Review Article

Nanostructure-based platforms-current prospective in ophthalmic drug delivery

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The topically applied drugs as drops are washed off from the eye in very short period, resulting in low ocular bioavailability of drugs. Number of approaches have been attempted to increase the bioavailability and the duration of action of ocular drugs. This review provides an insight into various novel approaches; hydrophilic nanogels, solid lipid nanoparticles, and nanosponges applied very recently in the delivery of insoluble drugs, prolonging the ocular residence time, minimize pre-corneal drug loss and, therefore, bioavailability and therapeutic efficacy of the drugs. Despite various scientific approaches, efficient ocular drug delivery remains a challenge for pharmaceutical scientists.

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The major diseases affecting the eye are macular degeneration, diabetic macular edema, cataract, proliferative vitreoretinopathy, uveitis, cytomegalovirus, and glaucoma.[1,2] More than 90% of the marketed ophthalmic formulations are as eye drops. These topically applied drugs as drops are washed off from the eye by different mechanisms (lacrimation, tear dilution, and tear turnover), resulting in low ophthalmic bioavailability of drugs.[3] Moreover, human cornea has epithelium, substantia propria and endothelium also restricts the ocular entry of drug molecules; as a result of these factors, less than 5% of administered drug enters the eye.[4] Major barriers to topical Ocular Drug Delivery are the high tear flow, rate of 16 ml per minute during waking hours (basal 0.5-2.2 ml/min) up to 300 ml/min in reflex stimulation of lacrimation.[5] The mucin present in the tear film has a protective role by forming a hydrophilic gel layer acts as a barrier to drug delivery systems.[6]

Number of approaches have been attempted to overcome these physiological barriers to increase the bioavailability and subsequently the therapeutic action of ocular medications.

These are broadly divided into two categories. The first approach is on use of the drug delivery systems that provide controlled and continuous delivery of medication. The second maximize corneal drug absorption and minimizing pre-corneal drug loss. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions, and ointments can be replaced by a more controlled, sustained, and continuous drug delivery, using a controlled release ocular drug delivery system.

These systems can achieve therapeutic action with a smaller dose and a fewer systemic and ocular side effects. Such systems include implantable systems, ocuserts, collagen shields etc., but the limitations of these systems include poor patient compliance due to high cost of the systems, inability of self-insertion, and need surgery.[7-9] Other approaches include increased viscosity of vehicle, which is based on the fact that the bioavailability of the applied drug can be enhanced by increasing the contact time between the drug and the ocular surface. Studies to-date indicate that this approach has only limited value, as the formulations are liquid and, therefore, subject to elimination from the eye by all the factors discussed earlier.[10]

The *in situ* gelling systems or phase transition systems were widely used to improve the ocular bioavailability of drugs, which are instilled in a liquid form and shift to a gel or solid phase in the cul-de-sac.[11-13] The phase transition is triggered by the pH of the tears, the temperature at the eye surface, or the electrolytes present in the tear film.[14,15] Recently, there is a growing interest in the development of a novel sustained nanostructured ophthalmic drug delivery system. This article provides very recent developments in the area of drug delivery to the eyes.

Hydrophilic Nanogels**:** Hydrogels can be defined as the polymeric networks with three-dimensional configuration capable of absorbing high amounts of water or biological fluids. The ability of hydrogels to absorb water is due to the presence of hydrophilic groups in polymers forming hydrogel structures.[16] Hydrogels were used for ophthalmic drug delivery in late 80's and in 90's with primary objective is to increase the residence time for better absorption.[17,18]

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These can be classified according to:[19]

- The nature of side groups (neutral or ionic)
- Mechanical and structural features (affine or phantom)
- Method of preparation (homo- or co-polymer)
- Physical structure (amorphous, semi crystalline, hydrogen bonded, supermolecular, and hydrocollodial)
- Physiologic responsiveness to environment stimuli (pH, ionic strength, temperature, electromagnetic radiation, etc.).

