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Review

Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review

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ABSTRACT

Cutaneous use of lipid nanoparticles (solid lipid nanoparticles, SLN and nanostructured lipid carriers, NLC) has been showing promising results. These systems consist of low viscosity aqueous dispersions, being usually employed by means of semi-solid formulations with adequate consistency for skin application.

This review addresses the cutaneous use of lipid nanoparticles for therapeutic and cosmetic applications. Initially, general information related to pharmaceutical semi-solid formulations is presented. Afterwards, the effects of SLN and NLC on the skin, and technological aspects related to semi-solid systems based on SLN or NLC are described. Finally, the most relevant studies related to the formulations based on SLN and NLC, for cosmetic and therapeutic applications, are reported.

Notwithstanding the cutaneous use of SLN and NLC has been proposed for both local and transdermal delivery, the reported studies show promising results only for local application. In this sense, more research is required to better understanding the interaction mechanisms of lipid nanoparticles with skin lipids. Furthermore, the development of standard methods for skin experiments with nanoparticles is necessary.

1. Introduction

Due to its large surface area, skin is the most accessible organ of the human body, being the local of election for topical application of drugs and cosmetics. Briefly, epidermis, dermis, hair follicles, sweat glands compose the skin, having the *stratum corneum* (SC) as the outermost lipid layer, creating an efficient barrier to the entry of substances into the body. The follicular and transepidermal (both intercellular and transcellular) are the main routes for bypassing molecules throughout the intact skin (Montagna, 1974; Trommer and Neubert, 2006). Health researchers are familiar with the skin structure and functions, and an extensive description of these is out of the scope of this work. The interested reader can find in references (Montagna, 1974; Brown et al., 2006; Trommer and Neubert, 2006; Agache et al., 2017) very good reviews related to this topic.

Conventional dosage forms for skin application typically have semi-solid consistency and include aqueous gels (*i.e.* hydrogels), hydrophobic ointments and gels (*i.e.* oleogels), or a mixture of both, aqueous and oily phases, like water-in-oil (W/O) or oil-in-water (O/W) creams. In these systems, the formulation external phase rules the molecules release. Thereby, hydrogels and O/W creams provide a fast release, while hydrophobic formulations originates a prolonged release. Furthermore, water-containing formulations are easier to apply and, therefore, preferred by consumers over high viscous lipid formulations. Because of their rheological properties (*i.e.* viscoelastic behavior), semi-solid formulations remain at the local of application for long periods, which prolong molecules delivery. Besides, these dosage forms are easy to apply and can transport a large variety of substances (Gupta and Garg, 2002; Hatahet et al., 2016).

Semi-solid systems have homogenous appearance and soft consistency and are employed for topic and systemic drug administration, protection and hydration of the application site. Their plastic properties allow a consistency modification when applying a minim mechanic force and, due to thixotropy, when this force stops, the formulation does not recover the initial consistency. Once viscosity of semi-solid systems tends to decrease with an increase of temperature, they are considered as thermoreversible systems. In addition, they must have adhesiveness, being possible their fixation to the application area (Fox,

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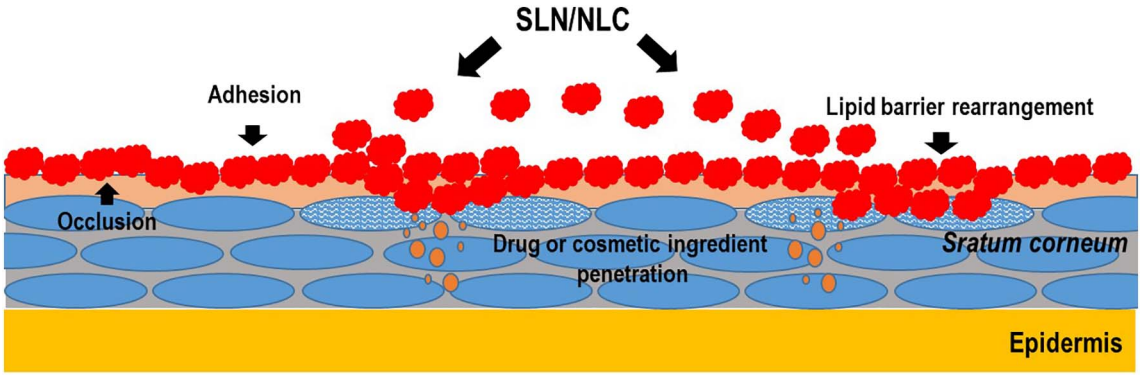

Fig. 1. Effects of lipid nanoparticles on the skin (modified after (Muller et al., 2011)).

2014).

There are a wide range of semi-solid dosage forms, which are classified with regard to their excipients nature, being most used the ointments, creams and gels (Gupta and Garg, 2002; Fox, 2014).

Formulations for skin application can be planned for local or transdermal delivery. The latter is allowed for drugs but not for cosmetic ingredients, and includes molecules diffusion trough skin layers into the systemic circulation, originating the therapeutic effect. In contrast, local delivery is normally related to dermal effects and is used for skin layers targeting, with minor/none systemic absorption (Brown et al., 2006).

