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Review Article

# TOPICAL AND SYSTEMIC DERMAL CARRIERS FOR PSORIASIS

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**ABSTRACT**

Psoriasis is a non-infectious, dry, inflammatory (autoimmune) skin disorder. Treatment approaches include phototherapy, topical, oral and other systemic drug delivery. However, owing to the side effects and incomplete cure accompanying the oral administration as well as phototherapy, the topical route seemed to be more satisfactory for the medical team. Dermal treatment ensuring percutaneous penetration is now highly recommended in topical indications for psoriatic patients, which can be achieved using pharmaceutical carriers. Several carrier systems loaded with antipsoriatic drugs have demonstrated promising results, with some of them strictly being confined to the skin and others allowing for systemic involvement also. The evolution in this area will present a more useful and safer therapy by minimizing the drugs' degradation and loss, and increasing their bioavailability and effectiveness. Since patients require at least three topical applications for almost a 1-year period to gain health benefit, a reduction in the cost of the treatment will be of real value. A distinction of these carriers is made in the current review, to allow the choice of the most suitable pharmaceutical carrier for psoriatic patients requiring either local and/or systemic involvement.

**Keywords**: Skin, Topical, Novel carriers, Psoriasis



## INTRODUCTION

The human skin consists of the epidermis, dermis, subcutaneous tissue and stratum corneum. The epidermis consists of 60 % phospholipids and 40 % ceramides, with a cellular structure represented by keratinocytes, antigen-presenting Langerhans cells, and pigment-producing melanocytes. A basement membrane containing extracellular proteins separates the epidermis from the dermis [1]. The vascular supply to the skin is provided by the dermis while the stratum corneum consists mainly of non-viable cells [2].

Several diseases are known to affect the skin, in which psoriasis is one of the most common. The name of the psoriasis disease is derived from the Greek word "psora" meaning "itch" [3]. It is a non-infectious, dry, inflammatory skin (autoimmune) disorder, caused by many environmental factors such as trauma, drugs, infection, alcohol, smoking and stress or is presented in association with other diseases such as Crohn's disease or HIV infection. The exact accurate origin of psoriasis remains unknown [4]. Psoriasis occurs when the immune system considers the skin cells as a pathogen and begins to send faulty signals *via* signaling molecules such as cytokines, chemokines and growth factors [3-6]. Pathogenic events include rapid multiplication of epidermal cells associated with keratinocyte hyperproliferation with abnormal cohesiveness and thickening of the stratum corneum, about 10times greater than normal, accompanied with an increase in transepidermal water loss leading to the formation of the red and white well known psoriatic plaques [5, 7]. Subsequently, activated T-cells are accumulated in the dermis and epidermis which are responsible for relapsing and remitting scaling, and in certain cases may lead to peeling off and exfoliation [8, 9].

The disease is considered mild if it affects less than 3% of the body, moderate if affecting 3-10 % of the body, and severe if more. Topical treatment is the first option for mild and moderate cases while phototherapy and systemic agents are preserved for topically-irresponsive patients [10]. Hence, dermal treatment ensuring percutaneous penetration would be highly recommended for psoriatic patients [11].

Owing to the presence of the stratum corneum; the skin natural barrier protecting it from potentially harmful environmental agents [12], the skin inherently shows limited drug permeation *via* the dermal/transdermal routes, preventing them from being delivered to target sites in optimum therapeutic amounts [13]. Stratum corneum is described by having brick-mortar arrangement, formed by its lipid matrix in which approximately 15 layers of enucleated dead cells (corneocytes) (brick) are embedded, surrounded by lipid lamellae (mortar) [14, 15]. "A domain mosaic model", is another suggestion for stratum corneum organization where its lipid layers form a highly lipophilic, water impermeable barrier presented in a gel like or crystalline form. The lipid matrix consisting of ceramides, free fatty acids and cholesterol, inhibits the loss of moisture from the skin to the outside, maintaining the homeostasis of the skin [12, 16].

Conventional topical delivery systems for treatment of psoriasis such as creams and ointments suffer from many disadvantages, such as poor percutaneous absorption and patient's discomfort due to greasiness and stickiness [9, 15, 17]. Lately, pharmaceutical carriers have been shown to provide a more useful antipsoriatic therapy, minimizing drug's loss and increasing both patient compliance and drug bioavailability. Safety will be another benefit for these carriers concentrating the fraction of drug at targeted tissues, while diminishing toxic side effects [4, 13, 18]. Besides overcoming physicochemical limitations of drugs such as poor solubility and short half-lives, these pharmaceutical carrier systems act as penetration enhancers across the stratum corneum or may serve as depot for prolonged release of dermally active molecules, possibly, due to their nanometer range. They also can act as rate limiting membrane barriers for systemic absorption [17, 19].

Based on the mode of action of pharmaceutical carriers of antipsoriatic drugs, categorization is made in the current review, based on whether the carrier would function topically or transdermally, achieving local or systemic actions respectively. Furthermore, since almost 10% of patients require at least three topical therapy switches over a 1-year period to gain health benefit, the identification of formulation penetrability will be an aid for medical needs in psoriasis treatment.

