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Research Article

Comparative review on conventional advanced occular drug delivery system

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ABSTRACT

Eye diseases are commonly encountered in a day to day life, which are most interesting and challenging for scientists. A newly development and particulate vesicular systems like liposomes, pharmacosomes and discomes are useful in delivering the drug for longer extent and helpful in systemic circulation. When the eye drops is administered in the inferior fornix of the conjunctiva, a very minute 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. The unique anatomy and physiology which content various type of barrier such as the different layer of cornea, sclera and cornea and retina. Including blood aqueous and blood retinal barrier, coroidal and conjuctival blood flow these review focuses on recent development in the convectional ophthalmic drug delivery system for eye having eye drop, eye ointment, aqueous gel, solid matrices and devices, nano-suspension,nano-particles, liposomes, neosomes, and ion-tophorosis to improve ophthalmic bioavailability of drug to an anterior chamber of the eye. Ocular drug delivery system provides the delivery of genes, and proteins to internal structure, which is inaccessible. In these review non conventional technologies such as nanotechnology, microspheres, micro-emulsion and ocular inserts would be developed in the pharmaceutical market.

Keywords: Eye; Ophthalmic Drug Delivery; Nanotechnology; Microsphere; Micro emulsion

INTRODUCTION

Relevant application of drugs to the eye is the well established route of administration in the treatment of various eye diseases like dryness, conjunctiva, eye flu, etc. The protective mechanisms of the eye such as blinking, baseline and reflex lacrimation, and drainage decrease the bioavailability of drug and also help to remove quickly foreign substances like the dust particles bacteria, including drugs, from the surface of the eye (Robinson, J.R., 1986). There are many eye diseases, which can be affected to the eye and also eye vision. Therefore, marketed ophthalmic dosage formulations are classified as conventional and non-conventional drug delivery systems. There are most commonly accessible to ophthalmic preparations such as drops and ointments about 70% of the eye dosage formulations in the market. But these preparations when instilled in to the eye they are rapidly drained away from the ocular surface due to blinking tear flow and lacrimal nasal drainage from the eye. Only a little amount of drug is available for its therapeutic effect resulting in frequent dosing application in the eye. So overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nano-suspension, micro-emulsion, iontophoresis and ocular inserts have been developed in last three decades enlarge the bioavailability of the drug as a sustained and controlled approach (Binstock, E.E., & Domb, A.J., 2006).

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Eye Anatomy and Physiology

The human eye is the important sense organ of the body, and its anatomy is quite complex. Eye can refract light and produce a focused image that can stimulate nervous system and allow the ability to see. The Structure of the eye and different Parts of the eye.

Aqueous Humor: It is a jelly-like substance situated in the frontal chamber of the eye.

Choroid: The choroid layer is located behind the retina and absorbs unused radiation.

Ciliary Muscle: The ciliary muscle is a ring-shaped muscle sensitively involved to the iris. It is important because contraction and relaxation of the ciliary muscle control the shape of the lens.

Cornea: Cornea is a clear transparent epithelial membrane. Light rays pass through the cornea to reach the retina the cornea is convex anterior and refracting light rays to focus them on the retained.

Iris: The iris is the visible coloured part of the eye and extends anteriorly from the ciliary body, lying at the

