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Review Article

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Nanotechnology in Ophthalmology

Gayatri Varikuti*

Department of Biochemistry, GITAM Institute of Science, GITAM University, Visakhapatnam, India

Correspondence to: Dr. Gayatri Varikuti, Department of Biochemistry, GITAM Institute of Science, GITAM University, Visakhapatnam, India, E-mail: gayatri.varikuti@gmail.com

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Despite various attempts, the delivery of ocular drugs appears to be a problem for pharmacologists. Most eye diseases are treated with topical applications of the drugs. But this does suffer from low bioavailability and other drawbacks. In recent years, Burgeoning interest in nano pharmaceutical products has produced several advances with a focus on engineering novel applications. Nanotechnology also provides disease detection capabilities at much earlier levels. Recent advances in research into the eye drug delivery system have provided important insights into developing drugs. Now we are looking at the recent discoveries and applications in ocular drug delivery of various nanosystems such as nanosuspensions, nanospheres, liposomes, and microemulsions.

Introduction

Nano and micro technology include the development and use of nanometerand micrometer-scale materials, devices, or systems. These technologies will play a critical role in many biomedical applications such as drug delivery, molecular imaging, biomarkers, and biosensors. The eye is a complex structure, divided by the number of layers of biological barriers from the rest of the body. Nevertheless, the close junctions of the corneal epithelium and the mucosal surface shield the internal ocular structures and tissues from the outside world. The ophthalmic use of drugs is the main route of administration for treating various eye disorders, and is well-accepted by patients; normally only a small amount of the drug administered penetrates the cornea to enter the target intraocular tissue due to corneal barriers and lacrimation dilution. Therefore, frequent instillation of concentrated solutions is necessary to obtain the desired therapeutic effect in both the eye's anterior and subsequent hemispheres. Yet this may cause damage to the cornea and adverse side effects arising from systemic drug absorption through the nasolacrimal duct. The key obstacle for the delivery of ocular drugs is therefore how to overcome such defensive barriers to achieve therapeutically efficient concentrations of drugs in the intraocular tissues. Improving the bioavailability, it is important to increase the efficacy of the drugs. To increase drug bioavailability and overcome these problems, several strategies have been developed and investigated, such as preparation of viscous solutions, micro/nanoparticles, and hydrogels. Ophthalmic products containing nanoparticles and provide a better approach to the limitations surrounding the penetration of ocular drugs. Understanding that, useful to circumvent the side effects related to drug delivery, to minimize direct cellular stimulation and to reduce the amount of medication used by increasing its bioavailability, ophthalmic drug systems using nanoparticles are supposed to provide an effective way to improve penetration of the ocular drug. This analysis addresses the utility of Nano and micro particulates in the delivery of ophthalmic drugs.

Nano Materials and Ocular Drugs

The particle size determines its functionality in terms of absorption, circulation residence, adhesion, deterioration, clearance [1,2]. The fate of the particles inside the body has been identified as 2 μm, trapped within the liver cells about 300-400 nm, collected and excreted by macrophages 200 nm, absorbed in spleen 100 nm, escaping from the blood vessels via the endothelial lining. Thus the movement of nanoparticles inside tissues is controlled by size. In the ophthalmic region, nanoparticles ranging from 10 to 1000 nm make it possible to improve the topical passage of large, water-insoluble molecules through the eye system barriers [3].

Superficial barriers hinder access to the precise place of action by direct and systemic medicines. Drug-loaded nanoparticles demonstrate extended residence periods for eye drops, improved drug capacity to penetrate deeper eye structure layers, and aqueous humor while reducing precorneal drug loss induced by rapid tear fluid turnover and reduced toxicity [4]. Techniques designed for transformation of nanoparticles from lipophilic to hydrophilic, and the regulation of eye irritation. Nano materials are very useful in the prolonged delivery of ophthalmic drugs [5,6].

