Nanostructured lipid carriers for targeting drug delivery to the epidermal layer

“Nanostructured lipid carriers have emerged as novel drug-delivery systems that could enable an epidermal targeting effect.”

Keywords: epidermal targeting • follicular • nanotechnology • skin

Targeted drug delivery to the epidermal layer could bring tremendous advantages over systemic administration on countless therapies. It is noninvasive, painless and easy to administer. Obviously the main advantage lies on the reason justifying any topical therapy itself, that is, a therapeutically relevant drug concentration is achieved at disease site preventing systemic exposure, hence, undesirable adverse effects. The challenge of topical cutaneous delivery is primarily to surpass the stratum corneum. Although very accessible, the stratum corneum lipid and protein domains restrict the diffusion of most pharmaceutically active molecules. Formulations or even specific formulation excipients may enhance drug-permeated amounts [1,2]. Generally molecules proven to be effective following topical administration are those of low molecular weight (not higher than 500 Da), relatively soluble in oil and water with an intermediary partition coefficient (Log P between 1 and 3 or even 4) and the very potent molecules that are able to exert the pharmacological effect in the micrograms per milliliter concentration range. Together with this last requirement comes the second challenge in cutaneous topical delivery, which is to restrict drug action to the disease site solely. The drug must not reach the dermis where it could be absorbed by the capillaries and reach systemic circulation. Since the stratum corneum, the outermost skin layer, is the main barrier for diffusion, how could delivery be targeted to the epidermis and release into the dermis be prevented? Even though tight junctions of the epidermis and the basal layer could impose

certain difficulty for drug diffusion, such a barrier can be considered as almost irrelevant when the stratum corneum is intact [3]. Consequently, the key aspect preventing systemic side effects following topical application is solely the low drug concentration. Ideally the amount of drug reaching the dermis, once distributed via systemic circulation, would not represent therapeutically relevant amounts. But as stated before, most frequently used molecules in topical cutaneous therapies are very potent.

Another aspect to be considered in cutaneous topical therapies is that many therapies are in fact intended for local effects in deeper tissues, as is the case of anti-inflammatories. Recent studies show deep dermal and/or subcutaneous delivery is a result of the mentioned dermal diffusion after the drug passed through the stratum corneum and epidermis, but also a result of the cutaneous vasculature transport, which seems to be ultimately influenced by the degree of drug plasma protein binding [4]. Indeed, our group has recently observed that when iontophoresis was applied on rat skin *in vivo*, the concentration of ketorolac, a highly plasma protein-bound drug (>99%), was superior in the biceps femoris muscle beneath the application site than in the contralateral muscle distal from the application site, clearly demonstrating a local enhanced topical drug delivery [5].

Moreover, epidermal targeting may not only be beneficial in terms of safety issues by preventing dermal exposure. Epidermal targeting could bring other benefits such as a better immunological response to antigens by taking advantage of antigen-presenting cells

Guilherme M Gelfuso

Laboratory of Food, Drug & Cosmetics (LTMAC), School of Health Sciences, University of Brasília (UnB), 70.910–900, Brasília, DF, Brazil

Marcílio SS Cunha-Filho

Laboratory of Food, Drug & Cosmetics (LTMAC), School of Health Sciences, University of Brasília (UnB), 70.910–900, Brasília, DF, Brazil

Tais Gratieri

Laboratory of Food, Drug & Cosmetics (LTMAC), School of Health Sciences, University of Brasília (UnB), 70.910–900, Brasília, DF, Brazil

*Author for correspondence:
tgratieri@gmail.com

FUTURE
SCIENCE

part of

fsg

of the epidermis [6]. In other cases, the dermatologic therapy requires certain drug accumulation at a specific structure site, as in the treatment of acne, a fungus infection or hair fall. In these cases therapy efficacy could be ameliorated with sustained drug release.

How to enhance drug permeation through the stratum corneum, yet maintain a reservoir for the drug to be continuously released through an extended period of time?

