
Chapter

15

COLLOIDAL CARRIERS IN THE TOPICAL TREATMENT OF DERMATOLOGICAL DISEASES

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Contents

15.1. INTRODUCTION	391
15.2. THE SKIN	392
15.3. BASIC CONCEPTS OF MICROEMULSIONS	393
15.3.1. Components of microemulsions	394
15.3.2. Characterisation of microemulsions.....	395
15.3.3. Enhancement mechanisms of microemulsions	395
15.4. MICROEMULSIONS AS COLLOIDAL DRUG CARRIERS FOR SKIN DISORDERS.....	396
15.4.1. <i>Acne vulgaris</i>	400
15.4.1.1. Microemulsion formulations of retinoids	401
15.4.1.2. Microemulsion formulations of hydroxy acids and antibacterial agents.....	401
15.4.1.3. Microemulsion formulations of antioxidant agents.....	402
15.4.2. Atopic dermatitis	402
15.4.2.1. Microemulsion formulations of topical corticosteroids	403
15.4.2.2. Microemulsion formulations of topical calcineurin inhibitors.....	404
15.4.3. Psoriasis	405
15.4.3.1. Microemulsion formulations in topical psoriasis treatment.....	405
15.4.4. Fungal infections	406
15.4.4.1. Microemulsion formulations of azole antifungals.....	406
15.4.4.2. Microemulsion formulations of allylamine/benzylamine antifungals.....	407
15.4.5. Viral infections of the skin.....	407
15.4.5.1. Microemulsion formulations in topical viral infection treatment.....	408
15.5. CONCLUSIONS.....	408
REFERENCES	409

15.1. INTRODUCTION

The common dermatological diseases, including acne, atopic dermatitis, eczema, psoriasis and microbial/fungal infections, affect the life quality of people worldwide. Skin disorders pose a continuous and serious threat to human health and life, and remain a major healthcare problem. Most of these skin disorders have been caused by inflammatory conditions and infectious pathogens. Topical treatment plays a crucial role in the treatment of skin diseases as it targets the drugs to the pathological sites within the skin and, minimises and/or prevents systemic side effects. The clinical efficiency of drugs applied topically depends on the concentration achieved in cutaneous tissues, which is mainly related to the ability of the compound to penetrate into tissue. The main limitation of topical treatment is mostly the poor penetration of drugs into deeper layers of skin, due to the unique barrier characteristics of *stratum corneum*, which is the outermost layer of the skin. The integrity of the skin barrier can be weakened in most dermatological diseases, and the enhancement of topical delivery efficacy is a great challenge for improving the localisation of drugs at the target sites for the treatment of dermatological diseases. As well as the barrier characteristics of skin, the physicochemical properties of drugs such as high lipophilicity and poor aqueous solubility also affect penetration across skin [1-3].

Different types of novel nano-sized drug carriers have been developed to overcome barriers to the dermal targeting of drugs in topical drug delivery [4]. Microemulsions are one of the colloidal carriers widely investigated for enhancing the localisation of the drugs at the targeted skin sites. Microemulsions are thermodynamically stable, optically isotropic, transparent dispersions of oil and water that are stabilised by an interfacial film of surfactant and co-surfactant. They offer the advantages of high drug solubilising capacity, long term stability, and ease of scale-up in manufacturing. Microemulsions have been intensively studied over recent decades by many scientists because of their great potential in pharmaceutical applications [4-6].

The present chapter focuses on background information about the structure of human skin, and microemulsions as colloidal drug carriers. The common dermatological diseases and the drugs used in their topical treatment are reviewed. Research studies in which focused on the development of microemulsions as a challenge for the effective treatment of skin disorders have also been summarised.

15.2. THE SKIN

The skin is the largest organ of the human body, accounting for more than 10 % of body weight and covering a surface area of approximately 2.0 m². It has a multi-lamellar structure that provides a physical barrier to protect organisms against environmental factors and to regulate heat and water loss from the body [7]. The skin also offers an ideal application site through which to deliver drugs for both local and systemic pharmacological effects, due to being easily accessible and having a large surface area [2]. It has excellent barrier functions against the penetration of drugs, however, due to the unique arrangement of its structure [3,8].

Morphologically, the skin consists of three main layers. From the outside to the inside these layers are the epidermis, the dermis, and the hypodermis (subcutaneous tissue). The epidermis is also composed of two distinct layers, the *stratum corneum* (non-viable epidermis) and viable epidermis [2,9]. The *stratum corneum* is located in the outermost layer of the epidermis. Although its thickness is only 10–20 µm, it is the main barrier of the skin [10]. It is formed primarily of keratin filled dead cells, which are called as corneocytes. The corneocytes are embedded in the bilayer lipid lamellar domain. The main lipids in the *stratum corneum* are ceramides, cholesterol and free fatty acids. The *stratum corneum* can be described as a brick and mortar organisation, in which the corneocytes are the bricks and the intercellular part of the lipid domain is the mortar [8,11]. The viable epidermis, ~ 100–150 µm thick, is responsible for formation of the *stratum corneum* and is itself also made up of different layers. From the outer to innermost, they are: *stratum granulosum*, *stratum spinosum*, *stratum germinativum (basale)* [12,13]. Cells proliferate in the basal layer, and viable cells differentiate and migrate through the skin surface. The morphological differentiation is formed between the *stratum granulosum* and *stratum corneum*, and the viable cells are changed to corneocytes. The viable epidermis layer is therefore a stratified epithelium composed of different layers. Each layer of the epidermis is defined by morphology, position and the differentiation state of keratinocytes [12,14]. As well as keratinocytes, there are melanocytes responsible for melanin production, merkel cells providing sensory perception and Langerhans cells with an immunological function [12]. In the epidermal barrier (epithelial layers and follicles), the tight junction proteins have been shown, and in diseased skin such as psoriasis, characterised by a compromised skin barrier, the localisation and expression of these proteins have been shown to be altered [15].