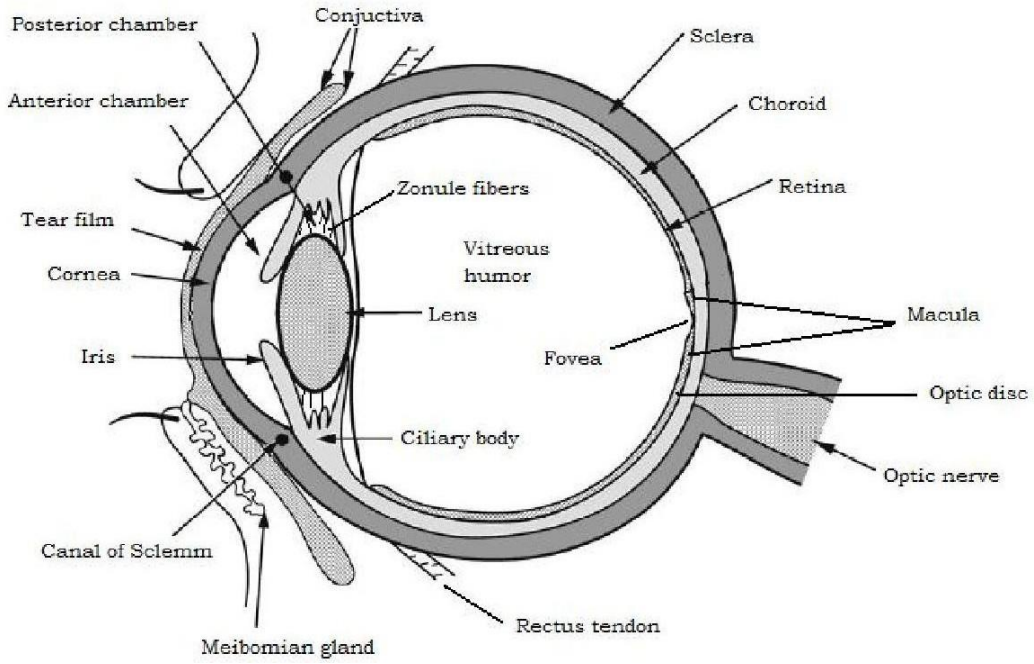

Figure 1: Structure of the eye

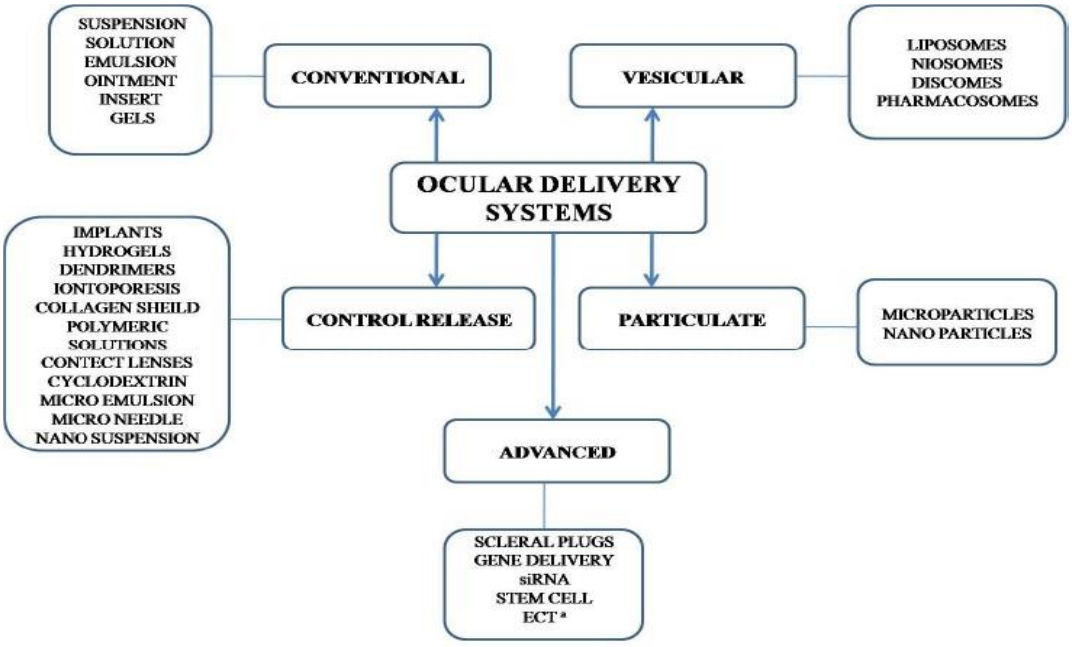

Figure 2: Different drug delivery systems for ocular therapy

rear the cornea and in front of the lens. It divides the anterior segment of the eye into anterior and posterior chambers, which contain aqueous fluid secreted by the ciliary body. The iris is abounding by parasympathetic and sympathetic nerves. Parasympathetic prompt constricts the pupil and sympathetic stimulation dilates it.