### Locally acting pharmaceutical carriers

### Vesicular systems

### Liposomes and niosomes

Liposomes are biodegradable, highly biocompatible spherical vesicles, composed of an internal aqueous core, suitable for loading hydrophilic drugs, surrounded by one or more natural or synthetic phospholipid layers arranged in a bilayer configuration enabling

hydrophobic active encapsulation [5,12]. Niosomes are non-ionic surfactant vesicles prepared by hydration of synthetic nonionic surfactants with or without cholesterol and other related lipids [20]. Niosomes are easier and cheaper to prepare than liposomes and are highly resistant to oxidation [4].

Liposomes represent the first generation of vesicular carriersfor topical drug delivery. Both liposomes and niosomes have the ability to concentrate the entrapped drug in the skin, while reducing its presence in other unwanted tissues, thus, minimizing the loss of entrapped drug and increasing its bioavailability and efficacy. They provide therapeutic activity in a controlled manner (reservoir) for a prolonged period of time. They also protect active entities from degradation sparing the treatment costs [21].

Liposomes owe their topical penetration ability to their affinity to the keratin layer of the skin [5]. They are hypothesized to either directly penetrate the intact skin, disintegrate on the surface of the skin with penetration of individual lipid molecules in stratum corneum, adsorb on the skin surface by fusion of their bilayer with skin lipids and subsequent direct transfer of the drug to stratum corneum, or create an occlusive effect leading to enhanced drug penetration [22]. Niosomes were postulated to penetrate the skin by diffusion reforming new smaller niosomes vesicles in the skin; interact with stratum corneum by fusion or adhesion, or modify the stratum corneum structure and making it more permeable. Due to their relative large particle size and non-flexible nature, both liposomes and niosomes are mainly usd for their local, rather than their systemic effects [4, 5, 22-24]. It was also reported that liposomes and niosomes serve as solubilisation matrix and penetration enhancers [25, 26].

Regarding psoriasis treatment, liposomes and niosomes were utilized by Agarwal *et al.* [27, 28] in delivering dithranol. Knudsen *et al.* [29] reported the delivery of greater amount of calcipotriol through the skin using liposomes with increased deposition in the stratum corneum. Ali *et al.* [30] disclosed the successful clinical use of liposomal methotrexate hydrogel in localized psoriasis with no psoriatic recurrence. Nagle *et al.*[31] also incorporated methotrexate in menthol containing liposomal gel reporting its enhanced retention in skin appendages and improved skin penetration. Also, methotrexate loaded niosomes exhibited better clinical efficacy than marketed methotrexate gel in psoriasis treatment with high topical deposition potential andof proven histopathological safety [32, 33]. Liposomes of retinoids showed increased photostability, and a manipulated permeation profile depending on the surface charge of the liposomes as outlined by Trapasso *et al.* [34]. Furthermore, Patil *et al.* [5] prepared tazarotene liposomes displaying lower skin irritation and slower drug release than currently available topical retinoids. In addition, liposomes enhanced the topical delivery of corticosteroids, as published by Umalkar *et al.* [35] stating that diflorasone diacetate liposomes were more efficient in the treatment of psoriasis than other conventional products. Schreier *et al.* and Shahiwala *et al.* [25, 26] delineated the improvement of the horny layer characteristics by reducing the transepidermal water loss and replenishing the lost skin lipids by the use of niosomal formulation.

**Lipid based systems**

**Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)**

SLNs are composed of high melting points physiological lipids such as triglycerides, carnauba wax, beeswax, cetyl alcohol, emulsifying wax, cholesterol, and cholesterol butyrate, which consolidate upon dispersion in water. SLNs are either formed by dispersion of the drug in the outer shell surrounding a lipidic core, or by dissolving the drug in the lipid matrix and surrounded by the outer shell [36]. If prepared by high-pressure homogenization, they will spare the use of organic solvents.

NLCs are tailored SLNs (oil loaded SLNs) composed of solid lipid matrix incorporating a liquid lipid such as soya bean oil, oleic acid, corn oil in the presence of an emulsifier. NLCs overcome limited drug loading, drug leakage and risk of gelation or drug expulsion during storage encountered with SLNs owing to the imperfect crystalline lattice of the former [37].

SLNs and NLCs offer many advantages for the topical route by providing controlled drug release, exhibiting limited toxicity due to their physiological lipid content, increasing drug permeation through stratum corneum due to their small lipid droplet size, and ensuring an occlusive effect, due to lipid film formation on the top of the stratum corneum, for better skin hydration [37-39]. Owing to their highly lipidic and non-flexible nature, SLNs and NLCs are confined to the topical rather than the transdermal treatment of skin diseases.

As examples of using SLNs in psoriasis field, tretinoin and isotretinoin encapsulated in SLNs showed higher uptake and enhanced skin targeting effect with good stability [36, 40]. Dithranol was also successfully loaded into SLNs for potential antipsoriatic applications [38, 41]. Moreover, SLNs co-encapsulating betamethasone dipropionate and calcipotriol displayed negligible skin irritation and better skin tolerability compared to commercial ointment [42].

