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RECENT ADVANCE OF NANOTECHNOLOGY FOR THE TREATMENT OF OCULAR DISEASE

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ABSTRACT

Nanoformulation are use as an alternative for traditional ophthalmic formulation. Their are various factors that creats problem in treatment of ocular disease like rapid elimination, enzymatic drug degradation, Protein binding and physiological barrier etc. All these factors cause reduction in intraocular residence time and poor bioavailability. Recent research study shows that nanoformulation can enhance the therapeutic efficacy and bioavailability of ocular drugs compared to conventional ocular formulation. The various research study in number of patent shows significant increase in therapeutic efficacy for various chronic disease states of both anterior and posterior ocular segments. The nanoformulation approach enhance the ocular bioavailability by reducing the drug protein binding, increasing the corneal resident time, enhancing the drug permeability and also providing a sustained drug release. United States Food and Drug Administration (USFDA) has approved ocular drugs employing nanotechnology and future developments.

KEYWORDS: Ocular drug delivery system, Patent, Nanotechnology, United States Food and Drug Administration.

INTRODUCTION

Ocular drug delivery is one of the most important rout of administration. The anatomical structure of eye provide a unique structure that prevent the entry of drug molecules. The cornea consists of three membranes: epithelium, endothelium, and inner stroma. The corneal epithelium, lipophilic in nature, acts as a selective barrier for small molecules and prevents the diffusion of macromolecules through the paracellular route. The stroma, located below

the epithelium, is a highly hydrophilic layer making up 90% of the cornea. The corneal endothelium consists of a single layer of flattened epithelium like cells which is responsible for maintaining normal corneal hydration. Because the cornea is characterized by lipophilic and hydrophilic structures, it act as an effective barrier to the absorption of both hydrophilic and lipophilic molecules.

There are two segments of eye one is anterior and other is posterior segment according to which rout of administration are differs as shown in figure1.

- For anterior segment drug delivery, common routes of administration are topical instillation and sub-conjunctival injection.
- For posterior segment drug delivery common routes include systemic dosing, periocular and intravitreal injections, and topical dosing.[1]

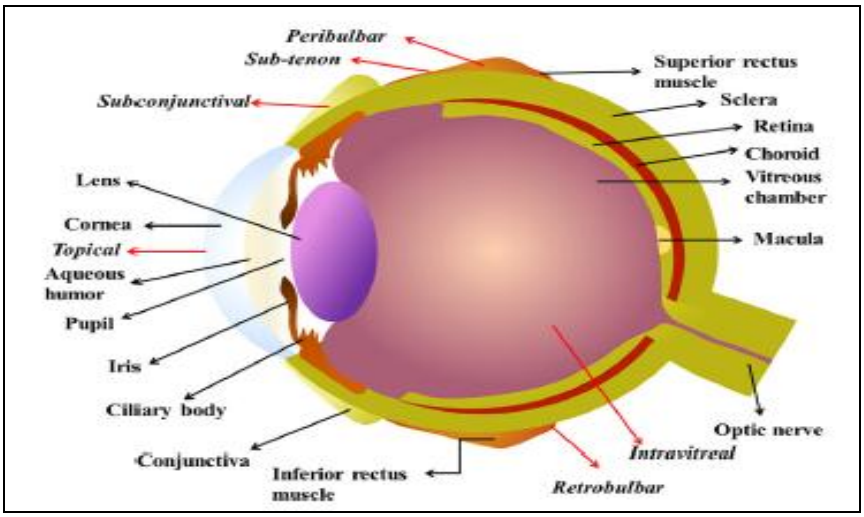

Figure 1: Ocular anatomy and administration routes of both traditional drugs and nanosystems: the black arrows shows different aya structures and the red arrows shows various administration routes.[2]

Topical ocular administration of drugs has two different purposes

- To treat superfcial eye diseases, such as infections (e.g., conjunctivitis, blepharitis, keratitis sicca).
- To provide intraocular treatment through the cornea for diseases such as glaucoma or uveitis.

More than 90% of the marketed ophthalmic formulations are in the form of conventional eye drops but these conventional systems cannot be considered optimal in the treatment of vision-

threatening ocular diseases because most of the drugs are washed from the eye by various mechanisms like lacrimation, tear dilution, and tear turnover.[1]

There are multiple of physiological barrier make topical drug delivery a challenging area for drug delivery as following:-

- Only ≤5% of drug in solution form is absorbed in the eye when administered topically. Drug loss is primary cause to rapid drug elimination from the cul-de-sac through lacrimation, blinking and tear turnover.
- Lacrimal protein drug binding,
- Drug metabolism by enzymes present in lacrimal fluid and
- Poor corneal permeability, are responsible for the poor drug bioavailability.
- Efflux transporte is primary barriers that cause poor drug absorption and bioavailability, primarily for anterior segment ocular drug delivery. A number of efflux transporters is present in the epithelial cells of various ocular tissues.

