

REVIEW ARTICLE

Colloidal drug delivery system: amplify the ocular delivery

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Abstract

Context: The ocular perceivers are the most voluntarily accessible organs in terms of location in the body, yet drug distribution to these tissues is one of the most intriguing and challenging endeavors and problematic to the pharmaceutical scientist. The most of ocular diseases are treated with topical application of conventional formulation, i.e. solutions, suspensions and ointment. Typically on installation of these conventional formulations, only <5% of the applied dose penetrates the cornea and reaches intraocular tissues, while a major fraction of the instilled dose is wastage due to the presence of many ocular barriers like external barriers, rapid loss of the instilled solution from the precorneal area and nasolacrimal drainage system. Systemic absorption caused systemic side effects varying from mild to life-threatening events. **Objective:** The main objective of this review is to explore the role of colloidal delivery of drug to minimize the drawbacks associated with them.

Methods: This review provides an insight into the various constraints associated with ocular drug delivery, summarizes recent findings and applications of colloidal delivery systems, i.e. nanoparticles, nanosuspensions, liposomes, niosomes, dendrimers and contact lenses containing nanoparticles have the capacity to distribute ocular drugs to categorical target sites and hold promise to revolutionize the therapy of many ocular perceiver diseases and minimized the circumscription of conventional delivery.

Conclusion: Form the basis of literature review, it has been found that the novel delivery system have greater impact to maximize ocular drug absorption, and minimize systemic absorption and side effects.

Keywords

Colloidal delivery system, eye, nanotechnology, ocular barriers, ocular transporter, pharmacokinetics

History

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Introduction

Ocular drug delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists. The anatomy, physiology and biochemistry of the eye provide a unique structure that restricts the entry of drug molecules at the required site of action. A suitable ocular formulation should release the drug overcoming the protective barriers of the eye without causing permanent tissue damage. For anterior-segment drug delivery common routes of administration are topical instillation and subconjunctival injection, whereas for posterior-segment drug delivery common routes include systemic dosing, periocular and intravitreal injections, and topical dosing. The topical ocular administration of drugs has two different purposes: to treat superficial eye diseases, such as infections (e.g. conjunctivitis, blepharitis, keratitis sicca) and to provide intraocular treatment through the cornea for diseases such as glaucoma or uveitis. For their favorable cost advantage, the greater simplicity of formulation development and production, and the good patient acceptability, >90% of the marketed ophthalmic formulations are in the

form of eye drops for soluble drugs; yet these conventional systems cannot be considered optimal in the treatment of vision-threatening ocular diseases, in that most of the drugs are washed off from the eye by various mechanisms (lacrimation, tear dilution and tear turnover). Moreover, the relatively impermeable corneal barrier restricts the entry of foreign substances. As a result, less than 5% of administered drug penetrates the cornea and reaches intraocular tissues (Lang, 1995; Araujo et al., 2009).

Drug delivery in ocular therapeutics is a challenging problem and is a subject of interest to scientists working in the multi-disciplinary areas pertaining to the eye, including chemical, biochemical, pharmaceutical, medical, clinical and toxicologic sciences. Recently, there has been increased attention focused on two main objectives:

- (i) to find or tailor-make newer, effective and safe drug molecules for various ocular conditions and diseases that are poorly controlled for conventional eye drops and
- (ii) to improve existing ocular dosage forms and exploits newer delivery systems for improving the ocular bioavailability of existing molecules.

Nanotechnology is the manipulation of matter on an atomic and molecular scale. It is a multi-disciplinary scientific field such as electronics, physical and material science; and manufacturing at a molecular or submicron level, is a

scientific field undergoing explosive development. The term nanotechnology derived from the Greek word “nano” meaning “dwarf” (Kayser et al., 2005; Sahoo et al., 2008). The dimensions are between ~ 1 and 1000 nm and this unique phenomena enable novel applications. Encompassing nanoscale science, engineering and nanotechnology involves imaging, measuring, modeling and manipulating matter at this length scale (Sahoo et al., 2003; Gupta & Kompella, 2006; Abdelkader et al., 2011). A part of this field is the development of nanoscale drug delivery devices. Nanoparticles (NPs) have been developed as an important drug delivery system (DDS).

The potential of nanocarriers as DDSs

There are many challenges associated to drug delivery like poor solubility of drug, bioavailability, delivery of peptides and proteins, large particle size, *in vivo* stability, intestinal absorption, sustained and targeted delivery to site of action, therapeutic effectiveness, generalized side effects, and plasma fluctuations of drugs (Torchilin, 2004; Kayser et al., 2005; Sultana et al. 2011). There are many novel drug delivery technologies overcome these challenges, using bioadhesive systems, transdermal patches, nanoscale devices, implants, microparticle systems and also route of delivering as nasal DDSs (Gondaliya & Pundarikakshudu, 2003; Labhasetwar, 2005; De la Fuente et al., 2010). But nanotechnology offers advantages that allow a more targeted drug delivery and controllable release of the therapeutic compounds. The major objective of nanotechnology as targeted drug delivery, i.e. control release of drug at target site, manipulating pharmacokinetic, pharmacodynamic, reduce dosing frequency, reduce toxicity and improve efficacy (Yih & Al-Fandi, 2006; Sahoo et al., 2008; Gupta et al., 2013; Singh et al., 2013).

Advantages of nanotechnology

- Nanostructures have the ability to protect drugs from the degradation in the gastrointestinal tract; the technology allows target delivery of drugs to various areas of the body.
- The technology enables the delivery of drugs that are poorly water soluble and can provide means of bypassing the liver, thereby preventing the first-pass metabolism.
- Nanotechnology increases oral bioavailability of drugs due to their specialized uptake mechanisms such as absorptive endocytosis and is able to remain in the blood circulation for a long time, releasing the incorporated drug in a controlled fashion, leading to less plasma fluctuations and minimized side effects.
- Nanoscale size materials are able to penetrate tissues and are easily taken up by cells, allowing for efficient delivery of drugs to target sites of action. Nanotechnology improves performance and acceptability of dosage forms by increasing their effectiveness, safety, patient adherence, as well as ultimately reducing health care costs.

Barriers in eye drug transport

The eyes are among the most readily accessible organs in terms of location in the body (Figure 1A), but drug delivery

to eye tissues is particularly problematic due to the presence of ocular barriers like tear film, cornea, conjunctiva and sclera.

Blood–ocular barrier

Systemic/intravitreal application is the main route of drug administration for many posterior-segment disorders, by which adequate concentrations of drug can be achieved and maintained in the retina and vitreous. The blood–ocular barrier is a barrier created by endothelium of capillaries of the retina and iris, ciliary epithelium and retinal pigment epithelium. It is a physical barrier between the local blood vessels and most parts of the eye itself, and stops many substances including drugs from travelling across it. Inflammation can break down this barrier allowing drugs and large molecules to penetrate into the eye. The blood–ocular barrier is composed of the blood–aqueous barrier (BAB) and the blood–retinal barrier (BRB). It protects the eye from entry of toxic substances and maintains the homeostatic control that underpins the ocular physiology (Singh et al., 2011).

The BAB is formed by the non-pigmented epithelium of the ciliary body, the posterior iris epithelium, the endothelium of the iris vessels with tight junctions of the leaky type, and the endothelium of Schlemm’s canal and controlled the secretion of the aqueous humor and its transport toward the posterior chamber. The passive permeability of the BAB depends on the ionic concentration gradients. The BAB is composed of iris capillaries and pigmentary epithelium, allows the transcellular transport by means of vesicles. The paracellular transport is controlled by the extension of the tight junctions. Associated with the ciliary and retinal pigment epithelium, the iris pigment epithelium seems to constitute an obstacle to the passage of type T activated lymphocytes. The BAB allows small lipophilic drugs to enter the uveal blood circulation and, consequently, facilitates their rapid elimination from the anterior chamber. In contrast, larger and more hydrophilic drugs are merely eliminated by aqueous humor turnover across the BAB (Thomas, 2013). The BRB is located in the posterior part of the eye and is composed of two cell types, namely the retinal capillary endothelial (RCE) cells and retinal pigment epithelial (RPE) cells which form the inner and outer BRB, respectively. The inner BRB covers the lumen of retinal capillaries and protects the retina from circulating molecules in the blood circulation (Gardner et al., 1999). The outer BRB displays tight barriers due to the presence of tight junctions (Zonula occludens). Specialized transport processes within the RPE together with robust barrier restrictiveness of RPE control the traverse of nutrients/compounds, allowing selective exchange of nutrients between the choroid and retina. Polarized RPE cells display a predominantly apical localization of Na^+ , K^+ -ATPase which regulates intracellular Na^+ and K^+ homeostasis. Retinal vascular leakage from loss of function of the BRB and subsequent macular edema are the main causes of visual loss and blindness in major eye diseases such as diabetic retinopathy (DR), age-related macular degeneration (AMD), retinal vein occlusion and uveitis (Klaassen et al., 2013).