Microemulsions

Micro emulsions are water and oil dispersions enabled by a mixture of surfactant and co-surfactant to reduce the interfacial stress. Typically these systems are distinguished by small droplet size (about 100 nm), higher thermodynamic stability, and a simple look. The parameters that can influence system stability are a selection of aqueous phase, organic phase, and surfactant / co-surfactant. Optimization of these components results in significant improvement of drug molecule solubility. i.e., the indomethacin, chloramphenicol [7,8]. Micro emulsion devices have also demonstrated increased permeation through the cornea, in addition to solubility. An oil in water device consisting of pilocarpine using lecithin, propylene glycol, PEG 200 as surfactant, co surfactant, and isopropyl myristate as designed to be nonirritating to the eye during the oil process [9]. Such formulations often provide a sustained release of drugs which reduces the drug administration

frequency. Pilocarpine, the micro emulsion-based device reduces the level of administration twice as opposed to four times that of traditional daytime eye drops. Because the combination of surfactant-co-surfactant increased permeation. Another micro emulsion device consisting of pilocarpine hydrochloride has been shown to transform in different ways, as with a shift in rheological parameters that have changed depending on the change in water content.A higher viscosity which retains the cornea formulation resulting in its enhanced effect. Timolol was laden into a 2-hydroxyethyl methacrylate gel in the micro emulsion method that was studied to modulate its movement through the gel [10]. Higher loading of the medication was achieved but was unable to monitor its release. A stable o / w and w/o emulsion were formulated in yet another attempt to deliver timolol. L The eye drop requirements of Polish Pharmacopeia V. Sirolimus, a highly lipophilic drug with an aqueous solubility of 2,6 μg / ml, were formulated in a micro emulsion system capable of holding 1 mg of drug in a system with excellent tolerability and stability. It developed an alcohol-free, micro emulsion-based formulation consisting of chloramphenicol. Compared to the commercially available formulation this formulation demonstrated excellent stability. While microemulsions have benefits, limitations in the selection of surfactant / co-surfactant systems, and toxicity associated with higher surfactant / co-surfactant concentrations typically restrict their use [11].

Nanosuspensions

It is characterized as a colloidal submicron system consisting of the poorly water-soluble material, suspended in a suitable dispersion medium, and stabilized by surfactants. Usually, they consist of colloidal carriers such as polymeric resins which are inert and help to improve drug solubility and thus bioavailability. They are also popular for their unirritating nature. Flurbiprofen contained in eudragit RS 100 ® and RL 100 ® polymer resins prevent myosis that may be induced during extracapsular cataract operations. The charge on the surface of the nanoparticles facilitates their adhesion to the cornea. Methylprednisolone acetate was encapsulated in a copolymer and tested for its impact on endotoxin-induced uveitis anti-inflammatory symptoms in rabbits [12,13]. Investigations have shown that nanosuspensions anti-inflammatory effect was more than micro-suspensions. So many studies in eudragit RS 100 done using piroxicam. In vivo investigations have demonstrated significant anti-inflammatory effects compared with micro-suspension. Nanosuspensions were developed in three different types of glucocorticoids; hydrocortisone, dexamethasone, and prednisolone. The vivo study suggested that the nanosuspensions significantly increased glucocorticoid absorption in the eyes. Such nanosuspensions often allow the controlled release of drugs and have become more effective over a longer period. Nanosuspensions also give formulation stability to the drug. Cloricromene (AD6) formulated by using the eudragit RS100 and RL100 in nanosuspensions. AD6-laden eudragit delayed nanoparticular suspension gave a substantial edge in improving the drug bioavailability and shelf life after ophthalmic application [14-16].

Nanoparticles

Nanoparticles classified as objects of less than 1μm in diameter, consisting of different biodegradable or non-biodegradable polymers, phospholipids, lipids, or metals. Those can be categorized as nanospheres or nanocapsules, based on whether the product was dispersed or coated evenly with the polymeric material. Research showed the migration of intact nanoparticles to the RPE cells after the intravitreal injection of suspension nanoparticles [17,18]. The migration led to the rupture of the internal limiting membrane (ILM) and activation of non-specific microglial retinal cells. These mild transient mechanisms also modify the permeability and anchoring mechanism of the ILM in the inflammatory cycle. Those findings are crucial for posterior-eye diseases. The utilization of nanoparticles and their distribution depends on the size of the nanoparticles. Fluorescein kinetics nanospheres studied after intravitreal injection into rabbits. In retinal cells other than the vitreous cavity and trabecular meshwork where only larger particles of diameter were distributed, nanospheres smaller than 200 nm were also observed. Those studies showed that how important particle size is in the distribution of ocular tissue. Many parameters of the formulation have to consider when constructing an optimal formulation. Drug and polymer surface charge interactions have played a significant role in the release of drugs from the polymer. Incomplete release of progesterone from the nanospheres of polybutylene cyanoacrylate resulted in the drug's surface charge communication with polymer. To topical drug delivery, a solid lipid nanoparticulate tobramycin system was developed. Compared with an aqueous solution of the drug, such a particulate layer may be maintained on the corneal surface and even on the conjunctival sac for a longer time. In vivo testing showed sustained release of the drug throughout 6 h compared with a short duration from an equal dose of eye drops. Recently, it has been studied how the ocular structure and distribution of the various sizes of nanoparticles differ in Sprague Dawley rats due to blood and lymph circulation. They noticed that particles with a size of 20 nm transported to a small extent across the sclera and no significant transport noted across the sclera-choroid-RPE. Such low permeation has to attribute to periodic circulation that plays a crucial role in clearing the particles of 20 nm. The post-mortem research found a higher concentration of particles in the ocular tissues in dead animals, which they inferred due to the lack of physiological barrier following periocular execution [19-22]. Nanospheres are of genuinely uniform sizes from 50 nm to 1000 nm. Drugs were encapsulated in synthetic and natural polymers that allow the drugs to be released locally and to enter tissue on a sustained basis. Polylactic acid, polyglycolic acid, and their copolymer, and PLGA are the most common substrates. PLA and PLGA injected intravitreous do not show any electrophysiological, histological toxicity in the retina. A GCV intraocular implant is a sustained-release product that is in vivo non-degradable and is used in AIDS patients for the treatment of cytomegalovirus retinitis. The 2000 nm particles were found in the intravitreal cavity and trabecula when fluorescent 2000 nm, 200 nm, and 50 nm nanospheres were injected into the vitreous body of the rabbits, whereas the 200 nm and 50 nm particles were found even inside the retina [23-26].