Fovea: The fovea is a small depression (approx. 1.5 mm in diameter) in the retina. This is the part of the retina in which high-resolution vision of fine detail is feasible.

Hyaloid: The hyaloid diaphragm divides the aqueous humour from the vitreous humour.

Lens: The lens on the eye is a flexible unit that consists of layers of tissue enclosed in a tough capsule. It is suspended from the ciliary muscles by the zonule fibers. Papilla: The papilla is also known as the "blind spot" and is located at the position from which the optic nerve leaves the retina.

Pupil: The pupil is the aperture through which light - and hence the images we see and "perceive" - enters the eye. This is formed by the iris. As the size of the iris notes only increases but also the size of the pupil decreases, likewise.

Retina: The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, then the hyaloid and finally, the vitreous humour be-

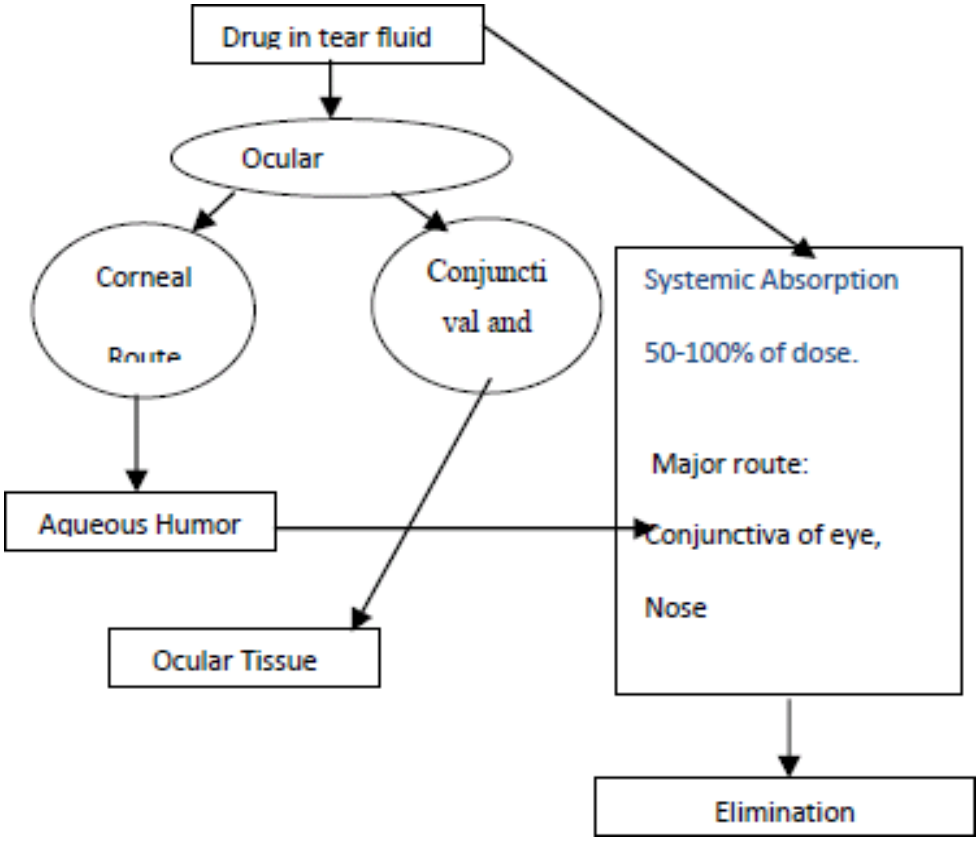

Figure 3: Route of administration to elimination in opthalmic drug delivery

fore getting the retina. The retina contains photosensitive elements that convert the light they detect into nerve impulses that are then sent to the brain along the optic nerve.

Optic Nerve: The optic nerve is the second cranial nerve and is responsible for vision. Each nerve contains roughly one million fibres transmitting information from the rod and cone cells within the retina.

