EXPERT OPINION

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Nanocarrier-based topical drug delivery for the treatment of skin diseases

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Introduction: Skin disorders will continue to cause complications in patients. At present, there is an expansion of research into dermatologic treatment due to a critical need for new treatment options to treat skin diseases.
Areas covered: The skin itself provides a natural barrier against particle penetration for topical delivery. However, it also offers a potential approach for the delivery of therapeutics, especially in diseased skin and via the openings of hair follicles. Recent innovation might be achieved in the field of dermatological treatment with improvement in the dermal localization of bioactives into the affected skin region, via novel nanocarriers that deliver the drugs directly to the target cells. After application, these nanocarriers can penetrate through the stratum corneum into viable skin and accumulate at the target site. However, noteworthy uptake does occur after damage and in certain diseased skin.
Expert opinion: Skin-targeted topical delivery by means of nanosystems, in order to produce sustained release and maintain a localized effect, will result in an effective treatment of various life-threatening dermatological conditions. In addition, research continues into the interactions between novel particles, skin and skin lipid, and the influence of particle composition on drug distribution within the skin strata.

Keywords: nanocarriers, skin, skin disorders, topical delivery

Expert Opin. Drug Deliv. (2012) 9(7):783-804

1. Introduction

Today, skin diseases and skin troubles are emerging aspects and afflict millions of people every day. Throughout history, skin diseases have mainly been caused by numerous infectious pathogens or inflammatory situations, which pose significant challenges. Skin-related diseases encompass a vast array of situations ranging in severity from benign to life threatening. Scientific data reveal that dermatologic diseases are very acute and commonly influence the populations in many developing countries. While these problems have not gained much attention from an international audience, there seems to be a high demand by healthcare workers for more consideration to be given to skin diseases [1].

Despite the great progress in dermatological treatments, many skin-associated problems are related especially to infectious skin disease and remain difficult to treat. Indeed, these problems depend on the type of pathogens involved, the integrity of skin layers and their structures and, moreover, the underlying medical condition of the patient [2]. There are various infectious diseases related to skin and hair follicles that might be due to bacterial, fungal and viral infection. However, skin tumors (benign and malignant) are basically derived from hair follicles and might represent a further concerning issue. Chronic inflammatory skin diseases such as psoriasis, atopic dermatitis and allergic contact dermatitis are the combined result of infiltration

10.1517/17425247.2012.686490 © 2012 Informa UK, Ltd. ISSN 1742-5247

Article highlights.

- Skin is the largest organ of the human body, which represents the outermost complex barrier between the body and the surrounding environment.
- Skin disorders are caused by numerous infectious pathogens or inflammatory situations, which pose significant challenges.
- Infectious skin-related disorders namely bacterial, fungal and viral skin disease affect people and cause the dermatologic illness.
- The chronic inflammatory skin diseases such as psoriasis, atopic dermatitis and allergic contact dermatitis are result of infiltration of inflammatory T cells.
- The success of topical therapy of skin diseases depends on the local and directed delivery of therapeutics to the diseased cells of the skin.
- Conventional topical formulation suffers the limitations with regard to patient compliance, safety and efficacy of the therapy.
- Nanosystems can proficiently control the release of therapeutic moiety on skin site with localized effect by creating the skin reservoirs.

This box summarizes key points contained in the article.

of inflammatory T cells with increased production of cytokines in the lesions (schematic representation shown in **Figure 1**) [3].

Several recent innovations have been made in the field of skin disease treatment as likewise with other fields. Intensive research proposes that the effective treatment of skin disorders requires timely identification, estimation and management of the causative agent and adoptability of efficient treatment, as well as drug administration via the optimal route with an optimized dosing schedule. To this end, there are a host of new treatment options available to combat skin disorders. In addition, the understanding of skin morphology, the barrier nature of stratum corneum, transport route in skin as well as barrier properties of diseased skin have expanded rapidly over the past few decades. This new knowledge has provided the recognition of molecular targets and the rapid progress for development of new, specific, targeted therapies for treating skin diseases.

The main objective of this review is to evaluate the different novel nanocarrier-based delivery systems used to improve the skin uptake of therapeutic moiety as well as the *in vitro* and *in vivo* studies performed with these types of carriers, along with their therapeutic potential for the therapy of skin-related disorders.

2. Skin

2.1 Skin structure

Skin is the largest organ of the human body, which represents the outmost complex barrier between the body and the surrounding environment. One of the major roles of the skin is to prevent invasion of microorganisms by creating a physical barrier from the external environment.

The defensive mechanism of skin not only presents physical protection but also offers immunological, metabolic and UV protection [4]. If the mechanisms that confer the barrier properties are well understood, they can be exploited as a port of entry for therapeutic substances such as drugs and vaccines.

The skin consists of three main layers: the outermost epidermis layer, which is about 50 – 150 µm thick, inner dermis layer about 250 µm thick and subcutaneous fat tissue. No blood vessels are present in the epidermis – therefore, nutrients have to diffuse across the dermal–epidermal junction to maintain its vitality. It consists of five layers, which, from the outside to the inside are the stratum corneum, stratum lucidum, stratum granulosum (granular layer), stratum spinosum (spinous layer) and stratum germinativum (basal layer). Viable epidermis consists of the epidermis without the stratum corneum (shown in **Figure 2**) [5].

The outermost part (15–20 µm) of the epidermis, named stratum corneum, is responsible for the barrier function of the skin. It consists of corneocytes (brick) that are embedded in a lamellar structure formed by intercellular lipids (mortar) that are rigid, desmosome-linked epithelial cells. The unique arrangement of this layer represents the basic skin permeation resistance that reduces the passage of molecules, especially of those that are larger than 500 Da [6]. Keratinocytes, melanocytes (melanin production), merkel cells (sensory perception) and Langerhans cells (immunological function) all might play an important role in the functioning of the viable epidermis. Keratinocytes differentiate and move upward from the basal layer to the outermost layer through a process termed keratinization. Along with the above cellular components, appendages including the pilosebaceous units (hair follicles and associated sebaceous glands), apocrine and eccrine sweat glands are also present. Stratum disjunctum, the outer layers of the stratum corneum, is mainly subjected for desquamation. Depending on anatomical site and age, the stratum corneum is completely renewed to maintain its optimum protective properties [7].

Substances are transported across the stratum corneum primarily by a passive diffusion process via three possible routes namely the transcellular, intercellular and appendageal routes [8]. Penetrants are mainly small molecules that preferentially move through the intercellular route. Lipophilicity and physicochemical properties such as molecular weight or volume, solubility and hydrogen bonding ability govern the diffusion rates. Lipid channels, which have been estimated to be 19 nm [9], are expected to physically restrict the free movement of particles suggesting that the stratum corneum could also present an additional barrier that is not present for small molecules. It is also evident that a large number of protein transporters are present in skin, which may play a supportive role in the active transport of drugs or other particles. Epithelial layers and follicles consist of several important elements as tight junction proteins whose localization and expression have been shown to be altered in the diseases characterized by a compromised skin barrier, such as psoriasis [8].

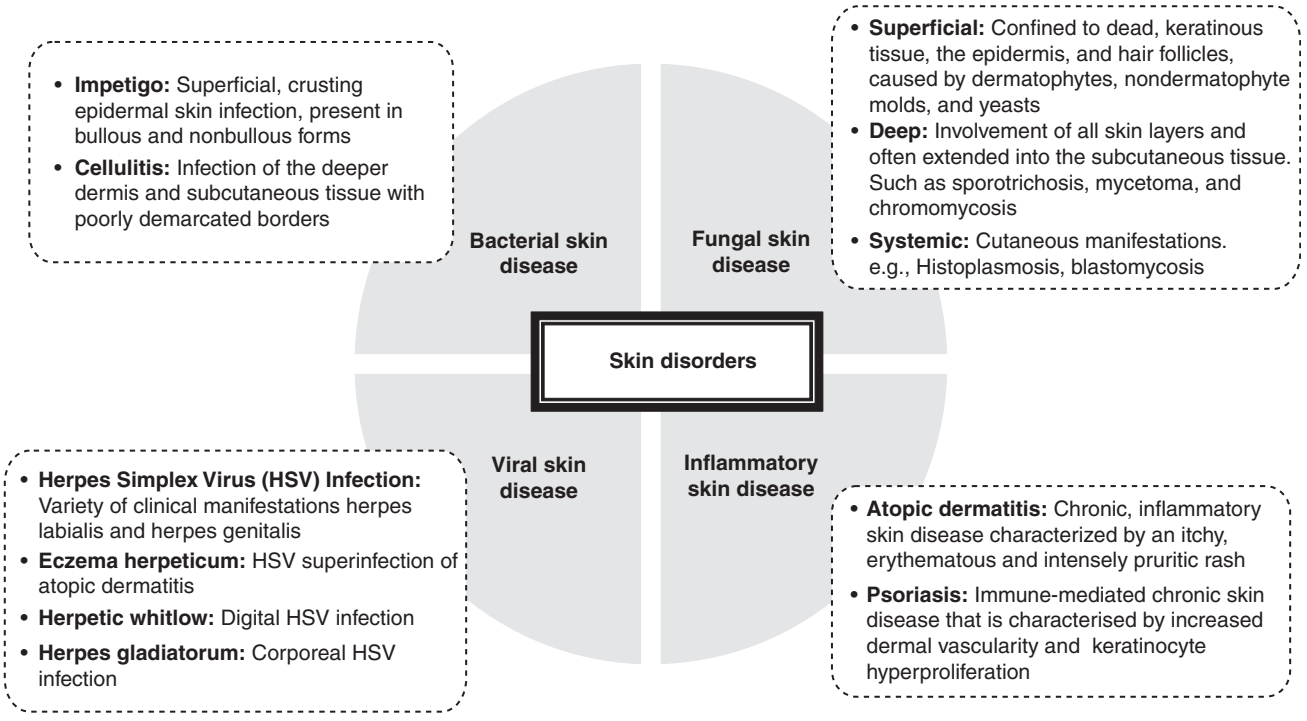

Figure 1. Schematic representation of various skin disorders and their origin.

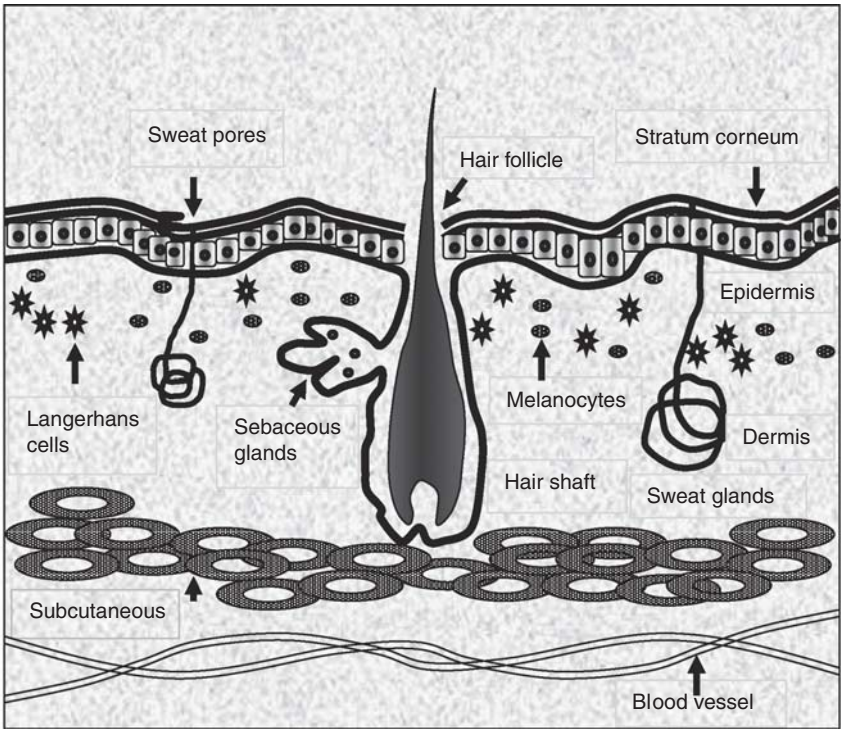

Figure 2. Diagrammatical representation of a cross section through human skin showing different cell layers and appendages.

