REVIEW ARTICLE

Topical Nano Drug Delivery for Treatment of Psoriasis: Progressive and Novel Delivery

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Abstract

Psoriasis is a chronic inflammatory disease influencing 1–3% of the all-inclusive community with significant hindrance to personal quality of life. These conditions may adversely influence the patient's quality of life and prompt psychosocial stretch. Psoriasis can be arranged as mild, moderate, and severe conditions. Mild psoriasis prompts the formation of rashes, and when it ends up moderate, the skin transforms into scaly. It is important to control and limit the indications of psoriasis to give patient long-lasting protection since psoriasis is not presently curable yet it can go into reduction, creating a normal/ordinary skin surface. Customary conventional treatments for psoriasis are utilized for the treatment of incorporate topical, oral, or systemic formulation yet have a potential for long-term danger and may not generally give adequate change of the illness. Dermal treatment guaranteeing percutaneous penetration is presently very suggested in topical signs for psoriatic patients, which can be accomplished utilizing pharmaceutical nanotransporters nanovesicle and nanoparticle and so forth. The advancement of novel treatments focusing on the pathogenesis of psoriasis presently gives new and efficient treatment alternatives such as nanoparticulate/nanovesicular gels, which are more powerful in diminishment of purities, scaling, and hyperkeratosis of psoriasis plaque. Because of high drug loading, productivity, and stability, novel transporter diminishes the scaly patches and decreases of humoral immunity. Point of the survey is to center around the effect of nanotechnology construct drug delivery approaches in light of different anti-psoriasis drugs delivery for the fruitful treatment of psoriasis with negligible poisonous or toxic response.

Key words: Hydrogel, nanogel, nanostructured lipid carrier, niosome, psoriasis, solid lipid nanoparticle

INTRODUCTION

Psoriasis is a typical chronic inflammatory infection with a complex pathophysiology and a strong genetic foundation[1,2] It is an immune-mediated systemic ailment sickness with specific skin contribution.[3] Progress in investigating, new biologic medications work honorably to treat psoriasis, and other new pharmaceuticals are close to the Food and Drug Administration (FDA) approval.[4] Drugs such as corticosteroids, cyclosporine, and methotrexate (MTX) pushed toward getting to be pillars for managing the illness. It impacts approximately 1–3% of the general public around the worldwide.[5] It might display at any age, in spite of the fact that a reasonable subgroup develops ailment before the age of 40 years, representing >75% of patients.[6] The contamination is depicted by layered, erythematous skin plaques, which indicate inflammatory cell invasion and neovascularization occurring in light of hyperproliferation of the epidermis with divided partition of keratinocytes and irregular arrangement of action of horn cell.[7,8] The essential type of psoriasis is perpetual plaque psoriasis speaking to around 85–90% of all cases.[9] Different types of psoriasis involve guttate psoriasis, erythrodermic, inverse, palmoplantar and localized, and additionally summed up pustular psoriasis. Around 80% of psoriasis patients have mild disease, with skin plaques covering under 10% of the body surface area (BSA). In any case, a few patients have direct to/or serious contamination, with more noticeable than 10% of the BSA commitment.[10,11]

In spite of late advances in the conventional treatment of psoriasis, topical operators speak to a pillar treatment for a

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greater part of patients with mild-to-moderate psoriasis, and additionally some with more serious infection. Treatment choice should be guided by the expectations and needs of each individual patient. More than 80% of psoriasis patients have localized disease that is agreeable to principally topical treatment.[10] Mild psoriasis is normally made do with topical treatment alone and accounts of the large part of patients. Direct to extreme psoriasis is normally treated with phototherapy, systemic treatments, or biological agent like monoclonal antibodies.[11] Studies revealed that, in the current, patients do not get ideal/good medicines and experience insufficient fulfillment with the efficacy of accessible topical medications as reflected by a high rate of resistance. In this manner, since psoriasis regularly requires long-lasting treatment, safe, advantageous, and successful topical regimens with great cosmetic acceptance.[12] However, there are as yet numerous information gaps in topical treatment for psoriasis with respect to efficacy and safety. We looked to methodically review the literature to decide these holes. There are many difficulties in topical delivery of medications. There will be inconstancy in percutaneous permeation because of the site, illness, age, and so forth. Skin irritation may happen and if the toxicities because of medication are more, the skin gets harmed. The first-pass metabolism impact of skin is likewise one of the difficulties for topical delivery.[13] Novel medication delivery has part of advantageous points. They increment efficacy with advancement in safety levels. Medication focusing on specificity and bringing down systemic toxic quality is the essential benefits of novel drug delivery system (NDDS).[14] In addition, they can enhance delivery rates and will avert biochemical degradation of pharmaceuticals.[15]

TYPES OF PSORIASIS

Psoriasis is believed to be an immune-mediated infection with a hereditary premise including a complex interrelationship between hyperplastic epidermal keratinocytes and a few immune cells compose including T-cells, neutrophils, dendritic cells, and macrophages. Psoriasis does not spread starting with one individual, then onto the next by contact, however, can be transmitted genetically.[16,17] From clinical point of view, psoriasis can be viewed as a wide range of different skin indications. The greater part of the lesions has normal characteristics including erythema, thickening, and squamae. Although size of lesion can change from a pinhead up to a distance across of 20 cm, fringes of lesions are normally round, oval, or polycyclic. In spite of the fact that it can influence any region, knees, elbows, lumbosacral district, scalp, and genital zone are most much of the time involved.[18] Psoriasis is analyzed based on clinical discoveries (skin rash, changes to nails, and joint association) and is normally clear. Sometimes, patients having atypical skin lesions that should be separated from tinea, mycosis fungoides, discoid lupus, or seborrheic dermatitis, or non-particular skin signs, for example, negligible scaling of the scalp, segregated flexural erythema, or genital lesions. Watchful evaluation of all body area may reveal undeclared, diagnostically helpful highlights, and a skin biopsy may periodically be shown. Different types of psoriasis are as follows and depicted in Figure 1.

Plaque psoriasis (psoriasis vulgaris)

It is also known as chronic stationary psoriasis and affects 85–90% of people with psoriasis. It appears as raised red-colored patches with silvery white scales. These lesions can be very itchy and painful, and in severe cases, they may even crack and bleed.