Advantages of controlled ocular drug delivery systems

- Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to the corneal surface.
- To provide targeting within the ocular globe to prevent the loss to other ocular tissues.
- To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
- To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
- To provide better housing of a delivery system.

Disadvantages

Various disadvantages of an ocular drug delivery system are given below.

- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen (Yusuf, A. &Lehmussaari, K., 2006).

Ophthalmic drug product may be classified according to route of administration

1. Topical

2. Intraocular

3. Systemic (oral and venous).

Absorption of drugs into the eye takes place either through corneal or non-corneal route.

Maximum absorption takes place through the cornea, which leads the drug into aqueous humor. Loss of the administered dose of drug, takes place place through spillage and removal by the naso-lacrimal apparatus. The non corneal route involves the absorption across the sclera and conjunctiva into the intra ocular tissues.

Table 1: List shows various ophthalmic marketed products in different formulation

Brand name	Drug	Dosage form	Use
Dichol	Carbachol	Sterile solution and prefilled syr-ings	in the treatment of glaucoma, also used in ophthalmic surgery.
Dilon	sodium hyaluronate	A sterilepyrogenic solution	use to protect eye tissues such as corneal endothelium during cataract removal, corneal transplant and glau-coma surgery.
REFRESH TEARS®	Hydroxypropyl-methylcelluose	Drops	As a eye lubricants and dryness of eye
RESTASIS®	Cyclosporine	emulsion	chronic dry eye (keratoconjunctivitis-sicca)
sREFRESH® Classic	Artificial tear fluid	convenien single use vials	moisturizes and relieves dry, irritated eyes
ciplox®	Ciprofloxacin	Drops	Eye infection and conjunctivitis
Geltear/ Vis-cotear	Corbomer	Bioadhesive gel	Lubricants, treatment of the symp-toms of dry eye such as soreness, burning, irritation or dryness
Macugen	Polyethylene glycol and vas-cular endothelial growth factor aptamer	Sterile solution intravitreous	Age-related macular degeneration
Timolol® XE	Timolol maleate	In-situ gel	Dry eye and keratoconjuctivitis
Ketolagsopth	Triaamicinolonemaleate and gramicidin	Ointment	Anti-infective, Anti-inflammatory and antiallergics
Acivir eye	Acyclovir	Ointment	Anti-infective
Ocupol	Polymixin-B sulphate	Drops and oint-ment	Bacterial infection, stye, corneal ulc-er, ulcerative blepharitis
PRED FORTE®	prednisolone acetate	suspensions	Antiallergic and anti-inflammatory

Conventional Drug Delivery Systems

Eye Drops

Drugs which are active in eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension. Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can convince retention of a solution into the eye (Mueller, W.H.&Deardroff, D.L., 1956). Less than5 % 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 (Urtti, A.&Pipkin, J.D., 1990). When the eye drops is administered in the inferior to the mix of the conjunctiva, the very minute 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 (Geroski, D.H, & Edelhauser, H.F., 2000).

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 these dosage form eyelids can limit its use. Pilopine HS gel containing pilocarpine was used to provide sustain the 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 the duration of action and enhancing ocular bioavailability of drugs (Sultana, Y & Jain, R., 2006).

Nanotechnology in ocular drug delivery system

The word Nanotechnology, arise from the greek word nano meaning drawf, technology means the application to the engineering, electronics, physical, material science medical and manufacturing at a molecular and a submicron level. Early promoter of nanotechnology, Albert franks, defined it as that area of science and technology where dimensions and tolerance are in the range of 0.1-100nm.The nanotechnology based drug delivery system like nanosuspension, solid nanoparticle, microemusion and liposomes have developed to solve the solution of various solubility-related problems of poorly water soluble drugs, likes dexamethsone, budenoside, gancyclovir and so on (Sahoo, S.K & Labhasetwar, V., 2003). Due to relative properties of the particle size charge, surface properties and relative hydrophobicity of (molecules) nananoparticles are developed to be successfully used in crossing the over-

coming absorption barriers (Kayser, O., 2005). Furthermore, nanocarriers are critical in order to exploit the emerging in pharmaceutical field of drug delivery systems and new gene therapies for the treatment of ocular disorders and other alternatives for topical drug delivery involve the use of liposomes, nano spheres, nanosuspension and nanoparticles and so on.