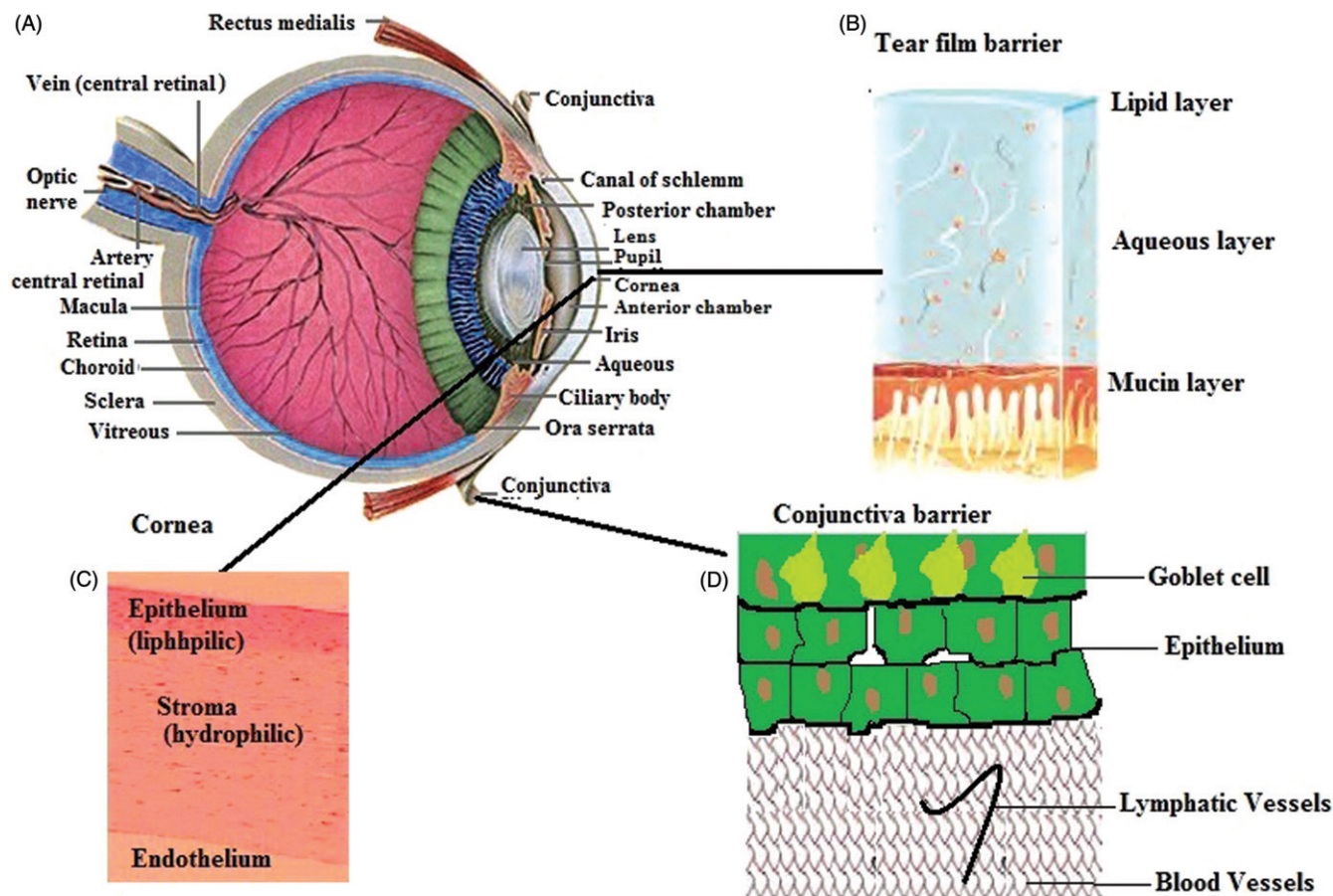


Figure 1. Different ocular barriers of topical drug delivery.

Tear film

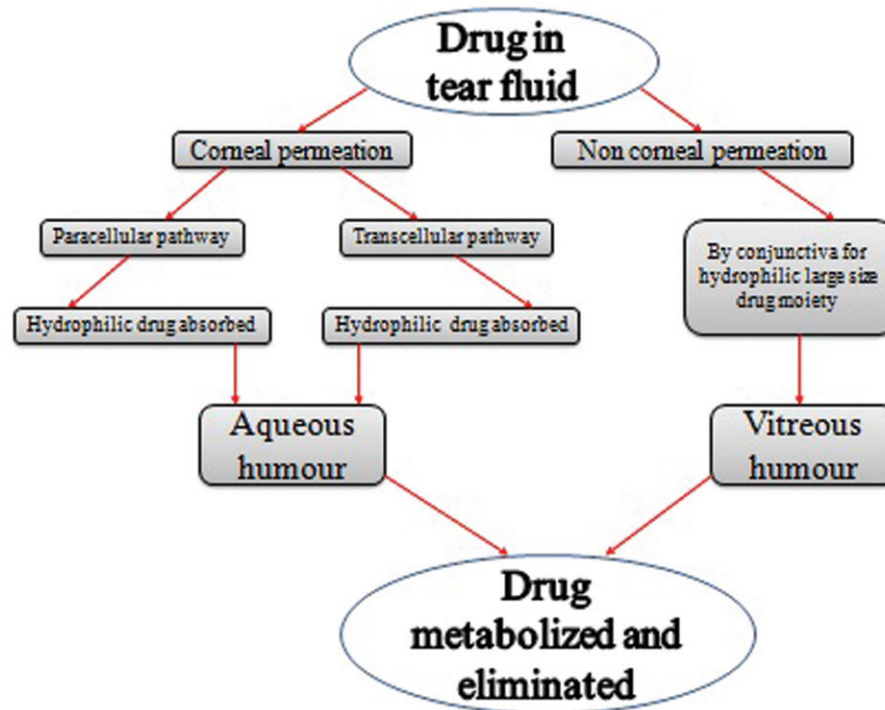
The tear (precorneal film) film is the liquid layer bathing cornea and conjunctiva. The film thickness is $\sim 3\text{--}10\ \mu\text{m}$ reported in published studies (King-Smith et al., 2000; Szczesna et al., 2006, 2007; Szczesna & Iskander, 2012). The tear film consist of three-layered structure comprising a lipid (oil) layer, an aqueous (water) layer and a mucus layer over the corneal epithelium as shown in Figure 1(B). Lipid layer is the most outer surface and polishes the corneal surface. It is produced by the meibomian glands and providing a smooth tear surface and retarding the rate of tear evaporation from the cornea. Mechanically traps and flushes out foreign bodies and chemicals, contains bacteriostatic substances that inhibit the growth of microorganisms. The aqueous layer produced by the lacrimal gland and is composed of water, proteins and other substances, such as lipocalin, lactoferrin, lysozyme and lactitin. This layer is responsible for control on infection, osmotic balance and water promoting spreading of the tear film. The innermost layer of the tear film is mucus layer. It is produced by goblet cells of the conjunctiva and acts as a hydrophilic layer (water soluble) and serves as an anchor for the tear film and helps it adhere to the eye. The tear film creates a smooth surface for light to pass through the eye, nourishes the front of the eye and provides protection from infection (Wolff, 1946, 1954; King-Smith et al., 2000; Craig, 2002; Montes-Mico et al., 2010; Stahl et al., 2012). Tear film which reduces

the effective concentration of the administrated drugs due to dilution by the tear turnover ($\sim 1\ \mu\text{l}/\text{min}$), accelerated clearance, and binding of the drug molecule to the tear proteins (Schoenwald, 1990; King-Smith et al., 2000; Her et al., 2013).

