Chapter 24

Corticosteroids for Skin Delivery: Challenges and New Formulation Opportunities

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http://dx.doi.org/10.5772/53909

1. Introduction

Currently, corticosteroids are the most widely used class of anti-inflammatory drugs. The introduction of topical hydrocortisone in the early 1950s provided great advantages over previously available therapies and initiated a new era for dermatological therapy. Their clinical effectiveness in the treatment of dermatological disorders is related to their vasoconstrictive, anti-inflammatory, immunosuppressive and anti-proliferative effects. Despite their benefit in the therapy of inflammatory diseases, topical corticosteroids (TC) are associated number of side effects that limit their use. Most TC are absorbed in quantities that can produce both systemic and topical side effects [1-2]. Table 1 shows the currently used TC in various dermatological disorders according to the British classification system [3]. In general, mild and moderate TC are used for long-term treatments while the potent and very potent products especially preferred for shorter regimes.

Over the years, research has focused on strategies to optimize the potency of steroids while minimizing adverse effects due to drug absorption across the skin. In other words, research focus no longer been on the synthesis of more potent derivatives but on safer one. Several attempts have been made to increase the safety of TC treatment, including new application schedules, special vehicles and new synthesized agents [4]. However, "ideal" TC have not yet been synthesized. They should be able to permeate the stratum corneum (SC) and reach adequate concentrations in the epidermis without reaching high systemic concentrations.

One of the approaches to reduce the adverse effects of TC is to enhance their permeability so as to reduce the topically applied dose [5]. Several approaches have been attempted, such as iontophoresis, electroporation or the application of eutectic mixtures [6,7]. However, the use of chemical penetration enhancers is the most widely used approach to increase skin delivery [8].

POTENCY	DOSE % (w/w)	TC
Mild		Hydrocortisone
	1	Hydrocortisone acetate
	0.25	Methylprednisolone
	0.05	Alclometasone dipropionate
	0.01-0.1	Dexamethasone
	0.0025	Fluocinolone acetonide
	0.75	Fluocortyn butyl ester
	0.5	Prednisolone
Moderate	0.05	Clobetasone butyrate
	0.02	Triamcinolone acetonide
	0.005	Fluocinolone acetonide
Potent	0.05	Betamethasone dipropionate
	0.1	Betamethasone valerate
	0.025	Fluocinolone acetonide
	0.1	Hydrocortisone butyrate
	0.05	Halometasone monohydrate
	0.1	Diflucortolone valerate
Very potent	0.1	Halcinonide
	0.05	Clobetasol propionate

Table 1. The currently used TC in various dermatological disorders [3]

TC are formulated in a variety of conventional vehicles, including ointments, creams, lotions and gels. In addition to conventional formulations several innovative systems such as nanoparticles, liposomes, microemulsions, foams and patches have been evaluated for different dermatological conditions. Colloidal drug carrier systems, such as liposomes and nanoparticles, could target TC to the viable epidermis, where the inflammatory reactions take place. In particular, liposomal preparations showed a strong affinity for the SC. Patents filed on topical nanoparticulate formulations also claimed the importance of colloidal drug carrier systems for this type of applications [9-12].

This chapter will review major innovations and advances in TC formulations based on the published articles and patent applications. The main factors influencing the effectiveness and bioavailability of TC will be also briefly discussed before emphasizing formulation alternatives.

2. Skin structure

The skin, in Latin called cutis, is considered the largest organ of the body, accounting more than 10% of the body mass and having an average surface of approximately 2 m^2. The

thickness of the skin is highly variable (average thickness of 1.5 mm), depending of several factors as the anatomic location, age and sex. The functions of the skin have been classified as protective, homeostatic, or sensorial. To maintain its characteristics, this organ is in a continual renewing process [13].

Anatomically, the skin consists on 3 basic layers: epidermis, dermis and subcutaneous tissues. Depending on the region considered, the epidermis is made of 4-5 sublayers that, from bottom to top, are: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum (present only in palm and soles) and SC or horny layer. In addition to these structures, there are also several associated appendages: hair follicles, sweat glands, apocrine glands, and nails [14].

The most important skin function is permeability barrier function. The outermost layer of the epidermis, the SC, with its peculiar structure, plays an important role in permeability barrier function [15]. Due to its barrier properties, the skin membrane is equally capable at limiting the molecular transport from and into the body. Overcoming this barrier function will be the purpose of skin drug delivery.

