



Drug Delivery Systems for Topical treatment of Inflammatory Skin Diseases

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Abstract

The skin is known to be the primary intact skin layer for the application of cosmetics and medicines. These nanocarriers, however, can enhance the distribution of molecules through hair follicles or impart a regulated pattern of release by making depots on the skin. Moreover, Many challenges may potentially face the topical delivery of medicaments through either the healthy or diseased skin. This is mainly owing to the strong protection offered by the barriers made of the skin. This paper displays the blocking nature of the skin, the difficult conditions of skin inflammatory diseases, options of effective treatment, and general categories of advanced topical drug delivery for better efficacy and safety. Solid lipid nanoparticles and other lipid-based nanocarriers are mentioned particularly with a further focus along with examples of opportunities for bioavailability enhancement of poorly absorbed active moieties and for more promising implementation in convenient and efficient topical remediation of skin inflammatory disorders.

Keywords: Skin inflammatory diseases; Gluco-corticosteroids; Topical drug delivery systems; Solid lipid nanoparticles.

Received on: 02. 3. 2021

Revised on: 20. 03. 2021

Accepted on: 24. 03. 2021

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1. Introduction

Skin is considered the largest body organ with 1.7 m² surface area and weighs almost fifth of the total body weight. The skin shields our bodies as a strong protection from any external environmental hazards. The breadth, skin-color, thickness and appendages distribution through the skin differ between the various body parts, according to the needs and function of these areas. The skin outermost lipid layer is the *stratum corneum* (SC), which is resembling a durable blockade/barrier versus

entrance of matters to the inner side of the body (Figure 1). Subsequently, SC is considered the main blockade of the integral skin for the application of medicaments and cosmetics (Lanigan and Zaidi, 2010).

For more than twenty centuries, dermatological description of the skin morphological structure has been well developed, which defined the skin as an important element in the "host-defense-system", which is known to comprise three major defenses;

a barrier, innate immunity and acquired immunity (Turvey and Broide, 2010). These three protection lines develop the utmost appropriate response versus any infectious and external dangers. In case these barriers were under attack, inflammation will be a main response. Inflammation can be simply renowned as a sequence of regenerative and protective body responses against pathological, injury or external foreign stimulus. Therefore, inflammatory skin diseases can be categorized as one of the ailments caused by the disruption of one or all of these defenses (Ballanti *et al.*, 2013). Any inflammatory skin disease partially simulates the response to threats or infections. Interestingly, the inflammatory skin diseases have not yet been fully categorized as the defects of which particular defense of the host-defense-system (Dainichi, Hanakawa and Kabashima, 2014). One popular example of inflammatory skin diseases is atopic dermatitis (AD), which is a chronic inflammatory skin ailment that frequently precedes allergic rhinitis or asthma. As AD diagnosed in more than 10% of children, AD is considered an important skin disorder with significant morbidity and costs to patients and families (Leung, 2000). Coherent topical treatment of AD imitates the understanding of the intricacy of the causal immunopathogenesis (Figure 2). Because of the inflammatory cascades complexity that potentially can initiate AD, a multipronged-tactic is needed for effective treatment, which includes skin hydration, identification and elimination of exacerbating factors, and topical corticosteroids (mainly Fluticasone propionate).

2. Topical gluco-corticosteroids:

From nearly half century, topical corticosteroids were familiarised to be utilized in medicine, which represented a weighty breakthrough in dermatological remediation. They were categorized to be in the main treatment guidelines of many inflammatory skin disorders, owing to their high effectiveness in alleviating inflammatory symptoms. Although it is strongly encouraged to report any detected adverse reactions, the reporting protocol in clinical practice is still imperfect. Therefore, the recorded data of safety and adverse reactions regarding topical corticosteroids are incomplete and considered neglectable in the literature (Hengge *et al.*, 2006). Dermal adverse reactions take place with treatment for long periods of time. Regarding children, and due to the higher ratio of their body surface area to