Cornea

The cornea is the transparent, dome-shaped window covering the front of the eye and one of the most densely innervated tissues on the surface of the body (Marfurt et al., 1989; Muller et al., 2003; Baspinar et al., 2008) (Figure 1C). It is a powerful refracting surface, providing two-third of the eye's focusing power. Because there are no blood vessels in the cornea, it is normally clear and has a shiny surface. It is $\sim 11.7\text{ mm}$ in diameter, $500\ \mu\text{m}$ thick in the center with $\sim 700\ \mu\text{m}$ at the periphery and radius of curvature of anterior surface $\sim 7.7\text{ mm}$ while the radius of curvature of the globe is $\sim 12\text{ mm}$ (Maurice & Mishima, 1984; Hitzenberger et al., 1994). The cornea consists of three layers: epithelium, stroma and endothelium and passes the mechanical barrier of foreign substances. Each layer possesses a different polarity and a rate-limiting structure for drug permeation. The corneal epithelium is of a lipophilic nature, and tight junctions among cells are formed to restrict paracellular drug permeation from the tear film and permeated lipophilic drugs (transcellular pathway). Hydrophilic charged cationic compounds permeate more easily through the cornea than anionic

Figure 2. Systemic representation of drug disposition model in the eye after topical instillation.



forms, because the corneal epithelium is negatively charged above its isoelectric point (Rojanasakul et al., 1992; Bourlais et al., 1998; Araujo et al., 2009). The highly hydrated structure of the stroma acts as a barrier to permeation of lipophilic drug molecules. Corneal endothelium is the innermost monolayer of hexagonal-shaped cells, and acts as a separating barrier between the stroma and aqueous humor. The endothelial junctions are leaky and facilitate the passage of macromolecules between the aqueous humor and stroma (Bourlais et al., 1998; Fischbarg, 2006; Araujo et al., 2009).

Conjunctiva

The conjunctiva is the thin, vascularized mucus membrane, transparent tissue that covers the outer surface of the eye. Histologically, the conjunctiva consists of non-keratinized, stratified squamous epithelium with interspersed goblet cells (Figure 1D). It involved in the formation and maintenance of the tear film. In addition, conjunctiva or episclera has a rich supply of capillaries and lymphatics (Sugar et al., 1957; Raviola, 1983; Robinson, 1993; Gausas et al., 1999; Singh, 2003); therefore, administrated drugs in the conjunctival or episcleral space may be cleared through blood and lymph. The conjunctival blood vessels do not form a tight junction barrier (King-Smith et al., 2000), which means drug molecules can enter into the blood circulation by pinocytosis and/or convective transport through paracellular pores in the vascular endothelial layer. The conjunctival lymphatics act as an efflux system for the efficient elimination from the conjunctival space. Recently, it has been reported that at least 10% of a small molecular weight hydrophilic model compound (sodium fluorescein), administered in the subconjunctival space, is eliminated via the lymphatics within the first hour in rat eyes (Lee et al., 2010). Therefore, drugs transported by lymphatics in conjunction with the elimination

by blood circulation can contribute to systemic exposure, since the interstitial fluid is returned to the systemic circulation after filtration through lymph nodes.

Sclera

The sclera (white of the eye) is white, fibrous collagen tissues, and has three layers (anterior to posterior): episclera, scleral stroma and lamina fusca and continued to cornea anteriorly (Figure 2A). Sclera provides the structural integrity that defines the shape and length of the eye (Newell, 1982; Ludwig, 2005; Pescina et al., 2011). Scleral permeability has been shown to have a strong dependence on the molecular radius; scleral permeability decreases roughly exponentially with molecular radius (Ambati et al., 2000). Additionally, the posterior sclera is composed of a looser weave of collagen fibers than the anterior sclera (Curtin, 1969; Miao et al., 2013), and the human sclera is relatively thick near the limbus (0.53 ± 0.14 mm), thin at the equator (0.39 ± 0.17 mm) and much thicker near the optic nerve ($0.9\text{--}1.0$ mm). Thus, the ideal location for transscleral drug delivery is near the equator at 12–17 mm posterior to the corneoscleral limbus (Myles et al., 2005; Qi et al., 2013). Hydrophobicity of drugs affects scleral permeability; increase of lipophilicity shows lower permeability; and hydrophilic drugs may diffuse through the aqueous medium of proteoglycans in the fiber matrix pores more easily than lipophilic drugs (Maurice & Polgar, 1977; Cruysberg et al., 2002; Wen et al., 2013).

Ocular transporters

The approach to improve bioavailability to ocular delivery is to modify the drug chemically (for solubility and lipophilicity improvement) or by novel DDS (colloidal delivery system). The transporters are membrane-bound proteins that play an important role in active transport of drug to across biologic

membranes and the presence on various ocular tissues, i.e. epithelia of the cornea, conjunctiva and retina. These transporters may be amenable to bind and transport specific-targeted ligands attached to drug moieties. Mainly two types of transporter systems are of interest in ocular drug delivery, i.e. efflux transporters and influx transporters. According to many researchers, the efflux transporters belong to the ATP-binding cassette superfamily, whereas influx transporters belong to the solute-carrier superfamily. Efflux transporters lower bioavailability by effluxing the molecules out of the cell membrane and cytoplasm. Prominent efflux transporters identified on ocular tissues include P-glycoprotein (P-gp), multidrug resistance protein (MRP) and breast cancer-resistance protein (BCRP). P-gp has an affinity to efflux lipophilic compounds in normal as well as in cancerous cells, possibly leading to emergence of drug resistance (Dey et al., 2004). Expression and functional activity of P-gp was identified on various ocular cell lines and tissues such as the cornea (Kawazu et al., 1999; Dey et al., 2003), conjunctiva (Yang et al., 2000) and retinal pigmented epithelium (RPE) (Constable et al., 2006). MRP works in a similar manner but effluxes organic anions and conjugated compounds. Influx transporters facilitate the translocation of essential nutrients and xenobiotics across biologic membranes. These include carriers for amino acids, peptides, vitamins, glucose, lactate and nucleoside/nucleobases. The most commonly applicable influx transporters for ocular drug delivery are amino acid and peptide transporters. These proteins may have a putative role in ocular drug delivery along with their physiologic role of transporting various amino acids and nutrients into ocular tissues. In nanotechnology base ocular delivery, the ocular transporter (influx) transported it to the targeted place by crossing the different ocular barriers which are described previously, whereas the formulation may also inhibit the efflux transporter (P-gp) and increase the bioavailability of drug (Gaudana et al., 2010). The increases in bioavailability of nanoformulation depend upon the type of polymer/lipid, charge, size and modification on surface of particles (Kompella et al., 2006).

Pharmacokinetic consideration

After topical administration of an ophthalmic drug solution, the drug is first mixed with the lacrimal fluid. The contact time of drug with ocular tissues is relatively short (1–2 min) because of the permanent production of lacrimal fluid (0.5–2.2 µl/min). Then, approximately half of the drug flows through the upper canaliculus and the other half, through the lower canaliculus into the lacrimal sac, which opens into the nasolacrimal duct. Drainage of lacrimal fluid during blinking (every 12 s) toward the nasolacrimal duct induces a rapid elimination of conventional dosage forms (Ahmed & Patton, 1987). The drug is absorbed into the retina–choroid via a corneal or sclero-conjunctival route, while the iris and ciliary body are presumably supplied via both the transcorneal and the extracorneal pathways.

Drugs penetrate across the corneal epithelium via the transcellular or paracellular pathway. Lipophilic drugs prefer the transcellular route, while hydrophilic drugs penetrate

primarily through the paracellular pathway, which involves passive or altered diffusion through intercellular spaces. The transcorneal penetration appears to be hindered by the binding of the drug to the corneal tissues. The cornea may act as a drug reservoir, slowly releasing the drug into the aqueous humor, where levels decrease very slowly (Merck, 2003). Then, drugs are distributed from the aqueous humor to the intraocular tissues, i.e. iris–ciliary body, lens, vitreous and choroids–retina and eliminated mainly via aqueous humor turnover and venous blood flow in the anterior uvea (Figure 2). It is suggested that ocular penetration via the scleroconjunctival route is more rapid (for a hydrophilic drug) than via the transcorneal route (Worakul & Robinson, 1997). Both transconjunctival absorption and transnasal absorption after drainage via the nasolacrimal duct are generally undesirable, not only because of the loss of active ingredient into the systemic circulation, but also because of possible side effects, for instance, the effects on the heart when beta-blockers are administered for the treatment of wide-angle glaucoma (Schoenwald, 1990; Meseguer et al., 1994; Jtirvinen et al., 1995).

Colloidal systems used as ocular delivery

Ocular drug delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists because of the critical and pharmacokinetically specific environment that exists in the eye. The anatomy, physiology and biochemistry of the eye provide a unique structure that restricts the entry of drug molecules at the required site of action and impervious to foreign substances. A suitable ocular formulation should release the drug overcoming the protective barriers of the eye without causing permanent tissue damage (Ghate & Edelhauser, 2006; Urtti, 2006). There are many routes of ocular administration like topical instillation and subconjunctival injection for anterior segment, whereas periocular and intravitreal injections, and topical dosing for posterior segment (Bu et al., 2007; Araujo et al., 2009; Bochot et al., 2011; Thrimawithana et al., 2011). Mostly superficial eye diseases, such as conjunctivitis, blepharitis or keratitis sicca and intraocular diseases, such as glaucoma or uveitis are treated by topical ocular administration of drugs formulation. On the other hand, drug targeting can be an efficient mode for the treatment intraocular disease such as DR, choroidal neovascularization, central retinal vein occlusion and intraocular solid tumors. There are three major objective of ocular targeting like enhancing drug permeation (e.g. iontophoresis and transscleral DDS); to control the release of drugs (e.g. micro spheres, liposomes and intraocular implants) and to target drugs (e.g. prodrugs with high molecular weight and immunoconjugates) (Yasukawa et al., 2004; Janoria et al., 2007).

