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Review

Designing lipid nanoparticles for topical ocular drug delivery

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ABSTRACT

Topically-applied dosage forms, such eye drops, are the most used formulations in the treatment of ocular diseases. Nonetheless, because of the special protection of the eye associated with the ocular surface, drug bioavailability and subsequent therapeutic efficiency obtained with these conventional dosage forms are very low. Recently, novel drug delivery systems have been proposed to solve the main drawbacks of conventional formulations. Nanotechnology, and more specifically lipid nanoparticles, have emerged as promising "modified eyedrops" with the purpose of improving therapeutic efficiency without compromising drug safety and patient compliance. The purpose of this review is to offer an overview of lipid nanoparticles as feasible alternatives to the conventional topically-applied dosage forms. We discuss the main limitations of topical ocular drug delivery and describe how correctly designed lipid nanoparticles can be highly valuable tools to overcome the constraints imposed by the ocular surface. Special emphasis is placed on the description of production methods and bulk materials used in the development of lipid nanoparticles for ophthalmic use and how both issues will determine the physicochemical and biopharmaceutical properties of the developed nanosystems.

1. Introduction

Ocular drug delivery (ODD) includes multiple pharmaceutical strategies to reach a therapeutic target in the eye through a variety of different routes. Topical administration, because of its simplicity, non-invasiveness, and high patient compliance, is the conventional and preferred route to achieve the therapeutic goal. In fact, topical formulations such as eyedrops represent 90% of the marketed dosage forms used in eye care (Patel et al., 2013). The purpose for topical ODD is two-fold. One is to treat anterior segment diseases affecting the ocular surface (OS), such as conjunctivitis, blepharitis, and keratoconjunctivitis sicca. The other purpose is to penetrate through the cornea to treat intraocular pathologies, such as glaucoma and uveitis (Araujo et al., 2009). Nevertheless, traditional drug therapies based on conventional dosage forms, i.e., eyedrops and ointments, typically have a low clinical success rate. This is attributed in part to the unfavorable physicochemical properties, i.e., low water solubility, of the active substances such as anti-infective agents, anti-inflammatories, and immunosuppressants, which are typically included in these formulations. Additionally, the highly impermeable milieu of the eye, especially the OS, limits the bioavailability and subsequent efficacy of the active agents. For this reason, high doses of drugs and frequent administration are necessary to maintain sufficiently high therapeutic levels at the site of action.

Multiple ODD systems have been proposed to overcome these limitations. These include hydrogels (Kirchhof et al., 2015), polymeric nanoparticles (Almeida et al., 2015), polymeric micelles (Mandal et al., 2017), nanosuspensions (Wang et al., 2016), and lipid-based nanocarriers (Gan et al., 2013). Lipid-based nanocarriers, a broad category comprised of liposomes, niosomes, cubosomes, nanoemulsions, nanomicelles, and lipid nanoparticles (LNs) have attracted enormous interest in recent years (Gan et al., 2013). These types of colloidal systems offer several advantages, including solubility enhancement of hydrophobic drugs, accurate adjustment of pharmacokinetic parameters, and drug protection from enzymatic degradation, all of which ultimately improve bioavailability (Souto et al., 2010).

The market of lipid colloidal systems for ODD is growing continuously. Since the approval of Restasis® (2002; Allergan, Irvine, CA, USA), an anionic nanoemulsion for the treatment of severe dry eye syndrome, and the marketing authorization of Ikervis® (2015; Santen

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Inc., Emeryville, CA, USA), a cationic nanoemulsion for the treatment of severe keratitis in adult patients with dry eye disease, other lipidic formulations have been developed (Pignatello et al., 2015). However, LN-based formulations are currently limited to research applications, and none are available for commercial use because they are in early developmental stages. Further investigation is necessary, both regarding the technological feasibility and safety after chronic exposure.

In this review, we analyze different elaboration methods and bulk materials commonly employed in the production of LNs for ODD, focusing on how they may influence the physicochemical and biopharmaceutical properties of the final formulation. We also describe different approaches to optimize these properties. Finally, as a case study, we summarize the available literature regarding the use of LNs in the topical administration of the immunosuppressant drug cyclosporine.

2. The OS as a barrier

Designing a formulation for topical ODD constitutes a pharmaceutical challenge for scientists due to the special protection of the eye against penetration of foreign substances. The anatomical barriers and physiological conditions of this organ limit the therapeutic efficacy of promising drugs if formulated as conventional dosage forms like eyedrops (Patel et al., 2013). Moreover, most therapeutic molecules have unfavorable physicochemical properties that prevent absorption and distribution through the ocular tissues, decreasing dramatically the fraction of drug that reaches the target tissue. Thus, the bioavailability in the anterior chamber is expected to be less than 5% for lipophilic substances and less than 0.5% for hydrophilic ones (Zhang et al., 2004). To follow a rational design in the formulation of novel dosage forms, it is necessary to understand the constraints that limit drug bioavailability once the drug contacts with the OS. These constraints, depicted in Fig. 1, can be divided in two categories: precorneal factors and the corneal barrier.