body weight, they are more susceptible to develop systemic reactions from topical medicaments. The furthest common adverse reactions consist of purpura, acne, rosacea, striae, perioral dermatitis, and atrophy. The magnitude of such adverse effects are directly related to the chemical properties of the vehicle, the drug, and its site of application (Hengge *et al.*, 2006). Pigmentation alterations, hypertrichosis, exacerbation of skin infections, and delayed wound healing are examples of adverse reactions that can be considered to be occurred with lower incidence. Glaucoma, adrenal insufficiency, and hyperglycaemia have also been recorded as systemic side effects of prolonged topical application (Hengge *et al.*, 2006). A good example of effective corticosteroid moiety is Fluticasone propionate (FP), which is an androstane synthetic glucocorticosteroid having potent anti-inflammatory dermal activity along with its activity on respiratory and high binding capacity to lung tissues (Michael *et al.*, 2000). Unlike the 21-carbon pregnane structure of the majority of the developed topical corticosteroids, FP is a modified 19-carbon androstane structure (Bleehen *et al.*, 1995). The greatest advantage of FP that differentiates it from other corticosteroids is its diminished potential for unwanted systemic effects, compared to its anti-inflammatory influence, such as hyperglycemia, glaucoma, and hypertension (Silva *et al.*, 2015). Regarding FP major drawbacks, its bioavailability is very low after topical or oral administration, due to limited absorption through the skin or from the gastrointestinal tract, and because of extensive first-pass metabolism (Soulele *et al.*, 2015).

3. Topical lipid-based drug delivery systems:

Utilizing lipid-based Nano delivery systems is a promising approach to enhance diffusion of molecules thru the *stratum corneum* (SC), as their lipophilicity can potentially ease crossing passage thru the intact lipid layer. The SC, as the outmost lipid layer of the skin, is representing a competent barrier against cutaneous entrance of substances into the internal structure of the body (Barua and Mitragotri, 2014). Consequently, the SC is considered the major barrier of the intact skin for cosmetics and medicaments application. However, these nanocarriers might improve delivery of molecules via hair follicles or impart a controlled release pattern by making depots on the skin

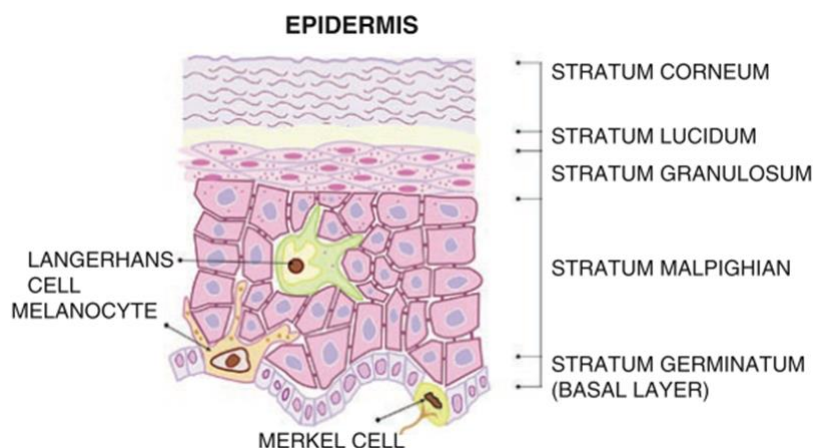


Figure 1. Skin structure (Lanigan and Zaidi, 2010).

(Vogt *et al.*, 2016). The following sections will detail various types of lipid-based delivery systems and their utilization for the remediation of inflammatory skin disorders.

3.1. Liposomes

Liposomes are characteristically fabricated from lecithin (natural phospholipids), which is the chief constituent of biological membranes. They are broadly utilized as delivery systems for lipophilic (carried inside the phospholipid bilayers) and hydrophilic (entrapped within the aqueous partition) molecules (Yoshida *et al.*, 2010). Liposomes can be with various sizes and lamellarity characteristic, which may be multilamellar (size > 0.5 μm), small unilamellar (size ranged between 20 to 100 nm), or large unilamellar liposomes (size > 100 nm) (Sherry *et al.*, 2013). Cholesterol is frequently used to enhance the bilayers' stability, which decreases the escape probability of the entrapped drug moiety. Antioxidants could also be used in formulating liposomes with better protection from phospholipid oxidation (Sala *et al.*, 2018). Regarding using liposomal formulation as delivery systems for dermal route, the skin barrier is principally hard to pass through owing to the complexity of the SC structure. A previous study informed that the prepared liposomal formulations were capable to interact with the lipids of SC to some extent and thus encouraging their diffusion and deposition into deeper layers of the skin (Plessis *et al.*, 1994). However, other studies on skin permeation displayed the weak role of ordinary liposomal vesicles to be effectively utilized in the remediation of skin diseases. On the other hand, liposomes were