3. Clinical limitations and side effects of TC

TC are successfully used in the treatment of several common cutaneous diseases but their major limitation is still their side effect potential. The most common side-effects occur locally in the areas of skin treated with the steroid. Probably the most well known is thinning of the skin (atrophy), which sometimes results in permanent stretch marks (striae). Fine blood vessels may swell and become prominent under the skin surface (telangiectasia), again a permanent change. In addition, there may be a temporary loss of pigment in the areas of skin treated; this may be more noticeable in dark-skinned people. Sometimes the skin may become allergic to the steroid, making the eczema appear to get worse. The skin may also bruise more easily and become more susceptible to infection.

The occurrence and severity of the side effects are depend on the duration of use, dosage, dosing regime and spesific drug used, along with individual patient variability. However, the highest risk factor seems to be prolonged use [16-18]. The concentration of corticosteroid in systemic circulation and risk of sytemic side effects are increased by prolonged therapy with TC. Systemic side-effects of TC, such as pituitary–adrenal axis suppression, should be taken into account when treating children. Children have a higher ratio of total body surface area to body weight (about 2.5- to 3-fold that of adults) and adrenal suppression may cause growth retardation.

The principle systemic side effects associated with TC are bodyweight gain, Cushing's syndrome, electrolyte imbalance, hypertension, diabetes mellitus, pseudoprimary aldosteronisim, growth retardation, osteoporosis peptic ulser and gastritis. In addition, TC are mostly capable of causing local side effects. One particularly important local side effect is epidermal thinning or atrophy [19]. This effect is characterized with the reduction in cell size and number of cell layers in epidermis. Other local side effects related to TC treatment

are steroid acne, rosacea, perioral dermatitis, corticoid acne, allergic contact dermatitis, hypopigmentation, glaucoma, cataracts, worsening of cutaneous infections and hypertrichosis [2]. Table 2 represents the possible local and systemic side effects of TC which are organized in subsections for tissue-organ level.

TISSUE - ORGAN	SIDE EFFECTS
Cardiovascular system	Hypertension
Endocrin system	Adrenal insufficiency, Cushing's syndrome, diabetes mellitus, bodyweight gain, pseudoprimary aldosteronism
Eye	Glaucoma, cataract
Immune system	Increased risk of infection, re-activation of latent viruses
Gastrointestinal	Peptic ulser, gastritis
Central nervous system	Behavioural changes, loss of memory/cognition
Skeleton and muscle	Growth retardation, osteoporosis
Skin	Atrophy, striae, allergic contact dermatitis, delayed wound healing, steroid acne, perioral dermatitis, rosacea, erythema, teleangiectasia, hypertrichosis, hypopigmentation

Table 2. The possible local and systemic side effects of TC

4. Classification of TC

TC are classified in two different ways by American and British National Formulary classification systems [20-21]. The American classification system includes seven potency groups while the British National Formulary contains four groups. In the former system, the potency of a product is defined by the corticosteroid, its concentration and the nature of the vehicle. On the other hand, The British classification system is irrespective of the topical vehicle used. According to the American classification sytem, it is important to note that the greater in potency for TC result in the greater therapeutic efficacy and side effects. Therefore, low-potency formulations should be used for long term treatments by physicians while the more potent products should be chosen for short periods and sites such as palms and soles, where low potency TC are ineffective [1,2].

5. Formulations of TC

It is well known that, besides the active molecule, the potency of each topical formulation can be influenced by vehicle characteristics. Vehicles should allow adequate release of the active compound, spread easily and be aesthetically pleasant [21]. Some important rules should be considered when choosing a vehicle; the solubility, release rate and stability of the therapeutic agent in the vehicle, the ability of the vehicle to hydrate the SC, the physical and chemical interactions of the vehicle with the skin and active molecule and also the phase, localization and extent of disease [22].

TC are formulated in a variety of conventional vehicles, including ointments, creams, lotions and gels. As mentioned previously, the character of the vehicle system defines the potency of topical preparations and its selection is crucial for product performance.

Ointments are semi-solid preparations intended for application to skin or mucous membranes. There are four types of ointment bases; hydrocarbon bases, absorption bases, emulsion bases and water-soluble bases. The potential of the absorption is affected by choice of the bases. Hence, appropriate selection of the base is important for the efficacy of the dermal therapy [23].