Even hydrogels have high water-absorbing ability; show a swelling behavior even instead of being dissolved in the aqueous surrounding environment. It is due to the critical crosslinks present in the hydrogel structure. Different Polymer(s) hydrated to different degrees (around 90% wt.), depending on the nature of the aqueous environment and polymer composition.

The natural, synthetic, and semi-synthetic polymers used in hydrogel preparations are classified as:[20,21]

- Natural polymers and their derivatives
  - Anionic: Alginic acid, pectin, carrageenan sulfate, dextran sulfate
  - Cationic: Chitosan, polylysine
  - Neutral: Dextran aragose
  - Amphipathic polymers: Collagen, carboxymethyl chitin, fibrin.
- Synthetic polymers: PEG-PLA-PEG, PEG-PLGA-PEG, PEG-PCL-PEG, PLA-PEG-PLA, PEG6CDs, PEGMMA
- Semi-synthetic polymers: P (PEG- co-peptides), alginate-g-(PEO-PPO-PEO), P (PLGA-co-serine), collagen acrylate, P (HPMA-g-peptide), P (HEMA/Matrigel)*.

*Abbreviations: PEG-Polyethylene glycol, PLA-Polylactic acid, PLGA- Polylactic-co-glycolic acid, PCL- Polycaprolactone, CDs- cyclodextrins, PEO-Polyethylene oxide, PPO- Polypropylene oxide, PHPMA- Polyhydroxypropylmethacrylamide, PHEMA-Polyhydroxyethylmethacrylamide, PEGMMA-Polyethylene glycol monoethyl ether monomethacrylate.

Yin HB *et al*. successfully synthesized a biodegradable triblock copolymer poly (ethylene glycol)-poly (*e*-caprolactone)-poly-(ethylene glycol) (PEG-PCL-PEG, PECE), which was flowing sol at low temperature and turned to non-flowing gel at body temperature.[14] The toxicity evaluation of PECE hydrogel as an *in-situ* sustained drug delivery for eyes was performed, including the biodegradability of PCTE hydrogel in the eye, its effect on *in vitro* cultured human lens, intraocular pressure, and ocular tissues.[14] The results showed that the prepared PECE hydrogel was biocompatible and biodegradable and safe candidate for sustained ophthalmic drug delivery. Tayel S. A *et al*. prepared controlled-release *in situ* ocular drug-loaded nanoemulsion (NE) gels of Terbinafine hydrochloride using oils (isopropyl myristate/ Miglyol® 812), surfactants (Tween® 80/Cremophor® EL), a co-surfactant (polyethylene glycol 400), and water. Drug pharmacokinetics of sterilized Formulation of Miglyol® 812, Cremophor® EL: Polyethylene glycol 400 (1:2) and water (5, 55 and 40%, w/w, respectively). *In-situ* NE gel and oily drug solution were evaluated in rabbit aqueous humor. The gels were transparent, pseudoplastic, mucoadhesive, and showed more retarded zero-order drug release rates with least ocular irritation potential, prolonged mean residence time, and increased bioavailability.[22] *In vivo* studies in rabbit eye showed a marked improvement in anti-inflammatory activity for Hydroxypropyl-β-cyclodextrin (HP-β-CD) based for pH-induced mucoadhesive hydrogel to treat uveitis.[23]

Ortega M D *et al*. designed and tested *in-vivo* the sustained release aqueous eye drops of dexamethasone, based on cyclodextrin (CD) nanogels. The nanogel eye drops (containing 25 mg dexamethasone per ml) were tested in rabbits and compared to the commercially available product Maxidex® (suspension with 1 mg dexamethasone per ml). One drop administration of the nanogel eye drops resulted in nearly constant dexamethasone concentration for at least 6 h in the tear fluid, whereas the concentration after administration of Maxidex® fell rapidly within 1 to 3 hrs. The dexamethasone nanogel eye drops were well tolerated with no macroscopic signs of irritation, redness, or other toxic effects.[24]

