DOI: https://doi.org/10.31351/vol29iss1pp12-32

Nanotechnology-Based Topical Drug Delivery Systems for Management of Dandruff and Seborrheic Dermatitis: An overview

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Abstract

Dandruff and seborrheic dermatitis (SD) are common skin disorders affecting the scalp and extending to other body sites in case of SD. They are associated with pruritus and scaling, causing an esthetical disturbance in the population affected. Treatment of such conditions involves using a variety of drugs for long terms, thus optimizing drug formulation is essential to improve therapeutic efficacy and patient compliance. Conventional topical formulations like shampoos and creams have been widely used but their use is associated with disadvantages. To overcome such effects, novel topical nanotechnology-based formulations are currently under investigation. In the following article, we highlight recently published formulation approaches used to improve topical dandruff/SD therapy.

Keywords: Dandruff, Seborrheic dermatitis, Topical therapy, Vanotechnology

أنظمة توصيل الأدوية الموضعية الجديدة المستخدمة في التهاب القشرة الدهنية والتهاب الجلد الدهني: نظرة عامة

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الخلاصة

قشرة الرأس والتهاب الجلد الدهني هي اضطرابات جلدية شائعة تصيب فروة الرأس ، وتمتد الى مواقع أخرى في الجسم في حالة التهاب الجلد الدهني. ترتبط هذه الحالات مع حكة وتقشر مما يسبب اضطرابا جماليا للمتأثرين بالحالة. ان علاج هذه الحالات يتضمن استخدام ادوية مختلفة وقد تكون هناك حاجة إلى علاج طويل الأجل ، وبالتالي فإن تحسين صياغة الدواء هو ضروري لتحسين الفعالية العلاجية وامتثال المريض. تم استخدام مجموعة متنوعة من المستحضرات الموضعية التقليدية مثل الشامبو والكريمات على نطاق واسع ولكن استخدامها مرتبط بمساوئ. للتغلب على هذه الآثار ، يتم حاليًا البحث عن تركيبات جديدة تعتمد على تقنية النانو .في المقالة التالية ، نسلط الضوء على مناهج الصياغة التي تم نشرها مؤخرًا والمستخدمة لتحسين علاج التهاب الجلد القشرة / والتهاب الجلد الدهني.

الكلمات المفتاحية : قشرة الرأس ، التهاب الجلد الدهني ، العلاج الموضعي ، تقنية النانو .

Introduction

Seborrhoeic dermatitis (SD) is a recurrent, chronic inflammatory skin condition, which has pink to red greasy-looking skin with yellowish flaky scales, accompanied by itching. It affects areas rich in sebaceous glands, such as scalp, face, chest and intertriginous areas [(1)]. Dandruff is considered as a mild or initial form of seborrheic dermatitis and appears as white or gray flakes in scalp, accompanied by itching with no apparent inflammation, and is considered as an embarrassing disorder [(2)].

There are many possible causes for dandruff/SD but most likely it is due to infection caused by Malassezia fungus species . Many factors are considered as possible contributors to the development of SD/dandruff which includes exogenous factors (e.g. humidity, heat and extended periods of sun exposure) and endogenous host factors (e.g. nutritional deficiency, stress, and immune response) [(3)]. Various topical treatment options are available such as antifungal agents, keratolytic agents and anti-inflammatory agents.

Nowadays, nanotechnology offers a revolutionary treatment for several skin diseases and proved to be safe and effective in the targeted delivery of many medicaments. This review article looks into some of the nanotechnology-based drug delivery systems with a focus on their potential role as next-generation carriers for medicaments used for topical therapy of dandruff/SD.

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Received: 8/12/2019
Accepted:1 /2 /2020

Topical pharmaceutical forms for the treatment of dandruff/seborrheic dermatitis

Conventional formulations

Many therapeutic agents are used for dandruff/SD and these are formulated in a variety of pharmaceutical preparations, including liquid preparations (solutions, shampoos, lotions, emulsions, hair oils), or semisolids preparations (ointments, creams, gels) so as to provide ease of application at multiple sites, along with maintaining effectiveness of the active agent. A summary of the main therapeutic agents used presently as different pharmaceutical formulations for management of dandruff/SD is represented in Table 1.

Table 1.Topical therapeutic agents used clinically for treatment of dandruff/SD *

Class	Drugs	Formulations available
Antifungals (Azoles)	Ketoconazole	1, 2% Shampoo 2% Cream 2% Foam 2% Gel 2% Emulsion
	Bifonazole	1% Shampoo 1% Cream 1% Gel
	Climbazole	0.5, 1 and 2 % Shampoo
	Fluconazole	2% Shampoo
	Miconazole	2% Shampoo 2% Rinse
	Clotrimazole	1% Cream
	Sertaconazole	2% Cream 2% Gel
	Flutrimazole	1% Shampoo 1% Gel
Antifungals (Hydroxy-pyridones)	Ciclopirox	1% Shampoo 0.77% Gel
	Ciclopirox olamine	1%, 1.5% Shampoo 1% Cream
	Piroctone olamine	1% Shampoo
Antifungals (Allylamines and benzylamines)	Terbinafine	1% Solution 1% Cream
	Naftifine	1% Gel
	Butenafine	1% Cream

Continue table 1. Topical therapeutic agents used clinically for treatment of dandruff/SD *.