Despite these challenges, a significant number of conventional marketed ophthalmic formulations are available as topical eye formulations. These are wide use mainly due to better patient compliance and lower production costs.

Retention time can be increase

- By using *viscosity builders* but they have limited scope because they can only use as liquid preparation which result in rapid drug clearance.
- Second option to use *penetration enhancer* but due to the highly sensitive nature of the cornea and conjuntival tissues, they may cause toxicity.
- Resins, mucoadhesive and thermogel also enhance the retention time.

In past few year, various approaches have been discovered for treatment of ocular diseases. Nanotechnology is one of the approach which is currently used for both anterior and posterior segment drug delivery. Nanotechnology based ophthalmic formulation have a potential to developed appropriate particle size that can ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Some of them have a great potential to improved ocular bioavailability.

Potential advantages of nano-scaled drug delivery systems in ocular therapy

(1) The possibility of self-administration by patients as eye drops.

(2) No impairment of sight because of small dimensions of the delivery systems.

(3) Protection against metabolic enzymes (such as peptidases and nucleases).

(4) Possible uptake into corneal cells.

(5) Prolonged drug release, reducing the need for repeated instillation or injection.

(6) Targeting toward affected tissues, reducing possible side effects and required dose.

Nanocarrier for ocular drug delivery

For the development of ocular drug delivery systems substantial efforts have been directed that would prolong the drug retention, and allowing the drug to remain in contact with the cornea for long time and increasing bioavailability. Nanoparticulate technology is used as an ophthalmic drug delivery that may enhance dosage form acceptability while providing sustained release in the ocular milieu. Particle size, particle size distribution, and stability constitute a major issue considered by formulation scientists when formulating dispersed systems, especially those intended for parenteral or ocular administration. Very small particles such as nanoparticles are well tolerated and possess adhesive properties, which could prolong the residence time of the drug in the cul-de-sac, prevent tear washout (due to tear dynamics), and increase ocular bioavailability. several nanocarriers have been developed for ocular drug delivery like lliposomes, dendrimers, nanoparticle, nanosuspension etc.as shown in figure.2. Table1 contain the list of some nanoformulation for anterior segment of eye that are in different phase of clinical trial and marketed nanoformulation. Table.2 contain list of some nanoformulation for posterior segment of eye that are in different phase of clinical trial and marketed nanoformulation.[1]

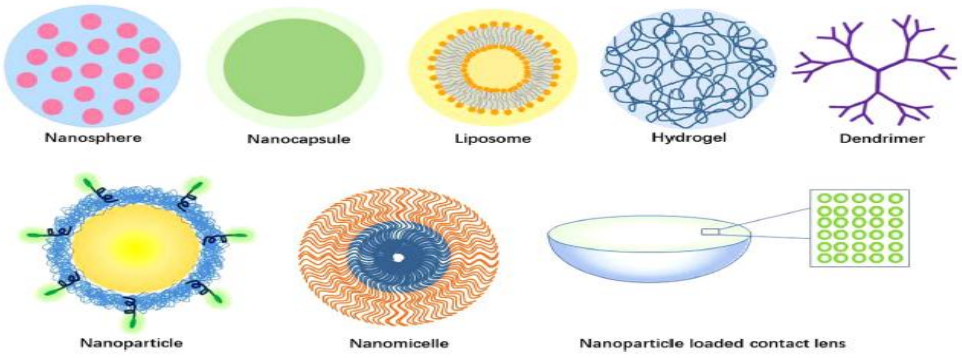

Figure 2: Schematic illustration of different nanotechnology-based ocular delivery systems.[2]

Table 1: Typical nanotechnology-based strategies for ocular anterior diseases application.[3]					
Formulation	**Material type**	**Payload**	**Size (nm)**	**Function**	**Clinical stage**
Nanowafer	Polymer	Axitinib	500	The drug loaded nanowafer was nontoxic and could treat corneal neovascularization more efficiently compared to the commercial eye drop even at a lower dosage.	Preclinical
Nanoparticle	Chitosan	Gene	~200	The nanoparticle showed superior transfection efficiency in anterior segment of the eye.	Preclinical
Hydrogel (Virgan)	Polymer	Ganciclovir	–	Topical treatment drug for herpes simplex virus infection in the eye.	Market
Nanosuspention	Polymer	Diclofenac	105	Enhanced penetration and retention effect in corneal tissues was achieved through topical administration.	Preclinical
Nanoparticle	Polymer	Flurbiprofen	200–300	Following topical administration of the formulation, an enhanced anti-inflammation effect was achieved towards to a built animal model.	Preclinical
Nanoparticle	Polymer	Dexamethasone sodium phosphate	100–500	The drug loaded nanoparticles could not cause inflammation in the eye and improved the efficacy for prevention of corneal graft rejection.	Preclinical
Nanoscale dispersed oilment	Polymer	–	100	The formulation not only retained the advantages of eye ointment, but also showed better efficacy in repairing the tear film and restoring the corneal surface.	Preclinical
Hydrogel	Polymer	Diclofenac	–	The micellar supramolecular hydrogel could extend the retention time on corneal surface and improve drug bioavailability in the eye.	Preclinical

