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A Review on Current Perspectives and Recent Advances in Ocular Drug Delivery System

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Abstract : The pitch of ocular drug delivery is one of the most appealing and challenging endeavours faced by the pharmaceutical scientist for past 10- 20 years. In ophthalmic formulation for the eye; like solutions, suspensions, and ointments are available in the market show drawbacks such as increased precorneal elimination, blurred vision and high variability in effectiveness. Eye is most remarkable organ due toits drug disposition features. Ideal ocular drug delivery must be able tosustain the drug release and to remain in the vicinity of front of the eye for prolong period oftime. Consequently it is imperative to optimize ocular drug delivery, one of the way to do sois by addition of polymers of various grades, improvement of viscous gel, development ofcolloidal suspension or using erodible or non erodible insert to prolong the precorneal drugretention. Lastly understanding species anatomical differences is useful for interpreting toxicological and pathological responses to the eye and is significant for human risk assessment of these important new therapies for ocular diseases. "Ocular drug delivery is one of the most interesting and exigent endeavours facing the pharmaceutical scientist. The challenge to the formulator is to outwit the protective barriers of the eye without causing permanent tissue damage.
Keywords : Intravitreal, ocular drug delivery, ocular insert**,** subconjunctival.

Introduction

The field of Ocular drug delivery has remained as one of the most taxing task & most fascinating and challenging Endeavours facing for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action[1, 2].Eye is most interesting organ due to its drug disposition features. In the earlier period, drug delivery to the eyehas been limited to topical application,redistribution into the eye followingsystemic direction or directsintraocular/periocular injections but now-a-days, Topical application of drugs to the eye is the well renowned route of administration for the healing of various eye diseases like dryness, conjunctiva, eye flu etc. For ailments of the eye, topical administration is usually preferred over systemic administration, before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route has to cross the precorneal barriers. These are the first barriers that slow the infiltration of an active ingredient into the eye and consist of the tear film and the conjunctiva.

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The medication, upon instillation, stimulates the protective physiological mechanisms, i.e., tear production, which exert a formidable defence against ophthalmic drug delivery[3]. The protective mechanisms of the eye such as Blinking, baseline and reflex lachrymator, 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[4].There are many eye diseases which can affect the eye and also eye vision. Therefore marketed ophthalmic dosage formulations are classified as conventional and non-conventional (newer) drug delivery systems. There are most frequently available ophthalmic preparations such as drops and ointments about 70% of the eye dosage formulations in market[5, 6].

Conventional drug delivery systems; which include solutions such as eye drop, a dosage form consisting of buffered, isotonic, aqueous solution or suspensions of the drug, 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[13]. Standard dropper used with conventional ophthalmic solution delivers about 50-75µl per drop and portion of these drops quickly drain until the eye is back to normal resident volume of 7µl. Because of this drug loss in front of the eye, very little drug is available to enter the cornea and internal tissue of the eye.

Actual corneal permeability of the drug is quite low and very small corneal contact time of the about 1-2 min in humans for instilled solution commonly lens than 10%[4].Consequently only small amount actually penetrates the cornea and reaches intraocular tissue[5] inhibited drug delivery to the eye is restricted due to these limitation imposed by the efficient protective mechanism[16]. Only a small amount of drug is available for its therapeutic effect resultant in frequent dosing application to the eyeSo overcome to these problems newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, into phoresis and ocular inserts have been developed in last three decades increase the bioavailability of the drug as a persistent and controlled manner.

Nanocarrier based approach seem to bemost attracting and are broadly investigated presently. it has been reportedthat 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[17]. 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 reward over conventional systems as they increase the efficiency of drug delivery by improving the release contour and also reduce drug toxicity. The rapid progress of the biosciences opens new potential 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 cure 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. It also provides the limitations of conventional delivery with a view to find contemporary approaches like vesicular systems, nano technology, stem cell therapy as well as gene therapy, oligonucleotide and aptamertherapy, protein and peptide delivery, ribozyme therapy for healing of various ocular diseases.

Ideal ophthalmic drug delivery must be able to uphold the drug release and to remain in the vicinity of front of the eye for protract period of time. Consequently it is imperative to optimize ophthalmic drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gel, development of colloidal suspension or using erodible or non erodible insert to prolong the precorneal drug retention. Bioadhesive systems utilized can be either microparticlesuspension[6]or polymeric solution. For petite and medium sized peptides major resistance is not size but charge, it is originated that cornea offers more conflict to negatively charged compounds as compared to positively charged compounds.