Class	Drugs	Formulations available
Corticosteroids	Hydrocortisone	0.1% Lotion 1% Solution 1% Liniment 1% Cream 1% Ointment
	Desonide	0.05% Lotion 0.05% Cream 0.05% Gel
	Alclometasone diporpionate	0.05 % Cream 0.05% Ointment
	Betamethasone valerate	0.12% Foam 0.1% Lotion 0.1% Cream
	Flucinolone acetonide	0.01% Shampoo 0.01% Solution
	Clobetasole propionate	0.05 % Shampoo
	Clobetasole 17-butyrate	0.05% Cream
	Mometasone furoate	0.1% Cream
Calcineurin Inhibitors	Tacrolimus	0.03, 0.1% Ointment 0.03 % Cream
	Pimecrolimus	1% Cream
Keratolytic agents	Salicylic acid	2, 3, 4% shampoo
	Salicylic acid /sulfur	Salicylic acid 2%, sulfur 2% shampoo Salicylic acid 3%, sulfur 5% shampoo
	Sodium sulfacetamide /sulfur	10% sodium sulfacetamide, 5% sulfur emollient foam
	Tar containing products	2, 3, 4% Solubilized coal tar extract shampoo 0.5, 1% whole coal tar shampoo 1, 5, 7% coal tar solution shampoo
	Salicylic acid/coal tar	10% Coal tar extract 2 or 3% salicylic acid shampoo
	Azelaic acid	15% Gel 15% Foam 20% Cream
	Propylene glycol	15% Solution 15% Shampoo 30% Liniment
	Urea/bifonazole	40% urea and 1% bifonazole ointment
Miscellaneous agents	Selenium sulfide	1, 2.25, 2.5% Shampoo
	Zinc Pyrithione	1, 2% Shampoo

Continue table 1. Topical therapeutic agents used clinically for treatment of dandruff/SD *.

Class	Drugs	Formulations available
	Lithium gluconate/succinate	8% Lithium succinate ointment 8% Lithium gluconate ointment or gel
	Metronidazole	0.75, 1% Gel
	Benzoyl peroxide	2.5, 5 and 10% Wash
	Glycerin	10% Lotion
	Hyaluronic acid (sodium salt)	0.2% Gel
	Calcipotriol	50 µg/ gm Cream 50 µg/mL Solution
	Tacalcitol	4 µg/ gm Cream 4 µg/ gm Ointment
	Nicotinamide (Vitamin B3)	4% Cream

*Note: Shampoos, foams, rinses and lotions are mostly used for treating dandruff/SD on the scalp; creams, emulsions and ointments are used to treat SD on face and body locations other than scalp; gels are used for scalp and non-scalp SD. Treatment duration is usually for up to 4 weeks.

Novel nanotechnology-based formulations

Dandruff/SD patients require regular, long-term use of therapeutic agents, mostly used on daily bases. These are usually available as several conventional topical dosage forms. There is a strong need to develop innovative pharmaceutical formulations which are aesthetically and cosmetically more acceptable to the patient, and can be conveniently incorporated into a patient's routine hair- or skin- care regimen to improve patient compliance. Nanotechnology has emerged as an innovative drug delivery approach, allowing controlled , sustained and targeted drug delivery thus minimize undesirable drug side effects while maintaining or improving therapeutic efficacy [4].

In the following sections, we highlight recently published work describing nanotechnology-based formulation approaches used to improve the efficacy of topically applied therapeutic agents used for dandruff/ SD management. Table 2 summarizes research conducted with various nanotherapeutics as topical drug delivery systems used for dandruff/SD.

Table 2. Summary of the most common nanocarriers for skin delivery of drugs used in dandruff/SD*

Nanocarrier	Dosage Form	Drug loaded	References
Microemulsion	Emulsion	Ketoconazole	7-11
		Clotrimazole	11
		Miconazole	15
		Sertaconazole	16
		Naftifine HCl	22
		Salicylic acid	23, 24
		Lactic acid	24
		Tacrolimus	25, 27

Continue Table 2. Summary of the most common nanocarriers for skin delivery of drugs used in dandruff/SD

Nanocarrier	Dosage Form	Drug loaded	References
Microemulsion	Gel	Ketoconazole	10, 14
		Fluconazole	12, 13
		Sertaconazole	17, 18
		Butenafine HCl	19, 20
		Terbinafine HCl	21
		Tacrolimus	26
Nanoemulsion	Emulsion	Ketoconazole	34-38
		Clotrimazole	39
Nanoemulsion	Gel	Ketoconazole	42
		Bifonazole	43
		Terbinafine HCl	44-46
Polymeric micelles	Dispersion	Clotrimazole	49
		Fluconazole	49
		Ketoconazole	50
Liposome	Dispersion	Fluconazole	55
		Miconazole	56-58
		Ketoconazole	36, 60-63
		Sertaconazole	82
		Terbinafine HCl	65, 66
		Ciclopirox olamine	68, 95
		Hydrocortisone	69, 71
		Betamethasone	69, 70
		Triamcinolone	69
Liposome	Gel	Ketoconazole	64
		Terbinafine HCl	67
		Hydrocortisone	71, 72
Transferosome	Dispersion	Miconazole	76, 77
		Fluconazole	79
		Clotrimazole	80
		Terbinafine HCl	91
		Hydrocortisone	85

