

Novel approaches for ocular drug delivery: A reviewAmandeep Singh^{1,2}, Tara Singh Dogra¹, Uttam kumar mandal², Raj kumar Narang^{1*}¹Department of Pharmaceutics, I. S. F. College of Pharmacy, Moga-142001, Punjab, India²Research scholar, Department of Pharmaceutical Sciences and Technology, Maharaja Ranjit Singh Punjab Technical University, Bathinda - 151001, Punjab, India.

Abstract: Nanocarrier have been recently studied for their relevance in ophthalmic drug delivery. These systems are capable to evade the ocular barriers that presently edge the efficacy of conventional treatments, as well as offer additional sustained release of drug, decreasing the administration frequency and increasing patient compliance. This review summarizes the ophthalmic drug delivery from conventional treatment to the utilization of nanocarriers as novel drug delivery system.

Key words: Drug delivery, Nanocarrier, Novel drug delivery system, Ocular, Emulsions, Implants

Introduction

Eye is special and profoundly organ on account of its perplexing capacity. Its life structures, physiology and natural chemistry make this organ carefully impervious to external substances. The test ahead of formulator is to detailing of particular sorts of dose structure which can't create any tissue harm of eye. For infection of the eye, topical organization is normally best more than the systemic organization. Anatomical contrast of each layer of the visual tissues can bring about a noteworthy obstruction for medication conveyed by any course, i. e., topical, intraocular and systemic. For any medication organization, firstly the medication atoms cross the precorneal obstruction, and then cross the corneal hindrance. Precorneal obstruction comprise of the tear (film) and the conjunctiva that moderate the conveyance of medication into the visual tissues furthermore in charge of decreased bioavailability of customary visual details. The centralization of imparted dosage begins diminishing inside of 2 minutes at precorneal territory in people. Cornea is the major organic barrier to infiltration of the solution (1,2). Ocular bioavailability of medication particle is additionally relying on couple of physiological properties of medication including, protein tying, drug digestion system, lacrimal seepage and so on and physiological components which can influence the medication's visual bioavailability (3). Figure 1 reveals the destiny of visual medication retention. In any case, for the most part of the visual details are rapidly lost amid

nasolacrimal seepage right away. Different types of dosage forms are used for different ocular diseases. Like the Conventional ocular dosage forms (eye solutions, suspensions, ointments etc), these are mostly used for ocular disease management. More than 90% of the promoted visual measurement structures are as eye drops, suspension, treatments, gels and so forth (4). These dosage forms are mainly target the ocular anterior segme. But due to the less contact time, these dosage forms have not more therapeutic effects on eye. To defeat these problems, novel ocular dosage forms are used for various ocular diseases. Like controlled ocular dosage form that are implants, ocular inserts, contact lenses, iontophoresis etc, have sustained release properties by slow degradation of polymer (5). They also enhance the retention time of drug in cul-de-sac of eye. The colloidal systems including liposomes, niosomes, nanoparticles etc, penetrate into the deeper tissues of eye and increase the ocular drug absorption. They additionally keep the metabolic system of medications from the catalysts that present at eye tissues (6). These can keep up medication movement at its site of activity and are suitable for inadequately water-solvent medications. The advanced ocular dosage forms like cyclodextrins, they increase the solubility of poorly aqueous soluble drug. Another is quality conveyance that conveys the nucleic acids to a particular site of eye. In this way, progressing research on Novel ocular dose

Corresponding Author:**Dr. Raj kumar Narang,**

Professor,

Department of Pharmaceutics, ISF College of Pharmacy,
Moga, Punjab, Postal Code: 142001, India.

E-mail: drrknisf@gmail.com



structures is help to defeat all detriments of conventional ocular dosage forms (7).

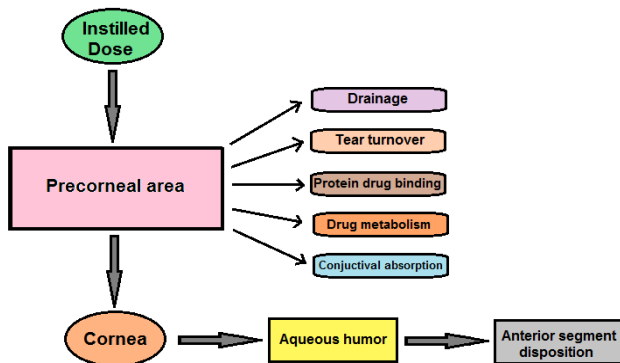


Figure 1. Fate of drug absorption by ocular rout

Required characteristics to optimize Ocular Dosage form are:

- Prolong contact time with ocular tissues.
- Good corneal penetration of drug.
- Non irritant and comfortable form for ocular tissues.
- Simple instillation of drug for the patient (8)

Different Conventional Ocular dosage form

Different conventional ocular dosage forms [figure. 2] are discussed below: -



Figure 2. Different types of conventional ocular dosage form.

Solutions

Greater part of topical ophthalmic arrangements accessible are as fluid arrangements since they are the most helpful, sheltered, tolerant consistence, in a flash dynamic and non-obtrusive type of visual medication organization. An eye arrangement gives strike medication saturation to topical drop instillation, following which its focus quickly low. The energy of low medication fixation may take after an inexact first request. Accordingly, to enhance drug saturation, contact time and visual bioavailability; different excipients might be mixeded to topically eye drops, for example, consistency enhancers, buffering operators, penetration enhancers. Table 1 demonstrates various advertised definitions of ordinary visual

measurements structure. Usually utilized thickness operators to improve precorneal living arrangement time and medication bioavailability incorporate polyvinyl alcohol (PVA), hydroxyl methylcellulose, sodium carboxyl methyl cellulose, hydroxypropyl methylcellulose (HPMC), carboxy methylcellulose and carbomers and some regular polymers (e.g. Hyaluronic corrosive (HA), guar gum, gellan gum and so on) has likewise been utilized to influence the thickness of the visual definition and hence improve bioavailability of drugs (9).