The dermis is about 1–2 mm thick, and located below the epidermis layer. It is made up of two main structures including fibrous proteins and glycosaminoglycans (GAG). Fibrous proteins are collagen, elastin, and fibronectin. In the GAG matrix, there are hyaluronic acid and chondroitin sulphates [2,9]. The dermis provides mechanical support for the skin. There

are also the fibroblasts, mast cells and dendritic cells in dermis layers. There are also several appendages including the pilosebaceous units (hair follicles and associated sebaceous glands), eccrine sweat and apocrine glands. The hypodermis (subcutaneous tissue) is located underneath the dermis layer. It acts as an anchor and provides support to connect the skin to the underlying muscle. Skin also has immunological functions due to having antigen-presenting cells, such as Langerhans cells, in the viable epidermis and dermal dendritic cells in dermis [16].

The diseased skin is mostly characterised by a diminished barrier function and altered lipid composition and organisation. Thus, the barrier features of the skin against penetration become less efficient in dermatological diseases such as atopic dermatitis, psoriasis, *etc.* The reduced barrier characteristics of the skin in atopic dermatitis are mainly due to a decrease in the amount of ceramides and the high proportion of hexagonal lateral packaging of the epidermal lipid [14,17]. There is also an irregular pattern of lipid organisation and irregular structure of protein particles of desmosomes [17]. In inflammatory skin disorders, namely dermatitis, psoriasis and fungal infections of the skin due to dermatophytes, leucocytes invade the skin. The thickness of the skin increases due to enhanced proliferation and the disturbed differentiation of keratinocytes. In the differentiation process, the nuclei and DNA of keratinocytes are degraded and, thus the amount of water in superficial skin is decreased to less than 20 % [18]. In psoriasis, the mitotic rate of the basal keratinocytes is ultimately high, and thus erythematous plaques with silvery scales at the skin surface are observed; the epidermis is thickened, and angiogenesis and the presence of inflammatory cells, such as dendritic cells, macrophages and T cells in the dermis, are increased [19].

15.3. BASIC CONCEPTS OF MICROEMULSIONS

Microemulsions are thermodynamically stable, fluid and isotropic colloidal nanocarriers with a dynamic microstructure that form spontaneously by combining appropriate amounts of oil, water, surfactant and co-surfactant [20,21]. The droplet size of microemulsions is usually in the range of 20–200 nm [22]. They are mostly prepared using the phase titration method and can be depicted with the help of pseudoternary phase diagrams. Pseudoternary phase diagrams provide the boundaries of the different phases (microemulsion, liquid crystalline, micelles) as a function of the component composition [5,22].

There has been increased interest in recent years in the use of topical vehicles that may modify drug penetration into the skin [23]. The most difficult aspect of the skin delivery of drugs is overcoming the barrier of the *stratum corneum*. Although the integrity of the skin barrier can be weakened in most of the

dermatological diseases, as mentioned above, there is still a need to deliver drugs into targeted skin layers in order to improve treatment efficacy and patient compliance. Various strategies have thus been employed with this aim, and among them microemulsion type colloidal carriers have been suggested as efficient promoters of drug localisation to skin [24,25].

15.3.1. Components of microemulsions

Microemulsions are mainly composed of oil and water phases which are successfully formulated using a combination of suitable surfactant and co-surfactant. A large number of oils, surfactants and co-surfactants are available which can be used as components of microemulsions, but a selection of the components suitable for pharmaceutical use involves a consideration of their toxicity and, if the systems are to be used topically, their irritation and sensitivity properties [22].

The optimal type of a microemulsion depends on the physicochemical properties of the drug; lipophilic drugs are preferably loaded to oil in water (o/w) type microemulsions whereas water in oil (w/o) type microemulsions are better carriers for hydrophilic drugs [21,26]. For lipophilic drugs, the ability of a microemulsion to maintain the drug in a dissolved state is strongly influenced by the solubility of the drug in the oil phase [23]. The ability of the selected oil to increase the region where the microemulsion is formed is equally important [20]. Fatty acids, alcohols, esters of fatty acids and alcohols, and medium chain triglycerides are among the most commonly used oil components in microemulsion systems [5].

