Review Article

# Review on nanotechnologies in ocular drug delivery

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## ABSTRACT

Treatment with traditional ocular dose structure has a wide range of issues such as obscured vision, loss of medication by seepage, irritation, non-maintain activity, persistent noncompliance, nature of medication, and so on furthermore diminishes the visual bioavailability of medication. To minimize these issues, novel ocular dose structures are utilized for some visual diseases. Distinctive novel ocular measurement frames like controlled dose shape that is inserts, liposomes, nanoparticles, visual supplements, contact lenses, iontophoresis, and so on, have managed the influx of medication particles by moderate degradation of the polymer. These measurement frames build the contact time of medication particles with ocular tissues, which infiltrates the medication particles into more profound tissues of the eye furthermore expands the visual bioavailability of medication. Novel medication conveyance through the ophthalmic course has real change for future perspectives.

**Keywords:** Emulsion, implants, nanomicelles, ocular delivery, solution, suspensions

## INTRODUCTION

The eye is a special and profoundly difficult organ on account of its perplexing capacity. Its life structures, physiology, and natural chemistry make this organ carefully impervious to external substances. The test before formulator is to detailing of particular sorts of dose structure which cannot create any tissue harm of eye{Lee, 1986 #3}. For infection of the eye, the 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, first, the medication atoms cross the precorneal obstruction, and then crosses the corneal hindrance. Precorneal obstruction comprises 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 min at precorneal territory in people.[1] The cornea is the major organic barrier to the infiltration of the solution. Ocular bioavailability of medication particle is additionally relying on a couple of physiological properties of medication including protein tying, drug digestion system, lacrimal seepage, and so on and physiological components that can influence the medication's visual bioavailability. In any case, for the most part of the visual details are rapidly lost amid nasolacrimal seepage right away. First, the medication in the definition is weakened with a tear in the circular drive of the eye, and this weakening cause diminishment of the transcorneal flux of the medication. The medication substance, pH, and tonicity of the dose structures can animate the tear creation. Topical uses of ophthalmic definitions are further made awkward by tear turnover, which is concerning 16% in humans. Because of these components generally under 5% of the medication achieves the watery funniness. Tying of medication to protein and digestion system in the precorneal region has been appeared to represent a further loss of the medication.[2]

Different types of dosage forms are used for various 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 eye drops, suspension, treatments, gels, and so forth. These dosage forms are mainly targeted to the ocular anterior segment. However, due to the less contact time, these dosage forms have not more therapeutic effects on the eye. Different topically connected medications are cleaned off from the ocular site by various components

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such as lacrimation, tear weakening, and tear turnover, bringing about poor visual bioavailability of medications. To overcome these problems, novel ocular dosage forms are used for various ocular diseases. Like controlled ocular dosage form that is implants, ocular inserts, contact lenses, and iontophoresis, has sustained-release properties by slow degradation of the polymer. They also increase the retention time of the drug in a cul-de-sac of the eye.[3] The colloidal systems including liposomes, niosomes, and nanoparticles, penetrate into the deeper tissues of the eye and increase the ocular drug absorption. They additionally keep the metabolic system of medications from the catalysts that present at eye tissues. 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 the poorly aqueous soluble drug. Another is the quality conveyance that conveys the nucleic acids to a particular site of eye. In this way, progressing research on novel ocular dose structures is helps to defeat all detriments of conventional ocular dosage forms.[3]

### Required characteristics to optimize ocular dosage form are

- Prolong contact time with ocular tissues
- Good corneal penetration of drugs
- Nonirritant and comfortable form for ocular tissues
- Simple installation of the drug for the patient.

## ADVANTAGES OF OCULAR DOSAGE FORM

- Easy to convenience and needle-free drug application
- Good penetration with water-soluble and low molecular weight drugs
- Quick ingestion of medication and quick onset of activity as a result of expansive retention surface region
- Avoidance of first-pass metabolic system
- Ocular bioavailability of medication is expanded by more corneal contact time.