The miceles have a diameter of about 100 nm or less. Due to the size of the micelles and the presence of a surfactant among the materials, nanoemulsions have good tissue permeability; Studies on DDSs have been conducted mainly in the field of ophthalmic drugs. Installing dexamethasone-containing microemulsions in the rabbit's eyes has been shown to contribute to improved intraocular permeability. Nanoemulsions, along with nanospheres and liposomes, are also unsuitable for long-term, controlled release of drugs [27,28].

Nanotechnology for the Eye Diseases

While most commonly used for the use of ophthalmic drugs, the topical route of administration suffers from rapid precorneal clearance, resulting in little or no delivery of drugs to the back of the eye. This route of administration can primarily benefit from Nano medicines that quickly bind to and/or internalize corneal and conjunctival epithelia in the surface eye tissues. Several approaches have been evaluated

to improve the adhesion of the ocular surface, including the use of polyethylene glycol, acrylic acid and other mucoadhesive polymers to improve corneal or conjunctival adhesion and therefore retention. These strategies in precorneal residence allowed minimal prolongation. On the other hand, positively charged polymeric materials can allow longer retention on the surface of the eye. It was determined using DPT dendrimers that dendrimers achieved rapid entry into human corneal epithelial cells and retained levels of gatifloxacin in the eye tissues for at least 24 hours.Although plasma membranes of cellular barriers allow the passive diffusion of small molecule drugs, they are more restrictive for the entry of usually hydrophilic small hydrophilic molecules, as well as macromolecules. Specialized mechanisms of cell entry may exist for the introduction of these poorly permeable molecules. Solute transporters, for example, can facilitate the entry of small molecules while proteins and large peptides can enter cells via endocytosis mediated by the receptor. The use of receptor-mediated endocytosis is an attractive approach for improving nanoparticles' cellular uptake. It can be assumed that a few protein or peptide ligands coated on a nanoparticle's surface could allow receptor interaction followed by nanoparticle internalization. Nanoparticles modified on their surface are referred to as functionalized nanoparticles, with special features for improved distribution. Such an approach may allow for the cell entry of a larger amount of drug encapsulated in the nanoparticle that otherwise would not reach the cells. Although selecting a receptor that is appropriate for a nanoparticle's cell entry, selecting a receptor that undergoes rapid internalization is crucial. Transferrin receptor is well known to be internalized and recycled. Further, earlier research indicated that deslorelin, a peptide agonist of luteinizing hormone-releasing hormone receptor, is internalized by respiratory epithelial cells. The possible benefit of conjugating transferrin or deslorelin on the surface of nanoparticles has been investigated for enhancing nanoparticle-cell sensitivity and absorption in ocular tissues. Nanoparticles functionalized with transferrin or deslorelin demonstrated rapid entry into the bovine cornea and conjunctive and improved absorption and trans-tissue transport in these tissues compared to non-functional nanoparticles.