A meticulous look toward the past of ocular delivery clearly accentuates eye drops as the principal and most frequently used formulation for ocular delivery. Although eye drops are easy to manufacture and patient compliant but their application is severely fraught with problems related to their poor bioavailability (1–10%). The poor bioavailability of eye drop may be due to attributed limited area of absorption, tight

junction of the superficial conjunctival epithelium, pre-systemic metabolism of drugs in the ocular milieu and non-specific binding with lacrimal proteins, blinking, transient residence time in cul-de-sac, and nasolacrimal drainage and rapid drainage of instilled dose from the site of application. The rapid drainage is associated with natural tendency of eye to maintain the residence volume at 7–10 μ l (Lang, 1995; Bu et al., 2007) which is much less than the normal volume instilled at once, i.e. 20–50 μ l. Rapid drainage is contributed by high turnover of lacrimation which results in very less residence time for drugs to be biologically available (Araujo et al., 2009). To overcome this drawback of conventional eye drop (less residence time), numerous novel formulation approaches like nanoparticulate systems, hydrogel vesicular systems, implantable systems, collagen shields and ocuserts have developed by researchers to increase the bioavailability of ophthalmic drugs by prolonging corneal/conjunctival epithelium residence time. These new delivery systems have many advantages such as increased residence time, controlled and sustained drug release over a longer period, reduction of side effects and better patient compliance in comparison to the conventional formulation for ocular delivery. This is possible by using of compatible biodegradable polymers (Ludwig, 2005; Mainardes et al., 2005; Gaudana et al., 2010).

Disadvantages (toxicology) nanotechnology

Various disadvantages are associated with nanotechnological preparation for ocular delivery. Many of them are given with needles, also some of them are as localized implantation. It is observed that the nanotechnological formulation showed interaction with tissues and cells, and the potential toxicity greatly depends on the actual composition of the nanoformulation. The toxicity depends on size of the product, which opens the potential for crossing the various biologic barriers within the body. Intravitreal injection of microspheres loaded with ganciclovir or poly(lactic-co-glycolic acid) (PLGA) with inert fluorochromes showed localized foreign-body reaction. PLGA microspheres loaded with 5-fluorouracil or retinoic acid have been used experimentally in proliferative vitreoretinopathy which is associated with localized multinuclear giant cell reaction (Bourges et al., 2006). Other disadvantages of microparticles and NPs are the risks of injection that intraocular injections may cause vitreous clouding and periocular injections may cause a foreign-body response (Herrero-Vanrell & Refojo, 2001). Other study revealed localized foreign-body reaction from partially degraded ganciclovir-loaded microspheres with mononuclear cells and multinucleated giant cells after 4 and 8 weeks of following intravitreal injection in rabbits, and it decreased substantially at 12 weeks (Short, 2008). Novel colloidal drug delivery of antibiotics, antifungals, antivirals and antimetabolic agents are less toxic than the free form because there is less free drug in contact with tissues. These systems protect poorly stable drugs from degradation also. An anatomical difference is useful for interpreting toxicologic and pathologic responses to the eye and is important for human risk assessment of these important new therapies for ocular diseases. Overall, nanotechnology has great impact in ocular

drug delivery after weighing the benefit risk ratio in the concerned area.

Advantages of colloidal ocular delivery

Advantages of colloidal ocular delivery are:

- sustained and controlled release of the drug at the targeted site;
- reduced frequency of administration;
- ability to overcome blood–ocular barriers, and efflux-related issues associated with the parent drug;
- overcome various stability-related problems of drug molecules, e.g. proteins and peptides; and
- the use of nanotechnology-based DDSs like nanosuspension, solid lipid NPs and liposomes has led to the solution of various solubility-related problems of poorly soluble drugs, like dexamethasone, budesonide, ganciclovir and so on (Kayser et al., 2005).

Colloidal (nanoparticulate based) ocular drug delivery

Nanoparticulate or colloidal dosage form are widely employed for the treatment of ocular disease. It would prolong the ocular retention of drug, allowing the drug to remain in contact with the cornea for longer duration, sustained release and thus increasing bioavailability. The dosage forms include microspheres, liposomes, niosomes, NPs, microemulsions (MEs), nanoemulsions (NEs), etc.

Microemulsions

MEs are currently of interest to the pharmaceutical scientist as promising drug delivery vehicles due to their long-term stability, ease of preparation, low toxicity and irritancy, considerable capacity for solubilization of a variety of drug molecules and great potential in bioavailability improvement (Soukharev et al., 2005; Djekic et al., 2008; Gupta & Moulik, 2008). MEs were first described by Hoar and Schulman (Fialho & da Silva-Cunha, 2004). They are dispersion of water, oil and a mixture of surfactants and co-surfactant, making a homogeneous, optically isotropic and thermodynamically stable and a small droplet size in the dispersed phase (<1.0 μ m) (Soukharev et al., 2005; Djekic et al., 2008).

MEs have attracted a great interest as DDS for topical ocular application because of small size, simple and inexpensive preparation, can be sterilized easily by filtration (Soukharev et al., 2005), low viscosity, greater ability as drug carrier, absorption promoter, and low surface tension of MEs, show spreading on the cornea mixing with the precorneal film constituents (Fialho & da Silva-Cunha, 2004). MEs as carriers for drugs to transport lipophilic and hydrophilic substances through their respective medium, i.e. an aqueous medium and lipid medium, and hence improve the bioavailability (Ma et al., 2008; Kesavan et al., 2013). The penetration enhancing property of surfactant and co-surfactant of MEs increases the drug permeability (drug uptake) and facilitates the passage of drug by corneal membrane. Moreover, MEs achieve sustained release of a drug applied to the cornea and higher penetration into the deeper layers of the ocular

structure and the aqueous humor than the eye drop. Due to prolonged release of drug from MEs, ocular delivery can decrease the frequency of application. Kesavan et al. (2013) developed MEs of dexamethasone and found that they are stable small globule size, have acceptable physicochemical behavior, good mucoadhesive properties, and ability to enhance bioavailability through its longer precorneal residence time sustained the release of the drug.

Due to the high-level indomethacin in ocular structure, aqueous humor in rabbit eyes was achieved upon topical instillation of chitosan NEs (CS NEs) as compared with indomethacin drug solution. The CS NPs prepared were capable to make contact intimately with the cornea thus giving a slow continuing drug release with long-term drug intensity, thus enhancing delivery to both internal and external ophthalmic tissues (Badawi et al., 2008).

Tayel et al. (2013a) developed alternative controlled-release *in situ* ocular drug-loaded NEs gels using isopropyl myristate/Miglyol 812, surfactants (Tween-80/Cremophor EL), a co-surfactant (polyethylene glycol 400) and water. The NEs was developed pseudoternary-phase diagrams technique and converted in gel by using gellan gum solution (0.2%, w/w). The optimized formulation [Miglyol 812, Cremophor EL:polyethylene glycol 400 (1:2) and water (5, 55 and 40%, w/w, respectively)] (NEs and gel) was evaluated *in vitro* and *in vivo* and showed the well transparency, rheologic behavior, mucoadhesive force and sustained drug release. On installation in rabbit eye it show good consistency, thermodynamically stable and no irritation and histopathologic assessment of ocular irritation. The gel have significantly ($p < 0.01$) higher C_{\max} , delayed T_{\max} , prolonged mean residence time and increased bioavailability as compared to terbinafine hydrochloride eye drop and decreased the frequent instillation and maintained effective aqueous humor concentrations.

Pathak et al. (2013) developed and evaluated novel pH-triggered nanoemulsified *in situ* gel (NE-ISG) for ophthalmic delivery of fluconazole. Pseudoternary-phase diagrams were constructed using capmul MCM (oil phase), Tween-80 (surfactant) and transcitol P (co-surfactant) to identify the NE region and form by spontaneous emulsification. The formulations were characterized for permeation, corneal irritation and corneal toxicity. The optimized NE *in situ* gels showed three-fold ($337.67 \mu\text{g}/\text{cm}^2$) higher *ex vivo* transcorneal permeation than commercial eye drops ($112.92 \mu\text{g}/\text{cm}^2$). Formulation dose not showed any visual signs of tissue damage. Hence, it can be concluded that NE gel may offer a more intensive treatment of ocular fungal infections due to higher permeation, prolonged precorneal residence time and sustained drug release along with higher *in vitro* efficacy, safety and greater patient compliance.