Table 2: Typical nanotechnology-based strategies for ocular posterior disease applications.[3]

Formulation	Material type	Payload	Size (nm)	Function	Clinical stage
Hydrogel	Polymer	Bevacizumab	–	The hydrogel showed a sustained release of Bevacizumab in suprachoroidal space of SD rats for 4 months.	Preclinical
Nanoparticle	Polymer	Latanoprost acid	80	The nanoparticles provided a sustained drug release by subconjunctival administration.	Preclinical
Hydrogel (Timoptic-XE)	Polymer	Timolol maleate	–	Topical treatment drug for glaucoma.	Market
Hydrogel	Polymer	Mitomycin C	–	The hydrogel showed good ocular compatibility and realized sustained release in intraocular after glaucoma surgery.	Preclinical
Liposome	Polymer	Bevacizumab	100–200	The system could pass through biological barriers by annexin A5 mediated endocytosis after topical administration.	Preclinical
Micelle	Polymer	Triamcinolone acetonide	200–350	A micelle combined gel system was well tolerated in rat eyes and had a sustained release for one year after intravitreal injection.	Preclinical
Dendrimer	Polymer	Gene	~50	The dendrimer-gene complex exhibited effective gene transfection in RPE cells.	Preclinical
Nanoparticle	Peptide/polymer	Gene	~180	The system could rescue the retina degeneration both histological and functional in a mouse model by subretinal injection.	Preclinical

Nanotechnology-based ocular delivery systems

1. Nanoemulsions

Emulsions are fine dispersion of tiny droplets of two immiscible liquids. Nanoemulsions are dispersion which contain dispersed phase of particle size is in submicron nanometer range. It contains one or more amphiphilic lipid or surfactants. Surfactant are molecules having a bipolar structure containing at least one hydrophilic part and one hydrophobic part. It is obtain by high pressure homogenization which provide translucent appearance of nanoemulsions with nanometer size (<100nm) of dispersed globules. Because of small particle size of dispersed phase, nanoemulsion are thermodynamically unstable so they required high concentration of surfactant to stabilized the formulation. This will lead to sticky feeling and intolerance in eye. Phospholipid are also commonly used in nanoemulsion which cause yellowish appearance and rancid odor after short period storage.

Table 3: US Patent of Nanoemulsion for ocular drug delivery systems.

Patent No.	Description
US6335022B1	These invention use *oxyethylenated* or *nonoxyethylenated sorbitan fatty esters* as surfactants. The inventor committed that use of surfactant containing oxyethylenated or non-oxyethylated sorbitan fatty esters, having a molecular weight >400 grams per mole, and are solid at temperatures ≤45°C can result in a stable formulation and use of amphiphilic lipids selected from the group of alkaline salt of cholesterol also increase stability. Inventor claim that this optimized ophthalmic nanoemusion can be used as effective delivery formulation for anti-glaucoma, anti-viral, anti-allergic, and anti-inflammatory agents.[3]
US6375960B1	ophthalmic nanoemulsion containing surfactants ethoxylated fatty ethers, ethoxylated fatty esters, and a mixture of both surfactants has been patented by the same inventor group. For improvement of bioavailability of ophthalmic formulation it is important to increase the residence time of drug. So for enhance the residence time it is important to increase the viscosity. Viscosity of nanoemulsion is increase by increasing the fraction of dispersed oil phase. Another method to increase the viscosity is by use of hydrophilic polymer which form a gel with continuous aqueous phase by increasing the viscosity. Water soluble polymers such as hydroxypropyl cellulose, algal derivatives, natural gums, synthetic polymers and copolymers of carboxyvinyl acid (carbopols)", are widely employed to improve the viscosity of ophthalmic formulations.[3]

2. Liposomes

Liposomal drug delivery systems discovered over 5 decades ago. Over a dozen liposome-based drug delivery systems is currently approved by the FDA and some are in various stages of development. The first liposomal system for drug delivery was Doxil, approved in 1995. As of 2015, most of the FDA-approved delivery vehicles are either fully liposomal or PEG-ylated. Liposomes are made up of one or more lipid bilayers separated by the aqueous buffer compartment and they are classified into three types:

- Multi-lamellar vesicles
- Small uni-lamellar vesicles(10 – 100 nm)
- Large unilamellar vesicles (0.1 – 10.0 μm)