Similarly, NLCs were also successful in topical psoriasis treatment. NLCs encapsulating psoralen were able to minimize permeation differentiation between normal and hyper proliferative skin compared to free drug in aqueous medium [43]. Agrawal *et al.* [44] developed acitretin loaded NLCs which displayed higher drug deposition, improvement of therapeutic response and reduction in local side effects compared to acitretin gel. Pople *et al.* [45] developed tacrolimus loaded NLCs for the treatment of psoriasis with better encapsulation efficiency, stability and enhanced skin deposition compared to the conventional product. Besides, they were also able to enhance occlusive properties, skin hydration potential, and reduce the transepidermal water loss. Pinto *et al.* and Agrawal *et al.* [46,47]prepared NLCs loaded with methotrexate, displaying higher skin penetration and better skin deposition than free methotrexate and methotrexate gel respectively. Lin *et al.* [48] successfully co-encapsulated the lipophilic calcipotriol and hydrophilic methotrexate showing enhanced drugs permeation and limited skin irritation. In addition to controlled release, methoxsalen NLCs were of enhanced drug stability [49]. High retention of fluocinolone acetonide in skin layers following the use of NLCs was proved by Pradhan *et al.* [50].

**Lipospheres**

Lipospheres are water dispersible solid micron or submicron sized particles composed of a solid hydrophobic core containing the bioactive drug molecule stabilized by a single monolayer of phospholipid molecules [51].

They are widely used in topical delivery owing to their solid lipid matrix, causing drug release over a prolonged duration with minimal systemic absorption. They also reduce transepidermal water loss due to lipid film formation on skin surface [51]. Only one report of their possible application in oral psoriasis treatment; cyclosporine lipospheres demonstrated better stability and improved bioavailability [52]. The need for lipid components during psoriasis treatment would encourage research to focus on their use.

**Nanoemulsions**

Nanoemulsions differ from microemulsions in that they are the same as regular emulsions with the particle size of the globules in the nanometer range. Unlike microemulsions, nanoemulsions are not formed spontaneously.

In topical field nanoemulsions improve skin hydration and drug permeation and provide low skin irritation and extended release of enclosed drugs [53, 54]. To authors' knowledge, only one attempt was made to test the efficacy of nanoemulsions in the topical treatment of psoriasis; in which Bernardi *et al.* [55] Developed rice bran oil nanoemulsion for possible treatment of psoriasis which was stable and showed low skin irritation based on its moisturizing activity.

**Polymeric carriers**

**Polymeric micelles**

Polymeric micelles are nanosized core/shell structures formed by self-assembly of amphiphilic block copolymers with hydrophobic

core and polyethylene glycol-hydrophilic shell in an aqueous milieu. They improve the solubilization of hydrophobic or poorly soluble drugs, provide sustained release, and protect the encapsulated drug from degradation [56].

For topical psoriasis treatment, Lapteva *et al.* [57] prepared methoxy-polyethylene glycol-dihexyl substituted polylactide (MPEG-dihexPLA) micelles and reported its higher efficiency for tacrolimus skin deposition in the stratum corneum, epidermis, and upper dermis, compared to the marketed ointment, with no systemic delivery. The same polymeric micelles were also used by the former group to load cyclosporin A, demonstrating deep skin penetration without concomitant systemic delivery [58].

**Polymeric nano and microspheres**

Polymeric microspheres are stable spherical polymer matrix system formed from naturally occurring polymers such as chitosan, collagen, albumin or cellulose, or synthetic polymers as polylactide co-glycolide (PLGA), polylactic acid or poly Ɛ caprolactone with particle size in the micrometer range (from 1 to 1000 μm) [59]. Typically, polymeric microspheres protect the entrapped drug from degradation or inactivation on the skin surface and provide controlled release of the incorporated drug whether it was lipophilic or hydrophilic [60, 61].

Upon encapsulation of clobetasol propionate in (PLGA) micro-spheres, they significantly delayed its release, with the authors expecting a decrease in its topical side effects [9]. PLGA microspheres also successfully encapsulated psoralen, with proven presence in rat skin [62]. Nanospheres are analogous to microspheres only differing in size. Nanosphere drugs are either entrapped or dispersed in the polymer matrix with biodegradable or non-biodegradable polymers [4].

Regarding psoriasis treatment, Kilfoyle *et al.* [63] prepared tryospheres (tyrosine derived polymeric nanospheres) with encapsulated paclitaxel providing sustained drug release over 72 h, in addition to achieving a reservoir of the drug in the epidermal layer. Batheja *et al.* [64] also confirmed the promising topical nature of tyrosine nanosphere encapsulated in a gel form.

**Nanocapsules**

They are nanoparticles consisting of a drug containing reservoir (cavity), surrounded by a polymeric or surfactant coat [65]. The drug may be present in a liquid form, solid form, or as a molecular dispersion in the cavity.

A successful use of nanocapsules in the topical treatment of psoriasis was attempted by Savian *et al.* [66] in which the nanocapsules dithranol provided reduced toxicity of the drug, encouraging its clinical use in psoriatic patients treated with dithranol to ensure their adherence to the therapy.