Following characteristics are required to optimize ocular drug delivery system:

- Good corneal penetration.
- Prolong contact time with corneal tissue.
- Simplicity of instillation for the patient.

- Non irritative and comfortable form (viscous solution should not provoke lachrymal secretion and reflex blinking)suitable rheological properties and concentrations of the viscous system.
- Following mucoadhesive polymers are used most of the times in various ophthalmic drug delivery systems.

Conventional Ocular Drug Delivery Systems

The conventional ophthalmic drug delivery systems are used in today's ocular disease treatment and preventions are solutions, suspensions, ointments and Bioadhesive polymer gel. In spite of considerable criticisms over the efficacy and efficiency of these conventional systems, such as limitation are such as bioavailability, sterility, dosing administration. So these preparations are comprehensively used in a majority of commercial products in pharmaceuticals market.

Liquids

The most popular and pleasing state of dosage forms for the eye because the drug in dissolved state results in the fastest inclusion from the eye surface or in the eye after passage through the cornea or the conjunctiva[7].

Solutions

Ophthalmic solutions are sterile solutions, essentially free from foreign particles, suitably compounded and packaged for instillation into the eye. Most widely used dosage forms to control drugs for the ocular therapy.

Aqueous ophthalmic solutions are generally manufactured by a process in which the dissolution of the active and other inactive ingredient (excipients/additives) after sterilization is achieved by application of heat or by sterile filtration. This prepared sterile solution may further be then mixed with other components such as sterilized solutions of viscosity including agents and additives. The batch is made upto final volume with additional sterile water. The stability of ophthalmic solutions and other dosage forms determine the shelf life and cessation dating of the product. The drug product is analyzed for physical, chemical and microbiological parameters throughout the shelf life[8].

Advantages:

- Simplicity of large scale manufacture

Disadvantages:

- Very short time interval of the solution due to its rapid elimination from the eye.
- The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration and the instilled volume.
- Its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage),
- The instability of the dissolved drug, and the necessity of using preservatives[3].

Sprays

Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for cycloplegic examination.

Aqueous Suspensions

Ophthalmic suspensions products is another part of the ocular drug delivery system and have many distinct recompense over others formulation. These are the best suited dosage form for drugs with dawdling dissolution. These dosage forms show significantly higher and sustained delivery in the eye. Recently developed drugs are generally hydrophobic poor solubility in water and aqueous medium. Formulation offers a sterile, preserved, effective, stable and pharmaceutically elegant. Ophthalmic suspensions are more complex and exigent when compared to ophthalmic (aqueous) solutions[9].

An ophthalmic suspension contains many inactive ingredients such as dispersing and wetting agents, suspending agents, buffers and preservatives. Wetting agents are used to decreases the contact angle between the solid surface and the wetting liquid. Generally used wetting and solubilizing agents are Benzalkonium chloride, Benzethonium chloride, Cetylpyridinium chloride, Nonoxynol 10, Octoxynol 9, Poloxamer, Polyoxyl 50 stearate, Polyoxyl 20 cetostearyl ether, Polyoxyl 40 stearate.

Suspending agents are used to avoid sedimentation and affecting the rheological behavior of a suspension. An ideal suspending agent should have to produce a structured vehicle and it should be inert and non-toxic. Generally ophthalmic suspension used suspending agents are includes cellulosic derivatives such as methyl cellulose, caboxy methyl cellulose, and hydroxyl propyl methyl cellulose, synthetic polymers such as carbomers, poloxamers, and polyvinyl alcohol. The selection of buffers and preservatives for suspension ophthalmic solutions in almost same as aqueous except that they must also be compatible with the flocculating systems.

In most ophthalmic suspension, the average particle size is less than 10 μm. The most competent method of producing such particle size is by dry milling. However, we milling may be desirable for potentially explosive ingredients. Other methods of particle size reduction include micro-pulverization, grinding, and controlled precipitation[10].

Upon administration into eye, particles reside at the delivery site and the drug is released from the particle through diffusion, chemical reaction, or ion-exchange mechanism. Certain technological problems faced with these formulations include the production of stable suspensions, uniform dose per unit volume, efficient drug entrapment, reproducible and large-scale manufacture, and uniform particle size.