Liposomes can encapsulate both hydrophilic and hydrophobic drug molecule. Liposomes shows promising effects over conventional ophthalmic dosage form due to protection of drug molecule from metabolic enzymes degradation on the conjunctival and corneal surface. To maintain the drug therapeutic activity for longer period of time liposomes can be use as eye drop. Liposome also protect drug molecule from enzymes present in tear fluid. Liposome membrane is flexible membrane and also support deformation stress. This feature make liposome suitable for intraocular injection for treatment of posterior site of ocular disease. Positive charge liposome disintegrate when it come in contact with negative charge mucin

membrane. Liposome used in various eye disease like dry eye, keratitis, Endophthalmitis, uveitis. Various research study are focused on coating the external part of liposome with bioadhesive and polymer that will enhance penetration for improvement of corneal penetration and conjunctival adhesion. Positive charge liposome shows highest corneal uptake and neutral liposome shows lowest corneal uptake.

Liposome are also used for delivery of vectors like genetic transfection, oligonucleotides and monoclonal antibodies. Retention of liposome on the corneal surface can be increase by suspending the liposomes in an aqueous medium which containing polymer having high viscosity. In some study investigators shows that by formulating the drug in mucoadhesive chitosan-coated liposomes the enhancement of bioavailability of ciprofloxacin hydrochloride has been observed.[3]

US Patents of Liposome for ocular drug delivery systems

Currently, there are good numbers of liposome-based drugs available for human use. Most of the liposomal drug formulations are available for intravenous and intramuscular (i.m.) applications. Liposomes for Photodynamic Therapy Visudyne, a product of Novartis, is the first light-activated drug available for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration (AMD).

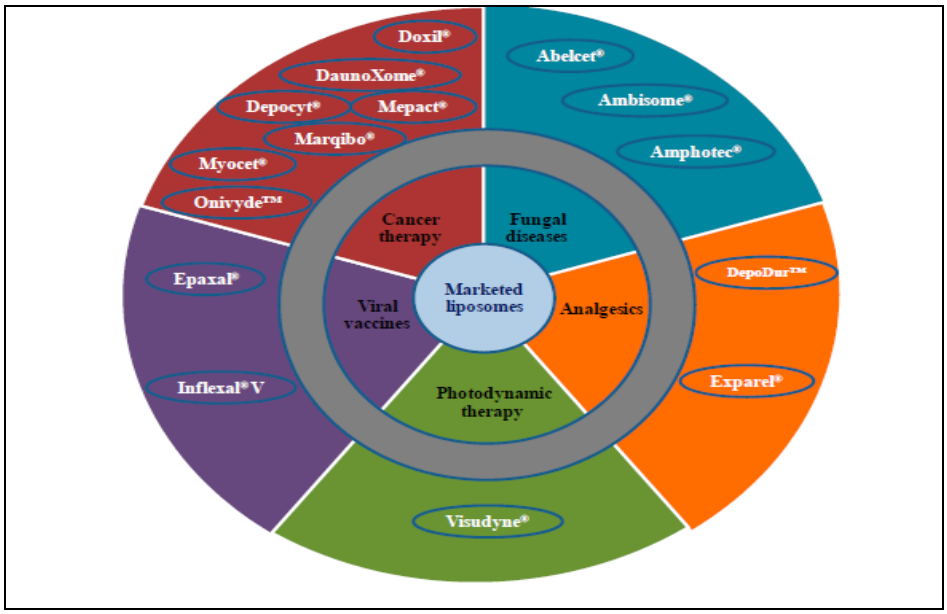

Figure 3: Therapeutic area covered by liposome-based product.[7]

In US 15 patents inventions reporting the successful use of liposomal technology for ophthalmic medications. One such patent is the development of liposomes containing 10–40

mole percent of an aminederivatized lipid component (-NH2 group is separated from a lipid polar head region by a carbon-containing spacer arm).

In a recent study, liposomes for sustained release of latanoprost have been prepared for the treatment of glaucoma. In the study, latanoprost-loaded egg-phosphatetidylcholine liposomes has been prepared using film hydration technique to achieve average particle size of 109 ± 18nm and encapsulation efficiency of 94 ± 5%. In vitro release and in vivo results shows that liposomes were more efficient in decreasing the intra ocular pressure compared to a daily dose of conventional topical formulation during a 90 day period.[7]

3. Nanosuspensions

Nanosuspensions are colloidal dispersion of submicron drug particles and also consist of polymer or surfactant as stabilizer. It is use for delivery of hydrophobic drugs. For ocular delivery, it provides several benefits like sterilization, ease of eye drop formulation, less irritation, increase precorneal residence time and increase bioavailability of drugs which are insoluble in tear fluid. The efficacy of nanosuspensions of glucocorticoids in improving ocular bioavailability has been shows in several research studies.