Continue Table 2. Summary of the most common nanocarriers for skin delivery of drugs used in dandruff/SD

Nanocarrier	Dosage Form	Drug loaded	References
Transferosome	Gel	Miconazole	78
		Ketoconazole	81
		Sertaconazole	82
		Bifonazole	83
		Sulphur and SA	84
		Tacrolimus	86
Ethosome	Dispersion	Fluconazole	55, 90
		Clotrimazole	80
		Ketoconazole	90
		Terbinafine HCl	91-93
		Ciclopiroxolamine	94, 95
		Tacrolimus	96
Ethosome	Gel	Terbinafine HCl	92, 93
Niosome	Dispersion	Miconazole	100
		Fluconazole	101
		Ketoconazole	102
		Ciclopirox olamine	103, 104
		Terbinafine HCl	105
		Naftifine HCl	106
		Benzoyl peroxide	108
Niosome	Gel	Ketoconazole	102
		Naftifine HCl	106
		Benzoyl peroxide	108
Polymeric nanoparticles	Dispersion	Hydrocortisone Betamethasone	113-115
		Tacrolimus	116-119
		Zinc pyrithione	120
			121

Continue Table 2. Summary of the most common nanocarriers for skin delivery of drugs used in dandruff/SD

Nanocarrier	Dosage Form	Drug loaded	References
Solid lipid nanoparticles (SLN)	Dispersion	Miconazole	127-129
		Fluconazole	130
		Ketoconazole	133
		Clotrimazole	137
		Hydrocortisone	140
		Betamethasone-17-valerate	140
		Clobetasol propionate	143
Solid lipid nanoparticles (SLN)	Gel	Bifonazole	132
		Ketoconazole	134-136
		Clotrimazole	135
		Terbinafine HCl	138
		Tacrolimus	148
Nanostructured lipid carriers (NLC)	Dispersion	Miconazole	128
		Fluconazole	131
		Ketoconazole	133
		Clotrimazole	137
		Betamethasone dipropionate	142
		Clobetasol propionate	144
		Tacrolimus	146
Nanostructured lipid carriers (NLC)	Ointment, Gel	Ketoconazole	135
		Clotrimazole	135
		Terbinafine HCl	139
		Betamethasone dipropionate	141
		Clobetasol propionate	145
		Tacrolimus	147, 148
Metallic nanoparticles	Dispersions	Silver	150-157
		Silver/ketoconazole	158, 159
		Sulphur	161, 162
		Selenium	163
		Zinc oxide	164
		Palladium	165

1. Microemulsions (MEs) and microemulsion gels

Microemulsions are clear/transparent, thermodynamically stable dispersions of oil and water stabilized by emulsifiers, with droplet diameter usually within the range of 10 -100 nm [(5)]. They have been widely studied to enhance the bioavailability of poorly soluble drugs, and represent an attractive option for enhanced dermal and transdermal administration of both hydrophilic and lipophilic drugs, as well as providing controlled or sustained drug release property [(6)].

Microemulsions have been used as carriers for antifungal drugs to ensure effective drug concentration levels in the skin after their dermal administration. Several microemulsion formulations and microemulsion based gels of azole antifungals (ketoconazole [(7-10)], clotrimazole [(11)], fluconazole [(12,13)], miconazole [(14, 15)], sertaconazole [(16-18)]) and allylamine/benzylamine antifungals (butenafine [(19,20)] , terbinafine [(21)] and naftifine [(22)]) have been developed with a view to provide controlled drug release and to enhance the skin permeability with the potential efficacy for eradication of cutaneous fungal infections. A study showing the benefits of microemulsion-loaded hydrogel over conventional topical preparations is seen with butenafine hydrochloride microemulsion-loaded hydrogel. Aerosol OT (surfactant), sorbitan monooleate (co-surfactant) and isopropyl palmitate (oil) were used in the preparation of microemulsion and carbopol 940 (1 %) was used as a gelling base for preparation of microemulsion-loaded hydrogel. The developed hydrogel has shown better ex vivo skin permeation and antifungal activity against Candida albicans when compared to marketed cream. The greater drug penetration-enhancing activity of microemulsions may be attributed to the combined effects of both the lipophilic and hydrophilic domains of microemulsions while the greater antifungal activity may be due to enhanced permeation of microemulsion oil globules containing drug through the fungal cell wall [(19)].

