribution into the eye following systemic administration or directs intraocular/periocular injections. Conventional drug delivery systems; which include solutions, suspensions, gels, ointments and inserts, suffer with the problems such as poor drainage of instilled solutions, tear turnover, poor corneal permeability, nasolacrimal drainage, systemic absorption and blurred vision.[2] Nanocarrier based approaches seem to be most attracting and are extensively investigated presently. it has been reported that particulate delivery system such as microspheres and nanoparticles; vesicular carriers like liposomes, niosomes, pharmacosomes and discomes improved the pharmacokinetic and pharmacodynamic properties of various types of drug molecules.[3] Emerging new controlled drug delivery systems such as dendrimers, microemulsions, muco-adhesive polymers, hydrogels, iontophoresis, collagenshelid, 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, nano technology, stem cell therapy as well as gene therapy, oligonucleotide and aptamer therapy, protein and peptide delivery, ribozyme therapy for treatment of various ocular diseases. Different drug delivery system for ocular therapy is shown in Figure 1.[4]

CONVENTIONAL DELIVERY SYSTEMS:

Eye Drops:

Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension.[5] Generally eye drops are used only for anterior segment disorders as adequate drug concentrations are not reached in the posterior tissues using this drug delivery method.[6] 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]

Ocuserts and Lacrisert:

Ocular insert (Ocusert) are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage.[9] Inserts are available in different varieties depending upon their composition and applications. Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca and was introduced by Merck, Sharp and Dohme in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea.[10]

VESICULAR SYSTEM:

Liposomes:

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 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 liposomes may bind.[13]

Niosomes and Discomes:

The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids. To avoid this niosomes are developed as 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. Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Vyas and co workers reported that there was about 2.49 times increase in the ocular bioavailability of timolol maleate encapsulated in niosome as compared to timolol maleate solution.[14] 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]

CONTROL DELIVERY SYSTEMS:

Implants:

For chronic ocular diseases like cytomegalovirus (CMV) retinitis, implants are effective drug delivery system. Earlier non biodegradable polymers were used but they needed surgical procedures for insertion and removal. Presently biodegradable polymers such as Poly Lactic Acid (PLA) are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs.[17] Intravitreal implants of fluocinolone acetonide were developed for the treatment of posterior segment and reported to control the ocular inflammation of retina.[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.[19] Positively charged 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.[20, 21]

Dendrimer:

Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility. Vandamme and co workers have developed and evaluated poly (amidoamine) dendrimers containing fluorescein for controlled ocular drug delivery. They determined the influence of size, molecular weight and number of amine, carboxylate and hydroxyl surface groups in several series of dendrimers. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups.[22]

Cyclodextrin:

Cyclodextrins (CDs) are cyclic oligosaccharides capable of forming inclusion complexes with many guest molecules.[23] CD complexes are reported to increase corneal permeation of drugs like dexamethasone, dexamethasone acetate, cyclosporine and pilocarpine resulted in higher bioavailability than the conventional eye drops.[24,25] This complexation of CD does not interrupt the biological membrane compared to conventional permeation enhancer like benzalkonium chloride. Due to inclusion, the free drug is not available, so drugs with inherent irritant properties can be successfully delivered by this approach. CD molecules are inert in nature and were found to be non irritant to the human and animal eye.[23]

Contact lenses:

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. 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.[26]

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. Collagen ophthalmic inserts are available for delivery of pilocarpine to the eye.[27]

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.[28] Selection of aqueous phase, organic phase and surfactant/co-surfactant systems are critical parameters which can affect stability of the system. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol for eye diseases.[29]

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.[30] The higher drug level in the aqueous humour was reported using Eudragit RS100 nanosuspensions for the ophthalmic controlled delivery of ibuprofen.[31]

Microneedle:

As an alternative to topical route Researchers have developed microneedle to deliver drug to posterior segment. The extent of lateral and transverse diffusion of sulforhodamine was reported to be similar across human cadaver sclera. 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.[32]

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. The partition coefficient

of ganciclovir found to be increased using an acyl ester prodrug, with substantially increased the amount of drug penetration to the cornea which is due to increased susceptibility of the ganciclovir esters to undergo hydrolysis by esterases in the cornea.[33]

Penetration Enhancers:

Transport of drug across the cornea is increased by increasing the permeability through corneal epithelial membranes. For such purpose Penetration enhancers can be used.[34] Examples of enhancers include actin filament inhibitors, surfactants, bile salts, chelators, and organic compounds. Selection of enhancer is critical due to unique characteristics and great sensitivity of the corneal conjunctival tissues. 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.[35]