Ammar et al. (2009) developed the dilutable NEs of dorzolamide hydrochloride for ophthalmic use and have numerous advantages as sustained effect and high ability of drug penetration into the deeper layers of the ocular structure and the aqueous humor. It prepared using different oils, surfactants and co-surfactants by applying pseudoternary-phase diagrams system. These NEs showed acceptable physicochemical properties and exhibited slow drug release and no sign of inflammation on Draize rabbit eye. Biologic

evaluation of dorzolamide hydrochloride NEs on normotensive albino rabbits indicated that these products had higher therapeutic efficacy, faster onset of action, and prolonged effect relative to either drug solution or the market product. Many researchers investigated the MEs/NEs ocular drug delivery, which are given in Table 1.

Nanosuspension

Nanosuspension made up of pure, poorly water-soluble drugs, suspended in an appropriate dispersion medium. Nanotechnology may be better utilized for drug compounds that form crystals with high energy content, which renders them insoluble in either organic (lipophilic) or hydrophilic media (Kayser et al., 2005). Polymeric NP suspensions, which are prepared from inert polymeric resins, can be utilized as important drug delivery vehicles, capable of prolonging drug release and enhancing bioavailability (Sahoo et al., 2008). Nanosuspension is free from irritation to cornea, iris or conjunctiva, and it is used as an inert carrier for ocular delivery. The Flurbiprofen (FLU)-loaded nanosuspensions are prepared by the quasi-emulsion solvent diffusion (QESD) technique, which generally avoids the toxic chemicals used in solvent evaporation techniques; they have great potential for ocular delivery (Kawashima et al., 1989; Pignatello et al., 2002). Thus, the use of nanosuspensions in ocular delivery is an attractive area, offering a great possibility to overcome the inherent difficulties associated with conventional ocular drug delivery.

Nanoparticles

NPs are one of the most-studied colloidal systems with the object of improving targeting of drug to organs and increasing drug bioavailability across biologic membranes. NPs are submicroscopic, colloidal system consisting of macromolecular substances that vary in size from 10 to 1000 nm. In NPs, the drug may be dissolved, entrapped, adsorbed, attached or encapsulated into the polymer matrix. Depending on the method of preparation, it can be classified into two groups: NPs (nanospheres) and nanocapsules and have different release profile of drug (Sahoo et al., 2003; Vandervoor et al., 2007).

Nanospheres are small solid spheres constituting of dense solid polymeric network having large surface area. Drugs can either be incorporated in the matrix system or adsorbed on the surface of the nanospheres. On the other hand, nanocapsules have small central cavity (oily droplet) surrounded by a polymeric membrane (Figure 3). NPs represent promising drug carriers for ophthalmic applications. After optimal binding to these particles, the drug absorption in the eye is enhanced significantly in comparison to eye drop solutions owing to the much slower ocular elimination rate of particles. Smaller particles are better tolerated by the patients than larger particles therefore NPs could be a very comfortably to be used for prolonged action ophthalmic DDS.

Different polymers can be used to fabricate NPs such as biodegradable polymers like polylactides, poly(D,L-lactides), PLGA, ϵ -caprolactone (Fessi et al., 1989; Aksungur et al., 2011; Gupta et al., 2011), polyacrylamide, polycyanoacrylate and poly(methyl methacrylate) (Zimmer et al., 1991; Wenger

Table 1. Colloidal approaches of various drugs for ocular delivery.

| Drug | Polymer | Formulation | Result | References |
|--|---------------------------------------|----------------------------|---|--------------------------------|
| Everolimus | Oil | ME | Stable, 8.64 ng/ml reached 30 min | Baspinar et al. (2008) |
| Pilocarpine | Oil | ME | Decreased IOP by 25% | Garty et al. (1994) |
| Dexamethasone | Oil | CS MEs | Enhance bioavailability | Kesavan et al. (2013) |
| Vitamin A palmitate | Oil | MEs | Provided better wettability and longer ocular retention | Ma et al. (2008) |
| Chloramphenicol | Oil | MEs | Tamibility increases remarkably than eye drop | Lv et al. (2005) |
| Dexamethasone | Oil | MEs | AUC two-fold higher than conventional | Fialho & da Silva-Cunha (2004) |
| Timolol | Oil | MEs | AUC 3.5-fold than timolol eye drop in aqueous humor | Gasco et al., 1989 |
| Betoxalol | CS | NPs | Marked reduction in IOP | Jain et al. (2013) |
| Cyclosporine | CS | NPs | Enhanced residence time at the corneal and conjunctival surfaces | Başaran et al. (2013) |
| Dorzolamide hydrochloride or timolol maleate | HS + CS | NPs | Produced a marked decrease in IOP | Wadhwa et al. (2010) |
| 5-FU | CS | NPs | Bioavailability NPs was significantly higher than 5-FU solution in aqueous humor of rabbit eye | Nagarwal et al. (2011) |
| Dorzolamide HCl and pramipexole HCl | CS | NPs | Show good mucoadhesion and <i>in vitro</i> release | Papadimitriou et al. (2008) |
| LCS-NP complex | CS | NPs | No cytotoxicity on conjunctival epithelial cell line IOBA-NHC and strong cellular uptake by corneal epithelium | Diebold et al. (2007) |
| Cyclosporine | CS | NPs | Prolonged control release cyclosporine to the cornea and conjunctiva in rabbit | Campos et al. (2001) |
| Metipranolol | CS | NPs | Decreases the systemic side effect | Losa et al. (1993) |
| 5-Fluorouracil (5-FU) | Sodium alginate–CS | NPs | Bioavailability NPs was significantly higher than 5-FU solution in aqueous humor of rabbit eye | Nagarwal et al. (2012) |
| Indomethacin | Poly(ϵ -caprolactone (PECL) | Nanocapsules, NPs | Enhance the corneal penetration and ocular bioavailability in rabbit eye | Calvo et al. (1996) |
| Ganciclovir | Albumin | NPs | Sustained release of ganciclovir over a days | Merodio et al. (2002) |
| Ganciclovir | Albumin | NPs | Increased antiviral activity against human cytomegalovirus infection | Irache et al. (2005) |
| Pilocarpine | Albumin | NPs | Increased the bioavailability of pilocarpine by ~50–90% (miosis), and 50–70% of IOP, respectively, compared to a pilocarpine solution | Zimmer et al. (1994) |
| Melatonin | PLGA | NPs | Produced a marked decrease in IOP | Musumeci et al. (2013) |
| Brimonidine and timolol maleate | PLGA | Hybrid hydrogel dendrimer | Effective IOP reduction over days | Yang et al. (2012) |
| Sparflaxacin | PLGA | NPs | Enhanced residence time and bioavailability in rabbit eye | Gupta et al. (2010) |
| Levofloxacin | PLGA | NPs | Enhanced residence time and bioavailability in rabbit eye | Gupta et al. (2011) |
| Flurbiprofen | PLGA nanospheres | Nanospheres | Enhanced the corneal permeation <i>ex vivo</i> | Vega et al. (2008) |
| Flurbiprofen | PLGA | NPs | Significant anti-inflammatory efficacy | Vega et al. (2006) |
| Carteolol | Polyalkylcyanoacrylate | NPs and Nanocapsules | Decrease in IOP was much more pronounced with carteolol incorporated into the colloidal carriers than with the commercial eye drops. | Heussler et al., 1993 |
| Metipranolol | Poly-isobutylcyanoacrylate PBCA/PECL | Nanocapsules | 10% reduction in IOP in 6 h | Losa et al. (1993) |
| Indomethacin and cyclosporine | PECL | Nanospheres | Five times superior corneal absorption than oily solution | Alonso et al. (1995) |
| Minocycline | Lipid | Liposomes | Enhance the therapeutic efficacy in retina after a subconjunctival injection | Kaiser et al. (2013) |
| Tacrolimus | Bile salts + lipid | Liposomes | 3–4-fold higher cellular uptake than conventional liposomes and sustained corneal permeation | Dai et al. (2013) |
| Diclofenac | Lipid | Surface-modified liposomes | Increased 1.8-fold concentration in retina–choroid compared to that of the unaltered diclofenac solution | Fujisawa et al. (2012) |
| Fluconazole | Lipid | Liposomes | Fluconazole-loaded liposomal formulation shown better action as compared to drug solution on Rabbits infected with <i>C. albicans</i> | Habib et al. (2010) |