Glucocorticoids are such widely use for the treatment of inflammatory conditions affecting anterior segment ocular tissues. These drugs requires frequent administration at higher doses which induce cataract formation, glaucoma, and damage optic nerve. Nanosuspension can improved ocular bioavailability of glucocorticoids. Various clinical study has been done in which the formulations were instilled into the lower cul-de-sac of the rabbit eye and intraocular pressure (IOP) was measured at frequent time intervals up to 12 h. This study shows that the area under percentage increase in IOP vs time curve (AUC) values for all the suspensions were higher than that for the respective drug solutions. The study shows that nanosuspension shows higher extent of drug absorption and more intense drug effects as compared with solutions. In another study, compared ocular bioavailability of hydrocortisone nanosuspensions with hydrocortisone solution in rabbits post topical instillation. The study shows that a sustained drug action which was represented in terms of changes in intraocular pressure was maintained up to 9 h for the nanosuspensions compared to 5 h for the drug solution.

From the results of these research studies, it can be concluded that nanosuspensions could be an efficient ophthalmic drug delivery system for delivery of poorly soluble drugs.

Nanosuspension can also be incorporated into hydrogels or ocular inserts for achieving sustained drug release for stipulated time period.[8]

US Patents of Nanosuspension for ocular drug delivery systems

Nanosuspension has emerged as an efficient and promising strategy for delivery of insoluble drugs due to its unique advantages like ease of modification, process flexibility, targeting capabilities, altered pharmacokinetic profile leading to safety and efficacy. These unique properties of nanosuspension have enabled its use in various dosage forms, including specialized delivery systems such as oral, parenteral, peroral, ocular and pulmonary routes. Currently, efforts are being directed by various research study to extend their uses in site-specific drug delivery. Large numbers of products based on nanosuspension are in the market and few product are under clinical trials. The commercialization potential of nanosuspension based techniques available, only wet milling technique has been successfully used for commercial production of nanosuspension. Nanosuspension based patents have formulation for oral route is well established and products for other routes will enter the market within short span. Among the various extensive potential of reaching faster in the market as compared to other nanotechnology based formulations. This review covers various aspects of techniques of preparation, route of administration and commercialization of nanosuspension with main focus on the recent patents granted in the field.

4. Nanoparticles

Nanoparticle are consist of small molecular drugs as well as proteins, peptides and nucleic acids for targeted delivery. The colloidal formulation system consist of a polymeric nanoparticles for ocular delivery.

Patents of Nanoparticles for ocular drug delivery systems

One **patent** (WO2012091278A2) on reversible hydrogel system consist of nanoparticles and nanospheres. It convert dilute solution of copolymer into hydrogel by mechanism of oxidation, light intensity and by mechanical stress. Nanocomposite are made up of combination of hydrogel and nanoparticle and form in-situ gel on injection into the eye in posterior segment. One more invention on inorganic nanoparticle which is useful for preventing uptake of biocides from ophthalmic composition by contact lenses. After that the inventors also shows that the uptake of biocides by contact lenses is minimized without effecting microbiological activity. Calcium phosphate nanoparticle shows great application in drug delivery system. Patent of calcium phosphate particle as an ocular drug delivery system

was shows in patent disclosure (WO2004050065A1) by Biosante Pharmaceuticals. Research have shown that ocular drugs can interact and bind with pigments, leading to decreased ocular bioavailability.[8]

5. Soft Contact Lenses

Soft contact lenses have been used in ophthalmic dosage form to prevent drug loss during drug administration. It reduce various side effect and enhance the efficacy of drug. It serve as a matrix for the drug nanoparticle. It contain lense with particle loaded in them which is very clear and it is not effect the vision due to the small particle size of formulation. Inventor report that particle size of this nanoparticle 9was ~50 nm to ~200 nm. Soft contact lenses are made up of hydrogel which is a three diamensional polymer network that absorbed required amount of aqueous medium. When it is submerged in the concentrated solution of drug then aqueous phase absorbed requisite volume of aqueous medium and take the drug into polymer mesh network through non specific absorption.

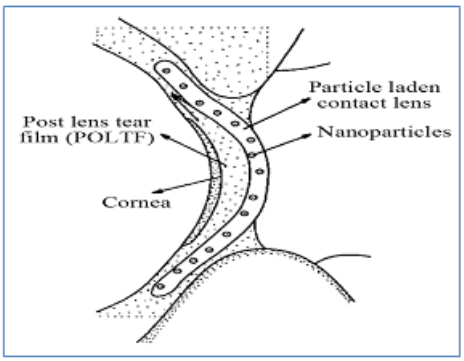

Figure 4: Schematic diagram of the novel particle-laden soft contact lens inserted in the eye.

It will improve bioavailability of drug when drug impregnated soft contact lenses wearing on the eye. The amount of drug penetrate through the cornea by using contact lenses is increased by five time higher than that released through the lachrymal fluid. By using this nanoformulation, drug remain in contact with high concentration of drug for long period of time and shows better penetration of drug.