The formulation of a ophthalmic suspension many problem occurred such asnon-homogeneity of the dosage form, settling of particles, cake formation, aggregation of the suspended particles.

A newer concept in suspensions is the use of microspheres or microparticulates. These are drug containing small polymeric particles (erodible, non-erodible, or ion-exchange resins) that are poised in a liquid carrier medium.

Emulsions

W/O micro-emulsions offer a promising alternative. They are thermodynamically steady 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 when administered in the eye, convert into the liquid crystalline state which releases the drug slowly and produce a sustained release preparation for the eye.

Anionic Emulsion

Anionic emulsion containing difluprednate 0.05%, Durezol™, Sirion Terapeutics) has recently been approved for the treatment of ocular inflammation. In the same pasture, a non-medicated anionic emulsion for eye lubricating purposes, in patients suffering from moderate to severe dry eye syndrome (Refresh Dry Eye Therapy®, Allergan), and two lipidic emulsions, indicated for the restoration of the lipid layer of the lacrimal fluid (Lipimix™, TubiluxPharma, and Soothe XP® Emollient, Bausch and Lomb), have been launched in the US and European markets.the cationic nanoemulsions have also made their way on to the market[11].

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. Novagali has screened most cationic lipids and has identified the composition of cationic emulsion droplet. Oily core solubilize the drugs, Phospholipids - stabilize the interface, and Oleylamine (brings the positive charges) was developed as a proprietary excipient. In case of **Back of the Eye (BOTE)** diseases, Novagali has designed cationic emulsions for non-invasive topical direction which allow the drug to migrate to the retina via the trans-scleral route from the cornea and conjunctiva which act as a reservoir.

Novel Ocular Drug Delivery Systems

Nanotechnology in ocular drug delivery system

The nanotechnology based drug delivery system like nanosuspention, solid nanoparticle microemusion and liposomes have developed to solve the solution of various solubility related problem of poorly water soluble drugs, likes dexamethsone, budenoside, gancyclovir and so on. 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[12]. In addition, 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, nanospheres, nanosuspension and nanoparticles and so on. Diverse nanoparticles based drug delivery systems are:

Microemulsion

Microemulsions were first described by 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.Micro emulsions have a transparent appearance, with thermodynamic steadiness and a small droplet size in the dispersed phase (aqueous and nonaqueous phase) (<1.0μm). Micro emulsions are an interesting substitute to ophthalmic formulation, due to their intrinsic properties and specific structure. They can be easily equipped through emulsification method, easily sterilized, and are more stable and have aelevated capacity for dissolving drugs. The ophthalmic o/w Micro emulsion could be advantageous over other formulation, because the incidence 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. The in-vivo experiments and preliminary studies on healthy volunteers have occurred a delayed effect and anboost in the bioavailability of the drug. This mechanism is based on the adsorption of the nanodroplets demonstrating the internal phase of the microemulsions, which act as a reservoir of the drug on the cornea and should decrease their drainage in limit namely, the product Cationorm® (NovagaliPharma, France) was launched in the European market for the treatment of dry eye symptoms.

Water-in-oil microemulsions (w/o ME) capable of undergoing a phase-transition to lamellar liquid crystals (LC) or bicontinuous ME upon aqueous dilution were formulated using Crodamol, sorbitan mono-laurate and polyoxyethylene 20 sorbitan mono-oleate, an alkanol or alkanediol as co-surfactant and water. The hypothesis that phase-transition of ME to LC may be induced by tears and serve to extendprecorneal custody 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 was investigated in rabbit eye using gamma scintigraphy. Results showed that sorbitan mono-laurate, polyoxyethylene 20 sorbitan mono-oleate and Crodamol ethyl oleate were non-irritant. However, all other cosurfactants investigated were irritant and their irritation was reliant on their carbon chain length. A w/o ME formulated without cosurfactant showed a protective effect when a strong irritant (0.1 M NaOH) was used as the aqueous phase. Precorneal consent studies revealed that the retention of colloidal and coarse dispersed systems was considerably greater than an aqueous solution with no significant dissimilarity 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[13].

Figure 1: Microemulsion

w/o micro-emulsions offer a promising alternative. They are thermodynamically steady 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 when administered in the eye, convert into the liquid crystalline state which releases the drug slowly and produce a sustained release preparation for eye.

