WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 13, Issue 2, 397-406. Review Article ISSN 2277–7105

DRUG DELIVERY SYSTEM FOR TOPICAL TREATMENT OF INFLAMMATORY SKIN DISEASES

Ravi Kumar Mehta*, Kritika Modak and Sudipta Modak

Department of Pharmaceutical Science, Jharkhand Rai University Ranchi Raja Ulatu Ranchi, India.

Article Received on
29 November 2023,

Revised on 19 Dec. 2023,
Accepted on 09 Jan. 2024

DOI: 10.20959/wjpr20242-31040

***Corresponding Author**
Ravi Kumar Mehta
Department of Pharmaceutical Science, Jharkhand Rai University Ranchi Raja Ulatu Ranchi, India.

ABSTRACT

The skin is known to be the primary intact skin layer for the application of cosmetics and medicines. One of the main goals in the galenic development of innovative topical treatment options for inflammatory skin diseases such as psoriasis and atopic dermatitis is to selectively deliver the drug at the inflammation site. Recent studies have highlighted the beneficial use of polymeric nanoparticles for anti-inflammatory therapy and topical anti-inflammatory drug delivery due to their ability to form a drug reservoir retaining the drug locally at the site of action. Our approach consisted in designing innovative topical semi-solid formulations of poly(lactic acid) (PLA) nanoparticles as anti-inflammatory drug vehicles for local treatment of inflammatory skin diseases. In the course of this work, five topical formulations containing fluorescent PLA nanoparticles were initially developed, and then screened depending on their physio-chemical properties, toxicity and delivery efficacy. The penetration and permeation of a fluorophore vectorized by PLA nanoparticles into healthy and inflammatory skin were assessed using an alternative device to classical Franz cells: Vitro BioPharma. All these investigations led to the selection of two satisfactory formulations out of five initial candidates.

KEYWORD: Skin inflammatory disease, Gluco-corticosteroids, Topical drug delivery system, Solid lipid nanoparticles.

1. INTRODUCTION

In a healthy state the skin act as a natural barrier to maintain a stable environment both within and outside the body however when they skin is disease the barrier to maintain our stable

environment both within and outside the body however when the skin is disease the various function is a compromised small molecule and microorganism can easily pass through the state nutrient including water and electrolyte easily lot from the body of city this balance and leading two disease order and many other parameter are just a few factors that might harm the skin barrier.[1] Skin is considered the largest body organs with surface area and weighs almost 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.[2] 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).[3] 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.[4]

Desoqi et al.

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.[5] 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).[6] 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).[7] 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.[8] 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).[9] 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).[10]

2. Topical gluco-corticosteroids

From nearly half century, topical corticosteroids were familiarized to be utilized in medicine, which represented a weighty breakthrough in dermatological remediation.[11] They were categorized to be in the main treatment guidelines of many 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.[12] Glaucoma, adrenal insufficiency, and hyperglycemia have also been recorded as systemic side effects of prolonged topical application (Hengge et al., 2006).[13] 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).[14] 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).[15] 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).[16] 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) inflammatory skin disorders, owing to their high effectiveness in alleviating inflammatory symptoms.[17] 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).[18] 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 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).[19] 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 system

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.[20] 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).[21] 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 impact a controlled release pattern by making depots on the skin.[22]

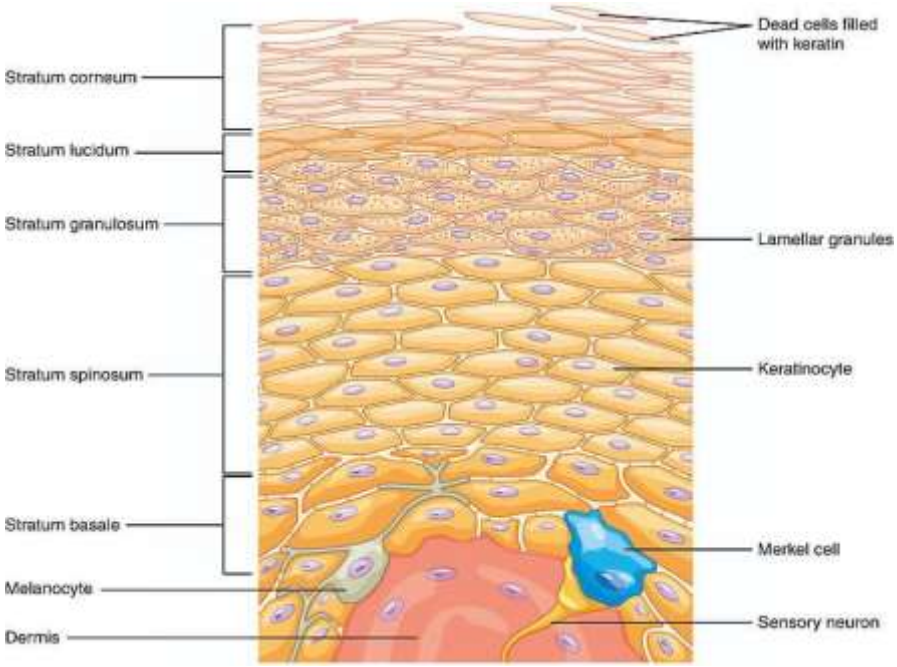

Figure 1: Skin structure epidermis.