## DISADVANTAGES OF OCULAR DOSAGE FORM

- Poor penetrability
- Rapid disposal of the medication through eye squinting with tear stream results in a short extent of remedial impact on the eye
- Some ocular formulations can cause irritation to the eye and that leads to patient discomfort.[4]

Different conventional ocular dosage form is shown in Figure 1.

### Solutions

The greater part of topical ophthalmic arrangements accessible is as fluid arrangements since they are the most helpful, sheltered, and tolerant consistence. To enhance saturation of drug, visual bioavailability, and contact time various excipients might be mixed to eye drops to enhance consistency, buffering operators,

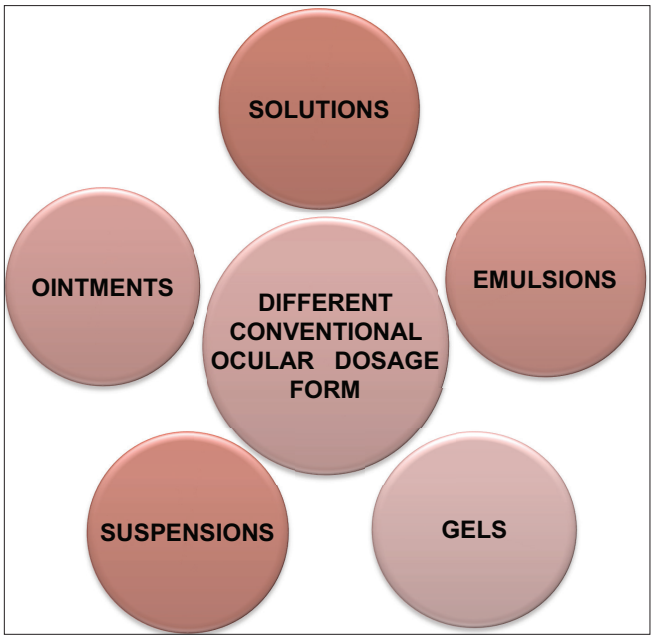


**Figure 1:** Different types of the conventional ocular dosage form

and enhance penetration. The use of polyvinyl alcohol, hydroxyl methylcellulose, sodium carboxyl methylcellulose (CMC), hydroxypropyl methylcellulose, CMC, and carbomers to utilized for influence in thickness and enhance bioavailability. Possible decisions of cushions and cradle limits are important to enhance drug bioavailability and in addition visual solace. The decisions of pH for the ophthalmic details are a key point for the formulator.[5] The dissolvability, solidness, and corneal penetrability of the visual medications are very reliant on the pH of the definitions. For the most part, visual arrangements are defined to the extent between pH 4 and 8.0. On the off chance that the pH of the visual plans is more than the physiological extent, visual distress might turn into the issue and might likewise bring about intemperate tearing additionally brings about fast flushing of the medication to the nasolacrimal organ. Pervasion enhancers in visual arrangements improve the visual bioavailability of the medication, yet few studies uncovered a nearby poisonous quality through penetration enhancers.[6] Thus, research is as yet being led to adjust the impact of pervasion improvers and assess its security over visual tissues.

### Suspensions

Suspensions are one more type of non-obtrusive visual measurement shape and offer particular focal points. It is characterized by finely isolated insoluble medication. Loads of the as of late created medications are hydrophobic in nature and furthermore have constrained dissolvability in water. Planning of clean, protected, proficient, steady, and the pharmaceutically rich suspension is further mixes and testing contrasted with normal ocular arrangements. A few of the troubles so as to a formulator are non-homogeneity in the measurements of ocular structure, cake development, collection of the suspended particles, and resuspendability.[7] Suspensions are actively steady other than thermodynamically insecure frameworks. The most skillful strategy for creating such a molecule size is by means

of dry processing. Then again, wet processing might be advantageous for conceivably flimsy fixings. Further strategies for molecule size lessening comprise smaller scale pummeling, granulating, and controlled precipitation.[8]