Scleral Buckling Materials

In some of the cases scleral buckling materials cause postoperative infections as they are used in retinal detachment surgery .To prevent this complication, scleral buckling materials can be made to absorb an antibiotic. Refojo and Thomos evaluated two common scleral buckling materials, gelatin film and solid silicone rubber impregnated with antibiotics, for their biological activity using agar plate method. They used commercial antibiotics preparations of chloramphenicol and lincomycin. Antibiotic impregnated gelatin disc and silicone rubber were prepared by immersing these devices into an aqueous antibiotic solution and then dried. They found sustained release of antibiotics form these devices. Refojo also investigated the sustained release of chloramphenicol sodium succinate and lincomycin hydrochloride from closed-cell silicone rubber scleral buckling material (sponge). These antibiotic-impregnated materials used in conjunction with standard preand postoperative therapy, can reduce the degree of infection in scleral buckling procedures[14].

Nanosuspensions

Nanosuspensions have emerged as a promising strategy for the competent 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[15].

Nanosuspension contains of pure, hydrophobic drugs (poorly water soluble),suspended in appropriate dispersion medium. Nanosuspension technology are utilised fordrug components that form crystals with high energy content molecule, which renders them insoluble in either hydrophobic or hydrophilic media.

Although nanosuspensions offer advantages such as more residence time in a cul-de-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 charge of the drug in lachrymal fluid controlled its release and increase ocular bioavailability. However, the intrinsic dissolution rate of the drug after application will diverge because of the constant inflow and outflow of lachrymal fluids.. However, a nanosuspension, by their inherent capability to improve the saturation solubility of the drug in media, also represents an ideal approach for ophthalmic delivery of hydrophobic drugs in eye. Furthermore, in earlier nanoparticulate nature of the drug allows to prolonged residence (ocular surface) in the cul-de-sac, giving sustained release of the drug. To accomplish sustained discharge of the drug, nanosuspensions can be incorporated or formulated with a suitable hydrogel or mucoadhesive base *(in- situgel)* or even in ocular inserts[16].

A recent advance has been developed for desired release; the drug is formulated with polymeric nanosuspensions particles laden with the drug. The bio erodible 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 quasi-emulsion and solvent diffusion method. 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 permissibility and in-vivo biological performance in animal. 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 Nanosuspension are formulated by the quasiemulsion solvent dispersal (QESD) method in which generally avoids using of toxic chemical. They are proved to great potential for ophthalmic application[17].

Vesicular or Colloidal Systems for Eye

Liposomes

A liposome is defined as a structure consisting of one or more concentric spheres of lipid bilayers alienated by water or aqueous buffer compartments. Liposomes are also biocompatible and biodegradable lipid vesicles made up of natural lipids with a diameter ranging from 25–10 000 nm in diameter.

Drug molecules depending upon their solubility are encapsulated in either the aqueous phase or the lipid bilayer. Thus, liposomes can accommodate both hydrophilic and lipophilic compounds, and it is possible to apply.

Liposomes can enhance corneal drug absorption, through their ability to come into intimate contact with the corneal and conjunctival surfaces which is enviable 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 prospect of ocular drug absorption. The corneal epithelium is thinly coated with negatively charged mucin to which the activist charged surface of the liposomes may bind.

According to their size, liposomes are known as,

- Small unilamellar vesicles (SUV), 25 to 100 nm in size that consist of a single lipid bilayer
- Large unilamellar vesicles (LUV), 100 to 400 nm in size that consist of a single lipid bilayer
- Multilamellar vesicles (MLV), 200 nm to several microns. (two or more concentric bilayers)
- Vesicles above 1 µm are known as giant vesicles