The outer layers of the stratum corneum are regarded as a moving, constantly renewable barrier. This upward migration might assist in providing a mechanism to prevent foreign bodies from invading the body and to eliminate pathogens, cancerous cells or solid particulate matter [10].

The dermis is located underneath the viable epidermis and it is the major site of cellular and fluid exchanges between the skin and the blood and lymphatic networks. The fibroblasts, mast cells and dermal dendritic cells (DCs) are important cell classes in the dermis. It also contains blood vessels, lymph vessels, nerves and an abundant level of collagen fibers [11]. An assembly of adipocytes linked by collagen fibers is located underneath the dermis, which forms a thermal barrier. Subcutaneous fat tissue stores energy and functions as a mechanical cushion for the body [12]. Structures penetrating the skin are appendages such as sweat glands, pilosebaceous units and hair follicles that originate either from the dermis or the subcutaneous fat tissue. These appendages form important discontinuities in the skin structure [11]. In addition to the barrier function, the skin has also important immunological functions and serves a vital role for the skin-residing antigen-presenting cells, such as Langerhans cells and dermal DCs, which coordinate with keratinocytes, mast cells and subsets of T lymphocytes [13].

It is also important to consider the barrier nature of diseased skin. As stated, there are limited data available on skin penetration of nanoparticles through diseased skin. The topical delivery by nanocarriers for local effects is generally to be used on diseased skin. Moreover, the barrier effects modulate disease and its impact on the penetration of nanoparticles is unknown. It was hypothesized that nanoparticles could penetrate these lesions more efficiently due to an altered stratum corneum, inflammation and increased keratinocyte turnover [8].

3. Designing of topical drug delivery system

A broad range of therapeutic indications are covered by drugs that are intended for topical/cutaneous administration. Although they have different molecular structures, they retain certain common physicochemical characteristics such as high lipophilicity and poor aqueous solubility. The drugs should possess log octanol/water partition coefficients value [log P] > 6.0. The formulation scientist has assured that the rate and extent of drug delivery are satisfactory to achieve therapeutic local concentrations in a reasonable time frame and provide sustained pharmacological action [14]. The effects of formulation on the absorption characteristics are much greater comparatively with topical drug delivery than any other route of drug administration [15]. The barrier function of the target biologic membrane provides a major challenge for optimal therapy. Deprived drug penetration of skin/nail/cornea limits their local bioavailability and drug efficacy. While the stratum corneum, corneal, mucosal and nail barriers all have different structures, they collectively present considerable restrictions to drug transport. Their epithelial architecture and physicochemical composition contribute principally to the barrier function. Delivery efficiency and therapeutic effect mainly depend on drug diffusion affinity and interaction between the formulation excipients and membrane components. Therefore, formulations and drugs should be better designed and modified for traversing a given biologic barrier. The correct balance between potency and deliverability has to be ensured to design and develop a formulation system so that optimum therapeutic drug levels can be achieved at the site of infection [14]. The stratum corneum acts as a barrier for topical drug delivery and its low permeability limits the delivery of drugs *via* the topical route. Various efforts, including various forms of formulation systems and strategies, have been investigated to surmount this permeability barrier. To overcome the complex array of enzymes and transporters in or through the skin, various systems for the delivery and transport of drugs have been studied including pro-drugs, soft-drugs or particle-bound drugs [16]. The success of topical therapy of skin diseases primarily depends on local and directed delivery of therapeutics to the diseased cells of the skin. Directed delivery has overcome the side effects resulting from unspecific delivery and systemic exposure, while local delivery requires that the drug is applied into skin where the main protective barrier, the stratum corneum, is not intact [17]. The literature abounds with studies on *in vitro* models that simulate diseased skin, which can improve the understanding of how the skin barrier affects penetration into and permeation across the skin. It was stated that skin disease therapy may resolve the initial condition, which can alter the skin barrier properties during the period of the treatment. Indeed, this variation can also influence the penetration profile of the administered drug substance [18].

4. Conventional approach

The majority of conventional topical preparations are intended to deliver the drug for a local, rather than a systemic action. Traditional therapies are proposed to act on the outer surface of the skin. Conventional topical treatment of the skin implies the use of ointments or creams. Drugs from such preparations partition upon application on the skin, producing a highly concentrated layer of active ingredient that is rapidly absorbed [19]. Moreover, sometimes the application of topical drugs results in lack of patient compliance due to problems such as greasiness and stickiness associated with the ointments. High concentration of active agents is required by these vehicles for effective therapy due to low efficiency of delivery system. It may also result in toxic reactions such as irritation, allergic reactions. Other drawbacks include uncontrolled evaporation of active ingredient and unpleasant odor [20]. The delivery from these systems is often unspecific, and the skin penetration can be very low with high variation. Two parameters are imperative for the drugs to be effective: they have to reach the site of action or deeper layers at significant amount, and they have to stay at the site in an

effective concentration for a certain time. Skin being the outermost organ can be easily accessed for drug application but this does not mean that the drug has an easy access route to the site of action. To increase the penetration of drugs across the skin layers, penetration enhancers, for example, dimethylsulfoxide or propylene glycol leads have been used. Use of penetration enhancers increase transport rate through the epidermal barrier but, in addition, it also increases unwanted effects due to an enhanced drug level in the blood. Reports indicate irritative or even toxic side effects of penetration enhancers that question their use in topical drug administration (**Table 1**) [21,22].

5. Current issues in skin disorder therapy: need of novel nanomedicine-based therapeutic strategy

As discussed in the previous section, conventional topical options suffer the limitations and are compromised with regard to patient compliance, safety and efficacy of the therapy [23]. To overcome these issues, novel drug delivery systems are being investigated that present the potential to reduce such erroneous characters without reducing the efficacy. They have also become available and opened up both opportunities/options for therapeutic strategies to treat skin diseases [24,25]. The new drug carrier systems with topical dermatics seem to provide the means for achieving unreachable goals and overtake the issues that are linked with conventional topical therapy. Pharmacokinetic data also show low absorption of drug from conventional formulation. All these subjects demand the need for the development of new carrier systems that could effectively improve skin penetration and reduce the undesirable side effects associated with the drug [26]. It is obvious that skin is a widely explored route, which can be reached directly for drug application; however, it does not automatically mean the drugs are getting to the right site of action (**Figure 3**) [22].

The applications of such novel nano-vehicle systems are able to deliver potent drugs to the preferred site in a very precise manner. The design of nanomedicines is based on nanosystems, which proficiently control the release of a therapeutic moiety to the affected region at the skin site with localized effect by creating skin reservoirs. Furthermore, nanosized particles and their narrow size distribution may allow an efficient site-specific skin targeting favoring greater drug retention [27]. The entrapment of active moiety in nanocarriers, which is an increasingly implemented strategy in skin targeting and topical delivery, may provide a base for a new generation of skin delivery of bioactive compounds. Such systems may enable sustained release, resulting in an extended activity or enhanced uptake and the possible reduction in adverse effects. Furthermore, encapsulated substances are shielded from degradation in the particles [28].

In the following section, the main representatives of nanocarriers particularly employed for skin targeting and their applications are discussed. One way of optimizing topical drug delivery to the skin is to employ particulate carriers such as liposomes, nano- and microemulsions and lipid nanoparticles and polymeric nanoparticles (**Figure 4**). The nanocarriers in particular have received attention owing to their ability to improve penetration across the stratum corneum and targeting properties. It is a well-known fact that skin acts as a negatively charged membrane. The presence of charge on the surfaces of nanocarriers influences their drug diffusion through the skin [29]. A positively charged delivery system would strongly interact with cells and has shown better permeability of the drug and prolonged pharmacological activity [30]. **Table 2** shows the work done recently with various nanotherapeutics as topical drug delivery systems.

5.1 Vesicular system

Liposomes are one of the most commonly used and most extensively studied topical drug delivery systems. Moreover, research is also being done into improving cutaneous delivery methods to reduce toxicity and consequently improving the therapeutic index. The field of liposomes is complex and involves equally basic science including chemistry, biology, biophysics and physics. Since the discovery of classic liposomes over 40 years ago by Bangham, liposomes have been most extensively investigated as potential carriers of drugs and biologically active molecules to date [31].

Liposomes are spherical vesicles made up of phospholipids, and by virtue of their compatibility with biological constituents, they can carry a range of drug payloads successfully [32]. Similar to biological membranes, they can encapsulate both water-soluble and lipophilic substances in their different phases. In regard to their potential in cutaneous delivery, it may be attributed to their lipid composition, which may be similar to epidermis enabling them to penetrate the epidermal barrier to a greater extent compared with other dosage forms.

On the basis of studies performed so far, liposomes are considered to be biodegradable and non-toxic. Liposomes can reportedly localize the drug effect on account of their dermal accumulation and drug reserve formation. Moreover, experiments were conducted to study the possible interaction between liposomes and keratinocytes using a reconstructed human skin [22]. The first liposomal topical product, a liposomal gel of the antifungal drug econazole (Pevaryl®; Cilag AG, Schaffhausen, Switzerland), was produced in 1994 in Switzerland [33]. According to the literature, almost every kind of therapeutic moiety can be encapsulated into liposomes. In our earlier study, we reported that fluconazole-loaded liposomal gel may be a promising option for cutaneous candidiasis (skin fungal infection treatment). This may be due to accumulation of drug-loaded liposomes in various strata of skin following the topical application. The formulation showed better antifungal activity due to localized drug-depot formation and subsequent controlled release of drug [34].

Use of nano-liposomal formulations in topical drug delivery has been found to improve the penetration of several entrapped agents into the skin. They have been proven to be

Table 1. Some of the drugs administrated through conventional topical preparations.

S. No.	Formulation	Drug	Indication
1	Gel	Ketoconazole	Antifungal
2	Cream	Sulconazole nitrate, Miconazole nitrate	Cutaneous dermatophytosis
3	Ointment	Tacrolimus	Vitiligo
4	Ointment	Tacrolimus	Atopic keratoconjunctivitis
5	Gel	Tazarotene	Psoriasis
6	Cream	Calcipotriol/betamethasone dipropionate combination	Psoriasis
7	Cream	Calcipotriol	Psoriasis
8	Gel	Methotrexate	Psoriasis
9	Gel	Tazarotene	Psoriasis
10	Ointment, cream, solution	Calcipotriene	Psoriasis
11	Propylene glycol–water–ethanol solutions	Minoxidil	Androgenic alopecia
12	Powders, parenterals, gels, creams and ointments	Miconazole	Candida infections, fungal infections
13	Cream, lotion, gels, ointments	Amphotericin B	Fungal skin infections