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.[36] A 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). Complexes were prepared with varying degrees of drug loading, such that the same PAA chain would have free -COOH groups for mucoadhesion along with ionic complexes of LB with COO^- groups. Thin films of the complexes dissociated to release the drug by ion exchange with synthetic tear fluid.[37]

Phase Transition Systems/Insitu 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.[38]

PARTICULATES (NANOPARTICLES AND MICROPARTICLES):

The maximum size limit for microparticles for ophthalmic administration is about 5-10 mm above which a scratching feeling in the eye can result upon ocular instillation. That is why microspheres and nanoparticles are promising drug carriers for ophthalmic application.[39] 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.[40] Similarly Poly butyl cyanoacrylate nanoparticles, containing pilocarpine into collagen shields, showed greater retention and activity characteristics with respect to the controls.[41] Nanospheres made up of poly lactic acid (PLA) coated with Poly Ethylene Glycol (PEG) shown better efficacy compared to conventional dosage form of Acyclovir for the treatment of ocular viral infections.[42] Microspheres of poly lacto gylcolic acid (PLGA) for topical ocular delivery of a peptide drug vancomycin were prepared by an emulsification/ spray-drying technique.[43]

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. The polymer implant containing genetically modified human RPE cells secretes ciliary neurotrophic factor into the vitreous humour of the patients' eyes. ECT can potentially serve as a delivery system for chronic ophthalmic diseases like neuroprotection in glaucoma, anti-angiogenesis in choroidal neovascularization, anti-inflammatory factors for uveitis.[44]

Gene Therapy:

Along with tissue engineering, gene therapy approaches stand on the front line of advanced biomedical research to treat blindness arising from corneal diseases, which are second only to cataract as the leading cause of vision loss.[45] Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex

virus, have been manipulated for use in gene transfer and gene therapy applications.[46] Topical delivery to the eye is the most expedient way of ocular gene delivery. However, the challenge of obtaining substantial gene expression following topical administration has led to the prevalence of invasive ocular administration.[45] Retroviral vectors have been widely used due to their high efficacy; however, they do not have the ability to transduce nondividing cells, leads to restrict their clinical use.[46] The advanced delivery systems that prolong the contact time of the vector with the surface of the eye may enhance transgene expression, thereby facilitate non-invasive administration.[45]

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.[47] 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.[48]

Protein and Peptide therapy:

Delivery of therapeutic proteins/ peptides has received a great attention over the last few years.[49] The intravitreous injection of ranibizumab is one such example. The designing of optimized methods for the sustained delivery of proteins and to predict the clinical effects of new compounds to be administered in the eye, the basic knowledge of Protein and Peptide is required.[50] However, several limitations such as membrane permeability, large size, metabolism and solubility restrict their efficient delivery. A number of approaches have been used to overcome these limitations. Poor membrane permeability of hydrophilic peptides may be improved by structurally modifying the compound, thus increasing their membrane permeability. Ocular route is not preferred route for systemic delivery of such large molecules. Immunoglobulin G has been effectively delivered to retina by trans scleral route with insignificant systemic absorption.[49]

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. The release profiles vary with the kind of polymers used, their molecular weights, and the amount of drug in the plug. The plugs are effective for treating vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vitrectomy.[51]

siRNA therapy:

For various angiogenesis-related diseases, the use of siRNA is considered as a promising approach.[52] Feasibility of using siRNA for treatment of choroidal neovascularization has been demonstrated using siRNA directed against vascular endothelial growth factor (VEGF) or VEGF receptor 1 (VEGFR1), and both of these approaches are being tested in clinical trials. Topical delivery of siRNAs directed against VEGF or its receptors has also been shown to suppress corneal neovascularisation. siRNA has become a valuable tool to explore the potential role of various genes in ocular disease processes. It appears that siRNAs may be valuable in the pathogenesis and development of new treatments for several ocular diseases, based on in vivo and in vitro studies.[53] However, its use in vivo remains problematic, largely due to unresolved difficulties in targeting delivery of the siRNA to the tumor cells. Viral gene delivery is very efficient however it currently lacks adequate selectivity for the target celltype. New encapsulated siRNA have been developed using liposomes, coupled-antibodies or others polymer vesicles. Therapeutic approach using siRNA provides a major new class of drugs that will shed light the gap in modern medicine.[52]

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. A number of factors have been

determined to contribute to the efficacy of antisense ON. One primary consideration is the length of the ON species. Lengths of 17–25 bases have been shown to be optimal, as longer ONs have the potential to partially hybridize with nontarget RNA species. Biological stability is the major barrier to consider when delivering both DNA and RNA oligonucleotides to cells. Protection from nuclease action has been achieved by modification of phosphate backbones, sugar moiety, and bases.[54]

Aptamer:

Aptamers are oligonucleotide ligands that are used for high-affinity binding to molecular targets.[55] They are isolated from complex libraries of synthetic nucleic acid by an iterative process of adsorption, recovery, and reamplification. 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.[55]

Ribozyme therapy:

RNA enzymes or ribozymes are a relatively new class of single-stranded RNA molecules capable of assuming three dimensional conformations and exhibiting catalytic activity that induces site-specific cleavage, ligation, and polymerization of nucleotides involving RNA or DNA. They function by binding to the target RNA moiety through Watson-Crick base pairing and inactivate it by cleaving the phosphodiester backbone at a specific cutting site. A disease named, Autosomal dominated retinitis pigmentosa (ADRP) is caused by mutations in genes that produce mutated proteins, leading to the apoptotic death of photoreceptor cells. Lewin and Hauswirth have worked on in the delivery of ribozymes in ADRP in rats shows promise for ribozyme therapy in many other autosomal dominant eye diseases, including glaucoma.[54]

Figure-1: Different drug delivery systems for ocular therapy

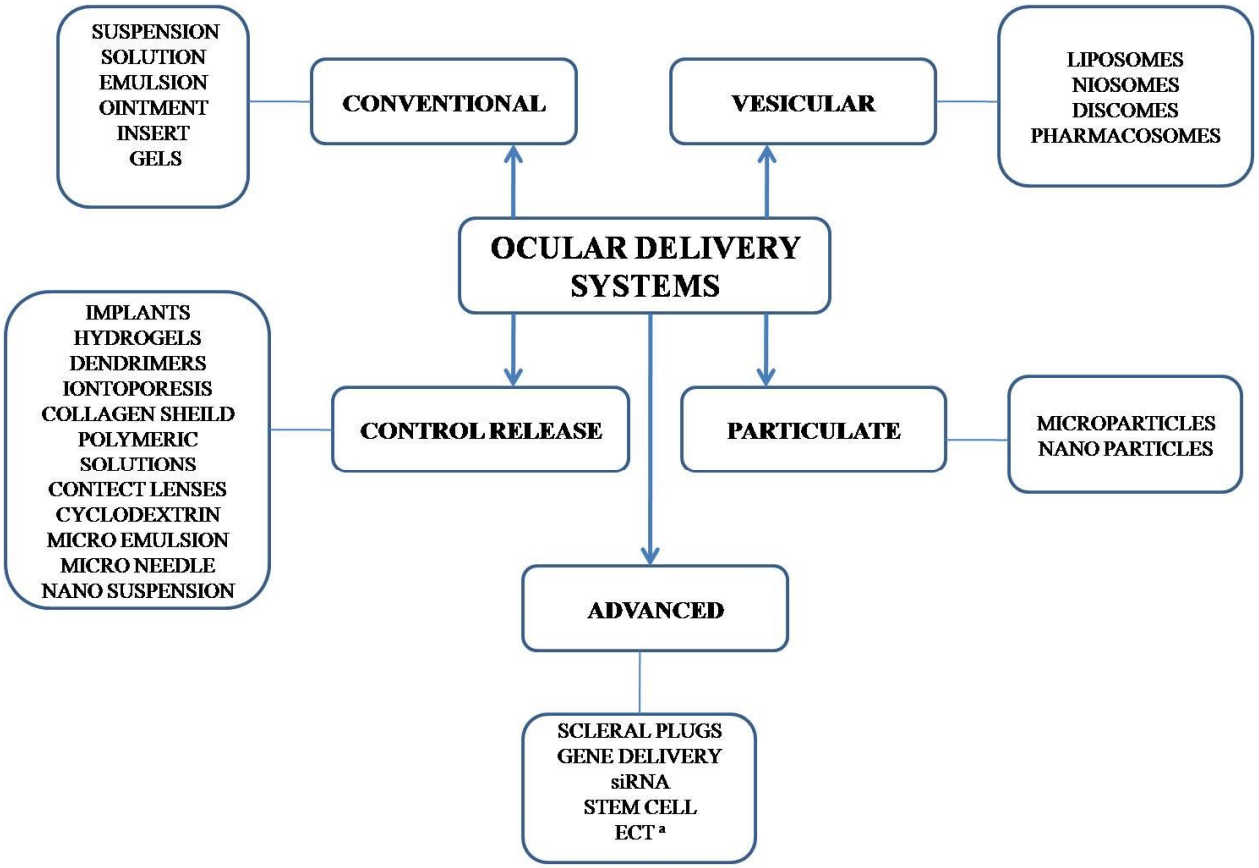

Fig 1. Different drug delivery systems for ocular therapy[4]
[a] Encapsulation Cell Technology

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. 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. Further developments are preferable which will eliminate the cons of these available advanced delivery systems and readily acceptable with the regulatory authorities as well.

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