(continued)

| Drug | Polymer | Formulation | Result | References |
|-----------------|----------------------|-------------|--|---------------------------|
| Ciprofloxacin | Lipid | Liposomes | Drug release in controlled manner | Mehanna et al. (2009) |
| Acetazolamide | Lipid | Liposomes | The positively charged and neutral liposomes exhibited greater lowering in IOP and a more prolonged effect than the negatively charged ones in rabbit eye | Hathout et al. (2007) |
| Acetazolamide | Lipid | Liposomes | Significant and prolonged decrease in IOP compared to the solution of free drug and plain niosomes | Guinedi et al. (2005) |
| Atenolol | Lipid | Liposomes | Marked reduction in IOP than solution formulation | Zaid et al. (2003) |
| ACV | Lipid | Liposomes | Positively charged liposomes increased absorption of ACV, because of a stronger binding effect to the cornea surface than occurs with negatively charged liposomes | Law et al. (2000) |
| Tropicamide | Lipid | Liposomes | Higher AUC values for tropicamide; this formulation was found to be more effective in dilating the pupil than drug-loaded neutral liposomes | Nagarsenker et al. (1999) |
| Oligonucleotide | Lipid | Liposomes | Prevent degradation and increase the residence time and efficacy | Bochet et al. (1998) |
| Acetazolamide | Lipid | Liposomes | Strong and sustained reduction in IOP in rabbits | Omaima et al. (1997) |
| Pilocarpine | Lipid | Liposomes | Prolonged duration of the miotic effect as compared to aqueous solutions and non-coated vesicles | Durrani et al. (1992) |
| Penicillin G | Lipid | Liposomes | More than four-fold flux increase across isolated rabbit cornea | Kaur et al. (2004) |
| Timolol maleate | Non-ionic surfactant | Niosomes | 1.7 times higher peak concentration of drug in aqueous humor as compare to the pure timolol maleate solution and 2.34 times AUC higher than TMS | Kaur et al. (2010) |
| Acetazolamide | Span 60 | Niosomes | Permeability increase and increased in aqueous humor drug concentration | Aggarwal et al. (2007) |

5-FU, 5-fluorouracil.

et al., 2011) and natural polymers like CS (Jain et al., 2013), gelatine (Vandervoort & Ludwig, 2004), sodium alginate (Zhu et al., 2012), albumin (Zimmer et al., 1994; Merodio et al., 2002) and tamarind kernel polysaccharide (Kaur et al., 2012a) can be used effectively for efficient drug delivery to the ocular tissues. Many of researchers conducted the study of nanoparticle drug delivery are found that it prevent the degradation of drug in ocular environment and release of drug over extended period of time give the desired effect (Javadzadeh et al., 2010; Gupta et al., 2011).

Studies conducted by Jain et al. (2013) in rabbits has shown that NPs showed gradual reduction of intraocular pressure (IOP) reaching peak value of 9.9 ± 0.5 mmHg, equivalent to $36.39 \pm 1.84\%$ reduction in IOP compared to control at the end of 5 h which was significantly higher ($p < 0.05$) as compared to marketed formulation.

Başaran et al. (2013) showed in an *in vivo* study that CS NPs of cyclosporine prolonged release of active agent due to positively charge of CS. This may be attributed to enhanced residence time at the corneal and conjunctival surfaces.

Sabzevari et al. (2013) studied the biodegradable poly beta-amino ester NPs of triamcinolone acetonide of anti-inflammatory effects in rabbit eye. It concluded that polymeric NPs of triamcinolone acetonide will provide as good anti-inflammatory effects as subconjunctival injection method and are better compared to other DDSs.

Wadhwa et al. (2009) reported that hyaluronic acid (HS) gave the synergistic effect for mucoadhesion in association with dorzolamide hydrochloride or timolol maleate-loaded CS NPs and revealed that CS–HA NPs show higher reduction in IOP level as compared to pure drug solution. Agnihotri & Vavia (2009) developed and evaluated diclofenac sodium-loaded PLGA NPs for ocular use and found good biocompatibility with the eye.

Jwala et al. (2011) studied PLGA NPs delivery of acyclovir (ACV) prodrug for the treatment of ocular herpes keratitis. It was found that NPs exhibited a biphasic release behavior, i.e. initial burst phase followed by sustained release because PLGA NPs may retard the degradation of prodrug in the precorneal area and further sustain the release in deep corneal tissues. Dispersion of NPs in thermosensitive gels completely eliminated the burst release phase.

Basaran et al. (2014) developed cyclosporine NPs for ocular delivery by spray-drying technique by using different grade (molecular weight) of CS and characterized *in vitro* and *in vivo*. The *in vitro* study showed sustained release. The *in vivo* study was done in sheep and the sample was analyzed by enzyme immunoassay. It showed prolonged release of active agent from positively charged chitosan formulations after 72 h of study in both aqueous and vitreous humor samples. This attributed is due to increase the corneal and conjunctival surfaces residence, so

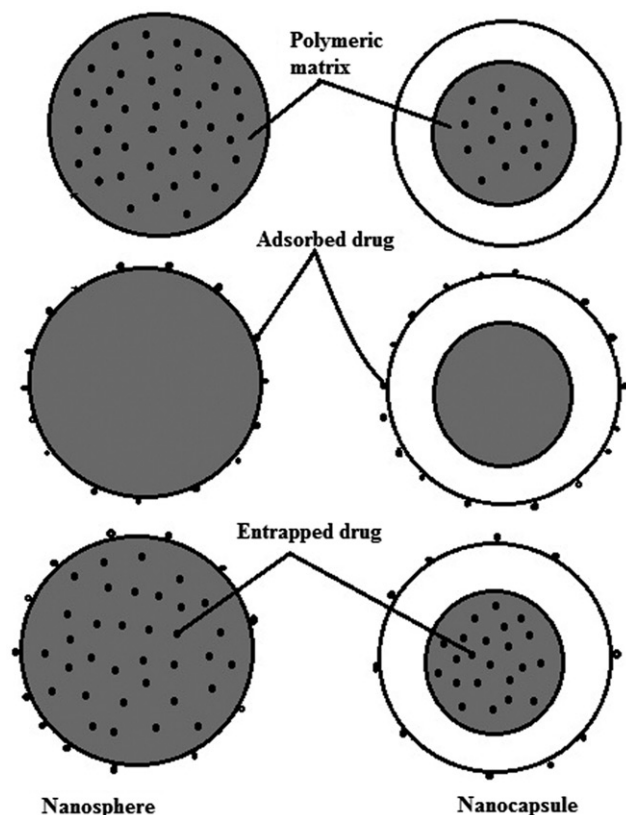


Figure 3. Different types of NPs.

concluded that CS have bioadhesive and permeation enhancing property.

Başaran et al. (2011) also developed cyclosporine A NPs using cationic Eudragit RS ocular application. The formulation was characterized *in vitro* and *in vivo*. NPs showed the extended release of incorporated drug. *In vivo* study showed prolonged residence time of cyclosporine A in the deeper layers (vitreous humor) of the eye due its positively charged nature of Eudragit RS.

Tayel et al. (2013b) formulated terbinafine hydrochloride NPs by positively charged Eudragit[®] RS100 and CS polymer in different ratio by nanoprecipitation technique using soybean lecithin (1%, w/v) and Pluronic[®] F68 as surfactant and stabilizer. The NPs have small particles size, zeta potential (73.29 to 320.15 nm and +20.51 to +40.32 mV) and sustained release profile in simulated tear fluid (pH 7.4). The NPs were physically stable at 4 and 25 °C. NP suspension showed significantly ($p < 0.05$) increased drug mean residence time and improved its ocular bioavailability; 1.657-fold in rabbit's aqueous humor as compared to terbinafine hydrochloride eye drops (0.25%, w/v).

Singh et al. (2013) prepared pH-triggered polymeric nanoparticulate *in situ* gel (NP-ISG) for ophthalmic delivery of acetazolamide. NPs were developed by nanoprecipitation method. NPs were spherical and small in size. Carbopol 934P as dispersed in optimized formulation form nanoparticulate *in situ* gels. The gel was selected as optimized formulation on the basis of gelation ability and residence time. *Ex vivo* transcorneal permeation study exhibited significantly higher acetazolamide permeation from NP-ISG5 ($74.5 \pm 2.20 \text{ mg/cm}^2$) and NP ($93.5 \pm 2.25 \text{ mg/cm}^2$) than eye

drops ($20.08 \pm 3.12 \text{ mg/cm}^2$) and acetazolamide suspension (16.03 ± 2.14). Modified Draize test with zero score indicated non-irritant property of NP-ISG5. Corneal toxicity study revealed no visual signs of tissue damage. Hypotensive effect on IOP in rabbits revealed that NP-G caused significant decrease in IOP ($p < 0.05$) in comparison to eye drops. It was concluded that NP-G higher permeation, prolonged precorneal residence time and sustained drug release along with higher *in vitro* efficacy, safety and patient compliance (Singh et al., 2013).