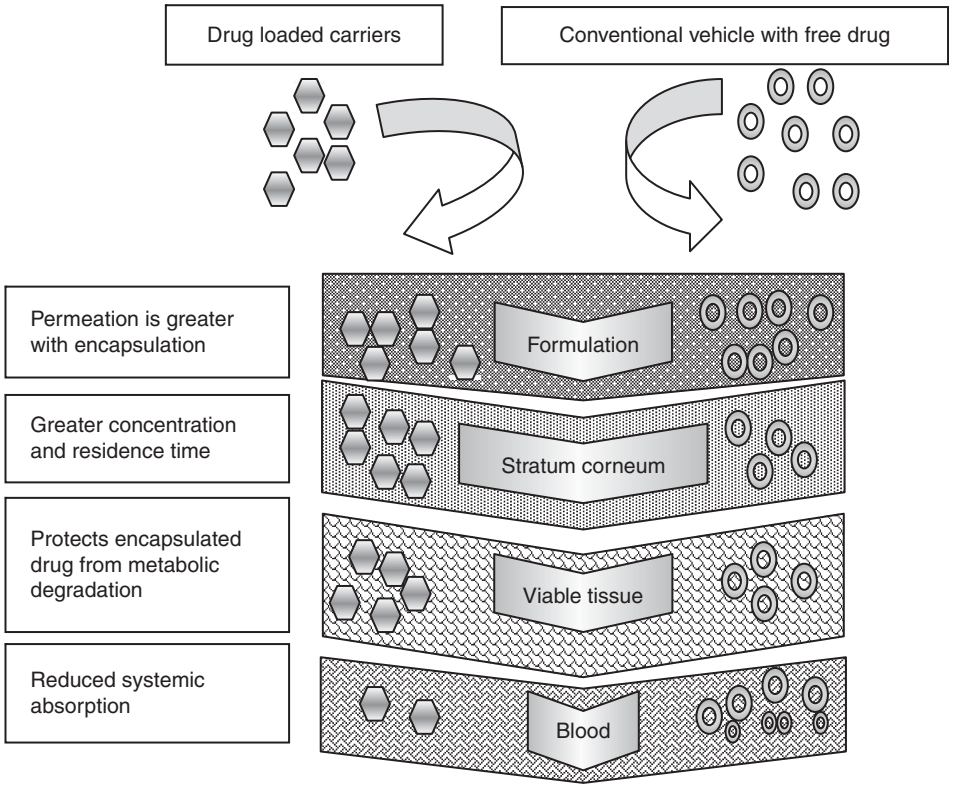

Figure 3. A schematic representation of drug transport through the skin and benefits of a carrier system.

a valuable module for follicular drug targeting. The first significant scientific study and contribution on liposomes in topical therapy was made and reported by Mezei and Gulasekharam in 1980 [35]. In this study, liposomal lotion presented a four- to fivefold higher retention of triamcinolone acetonide concentration in the epidermis and dermis, with lower systemic drug level as compared with conventional formulation. After this, numerous studies were conducted and conflicting results continued to be published concerning the effectiveness of liposomes. Recently, several *in vivo* and *in vitro* transport studies have reported that conventional liposomes might contribute to enhanced skin deposition of

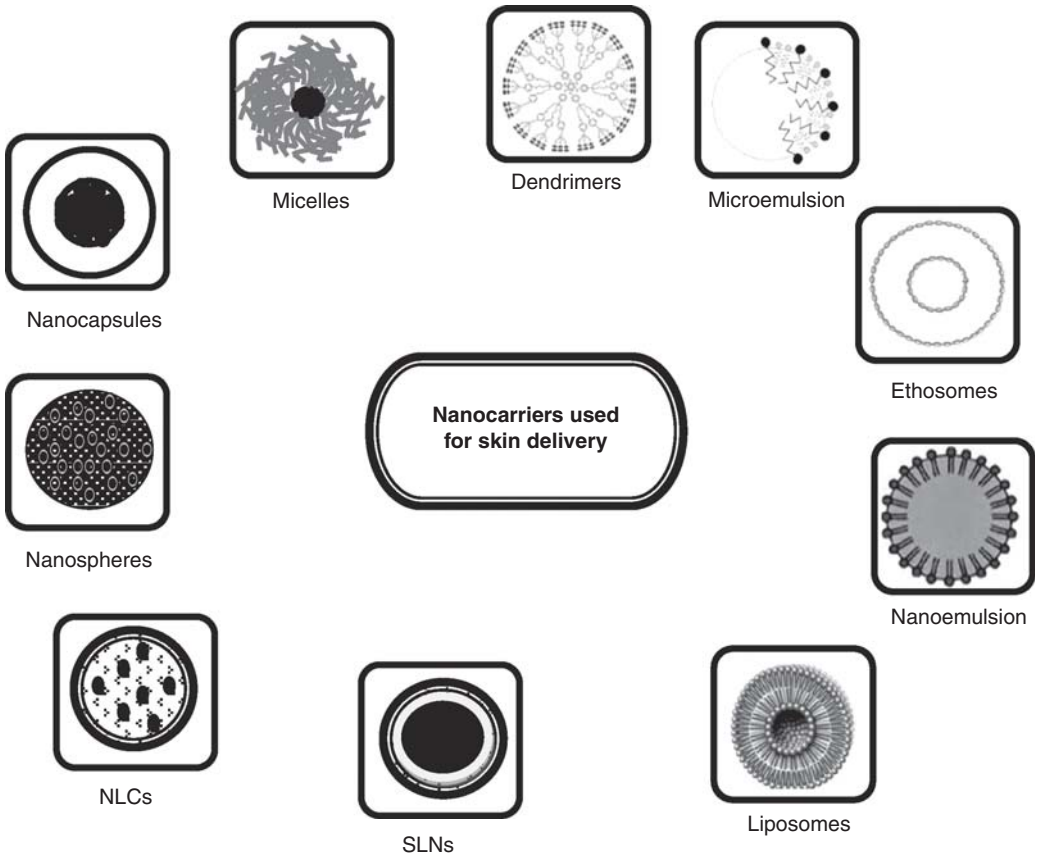

Figure 4. Pictorial view of novel nanocarriers used for skin delivery.

fluconazole [34] and tretinoin [36]. These results suggest that conventional liposomes could be useful for topical dermal delivery of these drugs. Despite the improved therapeutic value of liposomes, it has become evident that classical liposomes fail to penetrate the skin layers deeply – they remain confined to upper layers of the stratum corneum. Confocal microscopy studies suggest that intact liposomes do not penetrate into granular layers of the epidermis [37].

Researchers have also exploited the targeting potential of such vesicular structures to the appendages, especially the pilosebaceous units (hair follicles with their associated sebaceous glands). This area was extensively reviewed by El Maghraby *et al.* in 2006 [38] with an update. Vesicular preparations showed better results in acne vulgaris treatment compared with conventional preparations including alcoholic lotions [39]. This was considered to be strong evidence that vesicles can effectively target to skin appendages [38]. The *in vitro* permeation through hamster flank skin and *in vivo* deposition in hamster ear demonstrated the potential of liquid-state liposomes and surfactant vesicles for successful delivery of finasteride to the pilosebaceous unit [40]. To understand the influence of charge on vesicles, researchers investigated negatively charged vesicles and observed higher flux with negative as compared with positively charged vesicles, which ultimately enhanced drug accumulation in the superficial skin layers [41]. In one study, the positively charged vesicles of tretinoin provided permeation similar or even statistically higher ($p < 0.05$) than negatively charged vesicles [42].

5.2 Transfersomes

Deformable liposomes (Transfersomes) are a critical advancement in topical vesicular drug delivery and have the potential to dramatically improve drug delivery, as reported by Cevc, 1996 [43]. These first generations of elastic vesicles are reported to penetrate intact skin carrying the drugs, under non-occlusion conditions. They consist mainly of phospholipids with an edge activator that destabilizes lipid bilayers of the vesicles and contribute to the deformability of the bilayers. Sodium cholate, span 80, tween 80 and dipotassium glycyrrhizinate have successfully been employed as edge activators [44]. Several studies have reported that deformable liposomes are capable of improving *in vitro* skin delivery of various drugs [45,46] and of penetrating intact skin *in vivo*, transferring therapeutic amounts of drugs to the skin layers [47]. In a recent study, these vesicles were found to significantly improve ketotifen skin delivery, with an improvement of ketotifen skin deposition as compared with plain ketotifen skin permeation. Therefore, it was suggested that

Table 2. List of recent (Year 2008 onward) reported literature for various types of nanocarriers used for skin delivery.

Nanocarrier type	Materials used	Indications	Drug	Study findings	Ref.
Liposomes, niosomes	L-α-egg Phosphatidylcholine, Span-80, cholesterol	Cutaneous candidiasis	Fluconazole	The studies signify the potential of liposomal gel for topical delivery of fluconazole with increased accumulation of drug in various strata of skin *vis-à-vis* through sustained release of drug could maintain the localized effect, resulting in an effective treatment of a life-threatening cutaneous fungal infection	[34]
Transethosome	phospholipid, ethanol, water and oleic acid	Fungal infection	Voriconazole	Transethosomes enhanced both *in vitro* and *in vivo* skin deposition of drug in the dermis/epidermis region compared with deformable liposomes and conventional liposomes and control. Therefore, this novel carrier could serve as an effective dermal delivery for voriconazole	[58]
PEVs	Soy phosphatidylcholine, LipoidGmbH, Oramix, Transcutol, Labrasol	Inflammatory skin diseases	Tretinoin	PEVs are eligible for use as suitable carriers for tretinoin in skin disease treatment due to PEVs' ability to strongly interact with the intercellular lipids causing an enlargement of this region	[108]
PEVs	Soy lecithin, Dicetylphosphate, Labrasol, Transcutol, Cineole	Hair follicles associated with androgenic alopecia	Minoxidil	The most deformable PEVs, prepared with Labrasol® and cineole, were also able to deliver to the skin a higher total amount of minoxidil than the control thus suggesting that minoxidil delivery to the skin was strictly correlated to vesicle deformability and, therefore, to vesicle composition	[106]
PEVs	Phospholipon 90G, Transcutol, oleic acid	Local muscle inflammation	Diclofenac	This study shows the superior ability of the PEVs to enhance *ex vivo* drug transport of both hydrophilic and lipophilic diclofenac forms	[56]
Ethosomes	Soya PC, Ethanol, cholesterol	Skin fungal infections	Econazole nitrate	The results collectively suggest that because of the controlled drug release, better antifungal activity and good storage stability, ethosomal gel has tremendous potential to serve as a topical delivery system	[109]
Ethosomes	Soya phosphatidylcholine, ethanol, propylene glycol,	Candidiasis	Fluconazole	This formulation provides enhanced antifungal activity, better remission from the disease and reduces the therapy	[110]
Transfersomes	Egg phosphatidylcholine, sodium cholate, sodium deoxycholate, Tween 80, Span 80, Span 85.	Rheumatoid arthritis, osteoarthritis,	Diclofenac sodium	Transfersomes can significantly improve the *in vitro* skin delivery of drug compared with the marketed product (Olfen® gel) when applied non-occlusively. This enhancement is attributed to the synergistic ability of Transfersomes to act as drug carriers as well as permeation enhancers	[111]

Table 2. List of recent (Year 2008 onward) reported literature for various types of nanocarriers used for skin delivery (continued).

Nanocarrier type	Materials used	Indications	Drug	Study findings	Ref.
Pep-1 peptide-conjugated elastic liposomal	Phosphatidylcholine, Tween 80, N-[4-(*p*-maleimidophenyl)butyryl] phosphatidylethanolamine (MPB-PE),Pep-1 peptide	Atopic dermatitis	Taxifolin glycoside	Atopic dermatitis-associated immune responses including serum interleukine-4, immunoglobulin E and interferon-gamma were also regulated by topical application of elastic liposomes. In conclusion, the novel formulations showed substantial promise in the treatment of atopic dermatitis as a result of its desirable skin delivery-promoting capability	[112]
Ultradeformable archaeosomes	Soybean phosphatidylcholine, sodium cholate, and polar lipids	Topical adjuvants	Ovalbumin	The carrier system penetrate to the same skin depth (nearly 10 μm after 1 h on excised human skin), being the higher topical adjuvancy and higher phagocytic uptake related to its glycolipid content	[113]
NLCs	Compritol 888 ATO, Labrafac	Osteoarthritis, rheumatoid arthritis	Ketoprofen complex with cyclodextrin	This system improved entrapment efficiency, exhibited better drug permeation properties and ultimately enhanced the drug therapeutic efficacy	[114]
Lipid nanoparticles	Glyceryl trimyristate	Atopic dermatitis	Tacrolimus	This carrier has the potential for higher skin penetration and enhanced skin accumulation. Thus nanoparticles displayed superior performance, effective skin targeting and improved safety as compared with control	[115]
SLNs	Precirol ATO, cetylpalmitate, Dyanasan 116 polysorbate 80	Atopic dermatitis	Betamethasone-17-valerate	The studied system revealed that in both barrier-impaired and intact skin, a higher amount of drug substance remained in the skin during application of SLNs for 6, 16 and 24 h, as compared with the ointment. These results emphasize the applicability of SLNs to create a drug reservoir in skin, with the drug localized distinctively in the stratum corneum	[18]
SLNs	Stearic acid monostearin tristearin (TS) and compritol 888 ATO	Cutaneous candidiasis	Fluconazole	The antifungal activity shows that SLNs made up of compritol 888 ATO lipid could noticeably improve the dermal localization	[62]
SLNs	Stearic acid, Poloxamer 188, caprylic triglyceride	Fungal infection	Eugenol	The antifungal action of eugenol and tea tree oil is due to disruption of the membrane lipid packing, which leads to increase in the membrane permeability and promising alternative therapy in case of resistant fungal strains	[116]
SLNs and NLCs	Compritol 888 ATO, oleic acid, Egg phosphatidylcholine, Pluronic F-68	Cutaneous candidiasis	Fluconazole	NLCs provide a good skin targeting effect and may be a promising carrier for topical delivery of drug offering the sustained release and maintain the localized effect, resulting in an effective treatment of a life-threatening cutaneous fungal infection	[25]

Table 2. List of recent (Year 2008 onward) reported literature for various types of nanocarriers used for skin delivery (continued).