Ointment formulations are generally more effective than creams containing the same drug and they are especially preferred for infiltrated, lichenified lesions. In a comparative study, the absorption of clobetasol propionate from ointment and cream formulations was evaluated and it was reported that a greater amount of clobetasol propionate was absorbed from the ointment [24]. Ointments including well-known and new synthesized TC were formulated and they were still first-option for treatment of dermatological diseases. However, the greasy nature and hardness of the removal from the skin due to their lack of water-washability is their disadvantages.

Mobile dispersions intended for topical application are generally described as lotions and semi-solid systems as creams. Although, creams are usually emulsions of the oil-in-water type (aqueous creams) or water-in-oil type (oily creams), lotions are mostly oil-in-water emulsions [25]. Regarding to the phase of disease, lotions and creams are generally recommended in acute and subacute dermatoses. Good compliance is obtained by prescribing creams and lotions which are easily applied by patients rather than ointments in case of large extensional dermatoses. Sequeira et al. [26] filed a patent application which provided a corticosteroid lotion formulation exhibiting high vasoconstrictor and excellent anti-inflammatory activities in steroid responsive dermatoses. The addition of propylene glycol to a hydro-alcoholic lotion base exhibited and significantly higher vasoconstrictor activity than the corresponding lotion without propylene glycol.

Gels are semi-solid systems with dispersions of small or large molecules in an aqueose vehicle with a gelling agent. The gel formulations are suitable for topical delivery of drugs for treatment of diseases due to lack of irritating components. Pharmaceutical gel formulations for topical drug delivery include drug and gelling agent [27]. Gels based on carbopol, cellulose derivatives and chitosan are commonly used in the pharmaceutical and cosmetic industries [28, 29].

Recently, new hydrogel formulation intended for cosmetic use was introduced as a novel formulation of steroids for the treatment of atopic dermatitis. The formulation was prepared with carbopol-based polymer that contained 0.05% (w/w) of micronized desonide which is a well-known synthetic corticosteroid. This formulation was easily applied for atopic dermatitis patients aged 3 months. A wide variety of studies have been performed to validate the safety and efficacy of this product and these studies supported very favourable safety, tolerability and efficacy profile [30, 31].

Senyigit et al. [32] investigated the effect of vehicles (chitosan and sodium-deoxycholate gel) on the skin accumulation and permeation of two topical corticosteroids: clobetasol propionate and mometasone furoate. Commercial cream formulations containing the same amount of drug were also used for comparison. It was reported that sodium-deoxycholate gel formulation dramatically improved the amount of drug in the skin although chitosan gel produced the same skin accumulation as commercial creams for both active agents. In addition, all of these gel formulations did not induce the permeation.

For conventional formulations it can be stated that the effectiveness of the active agent is directly related to the composition of the formulation. In general, the potency of the corticosteroids in the formulations could be listed in order such as; ointments> gels> creams> lotions. This generalization was supported with a patent filed by McCadden [33]. The brief summary about conventional TC formulations including pharmaceutical characteristics, clinical usage, benefits and disadvantages were given in Table 3.

Formulation type	Pharmaceutical characteristics	Clinical usage	Benefits	Disadvantages
Ointment	Semi-solid preparations containing different types of ointment bases	Infiltrated, lichenified lesions	Occlusive property on the skin for inducing skin hydration at the skin-ointment interface	Greasy nature and hardness of the removal from the skin due to their lack of water-washability
Cream	Oil-in-water (aqueous creams) or water-in-oil (oily creams) type of emulsion	Acute and subacute dermatoses	Easy application and good patient compliance	Difficulty of spreadability and soiling linen and clothing during treatment for oily creams
Lotion	Generally oil-in-water emulsions	Acute and subacute dermatoses	Easy application and good patient compliance	Not suitable for use on dry skin
Gel	Dispersions formulated with a gelling agent	Suitable for all types of skin diseases	Easy application, easy to attach to the skin, good patient compliance and lack of irritating components	-

Table 3. The summary about conventional TC formulations

The activity of a TC formulation can be enhanced by adding a chemical penetration enhancer which may result in an increase of drug delivery into skin. Chemical penetration enhancers have been reviewed by several researchers and the authors underline the difficulty to select rationally a penetration enhancer for a specific permeant [34-36]. Recent studies showed that terpenes appear to be promising penetration enhancers for pharmaceutical formulations with favourable properties such as low cutaneous irritancy and possess good toxicological profile [32, 37].