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 to100 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.[23] 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 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.

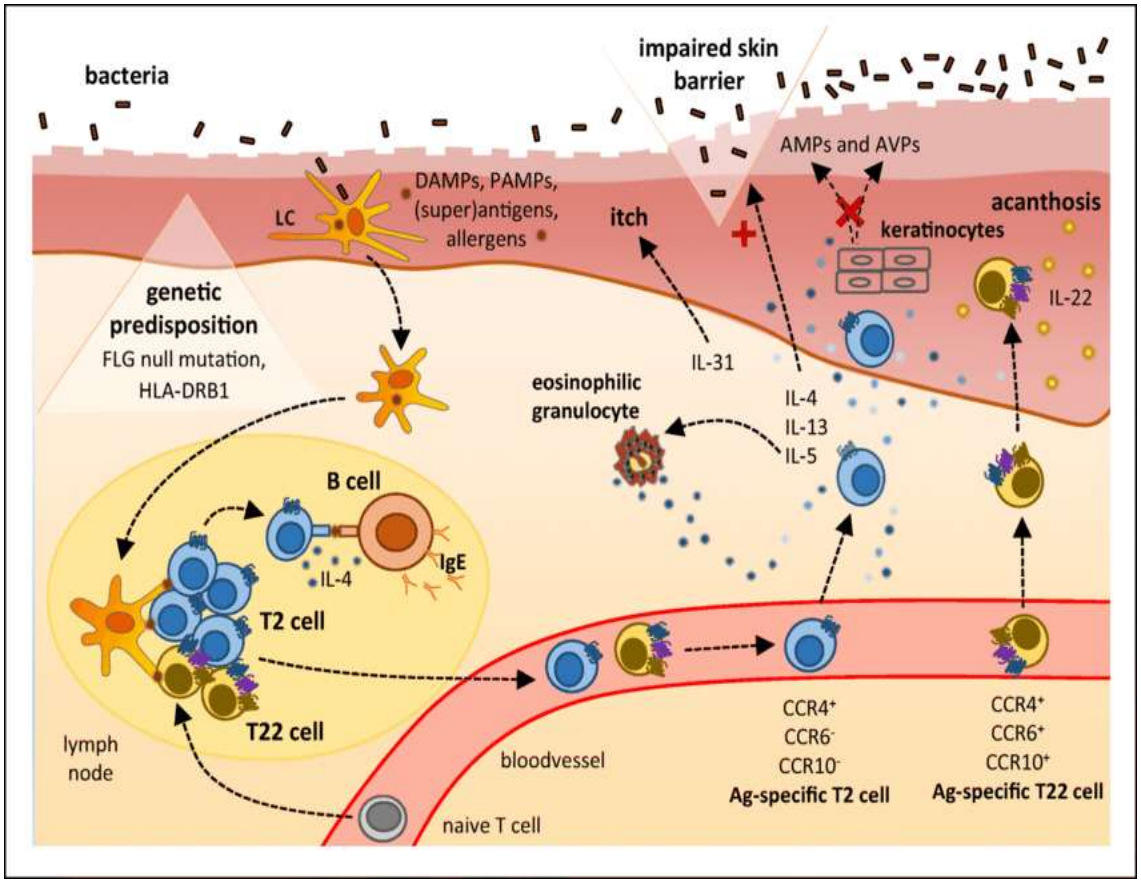

Figure 2: Atopic dermatitisimmunopathogenesis (Boguniewicz, 2004).

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.

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.