Nanocarrier type	Materials used	Indications	Drug	Study findings	Ref.
SLNs, NLCs and nanoemulsion	Cutina® CP, Dynasan®116, Carnauba Wax, Miglyol® 812, Plantacare® 810, Tween® 80	Skin protection from photo damage	Lutein	The nanocarriers were able to protect lutein against UV degradation. In SLN, only 0.06% degradation was observed after irradiation with 10 MED Minimal Erythema Dose), in NLC 6 – 8%, compared with 14% in the NE and may be employed as are potential dermal nanocarriers for lutein	[117]
Modified nanolipid carrier	Propylene glycol monocaprylate, Glyceryl trimyristate	Atopic dermatitis	Tacrolimus	The study concluded that successful development of novel modified nanolipid carrier using lipophilic solubilizers to increase the encapsulation efficiency of colloidal lipid carriers with advantage of improved performance in terms of stability and skin localization	[26]
Polymeric nanoparticles	poly(butyl cyanoacrylate	–	Econazole	The colloidal stability of the formulations was found to depend on the method of preparation, as well as on the type of colloidal stabilizer and may be used for topical delivery in near future	[118]
Polymeric bilayered nanoparticles	PLGA, Chitosan, oleic acid	Skin diseases	Spantide II and ketoprofen	Oleic acid-modified polymeric bilayered nanoparticles strongly suggested the improved drug delivery to the deeper skin layers	[119]
Nanogel	PLGA, Chitosan, oleic acid, Hydroxypropyl methyl cellulose and Carbopol	Inflammatory diseases	Spantide II, ketoprofen	Results suggested that bilayered nanoparticles have significant potential for the percutaneous delivery of Spantide II and ketoprofen to the deeper skin layers for treatment of various skin inflammatory disorders	[77]
Polymeric micelles	Methoxy-poly(ethylene glycol)- hexyl substituted polylactide (MPEG-hexPLA) block copolymers	Superficial fungal infections	Clotrimazole, econazole nitrate and fluconazole	The study showed that the significant increase in econazole skin deposition achieved using the MPEG-dihexPLA micelles and their ability to improve cutaneous drug bioavailability; this may translate into improved clinical efficacy *in vivo*. Moreover, these micelle systems may also enable targeting of the hair follicle and this will be investigated in future studies	[84]
Polymeric nanosphere gel	(PEG5K-b-oligo(desaminotyrosyl-tyrosine octyl ester suberate)-b-PEG5K triblock copolymer	–	Diclofenac sodium and Nile Red model drug	Tyrosine-derived nanospheres dispersed in gels offer promise for the topical delivery of lipophilic drugs and personal care agents to skin for treatment of cancers, psoriasis, eczema and microbial infections	[82]

Table 2. List of recent (Year 2008 onward) reported literature for various types of nanocarriers used for skin delivery (continued).

Nanocarrier type	Materials used	Indications	Drug	Study findings	Ref.
Lipid-core polymeric nanocapsules	Poly(ε-caprolactone) and sorbitan monostearate, caprylic/capric triglyceride mixture, polysorbate 80	Dermatological diseases	Tretinoin	Polymeric nanocapsules are able to protect nanoencapsulated drug against UVA radiation, being an important alternative to overcome its main pharmacotechnical limitation. Furthermore, skin permeation studies showed that this strategy was able to control the skin permeability of tretinoin and represent a useful tool in the development of topical nanomedicines containing tretinoin for the treatment of skin disorders	[120]
Dendrimers	PAMAM	Dermatologic therapy	Riboflavin	The water-soluble PAMAM dendrimers G2 and G3 can be successfully applied in cosmetic and dermatologic emulsions for weakly water-soluble vitamin	[121]
Microemulsion gel	Babchi oil, oleic acid, Tween 80, Transcutol-P	Psoriasis	Babchi oil (*Psoralea corylifolia*)	The results suggested that microemulsion gel is a potential vehicle for improved topical delivery of psoralen and that microemulsion gels are potential vehicles for improved topical delivery of babchi oil	[122]
Nanoemulsion Gel	Labrafac, Tween® 80 and Ethanol	Inflammatory diseases	Aceclofenac	From *in vitro* studies, it can be concluded that the developed nanoemulsion-based gel has great potential for topical drug delivery	[123]
Microspheres	PLGA	Cutaneous wound	Insulin	Study concluded that coverage of the scratch wounds was significantly faster in the presence of insulin released from microspheres than in the insulin-free control. Extended and sustained topical delivery of active insulin from a stable protein crystal-based reservoir shows promise in promoting tissue healing	[124]
Nanoemulsions	Phytosphingosine for the positive charge, Lipoid E80, α-tocopherol and Eutanol G, negative charge (myristic acid, stearic acid, 160 lauric acid and palmitic acid), Tween 80	Atopic dermatitis	Prednicarbate	The results showed that positively charged nanoemulsion containing prednicarbate show that its topical use could be advantageous for the therapy of atopic dermatitis, especially regarding phytosphingosine, which was responsible for the positive charge	[125]

these vesicles are more valuable for dermal than for transdermal delivery of ketotifen [48]. They could reportedly improve the skin deposition of 5-fluorouracil [49] and dipotassium glycyrrhizinate [50], hence were considered selectively useful for dermal delivery of these drugs.

5.3 Ethosomes

In the process of exploration of new approaches for enhanced cutaneous delivery, ethosomes were studied and explored as potential carriers in dermatologic area. Recently developed ethosomes by Touitou *et al.*, 2000 [51], exhibited enhanced skin delivery of contained drug. The only difference between conventional liposomes and ethosomes is that ethanol, instead of cholesterol, is used as constituent in ethosomes [52]. An ethanol content of up to 45% may be present in ethosomes, which is responsible for skin penetration resulting in drug delivery into deep layers of the skin. This may be due to the fact that ethanol plays a significant role in interaction between ethosomes and skin lipids. It is thought that intercalation of ethanol with the intercellular lipids enhances the lipid fluidity and decreases the density of the lipid multilayer. It includes interlipid penetration and permeation by the opening of new pathways due to the malleability and fusion of ethosome with skin lipids and drug release into deeper layers of the skin [53].

Literature abounds with studies that report excellent skin tolerability of ethosomes in human volunteers for as long as 48 h of application. In one study, the highly efficient delivery of antibiotics to deeper skin layers via stratum corneum intercorneocyte lipids was successfully possible with bacitracin-entrapped ethosomal dispersions. It was suggested that ethosomal applications into human cadaver and rat skin eliminate the side effects and other drawbacks associated with systemic treatment [54]. These systems could be used for the treatment of various dermatological disorders. Ethosomes are reported to improve skin delivery of various drugs [55].

5.4 Penetration enhancer-containing vesicles

Intensive research has led to the introduction and development of a new class of highly improved cutaneous delivery of minoxidil. The formulation mainly contained penetration enhancers. The penetration enhancer-containing vesicles (PEVs) were prepared using soya lecithin and different amounts of three penetration enhancers, 2-(2-ethoxyethoxy) ethanol (Transcutol), capryl-caproyl macrogol 8-glyceride (Labrasol) and cineole. The results showed that PEVs were able to give a statistically significant improvement of minoxidil deposition in the skin layers as compared with classic liposomes and penetration enhancer-containing drug ethanolic solutions. In addition, the most deformable PEVs, prepared with labrasol and cineole, were highly effective in the delivery of minoxidil in the skin suggesting that minoxidil delivery to the skin could correlate with the deforming of vesicles and, therefore, in turn relate to vesicle composition. Several studies have reported that acronym PEVs were introduced to identify the PEVs as carriers for dermal delivery of minoxidil and diclofenac [56,57]. These systems represent a judicious combination of liposome potential as carriers and penetration enhancer ability per se to modulate the order of stratum corneum packing, thus promoting the skin penetrance and hence the drug delivery.

5.5 Transethosomes

The area of vesicular drug delivery to the skin is identified to operate on the basis of composition of vesicles investigated. Therefore, a novel carrier, which can cover the advantages of both transfersomes and ethosomes, would be desirable as an elastic carrier in order to deliver drugs to dermis layer through stratum corneum barriers. Hence, it was exploited as another option, transethosomes, which consist of phospholipid, ethanol, water and edge activator. Researchers concluded that transethosome might be an opportunistic carrier effective for enhanced skin delivery of voriconazole [58].

5.6 Flexible nanosomes (SECosomes)

Significant research efforts have been devoted to designing effective carrier systems that could specifically deliver active agents to diseased sites. Hence, lipidic nanovesicles termed 'nanosomes' have been investigated for topical delivery. The nanosomes contain 1,2-dioleoyl-3-trimethylammonium propane chloride (DOTAP), cholesterol, surfactant (sodium cholate) and a higher percentage of ethanol, hence the name 'SECosomes' is used (surfactant–ethanol–cholesterol). The benefits of the synergistic effect of ethanol and surfactant provide an extreme flexible character and influence the skin penetration capacity of the SECosomes [59]. A recent study employed lipid-based nanosomes that enable the effective delivery of siRNA into human skin. The findings provide evidence that ultraflexible siRNA-containing nanosomes penetrate into the epidermis of freshly excised intact human skin and is able to enter into the keratinocytes. This system might be able to enhance efficient transfection of *in vitro* cultured cells and delivered siRNA through intact human skin where changes in the keratinocyte cell state are demonstrated [60].

5.7 Lipidic nanoparticles

The treatment of skin disease mainly implies application of a drug to skin with an impaired epidermal barrier and linked with the penetration profile of the drug substance as well as the carrier into the skin. To elucidate this, the effect of skin barrier damage on the penetration profile of various bioactives applied as solid lipid nanoparticles (SLNs) or nanostructured lipid nanoparticles (NLCs) composed of different lipids, varying in polarity, was studied. It is appreciated that the topical delivery of drugs in skin diseases by lipidic nanoparticles serves as an excellent tool in the dermatological field [18]. The SLNs of course present a great contribution in the administration of active molecules and simultaneously in the improvement of their therapeutic efficacy with a great degree of feasibility of incorporation of lipophilic and hydrophilic

drugs [61]. Moreover, their lipid core made from physiological lipids having high biocompatibility and biodegradability with their potential in epidermal targeting, follicular delivery and controlled release of active moiety with increased skin hydration due to greater occlusivity have been very well established [62,63].

NLCs, the new improved generation of lipid nanoparticles, are better in this respect as they overcome the problem associated with SLNs mainly relating to limited drug loading, risk of gelation and drug leakage during storage caused by lipid polymorphism [64]. NLCs consist of a mixture of especially very different lipid molecules; that is, solid lipid(s) is blended with liquid lipid(s). A blend of a liquid and solid lipid forms a less perfect crystalline structure with many imperfections providing more space for drug accommodation. The benefits of NLCs include the increased drug payload of actives compared with SLNs and inclusion of the active agents within the matrix of particles. Their applicability for dermatological applications was also confirmed by successful formulations and evaluation of some drugs for skin disease treatment [25,65].

