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REVIEW

Lipid Nanoparticles for Ocular Drug Delivery

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ABSTRACT

Despite numerous scientific efforts, efficient ocular drug delivery remains a challenge for pharmaceutical scientists. Delivery of ophthalmic drugs to the targeted ocular tissues is limited by many precorneal, dynamic and static ocular barriers. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. One of the promising strategies nowadays is the use of colloidal carrier systems characterized by a submicron-meter size. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) represent promising alternatives to conventional and very popular ocular carrier systems.

Key words: Ocular drug delivery; Lipid nanoparticles; Solid lipid nanoparticles; Nanostructured lipid carriers; Eye

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INTRODUCTION

The ocular route is one of the most delicate routes of drug delivery due to the unique physicochemical conditions of the eye[1,2]. However, the eye poses unique challenges relative to drug delivery. A major problem in conventional ophthalmic drug delivery is low drug bioavailability due to ocular anatomical and physiological constraints, which include the poor permeability of cornea, nasolacrimal drainage effect, and short retention time in the precorneal area[3,4]. Excessive liquids, both normally produced and externally delivered, rapidly drain from the eye[5,6]. The approaches to overcome the barriers related to the ophthalmic drug delivery a major aim. During the last periods, numerous drug delivery systems, such as liposomes[7], nanoemulsions[8], microemulsions[4], nanoparticles[9] have emerged as novel strategies[10].

Nanoparticles - a sole subgroup of wide area of nanotechnology - are sized between 1 and 200 nanometers. Nanoparticles may or may not display size-related properties that vary significantly from particles or bulk materials and atomic or molecular structures[11]. Lipid nanoparticles, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), are colloidal carriers with a lipid matrix. They are generally composed of lipids, surfactants and co-surfactants[12]. Lipid nanoparticles are alternative drug delivery systems to polymeric nanoparticles[13]. The lipid matrix is made from physiologically tolerated lipid components, which decreases the potential for acute and chronic toxicity[14].

Numerous drugs, e.g. antibiotics[4,6], plasmids[15], anti-inflammatory[16] and immuno-suppressive[9] agents, have been loaded into lipid nanoparticles for the treatment of ophthalmic disorders.

Puglia *et al* evaluated lipid nanocarriers for different application fields in ophthalmic treatment[17]. In another article the authors evaluated different surfactants on the technological properties and in vivo ocular tolerability of lipid nanoparticles[18]. In the current article lipid nanoparticles were described as preparation methods, characterizations and their results were discussed in recent years.

THE ANATOMY OF EYE

The eye is one of the most complex organs of the body. The eyeball has spherical shape and is about 1 inch across. It houses many structures that work together to facilitate sight. The human eye is covered of layers and internal structures, each of which performs different functions[19]. Anterior segment of the eye involves of front one-third of eye that mainly includes pupil, cornea, iris, ciliary body, aqueous humor, and lens while the posterior segment consists of the back two-thirds of the eye that includes vitreous humor, retina, choroid, macula, and optic nerve (Figure 1)[20,21]. The cornea is the most anterior part of the eye, in front of the iris and pupil[22]. It is approximately 0.5 mm thick in the center and 0.7 mm thick at periphery and composed of five layers. The sclera is the hard white sheath that forms the external layer of the eyeball. It maintains the shape of the eye as an approximately globe form[23]. The conjunctiva has leakier epithelium than the cornea and its surface area is also approximately 20 times larger than the cornea[23].

DELIVERY ROUTES AND ITS CHALLENGES OF OCULAR DRUG DELIVERY

There are numerous potential routes of ocular drug delivery. The selection of the route of administration depends primarily on the target tissue. The three primary approaches of delivery of ocular drugs to the eye are topical, local ocular (ie, subconjunctival, intravitreal, retrobulbar, intracameral), and systemic delivery[24,25]. Topical application is the most popular and preferred route due to ease application, low cost, patient compliance[26]. Although it has easy availability, the eye is well protected from drugs and foreign materials by numerous effective mechanisms such as blinking, tear flow, nasolacrimal drainage, which cause quick elimination of drugs from the eye surface[27]. Therefore, topically administered treatments are rapidly drained and result in less than 5% bioavailability[28]. After instillation of the eye drops, the flow of lacrimal fluid removes instilled compounds from the eye surface. Although the lacrimal turnover rate is only about 1 µl/min the extra volume of the instilled fluid is flown to the nasolacrimal channel rapidly[23].