Recently, it has been a great interest in developing new drug carriers for TC that may contribute to reduction of side effects. Therefore, in addition to previously mentioned conventional formulations several innovative systems such as nanoparticles, liposomes, microemulsions, foams and patches have been developed for TC.

Liposomes, microemulsions, solid lipid and polymeric nanoparticles have been proposed to increase percutaneous absorption of therapeutic agents while mitigating the damage to the skin barrier function [38,39]. Besides, the drug targeting to the skin or even to its substructures could be realized by micro- and nanoparticulate systems [40,41]. These drug carrier systems could target glucocorticoids to the viable epidermis, where the inflammatory reactions take place [9]. In particular, liposomal preparations showed strong affinity for the SC [42].

The loading of therapeutic agents into nanoparticles and administration to the skin using a simple vehicle offer many advantages over other traditional topical formulations, including enhanced formulation aesthetics, protection of unstable active agents against degredation, targeting of active agents to the skin layers and prolonged active agent release [43]. As a consequence of their proposed advantages in dermal/transdermal formulations two most common types of particles have been produced: Lipid nanoparticles and polymeric nanoparticles. The uses of lipid and polymeric nanoparticles for pharmaceutical formulations applied to skin have been reviewed by several authors [40, 44-46]. Most of the data reported on TC was obtained using lipid nanoparticles of differing lipid compositions.

The inclusion of prednicarbate into solid lipid nanoparticles (SLN) of various composition appeared to increase the penetration of the drug into human skin by 30% as compared to cream, permeation of reconstructed epidermis increased even 3-fold [47]. In a subsequent report SLN were shown to induce prednicarbate targeting in the epidermal layer in excised human skin and reconstructed epidermis [9]. Epidermal targeting was evidenced also for prednisolone, the diester prednicarbate and the monoester betamethasone 17-valerate included in solid lipid nanoparticles [48]. The authors hypothesized specific interactions of the drug-carrier complex and the skin surface, possible by the lipid nature and nanosize of the carrier. On the other hand, using the appropriate lipid combination, the skin retention of betamethasone 17 valerate was increased when SLN was used as a vehicle compared to a conventional formulations [49], both using intact skin as well as barrier impaired [50].

Clobetasol propionate was included in SLN as well [51]. SLN containing cream registered significant improvement in therapeutic response (1.9 fold inflammation, 1.2 fold itching) in terms of percent reduction in degree of inflammation and itching against marketed cream.

de Vringer disclosed a stable aqueous suspension of SLNs, comprising at least one lipid and preferably also at least one emulsifier for topical application to the body. According to this invention steroidal anti-inflammatory compound such as hydrocortisone, hydrocortisone-17α-butyrate, budesonide or TA, anti-proliferatives, anti-psoriatics, anti-eczema agents and dithranol could be succesfully incorporated into the suspension of SLNs. It was stated that a combination of two or more topically effective medicaments could also be used [52]. Senyigit et al. [53] prepared lecithin/chitosan nanoparticles containing clobetasol propionate and found a preferential retention in the epidermis while no permeation across the skin was observed. In vivo studies including transepidermal water loss measurements, anti-inflammatory effect and histological evaluation of the formulations on wistar albino rats were also performed and the results were promising (Data not published).

Liposomes are lipid vesicles prepared with phospholipids which have been shown to facilitate transport of drugs into and across skin [54]. Recently, many reports have been published on percutaneous enhancing property of liposomes for both hydrophilic and lipophilic compounds [55]. Liposomes do not only enhance the drug penetration into the skin by showing slow release, but also decrease the clearence of drug by minimizing its absorption into the systemic circulation [56]. Hence, the liposomes can improve the therapeutic effectiveness of TC while reducing systemic side effects. However, many stability problems are reported for liposomes.

Mezei et al. [57, 58] applied triamcinolone acetonide (TA) in liposomes and compared it with TA in Dermabase®. In this study, four- to five fold higher TA concentrations in the epidermis and dermis, with lower systemic drug levels were observed when the drug was delivered from liposomal lotion in comparison with conventional formulations of the same drug concentration.

Lasch and Wohlrab [59, 60] studied the skin distribution of cortisol and hydrocortison after application in a cream and liposomes. As a result, improved concentration-time profile was observed in skin layers by liposomes for both drugs.