Inverse psoriasis (flexural psoriasis)

It is characterized by bright red, shiny lesions which appear in skin folds such as armpits, groin area, and under breast. The condition becomes worst by friction and sweat and can be easily affected by fungal infections.

Nail psoriasis

Nail psoriasis occurs in 40–45% of people with psoriasis. It is characterized by pinhead sized depression in the nail, whitening of the nail, bleeding capillaries under the nail, yellow-red discoloration known as oil spot or salmon spot, subungual hyperkeratosis, onycholysis, and nail crumbling.

Erythrodermic psoriasis

It is very rare type of psoriasis and affects only 3% of people with psoriasis. It can take two forms: First, progressive chronic plaque psoriasis which becomes extensive and confluent and second, erythroderma which can lead to impairment of the thermoregulatory capacity of the body which further causes hypothermia, widespread inflammation on the body surface

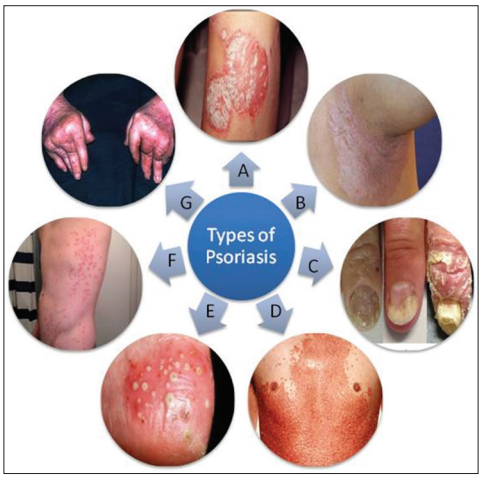

Figure 1: Types of psoriasis. (a) Plaque psoriasis, (b) inverse psoriasis, (c) nail psoriasis, (d) erythrodermic psoriasis, (e) pustular psoriasis, (f) guttate psoriasis, (g) psoriasis arthritis)

with severe itching, pain. and swelling. This form of psoriasis can be fatal.

Pustular psoriasis

It is characterized by raised bumps filled with non-infectious pus or pustules. These pustules can be localized commonly on the hands and feet, or it can be generalized with random widespread patches on any part of the body.

Guttate psoriasis

In Latin, guttate means "drops." Guttate psoriasis is characterized by small, red, and scaly tear-shaped drops with silvery scales which appear on arms, legs, and middle of the body. It is usually seen in persons younger than 30. It mostly occurs after an acute B hemolytic streptococcal infection of the pharynx or tonsil. The lesions can vary from 10 to 100.

Psoriatic arthritis

It is a chronic inflammatory arthritis which frequently occurs in an association with nails and skin psoriasis. It is characterized by painful inflammation of the joints and the surrounding connective tissues. It can occur in any joint but mostly affects the joints of toe and fingers which lead to dactylitis or sausage-shaped swelling on the fingers and toe. It can also affect the hips, knees, spine, and sacral.

PATHOPHYSIOLOGY OF PSORIASIS

There are two principle theories about the way physiology of psoriasis. The main hypothesis clarifies the advancement of psoriasis because of over the excessive growth and proliferation of the skin cells which is because of hyperproliferation of the epidermal cells and keratinocytes. In the second theory, T-cell-mediated immunity is the primary driver of irritation which prompts overabundance cell development. Excessive generation of the skin cell is a secondary reaction to the factor generated by the immune framework. Langerhans cell in the dermis goes about as an antigen presenting cell which relocates to the lymph node (site of T-cell). White blood cell actuation is because of presentation of Langerhans as unidentified antigen and furthermore because of costimulatory signals. A costimulatory signal is because of lymphocytes function-related antigen -3 and intracellular adhesive particle. Actuated T-cell travels back to the skin where it discharges cytokines. Cytokines discharged by T-cell in the dermis and epidermis cause release of (tumor necrosis factor) which prompts aggravation and epidermal hyperexpansion. Immunosuppressant therapy clears out psoriasis which supports the proof of immune-mediated model of psoriasis pathophysiology. Note: Lessen in T-cell count in HIV worsen psoriasis, since diminish in CD4 T-cell count, initiate the CD8 T-cell which fuel psoriasis in HIV patient.

CONVENTIONAL TREATMENT OPTION FOR PSORIASIS

Conventional treatment for psoriasis incorporates topical corticosteroids, tars, anthralin, Vitamin D analogs, tazarotene, and salicylic acids. These have an extremely toxic effect such as hepatotoxicity, nephrotoxicity, related to MTX and cyclosporine, teratogenicity with oral retinoids, and skin tumors with photo/chemotherapy. A survey from the United Kingdom has discovered that patients going toward topical treatment than systemic treatment. It is a direct result of the serious response, tedious, and insufficient outcomes. Thus, from latest 10 years, the better comprehension of the pathogenesis of psoriasis has incited the change of novel plans with potential less dangerous or side effect from drugs.[19]

Topical treatment

Topical treatment is the first-line treatment approach prescribed for patients with mild-to-moderate inflammatory disorders. It includes Vitamin D analog, corticosteroids, dithranol, tars retinoids, Tacrolimus (TAC), babchi oil, and methoxypsoralen (MOP) [Table 1]. Topical treatment reduces potential side effects which are associated with systemic treatments.

Vitamin D

Block keratinocyte separation and proliferation by diminishing the creation of interleukin (IL)-8. Vitamin D analogs tie to the intracellular Vitamin D receptor and after that dimerize. These units relocate to the nucleus, where they tie the Vitamin D response element, which specifically manages qualities associated with epidermal proliferation, inflammation, and keratinization. There are three Vitamin D analogs accessible to treat psoriasis: Calcitriol, tacalcitol, and calcipotriol.[20,21]

Topical corticosteroids

It remains the principal line treatment for generally mild-to-moderate plaque psoriasis; the proposed mechanism is to inhibit the formation of various inflammatory mediators such as prostaglandin and IL. Corticosteroids are all around utilized as a part of the cure for all types of psoriasis, both as monotherapy and as a supplement to systemic treatment. The real issue is tachyphylaxis, so for its prevention, it is prescribed to utilized with different treatment like betamethasone in addition to dithranol, psoralen plus ultraviolet A (UVA), and with calcipotriol.[22-24]

Topical dithranol

It is one of the most conventional medications for psoriasis; it produces helpful activity by following up on IL receptor of keratinocyte cell. The mechanism of activity of dithranol stays unclear, in spite of the fact that anthracyclines inhibit mitochondria by damaging the structure and function bringing