**Pharmaceutical carriers suitable for both local and systemic use**

**Vesicular systems**

**Transfersomes**

They are highly deformable and ultra flexible liposomes firstly developed by Cevc and Blume [67]. They consist of an inner aqueous core surrounded by lipid bilayers in addition to edge activators (single chain surfactants) such as Tweens, Spans, sodium cholate or deoxycholate [23, 68].

As transdermal delivery systems, transfer some have the advantage of being able to squeeze themselves through the intercellular regions of the stratum corneum which are less than one-tenth of their own diameter [15, 69]. They can either penetrate the skin *via* the intracellular or transcellular routes with destabilization of their lipid bilayer followed by an increase in their flexibility, making them more skin penetrating by diffusion following natural water gradient across the epidermis [4]. Even if skin pores are much smaller than the diameter of vesicles, transfer some are able to permeate without being ruptured, localizing high drug concentrations in the skin [24, 68, 70].

Regarding psoriasis treatment, transfer some have been shown to display three to four folds increase in permeation of methotrexate than normal liposomes [71]. In addition, Bhatia *et al.* [72] reported the significant efficacy of tamoxifen transfersomal gel compared to the conventional hydrogel in a mouse tail model of psoriasis.

**Ethosomes**

They are flexible vesicular carriers composed of phospholipids, ethanol (as edge activator) and water [73]. Ethanol also provides vesicles with a flexible nature allowing them to penetrate easily into the deeper layers of skin, achieving transdermal drug delivery [19].

As transdermal delivery systems, ethosomes promote skin permeation and penetration of drugs, owing to their high ethanol concentration, reacting with the polar head groups of the skin. Thus, they play an important role as permeation enhancer by disturbing the organization of skin lipid bilayer and increasing the fluidity of stratum corneum lipids [4, 74].

Ethosomeshave has been used successfully in the treatment of psoriasis. Dubey *et al.* [75]reported better permeation to deeper skin layers and greater retention of methotrexate and enhanced transdermal flux with ethosomes compared to the marketed product. Raza *et al.* [76] attempted the encapsulation of tretinoin in ethosomes, which displayed better biocompatibility and efficacy than marketed product. Zhang *et al.* [77] compared the encapsulation of psoralen in ethosomes with that of liposomes, reporting higher transdermal flux and skin deposition with the former. Better delivery of 5-aminolevulinic acid was also reported upon encapsulation in ethosomes with better delivery to the inflamed skin in hyperproliferative skin animal model than conventional products [78]. Upon incorporation in a gel, ethosomes were also proven to minimize the side effects caused by the photosensitivity of psoralen compared to conventional gel [79].

**Penetration enhancer-containing vesicles (PEVs)**

PEVs are analogous to transfer some, with the edge activator being replaced by a penetration enhancer such as 2-(2-ethoxyethoxy) ethanol (Transcutol®), capryl-caproyl macrogol 8 glyceride (Labrasol®), cineole and oleic acid [15,80]. This penetration enhancer has dual action as it improves vesicular fluidity and reduces the stratum corneum function [81]. Depending on the extent of deformability and the percentage of penetration enhancer, PEVs could either act as local or systemically acting dermal carrier.

The only attempt for the use of PEVs in the treatment of psoriasis was made by Srisuk *et al.* [6] who entrapped methotrexate in oleic acid-containing vesicles with a reported enhancement in permeability and transepidermal delivery than conventional liposomes, owing to their flexible nature and their content of penetration enhancer.

**Surfactant based systems**

**Microemulsions**

Microemulsions are thermodynamically stable isotropic dispersions involving oil and water stabilized by surfactant/cosurfactant film at the interface, and are classified into o/w and w/o types. Microemulsions have the advantages of ease of formation, small droplet size and high surface area providing better attachment of drug molecules [82]. Owing to their small droplet size and their high surfactant and cosurfactant content, microemulsions have proven themselves as an important transdermally oriented carrier.

Regarding psoriasis treatment, Alvarez-Figueroa and Blanco-Mendez [83], developed methotrexate containing microemulsion, showing better drug delivery than the solution form. In addition,Sah *et al.* [84] developed methoxsalen loaded microemulsion achieving ten folds better deposition in skin and proven transdermal flux than the marketed product. Behera *et al.* [85] also developed chitosan coated methoxsalen microemulsion providing controlled release and transdermal flux of the drug across the skin. Ali *et al.* [86] prepared turmeric oil containing microemulsions with high stability and low irritation. Furthermore, the immunosuppressive drug mycophenolate mofetil formulated as microemulsion based hydrogel displayed complete clearance of psoriatic plaques suggesting its effectiveness [87]. Upon inclusion in a gel, Ali *et al.* [88] were able to use babchi oil

microemulsion for the topical treatment of psoriasis, owing to its high content of psoralen. Results showed that the aforementioned formula provided high *in vivo* anti-inflammatory effects.