Regarding its function, the SC is the major barrier of the intact skin for drugs and cosmetic ingredients application. A promising strategy to improve molecules penetration throughout the SC is the use of nanosystems, since their lipophilicity ease the intact lipid layer crossing. In addition, these carriers might facilitate molecules delivery trough hair follicles or provide controlled release by creating depots on the skin (Vogt et al., 2016). In this context, lipid nanoparticles have been showing promising results to enhance molecules penetration up to epidermis, reducing systemic absorption, and provide chemical stability of compounds sensitive to light oxidation and hydrolysis (Puglia and Bonina, 2012; Montenegro et al., 2016).

There are few reports related to the transdermal permeation of lipid nanoparticles, reaching the bloodstream by crossing skin barrier or passing through hair follicles. Nonetheless, more studies are needed to confirm this effect (Qi et al., 2017).

This review addresses the use of lipid nanoparticles, namely solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), for skin application. In the first section, the mechanisms of lipid nanoparticles that become their skin application beneficial are described. Final section report the most relevant studies that are related to formulations based on SLN and NLC for cutaneous use, for cosmetic and therapeutic applications.

2. Lipid Nanoparticles for Cutaneous Use

Within the era of nanotechnology, lipid nanoparticles (*i.e.* SLN and NLC) are well known by researchers. Since their creation, in the nineties, the number of research groups studying these systems has been growing. Reasons for this are their easy accessible production methods and advantages over other colloidal carriers, particularly, non-toxicity. In this article, the main features of SLN and NLC are summarized. The interested reader can find elsewhere very good and complete reviews on this subject (Muller et al., 2000; Mehnert and Mader, 2001; Muller et al., 2002; Pardeike et al., 2009; Muller et al., 2011; Silva et al., 2012b; Silva et al., 2015; Beloqui et al., 2016; Geszke-Moritz and Moritz, 2016; Cunha et al., 2017).

Such as O/W nanoemulsions, lipid nanoparticles dispersions are heterogeneous systems with an inner lipid phase and an external aqueous phase, stabilized by one or two surfactants. However, contrary to nanoemulsions, lipid nanoparticles have an inner solid lipid phase, since these nanoparticles are totally (for SLN) or mainly (for NLC) composed by lipids that are solid at room temperature. This solid matrix allows the controlled release of encapsulated molecules and protect them from degradation, while increase the system long-term stability (Muller et al., 2000; Mehnert and Mader, 2001; Muller et al., 2011; Silva et al., 2015).

The two types of lipid nanoparticles, *i.e.* SLN and NLC, are classified according to their internal structure. SLN were first developed and are composed only by solid lipids, whereas NLC constitute an upgrade of the SLN and are composed by a mixture of solid and liquid lipids, despite the solid lipid is in higher amount to form the nanoparticle (Muller et al., 2002; Muller et al., 2011; Silva et al., 2015).

Among the different applications that have been proposed for SLN and NLC, the cutaneous use seems to be one of the most promising, for therapeutic and cosmetic purposes. In this field, different approaches have been studied, particularly, for transdermal and local drug delivery, and for hydrating and anti-age cosmetics. The latter include the first marketed products, which are based on NLC (Nanobase® from Yamanouchi and Cutanova® from Dr. Rimpler GmbH). Nonetheless, cutaneous therapeutic applications of SLN and NLC are the most studied, and reasons for the absence of commercial products are related with the complexity of regulatory issues that must be addressed before medicines reach clinics (Muller et al., 2011; Beloqui et al., 2016; Geszke-Moritz and Moritz, 2016; Desmet et al., 2017).

Cutaneous use of lipid nanoparticles (Fig. 1) present several advantages, such as the chemical protection of the incorporated substances, allowing the skin application of labile molecules that are difficult to transport in traditional semi-solid formulations; improved drug bioavailability, related to the possibility of modulating molecules release, promoting their skin penetration and retention. The latter has been explained by the lipid nanoparticles easiness to adhere to the SC, allowing encapsulated molecules reaching the deeper skin layers. These properties are related to the SLN and NLC physiological lipid composition that can interact with the SC, creating its lipid rearrangement, which eases molecules penetration. Furthermore, the nanoparticles small size also contribute to increase their adhesiveness and surface contact area, promoting the drug influx through the skin. Nonetheless, it is important to keep in mind that the molecules physicochemical properties also play an important role on their skin penetration performance (Beloqui et al., 2016; Kim et al., 2017; Sala et al., 2018). Müller and co-workers suggested that the cutaneous application of lipid nanoparticles promotes skin hydration by two mechanisms (Muller et al., 2002; Muller et al., 2011): i) formation of an occlusive film at SC surface that prevent water loss by evaporation, avoiding transepidermal water loss; ii) reinforce of the skin lipid film barrier by nanoparticles adhesion to the SC.

The follicular penetration route has also been explored for local treatment of alopecia by means of lipid nanoparticles. Depending on their size, after penetration in hair follicles, lipid nanoparticles can