Earlier studies recommended that both SLNs and NLCs serve a key role in topical route of application. These lipidic nanoparticles control the drug release profiles of incorporated bioactives [66,67]. Moreover, the small size ensures a close contact to the stratum corneum and can increase the amount of drug penetrating into skin. Hence, these carriers emerged as an important tool to supply the drug over a prolonged period of time and to reduce systemic absorption [68]. Epidermal targeting may successfully be exploited using SLN and NLC formulations [69,70], as well as for reducing the side effects especially during topical glucocorticoid treatment in conditions such as skin thinning and atrophy as they are associated with deeper layers of the skin, further systemic absorption can be eliminated [71].

Most of the studies based on SLNs relating to their properties as a topical drug delivery system have been conducted [62,25,18]. SLNs have shown to facilitate retention of the entrapped drug substance in the upper skin layers and to possess occlusive properties [72]. Aqueous SLN formulations were proposed for topical delivery of various glucocorticoids, for example, clobetasol propionate [73], or betamethasone valerate [74]. The occlusive character of the SLNs results from the small size and strong adhesive properties of the particles, which may ultimately lead to film formation on the skin and reduce the transepidermal water loss and possibly help to physically restore the barrier [75]. A recent study suggests that SLNs containing the corticosteroid betamethasone-17-valerate could efficiently be used for atopic dermatitis treatment. The researchers concluded that SLNs affect the drug substance penetration profile into and across the skin. Principally, the penetration profile of the drug into the skin was influenced by the type of lipids used in the SLN preparation and correlates to lipid polarity and drug substance solubility. As a result, SLNs can be used to facilitate the extent of drug accumulation conserve in the intact particulate structure. They may constitute dermal drug reserves especially in barrier-impaired skin and localized distinctively in the stratum corneum. But in intact skin, the reservoir effect was more pronounced and the drug partitioning into the different skin layers was found to be dependent on the lipid properties of the SLNs [18]. We have published previously the influence of various lipid cores on characteristics of SLNs designed for topical delivery of fluconazole for cutaneous candidiasis. The study supported that better antifungal activity in the case of compritol 888 ATO-based SLNs compared with stearic acid, monostearin and tristearin consisted SLNs, which could noticeably improve the dermal localization [62]. The previous studies demonstrated that SLN and NLC dispersion of ketoconazole and clotrimazole (antifungal drugs) were quite useful for skin targeting via topical route and notably offer localized effect [66,67]. Most of the studies could establish conclusively that SLNs and NLCs act as promising carriers for topical delivery. Recently, we have reported that NLCs have excellent ability as compared with SLNs, to increase drug accumulation in the various skin layers without any transdermal delivery by creation of a depot effect and as a result the maximal therapeutic antifungal fluconazole [25]. In one study, three psoralen derivatives were used for psoriasis treatments by encapsulating them in SLNs and NLCs. The results showed that enhanced permeation and controlled release of psoralen delivery were both achieved using the NLCs. Enhanced permeation can be helpful for improving the skin absorption of drugs, while sustained release is important for drugs with irritating effects at high concentrations, hence supplying the drugs over a prolonged period of time. This study provides supplementary evidence that NLCs have great potential for psoriasis therapies [76].

In one study, the modified lipid nanocarriers were formulated by modifying the lipid matrix so as to enhance the drug solubility in the lipid carrier by mixing solid lipid with lipophilic solubilizers (having very good solubility for the drug). The modified lipid nanocarriers contained the drug dissolved in the solubilizer nanopockets within the solid lipid particle matrix (i.e., drug/solubilizer/solid lipid/water). The tacrolimus-loaded system showed the enhanced encapsulation efficiency with the advantage of improved performance in terms of stability and skin localization. In the context of dermatopharmacokinetic parameters, the tacrolimus-loaded modified lipid nanocarriers presented the values of T_{max} and C_{max} to be significantly higher as compared with the reference, which indicated that tacrolimus could penetrate much more easily with this system than with ointment formulation. The area under the curve (AUC) values were less for reference formulation than modified lipid system, and relative bioavailability of this system was 2.2 times higher than the reference. The better transport of drug through the stratum corneum barrier could be correlated with better bioavailability and would lead to greater therapeutic effect at the site of action [26].

5.8 Polymeric nanoparticles

In the field of dermatology, increased attention has been given to polymeric nanoparticles to overcome the limitations associated with other lipid systems. The problems such as higher drug permeation, lower drug loading and phase stability issues are concerning factors and so their application for clinical use is restricted. Several non-toxic and biodegradable synthetic or semi-synthetic polymers, including polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone), chitosan, have shown promising results for topical drug delivery. The polymeric carriers have shown merits of controlled and sustained release via modification of polymer composition and reducing irritation associated with direct contact of drug with skin. PLGA-based nanoparticles may be useful in skin delivery as they propose a number of advantages including non-toxicity and biodegradability and entrapment of various therapeutic moieties [77]. The topical delivery of PLGA nanoparticles can be improved by modulating the particle surface by coating with chitosan. Chitosan is a cationic polysaccharide with many interesting biopharmaceutical properties and has been widely explored as a penetration enhancer in topical formulations [78]. Chitosan-modified PLGA nanoparticles might be able to improve the topical delivery in various aspects, such as incorporation of two drugs in inner and outer layers of the nanoparticles, increased stability of the macromolecules, reversal of zeta potential promoting skin adhesion and thus enhancing skin delivery and ability to conjugate with other molecules such as penetration enhancer through the free amino groups of chitosan. It was observed that in the case of polymeric nanoparticles, the drug permeation was higher due to gradual drug release from the nanoparticles on the skin surface but the intact nanoparticles were unable to permeate in deeper skin layers [79,80]. Others attempted to verify this aspect, but only a few of the researchers were able to show permeation of nanoparticles into the skin passively through the hair follicles, while in most cases, the nanoparticles were primarily restricted to the uppermost layers of the stratum corneum and unable to permeate the skin.

Despite the proposed benefits of topical polymeric nanoparticles, their utility is debatable to obtain prolonged skin retention and controlled release for the desired therapeutic effect. To successfully deliver a wide range of therapeutic agents, the correct system may be PLGA–chitosan bilayered nanoparticles with oleic acid into a proper gel matrix (Nanogel system) [81]. Nanogels are nano-sized networks of physically or chemically cross-linked polymeric particles. They may be useful for offering a uniform dispersion of the nano-carriers in the matrix and augment the contact time, which results in enhanced skin penetration of the bioactives [82]. A recent study investigated the skin-permeating nanogel system containing surface-modified polymeric bilayered nanoparticles along with a gelling agent entrapping two anti-inflammatory drugs, spantide II and ketoprofen. The findings support that nanogel has significant impact on the percutaneous delivery of drugs to the deeper skin layers and may be useful for the treatment of various skin inflammatory disorders. A similar approach could be extrapolated to treat other skin diseases such as fungal, bacterial, viral infections and skin cancers such as melanoma [77]. Abdel-Mottaleb *et al.*, 2011 [83], reported a comparative study between lipid nanocapsules (LNCs), SLNs, NLCs and polymeric nanoparticles for dermal delivery. They concluded that polymeric carriers showed fourfold greater accumulation in the skin compared with that of the LNCs and twice the accumulation of SLNs and NLCs. These findings support that the LNCs can be considered as a potential carrier with respect to SLNs and NLCs for the transdermal drug delivery while polymeric nanoparticles are more appropriate for localized drug delivery to the skin.

One of the recent efforts deals with the polymeric micelles, which have been explored as a drug carrier system in dermatotherapy. With their size, stability and capability to incorporate significant amounts of hydrophobic drugs in their core, these systems seem well suited for use with azole antifungals. In one recent study, novel amphiphilic methoxy-poly(ethylene glycol)-hexyl substituted polylactide (MPEG-hexPLA) block copolymer-based micelles incorporated clotrimazole, econazole nitrate and fluconazole. A noteworthy increase in the econazole nitrate in skin deposition was achieved using micelles. The study revealed their ability to improve cutaneous drug bioavailability and improved clinical efficacy *in vivo* [84]. The particle size of polymeric micelles is smaller (10 – 100 nm) as compared with other carriers, and it is a suitable approach for enhancing drug deposition into the skin. It was previously reported that the small size ensures a close contact to stratum corneum and greatly deposited in the viable epidermis well as dermis layer [68,85].

Dendrimers are a unique class of polymers and widely explored in drug delivery and imaging. They are usually 10 – 100 nm in diameter with multiple functional groups on their surface that makes them ideal carriers for targeted drug delivery. The pharmaceutical applications of dendrimers include nonsteroidal anti-inflammatory formulations, antimicrobial and antiviral drugs. The first investigational new drug application for a topical dendrimer-based drug named VivaGel (SPL7013 Gel) is a vaginal microbicide designed to prevent the transmission of sexually transmitted infections, including the human immunodeficiency virus and genital herpes and was formulated by Starpharma (Melbourne, Australia) [27].

5.9 Lipid–polymer hybrid system

Hybrid nanoparticles are polymeric nanoparticles enclosed by lipidic layers that merge the high biocompatible nature of lipids with its structural integrity afforded by polymeric nanoparticles. This system may be prepared by the modified emulsification-solvent-evaporation methods using lipid as surfactant. Generally, the biodegradable PLGA and phosphatidylcholine are used as the polymer and lipid models, respectively. They differ from polymeric nanoparticle with respect to their large size and higher drug-loading capacity [86].

However, all these properties make them attractive carriers in dermatologic therapy.

5.10 Miscellaneous system

Lipogels are based on fatty components and are obtained by gelling an oily phase with a lipophilic structure, using non-ionic surfactants. The type and concentration of the gelling agent can affect the structure on which the rheological characteristics of the preparation depend and consequently on the requirements of physical stability and consistency. Laithy and El-Shaboury 2002 studied fluconazole in a series of Cutina lipogels and a gel microemulsion using Jojoba oil as an oleogenous phase [87]. In general, they are opaque thermoreversible semisolids that are stable at room temperature for weeks [88]. In one study, *in vitro* pig skin permeation revealed that miconazole nitrate accumulated twice as much in the case of positively charged microemulsions than that from their negatively charged counterparts. Hence, the positively charged submicrometer emulsions might also bind to negatively charged sites of skin, confirming the potentiality of topically applied positively charged submicron emulsion [89] described in the paragraph below.

Microemulsions are clear, isotropic, thermodynamically stable dispersions of 2-immiscible liquids created by the presence of a suitable surfactant. These macroscopically monophasic systems possess a flexible interfacial film that is characterized by ultralow interfacial tension values. It was concluded that microemulsion as a potential formulation could enhance cutaneous drug delivery of both hydrophilic and lipophilic drugs compared with conventional vehicles [90]. Patel *et al.* [91] reported that ketoconazole, when used in microemulsion, was more efficiently penetrated into the skin as compared with saturated aqueous solution. The higher permeability rate may be due to the surfactants and the oily phase, which taken together act as penetration enhancers. Furthermore, the small particle size of the microemulsion makes it an excellent carrier for promoting *in vitro* skin permeation of ketoconazole. Some other studies for microemulsions were also reported by researchers including diclofenac sodium [92], itraconazole [93] and aceclofenac [94].

Nanoemulsions typically contain 20 – 500 nm large droplets, stabilized by surfactants. Basically, they are non-equilibrium structures and rely on energetic input to form, often from an emulsion. Nanoemulsion does not change on long term, for example, into a coalesced form. But shearing in the high-concentration range speeds up its physical deterioration. This may be questionable if a concentrated nanoemulsion is squeezed through a nano-porous membrane, such as skin. The topically used NB-00X products (nanoemulsion droplet based 200 nm based on NanoStat technology) were prepared for Herpes labialis caused by herpes simplex virus I.