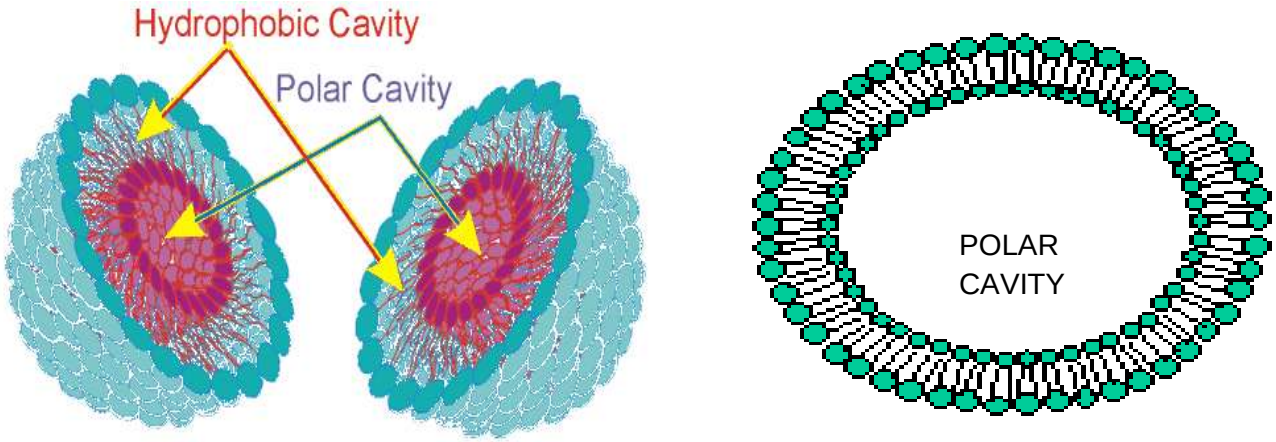

Figure 2: Liposome

Depending on the composition, liposomes can have a positive, negative, or neutral surface charge. The reason for this apparent disparity is not clear, but it is known that the corneal epithelium is thinly coated with negatively-charged mucin to which the positive surface charge of the liposomes may absorb more strongly.

Much research in the recent years has concentrated on the methods of increasing the precorneal residence of vesicles. Vesicles have been suspended in polymer solutions. The vesicles suspended in 1% HPMC or in 0.45% w/v solution of polyvinyl alcohol were retained on corneal surface for a significantly longer period than suspended in buffer[18].

Accumulation of drug in the cornea could transpire by endocytosis of the liposomes. In order to enhance adherence to the corneal/conjunctival surface, dispersion of the liposomes in mucoadhesive gels or coating the liposomes with mucoadhesive polymers was proposed. Several mucoadhesive polymers were employed are poly (acrylic acid) (PAA), hyaluronic acid (HA), chitosan, poloxame28. In order to extend the residence time at the site of administration, to increase efficacy, and to protect the oligonucleotides from degradation, the oligonucleotides were encapsulated in liposomes and disseminated in a thermo sensitive gel.Polymer concentration and the nature of the liposomes influence the release[19].

The *in vitro* and *ex- invitro* drug liberate studies profile showed that, there was slow and prolonged release of drug from all the formulations with zero order kinetics. The activity of liposome formulation was found to be appreciably lowered by the *in vivo* intraocular pressure and persistent for longer period of time which improves its physiological effectiveness. Thus, liposome offer a promising way fulfil the need for an ophthalmic drug delivery system that not only has the convenience of a drop, but that can be obliging to provide the localize drug action and maintain drug activity at its site of action for a longer period of time and minimizing frequency of drug administration with patient compliance.

Liposomes are a potentially functional ocular drug delivery system due to its structural diversity and versatility in physical uniqueness, but suffer from the disadvantage of instability (due to the hydrolysis of phospholipids normally used in their preparation), restricted drug-loading capacity, and technical difficulty in obtaining a sterile liposomal preparation.

Niosomes

The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and variable clarity 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 thedelivery of hydrophobic or amphiphilic drugs. Vyas and co-workers reported that there was about 2.49 times augment in the ocular bioavailability of timolol maleate encapsulated in niosome as compared to timolol maleate solution[20].

They are the vesicles formed by some members of the dialkylpolyoxyethylene ether non-ionic surfactant series. Vesicular system are formed when a mixture of cholesterol and a single-alkyl chain, non-ionic surfactant is hydrated.

Figure 3:Niosome

The resultant vesicles, termed as "niosomes", can entrap solutes, are osmotically active, and relatively stable. Neosomes behave in vivo like liposomes prolonging the circulation of entrapped drug, and altering its organ distribution and metabolic stability. Niosomes have also been reported as successful ophthalmic carriers.