Multi diseases affect the posterior eye segment including diabetic retinopathy and age-related macular degeneration requires ongoing care for several-year periods. The two main routes which could potentially deliver effective levels of drugs to the retina include intravitreal and periocular delivery routes. Frequent injections can lead to serious complications on either route, increasing safety concerns, and decreasing patient compliance. Sustained drug delivery devices can be used to supply the drug to the retina for extended periods to obviate or reduce the injection duration. These processes include particulate processes such as nanoparticles, and microparticles. The justification for using nanoparticles, as opposed to microparticles, is debatable when choosing a slow-release drug delivery device. While polymeric nanoparticles are successful in maintaining delivery relative to the drug in solution, they are generally not as successful in sustaining delivery as microparticles because of their high volume-to-surface ratio. For example, polylactide nanoparticles loaded with budesonide showed a high initial burst release followed by a very slow release rate unlike microparticles showing low burst release followed by higher release rats and more continuous release in vitro. In line with this, the rates of in vivo retinal drugs with microparticles were higher compared to nanoparticles on days 7 and 14 following periodic administration. In another in vivo test, triamcinolone acetonide microparticles especially administered retained drug levels in the retina for up to 60 days, while triamcinolone acetonide levels were undetectable for both suspended nanoparticles and drugs. Such experiments indicate that microparticles are more tolerant of drug levels *in vitro* and *in vivo* compared to nanoparticles or solution drugs [29]. Burst release of the drug from nanoparticles and microparticles may be decreased while embedded in a hydrogel, and the maximum duration of drug release may be increased. Though the above-mentioned hydrogels have demonstrated the potential to sustain drug delivery, the intravitreal route is an invasive route with potential injection-related adverse events such as vitrealhemorrhage and retinal and choroidal separation. Thus, it would be ideal to use topically applied hydrogel formulations which enhance the delivery of eye drugs. Hydrogels administered by the subconjunctival route have also shown sustained release and offer a safe alternative to intravitreal injections to target the posterior segment as well.

Diagnostics and Imaging of the Eye

We foresee a range of medical imaging applications for the eye based on developments in nanotechnology and nanomedicine. Light signals from nanoparticles and changes in emission properties as a function of the environment are useful indicators which can be used to determine disease biomarkers that are not invasive. One application based on the imaging is polychromatic angiography [30]. Current diagnostic imaging for retinal angiography is done by intravenously administering a fluorescent molecule, fluorescein, which permeates the diseased eye through the blood-retinal barrier but not in a normal healthy eye. This diagnostic technique cannot be distinguished early from late and is a diagnosis of retinal angiography all or none. A tool that can differentiate between early and late stage retinal angiography will enable a better assessment of disease progression, enhance the ability to select appropriate treatment and dosage, and allow monitoring of treatment and dosage effects. A polychromatic angiography diagnosis was suggested which can be differentiated early from intermediate and late stages of the disease and therefore provides many possible benefits in the treatment and management of retinal angiography. The theory is that in early-stage illness, small particles extravasate, but not larger particles, through the leaky vasculature or weakened blood barriers. During late-stage illness, however, both large and small particles spill through the vasculature or permeate through blood vessels and colocate in the tissue. If the small particles contain a colored dye different from the large particles, then the color can be tracked to monitor the disease stage. Detection of large as well as small particles suggests breakdown or dysfunction of blood vessels, while the detection of only small particles implies that there is a smaller breakdown or dysfunction [31].

Nanotechnology for Retinal Prosthesis

Ocular diseases such as diabetic retinopathy and age-related macular degeneration permanently damage the cells of the photoreceptor which impair vision. There are no therapies or approaches in these patients to restore vision and there is a need to develop methods that can restore vision. There are currently several implants and devices being studied for their ability to activate the retina to create visual hallucinations. Nanoscale materials are used to enhance contact with the surrounding tissue and thus to enhance biocompatibility. A nanophotonic device has been designed for optimum product properties such as reduced footprint, power consumption, and computational requirements of the current retinal prosthesis while reproducing high-resolution vision [32]. When designing silicon wafers, nanotopography, the deviation of a surface within a spatial wavelength of around 0.2 to 20 mm, is an important parameter. In other words, a surface with a high wavelength and low frequency is called a true topography of the nano surface. This

type of surface is used for bridging the difference between raw and flat surfaces. Indeed, the unique structure of nano topography has been shown to improve tissue integration and recovery from the injury of prosthetic devices [33].

Researchers used nanoparticles containing gene transcription factors and other modulating molecules that allow in vivo cell reprogramming as well as nanomaterials to induce selective differentiation of neural progenitor cells and create neural-mechanical interfaces.

