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A Study of Development and Optimization of Delivery System for the Management of Psoriasis

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ABSTRACT

This review offers insight into disease management of psoriasis and pharmaceutical approach for the effective drug delivery for the treatment of this disease. Several treatment regimens has been tried for psoriasis but rate of success is always limited as for as conventional system is concerned. This review deals in details about topical drug delivery in general and its challenges in designing effective drug delivery against psoriasis.

1. Introduction

Psoriasis is a chronic inflammatory skin disorder that may drastically affect the quality of life of an affected person. Different treatments are available for psoriasis and among this topical therapy are most commonly used in majority of patients. Psoriasis has genetic and life style triggers; the treatment guidelines involve continuous monitoring and lifelong care for the patients. Knowledge of the disease trigger factors and their role in precipitating the psoriasis is quiet important in the disease management. Care should be taken to avoid these psoriasis triggers. In recent years, new biological therapies have been introduced and several existing treatments have been improved giving new hope to people with psoriasis. Quality of life in a disease whether it's pre-treatment or post-treatment speaks a lot about its all-round impact on patients. Psoriasis has negatively effects on quality of life. Psoriasis is a lifelong, chronic, and recurrent disease. In a patient surveys conducted by the National Psoriasis Foundation between 2001 and 2008 in the USA, 33% of patients with mild disease and 60% of patients with moderate-to-severe psoriasis reported that their disease significantly affect their everyday life. Psoriasis can be as debilitating as many other serious medical or psychiatric conditions. The physical, psychological and social dimensions of life are negatively affected by the psoriasis and can be greater than those resulting from life-threatening illnesses such as myocardial infarction. Physical and mental rankings of psoriasis and other diseases, from best functioning (1) to worst functioning is (11). Physical rank of psoriasis is (10) just second to congestive heart failure (11) while mental rank is (9) which is third highest after depression (11) and chronic lung disease (10) but overall it has (10+9=19) rank which is highest amongst all disease.

The different types of psoriasis based on symptoms is given under:

Plaque Psoriasis
Guttate Psoriasis
Inverse Psoriasis
Erythrodermic Psoriasis
Pustular Psoriasis

According to Ayurveda, psoriasis (Sidhma Kushtam) occurs due to vitiation of doshas of Vata and Kapha. The reasons are use of incompatible food and accumulation of toxins etc.

Antipsoriatics		
Topical	Tars	Tar
	Antracens	Dithranol
	Psoralens	Trioxysalen – Methoxsalen
	Others	Fumaric acid – vitamina D (Calcipotriol, Tacalcitol, Calcitriol) – Tazarotene
Phototherapy		Artificial or natural light sources
Systemic	Psoralen	Methoxsalen – Bergapten- Trioxysalen
	Retinoids	Etretinate – Acitretin

Different treatment options are available to control and eliminate the symptoms of psoriasis. Nevertheless, most of them cannot be regarded as an ideal drug molecule. This may either be due to their inherent adverse effects or their improper incorporation in the conventional vehicles.

Topical Corticosteroids
Calcipotriene
Sequential Therapy with calcipotriene and super potent corticosteroids
Salicylic Acid
Coal Tar
Goeckerman's Regimen
Tazarotene
Calcineurin Inhibitors

2. Types Of Psoriasis:

Psoriasis can be classified into seven types as follows [6].

Table 1: Characteristics, affected areas and causes of various types of Psoriasis