### Ointments

Ocular ointments are semisolid dosage forms for topical application by and large comprising solid or semisolid hydrocarbon base. The various treatment bases are absorption bases (e.g., beeswax), water-dissolvable bases (e.g., macrogols), hydrocarbon bases (e.g., hard paraffin, microcrystalline wax), and vegetable oils (e.g., almond oil). The determination of hydrocarbon is dependent on biocompatibility. Treatments help to enhance visual bioavailability and maintain the arrival of medication. Certain drawbacks of ocular ointments are tolerated and secure, 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.[9]

### Emulsion

An emulsion is also the best approach to enhance both dissolvability and bioavailability of medications and both oils-in-water and water-in-oil are used. For the most part, ophthalmic emulsions are detailed by blending or scattering the dynamic fixing into an oil stage, suspending operators, including suitable emulsifying and blending with water overwhelmingly to shape a homogeneous oil-in-water emulsion.[10] The subsequent visual dose structure ought to have little oil beads, homogeneously suspended. Lesser watery dissolvability of the medication is the most well-known justification for defining an ophthalmic emulsion. The medication substance can be added to the stage in which it is solvent at the beginning of the assembling procedure and furthermore can be included after the emulsion is readied through a suitable scattering process. To avoid flocculation, creaming, and coalescence, manufacturers generally add surfactants.[11]

### Gels

Ocular gels are composed of mucoadhesive polymers (e.g., carboxymethylcellulose, carbopol, polycarbophil, and sodium alginate) that offer localized delivery of the drug to the eye. The gels showed longer residence times and increased drug bioavailability.[11]

## DRAWBACKS OF CONVENTIONAL OCULAR DOSAGE FORM

Conventional ocular dosage forms have various types of drawbacks, these are discussed below:-

- Loss of drug by drainage: Rapid loss of drug by drainage due to gravity, blinking reflex, induced lachrymation, and typical tear turnover
- Blurred vision: Various types of conventional ocular dosage forms, i.e., gels, and ointments can affect the normal vision of the eye. When these types of ocular formulation applied to the eye, the outer surface of the eye is covered. Hence, the normal vision of the eye can be disturbed
- Irritation: Some ocular formulations (e.g., eye solutions, suspensions, and emulsions) can cause irritation due to its excipients, i.e., buffering agents, antioxidants, and surfactants because these excipients can irritate to tissues of the eye
- Non-sustain action: Due to its conventional action, these formulations have 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 such as ointments and gels do not accept by some patients due to its difficult installation
- Nature of drug: The corneal absorption of the eye depends on the nature of the drug. To be effectively absorbed, the drug must have differential solubility, i.e., the ionized and non-ionized form.[12]

## Different anatomical barriers to restrict ocular dosage form

### *Tear as a barrier*

The main precorneal hindrance of the 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. The main constituents of the tear film are lipids, mucins, and water. The tear film is capable to wet the surface of the eye due to a film of mucin bound to the corneal and conjunctival epithelium. The tear film is very thin, about 5 μ, 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.[13]

### *Cornea as a barrier*

Corneal obstruction is an imperative mechanical and synthetic barrier that restricts the entrance of foreign substances into the visual site. The cornea is unmistakable, transparence, and avascular structure with normal breadth is 12 mm and thickness is 520 mm.

### *Conjunctiva as a barrier*

The conjunctiva assumes a significant part as a defensive obstruction on the visual exterior, and it adds to the arrangement and security of the tear film through the creation of bodily fluid glycoproteins and furthermore has a rich supply of vessels and lymphatics. A noteworthy part of the medication is lost to systemic dissemination even as an intersection of the conjunctiva. The remaining medication can enter by the sclera, which comprises generally of collagen and mucopolysaccharides. The veins of conjunctiva do not make a tight intersection hindrance, which implies drug atoms can come into the blood flow by pinocytosis. The conjunctiva lymphatic's function as an efflux framework for the effective expulsion from the conjunctival space.