Table 1: Showing brand name and dose of different topical agent use for psoriasis

Chemical (Vitamin D)	Brand name	Company	Dose/strength (%)
Calcipotriene (Vitamin D)	Dovonex	LEO Pharma	0.005
Clobetasol	Temovate	Lupin	0.05
Triamcinolone	Aristocort	Aristopharma	0.02
Fluocinolone	Synalar	Medimetrics	0.025
Betamethasone	Diprolene	Merk	0.05
Dithranol	Psoriatec	Biorga	1
Coal tar	DHS tar	Person and covey	0.5
Tazarotene	Tazorac	Allergan	0.1
Pimecrolimus and tacrolimus	Elidel Prograf	Valeant Astellas	1 5 mg
Babchi oil	–	SBL	–
Methoxsalen	Oxsoralen	Valeant	1
Salicylic acid		MG 217	2

about apoptosis.[25] This results in antiproliferative effects that produce an observable reduction in psoriatic plaques. Dithranol is less effective than topical corticosteroids or Vitamin D analogs.

Topical tar

It is produced by coal using high temperature (900–1200°C). Activity for psoriasis is achieved due to suppression of DNA synthesis, reduces the cell division of basal layer in epidermis.[26,27]

Topical retinoids

Like acitretin (Act) or 13 cis-trans-retinoic acid is a metabolite of Vitamin A. Possible mechanism is to inhibit the keratinocyte hyperproliferation and differentiation, but it has physiological effects such as regulation of epithelial cell growth and differentiation, sebum production, and collagen synthesis. Oral Act is indicated for severe psoriasis.[28-30]

Calcineurin inhibitors (pimecrolimus and tacrolimus)

TAC is a macrolide immunosuppressant; biologically it is isolated from the fermentation broth of *Streptomyces tsukubaensis* and is highly effective against immune inflammatory disorders. Topical calcineurin inhibitors are immune modulators. TAC has been shown to be effective for psoriasis of the face, intertriginous areas, and genital region. However, the efficacy of tacrolimus is more limited for plaque psoriasis.[31]

Mechanism of action involves the binding of it to cytoplasmic receptor, which is FK506-binding protein-immunophilin and then associates it with calcineurin and inhibits its phosphates activity, resulting in inhibition of T-lymphocyte activation (i.e., immunosuppression).[32,33]

Babchi oil (Psoralea corylifolia)

The most trusted Ayurvedic herb for blood purification and skin health. It is used for the treatment of psoriasis because its chief constituent is psoralen which is a photoactive furocoumarin that binds to DNA, which forms photoproducts with pyrimidine base when exposed to UV light. This action inhibits DNA synthesis and decreases the keratinocyte hyperproliferation.[34]

Methoxsalen (8-MOP)

8-MOP and its derivatives prevent hyperproliferative skin diseases when used along with long wavelength UVA light. However, due to certain limitations, it was developed into 8-MOP microemulsion gel form resulting in drug targeting, efficient promoter of the 8-MOP localization into the skin, reduces systemic side effect.[35]

Salicylic acid

It reduces psoriatic scales and softens the lesions. It is used in combined therapies with steroids, coal tar, and dithranol. When used in combination with steroids, it increases its efficacy by increasing the rate of penetration.[36]

Phototherapy

Short, non-consuming presentation to the sunlight enhances treating psoriasis and this treatment utilizing the sunlight is known as phototherapy. Lights of various wavelengths, UV beams of the sun, decrease the cell expansion or proliferation or repress the hypermultiplication and, furthermore, change the immune reaction, in this manner helping in treating psoriasis. Phototherapy incorporates limit band bright UVB, broadband UVB, and in addition to psoralen and UVA photochemotherapy.[37]

Systemic treatments

On the off chance that you have moderate to serious psoriasis, your specialist may propose "systemic drugs" that influence your whole body. They are typically utilized when the skin condition covers over 5–10% of your body and different other treatments have not worked such as phototherapy and topical formulations. While systemic treatment can help in treating psoriasis, but a considerable lot of the medications can cause genuine reactions [Table 2].

Act

This drug is made from Vitamin A and affects the way your skin cells grow and is shed. It works best when you pair it with light phototherapy. It works well to treat pustular psoriasis (a breakout of sore, red blisters, or pus bumps) and erythrodermic psoriasis, where most of your skin looks intensely red and peeling, as if it is burned. Retinoid regulates gene transcription by the action on nuclear receptor and reduces epidermal hyperplasia in psoriasis.[38]

Cyclosporine

It curbs your immune system and slows skin cell growth. It is reserved for severe cases of psoriasis when nothing else seems to work. Cyclosporine also carries risks like it can cause kidney problems, high blood pressure, and high cholesterol (CH).

MTX

MTX is a potent immune-modulating gold standard drug for severe, recalcitrant psoriasis. It is approved by the U.S. FDA in early 1972 for the treatment of psoriasis. MTX was approved for the treatment of mild to moderate psoriasis with oral and parenteral administration. It blocks the conversion of dihydrofolate to tetrahydrofolate; tetrahydrofolate is a cofactor for the formation of *de novo* synthesis. Recently, new mechanism has been found, MTX inhibits aminoimidazole carboxamide ribotide transformylase, resulting in accumulation of adenosine, which is a T-lymphocyte toxin, which may be responsible for immunosuppressive action.[39,40]

Hydroxyurea

This drug has fewer side effects than some of the stronger systemic medications, but it is also less effective. Hydroxyurea is metabolized in the body to produce a free radical nitric oxide, which inhibits the DNA synthesis. It is effective in psoriasis, due to the inhibition of dividing keratinocyte cell.[41]

Fumaric acid

It is a simple-structured dicarbonic acid. Inside the body, it is metabolized to produce mono and dimethyl fumarate, both these metabolites are called Fumaderm which shows anti-psoriatic activity. Possible mechanisms are (i) inhibiting the production of pro-inflammatory cytokines and adhesion molecules expression, (ii) inhibiting the D-cell differentiation, and (iii) reducing intracellular free radical generation. Its major side effect is gastrointestinal complications.[42]

Problems with psoriasis drug therapy

Treatment accessible for psoriasis comes with bunches of issues related like symptoms of their after ingestion and if the systemic medications are given topically they have permeation issue. Various topical medications can trouble your skin. After sometime, the health professional may recommend you change to various types of creams alongside different types of medicines such as phototherapy or pharmaceuticals you take by oral or with shots. Since the efficient concentration of medication is not get permeated through skin layer for better efficacy. The dry patches of skin you get with psoriasis can be irritated and uncomfortable. However, the correct treatment design can help. However, the prescription utilized for treatment has their own issues and reaction. The initial step is to utilize your topical psoriasis treatment precisely as directed by a physician. Changing to systemic treatment for psoriasis for delivery is right. However, you should know the dangers and advantages of it first. Topical treatment has the most minimal toxic reaction of antagonistic impact and lethality since it limits the medication to get into the systemic flow. Side effect with related to different psoriasis drug is depicted in Table 3.