The choice of the surfactant is another critical factor in the formulation of microemulsions, as it helps in the reduction of the interfacial tension by forming a film at the oil-water interface resulting in the spontaneous formation of microemulsions. The selected surfactant should microemulsify the oil and should also possess good solubilising potential for the selected drug candidate. Another crucial factor is the acceptability of the surfactant for the desired route of drug delivery. Non-ionic surfactants are mostly preferred for dermal delivery since they are well-known for their non-irritant nature [6,20]. Amongst the various surfactants, polysorbate 80 (Tween 80), sorbitan monooleate (Span 80), caprylocaproyl polyoxylglycerides (Labrasol) and phospholipids are widely used in the formulation of pharmaceutical microemulsions [20,26].

The incorporation of a co-surfactant, such as short- or long-chain alcohols or polyglycerol derivatives, in the microemulsion formulation reduces interfacial tension and increases the flexibility and fluidity of the interface by penetrating into the surfactant monolayer [5]. Diethylene glycol monoethyl ether (Transcutol), propylene glycol and poly(ethylene glycol) 400 are among the most preferred co-surfactants for dermal drug delivery [20].

15.3.2. Characterisation of microemulsions

In general, the effect of the surfactant to co-surfactant ratio, oil type and drug incorporation on the phase behaviour of the microemulsions have been characterised. Particle size and polydispersity index and the viscosity of the microemulsions are important parameters which should be identified. It has been shown that the size of the dispersed phase has an effect on drug transport into the skin [26,27]. The electrical conductivity of microemulsions has to be determined in order to identify whether the microemulsions are oil continuous or water continuous. Advanced techniques such as nuclear magnetic resonance (NMR) can be used to determine the location of the drug between the oil and water phase. From the skin delivery perspective, another important factor is the irritation potential of the oil, surfactant and co-surfactant. *In vitro* cytotoxicity tests have gained great interest for determining the biocompatibility and tolerability of microemulsions [24].

15.3.3. Enhancement mechanisms of microemulsions

The type of oil, surfactant and co-surfactant, the concentrations and ratios of these components and the type of microemulsion (o/w, w/o or bicontinuous systems) affect drug release and skin penetration from microemulsions [24]. Some of the potential mechanisms by which microemulsions would improve transport of drugs to the skin are described below and schematised in Figure 1 [21-23,27].

- Ingredients of microemulsions can modify the diffusional barrier of the *stratum corneum* either by perturbation/fluidisation of intercellular lipid bilayers or denaturation of intracellular keratin or modification of its confirmation.
- Due to the high solubilisation capacity of microemulsions an increased concentration gradient towards the skin can be reached.
- The ultralow interfacial tension and the continuously fluctuating interfaces of microemulsions can facilitate drug penetration into deeper skin layers compared to conventional formulations.
- The partitioning and solubility of drugs in *stratum corneum* could be increased depending on microemulsion composition.
- The internal phase can act as a drug reservoir resulting in controlled and sustained release from microemulsions.

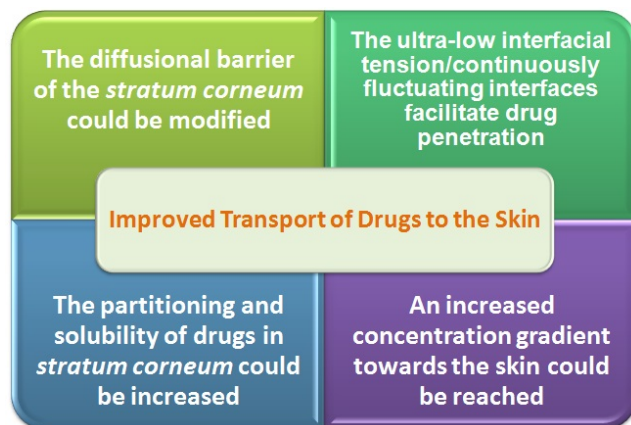


Figure 1. The potential mechanisms by which microemulsions would improve the transport of drugs to the skin

Microemulsions have additional advantages in drug delivery over conventional dermatologic formulations (emulsions, gels, *etc.*) such as improved shelf life due to their thermodynamic stability, ease of manufacture and scale-up because of the spontaneity of formation, and ability to entrap hydrophilic and hydrophobic drugs either alone or in combination. The encapsulation of therapeutic agents in the microemulsion structure can offer improvements in their chemical, photochemical and enzymatic stability [24].

Due to the broadness of the subject and the great number of studies published, this chapter will mainly focus on the influence of microemulsions as topical carriers in several common dermatological diseases discussed below. Even though a precise separation between the topical and transdermal delivery from microemulsions is not possible, most of the studies demonstrate that a more pronounced cutaneous drug localisation in skin layers, rather than percutaneous permeation, can be obtained with microemulsions [25,26].