Suspensions

Suspensions are one more type of non-obtrusive visual measurement shape and offer particular focal points. Suspension might be characterized as scattering of finely isolated insoluble medication in a watery dissolvable comprising of a suitable suspending and scattering specialists. The planning of a clean, protected, proficient, steady and pharmaceutically rich suspension is further mixes and testing contrasted with normal ocular arrangements (10). A few of the difficulty so as to a formulator ought to overcome amid the advancement of a suspension are non-homogeneity of the ocular measurements structure, settling, cake development, collection of the suspended particles, successful conservation, resuspendability and simplicity of production. Suspensions are actively steady other than thermodynamically insecure frameworks, keeping in mind left undisturbed for a long period of time, lead to collection of particles, sedimentation lastly hardening (11).

Ointments

Ocular ointments are semisolid dosage forms for topical application and large comprising of solid or semisolid hydrocarbon base of dissolving or softening point close to human body temperature. The inclination of a base relies on the clinical proposal for the balm. The distinctive sorts of treatment bases are Absorption bases (e.g. beeswax, fleece fat), Water-dissolvable bases (e.g. macrogols 200, 300, 400), Hydrocarbon bases (e.g. hard paraffin, delicate paraffin, microcrystalline wax), Vegetable oils (e.g. olive oil, coconut oil, sesame oil, almond oil), Emulsifying bases (e.g. emulsifying wax, cetrimide) (12). The determination of hydrocarbon is dependent on biocompatibility. Treatments help to enhance visual bioavailability and maintain the arrival of medication. It has a longer ocular contact time as compared to several ophthalmic solutions. After applying the ocular ointment, it decomposes into small drops of formulation, which stay for a longer period in conjunctival sac, therefore improving drug's bioavailability. Ocular ointments

have certain drawbacks, while they are well tolerated and secure, they can bring about obscuring of vision because of refractive list contrast among the tears and the non-fluid nature and infrequently have aggravating impacts. Ordinary created process for a visual balm incorporates micronization and disinfection of the medication by, ethylene oxide illumination, gamma light or dry warmth (13). In the event that Antimicrobial additives are required, for example, chlorobutanol or parabens are broken down in a mix of liquid petrolatum and mineral oil and cooled to on 40°C with perpetual blending to guarantee homogeneity. Sanitized and micronized dynamic is after that additional aseptically to the hot cleaned petrolatum/mineral oil mix with persistent blending until the treatment is uniform. The treatment is then pressed into presterilized ophthalmic tubes (14).

Emulsion

An emulsion based ocular detailing approach offers an advantage to improve both dissolvability and bioavailability of medications. There are two sorts of eye emulsions which are financially employed as

vehicles for dynamic pharmaceuticals: (1) oil in water (o/w) and (2) water in oil (w/o) emulsion frameworks. For visual dose structure, o/w emulsion is basic and generally favored in abundance of w/o framework. The reasons contain not as quite a bit of disturbance and better visual resilience of o/w emulsion. Various studies have confirmed pertinence of emulsions in improvement precorneal home time, giving support drug, drug corneal penetration discharge and along these lines improving visual bioavailability. For the mainly part, ophthalmic emulsions are detailed by blending or scattering the dynamic fixing into an oil stage, suspending operators, together with suitable emulsifying and blending with water overwhelmingly to shape a homogeneous oil-in-water emulsion. Each stage is commonly disinfected past to or amid rushing into the blending vessel. High-shear homogenation might be utilized to abatement oil bead size to sub-micron size which might show signs of improvement the physical dependability of the oil micelles so they don't consolidate (15).

Table 1. Some marketed formulations of conventional ocular dosage form

Ocular Dosage Form	Marketed Formulation	Drug	Indication	Advantages	Disadvantages
Solutions	Betnisol N Ciplox	Betamithasone Ciprofloxacin	Eye infection Conjunctivitis	Convenient. No effect on vision of patient.	Non-sustained action. Rapid drainage. loss of both solution and suspended solids.
Suspensions	Pred Fort Nevanac	Prednisolone acetate Nepafenac	Anti-allergic Anti-inflammatory	Patient compliance. Slow dissolution of drug.	Performance depend on drug properties. Patient non-compliance.
Emulsions	Restasis Enpred	Cyclosporine Difluprednate	Dry eye	Prolonged release of drug from vehicle. Improve drug stability.	Blurred vision.
Ointments	Acivir eye Chloromycetin	Acyclovir Chloramphenicolpalmitate	Eye infection Conjunctivitis	Inhibition of dilution by tears.	Poor patient compliance. Blurred vision.
Gels	GenTeal	Hydroxypropyl methylcellulose	Dry eye	Less blurred vision. Comfortable.	No rate control on diffusion. Matted eyelids after use.

Gels

Ocular gels are composed of mucoadhesive polymers (e.g. carboxymethylcellulose, carbopol, polycarbophil, sodium alginate etc) that tender localized delivery of drug to the eye. The gels have been shown to considerably longer residence times in the cul-de-sac by increased drug bioavailability. Typical gelling agents includes hyaluronic acid, cellulose derivatives, PVA and carbomer (16). These

polymers have a property recognized as bioadhesion that is attachment of a drug carrier to a specific biological tissue of eye and able to extend the contact time of the drug and thus enhance ocular bioavailability. These systems are further acceptable to patients while they are administered into the eyes like solution after which they undergo change in to gels. The polymers used in these systems shows reversible phase transition. The change in viscosity

can be due to adjust in pH, temperature and ionic strength. The purpose of the polymer assumes a noteworthy part in the discharge energy of the medication from the visual measurement structure. Various bioadhesive polymers are accessible with various level of mucoadhesive execution (17).