Intraocular (intravitreal or intraretinal) drug delivery is the most invasive route, in that it contains penetrating the eyeball and thus is not free of injection-related complications. Thus, compared with the other drug delivery routes, it reaches the highest bioavailability in posterior tissues[29,30]. However, this route causes to undesirable problems such as cataract, retinal detachment, vitreous hemorrhage, and endophthalmitis[31].

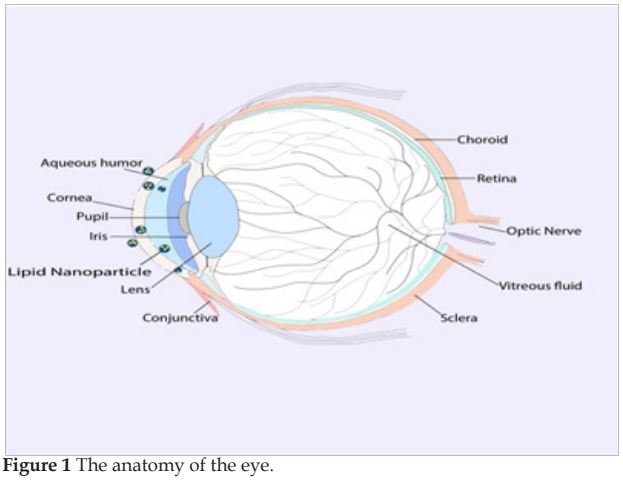

Figure 1 The anatomy of the eye.

Other than topical and intravitreal routes of delivery, periocular routes such as sub-tenon and subconjunctival routes can also be used to deliver drugs to the eye[32]. Subconjunctival injections have been used to deliver drugs at increased levels to the uvea. After subconjunctival injection drug must penetrate across sclera which is more permeable than the cornea. The scleral permeability is not dependent on drug lipophilicity and shows high permeability to the large molecules[23,33].

NANOTECHNOLOGY BASED OCULAR DRUG DELIVERY

Various efforts have been made to improve the the drug release and absorbing rate from formulations to enhance ocular bioavailability. The development of effective drug delivery systems that can transport and deliver a drug precisely and safely to its site of action is becoming a highly important research area for pharmaceutical researchers[34]. Various efforts in ocular drug delivery have been made to improve the bioavailability and to prolong the residence time of drugs applied topically onto the eye[35]. New alternative approach is to develop a drug delivery system that would circumvent the problems associated with the conventional systems, and provide the advantages of targeted delivery of drugs for extended periods of time and be patient-friendly. The latter requisite becomes more crucial in cases where the patient has to use the drug preparation throughout his life[36]. Use of nanotechnology has been advantageous for ocular drug delivery. The use of nanotechnology-based drug delivery systems such as microemulsions, nanosuspensions, nanoparticles, solid lipid nanoparticles, niosomes, dendrimers, and liposomes has led to the solution of various solubility-related problems of poorly soluble drugs, poor permeability and short retention time[37]. In addition nanotechnology based ophthalmic formulations are one of the approaches which are currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology-based drug delivery is also very efficient in crossing membrane barriers, such as the blood retinal barrier in the eye[38].

LIPID NANOPARTICLES

Nanoparticles are smaller than 1 micron and possibly as small as atomic and molecular length scales (~0.2 nm)[39]. Nanoparticles can have amorphous or crystalline form and their surfaces can act as carriers for liquid droplets or gases. They are commonly classified based on their dimensionality, morphology, composition, uniformity, and agglomeration[40]. Lipid nanoparticles made from lipids are especially attractive because of their enhanced biocompatibility imparted by the lipid. They are novel particulate drug delivery systems which have gained considerable interest since last decade[12]. During the last years, different materials have been entrapped into lipid nanoparticles, extending from lipophilic and hydrophilic molecules, including labile compounds, such as proteins and peptides[41,42,43].