### *Blood-retinal barrier*

It confines drug transport from blood to retina and framed by the endothelial cells of retinal color and veins of epithelial cells. The retinal shade epithelium (RPE) demonstration an indispensable part of keeping up the reasonability and capacity of the neural retina. The RPE is in charge of the disposal of liquid from the subretinal space keeping in

mind the end goal to hold the retinal bond and to continue through to the end retina in a condition of lack of hydration. On account of its tight intersections, the RPE goes about as solid obstruction, yet it is equipped for various particular transport forms. Just favored supplements are traded in the middle of choroid and retina, the transcellular and paracellular method for different atoms over the RPE is constrained. On account of their specific capacities, the RPE cells have specific. The RPE is in charge of the disposal of liquid from the subretinal space keeping in mind the end goal to hold the retinal bond and to continue through to the end retina in a condition of lack of hydration. On account of its tight intersections, the RPE goes about as solid obstruction, yet it is equipped for various particular transport forms. Just favored supplements are traded in the middle of choroid and retina, the transcellular and paracellular method for different atoms over the RPE is constrained morphologic and utilitarian extremity properties. Similar to the RPE, likewise retinal vessel dividers are severely porous to proteins (e.g., horse radish peroxidase) and little water-soluble substances (e.g., sodium fluorescein), while lipid-soluble substances can permeate retinal slim endothelial cells all the more essential.[14]

## ADVANCEMENT IN OCULAR DOSAGE FORM

Due to the various limitations of conventional ocular dosage forms [Figure 2], different types of advancements (such as liposomes, niosomes, nanosuspensions, dendrimers, and implants) have been created to build the contact time and bioavailability of medication.[15] These are discussed below: Some marketed formulation for conventional ocular drug delivery shown in Table 1.

### Ocular inserts

They are hygienic formulation with a solid or a semisolid consistency and offer an attractive approach to treat the eye problems by the use of the controlled release principles. Ocular inserts also offer the prospective benefit of improving bioavailability, increasing the contact time of drugs and reducing the dosing frequency. As of late, there has been a 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 few strategies at maintained, foreordained rate; however, the evacuations of supplements are essential after complete exhausting of medication from their definition. For the most part, solvent supplements are solid polymeric frameworks that experience moderate disintegration while discharging the medication atoms and do not require evacuation. At the point when addition is put in the eye, then swelling and in this way polymer chain unwinding and sedate dissemination occur discharging their medication atoms.[15]

### Implants

Intraocular implants are the most and grouped into two classifications that in light of debasement property first is biodegradable and second is non-biodegradable. Non-biodegradable intraocular implants offer durable discharge. Another class is biodegradable implants that are not required to uproot surgically. In case of implants drug delivery polymers like polycaprolactone, polyglycolic corrosive, polylactic are used. Surodex and Ozurdex are samples of biodegradable implants that are intended for the conveyance of dexamethasone to visual tissues.[16]

### Iontophoresis

Because of the non-intrusive nature of medication conveyance to both foremost and back portions of the 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 to intraocular infusions and inserts. Visual iontophoresis is protected, quick, and easy as well as convey more centralization of medication to a particular site of eye. The conveyance of anti-