Drawbacks of Conventional Ocular Dosage Form

Conventional ocular dosage forms have various types of drawbacks (figure 3), these are discuss below:-

- **Loss of drug by drainage:** Rapid loss of drug by drainage due to gravity, blinking reflex, induced lachrymation and typical tear turnover i. e. typical tear volume is around 7 ul, the flickering eye can hold a volume of up to 30 ul without spillage yet the drop volume is around 50 ul.
- **Blurred vision:** Various types of conventional ocular dosage forms i. e. gels, ointments etc, can affect on normal vision of eye. When these types of ocular formulation applied on eye, the outer surface of eye is covered. So, that the normal vision of eye can be disturbed.
- **Irritation:** Some ocular formulations (e.g. eye solutions, suspensions, emulsions, etc) can cause irritation due to its excipients i. e. buffering agents, antioxidants, surfactants, etc, because these excipients can irritate to tissues of eye.
- **Non-sustain action:** Due to its conventional action, these formulations has not sustained action. The rate of drug release is very fast in conventional ocular dosage form because the roles of controlled release polymers are nothing in this formulation.
- **Patient non compliance:** Various ocular formulations like ointments, gels, etc does not accepted by some patients due to its difficult installation.
- **Nature of drug:** The corneal absorption of the eye is depending upon the nature of drug. To be effectively absorbed, the drug must have differential solubility i. e. the ionised and non-ionised form (18).

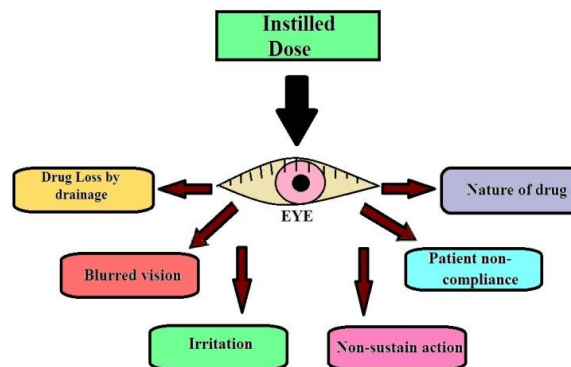


Figure 3. Different drawbacks of conventional ocular dosage form

Different Anatomical Barriers to Restrict Ocular Dosage Form

Tear as barrier: The main precorneal hindrance of eye is tear film which decreases the compelling convergence of the administrated drugs because of weakening by the tear turnover, quickened freedom, and medication tying with tear proteins. Figure 4 represents the pharmacokinetics of drug in tear fluid. The main constituents of the tear film are lipids, mucins and water. The tear film is capable to wet the surface of eye due to a film of mucin bound to the corneal and conjunctival epithelium. The tear film is very thin, about 5 microns, and is consisting of a sloppy mucin-gel covered by a thin layer of lipids. During irritation or emotional stress, when lacrimal production is extremely increased the water content of tears (19).

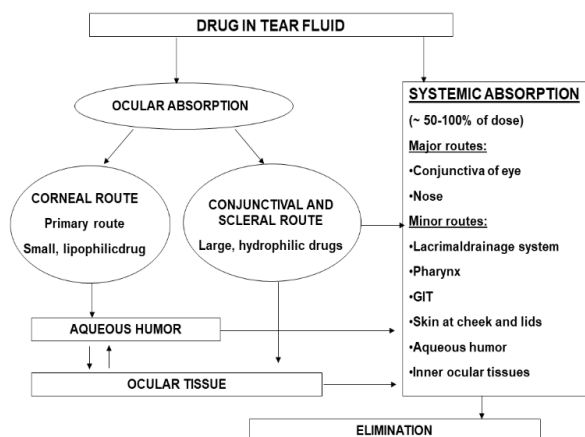


Figure 4. Pharmacokinetics of drug in tear fluid

Cornea as barrier

Corneal obstruction is an imperative mechanical and synthetic barrier, which limits the entrance of exogenous substances into the visual site and ensures the intraocular tissues. Figure 5 demonstrates defferent anatomical obstructions of eye. The cornea is a transparence and a vascular structure with normal breadth is 12 mm and thickness is 520 mm. fundamentally cornea is

comprising of five layers; corneal epithelium Bowman's layer, stroma, Descemet's film, storm cellular layer, and endothelium. Every layer has an alternate extremity and a rate-constraining course of

action for medication pervasion. Corneal epithelium is a lipid soluble in nature, and stretched intersections with cells are shaped to confine paracellular drug pervasion as of the tear film (20).