Mohammed et al. (2013) develop and studies the fluconazole-loaded chitin nanogels (Flu-CNGs) treatment of corneal fungal infections. Flu-CNGs have controlled-release pattern at prolonged period of time. Flu-CNGs are hemocompatible, cytocompatible and also showed very good cell uptake in human dermal fibroblast cells and penetration to the deeper sections of the porcine cornea with no signs of destruction or inflammation to corneal cells.

Kaur et al. (2012b) developed the spanlastics which consisted of spans and an edge activator prepared by the ether injection method and characterized for size, shape and the number of vesicles per milliliter by optical microscopy, entrapment efficiency, and *ex vivo* corneal permeability study. A three-tier safety of the novel formulation was established by the Ames test, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) assay, and in rabbits according to the OECD guidelines 404 and 405. Spanlastics were smaller in size (three times) and showed a better permeation in comparison to a corresponding niosomal formulation. The system showed an increase (three-fold) in the apparent permeability coefficient compared to the marketed formulation Zocon[®] (0.3% w/v solution of fluconazole) due to its elastic nature. The developed system was found to be stable for 2 months under refrigerated conditions and under extreme storage conditions. Safety was established in terms of genotoxicity (Ames test), cytotoxicity (MTT assay; mouse peritoneal macrophages), acute dermal/eye irritation/corrosion, and chronic eye irritation/corrosion tests (OECD guidelines). The developed system is novel and provides an effective and safe formulation of fluconazole.

Du Toit et al. (2013) developed and compared two specific embodiments of an ocular nanosystem (NS): one portraying a purely polymeric system, referred to as the chitosan-poly(ϵ -caprolactone) NS, and the other based on a composite lipoidal-polymeric NS architecture utilizing phospholipids, i.e. lipoidal-chitosan-poly(ϵ -caprolactone) NS. Investigations undertaken were implicit to warrant inclusion in an implantable system for the intelligent treatment of inflammatory disorders (specifically ocular afflictions). Results obtained highlighted the enhanced efficacy of both NS to an indomethacin suspension in terms of tissue permeation, cell uptake and anti-inflammatory activity. Furthermore, the size (134.3 versus 140.7 nm); surface charge (+49.4 versus +55.7 mV); drug incorporation efficiency (75.00 versus 67.20%); flux across the retinal pigment epithelium-choroid-sclera (0.002951 versus $0.001255 \text{ mgcm}^{-2}\text{h}^{-1}$); anti-inflammatory efficacy, demonstrated by a decrease in 4-chloro-7-nitrobenzo-2-oxa-1,3-diazole complex formation (0.0031 versus 0.0023 mmol/l) and decrease in NF κ B formation (decrease in relative optical

density of 0.2027 versus 0.2420); and enhanced inflammatory cell uptake, visualized via high-speed fluorescence and confocal microscopy, all highlighted the enhanced potential of the lipoidal system compared with the purely polymeric NS for potentially targeting inflammatory disorders of the posterior segment of the eye. Mechanics energy relationships revealed the favorable hydrophilic–lipophilic balance of the composite NS compared with the purely polymeric NS.

Liposomes

Liposomes were first introduced as the drug delivery carriers by Bangham et al. (1965). It is a bilayered lipid vesicles composed of altering aqueous compartments enclosed by lipid bilayers (mainly phospholipids and cholesterol) of natural and synthetic origin, and usually within the size range of 10 nm to 1 μ m or greater (Meisner & Mezei, 1995; Honda et al., 2013). Liposomes have advantages like (i) improve bioavailability of ophthalmic drugs after topical administration (Monem et al., 2000; Kaur & Kanwar, 2002; Wadhwa et al., 2009); (ii) no toxicity and low antigenicity (Van-Rooijen & Van Nieuwmegen, 1980); (iii) stable, biocompatible, biodegradable and metabolize *in vivo*; and (iv) encapsulating both lipophilic, hydrophilic and amphiphilic molecules (Klibanov et al., 1990), while hydrophilic drugs are entrapped in the aqueous layer and hydrophobic drugs are stuck in the lipid bilayers. Many researchers investigated those positive charged liposomes exhibited prolonged precorneal retention than negative and neutral charge liposome, due to electrostatic interaction with the negatively charged corneal epithelium, thus enhance drug absorption (Monem et al., 2000; Zaid et al., 2003; Danion et al., 2007; Balakrishnan et al., 2009; Dai et al., 2013). Hathout et al. (2007) reported acetazolamide liposome showed the positively charged and neutral liposomes exhibited greater lowering in IOP and a more prolonged effect than the negatively charged ones. It was suggested that liposomes have enhanced corneal penetration of drug by being adsorbed onto the corneal surface, with direct transfer of drug from liposomes to epithelial cell membranes. Drug loading capacity and entrapment efficiency of liposomes depends on many factors such as size of liposomes, concentration and types of lipid used, and physicochemical properties of therapeutic agent itself. The loading capacity and entrapment efficiency was low for Small unilamellar vesicles (SUV) in comparison to Multivesicular vesicles (MLV). However, Large unilamellar vesicles (LUV) provide a balance between size, loading capacity and entrapment efficiency (Ding et al., 2005; Jesorka & Orwar, 2008).

Bochot et al. (2011) reported phosphodiester (16-mer oligothymidylate) (pdT16) oligonucleotides encapsulated in liposome showed sustained release into vitreous humor and retina–choroid (37% even after 15 days) compared with the release from the solution and in a reduced distribution to the non-targeted tissues (sclera and lens) (Bandyopadhyay & Johnson, 2007).

Szulc et al. (1988) showed that the liposomal encapsulation of the hydrophilic drug and pilocarpine enhanced its pharmacologic effect in rabbits when using positively charged vesicles.

ACV containing positively charged unilamellar liposomes (LIPO-ACV) compared with pure ACV in solution and marketed ACV ointment containing same ACV concentrations (0.12%) showed that the liposomal formulation have highest drug concentration in the aqueous humor of rabbits compared to ointment and pure drug solution. The *in vitro* release profile liposomal formulation showed sustained release than the solution and ointment, it concluded that positively charged liposome bind to negatively charged corneal epithelium enhances the efficacy of ACV. These results indicate a significant advantage of ACV liposome as an alternative to ACV ointment (Chetoni et al., 2004). Sasaki et al. (2013) reported that surface modification of liposome with poly-L-lysine enhance the efficiency of coumarin-6 as a model drug and fluorescent marker to the retina delivery to the posterior segment of the eye. We found that surface modification with low molecular weight poly-L-lysine significantly increase the delivery as compare to high molecular weight, because aggregation of surface-modified liposomes increased particle size and hampered distribution to inner ocular tissue. Similarly many antiviral drugs like iododeoxyuridine, ganciclovir and ACV loaded in liposome (immunoliposome) reported for the treatment of ocular herpes infection (herpes simplex virus) (Norley et al., 1986).

Niosomes

Niosomes is a novel DDS having non-ionic surfactant, bilayered vesicular system formed by self-assembly of hydrated surfactant. Like liposome of delivering drug in controlled manner to enhance bioavailability and get therapeutic effect over a longer period of time (Karim et al., 2010; Mujoriya & Bodla, 2011). But liposome has some disadvantages like high cost and limited shelf life, and it may overcome these drawbacks by developing new vesicular system niosome (Mahale et al., 2012; Kumbhar et al., 2013). The vesicle suspension is water-based vehicle and this offers high patient compliance in comparison with oily dosage forms. They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and can entrap both hydrophilic and lipophilic drug with a wide range of solubilities. The bilayers of the niosomes protect the enclosed active pharmaceutical ingredient from the heterogenous factors present both inside and outside the body so can be used for labile and sensitive drugs (Khan et al., 2011).

Basha et al. (2013) developed Span 60-based nanovesicles with edge activator (Tween-80), sodium cholate or sodium deoxycholate of clotimazole. We found spherical unilamellar vesicle with an entrapment efficiency of 87.92% and displayed sustained antifungal effect over 12 h against *Candida albicans*. The area under the curve (AUC) of the optimized formulation was 3.09 times more than that of drug suspension with no sign of irritation after testing for ocular tolerance.

Hamdy et al. (2011) prepared and evaluated Span 60-based niosomes for ocular delivery of naltrexone hydrochloride (NTX) and found a five-fold increase in NTX entrapment efficiency. *Ex vivo* transcorneal permeation

studies conducted using excised cow corneas showed that niosomes were capable of controlling NTX permeation and enhance its corneal permeability, and were found practically non-irritant.

Bioadhesive-coated niosomal formulation of acetazolamide prepared from Span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendencies for reduction of IOP as compared to marketed formulation.

The CS-coated niosome of timolol maleate (0.25%) exhibited more effect for reduction IOP as compared to a marketed formulation with less chance of cardiovascular side effects compared to timolol solution (TMS; 0.25%) (Aggarwal et al., 2005).