Solid lipid nanoparticles (SLNs)

SLNs were developed at the beginning of the 1990s as an alternative carrier system to liposomes, emulsions and polymeric nanoparticles as a colloidal system for controlled drug delivery. SLNs consist

of a solid lipid, where the drug is normally incorporated, with an average diameter below 1 μm[44,45]. The common excipients used in SLN formulation are solid lipids, emulsifiers, co-emulsifiers and water[46]. They display major advantages such as controlled release, improved bioavailability, protection of chemically labile molecules, cost effective excipients, enhanced drug incorporation and extensive application range[47]. SLNs represent an interesting alternative to traditional colloidal carriers, such as emulsions, liposomes and polymeric nanoparticles. In recent years, many hydrophobic and hydrophilic drugs such as e.g. nifedipine, diazepam, desoxycorticosterone, cyclodextrin complexes with hydrocortisone and progesterone, doxorubicin, paclitaxel, tobramycin, timolol, pilocarpine, etc. have been incorporated into SLN, and administration of SLN by different routes (parenteral, oral, ocular, etc.) has been investigated[48,49,50].

Nanostructured lipid carriers (NLCs)

NLCs are drug delivery systems composed of both solid and liquid lipids as a core matrix. NLCs disclose some advantages for drug therapy over conventional carriers, including increased solubility, the ability to enhance storage stability, improved permeability and bioavailability, reduced adverse effect, prolonged half-life, and tissue-targeted delivery[51]. On account of the physiological and/or biodegradable lipids, this carrier system also exhibits an excellent tolerability[52].

RECENT STUDIES

Several features of SLN and NLC make them interesting carriers for ophthalmic applications (Table 1). These systems are commonly applied topically to the eye. Cavalli *et al*. developed a SLN system of tobramycin for topical ocular drug delivery. In vivo testing has shown sustained drug release over a period of 6 h compared to short duration from equal dose of eye drops[53].

Attama *et al* developed lipid nanoparticles containing sodium diclofenac combining the phospholipid, with high encapsulation efficiency applying the hot high-pressure homogenization technique. Permeation of sodium diclofenac through the cornea construct was improved by surfacing nanoparticles with phospholipid, which showed the performance of this formulation for ocular application[54].

Gökçe *et al* developed cyclosporine A loaded SLNs using Poloxamer 188 and Tween 80 as surfactant. Corneal cytotoxicity and cellular uptake tests performed in rabbit's corneal epithelial cell lines proved that cyclosporine A loaded SLNs were harmless and improved the penetration properties across the corneal cells[9].

Araujo *et al* prepared triamcinolone acetonide loaded NLC with high pressure homogenization using Precirol ATO5 and squalene as solid and liquid lipids respectively, and Lutrol F68 as surfactant for ocular antiangiogenic applications. The analyses confirmed that drug was mostly entrapped into the NLC, characterized by an amorphous matrix. Moreover in vivo Draize test showed no signs of ocular toxicity[55].

In recent studies baicalin loaded SLN was prepared by emulsification/ultrasonication method. In vitro release studies indicated that the baicalin loaded SLN retained the drug entity better than the baicalin solution. In the pharmacokinetics studies, the AUC value of baicalin loaded SLN was 4.0-fold versus the baicalin solution[56].

The other researchers developed flurbiprofen loaded NLCs in order to improve the bioavailability of drug used for the prevention of the inflammation. The ideal NLC presented a suitable average size for ocular delivery (228.3 nm) with a narrow size distribution (0.156), negatively charged surface (-33.3 mV) and high entrapment efficacy (~90%). In addition they have found that developed NLCs showed sustained release. Ideal NLC formulation did not show toxicity on ocular tissues[57].

Hao *et al* developed chloramphenicol loaded SLNs. These SLNs were successfully prepared by a modified method of melt-emulsion ultrasonication and low temperature-solidification technique. In vitro release studies showed a burst release at the initial stage followed by a prolonged release of chloramphenicol from SLN up to 48 hours. The authors found that the chloramphenicol loaded SLN could potentially be exploited as an ocular delivery system with improved drug entrapment efficiency and controlled drug release[58].

Liu *et al* prepared mangiferin loaded NLC formulations for the potential treatment of cataract. The optimized mangiferin loaded NLC formulation exhibited a sustained drug release with 3 months stability and 4.31-fold increase of in vitro corneal permeation. Furthermore, in vivo studies exhibited a high tolerance in the ocular tissues and prolonged drug retention capacity on the corneal surface. Finally, pharmacokinetic study suggested a 5.69-fold increase of ocular bioavailability compared with mangiferin solution[59].