Pilot study of contact lenses of timolol shows that contact lenses delivery can effectively lower the IOP. So soft contact lenses can be an attractive alternative to eye drop for delivery of drug for treatment of glaucoma. But limitation of contact lens delivery system is that it

require patients to wear contact lens at all time. Another limitation is that lenses are generally store in a hydrated storage condition, which cause drug to leach out of the lens over time.[4]

Advantages of medicated contact lenses are following

Comfort lens use in dry eye condition. Anti-dry eye formulation impregnated in the contact lens for prolong released in eye for improve the tolerance. Second is contact lens for patient which improved the patient compliance. Third are bandage lenses which is use for corneal wound healing and corneal erosion due to viral.

Method of drug delivery through contact lenses

Various methods for the drug delivery through use of contact lenses in the following subheadings.

1. First method is conventional method in which lens impregnated in the drug solution and then inserted into the eyes of patient.
2. Second method is chemical functionalization of hydrogel with drug molecule by using molecular molding method
3. Third method is molecular imprinting method which include preparation of contact lens in the presence of drug molecules which act as a mold that cause monomers to arranged themselves to their affinity.
4. Fourth method is encapsulation of drug in nanoparticle dispersed in the solution of monomer and form lenses when the polymerization occurs.[4]

US Patents of control lenses for ocular drug delivery systems

Recently various new progress has been established in the field of contact lenses drug delivery. New technology has been used that will enhance drug loading and controlled release. Each technic have some advantage and disadvantage with little effect on optical properties of lens. The type of the contact lenses and the technique of drug loading affect the residence time of the drug. In comparison with topical alternatives, contact lenses provide an increased residence time at the surface of the eye for efficacious therapy.

The use of polymers with varying width of channels in the matrix can control drug delivery rate which remains effective for longer periods. In this contest, soft contact lenses are more preferred due to their potential of increasing bioavailability of ophthalmic drugs. Approaches like molecular imprinting, particle-laden soft contact lenses, barrier approach, complexation have been proposed to improve the corneal drug delivery.[5]

Table 4: Market formulation of contact lense.[5]

Drugs used	Polymers/contact lens	Method of drug incorporation	Inference
Acetazolamide, timolol maleate	Balafilcon A	Discontinuous SSI methodology	Demonstrated the feasibility of preparing balafilcon A contact lenses using scCO2, ethanol and water by SSI
Acetazolamide or Ethoxzolamide	HEMA, zinc methacrylate, 1- or 4-vinylimidazole, and N-hydroxyethyl acrylamide	Bioinspired imprinted pHEMAhydrogels	Remarkable improvement in the performance as controlled release system
Azulene	HEMA + methacrylmide propyl trimethylammonium chroride	Molecular imprinting technique	Molecular imprinting is capable to store the anionic drug such as azulene based on ion-exchange reaction
Brimonidine tartrate	Acuvue contact lenses	Soaked in 0.1% brimonidine tartrate solution	Disposable contact lenses are able to uptake and release brimonidine tartrate in vitro
Ciprofloxacin, fluorescein	PLGA films over pHEMA	By ultraviolet light polymerization film coating process	PLGA film coated over pHEMA lenses sustained the release of drug, which can be controlled by changing either the ratio of drug to PLGA or the molecular mass of the PLGA used
Ciprofloxacin HCl	Lotrofilcon A, etrafilcon A, balafilcon A	Soaked in 0.3% ciprofloxacin-HCl	All materials released the drug too quickly to be effective as drug delivery device
Dexamethsone	ACUVUE, OASYS, NIGHT & DAY and O2OPTIX	Soaking of vitamin E loaded lens in drug solution	Vitamin E loading increases the drug release by 9 to 16 fold than non vitamin E loaded lenses
Diclofenac sodium	pHEMA and GMA	β-CD was grafted to the gel network and soaked in drug solution.	The hydrogels with pendant β-CD are particularly useful for the development of cytocompatible drug loaded SCLs.
Timolol	N-N-diethyllacrylamide, methacrylic acid, ethylene glycol dimethacrylate	Molecularly imprinted technique	Timolol loading capacity of the contact lenses as well as sustaining of drug release was improved by the molecular imprinting method

6. Spanlastics

Spanlastics contains concentric bilayers that is similar to liposomes. It can be Unilamellar or Multilamellar (MLVs). Depending on size of vesicles, these can be Small unilamellar (10-100 nm) or Large unilamellar (100-3000 nm). MLVs shows prolonged retention time as compared to SUVs of the same lipid composition. Spanlastics are spheroid structures and consisting of amphiphilic molecules acting as suitable matrices for bio encapsulation.[9]