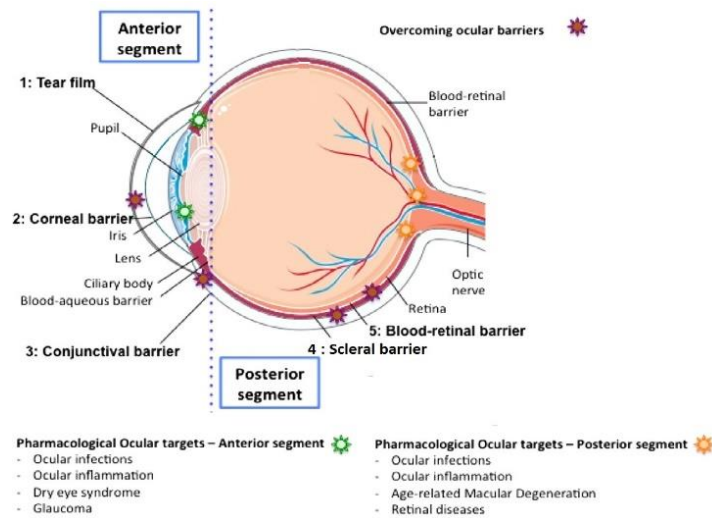


Figure 5. Different Anatomical barriers of eye for ocular dosage form

Conjunctiva as barrier

The conjunctival assumes important part as suspicious obstruction on the visual exterior, and it adds to the arrangement and security of the tear film during the creation of bodily fluid glycoproteins furthermore has a rich supply of vessels and lymphatics. A noteworthy part of the medication is lost to the systemic dissemination even as intersection the conjunctiva. The remaining medication can enter by the sclera, which include usually of collagen and mucopolysaccharides. To achieve the foremost eye through the non-corneal course, the medication needs to pass the bulbar conjunctiva, which is penetrable to medications of various extremity and size. Administrated drugs into the conjunctival or episcleral space may be washed through blood and lymph. The veins of conjunctiva don't make a tight intersection hindrance, which implies drug atoms can arrive into the blood flow by pinocytosis (21).

Sclera as barrier

The sclera primarily comprises of collagen strands and proteoglycans settled in an extracellular network. Scleral porousness has been appeared to bring about a solid reliance on the sub-atomic sweep; scleral penetrability diminishes generally exponentially with sub-atomic range. In addition, the back sclera is shaped of a looser weave of collagen strands than the front sclera, and the human sclera is similarly thick close to the limbus (0.53 ± 0.14 mm), slim at the equator (0.39 ± 0.17 mm), and much thicker near the optic nerve ($0.9-1.0$ mm). Subsequently, the perfect site for transscleral drug

conveyance is near the equator at 12–17 mm back to the corneosclerallimbus. Hydrophobicity of medication atoms influences scleral porousness; higher lipophilicity demonstrates lower penetrability and hydrophilic medications might distribute through the fluid medium of proteoglycans in the fiber network pores more just than lipid soluble medications. In addition, the charge of the medication atom additionally influences its porousness over the sclera. Absolutely charged atoms might demonstrate poor penetrability because of their coupling to the contrarily charged proteoglycan lattice (22).

Blood-retinal barrier

Blood-retinal barrier (BRB) confines drug transport instrument from blood into the retina. It is framed by the endothelial cells of retinal veins and the retinal color epithelial cells. The multiple layered neural retina is distanced by the subretinal space from the retinal shade epithelium (RPE) monolayer, which circulates the external surface of the neural retina from the choroid. In physiologic situation, the retina is immovably connected to the RPE. The RPE demonstration an indispensable part in keeping up the reasonability and capacity of the neural retina. The RPE is in charge of the disposal of liquid from the subretinal gap keeping in mind the end goal to hold retinal bond and to continue through to the end retina in a condition of lack of hydration (23).

Advancement in ocular dosage form

Due to the various limitations of conventional ocular dosage forms (figure 6) different types of

advancements (like liposomes, niosomes, nanosuspensions, dendrimers, implants, etc.) have been created to build the contact time and bioavailability of medication (24). These are discussed below:-

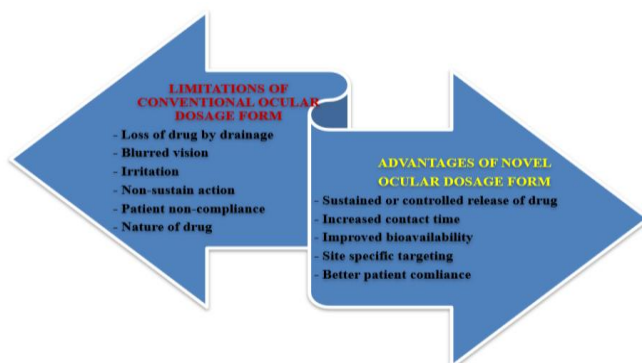


Figure 6. Various limitations of conventional ocular dosage form and advancements of novel ocular dosage forms

Ocular Inserts

Ocular inserts are hygienic formulation with a solid or a semisolid uniformity and their size and shape are specially considered for ophthalmic application. Ocular inserts offers an striking approach to conquer the eye problems by use of the controlled release principles. Ocular inserts also offer the prospective benefit of improving bioavailability, increasing the contact time of drug and reducing the dosing frequency. As of late, there has been blast of centrality in the polymer-based carrier for drug delivery. They are made out of various polymeric frameworks with or without medications. There are two sorts of supplements, insoluble and solvent additions. Insoluble additions are generally conveying drugs by a few of strategies at maintained, foreordained rate; however, the evacuations of supplements are essential after complete exhausting of medication from their definition (25).

Nanofiber based nanopatch

Recently, developments of nanofiber based nanopatch are more effective for ocular drug delivery. The nano-fibers patches are developed by using electrospinning. Electrospinning is one of the most excellent methods for the fabrication of nano-fibers. Due to very small diameter and higher surface area of nano-fibers patch, higher drug contents can be loaded in a very small portion of the nano patch. The developed nano-fibers patch can be successfully inserted to the cul-de-sac area of eye (26). The roles of polymers are most important for the formulation of nanofiber patch. The selection of polymers should be biodegradable and biocompatible in nature. Therefore, the

nanofiberpatch has slowdegradation property with time. Due to slow degradation, the releases of drug molecules are sustained. The physical characteristics and specific functional uses of selected polymer are depending on the degree of hydrolysis and polymerization (27).