Lecithin organogels are biocompatible having jelly-like phases, chiefly composed of hydrated phospholipids and appropriate organic liquid. Since they are thermodynamically stable and viscoelastic, they provide structural and functional benefits making them a system of keen interest to the pharmaceutical scientist. As they facilitate transport through topical route (for dermal or transdermal effect), several therapeutic agents have been formulated with it. Biphasic drug solubility, the desired drug partitioning, very low skin irritancy potential and the modification of skin barrier function by the organogel components are the factors that are responsible for the enhanced topical drug delivery. Lecithin organogels are prepared by spontaneous emulsification, and being thermodynamically stable, they possess prolonged shelf life. Muscle spasm as well as peripheral or neuropathic pain has been effectively treated by the topical application of digoxin containing Lecithin organogel formulation [95].

Hexasomes may be defined as reverse hexagonal phases comprised of hexagonally close-packed infinite water layers covered by surfactants monolayer, generally in submicrometer size range (200 nm). This carrier has the potential to be used as optional vehicle for drug delivery. The therapeutic moiety could be accumulated within the aqueous part or directly coupled to the lipid hydrophobic moieties oriented radially outward from the center of the water rods. Hence, these features make them suitable for improving the solubility of poorly water-soluble drugs and to transport therapeutic peptides and proteins by transdermal routes [96]. Cubosomes are nanoparticulate disperse system that may be prepared by the emulsification of cubic lipid phase in water. The size of cubosomes ranges from 10 to 500 nm in diameter and they seem like dots, square shaped, slightly spherical [97]. It is an efficient system for percutaneous delivery due to their high biocompatibility and bioadhesivity. In one study, it was concluded that this system represents an innovative approach to control the cutaneous absorption of indomethacin [98].

6. Mechanisms of topical drug delivery with nano-sized particulates

There are abundant studies that report that small size of particles allow close contact with superficial junctions of corneocyte and furrows between corneocyte which, in turn, may favor their accumulation for longer time allowing sustained drug release. As this concept is influential with liposomes, they are different in so far as they collapse, which is considered as compromising percutaneous penetration [99]. It was suggested that after vesicle application, ultrastructures of the intercellular lipids were changed showing that small hydrophilic head groups interact with human stratum corneum *in vitro* [100]. Kirjavainen *et al.* [37] revealed that vesicle composition may have a great effect, such as producing an enhancing effect (by skin pretreatment), while their lipidic part may penetrate deeply into the stratum corneum layer or may fuse and mix with skin lipids to loosen their structure. This effect was more pronounced in the case of liposomes containing dioleylphosphatidylethanolamine (DOPE) or lyso-phosphatidylcholine (lyso-PC). Researchers also explained another mechanism where the vesicles may adsorb on to the stratum corneum

surface with subsequent transfer of drug directly from vesicles to skin. The vesicles would be fused and mixed with the stratum corneum lipids with a resultant enhanced drug partitioning into the skin [101]. Foldvari *et al.* [102] showed the presence of integral liposomes in the dermis. They proposed that liposomes bearing the drug may be able to penetrate the epidermis. But this system was more superior to a conventional gel in the treatment of eczema but not for psoriasis. This may be due to the fact that vesicles can penetrate diseased skin with its ruptured stratum corneum (as in eczema) but cannot invade skin with hyperkeratosis, as in psoriasis [103].

Researchers explored basically two different mechanisms to identify a convincing explanation on deformable liposomes, which improve skin delivery of drugs. The first one suggests that invading vesicles enter the stratum corneum and carry vesicle-loaded drugs along into the skin. The other mechanism suggests that vesicles can act as penetration enhancers, whereby vesicle bilayers enter the stratum corneum and consequently adjust with the intercellular lipid lamellae with easier penetration of free drug into and across the stratum corneum [104]. In principle, the existence of edge activators in the vesicles might be the reason for vesicle deformability so that they could penetrate into intact skin with its dense stratum corneum lipid packing, which contain very small pores in comparison with the vesicle diameter. It appears that lesser vesicle size may negotiate superior drug deposition into deeper strata and penetration through skin, while large nano-aggregates may improve deposition only [105].

Several studies supported that ethosome vesicles may act as carrier systems; however, their mechanisms yet remain a matter of speculation. A synergistic mechanism was suggested between ethanol, vesicles and skin lipids: As stratum corneum lipid is densely packed and multilayered, ethanol can be interacted with lipid molecules, finally increasing the fluidity of the stratum corneum lipids with enhancing the membrane permeability. In addition, the ethosome itself may interact with the stratum corneum barrier and more easily penetrate into deeper layers of the skin. The drug release is quite possible in the deeper skin layers and its transdermal absorption could also be feasible with fusion of ethosomes with skin lipids and drug release at various points along the penetration pathway [51].

As in the case of PEV vesicles, we already have discussed in previous section that they have shown to possess the merits of liposome as carriers and penetration enhancer ability to adjust the order of stratum corneum packing thus promoting skin delivery [106]. While transethosome can encompass the advantages of both deformable liposomes and ethosomes that are suitable elastic carriers to deliver drugs to the dermis layer through stratum corneum barriers, it consists of high ethanol concentration and edge activator, which can enhance the skin permeation and deposition. Thus they appear to be a potential carrier for the dermal delivery of the drug [58].

In the subsequent section, we will consider the proposed mechanisms, illustrating this for lipidic nanoparticulate. SLNs and NLCs stay for a longer time at the site of application because of their pronounced adhesive character. The adhesion effect tends to increase with reducing particle size. Furthermore, the drug within the lipid matrix of the carrier system adheres to the carrier surface both facilitating contact to the outermost skin layers. In addition, a lipid film into the skin surface may facilitate dermal absorption because of an additional occlusive effect. Following the application of lipidic particles onto the skin surface, a structural change in particle structure may occur. Water evaporation results in a transition of the lipid matrix to a more highly ordered structure leading to drug expulsion, and final supersaturated solution must augment penetration into the tissue. Moreover, improved hydration, for the time being, opens the compact structure of the horny layer, and the permeability of the barrier increases. The surfactants used for SLN or NLC stabilization contribute to the penetration into human skin but only to a limited extent [101].

Polymeric nanoparticles do not penetrate into stratum corneum while follicular pathway has been reported as the primary penetration route for nanoparticles. Hence, they accumulate preferentially in skin furrows and hair follicles and create high local concentrations of loaded drugs that can subsequently diffuse into the viable layers of the skin. It is believed that it is a size-dependent phenomenon where smaller nanoparticles show highest penetration. The smaller size particles have a larger contact area with the skin surface. In addition, their viscosity also supports non-invasive occlusive film formation resulting in a depot at the skin surface. Hence, they may target the drug to the follicles followed by their accumulation, depot formation, and subsequent release of a drug may be used to provide more effective, sustained release. The size, composition and surface charge may have great influence on improvement of drug delivery to the deeper skin layers [84,107].

7. Conclusion

Skin disorders symbolize a primary category of dermatologic illnesses that directly account for substantial health and economic burden annually. The drawback linked with most of the marketed topical therapy is that many of them are associated with side effects of systemic circulation origin and will affect whole body rather than just the skin. Therefore, there is a need for an easy and non-invasive therapeutic approach and developing the more target oriented topical treatments. Ongoing research has provided novel topically based nano-aggregates for effective therapy. However, the numerous colloidal systems have been projected to improve topical drug delivery, but only the most energetic systems really could overcome the skin barrier and have the ability for customized pharmacokinetics. These nano-vehicles mainly increase or decrease the flux, adapt the drug depot location and size, and even selectively permeabilize the stratum corneum. The mechanisms of interaction of nano-aggregates with skin structures and their microenvironment, that is, furrows, hair

follicles, eccrine ducts, and so on, are absolutely significant for the enhancement of cutaneous drug delivery. The topically used nanomedicines offer promising opportunities in dermal delivery, and recent advances and modifications appear to have generated increased therapeutic potential. Amelioration and variation in their composition and structure result in vesicles with required tailored properties. Hence, nanosystems possess a promising, adjustable platform for the biocompatible, safe and effective topical delivery of therapeutics, since they did not induce any short-term cytotoxicity or morphological changes in stratum corneum.

8. Expert opinion

Skin diseases caused by numerous infectious pathogens or some inflammatory conditions impose significant challenges and are emerging targets. Indeed, these problems depend on the type of pathogens or other inflammatory skin conditions involved, the integrity of skin layers and the structures affected, moreover so the underlying medical condition of the patient. Intensive research suggests that the effective treatment of skin disorders need a timely identification, estimation and management of the disease and adoptability of efficient treatment.

To date, the topical treatment of skin diseases appears the most favorable choice. Yet the stratum corneum counteracts the penetration of bioactives into viable skin, and only a few percent of the applied drug is absorbed. Marketed topical preparations are associated with side effects relating drug absorption to systemic circulation and will thus affect more than just the skin. To achieve the localized effect, an easy and non-invasive option such as topical therapy is most desirable and ideal for this purpose. The recent innovations mainly focused on exploring the novel carriers such as vesicles, lipidic particles and particulate carriers. These nano-sized particles are of particular interest for topical treatment of skin diseases to increase skin penetration of drugs and to reduce side effects.

It has already been explored that skin lipids may impose discernible influence on the potential barrier of skin, since lipidic nano-aggregates may permit the lipid exchange with skin surface and emerged as a suitable option. Indeed, the nature of the lipid systems and the mode of drug interaction with the lipid matrix proved to be relevant as already have been discussed. The lipidic part of vesicles might deeply penetrate into the stratum corneum or may fuse and mix with skin lipids to loosen their structure and subsequent release of drug from vesicles to skin. Research suggests that vesicles can penetrate diseased skin with its ruptured stratum corneum but cannot invade intact skin in a more pronounced way. After application of lipidic particles on the skin surface, structural changes in the structure of the particle may be induced. Water evaporation results in a transition of the lipid matrix to a more highly ordered structure leading to favored drug release. The localized drug-supersaturated *in vivo* reserve must augment the penetration into the tissue. On the other hand, the polymeric particles do not penetrate to the stratum corneum; however, the follicular pathway has been the main penetration route for nanoparticles. Hence, they can accumulate in skin furrows and hair follicles and create high local concentrations of loaded drugs that can further diffuse to the viable layers of the skin.