15.4. MICROEMULSIONS AS COLLOIDAL DRUG CARRIERS FOR SKIN DISORDERS

Common dermatological diseases, including acne, atopic dermatitis, psoriasis and microbial/fungal infections, affect the life quality of people worldwide. Most of these skin disorders have been caused by inflammatory conditions and infectious pathogens. Topical delivery of drugs is always preferred for treating mild and localised dermatological conditions. The success of topical dermatologic therapies is dependent upon many factors, such as correct diagnosis, type of lesion being treated and the vehicle in which the active agent is delivered. The clinical efficiency of drugs applied topically depends on the

concentration achieved in cutaneous tissues, which is mainly related to the ability of the compound to penetrate into tissue. The enhancement of topical delivery efficacy is therefore a great challenge for improving the localisation of drugs into target sites in dermatological diseases. Different types of novel drug carriers could be an option to overcome the problems associated with conventional vehicles and to overcome the skin barrier to dermal targeting of drugs in topical drug delivery. Extensive review articles have been published, dealing with the nano-sized drug carriers intended for topical delivery of dermatological drugs [4,15,18,28-30]. The common dermatological diseases and the drugs used in their topical treatment are reviewed and research studies focused on microemulsions as a challenge for the effective treatment of these skin disorders are summarised below and in Table 1.

Table 1. Overview of topical microemulsion studies in common dermatological diseases

TREATMENT: ACNE	Drug	Oil phase	Surfactant	Co-surfactant	Aqueous phase	<i>In vitro</i> (skin/membrane) and <i>in vivo</i> studies	Ref.
	tretinoin	isopropyl myristate; transcuto P	tween 80 labrasol	propylene glycol	water	cellulose membrane	[31]
	retinoic acid	isopropyl myristate	soybean lecithin caprylyl/capryl glucoside	ethanol 1,2-hexanediol	phosphate buffer	polydimethylsiloxane membranes pig ear skin	[25]
	adapalene	oleic acid	tween 20	transcuto P	water	porcine ear skin	[32]
	salicylic acid	isopropyl myristate	tween 80	propylene glycol	water	-	[33]
	sodium salicylate	isopropyl myristate	tween 80	propylene glycol	water	cellulose membrane	[34]
	nadifloxacin	oleic acid	tween 80	ethanol	water	rat skin	[35]
	nadifloxacin	capryol 90	tween 80	transcuto P	water	rat abdominal skin	[36]
	clindamycin phosphate	isopropyl palmitate	aerosol OT	1-butanol	water	human epidermis	[37]
	nicotinamide	isopropyl palmitate	span 80	tween 80	water: isopropyl alcohol	newborn pig skin	[38]
	sodium ascorbyl phosphate	mygliol 812	labrasol	plurol oleique	water	cellulose membrane	[39]

Table 1. Continued

TREATMENT: ACNE	Drug	Oil phase	Surfactant	Co-surfactant	Aqueous phase	<i>In vitro</i> (skin/membrane) and <i>in vivo</i> studies	Ref.
	isotretinoin	isopropyl myristate	labrasol	cremophor EL plurol oleique solutol HS5	water	pig skin	[40]
	metronidazole	isopropyl myristate	lecithin	butanol	water	dialyzing tubing adult male/female patients	[41]
TREATMENT: ATOPIC DERMATITIS							
	hydrocortisone acetate	plurol oleique	labrasol	transcutol P labrafil	water	pig ear skin	[42]
	hydrocortisone acetate	eucalyptus oil	tween 80	ethanol isopropanol propylene glycol	water	cellulose membrane rabbit ear skin	[43]
	tacrolimus	cetiol B	phospholipon 90 G plantacare 2000 span 80 tagat S2	1,2-pentylene glycol	water	human skin	[44]
TREATMENT PSORIASIS							
	betamethasone dipropionate	oleic acid sefsol	tween 20	isopropyl alcohol	water	rat skin	[45]
	methotrexate	ethyl oleate	labrasol	plurol isostearique	sodium chloride solution	porcine skin	[46]
		myristic isopropyl ester	tween 80 span 80	1,2-octanediol	water		
	curcumin	eucalyptol	tween 80	ethanol	water	porcine skin	[47]

Table 1. Continued

TREATMENT: FUNGAL INFECTIONS	Drug	Oil phase	Surfactant	Co-surfactant	Aqueous phase	<i>In vitro</i> (skin/ membrane) and <i>in vivo</i> studies	Ref.							
	econazole nitrate	labrafil M1944	solutol HS15 span 80	transcutol P	water	rat skin	[48]							
	miconazole nitrate	1-decanol: 1-dodecanol	oramix® NS 10 lecithine	propylene glycol 1,2- hexanediol	phosphate buffer	pig ear skin	[49]							
	ketoconazole	lauryl alcohol	labrasol	ethanol	water	rat skin	[50]							
	clotrimazole	lemon oil isopropyl myristate	tween 80	<i>n</i> -butanol	water	cellulose membrane mice abdominal skin	[51]							
	sertaconazole	oleic acid	tween 80	propylene glycol	water	mice abdominal skin	[52]							
	terbinafine	oleic acid	labrasol	transcutol P	water	human cadaver skin	[53]							
	terbinafine	oleic acid	labrasol	transcutol P	water	rat skin	[54]							
	naftifine	oleic acid	cremophor EL cremophor RH40	transcutol P	water	pig skin	[55]							
								oxyresvera trol	isopropyl myristate	tween 80	isopropyl alcohol	water	shed snake skin	[56]
								penciclovir	oleic acid	cremophor EL	ethanol	water	mouse skin	[57,58]
acyclovir	isopropyl myristate captex 355 labrafac	tween 20	span 20	water dimethylsulfoxide	mice skin	[59]								