suggested to have the ability to permeate the skin in case the skin barrier is diminished as in skin cancer or other inflammatory disorder like psoriasis, as the skin permeability is highly elevated (Sala *et al.*, 2018). Nevertheless, investigations regarding the application of ordinary liposomes on injured skin are still in early progress.

3.2. Penetration enhancer-reinforced nanocarriers (PERNs)

Various delivery systems can contain penetration enhancers (PEs), which are able to solubilize the poorly soluble active moieties in solvents like water, and also offering an improved cutaneous permeability with a higher elasticity (Sala *et al.*, 2018). The first penetration enhancer-reinforced nanocarriers (PERNs) were ethosomes. The synergetic grouping of PEs and lipid-based nanovesicles is potentially expected to yield promising topical drug delivery systems. In addition, utilization of PEG 400 as PE and plasticizer can provide an appropriate deposition of the antioxidant agent quercetin in epidermis, which is reported in a previous research work (Chessa *et al.*, 2011).

For treating psoriasis, as the epidermis has a central role in psoriasis pathogenesis, the PERNs penetration to the epidermis layer is much more achieved than other ordinary lipid-based vesicles. Manca *et al.* work also displayed that PERNs application should be in a non-occlusive mode for obtaining an efficient dermal permeation (Manca *et al.*, 2013). Glycerol was also used to improve the flexibility of the lipid bilayer composition, which proved to increase PERNs elasticity and verified

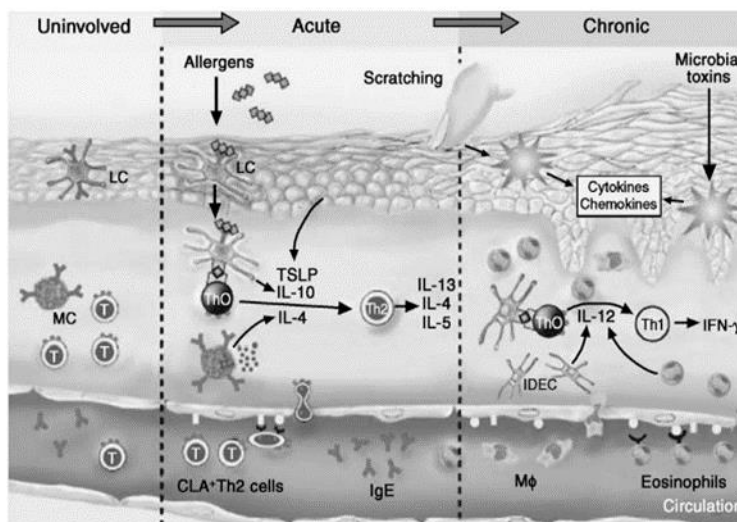


Figure 2. Atopic dermatitis immunopathogenesis (Boguniewicz, 2004).

the important role of glycerol. The enhanced skin penetration of PERNs was greatly noted comparison with the commercial reference products. Consequently, PERNs gathered all the benefits of the previously developed liposomal formulations.

3.3. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) have been offering auspicious outcomes to facilitate penetration of molecules reaching epidermis, and also offer additional stability for light sensitive compounds (Montenegro *et al.*, 2016). Cutaneous applications of SLNs display numerous advantages, like chemical protecting of the loaded drugs, enhancing drug bioavailability, in addition to the ability of controlling release of molecules, and encouraging their skin diffusion and retention (Figure 3) (Garcês *et al.*, 2018). Furthermore, the SLNs ability to adhere to the SC allows loaded molecules to reach deeper skin layers. These characteristics are interrelated to the physiological lipid composition of SLNs that enable interaction with the SC, generating its lipid reorganization, which affluences molecules diffusion (Al-maghrabi *et al.*, 2020). Moreover, the nano-sized property of SLNs also participates to increase surface contact area and hence, enhance their adhesiveness, and facilitate the drug influx thru the skin. However, the physicochemical properties of molecules also play a significant role on their performance in skin penetration, and such factors must be considered while utilizing SLNs for their topical delivery (Mudshinge *et al.*, 2011; Sala *et al.*, 2018).