Skin is considered to be the biggest and outermost organ of the human body. Among three vital layers of skin, epidermis works as a defensive boundary of the body.[43]

Topical treatment is the most affordable and convenient method for treating the sickness. Many patients when asked whether they have had any treatment derisively reply, "no, ointment balm," and must be affected, this is the most sensible way to deal with the skin treatment. A gel is the best strategy for carrying Active pharmaceutical ingredient (API) like MTX into contact with the skin. For the treatment of psoriasis, topical treatment is, for the most part, endorsed system since transdermal delivery of pharmaceutical is the essential line of the barrier for the psoriatic skin. Conventional types of medication delivery through the skin have come across over with numerous symptoms and other application challenges. Disruption of Subcutaneous (SC) and focusing on the more profound layers of skin is unrealistic with treatments, creams, and so forth. Along these lines, NDDS helps to overcome these impediments, thereby improves the bioavailability and capability of medication and is broadly utilized for the treatment of psoriasis recently. Restriction of medicines to dermis and epidermis can be accomplished by these NDDS.[43]

There is different investigational research that is going on to develop the effective and safe treatment of psoriasis shown in Figure 2.

Table 2: Available treatment of psoriasis

Brand name	Company name	Type	Dose (Mg)
MTX			
Folitrax	Ipca Laboratories Limited	Tablet	2.5. 5
Zexate	Dabur Pharma Limited	Tablet	2.5
Alltrex	Miracalus Pharma Private Limited	Tablet, injection	2.5 mg, 25 mg/ml
Beltrex	Neesee Healthcare Pvt., Ltd.	Tablet	5
Bio MTX	Biochem Pharmaceutical Industries Ltd.	Tablet, injection	2.5 mg. 2.5 mg/ml
Caditrex	Cadila Pharmaceuticals Ltd.	Injection	2 ml
Cytotrex	BDH Industries Ltd.	Tablet	2.5
Darmatrex	East West Pharma	Tablet	2.5, 7.5
Folitrax	Ipca Laboratories Ltd	Injection	25 mg/ml
Hi-Trex	VHB Lifesciences Inc. (Cytocare)	Tablet	2.5
Imutrex	Aronex Lifesciences Pvt., Ltd.	Tablet	2.5
Merex	Intas Pharmaceutical Ltd.	Injection	100 mg/ml
Methorex	Zydus Cadila Healthcare Ltd. (Biogen)	Injection	50 mg/2 ml
Neo MTX	Glaxo SmithKline Pharmaceuticals Ltd.	Injection	50
Nidtrex	Nidus Pharma Pvt., Ltd.	Tablet	2.5
Oncotrex	Sunrise International Labs Ltd.	Tablet, injection	2.5 mg, 50 mg/ml
Remtrex	Alkem Laboratories Ltd. (Cytomed)	Tablet	2.5
Trixilem	Elder Pharmaceuticals Pvt., Ltd.	Tablet	2.5
Zexate	Dabur Pharma Ltd.	Injection	25 mg/ml
Act			
Aceret	Glenmark Pharmaceuticals Ltd.	Capsule	10
Acetec	Dr. Reddy's Laboratories	Capsule	10
Acitrin	Ipca Laboratories Ltd.	Capsule	10
Acrotac	Ranbaxy Laboratories Ltd.	Capsule	10
Zoratame	Cipla Ltd.	Capsule	25
Hydroxyurea			
Cytodrox	Cipla Ltd.	Capsule/tablet	500
Droxiget	Gls Pharma Ltd.	Tablet	500
Durea	Samarth Pharma Pvt., Ltd.	Capsule/tablet	500
Gindrea	VHB Lifesciences Inc.	Capsule/tablet	500
Hondrea	Alkem Laboratories Ltd.	Capsule/tablet	500
Hydab	Dabur Pharma Limited	Capsule/tablet	500
Hytas	Novatech	Capsule/tablet	500
Myelostat	Zydus Cadila (German Remedies)	Capsule/tablet	500
Neodrea	VHB Lifesciences Inc.	Capsule/tablet	500
Oxyrea	Cadila Pharmaceuticals Ltd.	Capsule/tablet	500
Urdox	Zydus Cadila (German Remedies)	Capsule/tablet	500
Cyclosporine			
Arpimune	RPG Lifesciences Ltd.	Capsule	100
Graftin	Ranbaxy Laboratories Ltd.	Capsule	100, 50, 25
Imusporin	Cipla Limited	Capsule	25, 50, 100
Panimun Bioral	Ecolity (Panacea Biotec Ltd.)	Capsule	100

(Contd...)

Table 2: (*Continued*)

Brand name	Company name	Type	Dose (Mg)
Panimun Bioral	Ecolity (Panacea Biotec Ltd.)	Capsule	50, 25
Restasis	Allergan India Pvt., Ltd.	Injection	0.4 ml
Sandimmun Neoral	Novartis	Capsule	25
Sandimmun Neoral	Novartis	Solution	50 mg/ml