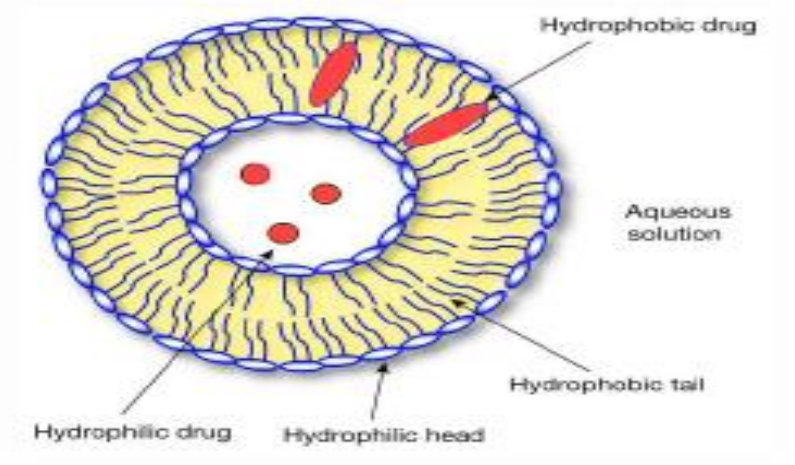

Figure 1.4 Structure of Spanlastic® Vesicle

Figure 5: Structure of Spanlastics vehicle.

Mechanism of penetration of Spanlastics

Edge activators (EAs) present in Spanlastics cause destabilization of lipid bilayers and increase the deformability of the vesicles. The surfactant present in these vesicles induce pores in lipid structures, such as membranes, and also increase solubilization (lysis) in the higher concentration range. Thus, elastic vesicles squeeze themselves under the influence of water gradient depending on the membrane bending energy that depends on its composition.

There are 2 mechanisms for drug penetration

1. The elastic vesicles reacts with the epithelial cell membrane and act as penetration enhancers, and subsequently modify the intercellular lipid lamellae.
2. The elastic vesicles can act as drug-carrier systems, in which intact vesicles carrying the drug pass through the intercellular spaces and reach across the biological membrane.[10]

Advantages

Spanlastics are biodegradable and non-immunogenic in nature. They protect the drug from biological environment by entrapping the drug within the lipid bilayer structure.

Both hydrophilic as well as lipophilic drugs can penetrate through biological membranes like cornea via Spanlastics system. The hydrophilic drug is incorporated within the aqueous compartment. Whereas, the lipophilic drug gets entrapped within the lipid bilayer membrane of the vesicular structure.

7. Ethoniosomes

Ethoniosomes are novel elastic nano-sized niosomes. Niosomes containing ethanol and minimum amount of cholesterol (ethoniosomes) could be effective ocular delivery systems for both water soluble and insoluble drugs.

Non-conventional types of spherical niosome are

- Asdiscomes (giant discoidal-shaped niosomes)
- polyhedral niosomes (multi-faceted niosomes)

Another non-conventional type of niosomes are spanlastic vesicles has been recently used for ocular administration. Spanlastic vesicles (SV) composed of Span 60 and Tween 80 (edge activator) in nano-sized ranges shows deformability/elasticity and enhanced ocular bioavailability compared with conventional niosomes. But these SVs did not contain cholesterol (a bilayer membrane stabilizer) which may cause physical instability problems like drug leakage and vesicle aggregations with aging (storage).

Preparation of ethoniosomes (EV)

Two methods (TFH and EI) are used to prepare EV formulations; the TFH is the conventional and mostly used method for preparation of the conventional niosomes and the EI method has been recently used to prepare elastic niosomes. Spanlastics are composed of Span 60 and Tween 80. High elasticity for the prepared EV could offer high deformability and penetrability through biological membranes intercellular membranes and minimize the possibility of vesicle rupture while penetrating through. With regard to ocular delivery, this concept could be valid for relatively porous membranes of the conjunctival/sclera route but not with exclusive tight junctions of the corneal.

Nano-sized ethoniosomes can show better spreading ability on lipophilic corneal epithelium, and enhance permeability of drugs by virtue of being surfactant based formulations and having exclusive deformability and ultra-flexibility characteristics.

Ethoniosomes which enabled to squeeze through porous conjunctival membranes and to lesser extent to the tight junctions of corneal epithelium and also due to better spreading ability on the lipophilic corneal surface.

These novel demonstrated ultra-deformability/flexibility, controlled drug release and good physical stability for at least 2 months at fridge temperature with good ocular tolerability and minimal ocular irritation as evidenced by the in-house modified Driaze's test. Further, they effectively reduced the IOP side effects due to suppressing rapid ocular absorption peaking without compromising the ocular bioavailability and anti-inflammatory effects for prednisolone derivatives. These findings warrant ethoniosomes as potential ocular delivery systems for both water soluble and insoluble drugs.[6]