Different nanoparticles based drug delivery systems are,

Microemulsion

Microemulsions were first described Hoar and Schulman. Microemulsion is a dispersion of water and oil that formulated with surfactants and co-surfactants in order to stabilize the surface tension of emulsion (Brigger.2002). Microemulsions have a transparent appearance, with thermodynamic stability and a small droplet size in the dispersed phase (<1.0µm). Microemusion is an interesting alternative to ophthalmic formulation, due to their intrinsic properties and specific structure. They can be easily prepared through emulsification method, easily sterilized, and are more stable and have a high capacity for dissolving drugs (Fialho, S.L., 2004) The ophthalmic o/w Microemusion could be advantageous over other formulations, because the presence of surfactants and co-surfactants increase the dug molecules permeability, thereby increasing bioavailability of drugs. Due to, these systems act as penetration enhancers to facilitate corneal drug delivery (Vandamme, T.F., 2002). The in-vivo experiments and preliminary studies in healthy volunteers have occurred a delayed effect and an increase in the bioavailability of the drug. This mechanism is based upon the adsorption of the nanodroplets representing the internal phase of the microemulsions, which act as a reservoir of the drug on the cornea and should decrease their drainage in the limit (Lawrence, M.J., 2000). Indeed, in 2002 the FDA approved the clinical use of an anionic emulsion containing cyclosporine a 0.05% for the treatment of the chronic dry eye. A similar formulation has recently been approved in the treatment of ocular inflammation. In the same field, a non-medicated anionic emulsion for eye lubricating purposes, in patients suffering from moderate to severe dry eye syndrome and two lipidicemulsions, indicated in the restoration of the lipid layer of the lacrimal fluid, have been launched in the US and European markets the cationic nanoemulsions have also made their way to the market.

Namely, the product Cationorm® was launched in the European market for the treatment of dry eye symptoms and two more products, based upon the same technology and intended to deliver cyclosporine A, are currently under registration or under clinical evaluation(Phase III).Water-in-oil microemulsions (w/o ME) capable undergoing a phase-transition to lamellar liquid crystals (LC) or continuous ME upon aqueous dilution were formulated using Crodamol, Sorbian monolaurate and polyoxyethylene 20 sorbitanmono-oleate, an alcohol or alkanediol as cosurfactant and water. The hypothesis that phase-transition of ME to LC may be induced by tears and serve to prolong precorneal retention was tested. The ocular irritation potential of components and formulations was assessed using a modified hen's egg chorioallantoic membrane test (HET-CAM), and the preocular retention of selected formulations were investigated in rabbit eye using gamma scintigraphy. showed that sorbitan monolaurate, polyoxyethylene 20 sorbitanmono-oleate and Crodamol ethyl oleate were non-irritant. However, all other co surfactants investigated were irritant and their irritation was dependent on their carbon chain length. Microemulsion formulated w/o without co surfactant showed a protective effect when a strong irritant (0.1 M NaOH) was used as the aqueous phase. Precorneal clearance studies revealed that the retention of colloidal and coarse dispersed systems was significantly greater than an aqueous solution with no significant difference between ME systems (containing 5% and 10% water) as well as o/w emulsion containing 85% water. Conversely, a LC system formulated without co surfactant displayed a significantly greater retention compared to other formulations.