Act: Acitretin, MTX: Methotrexate

Table 3: Types of side effect of different therapy used in psoriasis

Topical	Side effect
1. Corticosteroids	Local thinning of skin
2. Vitamin D	Skin irritation and do not applied on eyes, nose, and mouth
3. Anthralin	Stain on skin, cloth, skin burn, and irritation
4. Tazarotene	Skin burning, irritation, and sensitivity to sunlight. They do not apply on open wounds, face, eyes, nose, and also contraindicated in pregnancy
5. Salicylic acid	Hair fall due to weakness of hair stem
6. Coal tar	Inflammation of hair follicles and makes skin dry, sensitive to sunrays, and skin irritation
7. TAC	Burning sensation and pruritus at the site of application, risk of cutaneous infections, and long-term malignancy risk
Phototherapy treatments	
1. Light therapy	Minor skin burns, cancer, and sensitive to sunrays also include itching and red skin
2. UVB phototherapy	Redness, itching, dry skin, risk of cancer (melanoma), and sun sensitivity
3. Excimer laser	Skin redness and blistering
Systemic treatments	
1. MTX	Loss of appetite, upset stomach, fatigue, and feeling of tired. Slow down the production of WBC, RBC, and platelets. Cause toxicity in liver, lung, GIT, kidney, and nervous system
2. Retinoid	Eye weakness, problems in liver, birth defects, depression, joint pain, nose bleeding, hair fall and make skin, lips dry, and cracked
3. Hydroxyurea	Bone marrow problems and a higher chance of skin cancer
4. Cyclosporine	Cause high B.P, cancer, and damage kidney. Also enhance the risk of infection and make immune system slow
5. Injectables (MAbs)	Tuberculosis and heart failure. Pain at injection site, redness, swelling, and also include headache and lymphoma
6. Act (Soriatane)	Severe birth defects, hence, contraindicated for pregnant women and it also includes problems in liver and kidney

MAbs: Monoclonal antibodies, TAC: Tacrolimus, WBC: White blood cell, RBC: Red blood cell, Act: Acitretin, MTX: Methotrexate

NOVEL AND ADVANCE APPROACHES FOR PSORIASIS

Nanogel

Hydrogel nanoparticles, or nanogels, are generally comprised profoundly hydrated, cross-linked hydrophilic polymers. Nanogels can be developed to effect from outside stimuli, which can prompt changes in different properties including swelling, penetrability, viscoelasticity, and hydrophobicity (or hydrophilicity). The scope of external stimuli that can evoke such reactions includes photosensitivity and light exposer, changes in pH, ionic quality, and temperature and additionally presentation to magnetic fields, biological agent, and chemicals.[44,45] As comparison with other nanosize drug carriers, nanogel, show a properties like capacity to decrease off target impacts, stretch out medication flow time because of high stability compared to micelles, control drug discharge, to target particular tissues by means of conjugation of the nanogel surface with affinity ligands, to give security to the medication cargo from quick degradation, and to encourage crossing tissue barrier.[46]

PROPERTIES OF NANOGELS

1. Biocompatibility and degradability
2. Swelling property in aqueous medium

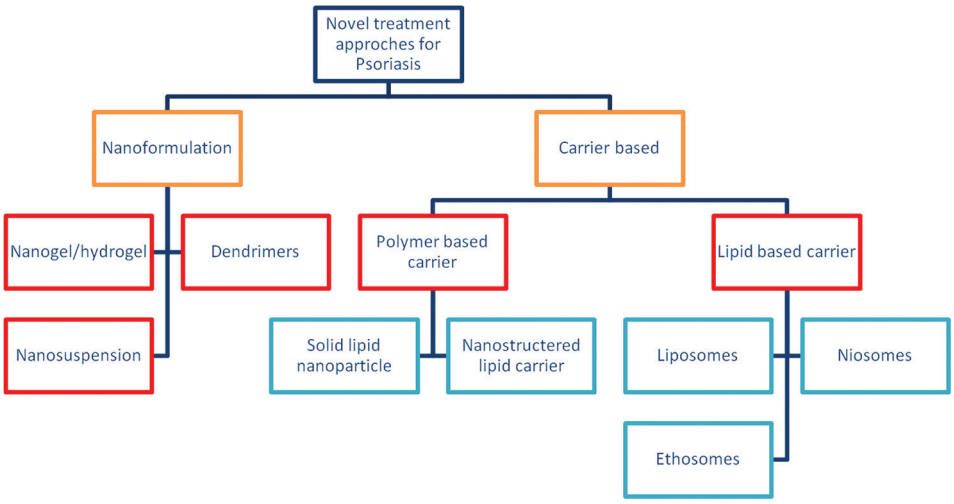

Figure 2: Novel approaches for the treatment of psoriasis

3. Higher drug-loading capacity
4. Increase solubility in its core and gel network
5. Non-immunological response
6. Hydrophilic and hydrophobic drugs loading.

Some of the research work had been carried out to formulate nanogel of different anti-psoriatic agent like Avasatthi *et al*. developed a nanogel by hot homogenization composed of MTX-loaded nanostructured lipid carrier (MTX-NLC) and then they evaluate its potential in imiquimod-induced psoriasis model to ameliorate symptoms of psoriasis. In its 48 h of study, MTX-NLC gel exhibited slow and prolonged release of MTX (47.32 ± 0.94% vs. 94.23 ± 0.79%) compared to MTX gel, and the PASI score is also get reduced in MTX-NLC formulation.[47] Like this way, Divya *et al.* focused on the development of an effective topical nanogel formulation of two anti-psoriatic drugs; Act and aloe-emodin using natural polymer chitin. They had done with *ex vivo* and *in vivo* studies in which *ex vivo* skin permeation studies using porcine skin confirmed the higher deposition of the systems at epidermal and dermal layers, which was confirmed further by fluorescent imaging. The *in vivo* anti-psoriatic activity study using Perry's mouse tail model and skin safety studies confirmed the potential benefit of the system for topical delivery of Act and AE in psoriasis.[48] The anti-psoriatic drugs loaded nanogel systems have proven to be an effective candidate for transdermal delivery in the dreadful disease psoriasis. The systems were found to be more stable at refrigerated condition as per the stability study.

Hydrogel

Hydrogels could be penetrated by the cross connecting of the polymer chain and provoke the formulation of polymer gel with high nuclear weight. Hydrogen loading is the essential component by which generous measure of water is entangled by the hydrogel.

Property

1. Highest absorption capacity
2. Desired rate of absorption
3. Highly durable and stable
4. Low cost
5. Photostability
6. Get neutralize in water
7. No toxic product formed after metabolism.