Korting et al. [61] compared the efficacy of betamethasone dipropionate encapsulated in liposomes and cream. The liposomes were prepared with egg lecithine and incorporated in a polyacrylate gel. The in vivo studies were carried out in patients with atopic eczema and psoriasis vulgaris. It was concluded that, betamethasone encapsulated in liposomes improved the antiinflammatory action, but not the antiproliferative effect.

Fresta et al. [62] prepared skin-lipid liposome formulations of different corticosteroids (hydrocortisone, betamethasone valerate and TA). They indicated that skin lipid liposomes showed a 6 and 1.3 fold higher blanching effect than control formulations of ointment and the phospholipid-based liposomes, respectively. Skin-lipid liposomes also produced a reduction in drug levels in the blood and urine. Consequently, this liposome formulation was proposed for improving the pharmacological effectiveness and reducing the systemic absorption of TC.

In order to overcome the stability problem of liposomes, new attempts have been maden and new drug carrier systems have been developed by adding some functional chemicals into the liposome structure. These systems are niosomes, transfersomes and ethosomes.

Niosomes, non-ionic surfactant vesicules, are widely studied as an alternative to liposomes for topical and transdermal drug delivery. Niosomes alleviate the disadvantages associated with liposomes, such as chemical instability, variable purity of phospholipids and high cost. In addition, they have the potential for controlled and targeted drug delivery to the skin [63-65]. Deformable liposomes (Transfersomes®) are the first generation of elastic vesicles introduced by Cevc [66]. They consist of phospholipids and an edge activator. An edge activator is often a single chain surfactant that destabilizes lipid bilayers of the vesicles and increases deformability of the bilayers [67-68].

Cevc et al. [69] investigated the regio-specificity potential of transfersomes which included different corticosteroids (hydrocortisone, dexamethasone and TA). They demonstrated that transfersomes ameliorate the targetability of all tested corticosteroids into the viable skin. They also suggested that the introduction of transfersomal corticosteroids creates new opportunities for the well controlled topical medication.

In another study performed by Fesq et al. [70], the efficacy of transfersomes was compared with commercially available cream and ointment formulations of TA in humans. According to the results of this study, 10-fold lower dose of TA in transfersome was found bioequivalent to conventional formulations as measured by erythema suppression. Ultrasonic measurements also revealed significantly reduced atrophogenic potential of transfersomes in comparison to commercial formulations.

Ethosome is another novel lipid carrier showing enhanced skin delivery and recently developed by Touitou. The ethosomal system is composed of phospholipid, ethanol and water. The use of high ethanol content was decribed for ethosomes although liposomal formulations containing up to 10% ethanol [71, 72].

Microemulsions are thermodynamically stable, transparent, isotropic, low-viscosity colloidal dispersions consisting of microdomains of oil and/or water stabilized by an interfacial film of alternating surfactant and cosurfactant molecules [73]. Microemulsions are effective formulations for the dermal and transdermal delivery of particularly lipophilic compounds like TC because of their solubilizing properties and also their components may act as penetration enhancers [74, 75].

Wiedersberg et al. [76] studied the dermato-pharmacokinetic properties of betamethasone valerate from two different formulations either in the reference vehicle consisting of medium chain triglycerides or in the microemulsion. The results showed that microemulsion significantly increased the extent of drug delivery into the SC.

In another study, the penetration behaviour of hydrocortisone from the microemulsion system and a commercialy available cream formulation containing the same amount of hydrocortisone (0.5%) was investigated. *Ex vivo* penetration studies on human breast skin were carried out and the drug contents in the different skin layers were measured. With regard to the cream, the results showed that, a higher percentage of hydrocortisone was found in the epidermis and dermis. This result pointed out the skin targeting effect achieved by microemulsion formulation [77, 78].

Formulation type	Pharmaceutical characteristics	Benefits	Disadvantages
Nanoparticles	Solid lipid nanoparticles include solid or the mixture of solid and fluid lipids Polymeric nanoparticles contain non-biodegradable and biodegradable polymers	Enhanced formulation aesthetics, protection of unstable active agents against degredation, targeting of active agents to the skin layers and prolonged active agent release	Mechanism of interaction between nanoparticles - skin structures and in vivo toxicity issues are need to be clarified
Liposomes	Lipid vesicles prepared with phospholipids	Percutaneous absorption enhancing property, slow release and decrease the clearence of drug by minimizing its absorption into the systemic circulation	Stability problems
Niosomes	Non-ionic surfactant vesicules	Alleviate the disadvantages associated with liposomes, such as chemical instability, variable purity of phospholipids and high cost. Controlled and targeted drug delivery to the skin.	Less effective drug delivery in comparison to liposomes
Transfersomes	Consist of phospholipids and an edge activator	Improved therapeutic risk-benefit ratio,due to better targeting and longer drug presence in the skin	-
Ethosomes	Composed of phospholipid, ethanol and water.	Improved dermal/transdermal delivery of lipophilic or hydrophilic molecules	The mechanism of action is not clear