15.4.1. *Acne vulgaris*

Acne vulgaris (acne) is a common skin disorder, affecting over 80 % of the population at some point in their lifetime. Acne is caused by follicular epidermal hyperproliferation and abnormal sebum production within pilosebaceous units in the skin. The anaerobic diphtheroid *Propionibacterium acnes* (*P. acnes*) has been demonstrated as the principal cause of inflammation in *acne vulgaris* [60,61]. *P. acnes* is naturally present deep within the follicle and contributes to the progression of acne realising pro-inflammatory mediators that lead to the formation of papules or pustules, which worsen the severity of the disease [62]. Other dermal bacterial flora such as *Staphylococcus epidermidis* and *Staphylococcus aureus* (*S. aureus*) may play a role in acne aetiology, particularly as secondary infections [60]. Acne can be classified as mild, moderate, or severe according to the morphology of lesions. The lesions of acne are clinically divided into inflammatory and non-inflammatory types [62].

When choosing medications to treat an individual with acne, several factors are considered, including the clinical type and severity of acne, skin type and the presence of scarring. Topical therapy is indicated for mild to moderate acne and mainly involves the application of retinoids, antibiotics, and antibacterial agents, whereas systemic therapy is required for severe acne (Table 2) [63].

Table 2. Topical agents in the treatment of *acne vulgaris*

Category	Antiacne compounds	
Retinoids	tretinoin adapalene moltretinide	isotretinoin tazarotene all- <i>trans</i> -retinoyl- β - -glucuronide
Hydroxy acids	glycolic acid lactic acid lipohydroxy acid	mandelic acid salicylic acid
Antibacterial agents	benzoyl peroxide clindamycin azelaic acid chloroxylenol metronidazole	erythromycin nadifloxacin azithromycin sodium sulfacetamide 5-amino levulinic acid
Antioxidants	nicotinamide	sodium ascorbyl phosphate

The active compounds in topical acne treatment are mainly delivered through conventional formulations such as solutions, gels, creams and lotions. The major disadvantages of topical treatment with conventional formulations are their potential to cause local side effects such as skin irritation. Drugs applied topically must also pass across the *stratum corneum* barrier and reach the site of action (the lipophilic environment of the pilosebaceous unit). Targeting the deeper layers of skin is not possible with conventional formulations, however. It could therefore be a good option to improve the skin uptake of antiacne drugs with a carrier facilitating skin targeting, while decreasing systemic exposure and toxicity. Microemulsion-type colloidal carriers have been used for the delivery of many drugs in topical dermatological therapy and they can be good alternatives to enhance the skin delivery of antiacne compounds.

15.4.1.1. Microemulsion formulations of retinoids

Retinoids normalise epidermal differentiation in skin, and topical retinoids perform many functions that directly affect the pathogenic steps associated with acne [64]. Tretinoin was the first retinoid used for the treatment of acne. The efficacy of conventional preparations is limited, however, by cutaneous irritation. Tretinoin microemulsions have been prepared and evaluated for their droplet size, stability, zeta potential, viscosity and conductivity. The optimised tretinoin microemulsion demonstrated an enhanced *in vitro* release profile compared to commercial gels and creams [31]. Trotta *et al.* evaluated the ability of microemulsion systems of both type, o/w or w/o, to deliver retinoic acid through *in vitro* pig skin. They observed a large increase in retinoic acid skin deposition from o/w microemulsion systems [25]. Adapalene was the first synthetic retinoid used in the treatment of acne. It is a highly lipophilic compound and it has been shown that adapalene penetration of the hair follicles is increased with microemulsions [32]. Microemulsion-type topical carriers for isotretinoin were investigated with the objective of improving skin uptake of the drug. After *in vitro* permeation studies, the dermal penetration of isotretinoin from microemulsions was investigated by tape stripping. Confocal laser scanning microscopy provided insights into the localisation of the drug in the skin. The interaction between the microemulsion components and *stratum corneum* lipids was studied by attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectroscopy. The results indicate that microemulsion-based novel colloidal carriers have the potential to enhance skin delivery and the localisation of isotretinoin [40].

15.4.1.2. Microemulsion formulations of hydroxy acids and antibacterial agents

Salicylic acid is a keratolytic agent used in topical products with antimicrobial actions. Microemulsions and gelled microemulsions have been reported as suitable carriers for the topical application of different concentrations of salicylic acid [33,34]. In order to develop alternative formulations for the

topical administration of the antibacterial compound nadifloxacin, microemulsions were evaluated by various researchers [35,36]. Nanocarrier-based microemulsion formulations of nadifloxacin have been found to be promising carriers, showing enhanced efficacy against *Propionibacterium* acne. Microemulsions were developed as alternative formulations to the topical delivery of clindamycin phosphate. Drug permeation through the human epidermis *via* microemulsions has been found considerably better than that *via* its solution, indicating the enhancement of skin permeation by clindamycin phosphate microemulsions [37]. A topical w/o type microemulsion of metronidazole was shown to be more effective in the reduction of inflammatory lesions and erythema compared to commercial gel products [41].