4. Utilization of lipid-based delivery systems for skin inflammatory diseases

As described earlier, corticosteroids, like FP and betamethasone, are broadly used in the treatment of inflammatory skin diseases such as AD, cutaneous lupus erythematosus, and psoriasis. The initial directions focused mainly on liposomes in order to enhance permeation of corticoids through the skin (Sala *et al.*, 2018). Afterwards, another trend was focused on more sophisticated nanocarriers rather as the ordinary liposomes with the unsatisfactory or limited enhancement in topical drug delivery (Korting *et al.*, 1990). Subsequently, a newly modified liposomes, that called transfersomes, was pronounced, as the transfersomes significantly boosted the transdermal delivery of many corticoids due to their adaptability and high elasticity. It is found that the modified lipid vesicles loading betamethasone can accumulate better in the dermis layer of the skin when compared to the deformable betamethasone-loaded liposomal–cyclodextrine complexes (Sala *et al.*, 2018). Moreover, compounds such as sodium deoxycholate (SDC) were also utilized as edge activator for the elaboration of deformable liposomal formulations with much improved size control, entrapment efficiency and skin permeability (Gillet, Compère, *et al.*, 2011). Interestingly, cyclodextrins utilization in the modified lipid-based vesicles formulation was also noted to increase the deformability of the vesicles.

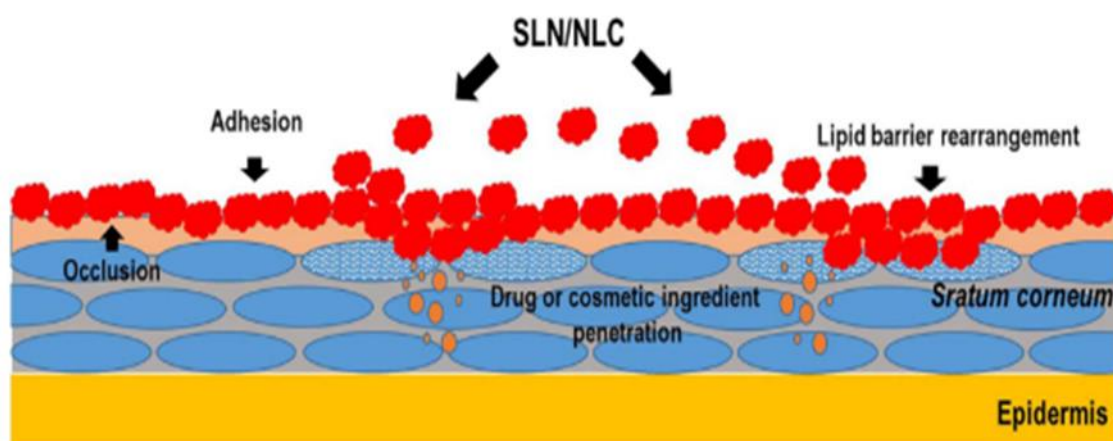


Figure 3. Effects of lipid nanoparticles on the skin (Garcês *et al.*, 2018).

However, and unfortunately, the deformable modified liposomal formulations were found to have more sensitivity to the ultracentrifugation than the non-deformable form of lipid-based vesicles (Gillet, Lecomte, *et al.*, 2011), and separation of the nanocarriers should be performed via another suitable technique.

5. Conclusion:

Topical drug delivery systems have a substantial influence in drug delivery. In our point of view, conventional liposomes still under investigation for further enhancing of their permeation through the skin, while solid lipid nanoparticles as well as the penetration-enhancer reinforced nanovesicles are considered competent delivery systems that show a distinguished characteristic after topical application and have promising impact for inflammatory skin diseases. These carriers can deliver topical medicaments through the harsh skin barriers via different mechanisms and therefore increase the amount of permeated medicament in comparison with the conventional formulations.

6. Declaration of interest:

The authors declare that they have no conflicts of interest.

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