Nanoparticles

Nanoparticles are the particle with a diameter of less than 1µm, containing of various biodegradable materials, such as natural and synthetic polymer, liposomes, lipids, phospholipids and even inorganic material. Biodegradable nanoparticles of polymers like polylactide (PLAs), polycyano acrylate, poly (d,l-lactides), natural polymers can be used effectively for efficient drug delivery to the ocular tissues.Pre-clinical Studies by Bourges in rabbits shows that nanoparticles of different size and electric charge, when injected into the vitreous, migrate through the retinal layers and tend to accumulate in the retinal pigment epithelium (RPE) cells. They found that presence of nanoparticles within the RPE cells up to four months after a single intra vitreous injection (Alany, R.G. & Davies, N.M., 2006). The movement of nanoparticles in the internal limiting-membrane (ILM) because of the modification of the vitreous interface structuresecondary to the presence of the PLA and poly (d,l-lactide-co-glycolide) (PLGA) (Bourges, J.L., 2003). The encapsulated nanospheres may also increase when in such as bioavailability of ophthalmic delivery. Recently, it reported that non-biodegradable polystyrene nanospheres observed within the neuroretina. Generally, nanoparticles act at the cellular level and followed to endocytosed/phagocytosed by cells, then resulting cell internalization of the encapsulated drug. The surface charge and the binding of the drug to the particles were found to be more important factors in the drug loading in case of nanoparticles. It proved, though being fully encapsulated in poly butyl cyano acrilate nanospheres, the drug progesterone not released properly, because of strong interaction between the drug and the poly-

mer(Lee, V.H.L., 1986). The albumin nanoparticles was used to a very efficient ocular delivery system for like CMV retinitis. They are biodegradable, non-toxic and have non-antigenic effects. Since high content of charged amino acids, albumin nanoparticles allow the adsorption of positively charged gancyclovir or negatively charged particles like oligonucleotides that increased the bioavailability (Lee, V.H.L., 1986). However, nanoparticles of natural polymers which are made up of like sodium alginate, chitosan, are very effective in intraocular penetration for some specific drugs, because of contact time with corneal and conjunctival surfaces studies results show the bioavailability of encapsulated indomethacin doubled when Poly(epsiloncaprolacton) (PECL) nanoparticles were coated with Chitosan (Irache, J.M., 2005). Greater corneal penetration enhancement was occurred, when PECL nanoparticles were coated with polyethylene glycol (PEG). All these studies lead us to believe that nanoparticles have great potential ophthalmic delivery systems for ocular tissues (Calvo, P., 1997.).

Nanosuspensions

Nanosuspension contains of pure, hydrophobic drugs (poorly water soluble), suspended suspended in an appropriate dispersion medium. Nanosuspension technology is utilized for drug components that form crystals with a high-energy content molecule, which renders them insoluble in either hydrophobic or hydrophilic media (Campos, A.M.D., 2003). Although nanosuspensions offer advantages such as more residence time in a culde-sac and avoidance of the high tonicity created by water-soluble drugs, their performance depends on the intrinsic solubility of the drug in lachrymal fluids after administration. Thus, the intrinsic solubility rate of the drug in lachrymal fluid controlled its releases and increases ocular bioavailability. However, the essential dissolution rate of the drug after application varies because of the constant inflow and outflow of lachrymal fluids. However, a nanosuspension, by their inherent ability to improve the saturation solubility of the drug in media, also represents an ideal approach for ophthalmic delivery of hydrophobic drugs in the eye. Moreover, in earlier nanoparticulate nature of the drug allows to prolonged residence (ocular surface) in the cul-de-sac, giving sustained release from the drug. To achieve sustained release from the drug, nanosuspensions can be incorporated or formulated with a suitable hydro gel or mucoadhesive base or even in ocular inserts (Kayser, O., 2005). Recent approaches been developes desired to release the drug is the formulation formulated with polymeric nanosuspensions particles loaded with the drug. Thebioerodible as well as water soluble/permeable polymers could be used to sustain and control the release of the medication. The nanosuspensions can be formulated by using the quasiemulsion and solvent diffusion method (Pignatello, R. &Bucolo, C 1998). The using acrylate polymers such as Eudragit RS 100 and Eudragit RL 100 in polymeric nanosuspensions of flurbiprofen and ibuprofen have been successfully formulated, and these have been characterized for drug loading, particle size, zeta potential, in-vitro drug release, ocular tolerability and invivobiological performance in animal (BeharCohen, F.F; Gautier, S., 2002). The flu is a non-steroidal anti-inflammatory drug (NSAID) that using in inflammation and antagonizes papillary construction during intraocular surgery. Since the flu-loaded Nanosuspensions are formulated by the quasiemulsion solvent diffusion (QESD) method in which generally avoids using of toxic chemical. They proved to great potential for ophthalmic application (Kalia, Y.N. &Naik, A., 2004).