Solid lipid nanoparticles: The promising approach nowadays is the use of colloidal carrier systems characterized by a submicron-meter size. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) represent alternatives to conventional ocular systems. Solid lipid nanoparticles are prepared with solid lipids. The majority of lipids used in the preparation are hydrogenated fatty acids like hydrogenated cottonseed oil (Lubritab™ or Sterotex™), hydrogenated palm oil (Dynasan™ P60 or Softisan™ 154), hydrogenated castor oil (Cutina™ HR), and hydrogenated soybean oil (Sterotex™ HM, or Lipo™).[25]

Number of publications describes the methods for preparation of SLN by micro emulsion, ultrasonication or high-speed homogenization, high pressure homogenization, solvent emulsification/evaporation, double emulsion method, and supercritical fluid technology.[25]

Li R *et al*. prepared and investigated methazolamide-loaded solid lipid nanoparticles (SLNs) for ocular delivery by emulsion-solvent evaporation method. Percentage decrease in intraocular pressure and ocular irritation was measured. Results indicated that methazolamide-SLNs had higher therapeutic efficacy, maximum action, more prolonged effect, and less ocular irritation than drug solution and commercial product.[26] Abul Kalam M *et al*. carried the investigations on gatifloxacin bioavailability to the eye using solid-lipid nanoparticles (SLN). SLNs were prepared by o/w-microemulsion method. C_{max} of gatifloxacin from SLNs showed 1.09-fold higher concentration as compared to conventional Eye-drops. The aqueous humor levels of gatifloxacin drug after single topical instillation asGate(®) Eye drops and positively charged SLN were measured. A 3.37-fold increase in the bioavailability was observed with the SLN containing formulation. This results that SLNs could enhance ocular bioavailability of gatifloxacin and increase its residence time in the eyes. Moreover, there were no signs of ocular irritation with the SLN formulations, indicating their relative safety compared to the marketed drops.[27,28] Seyfoddin A and Al-Kassas R investigated the ocular bioavailability of acyclovir solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). NLCs formulation showed faster permeation through the excised cornea followed by SLNs, indicating their potential enhanced corneal penetration properties.[29] Hippalgaonkar K *et al*. prepared the indomethacin-loaded solidlipidnanop articles of drug content 0.1% w/v for ocular delivery. Compritol(®) 888 ATO was selected as the lipid phase for the indomethacin-SLNs as indomethacin

exhibited a highest distribution coefficient and solubility in this phase. A dramatic increase in the chemical stability and *in vitro* corneal permeability of indomethacin was observed with the indomethacin-SLN formulation in comparison to the indomethacin solution of identical strength.[30]

Nanosponges: Nanosponges are encapsulating type of nanoparticles, which encapsulates the drug molecules within its core. By the method of associating with drugs, the nanoparticles can be classified into encapsulating nanoparticles, complexing nanoparticles, and conjugating nanoparticles. Nanosponges are tiny mesh-like structures, capable of carrying both lipophilic and hydrophilic substances.[31,32] The nanosponge is made up of a 'backbone' (a scaffold structure) of naturally degradable polyester. The polyester strands are mixed in solution with small molecules called cross-linkers that have an affinity for certain portions of the polyester. They 'cross link' segments of the polyester to form a spherical shape that has many pockets (or cavities) where drugs can be stored. The commonly used polymers in the preparation include cyclodextrins and its derivatives and cross linkers include ethyl cellulose and polyvinyl alcohol. Diphenyl carbonate, diaryl carbonates, diisocyanates, pyromellitic anhydride, glutaraldehyde.[33,34]

Nanosponges are prepared by:

- Solvent method in which the polymer is mixed with a suitable polar aprotic solvent such DMSO and dimethylformamide. Then, this mixture is added to excess quantity of the cross-linker, preferably in cross-linker/polymer molar ratio of 5 to 15. Carry out the reaction at temperature ranging from 10°C to the reflux temperature of the solvent, for time ranging from 1 to 48 h. After completion of the reaction, allow the solution to cool and recover the product by filtration under vacuum[35,36]
- Ultra-sound-assisted: In this method, the polymer and the cross-linker are mixed in a particular molar ratio in a flask. Then, it is placed in an ultrasound bath filled with water and heats it to 90°C. The mixture is sonicated for 5 hours. Then, allow the mixture to cool and break the product roughly. Wash the product with water to remove the unreacted polymer and subsequently purify.[37]

The major application of nanosponges is in the solubility enhancement. Cyclodextrin-based nanosponges improve the wetting and solubility of molecules with very poor solubility in water. The drugs are molecularly dispersed within the nanosponge structure, released as molecules, practically eliminating the dissolution step. Recently, Swaminathan S *et al*. investigated dexamethasone, a poorly soluble drug; nanosponges prepared by crosslinking of beta cyclodextrins with diphenyl carbonate for ocular delivery. The nanosponges of dexamethasone with beta-cyclodextrin were prepared with different cross-linking ratio 1:2, 1:4, and 1:8 for ocular applications. Encapsulation of the drug in cyclodextrins was done by incubation-lyophilization technique. Dexamethasone was loaded in the highest amount in formulation 1:4, as much as 10% w/w. *In vitro* release studies showed that release of the drug was found in controlled manner for five hours.[38]

Ophthalmic products toxicity evaluation

The *in-vivo* study on ophthalmic products is done on experimental animals, usually on rabbit's eye.[15,39-41] Preparation volume 50 µl is instilled topically in the center of the lower cul-de-sac. Tear film and aqueous humor samples are collected and analyzed. Eyes of the animal are observed for signs of irritation and injury. *In vitro* methods were developed with human corneal endothelial cells. Diclofenac sodium solid lipid nanoparticles (SLNs), prepared with goat fat and phospholipids evaluated using bio-engineered human cornea, produced from immortalized human corneal endothelial cells (HENC), stromal fibroblasts, and epithelial cells. Sustained release and high permeation of diclofenac sodium through the bio-engineered cornea were achieved.[42] The Bovine Corneal Opacity and Permeability (BCOP) assay has been accepted as a valid *in-vitro* alternative method to the Draize eye irritation test with the development of an improved laser light-based opacitometer (LLBO) for the analysis of the complete corneal surface instead of dual beam OP-KIT opacitometer.[43]

Confocal laser scanning microscopy study on the transport mechanism through the corneal epithelium of nanostructured lipid carrier was carried out in rabbits *in vivo*. The corneas were isolated and rinsed in physiological saline to remove the adhesive fluorescence fragment. After 30 minute administration in to eyes, the interaction with corneal epithelia to be investigated by observing the corneal samples using confocal laser scanning microscopy (CLSM).[44]

The EpiOcular tissue model is a new *in-vitro* test method for ocular irritation, produced by MatTek Corporation tissue production facilities. The EpiOcular tissue model shows *in-vivo* like morphological and growth characteristics that are uniform and highly reproducible. The tissue consists of highly organized basal cells, which progressively flatten out as the apical surface of the tissue similar to the normal *in-vivo* corneal epithelium. The endpoint used is the determination of extent of cytotoxicity.[45] The validation of EpiOcular eye irritation test was performed with 60 chemicals.[46] This test could be applied as an alternate to rabbit eye test in the toxicological assessment of ophthalmic preparations.

Conclusion

Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the eye as well as to slow drug release from the delivery system and minimize pre-corneal drug loss. Nanostructured platforms provide the effective ways for delivery of insoluble drugs to the target site. As these platforms for ophthalmic delivery are very recent and the research continues, formulation factors such as loading of drug, release rate, stability, and therapeutic effectiveness for these needs to be optimized.

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