**Polymeric nanoparticles**

**Dendrimers**

They are nanosized highly branched macromolecules with a large number of surface groups branching from a central unit, and an internal core that act as a compartment for housing drugs [89]. Drugs may rest in the central unit or interact with functional groups with electrostatic or covalent bonds with drug release achieved by enzymatic degradation or change in pH or temperature4. In the topical/transdermal fields, dendrimers facilitate drug diffusion and enhance drug penetration owing to their small nanometer size. Topical and transdermal psoriasis treatment can be achieved with dendrimers, depending on their type and generation. Agrawal et al. [90] prepared dendrimers loaded with dithranol with prolongation of drug retention in the skin and greater skin permeation compared to plain drug solution. The effective conjugation of 8-methoxypsoralen with dendrimers facilitated transdermal skin permeation for PUVA (psoralen-UV-A) therapy [91].

## CONCLUSION

The incidence of the autoimmune disease "psoriasis" has increased in the past few years. The conventional forms of antipsoriatic drugs used such as creams, ointments and gels are starting to become outdated as they don't provide complete cureowing to poor drug absorption and patient in compliance. In this review, we have made a survey on the pharmaceutical carriers used for antipsoriatic drugs which were able to overcome the disadvantages encountered with the conventional forms and provide superiority in overcoming the barrier properties of the stratum corneum. An emphasis on whether the pharmaceutical carrier could be used for topical or transdermal effects was made in the current manuscript. This will serve as a guide for career choice, based on the treatment rationale.

## CONFLICT OF INTERESTS

The authors report no conflicts of interest

## REFERENCES

1. Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interventions Aging 2006;1:327–48.
2. Imura T, Sakai H, Yamauchi H, Kaise C, Kozawa K, Yokoyama S, Abe M. Preparation of liposomes containing Ceramide 3 and their membrane characteristics. Colloids Surf B 2001;20:1–8.
3. Su YH, Fang JY. Drug delivery and formulations for the topical treatment of psoriasis. Expert Opin Drug Delivery 2008;5:235-49.
4. Pradhan M, Singh D, Singh MR. Novel colloidal carriers for psoriasis: Current issues, mechanistic insight and novel delivery approaches. J Controlled Release 2013;170:380–95.
5. Patil P, Bhowmik M, Pandey GK, Joshi A, Dubey B. Design and evaluation of tazarotene loaded liposome gel for the effective treatment of psoriasis and acne. J Biomed Pharm Res 2013;2:19-29.
6. Srisuk P, Thongnopnua P, Raktanonchai U, Kanokpanont S. Physico-chemical characteristics of methotrexate-entrapped oleic acid-containing deformable liposomes for *in vitro* transepidermal delivery targeting psoriasis treatment. Int J Pharm 2012;427:426–34.
7. Motta S, Monti M, Sesana S, Mellesi L, Ghidoni R, Caputo R. Abnormality of water barrier function in psoriasis, role of ceramide fractions. Arch Dermatol 1994;130:452-6.
8. Lau WM, White AW, Heard CM. Topical delivery of a naproxen dithranol co-drug: *in vitro* skin penetration, Permeation, and Staining. Pharm Res 2010;27:2734-42.
9. Badilli U, Sen T, Tarımcı N. Microparticulate based topical delivery system of clobetasol propionate. AAPS PharmSciTech 2011;12:949-57.
10. Kuchekar AB, Pujari RR, Kuchekar SB, Dhole SN, Mule PM. Psoriasis: a comprehensive review. Int J Pharm Life Sci 2011;2:857-77.
11. Vincent N, Ramya DD, Vehda HB. Progress in psoriasis therapy via novel delivery systems. Dermatol Rep 2014;6:5451.
12. Park SN, Lee MH, Kim SJ, Yu ER. Preparation of quercetin and rutin-loaded ceramide liposomes and drug-releasing effect in the liposome-in-hydrogel complex system. Biochem Biophys Res Commun 2013;435:361-6.
13. Akhtar N, Pathak K. Cavamax W7 composite ethosomal gel of clotrimazole for improved topical delivery: development and comparison with ethosomal gel. AAPS PharmSciTech 2012;13:344-55.
14. Sahle FF, Metz H, Wohlrab J, Neubert RH. Lecithin-based microemulsions for targeted delivery of ceramide AP into the stratum corneum: formulation, Characterizations, and *in vitro* release and penetration studies. Pharm Res 2013;30:538-51.
15. Gupta M, Agrawal U, Vyas SP. Nanocarrier-based topical drug delivery for the treatment of skin diseases. Expert Opin Drug Delivery 2012;9:783-804.
16. Groen D, Poole DS, Gooris GS, Bouwstra JA. Investigating the barrier function of lipid skin models with varying compositions. Eur J Pharm Biopharm 2011;79:334-42.
17. Suresh PK, Singh P, Saraf S. Novel topical drug carriers as a tool for the treatment of psoriasis: Progress and advances. Afr J Pharm Pharmacol 2013;7:138-47.
18. Tokudome Y, Saito Y, Sato F, Kikuchi M, Hinokitani T, Goto K. Preparation and characterization of ceramide-based liposomes with high fusion activity and high membrane fluidity. Colloids Surf B 2009;73:92–6.
19. Prasanthi D, Lakshmi PK. Vesicles–mechanism of transdermal permeation: a review. Asian J Pharm Clin Res 2012;5:18-25.
20. Kumar GP, Rajeshwarrao P. Nonionic surfactant vesicular systems for effective drug delivery—an overview. Acta Pharm Sin B 2011;1:208–19.
21. Nasr M, Mansour S, Mortada ND, Elshamy AA. Vesicular aceclofenac systems: a comparative study between liposomes and niosomes. J Microencapsul 2008;25:499-512.
22. Sinico C, Manconi M, Peppi M, Lai F, Valenti D, Fadda AM. Liposomes as carriers for dermal delivery of tretinoin: *in vitro* evaluation of drug permeation and vesicle–skin interaction. J Controlled Release 2005;103:123–36.
23. Elsayed MM, 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.
24. El Zaafarany GM, Awad GA, Holayel SM, Mortada ND. Role of edge activators and surface charge in developing ultra deformable vesicles with enhanced skin delivery. Int J Pharm 2010;397:164–72.
25. Schreier H, Bouwstra J. Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. J Controlled Release 1994;30:1–15.
26. Shahiwala A, Misra A. Studies in topical application of niosomally entrapped nimesulide. J Pharm Pharm Sci 2002;5:220-5.
27. Agarwal R, Katare OP, Vyas SP. Preparation and *in vitro* evaluation of liposomal/niosomal delivery systems for antipsoriatic drug dithranol. Int J Pharm 2001;228:43-52.
28. Agarwal R, Saraswat A, Kaur I, Katare OP, Kumar B. A novel liposomal formulation of dithranol for psoriasis: preliminary results. J Dermatol 2002;29:529-32.
29. Knudsen NØ, Rønholt S, Salte RD, Jorgensen L, Thormann T, Basse LH, *et al*. Calcipotriol delivery into the skin with PEGylated liposomes. Eur J Pharm Biopharm 2012;81:532-9.
30. Ali MF, Salah M, Rafea M, Saleh N. Liposomal methotrexate hydrogel for treatment of localized psoriasis: preparation, characterization and laser targeting. Med Sci Monit 2008;14: PI66-74.
31. Nagle A, Goyal AK, Kesarla R, Murthy RR. Efficacy study of vesicular gel containing methotrexate and menthol combination on parakeratotic rat skin model. J Liposome Res 2011;21:134-40.
32. Lakshmi PK, Devi GS, Bhaskaran S, Sacchidanand S. Niosomal methotrexate gel in the treatment of localized psoriasis: phase I and phase II studies. Indian J Dermatol Venereol 2007;73:157-61.
33. Abdelbary AA, Abou Ghaly MH. Design and optimization of topical methotrexate loaded niosomes for enhanced