Implants

Intraocular implants are for the most part utilized to give limited controlled medication discharge over a developed period. It can be grouped into two classifications that in light of debasement property (1) biodegradable and (2) non-biodegradable. These intraocular implants have been connected in the treatment of visual infections influencing both foremost and back fragments of eye (28). Some implantables have been utilized for visual medication conveyance especially for the management of endless vitreoretinal infections. Non-biodegradable intraocular implants offer durable discharge by accomplishing near zero request discharge energy. Cases of non-biodegradable implants are Vitrasert and Retisert. Another class is biodegradable implants that are not required to uproot surgically. Biodegradable polymers that utilization in implants are polycaprolactone, polyglycolic corrosive, polylactic corrosive and so forth. Surodex and Ozurdex are samples of biodegradable implants which are intended for the conveyance of dexamethasone to visual tissues (29).

In-situ gelling systems

In-situ hydrogels are polymeric arrangement which can be conveyed as fluid upon instillation and experience stage move in parkway of the eye to frame gel and this gives a reaction to natural boosts like change in pH, temperature (30). Moderate medication seepage from the eyeball surface can bring about by this property and expansion the bioavailability of the dynamic fixings. Polymers like poloxamer, gellan gum, cellulose acetic acid derivation phthalate and so on utilized in adding to these medication measurements frames while dynamic fixings are utilized as a part of the different explores on in situ gels incorporate fluconazole, ganciclovir, ciprofloxacin hydrochloride, timolol maleate and pilocarpine (31).

Contact lenses

Contact lenses are thin and twisted shape plastic plates and the created design help to cover the cornea of eye. After establishment, contact lens sticks to the tear film over the corneal layer because of the surface pressure. Drug stacked contact lens have been intended for visual conveyance of numerous medications, for example, β -blockers, antihistamines

and antimicrobials (32). The first and most generally utilized polymer as a part of the advancement of contact lenses was the cross-connected poly (2-hydroxyethyl methacrylate) with little amount of ethylene glycol dimethylacrylate. As of late, different examines have been led on utilizing silicon-based lenses (33). Centrality in contact lenses still develops, which is built up by bring up in the quantity of examination articles on its utilization distributed lately. Distinctive samples of medications whose pharmaceutical availability from lenses was scrutinized involve timolol, dexamethasone, ciprofloxacin and cyclosporine (34).

Iontophoresis

Because of non-intrusive nature of medication conveyance to both foremost and back portions of eye, visual iontophoresis has increased huge consideration. It requires electric current which is connected to improve ionized medication infiltration into visual tissues. This type of conveyance can conquer the potential reactions related with intraocular infusions and inserts (35). Visual iontophoresis is protected, quick and easy as well as convey more centralization of medication to particular site of eye. The conveyance of anti-infection agents by iontophoresis technique has brought about critical to less bacterial settlements in cornea when contrasted with the eye drops. Different cases of anti-toxins successfully utilized are tobramycin, gentamicin, and ciprofloxacin however not for vancomycin due to its high atomic weight (36).

Micro Needles

Microneedle based strategy is a developing and negligibly intrusive type of medication conveyance framework to back visual tissues. This strategy might give proficient treatment way to deal with vision debilitating back ophthalmic infections. Microneedle based organization methodology might lessen the danger and inconveniences related with intravitreal infusions (37). Likewise, this methodology might keep away from blood retinal barrier and transport restorative medication levels to retina/choroid. Microneedles are custom intended to enter just the many microns into sclera, in order that harm to more profound visual tissues might be stayed away from furthermore store drug with bearer framework into the sclera or into the slight gap present in the middle of sclera and choroid called "suprachoroidal space" (SCS). Suspensions, Nanoparticles and microparticles were likewise conveyed into the sclera by microneedles (38).

Liposomes

Liposomes are the lipid containing vesicular framework comprises with one or more phospholipid bilayers ensnaring a watery center. The size scope of liposomes as a rule between 0.08 to 10.00 μm yet in view of the size and phospholipid bilayers, the liposomes can be named little estimated unilamellar vesicles (10–100 nm), huge measured unilamellar vesicles (100–300 nm) and multilamellar estimated vesicles (contains more than one bilayers (39). For visual applications, liposomes mean perfect medication conveyance frameworks because of its brilliant biocompatibility, cell film like course of action and capacity to entangle both hydrophilic and hydrophobic medication atoms furthermore have great adequacy for both front and back fragment of eye. They are likewise having a close contact time with corneal and conjunctival surfaces which is important for medications that are inadequately ingested. The adversely charged mucin on corneal epithelium might tie with positive charged liposomes (40).

Niosomes and Discomes

Niosomes are bilayered auxiliary vesicles that made up of the non-ionic surfactant furthermore equipped for embodying both lipophilic and hydrophilic medication atoms. In a late way to deal with the conveyance of cyclopentolate, niosomal drug conveyance framework was produced. It discharged the medication particles autonomous of pH bringing about boss upgrade of visual bioavailability (41). Niosomal conveyance arrangement of covered (chitosan or carbopol) containing timolol maleate indicated noteworthy IOP bringing down result in rabbits when contrasted with timolol maleate arrangement. Another novel medication conveyance framework that is discomes has been created. These are huge structures framework with a size scope of 12–16 μm determined by consolidating nonionic surfactant Solutan C24 in niosomes. Principle favorable position of this framework was less systemic waste as a result of the expansive size reach and vast living arrangement time in the circular drive of eye because of their circle shape. Drug (Timolol maleate) was effectively captured in both discomes and niosomes. In vivo rate and extent of the medication containing discomes was superior to the niosomes (42).

Nanoparticles

Nanoparticles are the colloidal transporter framework with size scope of 10 to 1000 nm. For ocular medication conveyance, nanoparticles are normally made out of lipids, proteins, manufactured or regular polymers, for example, egg whites, poly

(lactide-co-glycolide) (PLGA), sodium alginate, chitosan, polylactic corrosive (PLA) and polycaprolactone (PCL). In nanocapsules, drug particles are encased inside the polymeric shell despite the fact that in nanospheres; medication is consistently scattered all through polymeric network (43). Nanoparticles speak to critical results for visual medication conveyance on account of its little size extent prompting low bothering and managed discharge property. Then again, as fluid arrangements, drug containing nanoparticles might be killed quickly from precorneal compartment of eye. Along these lines, for topical organization of nanoparticles with mucoadhesive properties have been produced to build the precorneal home time. Chitosan, Polyethylene glycol (PEG) and hyaluronic corrosive are usually used to enhance precorneal living arrangement time of nanoparticles (44).