Salicylic acid (SA) is a keratolytic agent with antimicrobial actions that have been used in topical products for the treatment of SD and dandruff. However, the topical use of SA is associated with burning sensation and irritancy. To minimize skin irritation and increase SA solubility, microemulsion loaded with SA was prepared and provided a better option for topical delivery with enhanced solubility in all the studied concentrations [(23)]. In another study, a microemulsion composed of 12% salicylic acid and 4% lactic acid was prepared. This was composed of Tween 80 as surfactant, propylene glycol as a co-surfactant, castor oil, ethyl alcohol and purified water. Increasing the concentration of surfactant or co-surfactant, the microemulsion region becomes larger. Such microemulsion could be a suitable vehicle for topical treatment of psoriasis, scaly patches, ichthyoses, dandruff, corns, calluses, and warts on the hands or feet [(24)].

Topical calcineurin inhibitors tacrolimus and pimecrolimus have shown safety and efficacy in the treatment of SD as an alternative to corticosteroids. Tacrolimus is a lipophilic drug that is commercially formulated as a lipophilic ointment. A microemulsion-type colloidal carrier, as well as microemulsion based hydrogel of tacrolimus, were developed to improve the dermal availability of tacrolimus [(25-27)].

2. Nanoemulsions (NE) and nanoemulgels

Nanoemulsions are biphasic dispersion of two immiscible liquids; an oily system dispersed in an aqueous system or an aqueous system dispersed in an oily system, stabilized by an amphiphilic surfactant. The droplet sizes in nanoemulsions are usually in the range of 100 - 400 nm. Recently, the term nanoemulsions have been used specifically for systems having droplet diameter smaller than 250 nm that are in a metastable state compared with microemulsions [(28)]. Depending on constituents and relative distribution of the internal dispersed phase/phases and the external phase, nanoemulsions are termed as biphasic (o/w or w/o) or multiple nanoemulsions (w/o/w) [(29)].

Nanoemulsions offer several advantages for topical and transdermal delivery; they can be used to deliver both lipophilic and hydrophilic drugs to the skin or mucous membranes, have the capacity for site-specific drug targeting and delivery as well as their ability to increase the solubility and dispersion of drugs onto skin, thus will enhance skin permeation, extend the release of drugs and minimize their side effects by reducing the administrated dose. They are transparent/ translucent with a pleasant appearance that can be washed away easily after application and provide good skin hydration in cosmetic products [(30, 31)]. On the other side, the disadvantage of these systems is their instability during storage and the fact that their preparation requires expensive, high energy input instruments as they require smaller amounts of surfactants compared to microemulsions [(32, 33)].

Antifungals are widely used in the treatment of SD. They are characterized by poor aqueous solubility and therefore have poor dispersibility in topical vehicles. Formulation of antifungals as nanoemulsions enhances their solubility, and, subsequently, improves their subcutaneous absorption, and increases their efficacy for topical use. Nanoemulsions of antifungal drugs for topical use were developed for ketoconazole [(34-38)] and clotrimazole [(39)].

The use of topical nanoemulsions is limited due to their low viscosity and spreadability; such a problem is solved by the incorporation of gelling

agents to nanoemulsions and thus converting them to nanoemulgels [40]. The latter can accommodate a higher amount of drugs due to their better solubilization capacity. Moreover, because of their adhesion, nanoemulgels provide longer retention time and higher skin penetration along with the achievement of controlled drug release profile at the target site with fewer side effects [41]. A variety of nanoemulgel formulations for the treatment of fungal infection incorporating ketoconazole [42], bifonazole [43] and terbinafine hydrochloride [44-45] have been formulated as a mean of more effective topical drug delivery system. A comparative assessment between terbinafine nanoemulgel for ex vivo drug permeation and in vivo antifungal activity compared to the marketed product, Lamisil® emulgel was conducted. Results showed that skin permeation and in vivo antifungal activity of terbinafine for Candida infection from all the prepared nanoemulsion based gel formulae was improved significantly over the marketed emulgel [46].

3. Polymeric micelles (PMs)

Polymeric micelles are nanoscopic core-shell structures with diameters typically smaller than 100 nm, formed by self-aggregation of amphiphilic block copolymers dispersed in aqueous media, with the hydrophobic part of the polymer on the inside (core) and hydrophilic part on the outside (shell). PMs have great potential as a drug delivery system as they increase the solubilization of poorly soluble molecules, provide sustained-release properties, and increase drug stability by the protection of encapsulated substances from degradation [47]. Despite their promising potential, significant problems have impeded the progress of PM and limited their applications as drug delivery systems, mainly due to lack of stability, limited polymers for use and lack of suitable methods for large-scale production. [48]

Researches have been conducted to utilize PMs as drug delivery systems for different azole antifungal compounds using different copolymers. In one study, different azole antifungal compounds (clotrimazole, fluconazole, and econazole nitrate) were loaded in polymeric micelles with different copolymers. The best formulation was provided by the MPEG-dihexPLA micelles loaded with econazole and incorporated with an efficiency of 98.3%. This micelle formulation showed significantly higher penetration than its commercial liposomal gel (Pevaryl®) in both the porcine and human skins. The authors concluded that better skin delivery is due to the smaller size of formulation while the commercial formulation containing numerous penetration enhancers [49]. Another study reported that ketoconazole incorporated into methoxy poly (ethylene glycol)-b-poly (δ-valerolactone) copolymeric micelles had 86-fold higher water-solubility than crude ketoconazole, and showed activity similar to crude drug with no skin irritation. In addition, the drug-loaded micelles demonstrated enhanced drug deposition in mice skin with no penetration through skin, as compared to marketed ketoconazole cream indicating selective skin delivery [50].