management of psoriasis: Application of Box-Behnken design, *in-vitro* evaluation, and *in-vivo* skin deposition study. Int J Pharm 2015;485:235-43.

34. Trapasso E, Cosco D, Celia C, Fresta M, Paolino D. Retinoids: new use by innovative drug-delivery systems. Expert Opin Drug Delivery 2009;6:465-83.
35. Umalkar DG, Rajesh KS. Formulation and evaluation of liposomal gel for the treatment of psoriasis. Int J Pharma Bio Sci 2013;4:22–32.
36. Mandawgade SD, Patravale VB. Development of SLNs from natural lipids: application to topical delivery of tretinoin. Int J Pharm 2008;363:132–8.
37. Joshi M, Patravale V. Nanostructured lipid carrier (NLC) based gel of celecoxib. Int J Pharm 2008;346:124–32.
38. Shahwal VK. Preformulation studies and preparation of dithranol are loaded solid lipid nanoparticles. Int J Biomed Res 2012;3:343-50.
39. Dubey A, Prabhu P, Kamath JV. Nanostructured lipid carriers: a novel topical drug delivery system. Int J PharmTech Res 2012;4:705-14.
40. Liu J, Hub W, Chen H, Nib Q, Xu H, Yang X. Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. Int J Pharm 2007;328:191–5.
41. Gambhire MS, Bhalekar MR, Shrivastava B. Investigations in photostability of dithranol incorporated in solid lipid nanoparticles. Pharm Chem J 2012;46:256-61.
42. Sonawane R, Harde H, Katariya M, Agrawal S, Jain S. Solid lipid nanoparticles loaded topical gel containing combination drugs: an approach to offset psoriasis. Expert Opin Drug Delivery 2014;11:1833-47.
43. Fang JY, Fang CL, Liu CH, Su YH. 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.
44. Agrawal Y, Petkar KC, Sawant KK. Development, evaluation and clinical studies of Acitretin loaded nanostructured lipid carriers for topical treatment of psoriasis. Int J Pharm 2010;401:93-102.
45. Pople PV, Singh KK. Development and evaluation of colloidal modified nano lipid carrier: application to topical delivery of tacrolimus, Part II–*in vivo* assessment, drug targeting, efficacy, and safety in treatment for atopic dermatitis. Eur J Pharm Biopharm 2013;84:72-83.
46. Pinto MF, Moura CC, Nunes C, Segundo MA, Costa Lima SA, Reis S. A new topical formulation for psoriasis: Development of methotrexate-loaded nanostructured lipid carriers. Int J Pharm 2014;477:519–26.
47. Agrawal YO, Mahajan HS, Surana SJ. Development of methotrexate nanostructured lipid carriers for topical treatment of psoriasis: Optimization, evaluation, and in vitro studies. World Academy Sci Eng Technol Pharmacol Pharm Sci 2015;2:294.
48. Lin YK, Huang ZR, Zhuo RZ, Fang JY. The combination of calcipotriol and methotrexate in nanostructured lipid carriers for topical delivery. Int J Nanomedicine 2010;5:117-28.
49. Shinde G, Rajesh KS, Prajapati N, Murthy RSR. Formulation, development, and characterization of nanostructured lipid carrier (NLC) loaded gel for psoriasis. Pharm Lett 2013;5:13-25.
50. Pradhan M, Singh D, Murthy SN, Singh MR. Design, characterization, and skin permeating potential of fluocinolone acetonide loaded nanostructured lipid carriers for topical treatment of psoriasis. Steroids 2015;101:56-63.
51. Nasr M, Mansour S, Mortada ND, El Shamy AA. Lipospheres as carriers for topical delivery of aceclofenac: preparation, characterization and *in vivo* evaluation. AAPS PharmSciTech 2008;9:154-62.
52. Avramoff A, Khan W, Ezra A, Elgart A, Hoffman A, Domb AJ. Cyclosporin pro-dispersion liposphere formulation. J Controlled Release 2012;160:401–6.
53. Abolmaali SS, Tamaddon AM, Fakhr Sadat Farvadi FS, Daneshamuz S, Moghimi H. Pharmaceutical nanoemulsions and their potential topical and transdermal applications. Int J Plasma Sci 2011;7:139-50.
54. Salim N, Basri M, Rahman MB, Abdullah DK, Basri H. Modification of palm kernel oil esters nanoemulsions with hydrocolloid gum for enhanced topical delivery of ibuprofen. Int J Nanomed 2012;7:4739-47.