15.4.1.3. Microemulsion formulations of antioxidant agents

A microemulsion containing nicotinamide has been evaluated for its characteristics, stability and skin penetration and retention. The microemulsion system has been found stable and provided a greater amount of skin retention than skin penetration, resulting in its suitability as an antiacne product [38]. Sodium ascorbyl phosphate is the hydrophilic derivative of ascorbic acid and is used in many cosmetic and pharmaceutical formulations because of the antioxidant activity. Microemulsions were selected as carrier systems for the topical delivery of sodium ascorbyl phosphate and it was shown that the drug maintained its stability and demonstrated sustained release when incorporated in the inner phase of the microemulsions [39].

15.4.2. Atopic dermatitis

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease with a wide range of severity [65]. It is one of the most common skin disorders and affects approximately 20 % of children and 1–3 % of adults in developed countries [66]. In AD, skin barrier abnormalities are associated with a deficiency in ceramides and antimicrobial peptides, and function mutations in the filaggrin gene, which encodes for the filament aggregating protein, are also reported. A filaggrin mutation contributes to a disrupted epidermal barrier, increased trans-epidermal water loss, and inflammation. There are also many exogenous factors that can exacerbate barrier dysfunction in AD, specifically soaps and surfactants in detergents that accelerate corneocyte and lipid degradation. In genetically predisposed people the activation and skin-selective homing of peripheral-blood T cells and effector functions in the skin represents sequential immunologic events in the pathogenesis of atopic dermatitis [67]. Patients with AD are susceptible to a variety of secondary cutaneous infections such as *S. aureus* infections. The cutaneous and nasal colonisation of *S. aureus* exacerbates AD symptoms and the density of *S. aureus* colonisation correlates with AD clinical severity [66].

AD treatment requires a multi-therapeutic approach including short-term treatment to control AD flares as well as longer-term strategies to control symptoms between flares and to prolong the time until the next flare. Topical corticosteroids and more recently topical calcineurin inhibitors are preferred in the topical treatment of AD [68,69]. The use of emollients in AD treatment is considered supportive because hydration of the skin helps to improve the dryness, the pruritus and restore the disturbed skin barrier, and may also lead to a reduction of steroid therapy [67]. In topical therapy the treatment and prevention of acute inflammatory processes is essential to avoid exacerbation of the disease. Novel colloidal carriers could be an option for overcoming the problems associated with conventional vehicles.

15.4.2.1. Microemulsion formulations of topical corticosteroids

Topical corticosteroids are recommended as first-line therapy in AD treatment. Although they provide rapid relief, the major problem in treatment is corticophobia, which is related to potential local side-effects (striae, petechiae, telangiectasia, atrophy, and acne or rosacea), associated with long term topical corticosteroid usage. They are therefore preferred for use over short periods (5–7 days) to settle eczema flare ups [67]. Topical corticosteroids are classified in Table 3 on the basis of their relative potency class. Clobetasol propionate is a super potent corticosteroid of the glucocorticoid class used to treat various skin disorders including atopic dermatitis, psoriasis and vitiligo. It suppresses the immune system by reducing immunoglobulin action and like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. Microemulsion and microemulsion-based gel formulations were evaluated as a vehicle for the dermal delivery of clobetasol propionate. Microemulsion based gel formulation showed significant changes in skin structure and the visualisation of cutaneous uptake *in vivo* using laser scanning microscopy-confirmed targeting of clobetasol propionate to the epidermis and dermis layers [70,71]. The permeation of hydrocortisone from microemulsions across *in vitro* animal membranes was examined and it has been proposed that gel and ointment formulations of hydrocortisone could be more suitable when it is desirable to restrict drug absorption only to the diseased skin area. Microemulsion carriers promote the transdermal permeation of hydrocortisone which in turn could lead to the occurrence of systemic side effects [42,43].

Table 3. Classification of topical corticosteroids

Relative potency class	Topical corticosteroid
1 – Super potent	clobetasol propionate halobetasol propionate
2 – Potent	betamethasone dipropionate desoximetasone fluocinonide
3 – Upper mid-strength	betamethasone dipropionate betamethasone valerate fluticasone propionate triamcinolone diacetate
4 – Mid-strength	hydrocortisone valerate mometasone furoate
5 – Lower mid-strength	betamethasone valerate fluticasone propionate hydrocortisone butyrate hydrocortisone valerate triamcinolone acetonide
6 – Mild	alclometasone dipropionate desonide fluocinolone acetonide
7 – Least potent	hydrocortisone

15.4.2.2. Microemulsion formulations of topical calcineurin inhibitors

Topical calcineurin inhibitors tacrolimus and pimecrolimus are approved for second-line therapy for the treatment of AD when the use of topical corticosteroids is ineffective or inadvisable [69,72]. They inhibit activation of T cells and mast cells by blocking calcineurin and suppressing inflammatory cytokines and other mediators of the allergic inflammatory reaction [64]. In contrast to corticosteroids, topical calcineurin inhibitors do not lead to skin atrophy [67]. Tacrolimus and pimecrolimus have demonstrated short-term (3 weeks) and long-term (24 months) safety and efficacy in the treatment of AD in adults and children [73]. Tacrolimus is a lipophilic and high-molecular weight (MW : 822.05) molecule and is commercially formulated as a lipophilic ointment. A sufficient bioavailability in the living epidermis is essential for the efficacy of tacrolimus, which cannot be achieved by conventional formulations. To overcome this, a microemulsion-type colloidal carrier has been developed, and it was shown that microemulsions provided significantly higher bioavailability of tacrolimus in the intended skin compartment than the commercially established reference preparation [44].