Aggarwal et al. (2004) developed topical niosomes of acetazolamide for treatment of glaucoma. The formulation was prepared by using Span 60 cholesterol, dicetyl phosphate and stearylamine by different methods. It was found that the reverse-phase evaporation method (REV) gave the maximum drug entrapment efficiency (43.75%) as compared with ether injection (39.62%) and film hydration (31.43%) techniques. Drug entrapment efficiency varied with the charge and the percent entrapment efficiency for the REV method was 43.75, 51.23 and 36.26% for neutral, positively charged and negatively charged niosomes, respectively. Corneal permeability studies showed that the percent permeation and the apparent permeability coefficient for the charged niosomes were less than for the neutral ones. Further, the IOP-lowering effect of the developed formulations was compared with that of a marketed formulation of dorzolamide 2%, a topical carbonic anhydrase inhibitor. The developed niosomal formulations of acetazolamide showed a comparable physiologic effect (33% reduction of IOP in REV1bio and 37% reduction in dorzolamide) with duration of up to 6 h. The developed formulations can form a cost-effective treatment plan, a safe, which is especially important in the treatment of glaucoma.

Various colloidal DDSs used in ophthalmic research are listed in Table 1.

Dendrimers

Dendrimers are particularly auspicious potentially usable in numerous applications. It is tree-like highly branched synthetic nanostructure polymers with a 3D structure. These very monodisperse molecules are composed of an initiator core, interior layers of repeating units, and multitudinous terminal groups (Jain & Gupta, 2008). Their branched layered architectures displaying a high number of controlled terminal groups is, in particular, very promising for biomedical applications (Bai et al., 2006; Newkome & Shreiner, 2008; Kambhampati & Kannan, 2013). They are classified by the number of branches and terminal groups. Various cores and units can be used, which can change the properties and shape of the dendrimer. Concerning drug delivery, can be achieved by coupling a drug through one of two approaches. Hydrophobic drugs can be complexed within the hydrophobic dendrimer interior to make them water soluble or drugs can be covalently coupled onto the surface of the dendrimer. Dendrimers can either attach to a therapeutic agent by a permanent or separable bond to the end groups or be enclosed within the dendrimer itself. Because of its multiple terminal

groups and its polymer backbone, dendrimers can have multiple functionalities. In addition, dendrimers have been shown to be capable of bypassing efflux transporters and enable the efficient transport of drugs across cellular barriers (Yang & Kao, 2006; Samad et al., 2009).

Vyas et al. (1998) reported that there was about a 2.48 times increase in the ocular bioavailability of timolol maleate encapsulated in niosomes as compared to timolol maleate solution.

Dendrimeric structures are of particular interest in the field of drug delivery due to their peculiar structural properties including controllable internal cavities bearing specific species for the encapsulation of guest drugs and external periphery with 3D multiple functional moieties for solubilization, conjugation of bioactive compounds and targeting molecules, and recognition purposes. The main successes of dendrimers resulted in their appropriate, reproducible and optimized design parameters addressing physicochemical limitations of classical drugs (e.g. solubility, specificity, stability, biodistribution and therapeutic efficiency) (Jain & Gupta, 2008; Gajbhiye et al., 2009) and their ability to overcome biologic issues to reach the right target(s) (e.g. first-pass effect, immune clearance, cell penetration, off-target interactions). Improvement of pharmacokinetic (PK) and pharmacodynamic (PD) behaviors of both drug–dendrimer conjugates and drug–dendrimer encapsulates versus plain drugs demonstrates their strong potentials in medicine as nanocarriers (Gajbhiye et al., 2009; Mintzer & Grinstaff, 2011).

The most commonly used dendrimers in nanomedicine are polyamidoamines (PAMAM), poly(L-lysine) scaffold dendrimers (PLL), polyesters (PGLSA-OH), polypropylimines (PPI), poly(2,2-bis(hydroxymethyl) propionic acid scaffold dendrimers (bis-MPA) and aminobis (methylenephosphonic acid) scaffold dendrimer.

Cyclodextrins-based ocular delivery system

Cyclodextrins are a group of homologous cyclic oligosaccharides with a hydrophilic outer surface consisting of six, seven or eight glucose units, namely α , β , γ cyclodextrin, respectively. Although soluble in water, cyclodextrins have a lipophilic cavity in the center. Cyclodextrins have mainly been used as complexing agents to increase aqueous solubility of poorly soluble drugs, and to increase their bioavailability and stability in solutions and reduced side effects. Cyclodextrins are novel, chemically stable adjuvants that enhance ocular bioavailability of ophthalmic drugs without affecting the barrier function of the eye or increasing the viscosity of the aqueous eye drop formulation (Loftsson & Masson, 2001).

Kristinsson et al. (1996) studied the ocular absorption of dexamethasone eye drops containing 2-hydroxypropyl- β -cyclodextrin was also tested in human patients and compared with Maxidex A (0.1% dexamethasone alcohol suspension). Patients received the eye drops at a certain time prior to cataract surgery and at the time of cataract surgery. The concentration of dexamethasone in the aqueous humor was significantly higher ($p < 0.001$) and the AUC was 2.6 times higher with the 0.32% cyclodextrin dexamethasone eye drop solution than with Maxidex A.

Sasamoto et al. (1991) testing the same cyclosporine- α -cyclodextrin complex to increase drug solubility, recommended topical α -cyclodextrin-cyclosporin as treating anterior uveitis in rats with the same efficacy as topical fluorometholone solution.

Contact lenses containing NPs

The success of the therapy of eye ailments with ophthalmic drug delivery through contact lens is an alternative approach for treatment ocular diseases. It have a much longer residence time in the post-lens tear film, compared with 2 min in the case of topical application as eye drops achieving sufficient drug concentration on the cornea for a sufficient period of time. This longer residence time enhances drug permeation through minimizes drug absorption into the blood stream through the conjunctiva or nasolacrimal duct the leading to improved bioavailability, lower required dosage and less frequent drug application, thereby improving patient adherence. The nanoformulation such as NPs, liposomes and niosomes dispersed throughout the contact lens materials. The drug release from the lens in slow continuous manner by diffusion mechanism were from trapped drug from the particles and gel matrix, first drug diffused out from the particles and reaches on surface and contact with lens materials, so it provided the action for longer period of time (Hiratani et al., 2005; Lavik et al., 2011).

Kim et al. (2014) developed nanodiamond (ND)-embedded contact lens, capable of lysozyme-triggered release of timolol for sustained therapy. We found that ND-embedded lenses composed of enzyme-cleavable polymers allow for controlled and sustained release of timolol in the presence of lysozyme. Retention of drug activity is verified in primary human trabecular meshwork cells. These results demonstrate the translational potential of an ND-embedded lens capable of drug sequestration and enzyme activation.

Future prospect

Nanotechnology formulation have multiple application in ophthalmology due its small size provide the convenience of a drop, maintain drug activity at the site of action and are suitable for poorly water-soluble drugs. It can be help to treat many complex eye disorders like glaucoma, cataract and retinal disease through number of nanoformulation like NPs, NEs, niosome, liposome. Nanotechnology can be used to fabricate nanodevices for the treatment of eye surgeries like retinal detachment, blood-ocular barriers, cataract, cornea and glaucoma. This technology can be used to formulate difference delivery like topical, intravitreal, transscleral, implantable, contact lens, etc. Moreover, the development of different nanotechnology-based tools like ND particles have been utilized for numerous applications in biomedical imaging, sensing and therapeutic delivery. Nanotechnology can also help to develop an effective and robust DNA NP therapy for the treatment of genetically based blinding diseases. It can even help in generation of scaffolds for tissue bioengineering, especially for neural stem cells and also use of these for the delivery of growth factors and the stem cells.

Conclusion

In recent years, considerable research has been directed toward developing colloidal system for ocular delivery. Effective treatment of ocular diseases is a formidable challenge for scientists in the field because presence of the ocular barriers of both ocular segments. The challenges in drug delivery to ocular tissues have been partially met by the identification of transporters and modification of drug substances to target these transporters. The transporters aids in targeting specific tissues thereby lowering side effects and improving bioavailability. In general, the most used animal species in ocular field is the rabbit; however, although the rabbit eye is comparable to the human eye in terms of size, it has differences such as higher surface sensitivity, lower tear production, lower blinking frequency and higher mucus production. All these factors could probably improve the mucoadhesion and reduce clearance from the ocular surface; this could increase the ocular residence time of systems. Several approaches have been proposed for ocular delivery namely, MEs, NEs, nanosuspension, NPs, liposomes, niosome, dendrimer, etc. as drug carriers and substantially improve the periocular administration.

Declaration of interest

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