Many strategies reached the market in the last few years taking advantage of biocompatible permeation enhancers, film technology and development of occlusive patches, among others. But perhaps one of the strategies with the most potential to render the better patient compliance is the use of nanostructured lipid carriers (NLC).

NLC are a second-generation of solid lipid carriers formulated to increase drug loading, by mixing unsaturated, amorphous (spatially different lipids) or liquid lipids (oils) to the solid lipids. NLC show a number of advantages over conventional formulations. They are normally composed of biodegradable and biocompatible lipids, at physiological temperature; they adhere to the skin and may form an occlusive film increasing skin hydration and drug permeation [7]. But a key factor leading to both an enhanced and sustained drug release may be the route of permeation. Traditional permeation routes across the skin are transcellular and intercellular. The hair follicles (HF) have for long been considered of minor importance as penetration shunts because of their relatively small area (0.1%) [8]. However, when nanostructured carriers are applied on the skin such a concept needs to be revised. Recent data have demonstrated that nanoparticles used in pharmaceutical formulations are too large to penetrate through the intercellular pathways of the stratum corneum. Even with physical stimulus or massage only minor particle accumulation can be seen in the first external layers of the stratum corneum [9]. How to explain the enhanced drug permeation from NLC so broadly observed [10]? There are two mostly accepted explanations, either the permeation enhancement through the stratum corneum followed by drug diffusion from the particles into the skin, which can be attributed to three main reasons: phospholipids acting as permeation enhancers; film formation leading to occlusion, as previously mentioned and higher diffusion due the larger contact surface area [11]; or, particle accumulation into the follicular casts followed by drug diffusion from the particles into the skin [12]. The difference is, in the latter, both permeation enhancement and sustained release are feasible due to the larger storage volume of HF casts. Even though NLC could also sustain

delivery at the skin surface, the contact time before the formulation is washed off or removed by clothing contact or sweat, is expected to be lower from the surface than from the interior of HF casts. In addition, the stratum corneum barrier seems to be less effective in the lower part of the infundibulum. Thus, once accumulated in the HF canal, substances can continuously diffuse to surrounding epithelia [13].

There is not yet a consensus to which particle properties would lead to highest epidermal targeting effect, independently of it being a lipid or polymeric nanoparticle. Size, surface charge and composition material exert influence on the skin permeation and pharmacodynamics of encapsulated drugs [14,15]. Also, drug characteristics, as mentioned, and degree of plasma protein binding, may ultimately influence the targeting potential and nanoparticle penetration depth into HF, since a capillary network surrounds this structure, especially when in the anagen phase [13]. As the HF extends deep into the dermis or even in the subcutaneous fat, after follicular accumulation there may be a fast access to such deeper compartments leading to enhanced local delivery and not only targeting the drug to the epidermal layer. Therefore, generalizations are not possible and studies evaluating the delivery of each molecule in each particular NLC formulation are needed.

Recently we have demonstrated NLC could be used for epidermal targeting of clobetasol propionate (CP). CP has indeed excellent characteristics to be encapsulated in lipid carriers, that is, low water solubility (2 µg/ml) and an oil/water partition coefficient log value of 3 (log P). It is a potent corticosteroid widely used in the treatment of various skin disorders but often related to systemic and cutaneous adverse effects. CP-loaded NLC produced with 1/5 of the drug dose used in commercial formulations lead to 81-fold permeation enhancement effect in the epidermis when compared with the commercially available formulation [16]. Still, such a study evaluated drug retained amounts within the stratum corneum, epidermis and dermis, not specifically evaluating follicular accumulation. Therefore, it was not possible to distinguish which mechanism predominantly led to such drug epidermal targeting, if permeation enhancement through the stratum corneum, or follicle accumulation.

In summary, in the past few years it has been clear NLC may bring several advantages to topical therapies. We believe that to better understand which factors and mechanisms contribute to epidermal targeting, there will need to be more focus of future research in the field.