Nanosuspensions

Nanosuspensions are colloidal scattering in which submicron drug particles are balanced out by polymer (s) or surfactant (s). It is developed as promising methodology for conveyance of hydrophobic medication particles. For visual medication conveyance, it gives heaps of favorable circumstances, for example, disinfection, less disturbance, simplicity of eye drop detailing, increment precorneal living arrangement time and change in visual medications bioavailability which are insoluble in tear liquid (45). The viability of nanosuspensions in enhancing visual bioavailability of glucocorticoids class of medication has been shown in a few exploration studies. Glucocorticoids, for example, hydrocortisone, dexamethasone and prednisolone are generally suggested for the management of provocative environment influencing front fragment of eye. These medications require regular organization at higher measurements in current treatment which actuate harm optic nerve, waterfall development and glaucoma. The visual bioavailability of a range of glucocorticoids (prednisolone, hydrocortisone and dexamethasone) from nanosuspensions, microcrystalline suspensions and arrangements. The visual measurement structures were imparted into the circular drive of the rabbit eye and intraocular weight (IOP) was computed at incessant time interims up to 12 h. The territory under rate bring up in IOP versus time bend (AUC) values for all the medication containing suspensions were advanced than the particular medication arrangements (46).

Nanomicelles

Nanomicelles are the most typically utilized transporter frameworks to define the helpful

specialists as clear watery arrangements. In expansive, these nanomicelles are readied with amphiphilic atoms. These particles might be surfactant or polymeric structure in nature. In no time, significantly hobby is being demonstrated towards the improvement of nanomicellar detailing based innovation for ophthalmic drug conveyance (47). Also, micellar definition can increase the bioavailability of the helpful specialists in visual tissues. A few endeavors are additionally being made to utilize nanomicelles for the back visual medication conveyance of eye. As of late, the creators have made a critical stride to convey remedial specialists to the back visual tissues with the assistance of topical drops of blended nanomicellar plans. Drawn out micellar course was accomplished by controlling the polymer to medication charge proportions. Creators speculate that more drawn out systemic micellar course might help in enhanced pervasion and maintenance impact at neovascularization site. Micellar plans were seen to specifically accumulate at the pathologic neovascular site to a more prominent level than in typical tissues (48).

Dendrimers

Dendrimers are nanosized, very fanned, star molded polymeric conveyance frameworks. These stretched polymeric frameworks are existing in various atomic weights with terminal end amine, carboxyl or hydroxyl useful gathering. Dendrimers are being utilized as bearer frameworks as a part of medication conveyance. Decision of sub-atomic weight, size, sub-atomic geometry, surface charge and utilitarian gathering are not kidding to convey drugs. The greatly spread structure of dendrimers permits osmosis of extensive variety of medication particles, for example, hydrophobic and additionally hydrophilic. In visual medication conveyance, couples of skilled results were accounted for with these to a great degree expanded polymeric frameworks (49).

Cyclodextrins

The Cyclodextrins (CDs) identified with a gathering of cyclic oligosaccharides fit for framing consideration buildings. Amid CD complexation, fluid dissolvability of hydrophobic medications can be enhanced without changing their atomic structure and their fundamental capacity to pervade organic films. Drug particles having lower fluid solvency have been conveyed as the CD buildings. These buildings have been affirmed to increment corneal penetration of medication particles like cyclosporine, dexamethasone etc. Cd complexation can essentially

expand the visual bioavailability of inadequately water solvent medications (50).

Gene Delivery

As of late, diverse techniques have been received to convey nucleic acids to a focusing on location inside of the eye. Created conveyance framework for siRNAs, antisense ODNs or aptamers is a testing errand for scientists in visual medication conveyance field in view of solvency of the dynamic medication, high atomic weight, size, surface charge and inborn complexities related with the arrangement of visual tissues like retina, cornea and so forth (51).

Future of nanomedicines

The science of nanomedicine is presently the most attractive areas of research. A lot of research in this field in the last two decades has previously lead to the filling of 1500 patents and conclusion of several dozens of clinical trials. As outlined in the different sections over cancer appears to be the best illustration of diseases where both its diagnosis and therapy have advantage from nonmedical technologies. The variety of types of nanoparticles for the delivery of the precise quantity of drug to the affected cells such as the cancer cells, without disturbing the physiology (51). The application of nanomedicine is positively the trend that will stay to be the future of research and development.

The examples of nanoparticles illustrated in these communications are not regular in their size, with several truly measuring in nanometers even as others are measured in sub-micrometers (over 100 nm). Further research on materials with additional reliable uniformity and drug release capacity would be the supplementary for research. The significant amount of progress in the use of metals-based nanoparticles for investigative purposes. Even though the awesome perceptive of the future prospect of nanomedicine and nano-drug delivery system, its actual impact in healthcare system, even in cancer therapy remains to be very limited. This feature to the field creature a new region of science with only two decades of genuine research on the subject (52).

The markers of diseased tissues together with key biological markers that permit complete targeting without varying the normal cellular process is one chief potential area of research. Eventually, the relevance of nanomedicine will go forward with our increasing awareness of diseases at molecular level or that mirrors a nanomaterial-subcellular size similar marker identification to open up avenues for new diagnosis/therapy. Thus, understanding the

molecular signatures of disease in the future will lead to advances in nanomedicine applications. As nanomedicines expand attractiveness, their affordability would be a different area of research that desires further research input.