4. Liposomes

Liposomes are colloidal spherical nanoparticle vesicles, composed of one or more lipid bilayers that can be produced from cholesterols, non-toxic surfactants, sphingolipids, glycolipids, long-chain fatty acids, and even membrane proteins. They have an aqueous core and can transport hydrophilic or hydrophobic drugs [51, 52].

Topical liposome formulations offer several advantages; they act as a solubilizing matrix for poorly soluble drugs, provide good skin penetration, associated with improved therapeutic efficacy and reduced side effects. They also act as a local depot that provides sustained drug release. However, the disadvantages of liposomes are associated with their low solubility, physical and chemical instabilities after long-term storage [53, 54].

Liposomes and liposomal gels have been used as a drug delivery system for a variety of antifungal drugs including fluconazole [55], miconazole [56-58], ketoconazole [59-64], terbinafine [65-67] and ciclopirox olamine [68]. Liposomal dispersions and liposomal gels have also been developed for a variety of corticosteroids to increase their dermal delivery and hence, improve their topical bioavailability, reflected by improved therapeutic effect and reduced side effects. Among the corticosteroids studied which have the potential for use in dandruff/SD are hydrocortisone, betamethasone, and triamcinolone [69-71]. However, increased percutaneous penetration and efficacy combined with a decreased toxicity cannot be found for all steroids; the liposome characteristics can vary according to size, shape, surface charge and lipid composition [72].

Despite the improved therapeutic value of liposomes, it has become evident that classical liposomes remain confined to upper layers of the stratum corneum and fail to penetrate the skin layers deeply [73]. To improve the elasticity of conventional liposomes, researchers have found and a new family of liposomal structures called transferosomes.

5. Transferosomes

Transferosomes, also known as ‘deformable liposomes’ or ‘elastic liposomes’ are highly elastic vesicular systems, consisting of a complex lipid bilayer surrounding water-filled core. They differ from liposomes by the presence of edge activators (surfactants) in the lipid bilayer of vesicles; this will contribute to the deformability of the bilayers and provides transferosmes with better

skin penetration ability [74]. Transferosomes are used for topical or systemic administration of various hydrophilic and lipophilic drugs delivering them either into or through the skin; they have the ability for sustained release action with high efficiency. The main disadvantage of transferosomes is related to their chemical instability and cost of formulation [75].

There have been numerous studies involving transferosomes and transferosomal gels as a drug delivery system for a variety of drugs useful for SD. Antifungal drugs like miconazole [76-78], fluconazole [79], clotrimazole [80] ketoconazole [81], sertaconazole [8282] and bifonazole [83] were successfully encapsulated into transferosomes and transferosomal gels for topical delivery.

In one study, miconazole transferosomes with a high encapsulation efficiency ranging from (67.98 ± 0.66%) to (91.47 ± 1.85%), with small particle sizes ranging from (63.5 ± 0.604 nm) to (84.5 ± 0.684 nm) were prepared. The optimized formulation of miconazole transfersomes was incorporated into a Carbapol 934 gel base and showed higher antifungal activity than marketed product (Daktarin® cream 2%), were the steady state flux after 24 h for miconazole transfersomal gel was 85.968 µg cm^{-2} h^{-1} as compared to a value of 72.488 µg cm^{-2} h^{-1} for Daktarin®cream 2%. This could be attributed to the high deformability and flexibility of transfersomes, which allowed them to overcome skin barrier properties [78].

Sulfur and salicylic acid are effective for topical delivery in many skin-care products of many clinical conditions including SD due to their anti-inflammatory and keratolytic activities. Topical transferosomal gels of sulfur and salicylic acid were formulated and have shown an enhanced skin penetration compared with conventional gels [84]. Transferosomes have also been used for the delivery of anti-inflammatory agents such as hydrocortisone [85] and tacrolimus [86] with improved site-specificity and overall drug safety compared with traditional topical formulations, making such carrier a suitable one for the treatment of inflammatory skin disorders.

A study reported the prepartion of tacrolimus transfersomes using different kinds of surfactants (sodium cholate, tween 80 and span 80). Tween 80 was selected as the optimal carrier owing to the best deformability and the highest drug retentions. The optimized transferosomal formulations were further made into gel and in vitro drug release after 24 h of transferosomal gel and liposomal gel was 2.8 times and 2.3 times higher than the commercial ointment (Protopic®). The optimized tacrolimus transferosomal gel displayed highest skin retentions compared with liposomal gel and commercial ointment. The amounts of tacrolimus in epidermis and dermis from transferosomal gel were 3.8 times and 4.2 times respectively as much as ointment, while liposomal gel was only 1.7 times and 1.4 times respectively as compared to ointment. In vivo therapy of mice atopic dermatitis, tacrolimus transferosomal gel took effect more quickly than liposomal gel and commercial ointment. Thus transferosomes displayed superior performance and effective skin target for topical delivery of tacrolimus [86].