Niosomes of brimonidine tartrate are authorized that niosomes is a significant vesicular carrier scheme for therapeutic effectiveness as helpful to increase the duration of action and decrease in dose frequency. During evaluation of drug preparation it follows zero order kinetics and show prolong release of drug. The activity of niosome formulation was found to be lowered significantly by the *in vivo* intraocular pressure and continual for long period of time which encourages its physiological effectiveness. Thus, niosomes offer a promising way to fulfil the need for an ophthalmic drug delivery system that not only has the convenience of a drop, but that can localize and maintain drug activity at its site of action for a longer period of time thus allowing for a sustained action; minimize frequency of drug supervision with patient compliance.

Discosomes

Disc shaped neosomes are known as discosomes. Discosomes are large structures formed by solubilization of niosomes with a non-ionic surfactant.

Advantages:

- Large size (12-60 µm) prevents their drainage into the systemic pool.
- Better adherence of the system to the cornea.
- Disc shaped provides for a better fit in the cul-de-sac of the eye.

Non-ionic surfactant-based discoidalniosomes (discosomes) of timolol maleate have been reported to be promising systems for the controlled ocular administration of water-soluble drugs, with zero order drug release. *In vivo* studies showed that discomes released the contents in a biphasic profile if the drugwas loaded using a pH gradient technique. Discomes may act as potential drug delivery carriers as they released drug in a sustainedmanner at the ocular site.

Pharmacosomes

This is the term used for pure drug vesicles formed by the amphiphilic drugs.

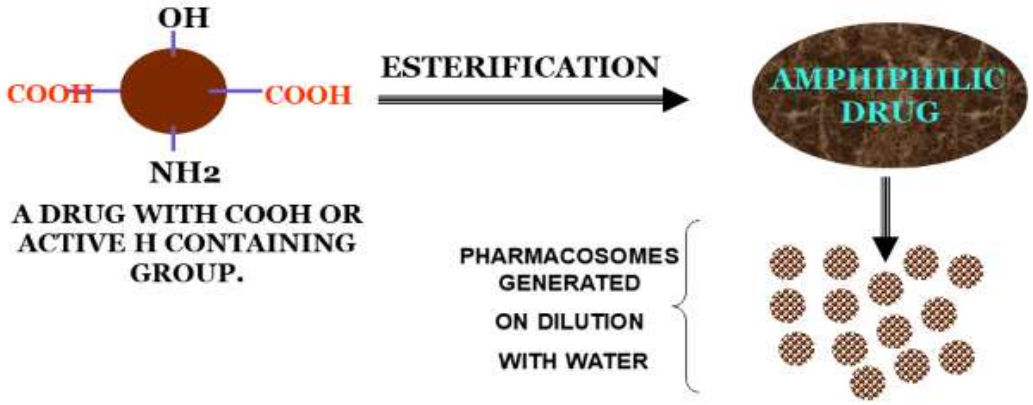

Figure 4:Pharmacosome

Any drug possessing a free carboxyl group (-COOH) or an active hydrogen atom (–OH, NH_2) 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 transformed to pharmacosomes on dilution with water. The pharmacosomes show decreased drug metabolism, facilitated transport across the cornea, and controlled release profile.

Particulates (Nanoparticles and Microparticles) System

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 polylactides (PLAs), polycyanoacrylate, poly (d,l-lactides), natural polymers can be used effectively for efficient drug delivery to the ocular tissues.

Aqueous suspensions one of the conventional ophthalmic formulations contain a sparingly soluble drug in a finely divided particulate form which is pendant in saturated solution of the drug. The drug particles as well as solution portion of the suspension are drained into the lachrymal systems on instillation of the suspension leaving behind some of the suspended drug particles. The suspension advance shows improved drug bioavailability by manipulation of particle size only for water insoluble drugs. For drugs that are water soluble the nanoparticles approach has been considered. Nanoparticles are particulate drug delivery systems 10-1000 in size in which the drug may be dispersed, encapsulated, or absorbed. Nanoparticles for ophthalmic drug liberation have been mainly produced by emulsion polymerization. In this process a scantily soluble monomer is dissolved in the continuous phase which can be aqueous or organic. Polymerization is started by chemical instigation or by irradiation with gamma rays, ultra violet or visible light. The resources that have been mainly used fur ophthalmic nanoparticles are polyalkyl cyanoacrylates[21].