Conclusion

The potential for the development of novel medication conveyance frameworks including polymeric frameworks is limitless and more up to date polymers would fill the need of controlled and managed conveyance for treating ophthalmic sicknesses. The recent novel ocular formulation provides sustained release of drug at particular eye site. With the help of various polymers bioavailability of drugs can be enhanced. Combination of various drugs with polymer coating is a better way to deliver the drug in control manners.

References


1. Kels BD, Grzybowski A, Grant-Kels JM. Human ocular anatomy. *Clinics in dermatology*.1; 33(2) (2015):140-6.
2. Casper DS, Sparrow JR. *Orbital and Ocular Anatomy. The Columbia Guide to Basic Elements of Eye Care*. Springer, Cham 2019 (pp. 3-25).
3. Rathore KS, Nema RK. Review on ocular inserts. *Int J PharmTech Res*. 1(2): (2009) 164-9.
4. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. *The AAPS journal*. 1;12(3) (2010 Sep): 348-60.
5. Chen H. Recent developments in ocular drug delivery. *Journal of drug targeting*.14;23(7-8): (2015 Sep) 597-604.
6. Morrison PW, Khutoryanskiy VV. Advances in ophthalmic drug delivery. *Therapeutic delivery*.;5 (12) (2014 Dec) 1297-315.
7. Bhattacharjee A, Das PJ, Adhikari P, Marbaniang D, Pal P, Ray S, Mazumder B. Novel drug delivery systems for ocular therapy: With special reference to liposomal ocular delivery. *European journal of ophthalmology*.;29(1) (2019 Jan):113-26.
8. Bucolo C, Drago F, Salomone S. Ocular drug delivery: a clue from nanotechnology. *Frontiers in pharmacology*. 25;3 (2012 Oct)188.
9. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. *World journal of pharmacology*.2(2) (2013):47.

10. Ghate D, Edelhauser HF. Ocular drug delivery. Expert opinion on drug delivery. 1;3 (2) (2006 Mar)275-87.
11. Achouri D, Alhanout K, Piccerelle P, Andrieu V. Recent advances in ocular drug delivery. Drug development and industrial pharmacy. 1;39 (11) (2013 Nov) 1599-617.
12. Al-Amri AM. Long-term follow-up of tacrolimus ointment for treatment of atopic keratoconjunctivitis. American journal of ophthalmology. 1;157(2) (2014 Feb):280-292
13. Hessen M, Akpek EK. Dry eye: an inflammatory ocular disease. Journal of ophthalmic & vision research.;9(2) (2014 Apr):240-253.
14. Ali Y, Lehmussaari K. Industrial perspective in ocular drug delivery. Advanced drug delivery reviews. 15;58(11)(2006 Nov):1258-68.
15. Gote V, Sikder S, Sicotte J, Pal D. Ocular Drug Delivery: Present Innovations and Future Challenges. Journal of Pharmacology and Experimental Therapeutics. 1 (2019 Jan) j100-119.
16. Nayak AK, Bera H. In situ polysaccharide-based gels for topical drug delivery applications. InPolysaccharide Carriers for Drug Delivery 2019 Jan 1 (pp. 615-638).
17. Subrizi A, del Amo EM, Korzhakov-Vlakh V, Tennikova T, Ruponen M, Urtti A. Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties. Drug discovery today. 2019 Feb 7.
18. Majeed A, Khan NA. Ocular in situ gel: An overview. Journal of Drug Delivery and Therapeutics. 15;9(1): (2019 Jan)337-47.
19. Sharma OP, Patel V, Mehta T. Nanocrystal for ocular drug delivery: hope or hype. Drug delivery and translational research. 1;6(4)(2016 Aug)399-413.
20. Skalicky SE, Petsoglou C, Gurbaxani A, Fraser CL, McCluskey P. New agents for treating dry eye syndrome. InStudies on the Cornea and Lens 2015 (pp. 115-129).
21. Ruponen M, Urtti A. Undefined role of mucus as a barrier in ocular drug delivery. European Journal of Pharmaceutics and Biopharmaceutics. 1;96:(2015 Oct)442-6.
22. Nettey H, Darko Y, Bamiro OA, Addo RT. Ocular barriers. InOcular Drug Delivery: Advances, Challenges and Applications 2016 (pp. 27-36). Springer, Cham.
23. Cunha-Vaz J, Marques FB, Fernandes R, Alves C, Velpandian T. Drug transport across blood-ocular barriers and pharmacokinetics. InPharmacology of Ocular Therapeutics 2016 (pp. 37-63). Adis, Cham.
24. Yellepeddi VK, Palakurthi S. Recent advances in topical ocular drug delivery. Journal of Ocular Pharmacology and Therapeutics. 2016 Mar 1;32(2):67-82.
25. Kuno N, Fujii S. Recent advances in ocular drug delivery systems. Polymers.;3(1)(2011 Mar)193-221.
26. Shahriar SM, Mondal J, Hasan MN, Revuri V, Lee DY, Lee YK. Electrospinning nanofibers for therapeutics delivery. Nanomaterials.;9(4)(2019 Apr)53-67
27. Singh A, Rath G, Singh R, Goyal AK. Nanofibers: An effective tool for controlled and sustained drug delivery. Current drug delivery. 1;15(2)(2018 Feb)155-66.
28. Stevenson CL, Santini Jr JT, Langer R. Reservoir-based drug delivery systems utilizing microtechnology. Advanced drug delivery reviews. 1;64(14)(2012 Nov) 1590-1602.
29. Rawas-Qalaji M, Williams CA. Advances in ocular drug delivery. Current eye research. 1;37(5):(2012 May)345-56.
30. Rupenthal ID, Green CR, Alany RG. Comparison of ion-activated in situ gelling systems for ocular drug delivery. Part 1: physicochemical characterisation and in vitro release. International journal of pharmaceutics. 15;411(1-2):(2011 Jun)69-77.
31. Agrawal AK, Das M, Jain S. In situ gel systems as 'smart' carriers for sustained ocular drug delivery. Expert opinion on drug delivery. 1;9(4):(2012 Apr)383-402.
32. Maulvi FA, Soni TG, Shah DO. A review on therapeutic contact lenses for ocular drug delivery. Drug delivery. 12;23(8):(2016 Oct)3017-26.
33. Yasin H, Yousaf Z. Synthesis of hydrogels and their emerging role in pharmaceutics. InBiomedical Applications of Nanoparticles 2019 Jan (pp. 163-194).
34. Mehta P, Haj-Ahmad R, Al-Kinani A, Arshad MS, Chang MW, Alany RG, Ahmad Z. Approaches in topical ocular drug delivery and developments in the use of contact lenses as drug-delivery devices. Therapeutic delivery.8(7):(2017 Jul)521-41.