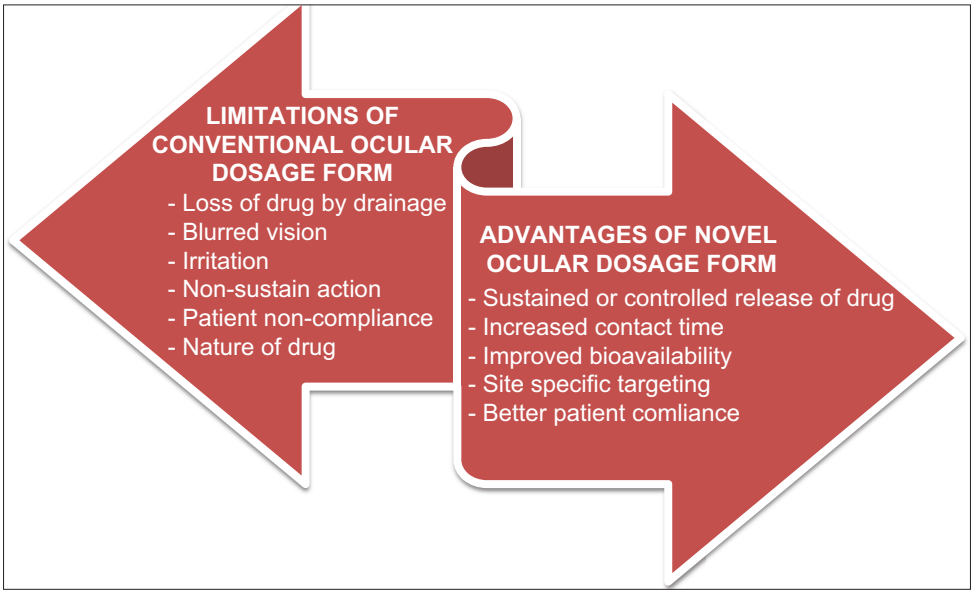


**Figure 2:** Various limitations of conventional ocular dosage form and advancements of novel ocular dosage forms

**Table 1: Some marketed formulation for conventional ocular drug delivery**

| Ocular dosage form | Marketed formulation | Drug | Indication | Advantages | Disadvantages |
|---|---|---|---|---|---|
| Solutions | Bennison N | Betamethasone | Eye infection | Convenient | Non-sustained action |
| | Ciplox | Ciprofloxacin | Conjunctivitis | No effect on the vision of the patient | Rapid drainage |
| Suspensions | Pred forte | Prednisolone acetate | Anti-allergic | Patient compliance | Loss of both solution and suspended solids |
| | Nevada | Nepafenac | Anti-inflammatory | The slow dissolution of the drug | Performance depends on drug properties |
| Emulsions | Restasis | Cyclosporine | Dry eye | Prolonged-release of drug from the vehicle | Patient non-compliance |
| | End | Difluprednate | | | Blurred vision |
| Ointments | Acivir eye | Acyclovir | Eye infection | Improve drug stability | Poor patient compliance |
| | Chloromycetin | Chlorampthenicolpalmitate | Conjunctivitis | Inhibition of dilution by tears | Blurred vision |
| Gels | GenTeal | Hydroxypropyl methylcellulose | Dry eye | Less blurred vision<br>Comfortable | No rate control on diffusion<br>Matted eyelids after use |

infection agents by iontophoresis technique has brought about critical to less bacterial settlements in the cornea when contrasted with the eye drops. Different cases of antitoxins successfully utilized are tobramycin, gentamicin, and ciprofloxacin, however, not for vancomycin due to its high atomic weight.[17]

## Gene delivery

As of late, diverse techniques have been received to convey nucleic acids to focusing on location inside of the eye. Created conveyance framework for RNAs, antisense oligonucleotides, or aptamers is a testing errand for scientists in visual medication conveyance field in view of the solvency of the dynamic medication, high atomic weight, size, surface charge, and in born complexities related with the arrangement of visual tissues such as retina and cornea.[18]

# CONCLUSION

Ophthalmic dosage forms have been a major test for formulators. Ordinary measurement frames have different downsides because of its quick waste and less contact time. Complex eye structure is additionally enormous hindrance to the conveyance of medication. Headway in ophthalmic dose shapes offers viable and defensive methods for the treatment for visual infections. Change of non-invasive conveyance strategies will reform visual medication conveyance. 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 for controlled and managed conveyance for treating ophthalmic sicknesses. Propels in nanotechnology conveyance strategies will stay in the front line of new and novel ophthalmic medication conveyance frameworks.

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