Kumar *et al*. studied the efficacy and safety of a recently marketed topical MTX (0.25%) preparation in a hydrogel base in 14 adult patients with palmoplantar lesions. They conclude that MTX 0.25% in a hydrophilic gel is well tolerated but is not very effective in controlling the lesions of psoriasis on the palms and soles. A higher concentration in a different base with better penetration could possibly provide better results.[49] Baboota *et al*. work was to test the hypothesis that the addition of corticosteroid such as BD and a keratolytic agent such as salicylic acid in nanocarrier-based microemulsions or hydrogel formulation would result in enhancement and sustaining of corticosteroid delivery rate, leading to better anti-psoriatic activity. There *in vivo* anti-inflammatory activity indicated 72.11–43.96% inhibition of inflammation of hydrogel versus marketed formulation, respectively. They find that the developed microemulsion gel containing BD and salicylic acid provided sustained and good anti-inflammatory activity for the treatment of psoriasis.[50] Gabriel *et al.* developed a composite hydrogel for improved topical delivery of the poorly soluble drug TAC to psoriasis lesions. Skin delivery of TAC composite hydrogel in an imiquimod-induced psoriasis mouse model was found to be twice as high as for the commercial formulation. This gives indication that the TAC composite hydrogel showed significant improvement in the *in vivo* and histopathological features of the imiquimod-induced psoriasis model.[51] From all the above study, a safe and effective hydrogel formulation can be prepared for the treatment psoriasis, which can provide

enhance permeation of the drug, reduced dosing frequency, and can sustain the drug release for the desired period of time.

Liposome

Liposomes are vehicles typically used as transdermal delivery of medication which is varied in their membrane from other vesicles, vesicle size, and CH content. There are numerous components that can enhance the dermal localization of liposomes through the skin, for example, size, charge, fluidity, etc. Surfactants have a basic part in the permeation of drug through SC. Unsaturated phosphatidylcholine (PC) species from natural sources (egg or soybean PC) give considerably more penetrable and less steady bilayers, while the saturated phospholipids with long acyl chains (for instance, dipalmitoyl PC) shape a rigid, rather an impermeable bilayer structure.

Application of liposomal delivery system

1. Solubility of lipophilic and amphiphilic drugs
2. Passive targeting to the cells of the immune system
3. Sustained release system
4. Improved penetration into tissues
5. Increased stability through encapsulation
6. Reduce the toxicity of the encapsulated agent like amphotericin B.

Srisuk *et al.* investigated the physicochemical characteristics and *in vitro* permeability of MTX-entrapped deformable liposomes. They formulated lipid vesicle from PC and oleic acid (OA), comparing with those of MTX-entrapped conventional liposomes prepared from PC and CH by thin-film hydration method. MTX entrapped in PC: CH is more stable in size and loading than other; however, the MTX-entrapped PC: OA liposomes enhanced the skin permeability characterized by the higher concentration and flux of MTX diffused across or accumulated in the epidermis and dermis layers of porcine skin.[40] Agarwal *et al.,* they prepared a novel, aqueous gel-based, and liposome-entrapped formulation of dithranol. They conducted clinical study of 19 plaques of psoriasis in nine adult patients which were treated for 6 weeks in a prospective, open-label trial. These preliminary results indicate that liposomal dithranol gel has potential advantages over presently available preparations with enhanced effectiveness.[52] Trotta *et al.* tested deformable liposome of MTX entrapped in PC or hydrogenated lecithin and dipotassium glycyrrhizinates surfactant. At the end of the skin permeation assay using deformable liposomes, up to 50% of the administered dose was found in the skin. They conclude that liposomes containing KG may be of value for the topical administration of MTX in the treatment of psoriasis.[53] Priyanka *et al*. worked on designing and evaluation of tazarotene-loaded liposome gel. Tazarotene has side effect on topical therapy such as peeling, dryness, irritation, and burning with its use, mostly during the early weeks of therapy. However, liposomal formulation of tazarotene improves the topical delivery by enhancing their dermal localization with concomitant reduction in their side effects.[54] All the study stabilized that topical liposomal formulation is effective in the treatment of limited chronic plaque psoriasis with a satisfactory safety profile. Future clinical trials should assess liposomal cyclosporine in larger study populations.

Solid lipid nanoparticle (SLN)

Due to their remarkable size-dependent properties, lipid nanoparticles offer to develop new therapeutics. SLNs hold awesome guarantee for achieving the objective of controlled and site medication delivery and thus have pulled into wide consideration of scientists. SLNs are either shaped by dispersion of the drug in the external shell encompassing a lipidic core, or by dissolving the medication in the lipid network and encompassed by the external shell. Mainly SLN are prepared by high pressure homogenization. SLNs offer numerous points of interest for the topical course by giving controlled medication release, displaying restricted harmfulness because of their physiological lipid content, expanding drug penetration through stratum corneum because of their little lipid droplet size, and guaranteeing an occlusive impact, because of lipid film formation on the top of the stratum corneum, for better skin hydration.[55] SLNs have been utilized in the pharmaceutical business for controlled drug discharge and expanding the bioavailability of loaded active substance by changing the disintegration rate in parenteral (intravenously, intramuscularly, or hypodermically), oral, and rectal treatments, in ophthalmology, and in outer use such as dermatology and cosmetics.

The key advantages of SLN are as follows

- Controlled release and orientation of active substance
- Increase of the active substance stability
- The capability to include lipo-and hydro-philic substances
- No biotoxicity
- No necessity to use organic solvents
- No problems related to large-scale production and sterilizing
- High loading (drug loaded).

Misra *et al.* developed MTX-loaded SLN, incorporated it in suitable gel base by hot microemulsion technique, and evaluated it *in vitro* and clinically on 24 patients to justify the role of the developed gel in the treatment of psoriasis. They founded that patients who showed progressive remission of lesions, desquamation, followed by decreased erythema and infiltration were considered effectively treated.[56] Arora *et al*. developed ultra-small SLN and NLC encapsulating cyclosporine and calcipotriol. On conducting anti-psoriatic efficacy in BALB/c mice (evaluated on the basis of cytokine levels and skin morphology), they highlighted that potential of drug-loaded NLC significantly higher as compared to drug-loaded SLN and marketed formulation Betagel in

treating psoriasis.[57] Sonawane *et al*. developed effective combination drug therapy (betamethasone dipropionate and calcipotriol-loaded SLN) for topical treatment of psoriasis by hot homogenization technique. They conducted *in vitro* and *in vivo* studies in which *in vitro* (HaCaT cell line) study demonstrated that SLNs delayed the abrupt growth of keratinocytes, while *in vivo* mouse tail model showed that SLNs gel significantly decreased the epidermal thickness and increased melanocyte count in comparison to commercial ointment.[58] Findings of the studies suggest that there is significant improvement in therapeutic index in the treatment of psoriasis by SLN gel base developed in this investigation over plain drug gel currently available in the market.