6. Ethosomes

Ethosomes are a slight modification of liposomes. They are soft vesicles made of phospholipids, containing a high content of ethanol (20–45%) and water [87]. Compared to liposomes, skin penetration capacity of ethosomes is higher due to the capability of ethanol to cause disturbance of skin lipids, making this carrier system suitable for dermal and transdermal delivery of hydrophilic and lipophilic drugs. As with other lipid-based vesicular systems, stability is a major challenge for ethosomes [88, 89].

Ethosomes and ethosomal gels represent an efficient carrier for a variety of therapeutic agents used in the treatments of skin infection and inflammatory conditions, including SD. However, clinical studies are lacking but many researches have been conducted to prepare ethosomal formulations for a variety of antifungal agents including fluconazole [55], clotrimazole [80], ketoconazole [90], terbinafine [91-93] and ciclopirox olamine [94, 95]. In one study, tacrolimus ethosomes were prepared and showed lower vesicle size and higher encapsulation efficiency as compared with traditional liposomes. In addition, tacrolimus ethosomes permeated to a greater degree than from commercial ointment (Protopic®) suggesting the greater penetration ability to the deep strata of the skin for ethosomes [96] .

7. Niosomes

Niosomes are vesicular nanocarriers similar to liposomes except that they are composed of mixtures of non-ionic surfactants, cholesterol and may contain small amounts of phospholipids [97]. They can be used as carriers for hydrophilic or lipophilic drugs but are more popular than liposomes in the field of topical drug delivery due to their higher chemical stability because of using surfactant instead of phospholipids during their preparation, low production cost, high loading capacity and their ability to provide sustained drug release pattern [98, 99].

In recent years, there have been much research on the use of niosomal dispersions and niosomal gels for the delivery of a variety of antifungal drugs such as miconazole [100], fluconazole [101], ketoconazole [102], terbinafine hydrochloride [103], naftifine hydrochloride [104] and ciclopirox olamine [105]. In one study, ciclopirox olamine niosomes were prepared using span 60,

cholesterol, diacetyl phosphate. The obtained niosomes were in the size range of 170–280 nm, with entrapment efficiency 38–68%. A niosomal gel of the optimized batch was prepared by incorporating the niosomal dispersion in a 2% (w/w) carbopol 940 P. Deposition of ciclopirox olamine into rat skin from niosomal dispersion and its gel was significantly higher than that of plain ciclopirox olamine solution and its marketed product. Such findings suggest that niosomes are promising tools for cutaneous retention of ciclopirox olamine with expected reduction in the frequency of the application of the dosage form [106]. Benzoyl peroxide is widely used in the treatment of acne but has also been effective for the treatment of trunk and facial SD due to its antibacterial and keratolytic effects. [107(107)] Benzoyl peroxide loaded niosomes have been prepared to increase its solubility and was incorporated into gel by adding it to 1% carbopol 934 base to increase skin contact time to gain maximum benefits of the treatment. The prepared niosomal gel was advantageous because it controlled the release of the drug and enhanced its transdermal permeation. Skin irritation studies conducted on mice showed that optimized niosomal gel formulation cause significant reduction in inflammation with very less irritation in comparison with plain benzoyl peroxide solution [108].

8. Polymeric nanoparticles (PNs)

Polymeric nanoparticles are solid colloidal particles with a diameter ranging from 1-1000 nm. They are made of non-biodegradable or biodegradable polymers (natural, semi-synthetic or synthetic) in which the active ingredient is dissolved, encapsulated, adsorbed or chemically attached. There are two types of nanoparticles depending on the preparation process: nanospheres and nanocapsules. Nanospheres have a monolithic-type structure (matrix) in which drugs are dispersed, encapsulated within the particles or adsorbed onto their surfaces, whereas nanocapsules have the drug confined in cavity of liquid core and surrounded by a polymeric membrane [109, 110]. Polymeric nanoparticles have been extensively studied as promising particulate carriers in the pharmaceutical and medical fields due to their subcellular size, potential to protect unstable active ingredients, ability to enhance the skin permeation poorly water-soluble lipophilic drugs, as well as their utility in providing controlled- and sustained-drug delivery [111]. Despite their proposed benefits, topically applied nanoparticles remain localized to proximal glands and hair follicles and are unable to deeply penetrate the stratum corneum; this makes their utility in obtaining prolonged skin retention and controlled release for the desired therapeutic effect debatable [112].

Many anti-inflammatory agents have been developed as PNs, including hydrocortisone [113-115], betamethasone [116-119] and tacrolimus [120] with the aim of increased drug permeability through lipid membranes, long-term drug release potential as well as providing a safer approach for the treatment of dermatitis. Zinc pyrithione (ZPT), a widely used agent in anti-dandruff shampoos was prepared as nanoparticles with primary particle diameters in the range of 20-200 nm. It is expected that particles smaller than 25 nm in diameter would not be expected to significantly scatter light, and produce a clear anti-dandruff shampoo formulation, which exhibit a higher activity, be distributed more effectively on the scalp, and will require a less thickening agent in the shampoo formulation to ensure its stability against settling than the standard form of ZPT [121].