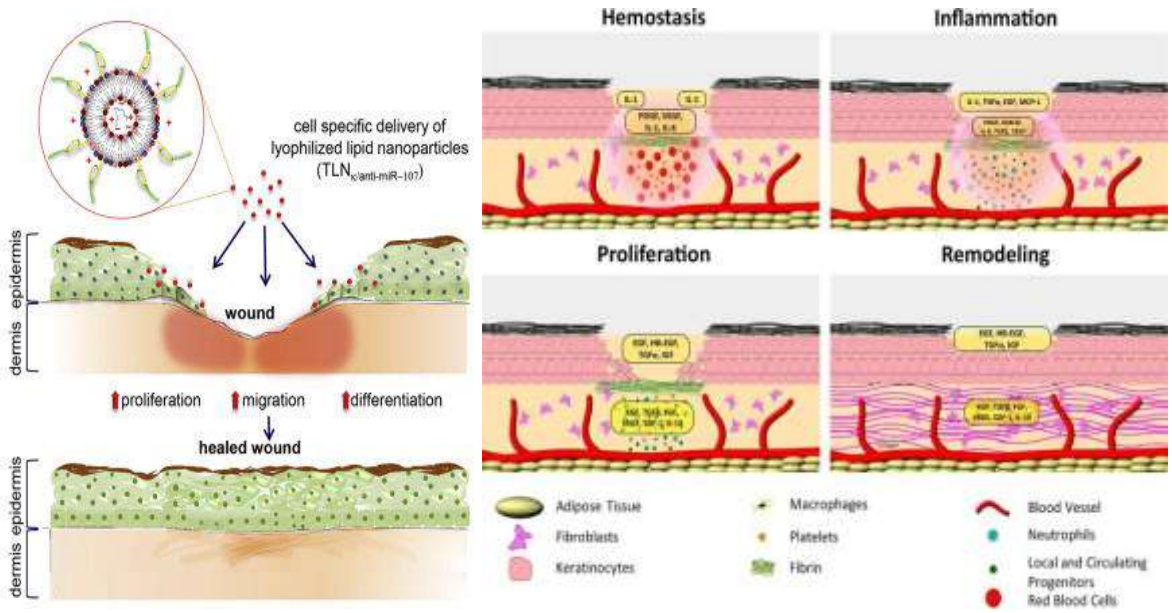

Figure 3: Effects of lipid nanoparticles on the skin.

CONCLUSION

Topical drug delivery systems have a substantialinfluence in drug delivery. In our point of view, conventional liposomes still under investigation forfurther enhancing of their permeation through theskin, while solid lipid nanoparticles as well as the penetration-enhancer reinforced nanovesicles areconsidered competent delivery systems that show adistinguished characteristic after topical applicationand have promising impact for inflammatory skindiseases. These carriers can deliver topicalmedicaments through the harsh skin barriers viadifferent mechanisms and therefore increases.

ACKNOWLEDGEMENT

It gives me immense pleasure to express deepest sense of gratitude and sincere thanks to my highly respected and esteemed guide Prof. Kritika modak, Prof. Sudipta modak, Department of pharmaceutical science, Jharkhand Rai University Raja Ulatu Ranchi, India for his valuable guidance, encouragement and help for completing this work. His useful suggestions for this whole work and co-operative behaviour are sincerely acknowledged. I also wish to express my gratitude to Prof. Kritika modak, Prof. Sudipta modak jharkhand Rai University, Ranchi for his kind hearted support. I am also grateful to my faculty members for their constant support and guidance. I also wish to express my indebtedness to my parents as well as my family members whose blessings and support always helped me to face the challenge ahead. At the end I would like to express my sincere thanks to all my friends and others who helped me directly or indirectly during this project work.

REFERENCES

1. Al-maghrabi, P. M.et al. Solid lipidnanoparticles : a prospective approach for topical drug delivery. Records of Pharmaceutical and Biomedical Sciences, 2020; 4(2): 8– 16.
2. Ballanti, E.et al. Complement andautoimmunity. Immunologic Research, 2013; 56(2 – 3): 477 –491. doi: 10.1007/s12026-013-8422-y.
3. Barua, S. and Mitragotri, S. Challengesassociated with penetration of nanoparticles acrosscell and tissue barriers: A review of current statusand future prospects. Nano Today, 2014; 9(2): 223 -243. doi:10.1016/j.nantod.2014.04.008.
4. Bleehen, S. Set al. Fluticasonepropionate0.05% cream in the treatment of atopic eczema: Amulticentre study comparing once-daily treatmentand once-daily vehicle cream application versustwice-daily treatment.British Journal of Dermatology, 1995; 133(4): 592 – 597. doi:10.1111/j.1365-2133.1995.tb02711.x.
5. Boguniewicz, M. Topical treatment of atopicdermatitis. Immunology and Allergy Clinics of North America, 2004; 24(4): 631 – 644. doi:10.1016/j.iac.2004.06.011.
6. Chessa, M. et al. Effect of penetrationenhancer containing vesicles on the percutaneousdelivery of quercetin through new born pig skin. Pharmaceutics, 2011; 3(3): 497– 509. doi:10.3390/pharmaceutics3030497.
7. Dainichi, T., Hanakawa, S. and Kabashima, K. Classification of inflammatory skin diseases:A proposal based on the disorders of the three-layered defense systems, barrier, innate immunityand acquired immunity. Journal of Dermatological Science, 2014; 76(2): 81 – 89. doi:10.1016/j.jdermsci.2014.08.010.
8. Garcês, A. et al. Formulations based on solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) for cutaneous use: A review. European Journal of Pharmaceutical Sciences, 2018; 112: 159–167. doi: 10.1016/j.ejps.2017.11.023.
9. Gillet, A., Compère, P., et al. Liposome surface charge influence on skin penetration behaviour. International Journal of Pharmaceutics, 2011; 411(1–2): 223–231. doi: 10.1016/j.ijpharm.2011.03.049.
10. Gillet, A., Lecomte, F., et al. Skin penetration behaviour of liposomes as a function of their composition. European Journal of Pharmaceutics and Biopharmaceutics, 2011; 79(1): 43–53. doi: 10.1016/j.ejpb.2011.01.011.
11. Hengge, U. R. et al. Adverse effects of topical glucocorticosteroids. Journal of the American Academy of Dermatology, 2006; 54(1): 1–15. doi: 10.1016/j.jaad.2005.01.010.