Hippalgaonkar *et al* developed indomethacin loaded solid lipid nanoparticles for ocular delivery. They have reported a dramatic increase in the corneal permeability of indomethacin with the SLN

Table 1 Examples of drugs incorporated in SLN or NLC, used lipid, surfactant and preparation method.

SLN/NLC	Drug	Lipid/surfactant	Production method	Ref.
SLN	Tobramycin	Stearic acid/ Epikuron 200	Warm o/w microemulsion method	[53]
SLN	Diclofenac sodium	Phospholipon 90G/ Tween 80	Hot homogenization using high-pressure homogenizer	[54]
SLN	Cyclosporin A	Compritol 888 ATO/ Poloxamer 188 and Tween 80	High shear homogenization and ultrasound method	[9]
NLC	Triamcinolone acetonide	Precirol ATO5 and squalene/ Lutrol F68	High pressure homogenization	[55]
SLN	Baicalin	Triglyceride and soya phospholipids SL-100/ Poloxamer 188	Emulsification/ultrasonication method	[56]
NLC	Flurbiprofen	Stearic acid and castor oil / Tween 80	Hot high pressure homogenization method	[57]
SLN	Chloramphenicol	Glyceryl monostearate/ Poloxamer 188	Melt-emulsion, ultrasonication and low temperature-solidification technique	[58]
NLC	Mangiferin	Glyceryl monostearate, Gelucire 44/14, Miglyol812 / Tween 80 and Labrasol	Ultrasonication method	[59]
SLN	Indomethacin	Compritol 888 ATO/ Poloxamer 188 and/or Tween 80	Hot homogenization method	[60]
NLC	Genistein	Compritol 888 ATO, Miglyol 812 N and Gelucire 44/14 / Cremphor® EL and Egg phosphatidylcholine	Melt-emulsification technique	[61]
NLC	Ofloxacin	Compritol HD5 ATO, oleic acid, Tween 80	High pressure homogenization method	[6]

formulation in comparison to the indomethacin solution[60].

Zhang *et al* prepared genistein loaded NLC using the melt-emulsification technique in the recent ocular studies. The developed genistein loaded Eudragit RS 100 modified NLC showed extended precorneal clearance and a 1.22-fold increase in AUC compared with the bare NLC. The Eudragit RS 100 modification also significantly increased corneal penetration producing a 3.3-fold increase in apparent permeability coefficients. Draize and cytotoxicity testing confirmed that the developed NLCs were found nontoxic to corneal cells[61].

Many formulation parameters have to be considered in designing an ideal formulation. Surface charge interaction of the drug and polymer has played an important role in drug release from the polymer[62]. Bio-compatibility and mucoadhesive properties of SLNs improve their interaction with ocular surface and extend corneal residence time of the drug, with the aim of ocular drug targeting.

In the recent days to further improve precorneal residence time, the surface lipid nanoparticles were coated with chitosan. Chitosan has mucoadhesive properties due to generating molecular attraction forces by electrostatic interactions with the negative charge of the eye surface[63]. For instance, Üstündağ Okur *et al* developed nanostructured lipid carriers and modified with chitosan oligosaccharide lactate for topical ocular application. They have found that NLCs remained 20- 40 min on the eye surface. The longest precorneal retention time was determined with chitosan modified NLCs as 40-60 min[6].

In another recent study the authors prepared NLC based inserts by means of high shear homogenization and 0.75% chitosan oligosaccharide lactate (COL) was added for ocular ofloxacin delivery for treatment of bacterial keratitis. These NLCs were used for preparing inserts by solvent casting evaporation. The developed NLC based inserts were evaluated characterization, in vitro release, microbiological, ex vivo and in vivo studies. The pre-ocular retention time was enhanced up to 24 h and Cmax was increased almost six times in comparison with commercial in the in vivo studies[2].

CONCLUSION

Effective treatment of ocular diseases is a formidable challenge for scientists in the field because the eye is one of the most complex organs in the human body. Drug delivery to the eye is hampered by anatomical factors, including the corneal epithelium, the blood–aqueous barrier and the blood–retinal barrier. Development of new drug candidates and novel delivery techniques for treatment of ocular diseases has recently accelerated. SLN and NLC are colloidal systems still being developed for ocular administration. The technology used to produce lipid nanoparticles is feasible in the laboratory, and easily reproducible at an industrial scale. These lipid nanoparticles are possible novel drug delivery systems in drug market for ophthalmic applications.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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