15.4.3. Psoriasis

Psoriasis is an immune-mediated disorder which is characterised by relapsing episodes of inflammatory lesions and hyperkeratotic plaques. It is known to be the most prevalent autoimmune disease in humans and ranges in severity from mild to severe [73,74]. The goals of psoriasis treatment are to gain initial and rapid control of the disease process, decrease the percentage of body surface area affected, decrease plaque lesions and improve a patient's quality of life. Topical therapies are preferred to treat mild and localised psoriasis, and phototherapy or systemic therapy is reserved for severe forms. Conventional topical formulations are inefficient in providing a targeted effect and patient noncompliance remains a critical limitation in the effective treatment of psoriasis [75,76].

For the past 60 years the mainstay of the topical treatment of psoriasis has been corticosteroids. They are available in a variety of formulations, with potencies ranging from superpotent to least potent (Table 3) and are frequently used in combination with other forms of topical treatment such as Vitamin D analogues. The Vitamin D3 analogues calcipotriene and calcitriol, topical retinoids (tazarotene), topical tars, anthralin and keratolytics (salicylic acid, urea and glycolic acid) are the other therapy options in mild psoriasis treatment [74,76]. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) have been found less effective in treating psoriasis than AD and the most frequently reported adverse event is skin irritation at the application site [75,77].

Novel colloidal carriers such as microemulsions can be effective alternatives in alleviating the side effects associated with the available therapeutic agents. Microemulsions can provide enhanced administration of drugs to the epidermis and dermis and the excess growth of skin cells in psoriasis could be controlled more easily this way [78].

15.4.3.1. Microemulsion formulations in topical psoriasis treatment

Betamethasone dipropionate, an upper-mid strength topical corticosteroid, has been prepared as a microemulsion and a microemulsion-based gel formulation together with salicylic acid for the treatment of psoriasis. The microemulsion based gel formulation has been found safe and effective and permeation of both drugs was enhanced when compared to the conventional gel formulation [45]. Methotrexate is one of the most effective systemic agents for the treatment of severe psoriasis. The traversing efficiency of methotrexate from microemulsion and solution formulation has been studied and it was found that the microemulsion formulation may be of value in the topical administration of methotrexate [46].

15.4.4. Fungal infections

Infections caused by pathogenic fungi and limited to the human skin, nails, hair and mucosa, are referred to as superficial fungal infections. Dermatophytes are one of the most frequent causes of tinea and onychomycosis. Candidal infections are also among the most widespread superficial cutaneous fungal infections. Despite the fact that fungal infections are rarely life threatening, they are important because of their worldwide increased incidence, person-to-person transmission, and morbidity [79].

The topical treatment of fungal infections has several advantages, including targeting the site of infection, a reduction of the risk of systemic side effects, enhancement of the efficacy of treatment and high patient compliance. The main classes of topical antifungals are the polyenes, azoles, allylamine/benzylamines and hydroxypyridones (Table 4). Currently, these antifungal drugs are commercially available in conventional dosage forms such as creams, gels, lotions and sprays [80].

Table 4. Topical Antifungal Compounds

Category	Topical antifungal compound
Azoles	econazole, miconazole, ketoconazole clotrimazole, oxiconazole, sertaconazole sulconazole
Allylamines/benzylamines	terbinafine, naftifine, butenafine
Polyenes	nystatine
Hydroxypyridones	ciclopirox

The efficiency of topical antifungal treatment depends on the penetration of drugs through the target tissue. Antifungal drugs should reach effective therapeutic levels in viable epidermis after dermal administration. In this context, the formulation may play a major role in the penetration of drugs into skin [81]. New approaches to the topical treatment of fungal infections of the skin encompasses new delivery systems for approved and investigational compounds. Microemulsions are among those new carriers used to ensure effective drug concentration levels in the skin after the dermal administration of antifungals.