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. 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 superior retention and bustle characteristics with respect to the controls. Nanospheres made up of poly lactic acid (PLA) coated with Poly Ethylene Glycol (PEG) shown better efficacy compared to conventional amount form of Acyclovir for the treatment of ocular viral infections. Microspheres of poly lacto gylcolic acid (PLGA) for topical ocular delivery of a peptide drug vancomycin were prepared by an emulsification/ spray-drying technique.nanoparticles microspheres provide the promising drug carriers for ophthalmic applications. The binding of drugs depends on the physicochemical properties of the drugs and polymer used, as well as of the nano and microparticle material and also on the developed process for these particles. After optimal drug binding to these particles, the ocular bioavailability of a number of drugs is significantly enhanced in comparison to normal aqueous eye drop solutions as increased solubility. Generally, smaller particles are better tolerated by the patients than larger particles (no irritation). For this reason especially nanoparticles may be preferred for long-acting ocular drug delivery systems, although larger microparticles showed slower elimination kinetics from the precorneal compartment.

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 topicaldrug administration like pilocarpine[21].

Advanced Ocular Drug 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, incessant, and long-term delivery of therapeutic proteins directly to the posterior regions of the eye. The polymer implant containing genetically tailored human RPE cells secretes ciliaryneurotrophic factor into the vitreous humour of the patients' eyes. ECT can potentially serve as a delivery structure for chronic ophthalmic diseases like neuroprotection in glaucoma, anti-angiogenesis in choroidal neovascularization, anti-inflammatory factors for uveitis[22].

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 foremost 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 application. Topical delivery to the eye is the most expedient way of ocular gene delivery. However, the dare of obtaining substantial gene expression following topical administration has led to the prevalence of invasive ocular administration. Retroviral vectors have been widely worn due to their high efficacy; however, they do not have the aptitude to transduce nondividing cells, leads to restrict their clinical use.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[23].

tem cell Therapy

Emerging cell therapies for the restoration of sight have resolute on two areas of the eye that are critical for visual function, the cornea and the retina. 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[24].

Protein and Peptide therapy

Delivery of therapeutic proteins/ peptides has received a great attention over the last few years. The intravitreous inoculation of ranibizumab is one such example. The designing of optimized methods for the sustained delivery of proteins and to envisage the clinical effects of new compounds to be administered in 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 enhanced by structurally modifying the compound, thus mounting 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 irrelevant systemic absorption[25].

Scleral Plug therapy

Scleral plug can be implanted using a effortless 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 necessitate vitrectomy[26].

siRNA therapy

For various angiogenesis-related diseases, the use of siRNA is considered as a promising approach. Feasibility of using siRNA for action 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 repress 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. However, its use in vivo remains problematic, largely due to unresolved hitches in targeting delivery of the siRNA to the tumor cells. Viral gene delivery is very competent however it currently lacks adequate selectivity for the target cell type. New encapsulated siRNA have been developed using liposome, 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[27].

Oligonucliotide therapy

Oligonucleotide (ON) therapy is based on the principle of jamming 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 restrain protein synthesis, the ribonuclease H mechanisms is the most important. A number of factors have been resolute 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 amendment of phosphate backbones, sugar moiety, and bases[28].

Aptamer

Aptamers are oligonucleotide ligands that are used for high-affinity binding to molecular targets. They are isolated from complex of synthetic nucleic acid by an iterative process of adsorption, revival, and reamplification. They bind with the target molecules at a very low level with soaring specificity. One of the earliest aptamers studied structurally was the 15 merDNA aptamer against thromb.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[29].

Ribozyme therapy

RNA enzymes or ribozymes are a moderately 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 precise 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 loads of other autosomal dominant eye diseases, including glaucoma[30].

Conclusion

New ophthalmic delivery system includes ocular inserts, collagen shields, ocular films, disposable contact lens and other Novel drug delivery systems like hiosomes 20 and nanoparticles. A newer drift is a permutation of drug delivery technologies for improving the therapeutic response of a non efficacious drug. This can give a superior dosage forms for topical ophthalmic application. Among these drug delivery systems, only few commodities have been, commercialized. An ideal system should have efficient drug concentration at the target tissue for a tended period of time with minimum systemic effect. Patient acceptance is very important for the design of any secure ophthalmic drug delivery system. Major Improvements are required in each system like improvement in sustained drug release, large scale manufacturing and stability.

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