2.1. Precorneal factors

Immediately after instillation, the administered drug is exposed to various physiological mechanisms of the eye that lead to a partial loss of the administered dose. Under normal conditions, the tear film is renewed at a rate of 16% per minute (Mishima et al., 1966); thus, only a few minutes are needed for a complete removal of the formulation from the OS. Furthermore, tear production is increased in the presence of irritating substances that are contained in some formulations (Loftssona and Jarvinen, 1999). The normal tear volume is only 7 μL and the maximum capacity of the precorneal tear film when the eye is not blinking is 30 μL, which is reduced to 10 μL during blinking. This results in a limited retention capacity of the instilled volume, which usually is about 50 μL for the conventional dosage forms. The excess formulation is quickly drained from the eye through the nasolacrimal duct, potentially leading to undesirable systemic effects (Urtti and Salminen, 1993).

Tears contain about 0.7% protein under normal conditions (Mikkelson et al., 1973), but this percentage can increase during disease. This aspect is of particular interest for two reasons. First, many drugs are metabolized by the action of certain enzymes such as cytochrome P-450, esterases, and peptidases (Duvvuri et al., 2004). Second, drug-protein complexes can be formed that reduce the fraction of free drug available for absorption (Mikkelson et al., 1973). In addition, drugs are absorbed by other tissues aside from the cornea. For instance the conjunctiva, which has a larger surface than the cornea, has 2–30 times higher permeability than the cornea (Wang et al., 1991). This non-productive absorption leads not only to a reduction in drug therapeutic efficacy, but also to an increase in the systemic absorption with associated undesirable effects (Urtti et al., 1994).

2.2. The corneal barrier

One of the most important functions of the cornea is the protection

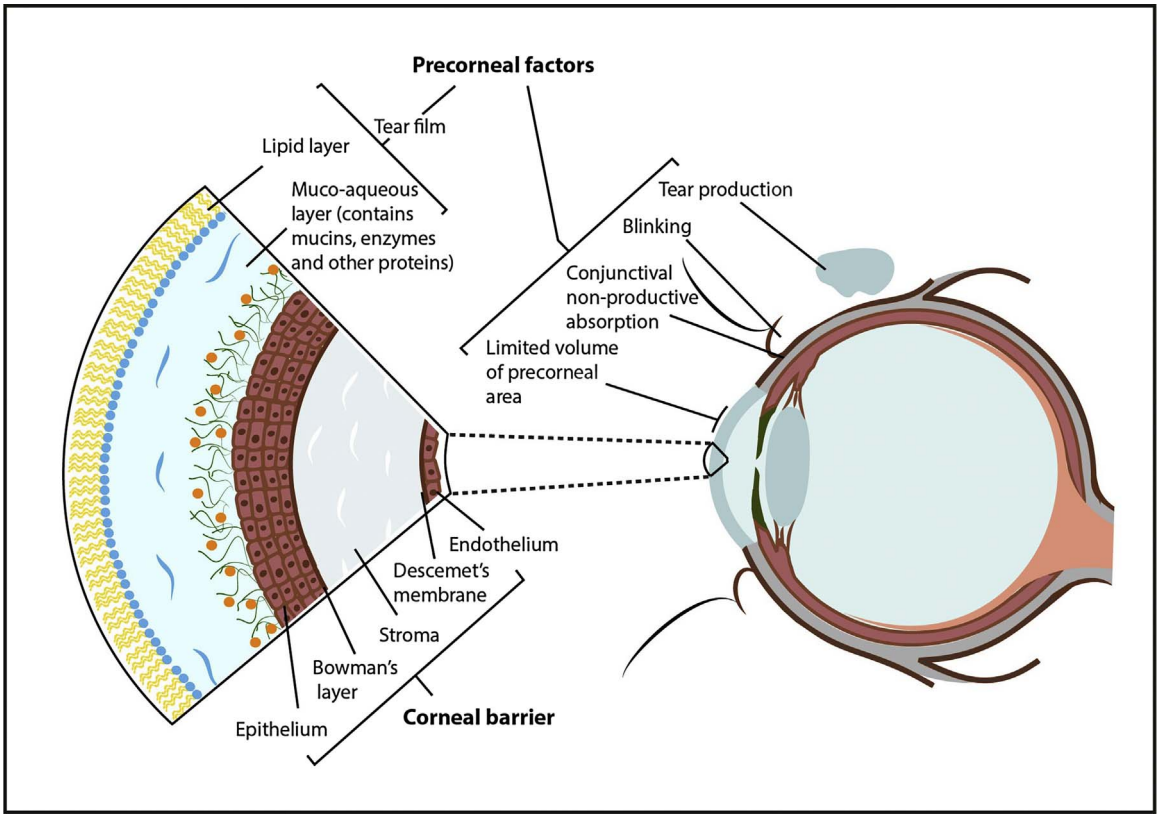

Fig. 1. Representation of the main ocular factors and barriers that any delivery system must overcome to access the therapeutic target after topical administration.