Future perspective

NLC have emerged as novel drug-delivery systems that could enable an epidermal targeting effect. Given the

wide range of pharmacologically active molecules with low skin permeation and severe systemic adverse effects or high cost associated with drug dose, the development of novel systems leading to an enhanced and targeted cutaneous delivery seems rational and may allow for improved therapeutic efficacy with fewer side effects. Further studies focusing in understanding particle and drug properties that would lead to higher follicular accumulation and/or epidermal targeting effect are expected in the near future.

Financial & competing interests disclosure

The authors acknowledge the financial support of *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)*, Brazil; *Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)*, Brazil, and *Fundação de Apoio à Pesquisa do Distrito Federal (FAPDF)*, Brazil. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

References

- Quintao WDC, Matos BN, Reis TA, Barreto LCD, Gratieri T, Gelfuso GM. Influence of monoolein on progesterone transdermal delivery. *Braz. J. Pharm. Sci.* 51(4), 923–929 (2015).
- Barry BW. Breaching the skin's barrier to drugs. *Nat. Biotechnol.* 22(2), 165–167 (2004).
- Andrews SN, Jeong E, Prausnitz MR. Transdermal delivery of molecules is limited by full epidermis, not just stratum corneum. *Pharm. Res.* 30(4), 1099–1109 (2013).
- Dancik Y, Anissimov YG, Jepps OG, Roberts M. Convective transport of highly plasma protein bound drugs facilitates direct penetration into deep tissues after topical application. *Brit. J. Clin. Pharmacol.* 73(5), 841–841 (2012).
- Gratieri T, Pujol-Bello E, Gelfuso GM, De Souza JG, Lopez RFV, Kalia YN. Iontophoretic transport kinetics of ketorolac *in vitro* and *in vivo*: demonstrating local enhanced topical drug delivery to muscle. *Eur. J. Pharm. Biopharm.* 86(2), 219–226 (2014).
- Hansen S, Lehr CM. Transfollicular delivery takes root: the future for vaccine design? *Expert Rev. Vaccines* 13(1), 5–7 (2014).
- Muller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. *Adv. Drug Deliv. Rev.* 54, S131–S155 (2002).
- Moser K, Kriwet K, Naik A, Kalia YN, Guy RH. Passive skin penetration enhancement and its quantification *in vitro*. *Eur. J. Pharm. Biopharm.* 52(2), 103–112 (2001).
- Gratieri T, Schaefer UF, Jing LH *et al.* Penetration of quantum dot particles through human skin. *J. Biomed. Nanotechnol.* 6(5), 586–595 (2010).
- Firooz A, Namdar R, Nafisi S, Maibach HI. Nano-sized technologies for miconazole skin delivery. *Curr. Pharm. Biotechnol.* 17(6), 524–531 (2016).
- Schafer-Korting M, Mehnert WG, Korting HC. Lipid nanoparticles for improved topical application of drugs for skin diseases. *Adv. Drug Deliv. Rev.* 59(6), 427–443 (2007).
- Chia-Lang Fang IaA, Yi-Ching Li, Jia-You Fang. Delivery and targeting of nanoparticles into hair follicles. *Ther. Deliv.* 5(9), 16 (2014).
- Fiorenza Rancan AV. Getting under the skin: what is the potential of the transfollicular route in drug delivery? *Ther. Deliv.* 5(8), 3 (2014).
- Wu X, Biatry B, Cazeneuve C, Guy RH. Drug delivery to the skin from sub-micron polymeric particle formulations: influence of particle size and polymer hydrophobicity. *Pharm. Res.* 26(8), 1995–2001 (2009).
- Verma DD, Verma S, Blume G, Fahr A. Particle size of liposomes influences dermal delivery of substances into skin. *Int. J. Pharm.* 258(1–2), 141–151 (2003).
- Silva LaD, Andrade LM, De Sa FaP *et al.* Clobetasol-loaded nanostructured lipid carriers for epidermal targeting. *J. Pharm. Pharmacol.* 68(6), 742–750 (2016).