Sr. No	Types	Characteristics	Affected Areas	Causes
1.	Plaque Psoriasis: The Most common form of psoriasis. About 80–85% of those who have psoriasis have this type.	Characterized by inflamed skin covered with silvery-white scaly skin. plaques itch or may be painful.	Elbows, knees, scalp and lower back.	Rubbing of skin, infection, medicines, alcohol, stress, smoking, and sunlight.
2.	Guttate Psoriasis: It is usually triggered by a bacterial infection such as streptococcal throat infection and often starts in childhood or young adulthood and affects about 18% of all psoriasis patients.	Characterized by numerous small scaly, red or pink drop like lesions.	Chest, arms, legs.	Streptococcal infection, bacterial or viral infections, injury to skin, e.g., cuts, burns, and insect bites, medicines, stress, sunburn, and alcohol.
3.	Inverse Psoriasis: Also known as Flexural Psoriasis. About 18% of those who have psoriasis have this type.	Characterized by bright red lesions that are smooth and shiny.	In the armpits, groin, under the breasts, and in other skin folds around the genitals and the buttocks.	Yeast overgrowth, high sensitivity to friction or sweating.
4.	Postural Psoriasis: Less than 5% of patients who have psoriasis have this type.	Characterized by white blisters of non-infectious pus surrounded by red skin.	Smaller areas on the hands, fingertips, or feet.	Overexposure to UV light, pregnancy, systemic steroids, infections, stress, and sudden withdrawal of systemic medications or potent topical steroids.
5.	Erythrodermic Psoriasis: It is a rare form of psoriasis and affecting 1-6% of psoriasis cases.	Characterized by widespread, fiery redness of the skin shedding of scales in sheets.	It affects most of the body surface.	Use of steroid, severe sun burn, emotional stress, alcoholism, infection, allergy.
6.	Nail Psoriasis: About 50–80% of those who have psoriasis have this type.	Change in nail color, little pits in nails, lines across nails, white area on nail plate, thickening of skin under nail, loosening of nail.	Toenails and fingernails.	Combination of genetic, environmental, and immune causes

3. Causes:

The cause of psoriasis is not fully understood, but there are several factors responsible which include genetics, environmental factors and the immune system.

¬ Genetics: It plays a major role in the development of this disease. Approximately 10% of the general populations have genes which are predisposed to psoriasis; But out of 10% only 1-3% of the populations develops the disease. Family with history of psoriasis has higher chance to develop this disease. Identical twin studies suggested a 70% chance of a twin developing psoriasis, if the other twin has the disease. The chance of developing disease is 20% in case of non-identical twin. These studies suggest both genetic and environmental factors are responsible in developing psoriasis [13].

¬ Environmental factors: Certain environmental factors trigger the psoriasis gene to become active. Some of the factors are [14]:

- Infections, such as streptococcal throat or skin infections
- Injury to the skin, such as a cut or scrape, a severe sunburn
- Stress
- Cold weather
- Smoking
- Obesity
- Heavy alcohol consumption
- Folate and vitamin B12 deficiency
- Certain medications like lithium, which is prescribed for bipolar disorder; high blood pressure medications such as beta blockers and antimalarial drugs.
- Co-morbidities of psoriasis: Psoriasis is associated with high morbidity and great level of psychological stress. The co-morbidities of psoriasis are:
  - Psoriasis arthritis
  - Cardiovascular disease and metabolic syndrome
  - Crohn's disease
  - Cancer.

¬ Immune system: In a normal healthy individual, T-cells which is a part of White blood cells (WBC's) , protect the body against infection by identifying &destroying foreign material. But, in psoriasis, T-cells are over-activated. Over-activation of T cells trigger other immune responses like dilation of blood

vessels in the skin around the plaques, stimulation of inflammatory chemical signal (cytokines) such as tumor necrosis factor- α,interleukin-1 β,interleukin-6,interleukin-36 and interleukin-22.These secreted inflammatory signals stimulate T-cells proliferation which causes an ongoing cycle in which new skin cells move to the outermost layer of skin too quickly, in days rather than weeks leading to formation of dead skin which is built up in thick, scaly patches on the skin's surface.