15.4.4.1. Microemulsion formulations of azole antifungals

Microemulsion formulations of econazole nitrate have been prepared, characterised and the percutaneous permeation of econazole nitrate *in vitro* through rat skin was investigated. It was concluded that microemulsions enhanced drug retention in the skin and may be promising vehicles for the effective percutaneous delivery of econazole nitrate [48]. It was reported that

skin accumulation of miconazole nitrate from positively charged microemulsions increased significantly when compared with accumulation from their negatively charged counterparts. The increased accumulation has been attributed to the interaction between the positive microemulsion system and negatively charged skin sites [49]. The percutaneous absorption of ketoconazole from microemulsions was enhanced, and histopathological investigations on rat skin demonstrated the safety of prepared microemulsions for topical delivery of ketoconazole [50]. Clotrimazole topical microemulsions and microemulsion based gels have been prepared and evaluated for their stability, droplet size, viscosity, *in vitro* release across cellulose membrane and drug retention in skin. Both prepared formulations achieved significantly higher skin retention for clotrimazole over clotrimazole commercial cream [51]. A microemulsion-based hydrogel has been studied as a topical delivery system of sertaconazole for effective treatment of cutaneous fungal infections. The inhibition zone of the microemulsion-based hydrogel formulation against *Candida albicans* (*C. albicans*) was found to be higher in comparison with sertaconazole commercial cream. The drug retention capacity of the microemulsion hydrogel was also higher than that of commercial cream and did not cause any irritation in skin sensitivity studies on rabbits [52].

15.4.4.2. Microemulsion formulations of allylamine/benzylamine antifungals

A microemulsion-based terbinafine gel has been developed for the treatment of onychomycosis. The optimised microemulsion-based gel formulation demonstrated better penetration and retention of terbinafine in the human cadaver skin as compared to the commercial cream. Terbinafine microemulsion in the gel form also showed better activity against *C. albicans* and *Trichophyton rubrum* than the commercial cream [53]. In another study, a microemulsion formulation of terbinafine was developed and optimised with a view to provide controlled drug release and to enhance the skin permeability of terbinafine. It was found that the optimised microemulsion formulation showed better anti-fungal activity against *C. albicans* and *Aspergillus flavus* than the marketed product [54]. The effect of microemulsion-type colloidal carriers of naftifine on pig skin has been investigated by attenuated total reflectance infrared spectroscopy *in vitro*. The results revealed that treatment with microemulsion formulations lead to intercellular lipid bilayer disruption in the *stratum corneum*. Tape stripping studies showed that naftifine was in the lower layers of the skin after 24 h of treatment with microemulsion formulations [55].

15.4.5. Viral infections of the skin

Herpes simplex viruses (more commonly known as herpes) are categorised into two types: *herpes simplex* type 1 (oral herpes) and *herpes simplex* type 2 (genital herpes). Most commonly, herpes type 1 causes herpetic lesions around

the mouth and lips. Following a primary infection, the virus may become latent within nerve ganglia and recurrent infections may occur. Topical antiseptics or antibiotics may prevent secondary infections and antiviral compounds may be effective in reducing the length and severity of attacks [82].

15.4.5.1. Microemulsion formulations in topical viral infection treatment

Microemulsion-based formulations for the topical delivery of acyclovir have been developed. *In vivo* antiviral studies showed that a single application of acyclovir microemulsion formulation resulted in complete suppression of the development of herpetic skin lesions [59]. The skin irritation potential and pharmacodynamics of penciclovir loaded microemulsion were investigated. Male guinea pigs were employed as animal models which were infected with *herpes simplex* virus type 1 in a pharmacodynamics study. The results indicated that compared with commercial penciclovir cream, penciclovir microemulsion could significantly inhibit the replication of *herpes simplex* virus type 1 in skin [57]. Microemulsion-based hydrogel as a topical delivery system for penciclovir has been investigated. The results of permeation test *in vivo* in mice showed that compared to the commercial cream, microemulsion-based hydrogel and microemulsion could significantly increase the permeation of penciclovir into both epidermis and dermis. Skin irritation tests in rabbits demonstrated that multiple applications of microemulsion-based hydrogel of penciclovir did not cause any erythema or oedema [58]. The permeating ability of oxyresveratrol in microemulsion was evaluated, and the efficacy of oxyresveratrol microemulsion in cutaneous *herpes simplex* virus type 1 infection in mice was examined. In cutaneous infection in mice, at 20 %, 25 %, and 30 % w/w, oxyresveratrol microemulsion topically applied five times daily for seven days after infection, was significantly effective in delaying the development of skin lesions and protection from death compared to the untreated control [56].

15.5. CONCLUSIONS

Dermatological skin disorders due to fungal, viral bacterial infections, and inflammatory reasons can seriously affect people's quality of life. Although there have been some great innovations in treatment, many of problems related to skin diseases remain difficult to treat efficiently. In particular, the adequate skin penetration of drugs in the target layers is a great challenge in topical therapy. The integrity of the skin barrier can be weakened in most of the dermatological diseases, such as atopic dermatitis and psoriasis. There is a need to target drugs into skin layers since the conventional dosage forms such as creams, ointments, and gels can be inefficient in achieving the required drug concentrations in the target cutaneous tissues. The development of novel carriers would have advantages in terms of the enhancement of both

therapeutic aspects and improvement of patient compliance. Today, only a few products with nano-sized carriers have been approved for topical treatment and are on the market, but there have been great efforts made, and a considerable amount of research focused on the optimisation of nano-sized novel carriers for skin delivery. Numerous strategies including optimisation of colloidal carriers such as microemulsions have emerged over recent years to optimise the targeted delivery of drugs into skin layers, and some promising data, to some extent, has been published.

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