Nanotechnology promises for the minuscule effects, but most of these visions are hypothetical at this point. Currently, the biggest pitfalls of the molecular manufacturing pattern have not yet been explored, hence their benefits/drawbacks will remain the dominant focus of researchers. Various therapeutic products based on ultra-adaptable, self-regulating, nano-sized particles are marketed and some have reached the clinical level. The first topical liposomal product, a 'liposome gel' of econazole (antifungal drug) (Pevaryl®; Cilag AC), has been approved in Switzerland, while 'VivaGel' is an example of a dendrimer-based product and was formulated by Starpharma (Melbourne, Australia). Another one is the topically used NB-00X product (nanoemulsion droplet based 200 nm based on NanoStat technology), which has progressed for Herpes labialis caused by herpes simplex virus I. IDEA AG, the biopharmaceutical company, announced the start of developing targeted therapeutics based on the novel Transfersome carriers (topically applied dosages of IDEA-033) currently in Phase III trials in Europe for the treatment of signs and symptoms related to osteoarthritis of the knee. Nevertheless, many questions arise, which remain to be unexplored and addressed. In the context with safety, the environmental effects and the potential effects on the health are major issue for manufacturing of these particles. Finally, it is hoped that the application of nanotherapeutics is limitless, but the development of safety guidelines by the manufacturers should strongly be considered.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Sigmundsdottir H. Improving topical treatments for skin Diseases. Trends Pharmacol Sci 2010;31:239-45
2. Fleischer AB Jr, Feldman SR, Rapp SR. The magnitude of skin disease in the United States. Dermatol Clin 2000;18:xv-xxi
3. Dawson AL, Robert PD, Dirk ME. Infectious skin diseases: a review and needs assessment. Dermatol Clin 2012;30:141-51
4. Roberts MS, Walters KA. Human skin morphology and dermal absorption. In: Roberts MS, Walters KA, editors. Dermal Absorption and Toxicity Assessment. Informa Healthcare, New York; 2008. p. 1-15
5. Bissett DL. Anatomy and biochemistry of the skin. In: Kydonieus F, Berner B, editors. Transdermal Delivery of Drugs. Volume 1 CRC Press, Inc., Boca Raton; 1987. p. 29-42
6. Erdogan S. Liposomal nanocarriers for tumor imaging. J Biomed Nanotechnol 2009;5:141-50
7. Bouwstra JA, Honeywell-Nguyen PL. Skin structure and mode of action of vesicles. Adv Drug Deliv Rev 2002;54:41-55
8. Prow TW, Grice JE, Lin LL, et al. Nanoparticles and microparticles for skin drug delivery. Adv Drug Deliv Rev 2011;63:470-91
9. Merwe D, van der, Brooks JD, Gehring R, et al. A physiologically based pharmacokinetic model of organophosphate dermal absorption. Toxicol Sci 2006;89:188-204
10. Langbein L, Grund C, Kuhn C, et al. Tight junctions and compositionally related junctional structures in mammalian stratified epithelia and cell cultures derived there from. Eur J Cell Biol 2002;81:419-35
11. Schaefer H, Redelmeier TE. Skin Barrier: Principles of Percutaneous Absorption. Karger, Basel; 1996
12. Barry BW. Dermatological Formulations: Percutaneous Absorption. Marcel Dekker, New York; 1983
13. Suzanne MB, Zhi D, Elly R, et al. Advances in transcutaneous vaccine delivery: do all ways lead to Rome? J Control Release 2010;148:266-82
14. Robert EM, Kalia YN. New developments in topical antifungal therapy. Am J Drug Deliv 2006;4:231-47
15. Gabard B, Elsner P, Surber C, Treffel P. Dermatopharmacology of Topical Preparations: a Product-Development Oriented Approach. Springer-Verlag, Berlin; 2000
16. Dancik Y, Jepps OG, Roberts MS. Beyond stratum corneum. In: Roberts MS, Walters KA, editors. Dermal Absorption and Toxicity Assessment. Informa Healthcare, Inc., New York; 2008. p. 209-50
17. Garcia OP, Hansen SH, Shah VP, et al. Impact of adult atopic dermatitis on topical drug penetration: assessment by cutaneous microdialysis and tape stripping. Acta Derm Venereol 2009;89:33-8
18. Jensen LB, Petersson K, Nielsen HM. In vitro penetration properties of solid lipid nanoparticles in intact and barrier-impaired skin. Eur J Pharm Biopharm 2011;79:68-75
19. Nacht S, Katz M. The microsponge: A novel topical programmable delivery system. In: Osborne DW, Amman AH, editors. Topical Drug Delivery Formulations. Marcel Dekker Basel, New York; 1990. p. 299-325
20. Pradhan SK. Microsponges as the versatile tool for drug delivery system. Int J Res Pharm Chem 2011;1:243-58
21. Barry BW. Penetration enhancers. In: Shroot B, Schafer H, editors. Skin Pharmacokinetics. Karger, Basel; l987. p. 121-7
22. Schmid MH, Korting HC. Therapeutic progress with topical liposome drugs for skin disease. Adv Drug Deliv Rev 1996;18:335-42
23. Teichmann A, Heuschkel S, Jacobi U, et al. Comparison of stratum corneum penetration and localization of a lipophilic model drug applied in an o/w microemulsion and an amphiphilic cream. Eur J Pharm Biopharm 2007;66:159-64
24. Castro GA, Coelho ALLR, Oliveira CA, et al. Formation of ion pairing as an alternative to improve encapsulation and stability and to reduce skin irritation of retinoic acid loaded in solid lipid nanoparticles. Int J Pharm 2009;381:77-83
25. Gupta M, Vyas SP. Development, characterization and in vivo assessment of effective lipidic nanoparticles for dermal delivery of fluconazole against cutaneous candidiasis. Chem Phys Lipids 2012. doi:10.1016/j.chemphyslip.2012.01.006

•• **This study reported that NLCs provide a good skin-targeting effect and may be a promising carrier for topical delivery of fluconazole, offering the sustained release and maintaining the localized effect, resulting in an effective treatment of a life-threatening cutaneous fungal infection.**

26. Pople PV, Singh KK. Development and evaluation of colloidal modified nanolipid carrier: application to topical delivery of tacrolimus. Eur J Pharm Biopharm 2011;79:82-94
27. Bawarski WE, Chidlowsky E, Bharali DJ, Mousa SA. Emerging nanopharmaceuticals. Nanomed Nanotechnol Biol Med 2008;4:273-82

• **This review will provide a brief discussion of the major nanopharmaceutical formulations as well as the impact of nanotechnology into the future.**

28. Zhang L, Pornpattananangkul D, Hu CMJ, Huang CM. Development of nanoparticles for antimicrobial drug delivery. Curr Med Chem 2010;17:585-94
29. Katahira N, Murakami T, Kugai S, et al. Enhancement of topical delivery of a lipophilic drug from charged multilamellar liposomes. J Drug Target 1999;6:405-14
30. Martin P, Youenang P, Daniel K, Simon B. Positively and negatively charged submicron emulsions for enhanced topical delivery of antifungal drugs. J Control Release 1999;58:177-87
31. Vanniasinghe AS, Bender V, Manolios N. The potential of liposomal drug delivery for the treatment of inflammatory arthritis. Semin Arthritis Rheum 2009;39:182-96

32. Tamilvanan S, Venkateshan N, Ludwig A. The potential of lipid-and polymer-based drug delivery carriers for eradicating biofilm consortia on device-related nosocomial infections. J Control Release 2008;128:2-22

33. Schreier H, Bouwstra J. Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. J Control Release 1994;30:l-15

34. Gupta M, Goyal AK, Paliwal SR, et al. Development and characterization of effective topical liposomal system for localized treatment of cutaneous candidiasis. J Liposome Res 2010;20:341-50

35. Mezei M, Gulasekharam V. Liposomes – a selective drug delivery system for the topical route of administration: lotion dosage form. Life Sci 1980;26:1473-7

36. Trapasso E, Cosco D, Celia C, et al. Retinoids: new use by innovative drug-delivery systems. Expert Opin Drug Deliv 2009;5:465-83

37. Kirjavainen M, Urtti A, Jaaskelainen I, et al. Interaction of liposomes with human skin in vitro – the influence of lipid composition and structure. Biochim Biophys Acta 1996;1304:179-89

38. El Maghraby GM, Williams AC, Barry BW. Can drug bearing liposomes penetrate intact skin? J Pharm Pharmacol 2006;58:415-29

39. Skalko N, Cajkovac M, Jalsenjak I. Liposomes with clindamycin hydrochloride in therapy of acne vulgaris. Int J Pharm 1992;85:97-101

40. Tabbakhian M, Tavakoli N, Jaafari MR, Daneshamouz S. Enhancement of follicular delivery of finasteride by liposomes and niosomes: in vitro permeation and in vivo deposition studies using hamster flank and ear models. Int J Pharm 2006;323:1-10

41. Montenegro L, Panico AM, Ventimiglia A, Bonina FP. In vitro retinoic acid release and skin permeation from different liposome formulations. Int J Pharm 1996;133:89-96

42. Sinico C, Manconi M, Peppi M, et al. Liposomes as carriers for dermal delivery of tretinoin: in vitro evaluation of drug permeation and vesicle–skin interaction. J Control Release 2005;103:123-36

43. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration, and transdermal drug delivery. Crit Rev Ther Drug Carrier Syst 1996;13:257-388

44. Honeywell-Nguyen PL, Bouwstra JA. Vesicles as a tool for transdermal and dermal delivery. Drug Discov Today Technol 2005;2:67-74

45. Trotta M, Peira E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. Int J Pharm 2004;270:119-25

46. Boinpally RR, Zhou SL, Poondru S, et al. Lecithin vesicles for topical delivery of diclofenac. Eur J Pharm Biopharm 2003;56:389-92

47. Cevc G, Blume G. New, highly efficient formulation of diclofenac for the topical, transdermal administration in ultradeformable drug carriers, transfersomes. Biochim Biophys Acta 2001;1514:191-205

48. Elsayed MAA, Abdallah OY, Naggar VF, Khalafallah NM. Lipid vesicles for skin delivery of drugs: reviewing three decades of research. Int J Pharm 2007;332:1-16

49. El Maghraby GM, Williams AC, Barry BW. Skin delivery of 5-fluorouracil from ultradeformable and standard liposomes in-vitro. J Pharm Pharmacol 2001a;53:1069-77

50. Trotta M, Peira E, Debernardi F, Gallarate M. Elastic liposomes for skin delivery of dipotassium glycyrrhizinate. Int J Pharm 2002;241:319-27

51. Touitou E, Dayan N, Bergelson L, et al. Ethosomes – novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. J Control Release 2000;65:403-18

52. Liu J, Hu G. Advances in studies of phospholipids as carriers in skin topical application. J Nanjing Med Uni 2007;21:349-53

53. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 2001;14:101-14

54. Godin B, Touitou E. Mechanism of bacitracin permeation enhancement through the skin and cellular membranes from an ethosomal carrier. J Control Release 2004;94:365-79

55. Paolino D, Lucania G, Mardente D, et al. Ethosomes for skin delivery of ammonium glycyrrhizinate: in vitro percutaneous permeation through human skin and in vivo anti-inflammatory activity on human volunteers. J Control Release 2005;106:99-110

56. Manconi M, Sinico C, Caddeo C, et al. Penetration enhancer containing vesicles as carriers for dermal delivery of tretinoin. Int J Pharm 2011;412:37-46

• **Penetration enhancer containing vesicles seem to be the most appropriate formulations for tretinoin dermal delivery. This investigation reported that drug deposition and permeation in the skin was found to be affected by PEV composition.**

57. Mura S, Manconi M, Sinico C, et al. Transcutol containing vesicles for topical delivery of minoxidil. J Drug Target 2011;19:189-96

58. Song CK, Balakrishnan P, Shim C, et al. A novel vesicular carrier, transethosome, for enhanced skin delivery of voriconazole: characterization and in vitro/in vivo evaluation. Colloids Surf B Biointerfaces 2012;1:299-304

•• **The transethosomes enhanced both *in vitro* and *in vivo* skin deposition of voriconazole in the dermis/epidermis region compared with other one. Therefore, this novel carrier transethosomes could serve as an effective dermal delivery for voriconazole.**

59. Bird DK, Schneider AL, Watkinson AC, et al. Navigating transdermal diffusion with multiphoton fluorescence lifetime imaging. J Microsc 2008;230:61-9

60. Barbara G, Van GM, Sien B, Stefaan C. Flexible nanosomes (SECosomes) enable efficient siRNA delivery in cultured primary skin cells and in the viable epidermis of ex vivo human skin. Adv Funct Mater 2010;20:4077-90

61. Shah AK, Date AA, Joshi MD, Patraval VB. Solid lipid nanoparticles (SLN) of tretinoin: potential in topical delivery. Int J Pharm 2007;345:163-71

62. Gupta M, Tiwari S, Vyas SP. Influence of various lipid core on characteristics of SLNs designed for topical delivery of fluconazole against cutaneous candidiasis. Pharm Dev Technol 2011; doi:10.3109/10837450.2011.598161

63. Mandawgade SD, Patravale VB. Development of SLNs from natural

lipids: application to topical delivery of tretinoin. Int J Pharm 2008;363:132-8

64. Muller RH, Mader K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery-a review of the state of the art. Eur J Pharm Biopharm 2000;50:161-77

65. Pardeike J, Hommoss A, Muller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. Int J Pharm 2009;366:170-84

66. Souto EB, Wissing SA, Barbosa CM, Muller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm 2004;278:71-7

67. Souto EB, Muller RH. SLN and NLC for topical delivery of ketoconazole. J Microencapsul 2005;22:501-10

68. Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. Int J Pharm 2008;346:124-32