35. Eljarrat-Binstock E, Domb AJ. Iontophoresis: a non-invasive ocular drug delivery. *Journal of Controlled Release*.110(3):(2006 Feb 21)479-89.
36. Eljarrat-Binstock E, Raikup F, Frucht-Pery J, Domb AJ. Hydrogel probe for iontophoresis drug delivery to the eye. *Journal of Biomaterials Science, Polymer Edition*. 1;15(4):(2004 Jan)397-413.
37. Thakur Singh RR, Tekko I, McAvoy K, McMillan H, Jones D, Donnelly RF. Minimally invasive microneedles for ocular drug delivery. *Expert opinion on drug delivery*. 3;14(4):(2017 Apr) 525-37.
38. Patel SR, Berezovsky DE, McCarey BE, Zarnitsyn V, Edelhauser HF, Prausnitz MR. Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. *Investigative ophthalmology & visual science* 1;53(8):()4433-41.
39. Bhattacharjee A, Das PJ, Adhikari P, Marbaniang D, Pal P, Ray S, Mazumder B. Novel drug with special reference to liposomal ocular delivery. *European journal of ophthalmology*.29(1):(2019 Jan)113-26.
40. Meng T, Kulkarni V, Simmers R, Brar V, Xu Q. Therapeutic implications of nanomedicine for ocular drug delivery. *Drug discovery today*. 2019 May 15.
41. Swain S, Beg S, M Babu S. Liposomes as a novel carrier for lipid-based drug delivery: current and future directions. *Recent patents on drug delivery & formulation*. 1;10(1):(2016 Apr)59-71.
42. Sahoo SK, Dilnawaz F, Krishnakumar S. Nanotechnology in ocular drug delivery. *Drug discovery today*. 1;13(3-4):(2008 Feb)144-51.
43. Battaglia L, Serpe L, Foglietta F, Muntoni E, Gallarate M, Del Pozo Rodriguez A, Solinis MA. Application of lipid nanoparticles to ocular drug delivery. *Expert opinion on drug delivery*. 1;13(12):(2016 Dec)1743-57.
44. Agrahari V, Patel SP, Dhall N, Aulgur Z, Thukral S, Yang X, Conley R, Mitra AK. Nanoparticles in thermosensitive gel based composite nanosystem for ocular diseases. *Drug delivery and translational research*. 1;8(2):(2018 Apr) 422-35.
45. Bachu R, Chowdhury P, Al-Saedi Z, Karla P, Boddu S. Ocular drug delivery barriers – role of nanocarriers in the treatment of anterior segment ocular diseases. *Pharmaceutics*. 10(1):(2018 Mar)28-40.
46. Srinivasarao DA, Lohiya G, Katti DS. Fundamentals, challenges, and nanomedicine-based solutions for ocular diseases. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*. 11(4): (2019 Jul)154-166.
47. Mandal A, Patel P, Pal D, Mitra AK. Multi-Layered Nanomicelles as Self-Assembled Nanocarrier Systems for Ocular Peptide Delivery. *AAPS PharmSciTech*. 1;20(2)(2019 Feb):66-76
48. Gote V, Sikder S, Sicotte J, Pal D. Ocular Drug Delivery: Present Innovations and Future Challenges. *Journal of Pharmacology and Experimental Therapeutics*. 2019 Jan 100-119.
49. Özsoy Y, Güngör S, Kahraman E, Durgun ME. Polymeric micelles as a novel carrier for ocular drug delivery. In *Nanoarchitectonics in Biomedicine 2019 Jan 1* (pp. 85-117).
50. Amadio M, Kaarniranta K, Xu H, Smedowski A, Ferrington DA. Molecular Mechanisms Underlying Age-Related Ocular Diseases. *Oxidative medicine and cellular longevity*. 2018:76-86
51. Balaggan KS, Ali RR. Ocular gene delivery using lentiviral vectors. *Gene therapy*. 19(2):(2012 Feb)145-155.
52. Mourelatou EA, Sarigiannis Y, Petrou CC. Ocular Drug Delivery Nanosystems: Recent Developments and Future Challenges. *Drug Delivery Nanosystems: From Bioinspiration and Biomimetics to Clinical Applications*. 2019 Jan 92-102).

Cite this article as:

Amandeep Singh, Tara Singh Dogra, Uttam Kumar Mandal, Raj Kumar Narang. Novel approaches for ocular drug delivery: A review. *International Journal of Bio-Pharma Research*, Volume 8, Issue 7 (2019) pp. 2722-2732.

 <http://dx.doi.org/10.21746/ijbpr.2019.8.7.2>

Source of support: Nil; **Conflict of interest:** Nil.