Nanotechnology – Current & Future Developments

The scope of nanotechnology increase with a time for ophthalmic delivery of drug. Cyclosporin (Restasis) was the first drug that was marketed as ophthalmic nanoemulsion approved by FDA for the treatment of dry eyes. It is preservative free anionic nanoemulsion. Recent research study on dorzolamide nanoemulsion shows successful development of nanoemulsion for the treatment of glaucoma. Various study shows that nanoemulsion formulation shows great physiochemical properties, sustained drug release high therapeutic efficacy, fast onset of action compared to marketed conventional formulation in solution form. Cycokat is also the nanoemulsion of cyclosporine and it is use marketed for treatment of dry eye disease. Recently, Insite vision has been developed as drug delivery vehicle and Durasite(Besifloxacin) has been also approved by FDA for treatment of bacterial conjunctivitis. The technology involved in the preparation of Drasite utilizing polycarbophil as a biodegradable matrix for holding drug microparticle that increase drug retention time Cyclokat is also a novel nanoemulsion formulation of Cyclosporin A, which is currently in the market for the treatment of dry eye disease. The formulation is based on the Novasorb® technology developed by Novagali Pharma, that uses novel cationic nanoemulsion methodology for topical drug delivery. The Novasorb technology is known to improve bioavailability by interacting with anionic eye surface. Catioprost is another marketed nanoemulsion formulation of glaucoma drug. The formulation is also based on Novasorb technology and is a preservative-free cationic emulsion.

Recently, In Site Vision (USA) developed an innovative drug delivery vehicle, Durasite (polycarbophil, edentate disodium dihydrate and sodium chloride), as a platform for wide array of ocular drugs. FDA approved a Dura Site formulation containing Besifloxacin to treat bacterial conjunctivitis (pink eye). The technology involves utilizing polycarbophil as a

biodegradable matrix for holding drug microparticles for increased drug retention time. Challenges and perspective.[3]

Challenges Nanotechnology has been proven to be a powerful and effective tool for treatment and detection of ocular diseases by fabricating nanosystems. In this review, we have focused on advances in design and development of nanosystems for various ocular diseases.

Several nanosystems with different payloads have shown great potential in ocular delivery either in vitro or in vivo. However, several challenges still remain to be addressed in future studies, including:

(1) Among numerous studies of ocular disorder therapy by nanotechnology, many studies are focused on in vitro studies, and less in vivo studies have been accomplished. In the future, more efforts should be made in this area and animal models especially the ocular cancers model should be established.

(2) Although the rabbit is most commonly used animal because of the comparable size of human eye, rabbit eye has a higher surface sensitivity, higher mucus production and lower blinking frequency, lower tear production99. These differences would lead to a better result of bioadhesion and retention in the ocular surface thus made the effect of nanosystems unauthentic to human beings.

(3) For targeted delivery, the biomarkers are the most common types of target. As a result the ocular disease related biomarkers should be fully understood as well as the cellular and molecular mechanism of their functions.

(4) It is reported that nanoparticles seem to grow in size and aggregate inside the tissues after intravitreous injection or other administration route. This phenomenon could decrease the delivery efficiency and affect drug distribution.

Further studies need to improve our understanding of the fundamentals of nanoparticles and facilitate development of proper delivery routes for application. Perspective Considering the above aspects which deserve more efforts, nanotechnology has great application potential in ocular disease therapy and diagnosis. As a unique and relatively closed organ, the eye is always considered to be a perfect research object for gene and drug delivery because the systemic circulation is usually omitted. Data from wiley website revealed that more than 1500 gene therapy clinical trials for ophthalmology are underway100. There are various nanomaterials used for nanosystem fabrication. However, their toxicities are not completely understood in the eye, especially for those repeated dosage materials. It seems that colloidal

carriers and some FDA approved materials have more potential in application. In addition to delivery systems, future non-invasive delivery routes will be emphasized for ocular diseases in both segments. Finally, all-in-one systems which might combine diagnostic and therapeutic functions may be introduced to enable visual tracking during the ocular disease treatment.[2]

CONCLUSION

The review discusses in detail, the development of ocular nanoformulation approaches like calcium phosphate (CaP) nanoparticles, nanoemulsions, polymeric nanoparticles, nanomicelles, soft contact lenses, ophthalmic liposomal formulations and patent inventions reported from promising therapeutic outcomes utilizing the nanoformulation approaches. Recent studies shows that significant enhancement of therapeutic outcome by use of nanoformulation systems for chronic disease states of both anterior and posterior ocular segments. Various research studies shows improved therapeutic efficacy, increased drug bioavailability and decreased toxicity with the use of nanoformulations, compared to conventional treatment approaches. From the promising research data reported in patent disclosures, nanoformulation strategy can primarily benefit chronic anterior segment ocular diseases (Glaucoma, Dry Eye, Conjunctivitis, Uveitis, Choroidal Neovascularization) and also posterior segment ocular diseases (Age Related Macular Degeneration). In light of promising inventions, extensive research is in progress to delineate nanoformulation approach applicable for broad ocular disease states. Now various research are focus on development of nanocarrier which could reach targeted ocular tissue, including back of the eye tissues, post non-invasive mode of drug administration.

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