Formulation type	Pharmaceutical characteristics	Benefits	Disadvantages
Microemulsions	Thermodynamically stable, transparent, isotropic, low-viscosity colloidal dispersions consisting of microdomains of oil and/or water stabilized by an interfacial film of alternating surfactant and cosurfactant molecules	Ease of manufacturing and high loading capacity. Effective formulations for the dermal and transdermal delivery of particularly lipophilic compounds.	-
Patches	Drug delivery systems intended for skin application	Provides the administration of effective and known drug amount to the skin and the occlusive effect	Skin irritation
Foams	Incorporate active agents, solvents, co-solvents, surfactants and propellants in a sealed canister under pressure	More convenient topical drug delivery with easy application and spreadability characteristics in comparision to other topical dosage forms	-

Table 4. The summary about innovative TC formulations

Patches are other innovative drug delivery systems intended for skin application in view of achieving local or systemic effect. The patch provides the administration of effective and known drug amount to the skin [79].

The occlusive effect of Actiderm® (hydrocolloid dermatological patch) has been studied on the percutaneous penetration of several drugs including corticosteroids. It was found to be effective in controlling and sustaining the localized delivery of the steroid into the skin and enhancing the healing of dermatological disorders [80, 81].

Ladenheim et al. [82] investigated the effect of occlusion on *in vitro* TA penetration using hydrocolloid containing patches by measuring transepidermal water loss. They found that the diffusion rate of TA was increased 3-4 fold when applied occluded patch in comparison with unoccluded. Same research group was also evaluated the occlusive properties of a range of hydrocolloid patches containing TA on the drug penetration *in vivo* using visual assessment and the graded multiple-measuremet procedure. They concluded that these patch formulations showed great potential for localized prolonged delivery of drugs to the skin, which would be desirable for the topical use of other corticosteroids [83].

More recently, novel foam formulations of TC have been developed and proposed as alternative therapy to conventional formulations. They offer more convenient topical drug delivery with easy application and spreadability characteristics in comparision to other topical dosage forms [84, 85].

A novel foam formulation with enhanced BMV bioavailability has been shown to be superior in efficacy when compared with a lotion in the treatment of disease, without an concomitant increase in toxicity [86]. Another study has been performed comparing the ability of a foam formulation to release the active ingredient (betamethasone benzoate) with ointment, gel, and cream formulations. It was found that the release of betamethasone benzoate from the foam formulation better than the release from the cream [87].

The thermolabile and low-residue foam formulations of corticosteroids (betamethasone valerate and clobetasol propionate) are available in USA market. These foam formulations are associated with better patient compliance and improvements in quality of life [88, 89]. Table 4 summarizes the new drug carrier formulations of TC.

6. Conclusion

Current therapy of dermatological disorders with conventional dosage forms including TC is insufficient due to the low absorption rate and the risk of side effects. Therefore, it is necessary to synthesize the new topical corticosteroid molecules with adequate anti-inflammatory activity and minimal side effects. Fluticasone propionate, mometasone furoate and prednicarbate are very promising molecules showed lower side effects and better tolerability as a member of new generation TC. Also, improved dermal absorption of established TC may be obtained by new designed vehicle system as an alternative to conventional formulation. Recently, lipid and polymeric based carriers such as liposomes, niosomes, transfersomes, ethosomes, microemulsions and nanoparticles have been studied intensively and the potential of these carrier systems have also been described. Another alternative approach for TC treatment is a combined therapy which is more effective than in case of drug alone. The combined use of TC and synthetic vitamin D analogues such as calcipotriol would be promising for the treatment of inflammatory skin diseases. I

In conclusion, due to the difficulty of synthesizing new steroid molecules, developing the novel alternative drug carrier systems which improve the risk-benefit ratio of TC would be more beneficial in topical corticosteroid treatment. Besides, more in vivo study is required to validate the ability of new formulations in enhancing topical delivery of corticosteroids.

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