55. Bernardi DS, Pereira TA, Maciel NR, Bortoloto J, Viera GS, Oliveira GC, *et al*. Formation and stability of oil-in-water nanoemulsions containing rice bran oil: *in vitro* and *in vivo* assessments. J Nanobiotechnol 2011;9:4.
56. Croy SR, Kwon GS. Polymeric micelles for drug delivery. Curr Pharm Des 2006;12:4669-84.
57. Lapteva M, Mondon K, Möller M, Gurny R, Kalia YN. Polymeric micelle nanocarriers for the cutaneous delivery of tacrolimus: a targeted approach for the treatment of psoriasis. Mol Pharm 2014;11:2989-3001.
58. Lapteva M, Santer V, Mondon K, Patmanidis I, Chiriano G, Scapozza L, *et al*. Targeted cutaneous delivery of ciclosporin A using micellar nanocarriers and the possible role of inter-cluster regions as molecular transport pathways. J Controlled Release 2014;196:9-18.
59. Saralidze K, Koole LH, Knetsch LW. Polymeric microspheres for medical applications. Materials 2010;3:3537-64.
60. Rolland A, Wagner N, Chatelus A, Shroot B, Schaefer H. Site-specific drug delivery to pilosebaceous structures using polymeric microspheres. Pharm Res 1993;10:1738-44.
61. Nasr M, Awad GA, Mansour S, Al Shamy A, Mortada ND. A reliable predictive factorial model for entrapment optimization of a sodium bisphosphonate into biodegradable microspheres. J Pharm Sci 2011;100:612-21.
62. Gomes AJ, Luardi CN, Lunardi LO, Pitol DL, Machado AE. Identification of psoralen loaded PLGA microspheres in rat skin by light microscopy. Micron 2008;39:40-4.
63. Kilfoyle BE, Sheihet L, Zhang Z, Laohoo M, Kohn J, Michniak-Kohn BB. Development of paclitaxel-tyro spheres for topical skin treatment. J Controlled Release 2012;163:18-24.
64. Batheja P, Sheihet L, Kohn J, Singer AJ, Michniak-Kohn B. Topical drug delivery by a polymeric nanosphere gel: Formulation optimization and *in vitro* and *in vivo* skin distribution studies. J Controlled Release 2011;149:159-67.
65. Nasr M, Abdel-Hamid S. Lipid-based nanocapsules: a multitude of biomedical applications. Curr Pharm Biotechnol 2015;16:322-32.
66. Savian AL, Rodrigues D, Weber J, Ribeiro RF, Motta MH, Schaffazick SR, *et al*. Dithranol-loaded lipid-core nanocapsules improve the photostability and reduce the *in vitro* irritation potential of this drug. Mater Sci Eng C 2015;46:69-76.
67. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochim Biophys Acta 1992;1104:226-32.
68. Chaudhary H, Kohli K, Kumar V. Nano-transfersomes as a novel carrier for transdermal delivery. Int J Pharm 2013;454:367–80.
69. Cevc G, Schatzlein A, Blume G. Transdermal drug carriers: basic properties, optimization and transfer efficiency in the case of epicutaneously applied peptides. J Controlled Release 1995;36:3-16.
70. Malakar J, Sen SO, Nayak AK, Sen KK. Formulation, optimization and evaluation of transferosomal gel for transdermal insulin delivery. Saudi Pharm J 2012;20:355–63.
71. Trotta M, Peira E, Carlotti ME, Gallarate M. Deformable liposomes for dermal administration of methotrexate. Int J Pharm 2004;270:119-25.
72. Bhatia A, Singh B, Wadhwa S, Raza K, Katare OP. Novel phospholipid-based topical formulations of tamoxifen: evaluation for antipsoriatic activity using mouse-tail model. Pharm Dev Technol 2014;19:160-3.
73. Bseiso EA, Nasr M, Sammour OA, Abd El Gawad NA. Recent advances in topical formulation carriers of antifungal agents. Indian J Dermatol Venereol 2015;81:457-63.
74. Chourasia MK, Kang L, Chan SY. Nanosized ethosomes are bearing ketoprofen for improved transdermal delivery. Results Pharm Sci 2011;1:60–7.
75. Dubey V, Mishra D, Dutta T, Nahar M, Saraf DK, Jain NK. Dermal and transdermal delivery of an anti-psoriatic agent via ethanolic liposomes. J Controlled Release 2007;123:148-54.
76. Raza K, Singh B, Lohan S, Sharma G, Negi P, Yachha Y, *et al*. Nano-lipoidal carriers of tretinoin with enhanced percutaneous absorption, photostability, biocompatibility and anti-psoriatic activity. Int J Pharm 2013;456:65-72.