12. Korting, H. C. et al. Liposome encapsulation improves efficacy of betamethasone dipropionate in atopic eczema but not in psoriasis vulgaris. European Journal of Clinical Pharmacology, 1990; 39(4): 349–351. doi: 10.1007/BF00315408.
13. Lanigan, S. and Zaidi, Z. Skin: Structure and Function Skin. in Dermatology in Clinical Practice, 2010; 1–15. doi: 10.1007/978-1-84882-862-9.
14. Leung, D. Y. M. Atopic dermatitis: New insights and opportunities for therapeutic intervention. Journal of Allergy and Clinical Immunology, 2000; 105(5): 860–876. doi: 10.1067/mai.2000.106484.
15. Manca, M. L. et al. Glycerosomes: A new tool for effective dermal and transdermal drug delivery. International Journal of Pharmaceutics, 2013; 455(1–2): 66–74. doi: 10.1016/j.ijpharm.2013.07.060.
16. Michael, Y. et al. The physico-chemical properties of salmeterol and fluticasone propionate in different solvent environments. International Journal of Pharmaceutics, 2000; 200(2): 279–288. doi: 10.1016/S0378-5173(00)00397-5.
17. Montenegro, L. et al. From nanoemulsions to nanostructured lipid carriers: A relevant development in dermal delivery of drugs and cosmetics. Journal of Drug Delivery Science and Technology, 2016; 32: 100–112. doi: 10.1016/j.jddst.2015.10.003.
18. Mudshinge, S. R. et al. Nanoparticles : Emerging carriers for drug delivery. Saudi Pharmaceutical Journal, 2011; 19(3): 129–141. doi: 10.1016/j.jsps.2011.04.001.
19. Plessis, J. d. et al. The influence of particle size of liposomcs on the deposition of drug into skin. International Journal of Pharmaceutics, 1994; 103: 277–282.
20. Sala, M. et al. Lipid nanocarriers as skin drug delivery systems: Properties, mechanisms of skin interactions and medical applications. International Journal of Pharmaceutics, 2018; 535(1–2): 1–17. doi: 10.1016/j.ijpharm.2017.10.046.
21. Sherry, M. et al. Essential oils encapsulated in liposomes: A review. Journal of Liposome Research, 2013; 23(4): 268–275. doi: 10.3109/08982104.2013.819888.
22. Silva, C. O. et al. Polymeric nanoparticles modified with fatty acids encapsulating betamethasone for anti-inflammatory treatment. International Journal of Pharmaceutics, 2015; 493(1–2): 271–284. doi: 10.1016/j.ijpharm.2015.07.044.
23. Soulele, K. et al. Population pharmacokinetics of fluticasone propionate/salmeterol using two different dry powder inhalers. European Journal of Pharmaceutical Sciences, 2015; 80: 33–42. doi: 10.1016/j.ejps.2015.08.009.
24. Turvey, S. E. and Broide, D. H. Innate immunity. Journal of Allergy and Clinical Immunology, 2010; 125(2): S24–S32. doi: 10.1016/j.jaci.2009.07.016.

25. Vogt, A. et al. Nanocarriers for drug delivery into and through the skin — Do existing technologies match clinical challenges? Journal of Controlled Release, 2016; 242: 3–15. doi: 10.1016/j.jconrel.2016.07.027.
26. Yoshida, P. A. et al. Liposomes incorporating essential oil of Brazilian cherry (Eugenia uniflora L.): Characterization of aqueous dispersions and lyophilized formulations. Journal of Microencapsulation, 2010; 27(5): 416–425. doi: 10.3109/02652040903367327.