Iontophoresis

Iontophoresis technique is used to depth penetration of topically applied drug loaded nanoparticles iontophoresis is a method for enhancing charged drug penetration in to anterior and posterior ocular structures, by using a low electric current. The mechanisms of drug penetration are followed by iontophoresis of electrorepulsion elecro-osmosis and current-induced tissue damage (Lee, V.H.L. & Robinson, J.R., 1986). However, each drug has to be evaluated for its penetration capacity and pharmacokinetically profile, due to different physicochemical properties to the drug molecules. This novel approach of charged nanoparticles iontophoresis can benefit from deep penetration, regardless of drug's ionic activity strength and diffusion capacity in ocular tissues, (Lang, J. C., 1995). It controlled and sustained release from the drug for better therapeutic activity, targeting to a specific desired tissue and localized tissues (Alany, R.G., & Davies, N.M., 2006).

Advantages

- Increases the bioavailability and decreases the adverse effects.
- Iontophoresis of charged nanoparticles as drug carriers, providing a long duration therapeutic activity.
- Topical ophthalmic preparation and easy to apply.
- Good drug penetration to the anterior and posterior segments of the eye by topically.

Advanced drug delivery system

Cell Encapsulation

The entrapment of immunologically isolated cells with hollow fibres or micro capsules before their administration to 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 the ciliary neurotrophic factors into the vitreous humour of the patients' eyes. ECT can potentially serve as a delivery system for chronic ophthalmic diseases like neuro protection in glaucoma, anti-angiogenesis in

choroidal neovascularization, anti-inflammatory factors for verities (Tao, W., 2006).

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. Several kinds of viruses, including adenovirus, retrovirus, adeno-associated virus, and herpes simplex, which are second only to cataract as the leading cause of vision loss. 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. Topical delivery to the eye is the most convenient 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. 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 (Klausner, E.A.& Chapman, R.L., 2007). The advanced delivery systems that prolong the contact time of the vector with the surface of the eye may enhance trans gene expression, there by facilitate non-invasive administration.

Stem cell Therapy

Emerging cell therapies for their storation of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina (Selvam, S.& Thomas, P.B., 2006). 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 the corneal epithelium. The sources of limbal cells include donors, auto grafts, cadaver eyes, and (recently) cells grown in culture. Stem-cell Therapy has demonstrated great success for certain maladies of the anterior segment (Pellegrinia, G. &Arsenijevicc, Y., 2007).

Protein and Peptide therapy

Delivery of therapeutic proteins/peptides has received a great attention over the last few years. The intra vitreous injection of ranibizumab is one such example (Levin, L.A.&Ritch, R., 2004). The designing of optimized methods for the sustained delivery of proteins and to predict the clinical effects of new compounds to be administered to the eye, the basic knowledge of Protein and Peptide is required. 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 a large molecules. Immunoglobulin G has been effectively delivered to the retina by transscleral route with insignificant systemic absorption (Ambati, J.& Gragoudas, E.S., & Miller, J.W., 2000).

Scleral Plug therapy

Scleral plug can be implanted using a simple procedure at the pars plana region of the 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, there in the plug. The plugs are effective for treating vitreo retinal diseases such as proliferatives vitreo retinopathy. Cytomegalo virus retinitis responds to repeat intravitreal injections and for Vitreo, retinal disorders that require vitrectomy (Sanharawi, M.E.& Kowalczuk., 2010).

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 unreachable diseases or syndromes of eyes. The most widely developed drug delivery system is represented by the conventional and non-conventional ophthalmic formulations to polymeric hydrogels, nanoparticle and nanosuspensions, microemulsions, iontophoresis and ocular inserts. Ocular delivery based formulations could be making more acceptable and admirable drug delivery systems by using the biodegradable and water soluble polymers.

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