77. Zhang YT, Shen LN, Wu ZH, Zhao JH, Feng NP. Comparison of ethosomes and liposomes for skin delivery of psoralen for psoriasis therapy. Int J Pharm 2014;471:449-52.
78. Fang YP, Huang YB, Wu PC, Tsai YH. Topical delivery of 5-aminolevulinic acid-encapsulated ethosomes in a hyperproliferative skin animal model using the CLSM technique to evaluate the penetration behavior. Eur J Pharm Biopharm 2009;73:391-8.
79. Kumari S, Pathak K. Cavamax W7 composite psoralen ethosomal gel versus cavamax W7 psoralen solid complex gel for topical delivery: a comparative evaluation. Int J Pharm Investig 2013;3:171-82.
80. Bsieso EA, Nasr M, Moftah NH, Sammour OA, Abd El Gawad NA. Could nanovesicles containing a penetration enhancer clinically improve the therapeutic outcome in fungal skin diseases. Nanomedicine (Lond) 2015;10:2017-31.
81. Romero EL, Morilla MJ. Highly deformable and highly fluid vesicles as potential drug delivery systems: theoretical and practical considerations. Int J Nanomed 2013;8:3171-86.
82. Hathout RM, Nasr M. Transdermal delivery of betahistine hydrochloride using microemulsions: physical characterization, biophysical assessment, confocal imaging and permeation studies. Colloids Surf B 2013;110:254-60.
83. Alvarez-Figueroa MJ, Blanco-Méndez J. Transdermal delivery of methotrexate: iontophoretic delivery from hydrogels and passive delivery from microemulsions. Int J Pharm 2001;215:57–65.
84. Sah AK, Jain SK, Pandey RS. Microemulsion based hydrogel formulation of methoxsalen for the effective treatment of psoriasis. Asian J Pharm Clin Res 2011;4:140-5.
85. Behera J, Keservani RK, Yadav A, Tripathi M, Chadoker A. Methoxsalen loaded chitosan coated microemulsion for effective treatment of psoriasis. Int J Drug Delivery 2010;2:159-67.
86. Ali MS, Alam S, Imam FI, Siddiqui MR. Topical nanoemulsion of turmeric oil for psoriasis: characterization, ex vivo and *in vivo* assessment. Int J Drug Discovery Technol 2012;4:184-97.
87. Sharma K, Bedi N. Microemulsion based hydrogel of mycophenolate mofetil for the treatment of psoriasis. Curr Trends Biotechnol Pharm 2014;8:359-71.
88. Ali J, Akhtar N, Sultana Y, Baboota S, Ahuja A. Antipsoriatic microemulsion gel formulations for topical drug delivery of babchi oil (Psoralea corylifolia). Methods Find Exp Clin Pharmacol 2008;30:277-85.
89. Nasr M, Najlah M, D'Emanuele A, Elhissi A. PAMAM dendrimers as aerosol drug nanocarriers for pulmonary delivery via nebulization. Int J Pharm 2014;461:242-50.
90. Agrawal U, Mehra NK, Gupta U, Jain NK. Hyperbranched dendritic nanocarriers for topical delivery of dithranol. J Drug Target 2013;21:497-506.
91. Borowska K, Wołowiec S, Głowniak K, Sieniawska E, Radej S. Transdermal delivery of 8-methoxypsoralene mediated by polyamidoamine dendrimer G2.5 and G3.5--*in vitro* and *in vivo* study. Int J Pharm 2012;436:764-70.