9. Lipid nanoparticles: solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)

Solid lipid nanoparticles (SLNs) are nanosized spherical structures composed of a coat of aqueous surfactant monolayer surrounding a high melting point lipid core that remain in a solid-state at the room as well as body temperature [122]. SLNs can effectively encapsulate and solubilize lipophilic and hydrophilic drugs, but lipophilic drugs can be better delivered by solid-lipid nanoparticle [123]. SLNs hold great promise to achieve controlled site-specific drug delivery and increase in skin hydration. However, drawbacks associated with SLNs are uncontrolled drug expulsion from the carrier and limited drug loading capacity [124] .

Nanostructured lipid carriers (NLCs) are modified generations of SLNs consisting of a matrix composed of solid and liquid lipids, stabilized by an aqueous surfactant solution. The incorporation of liquid lipid causes structural imperfections of solid lipids to form a crystal lattice with many spaces. Such arrangement increases spaces and allows for higher drug loading capacity [125].

Lipid nanoparticles (SLN, NLC) have been reported as suitable carrier systems to control the penetration/permeation of highly lipophilic drugs and offer epidermal, follicular targeting, as well as controlled release of drugs, protecting them from degradation and enhancing their stability [126]. SLNs and NLCs are among the nano-carriers that have conquered a better place in topical preparations and are applied either as an aqueous dispersion or incorporated in a suitable liquid or semi-solid preparations to provide an appropriate formulation for application upon the skin. They have been used to improve drug absorption by the skin for a variety of drug molecules intended for the topical treatment of multiple diseases.

The development of SLNs/NLCs of antifungals might have a significant advantage for their clinical use. Antifungals drugs such as miconazole nitrate [127-129], fluconazole [130, 131] , bifonazole [131, 132] ,

ketoconazole [133-136] , clotrimazole [137] and terbinafine hydrochloride [138, 139] formulated as SLNs /NLCs upon incorporation into suitable semi-solid preparations, have the potential to provide targeted and sustained drug release pattern, with reduction of fungal burden in the infected area. Such findings could be exemplified with miconazole nitrate loaded SLN [127]. SLN dispersions exhibited average size between 244 and 766 nm. All the dispersions had high entrapment efficiency ranging from 80% to 100%. Miconazole nitrated-SLN gel (2%) was prepared by incorporation with carbopol 940 gel base (0.3–1.0%), out of which 0.5% concentration showed good consistency. Miconazole nitrated-SLN gel produced significantly higher deposition of the drug in skin (57±0.65%) than marketed gel (30%±0.87) and this colloidal nanoparticulate gel, being sumbicron in size, enhances the drug penetration into the skin, remains localized for a longer period of time in skin as compared to conventional gel, thus enabling better drug targeting to the skin.

Incorporation of corticosteroids, such as hydrocortisone, betamethasone valerate and dipropionate [140-142], clobetasol propionate [143-145] into lipid nanoparticles enable such drugs to be deposited on skin with reduced systemic exposure and reduced local side-effects along with providing sustained release of drug in addition to more efficient penetration into skin layers than traditional formulations. Tacrolimus, a calcineurin inhibitor, used in treatment of SD mainly due to its anti-inflammatory effects, is not associated with the side effect profile of corticosteroids but topically is reported to have low penetration rate through the skin. A solid lipid nanoparticle (SLN), nanostructured lipid carrier (NLC) and modified nano-lipid carrier formulations of tacrolimus were developed to overcome such a problem and subsequently improve its bioavailability [146- 148].

10. Metallic nanoparticles (MNs)

Recent advances in nanotechnology are the development of inorganic nanoparticles that remain stable for long periods and are useful for specific targeting and controlled release of carried drugs in the skin [149]. A variety of metallic nanoparticles have been used in the treatment of a variety of skin diseases including SD.

Antidandruff shampoos have become popular in the treatment of dandruff using agents that combat the growth of the causative agent, Malassezia furfur. Recently, this yeast has developed resistance towards the commonly used antidandruff drugs, and as a result, it is necessary to develop a new class of novel antidandruff shampoos.

Silver nanoparticles (AgNP) were developed for their bactericidal properties and used in the treatment of infectious diseases and have been used in several biomedical products, including wound or burn dressings [150]. They have also been investigated as a potential fungistatic agent for various clinically relevant fungi including M. furfur involved in scalp related diseases such as dandruff. It is also reported that AgNP may also have significant anti-inflammatory effects [151, 152]. The activity of silver nanoparticles depends on factors such as sensitivity to silver, the concentration of nanoparticles in the formulation, and their shape [153(153)].