Nanosuspension

Nanosuspensions are submicron colloidal dispersion system of nanosized medicate particles stabilized by surfactants. Nanosuspensions consist of the low water dissolvable drug with no matrix material suspended in the dispersion. These can be utilized to improve the dissolvability of medications that are ineffectively solvent in water and in addition lipid media. Because of good dissolvability, the rate of flooding of the active compound increments and the greatest saturation level is achieved quicker.[59]

Advantages of nanosuspension

- Enhance the solubility and bioavailability of drugs
- Suitable for hydrophilic drugs
- Higher drug loading can be achieved
- Dose reduction is possible
- Enhance the physical and chemical stability of drugs
- Provides a passive drug targeting.

Yang *et al*. had conducted the studies on solid in oil nanosuspensions which was a kind of oil-based nanocarriers. The oil-based nanocarriers help in the penetration of MTX through SC. Compared to other conventional drug delivery systems such as liposomes and niosomes, the S/O nanocarriers possessed higher penetration capacity.[60] Due to lipophilic nature and nano level size of the carrier, it could enhance the permeation capacity. The absence of water in the formulation makes it as an anhydrous medium so that the risk of oxidation and biochemical degradation could be reduced effectively.

Nanostructured lipid carriers

NLC might be a contrasting option to different nanocarriers. NLCs are a helpful nutraceutical delivery system with high drug loading, encapsulation efficiency, productivity, and strength. They may increase, bioavailability and stability of bioactive compounds, and give controlled arrival of loaded materials. NLCs have been accounted for to be an alternative system to liposomes, microparticles, SLNs, emulsion, and their polymeric counterparts because of their various advantages.[57] Advantages of NLCs are such as

- Better physical stability
- An advanced and efficient carrier system, in particular, for lipophilic substances
- Controlled particle size
- Increase of skin occlusion
- High entrapment of lipophilic drugs and hydrophilic drugs
- Increase of skin hydration and elasticity
- Increased dispersability in an aqueous medium.

Pinto *et al*. aimed to develop and assess the potential of NLCs loaded with MTX by hot homogenization technique in combination with ultrasonication as a new approach for topical therapy of psoriasis. Evaluation of the *in vitro* skin permeation of MTX in their study showed its capability to go through the skin barrier when loaded within NLCs formulation which confirms the high potential of NLC as carriers for MTX and feasibility for topical delivery. Patient compliance should be increased, as topical application is much more comfortable.[61] Gajanan Shinde done work on methoxsalen which is a powerful anti-psoriatic agent. The purpose was to prepare and evaluate methoxsalen-loaded NLCs based gel. NLC-based gel was not shown skin irritation and shown prolong release up to 24 h. There was insignificant change in pH, drug content and *in vitro* release indicating the developed NLC were fairly stable.

Niosome

Niosomes were postulated to penetrate the skin by diffusion reforming new smaller niosomes vesicles in the skin, interact with stratum corneum by fusion or adhesion, or modify the stratum corneum structure and making it more permeable. Niosomes are microscopic lamellar structure formed on admixture of a non-ionic surfactant, CH, and diethyl ether with subsequent hydration in aqueous media. They behave *in vivo* like liposomes prolonging the circulation of entrapped drug and altering its organ distribution.[62]

Application

1. Accommodate hydrophilic, lipophilic, as well as amphiphilic drug moieties
2. Flexibility in their structural characteristic
3. Restrict the drug to its therapeutic site so prevent from clearance.
4. Niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug
5. Biodegradable, biocompatible, and non-immunogenic.

Lakshmi *et al*. prepared niosomal by lipid layer hydration method of MTX in chitosan gel and test the same for irritation and sensitization on healthy human volunteers followed by assessing the efficacy of the gel through double-blind placebo-controlled study on psoriasis patients and also comparing its efficacy with a marketed MTX gel. In human

repeated insult patch test, they did not find any significant irritation or sensitization on healthy human volunteers. In comparison to placebo and marketed gels, niosomal MTX gel reduces the total score from 6.2378 ± 1.4857 to 2.0023 ± 0.1371. Therefore, studies show that niosomal MTX gel is more efficacious than placebo and marketed MTX gel.[63] Almaghrabi *et al*. prepared and characterized of Act-loaded niosomes film hydration method for psoriasis because Act is used for the treatment of psoriasis orally. However, its systemic side effects and teratogenicity, the clinical administration is highly limited. Hence, topical administration of Act may reduce the systemic toxicity while increasing local bioavailability in the skin. Their Act-loaded niosomes showed a biphasic drug release pattern with an initial sustained release phase for up to 8 h followed by a steady drug release phase. They conclude that the drug retention on the skin gives the best result in treatment without leading to therapeutic levels in the systemic circulation.[64] The major findings of the studies reveal that the niosomal gel used as a topical agent significantly resolved psoriatic lesions and was shown to be quite effective in treating patients without any side effect.

Ethosomes

Topical delivery of drugs by liposomal formulations has attracted considerable interest in recent decades because of the improved therapeutic effects. However, conventional liposomes do not permeate deeply into the skin. Their particle size distribution is uneven and they remain confined to the epidermis. Touitou *et al.* discovered a novel type of liposomes, namely ethosomes. Ethosomes are composed of phospholipids, water, and a high concentration of ethanol, usually about 20–45% (https://www.ncbi.nlm.nih.gov/pubmed/10699298). Due to a liquid and flexible lipid bilayer, ethosomes are easily deformable and may permeate deep into the skin, thus enhancing drug delivery. Moreover, they increase drug deposition in the skin and enhance its permeability in scar tissue. Zhang *et al*. aimed to improve skin permeation and deposition of psoralen using ethosomes and to investigate real-time drug release in the deep skin in rats. *In vivo* skin microdialysis showed that the peak concentration and area under the curve of psoralen from ethosomes were approximately 3.37–2.34 times higher, respectively, than those of psoralen from the tincture. Moreover, it revealed that the percutaneous permeability of ethosomes was greater when applied to the abdomen than when applied to the chest or scapulas (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3904810/).