Conclusion

Nanotechnology is definitely an innovative technology, which helps to solve all the limitations faced by other distribution paths. Because of its flexibility in the sense that the formulation can be modified to deliver the medication via different routes such as nasal, parenteral and other mucosal routes, and is approved for use in humans by regulatory agencies. In the ophthalmic sector, some of the products are available on the market. As this is still a budding technology and there is still a lot of work to do.

References

1. Adibi SA (1997) Renal assimilation of oligopeptides: physiological mechanisms and metabolic importance. Am J Physiol 272:E723-E736.https://doi.org/10.1152/ajpendo.1997.272.5.e723
2. Atluri H, Anand BS, Patel J, Mitra AK (2004) Mechanism of a model dipeptide transport across blood-ocular barriers following systemic administration. Exp Eye Res 78:815-822.https://doi.org/10.1016/j.exer.2003.10.020
3. Winkler BS (1981) Glycolytic and oxidative metabolism in relation to retinal function. J Gen Physiol 77:667-692.https://doi.org/10.1085/jgp.77.6.667
4. Ammar HO, Salama HA, Ghorab M, Mahmoud AA (2009) Nanoemulsion as a potential ophthalmic delivery system for dorzolamide hydrochloride. AAPS PharmSciTech 10:808-19.https://doi.org/10.1208/s12249-009-9268-4
5. Baba K, Tanaka Y, Kubota A, Kasai H, Yokokura S, et al. (2011) A method for enhancing the ocular penetration of eye drops using nanoparticles of hydrolyzable dye. J Control Release 153:278-287.https://doi.org/10.1016/j.jconrel.2011.04.019
6. Brubaker RF, Bourne WM, Bachman LA, McLaren JW (2000) Ascorbic acid content of human corneal epithelium. Invest Ophthalmol Vis Sci 41:1681-1683.
7. Ansari MJ, Kohli K, Dixit N (2008) Microemulsions as potentialdrug delivery systems: a review. PDA J Pharm SciTechnol 62:66-79.
8. Vandamme TF (2002) Microemulsions as ocular drug delivery systems: recent developments and future challenges. Prog Retin Eye Res 21: 15-34.https://doi.org/10.1016/s1350-9462(01)00017-9
9. Gautam N, Kesavan K (2017) Development of microemulsions for ocular delivery. Therapeu Deliv 8:313-530.https://doi.org/10.4155/tde-2016-0076
10. Chan J, Maghraby GM, Craig JP, Alany RG (2007) Phase transition water-in-oil microemulsions as ocular drug delivery systems: in vitro and in vivo evaluation. Int J Pharm 328:65-71.https://doi.org/10.1016/j.ijpharm.2006.10.004
11. Li CC, Abrahamson M, Kapoor Y, Chauhan A (2007) Timolol transport from microemulsions trapped in HEMA gels. J Colloid Interface Sci 315:297-306.https://doi.org/10.1016/j.jcis.2007.06.054
12. Kaur IP, Kanwar M (2002) Ocular preparations: the formulation approach. Drug DevInd Pharm 28:473-493.https://doi.org/10.1081/DDC-120003445
13. Adibkia K, Shadbad MR, Nokhodchi A, Javadzedeh A, Barzegar-Jalali M, et al. (2007) Piroxicam nanoparticles for ocular delivery: physicochemical characterization and implementation in endotoxin-induced uveitis. J Drug Target 15:407-416.https://doi.org/10.1080/10611860701453125
14. Bucolo C, Maltese A, Maugeri F, Busà B, Puglisi G, et al. (2004) Eudragit RL100 nanoparticle system for the ophthalmic delivery of cloricromene. J Pharm Pharmacol 56:841-846.https://doi.org/10.1211/0022357023835
15. Kassem MA, Abdel-Rahman AA,Ghorab MM, Ahmed MB, Khalil RM (2007) Nanosuspension as an ophthalmic delivery system for certain glucocorticoid drugs. Int J Pharm 340:126-133.https://doi.org/10.1016/j.ijpharm.2007.03.011
16. Pignatello R, Ricupero N, Bucolo C, Maugeri F, Maltese A, et al. (2006) Preparation and characterization of eudragit retard nanosuspensions for the ocular delivery of cloricromene. AAPSPharmSciTech 7:E192-E198.https://doi.org/10.1208/pt070127