Silver nanoparticles can be synthesized from eco-friendly, cost-effective biological systems making them amenable to large-scale industrial production and are considered as cost-effective fungistatic agents in shampoo formulations for treating scalp problems, especially knowing that very small amount is required for producing desired antidandruff activity. There have been many reports using silver nanoparticles during the formulation of antidandruff shampoo with effective antifungal activity [154-157]. A hybrid system of ketoconazole complexed with silver nanoparticles have been synthesized to enhance the activity against Malassezia furfur. The anti-dandruff activity was highest with ketoconazole coated AgNp when compared to ketoconazole and AgNp individually [158, 159].

There have been studies indicating that Ag NPs are toxic to the mammalian cells [160] therefore, sulfur nanoparticles were developed as a safer, more cost-effective alternative to silver nanoparticles as these are reported to possess broad-spectrum antimicrobial activity, as well as extensive antifungal activity against M. furfur, the main causative agent of dandruff [161, 162] .

Other metallic nanoparticles with potential anti-dandruff activity due to their antifungal activities against Malassezia include selenium nanoparticles (SeNPs) [163] with reported higher potency than the known anti-dandruff agent, selenium sulphide; zinc oxide nanoparticles (ZnO NPs) [164] and palladium nanoparticles (Pd NPs) [165] reported to have antimicrobial as well as anti-dandruff activity. However, clinical research work is required before such metallic nanoparticles are introduced into anti-dandruff preparations.

The potential benefits of the previously mentioned nanotechnology approaches over the conventional dosage forms and potential advantages of each nanotechnology formulation compared to the other nanotechnology techniques are summarized in Table 3.

Table 3. Potential benefits of novel nanotechnology approaches over the conventional dosage forms and potential advantages of nanotechnology approach compared to the other nanotechnology approaches

Novel nanotechnology approach	Potential benefits of nanotechnology approach over conventional approach	Potential benefits of specified nanotechnology approach over other nanotechnology approaches	References
Microemulsions (MEs) and nanoemulsions (NEs)	Emulsions are coarse dispersions with cloudy/ opaque semi-solid consistency whereas ME and NEs are clear/transparent colloidal dispersion with fluid consistency, suitable for delivering both lipophilic and hydrophilic drugs with higher stability, bioavailability and permeation than emulsions or conventional semisolids, with the capacity for site-specific drug targeting	Compared to other nanosystems, ME and NE offer advantages in terms of simplicity and stability.	166
Polymeric micelles	Solubilization of poorly soluble molecules, protection of encapsulated substances from degradation, thus enhanced stability and efficacy of encapsulated drugs as well as sustained and targeted delivery to desired site.	Limited benefit over other nanotechnology approaches due to lack of stability, low drug loading capacity, limited polymers for use and lack of suitable methods for large-scale production.	48
Liposomes, transferosomes and ethosomes	Suitable carriers for both lipophilic and hydrophilic drugs, with better skin penetration, reduced side effects, improved therapeutic efficacy and stability of encapsulated drugs as well as ability to provide local drug depot, with sustained drug release action.	Improved localized as well as transdermal skin delivery of drugs	167
Niosomes	Suitable carriers for both lipophilic and hydrophilic drugs, enhanced bioavailability, targeted delivery, and slow drug release.	Compared to lipid vesicles, niosomes are more stable, with higher drug loading capacity leading to reduction of dose, delayed clearance and ease of modification with lower production cost.	168
Polymeric nanoparticles	Enhance lipophilic drug penetration through skin, with ability to protect unstable active ingredients and reduce skin irritation, with sustained drug release ability over prolonged periods of time.	Limited degree of enhancement in skin permeation and localization in the hair follicles; this may promote potential application of delivery of drugs to site of application during the treatment of dermatological conditions.	111

Continue Table 3.Potential benefits of novel nanotechnology approaches over the conventional dosage forms and potential advantages of nanotechnology approach compared to the other nanotechnology approaches

Novel nanotechnology approach	Potential benefits of nanotechnology approach over conventional approach	Potential benefits of specified nanotechnology approach over other nanotechnology approaches	References
Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)	Effectively encapsulate and solubilize both lipophilic and hydrophilic drugs, with ability to improve penetration and follicular targeting, thus increases bioavailability. Additionally, skin hydration effect is observed due to occlusive properties of lipid nanoparticles.	Higher stability and ability to protect chemically labile drugs against decomposition than lipid vesicles. NLC provide greater drug loading and better stability compared to SLN.	126
Metallic nanoparticles	Useful for controlled, localized and targeted drug release in the skin.	Good stability in addition to antimicrobial properties in some types of metallic nanoparticles.	149

Conclusions

Dandruff and SD are stubborn skin disorders that require symptomatic relief against pruritus and long-term therapy using antifungal, keratolytic and anti-inflammatory agents to clear symptoms, as well as the need to maintenance therapy to help maintain remission. Nanotechnology offers a new approach in the treatment of dandruff/SD with the potential to better targeting, enhanced penetration and sustained delivery of active therapeutic agents. However, reported clinical studies using such drug delivery systems in topical applications have been limited. Consequently, further clinical investigative studies are required to elucidate the effectiveness of nanotechnology in the topical treatment of dandruff/SD.

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