69. Teeranachaideekul V, Boonme P, Souto EB, et al. Influence of oil content on physicochemical properties and skin distribution of nile red-loaded NLC. J Control Release 2008;128:134-41

70. Stecova J, Mehnert W, Blaschke T, et al. Cyproterone acetate loading to lipid nanoparticles for topical acne treatment: particle characterisation and skin uptake. Pharm Res 2007;24:991-1000

71. Wiedersberg S, Leopold CS, Guy RH. Bioavailability and bioequivalence of topical glucocorticoids. Eur J Pharm Biopharm 2008;68:453-66

72. Santos MC, Mehnert W, Schaller M, et al. Drug targeting by solid lipid nanoparticles for dermal use. J Drug Target 2002;10:489-95

73. Hu FQ, Jiang SP, Du YZ, et al. Preparation and characteristics of monostearin nanostructured lipid carriers. Int J Pharm 2006;314:83-9

74. Sivaramakrishnan R, Nakamura C, Mehnert W, et al. Glucocorticoid entrapment into lipid carriers characterization by parelectric spectroscopy and influence on dermal uptake. J Control Release 2004;97:493-502

75. Wissing S, Lippacher A, Muller A. Investigations on the occlusive properties of solid lipid nanoparticles (SLN). J Cosmet Sci 2001;52:313-24

76. Fang JY, Fang C, Liu C-H, Su Y-H. Lipid nanoparticles as vehicles for topical psoralen delivery: solid lipid nanoparticles (SLN) versus nanostructured lipid carriers (NLC). Eur J Pharm Biopharm 2008;70:633-40

• **The study indicated that the NLCs can potentially be exploited as carriers with improved drug permeation for psoriasis therapies.**

77. Shah PP, Desai PR, Patel AR, Singh MS. Skin permeating nanogel for the cutaneous co-delivery of two anti-inflammatory drugs. Biomaterials 2012;33:1607-17

78. Senyigit T, Sonvico F, Barbieri S, et al. Lecithin/Chitosan nanoparticles of clobetasol-17-propionate capable of accumulation in pig skin. J Control Release 2010;142:368-73

79. Alvarez-Roman R, Naik A, Kalia YN, et al. Enhancement of topical delivery from biodegradable nanoparticles. Pharm Res 2004;21:1818-25

80. Luengo J, Weiss B, Schneider M, et al. Influence of nanoencapsulation on human skin transport of flufenamic acid. Skin Pharmacol Physiol 2006;19:190-7

81. Samah NA, Williams N, Heard CM. Nanogel particulates located within diffusion cell receptor phases following topical application demonstrates uptake into and migration across skin. Int J Pharm 2010;401:72-8

82. Batheja P, Sheihet L, Kohn J, et al. Topical drug delivery by a polymeric nanosphere gel: formulation optimization and in vitro and in vivo skin distribution studies. J Control Release 2011;149:159-67

83. Abdel-Mottaleb MMA, Neumann D, Lamprecht A. Lipid nanocapsules for dermal application: a comparative study of lipid-based versus polymer-based nanocarriers. Eur J Pharm Biopharm 2011;79:36-42

•• **This investigation presented that the lipid nanocapsules can be considered as efficient as SLNs and NLCs for the transdermal drug delivery while polymeric nanoparticles are more suitable for localized drug delivery to the skin.**

84. Bachhav YG, Mondon K, Kalia YN, et al. Novel micelle formulations to increase cutaneous bioavailability of azole antifungals. J Control Release 2011;153:126-32

85. Verma DD, Verma S, Blume G, Fahr A. Particle size of liposomes influences dermal delivery of substances into skin. Int J Pharm 2003;258:141-51

86. Cheow WS, Hadinoto K. Factors affecting drug encapsulation and stability of lipid–polymer hybrid nanoparticles. Colloids Surf B Biointerfaces 2011;85:214-20

87. El laithy HM, El-Shaboury KMF. The development of cutina lipogels and gel microemulsion for topical administration of fluconazole. AAPS PharmSciTech 2002;3:1-9

88. Murdan S, Gregoriadis G, Florence AT. Novel sorbitan monostearate organogels. J Pharm Sci 1999;88:608-14

89. Salerno C, Carlucci AM, Bregni C. Study of in vitro drug release and percutaneous absorption of fluconazole from topical dosage forms. AAPS PharmSciTech 2010;11:986-93

90. Peira E, Carlotti ME, Trotta C, et al. Positively charged microemulsions for topical application. Int J Pharm 2008;346:119-23

• **This study suggests that positively charged microemulsions could be used to optimize drug targeting without a concomitant increase in systemic absorption.**

91. Patel MR, Patel RB, Parikh JR, et al. Investigating the effect of vehicle on in vitro skin permeation of ketoconazole applied in O/W microemulsions. Acta Pharmaceutica Sciencia 2010;52:65-77

92. Dima S, Popescu M. Topical delivery of diclofenac using microemulsion systems. Roumanian Biotech Lett 2008;13:49-55

93. Lee EA, Balakrishnan P, Song CK, et al. Microemulsion-based hydrogel formulation of itraconazole for topical delivery. J Pharm Invest 2010;40:305-11

94. Shah RR, Magdum CS, Patil SS, Niakwade NS. Preparation and evaluation of aceclofenac topical microemulsion. J Pharm Res 2010;9:5-11

95. Charles L, Matthew D. Cardiac glycosides for treating muscle pain and spasm. US20030229029; 2003

96. Hirlekar R, Jain S, Patel M, et al. Hexosomes: a novel drug delivery system. Curr Drug Deliv 2010;7:28-35

• **This report concluded that special properties of hexosomes are used to improve solubility of poorly water-soluble drugs and to transport therapeutic moiety by transdermal route.**

97. Thadanki M, Srivalli P, Prabha K. Overview of cubosomes: a nano particle. Int J Res Pharm Chem 2011;1:535-41

98. Elisabetta E, Carmelo P, Markus D, Lydia P. Production and characterization of cubosomes: a new tool for percutaneous administration of lipophilic drugs. Proc. 5th world meetings. Pharm Biopharm Pharm Technol 2006;1-2

99. Cevc G. Lipid vesicles and other colloids as drug carriers on the skin. Adv Drug Deliv Rev 2004;56:675-711

100. Hofland HEJ, Bouwstra JA, Bodde HE, et al. Interaction between liposomes and human stratum corneum in vitro: freeze fracture electron microscopical visualization and small angle X-ray scattering studies. Br J Dermatol 1995;132:853-66

101. Schaller M, Korting HC. Interaction of liposomes with human skin: the role of the stratum corneum. Adv Drug Deliv Rev 1996;18:303-9

102. Foldvari M, Gesztes A, Mezei M. Dermal drug delivery by liposome encapsulation: clinical and electron microscopic studies. J Microencapsul 1990;7:479-89

103. Korting HC, Zeinicke H, Schafer KM, Falco OB. Liposome encapsulation improves efficacy of betamethasone dipropionate in atopic eczema but not in psoriasis vulgaris. Eur J Clin Pharmacol 1990;39:349-51

104. Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Deformable liposomes and ethosomes as carriers for skin delivery of ketotifen. Pharmazie 2007;62:133-7

105. Valenta C, Janisch M. Permeation of cyproterone acetate through pig skin from different vehicles with phospholipids. Int J Pharm 2003;258:133-9

106. Mura S, Manconi M, Sinico C, et al. Penetration enhancer-containing vesicles (PEVs) as carriers for cutaneous delivery of minoxidil. Int J Pharm 2009;380:72-9

107. Vogt A, Combadiere B, Hadam S, et al. 40 nm, but not 750 or 1,500 nm, nanoparticles enter epidermal CD1a+ cells after transcutaneous application on human skin. J Invest Dermatol 2006;126:1316-22

108. Manconi M, Caddeo C, Sinico C, et al. Ex vivo skin delivery of diclofenac by transcutol containing liposomes and suggested mechanism of vesicle–skin interaction. Eur J Pharm Biopharm 2011;78:27-35

• **This work shows the superior ability of the PEVs to enhance *ex vivo* drug transport of both hydrophilic and lipophilic diclofenac forms.**

109. Verma P, Pathak K. Nanosized ethanolic vesicles loaded with econazole nitrate for the treatment of deep fungal infections through topical gel formulation. Nanomed Nanotechnol Biol Med 2011. doi:10.1016/j.nano.2011.07.004

• **The results suggest that because of the controlled drug release, better antifungal activity and good storage stability, econazole-loaded ethosomal gel has tremendous potential to serve as a topical delivery system.**

110. Bhalaria MK, Naik S, Misra AN. Ethosomes a novel delivery system for antifungal drug in the treatment of topical fungal diseases. Indian J Exp Biol 2009;47:368-75

111. El Zaafarany GM, Awad GAS, Holayel SM, Mortada ND. Role of edge activators and surface charge in developing ultradeformable vesicles with enhanced skin delivery. Int J Pharm 2010;397:164-72

112. Kang MJ, Kang MJ, Eum JY, et al. Pep-1 peptide-conjugated elastic liposomal formulation of taxifolin glycoside for the treatment of atopic dermatitis in NC/Nga mice. Int J Pharm 2010;402:198-204

113. Higa Leticia H, Priscila S, Ana PP, et al. Ultradeformable archaeosomes as new topical adjuvants. Nanomed Nanotechnol Biol Med 2012. doi.org/10.1016/j.nano.2012.02.008

114. Cirri M, Bragagni M, Mennini N, Mura P. Development of a new delivery system consisting in ''drug – in cyclodextrin – in nanostructured lipid carriers'' for ketoprofen topical delivery. Eur J Pharm Biopharm 2012;80:46-53

115. Pople PV, Singh KK. Targeting tacrolimus to deeper layers of skin with improved safety for treatment of atopic dermatitis. Int J Pharm 2010;398:165-78

116. Garg A, Singh S. Enhancement in antifungal activity of eugenol in immunosuppressed rats through lipid nanocarriers. Colloids Surf B Biointerfaces 2011;87:280-8

117. Mitri K, Shegokar R, Gohla S, et al. Lipid nanocarriers for dermal delivery of lutein: preparation, characterization, stability and performance. Int J Pharm 2011;414:267-75

118. Yordanov G. Influence of the preparation method on the physicochemical properties of econazole-loaded poly (butyl cyanoacrylate) colloidal nanoparticles. Colloids Surf A Physicochem Eng Aspects 2012. doi.org/10.1016/j.colsurfa.2011.12.060

119. Shah PP, Desai PR, Singh M. Effect of oleic acid modified polymeric bilayered nanoparticles on percutaneous delivery of spantide II and ketoprofen. J Control Rel 2012;158:336-45

120. Ourique AF, Melero A, Bona da Silva C, et al. Improved photostability and reduced skin permeation of tretinoin: development of a semisolid nanomedicines. Eur J Pharm Biopharm 2011;79:95-101

121. Filipowicz A, Wołowiec S. Solubility and in vitro transdermal diffusion of riboflavin assisted by PAMAM Dendrimers. Int J Pharm 2011;408:152-6

122. Ali J, Akhtar N, Sultana Y, et al. Antipsoriatic microemulsion gel formulations for topical drug delivery of babchi oil (Psoralea corylifolia). Methods Find Exp Clin Pharmacol 2008;30:277-85

123. Modi JD, Patel JK. Nanoemulsion-based gel formulation of aceclofenac for topical delivery. Int J Pharm Pharm Sci Res 2011;1:6-12

124. Michael H, Manuela M-G, Barron Annelise E, et al. Sustained prolonged topical delivery of bioactive

human insulin for potential treatment of cutaneous wounds. Int J Pharm 2010;398:146-54

125. Baspinar Y, Borchert H. Penetration and release studies of positively and negatively charged nanoemulsions – is there a benefit of the positive charge? Int J Pharm 2012. doi.org/10.1016/j.ijpharm.2012.03.040

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