17. Tak RV, Pal D, Gao H, Dey S, Mitra AK (2001) Transport of acyclovir ester prodrugs through rabbit cornea and SIRC-rabbit corneal epithelial cell line. J PharmaceuSci 90:1505-1515.https://doi.org/10.1002/jps.1101
18. Li VH, Wood RW, Kreuter J, Harmia T, Robinson JR (1986) Ocular drug delivery of progesterone using nanoparticles. J Microencapsul 3:213-218.https://doi.org/10.3109/02652048609031575
19. Chetoni P, Burgalassi S, Monti D, Tampucci S, Tullio V, et al. (2016) Solid lipid nanoparticles as promising tool for intraocular tobramycin delivery: Pharmacokinetic studies on rabbits. Eur J Pharmaceu Biopharmaceu 109:214-223.https://doi.org/10.1016/j.ejpb.2016.10.006
20. Xu Q, Kambhampati SP, Kannan RM (2013) Nanotechnology approaches for ocular drug delivery. Middle East Afr J Ophthalmol 20:26-37.https://dx.doi.org/10.4103/0974-9233.106384
21. Amrite AC, Kompella UB (2005) Size-dependent disposition of nanoparticles and microparticles following subconjunctival administration. J Pharm Pharmacol 57:1555-1563.https://doi.org/10.1211/jpp.57.12.0005
22. Kruh GD, Guo Y, Hopper-Borge E, Belinsky MG, Chen ZS (2007) ABCC10, ABCC11, and ABCC12. Pflugers Arch 453:675-684.https://doi.org/10.1007/s00424-006-0114-1
23. Peterson MJ, Sarges R, Aldinger CE, MacDonald DP (1979) CP-45,634: a novel aldose reductase inhibitor that inhibits polyol pathway activity in diabetic and galactosemic rats. MetabolClinExp 28:456-461.https://doi.org/10.1016/0026-0495(79)90056-8
24. Yang JJ, Ann DK, Kannan R, Lee VH (2007) Multidrug resistance protein 1 (MRP1) in rabbit conjunctival epithelial cells: its effect on drug efflux and its regulation by adenoviral infection. Pharm Res 24:1490-1500.https://doi.org/10.1007/s11095-007-9267-7
25. Karla PK, Quinn TL, Herndon BL, Thomas P, Pal D, et al. (2009) Expression of multidrug resistance associated protein 5 (MRP5) on cornea and its role in drug efflux. J OculPharmacolTherapeu 25:121-132.https://doi.org/10.1089/jop.2008.0084
26. Nakano M, Lockhart CM, Kelly EJ, Rettie AE (2014) Ocular cytochrome P450s and transporters: roles in disease and endobiotic and xenobiotic disposition. Drug Metabol Rev 46:247-260.https://doi.org/10.3109/03602532.2014.921190
27. Sahoo SK, Dilnawaz F, Krishnakumar S (2008) Nanotechnology in ocular drug delivery. Drug Disc Today 13:144-151.https://doi.org/10.1016/j.drudis.2007.10.021
28. Majumdar S, Nashed YE, Patel K, Jain R, Itahashi M, et al. (2005) Dipeptide monoester ganciclovirprodrugs for treating HSV-1-induced corneal epithelial and stromal keratitis: in vitro and in vivo evaluations. J OculPharmacolTherapeu 21:463-474.https://doi.org/10.1089/jop.2005.21.463
29. Shirasaki Y (2008) Molecular design for enhancement of ocular penetration. J Pharm Sci 97:2462-2496.https://doi.org/10.1002/jps.21200
30. Liang WJ, Johnson D, Jarvis SM (2001) Vitamin C transport systems of mammalian cells. MolMembrBiol 18:87-95.https://doi.org/10.1080/09687680110033774
31. Peng CC, Bengani LC, Jung HJ, Leclerc J, Gupta C, et al. (2011) Emulsions and microemulsions for ocular drug delivery. J Drug Deliv Sci Technol 21: 111-121.https://doi.org/10.1016/S1773-2247(11)50010-3
32. Sasaki H, Yamamura K, Mukai T, Nishida K, Nakamura J, et al. (1999) Enhancement of ocular drug penetration. Crit Rev Therapeu Drug Carr Sys 16: 62.https://doi.org/10.1615/critrevtherdrugcarriersyst.v16.i1.20
33. Gunda S, Hariharan S, Mitra AK (2006) Corneal absorption and anterior chamber pharmacokinetics of dipeptide monoester prodrugs of ganciclovir (GCV): in vivo comparative evaluation of these prodrugs with Val-GCV and GCV in rabbits. J OculPharmacolTher 22: 465-476.https://doi.org/10.1089/jop.2006.22.465