Dendrimer

The hyperbranched polypropylene imine (PPI) dendrimer generated a great deal of interest in controlled and targeted drug delivery due to their monodispersity, high density of peripheral functional group, well-defined precise shape and size, surface chemistries, host–guest interaction chemistry, interior cavities for higher entrapment of biomolecules, and multivalency (https://www.ncbi.nlm.nih.gov/pubmed/19099452). In just a couple of decades, dendrimers have attained recognition among the few leading systems in solubility enhancement, gene therapy, cancer, malaria, acquired immunodeficiency syndrome, microbial infections (fungal, viral, bacterial, and protozoal), tissue regeneration and remodulation, and imaging and diagnostic application. Several studies have shown that dendrimers increase the skin permeation of lipophilic drugs by increasing their water solubility. Udita Agrawal *et al*. investigated the potential of PPI dendrimers to deliver dithranol (DIT) topically and to evaluate its encapsulation, permeation, and skin irritation potential. Their study found the enhanced accumulation of DIT through dendrimer carrier within the skin which might help optimize and targeting the drug to the epidermal and dermal sites, thus creating new opportunities for well-controlled, modern topical application of DIT for the treatment of psoriasis (https://www.ncbi.nlm.nih.gov/pubmed/23594093).

FUTURE PROSPECTUS

Despite proven efficacy and safety of conventional drugs in psoriasis, there is a continued need for more effective and better-tolerated agents with different mechanisms of action for the treatment of recalcitrant lesions and for improved patient adherence. These newer developments include newer combinations, better formulations, newer investigational agents, or a comeback of older traditional therapies. Advances in nanoformulation help to solve the permeation problem of many of the drug use in psoriasis by entrapping the drug in vesicular compartment. However, there is some stability issue with nanoformulation. As there is tremendous increment in the usage of nanomaterials, it is a matter of concern that whether these materials can cause unexpected biological effects or not. All the vesicles in a dispersed aqueous system may suffer from some chemical problems associated with the degradation by hydrolysis or oxidation as well as physical problems such as sedimentation, aggregation, or fusion during storage. The provesicular concept has evolved to resolve the stability issues pertaining to the conventional vesicular systems, i.e., liposome and niosome. Provesicular systems are composed of water-soluble porous powder as a carrier, on which one may load phospholipids/non-ionic surfactants (liposome or niosomes, respectively) and drugs dissolved in organic solvents. The resultant dry-free flowing granular product which is formed could be hydrated immediately before use, and because of this reason, it can avoid various problems associated with aqueous vesicular dispersions. This includes proliposomes, proniosomes, dry granular liposomes, and protransfersomes. They avoid the problems of physical stability such as fusion, aggregation, sedimentation, and leakage on storage, chemical stability drug delivery improves bioavailability and minimum side effects. It is biodegradable, biocompatible, and non-immunogenic to the body.[65]

Other issues are toxicity of polymer used. Nanoformulations being in nanosize possessed easy access into the skin and provide deeper skin penetration. These carriers can transport drugs to the targeted tissue and thus gained tremendous interest in recent years. If the nanoparticles are serving as biomolecule carriers for *in vivo* applications, then it is important to understand the overall stability of the interaction of the carrier particle with the loaded biomolecules under several biophysical conditions.[65] Like nanoparticle >100 nm can be internalized by any cell through endocytosis that can ultimately pose more harm to the biological system. Hence, to eliminate these problems with non-biodegradable polymers, biodegradable material takes newer attention in market. The biodegradable materials are natural and synthetic in origin and by enzymatic or non-enzymatic actions can be degraded easily when used *in vivo* to produce biocompatible, toxicologically safe by-products which can be easily eliminated by the normal metabolic pathways of the body such as poly(ethylene glycol), poly(N-vinylpyrrolidone), polyoxazoline, and natural proteins such as albumin and casein, chitosan, dextran, alginate, and gelatine-based nanoparticles.

Numerous herbal topical drugs have been showcased worldwide to anticipate psoriasis. It is attractive to utilize natural agent as an elective treatment for psoriasis that causes a fewer toxic reaction. There are numerous focal points of utilizing natural medications including patient compliances, fewer symptoms, simple availability, low expenses, and more than one method of biochemical activity for psoriasis treatment. In this way, scientists are studying new herbal treatment items, which can possibly be an option for conventional medications in psoriasis treatment.[66] Some of the drugs under clinical trial for psoriasis are Aloe vera, *Baphicacanthus cusia*, *Curcuma longa*, *Indigo naturalis*, *Hypericum perforatum, etc.*

REGULATIONS FOR NANOTECHNOLOGY-BASED PRODUCT

In India

Regulation in India is still at its initial stage. Efforts have been taken by the Government of India to extend the research of nanotechnology in academic institutions, R and D, and National laboratories through financial assistance. Nanotechnology Sectional Committee was formed in March 2007 by the Bureau of Indian Standards to look into the standardization for nanodevices, sensors, transistors, initiators, etc.

The organization did not include consumer products in their agenda as standards for these products require advanced technologies and trained personnel in which the country is lacking significantly.[67]

In USA

Nanotechnology was not regulated specifically by the US - FDA in the past as it holds the view that it regulates products and claims regarding them but not technology. Further, it believes that its existing technologies are self-sufficient for nanotechnology testing. It has placed nanotechnology in critical path project and wants to take the research done by a manufacturer to develop standards and testing procedure to verify their technology. The US FDA has also constituted the National Nanotechnology Initiative and nanotechnology task force to evaluate the current regulatory approaches which will help in developing safe and effective products.[68]

CONCLUSION

The frequency of the autoimmune sickness “psoriasis” has expanded in a previous couple of years. The conventional types of anti-psoriatic drugs used, for example, creams, balms, and gels are beginning to become obsolete as they do not give complete prevention or treatment due to poor absorption and patient in compliance. Utilization of high dosage of these medications uses of conventional product produce side effect and different issue so that to limit these problems with conventional treatment and to enhance the targeting, NDDSs are favored particularly for mild and moderate psoriasis. In this review, we have made a review on the pharmaceutical carrier utilized for anti-psoriatic drugs which could overcome the inconveniences encountered with the conventional system and give predominance in overcoming the penetration properties of the stratum corneum. An emphasis on whether the pharmaceutical carrier could be utilized productively for the topical delivery of anti-psoriatic drug.

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