4. Pathophysiology:

Psoriasis is immune mediated disease which is generally caused by faulty signal of own immune system. It is believed that psoriasis develops when skin cells multiply at a faster rate as compared to normal skin cells growth rate. Normally, the skin cells mature and shed from the skin's surface every 28 to 30 days. In case of psoriasis, the skin cells mature in 3 to 6 days and move to epidermis. Instead of being shed, the skin cells accumulate on epidermis and cause visible lesions. There are mainly two hypotheses involved in the development of the disease. The first hypothesis states that psoriasis is primarily a disorder of excessive growth and reproduction of skin cells. The second hypothesis states that the disease is an immune mediated disorder in which the excessive reproduction of skin cells is secondary to factors produced by the immune system. Antigen-presenting cells in the skin, such as Langerhans cells, are believed to migrate from the skin to regional lymph nodes, where they interact with T cells. A number of co-stimulatory signals ,triggers an immune response, leading to T cell activation and the release of cytokines. Co-stimulatory signals are initiated via the interaction of adhesion molecules on the antigen-presenting cells, such as lymphocyte function-associated antigen (LFA)-3 and intercellular adhesion molecule, with their respective receptors CD2 and LFA-1 on T cells. These T cells are released into the circulation and traffic back into the skin. Reactivation of T cells in the dermis and epidermis and the local effects of cytokines such as tumor necrosis factor lead to the inflammation, cell mediated immune responses, and epidermal hyper-proliferation observed in persons with psoriasis. Current research suggest that the inflammation involved in the disease is because of immune system and most likely initiated and maintained by T cells in the dermis.

5. Novel Drug Delivery Systems For Psoriasis:

Conventional therapy has many limitations which include poor drug solubility, insufficient drug concentration due to poor absorption, low permeability, rapid metabolism and elimination, drug distribution to other tissues combined with high drug toxicity and short half-life [39]. Novel drug delivery systems (NDDS) is a promising strategy to overcome these side-effects and offer many advantages which include increased safety and efficacy, drug targeting specificity and lowering of systemic drug toxicity.Stratum corneum (SC) is the main barrier in percutaneous absorption of topically applied drugs. Small and relatively narrow size distribution with novel carriers permit site specific delivery to the skin with improved drug solublization of hydrophobic drugs and better bioavailability. Nanocarriers play an important role in drug delivery to the target site for control and prevention of the disease. Such carriers have become the first choice to deliver anti-psoriatic drugs, due to their various characteristics such as:

- Excellent biocompatibility and biodegradability
- Non-toxic and degradable nature
- Easily eliminated from the body
- Stable at physiological and atmospheric conditions
- Longer duration of action
- Sustained and controlled drug release to the target site.

6. Skin As Delivery Target

The skin, called cutis in Latin (term cutaneous derived from it), is the largest organ of the body counting more than 10% of the total body mass. Its large surface area of around two square meters considered essential for the survival as it is in direct contact with the environment providing multifunctional activity against varying conditions. For pharmaceutical technologist's approach skin presents tremendous opportunities for drug delivery and overcoming the barrier function of it has become the essence in the design of topical drug delivery systems. Thus, before going for topical formulations it is necessary to study skin and its barrier function thoroughly. The human skin is organized into two distinct layers, namely the outermost epidermis and the layer below epidermis is called dermis (Figure 1). Beneath the dermis are subcutaneous fatty tissues. Bulbs of hair embedded in to these fatty tissues. The highly vascular dermis is made up of a connective tissue containing network of blood vessels, hair follicles, pilosebaceous units and sweat glands. The epidermis is avascular in nature and has five numbers of different layers, which, from outermost to bottom, are stratum corneum (also called Horny layer), stratum lucidum presents only in thick skins, stratum granulosum (Granular layer), stratum spinosum (Prickly cell layer) and stratum germinativum (Growing layer). The stratum corneum consists of corneocytes which is dead epidermal cells rich in keratin and surrounded by crystalline intercellular lipid domains. In addition to the almost impermeable corneocytes, the barrier function of stratum corneum is offered by the presence of a unique mixture of lipids in the intercellular spaces of it. These lipids, though acting as barriers, can provide a passage for permeation of exogenous chemicals, including drugs. Therefore, drug delivery across the stratum corneum has become the real challenge in the design of topical drug delivery systems3 . Absorption through skin generally takes place either by transepidermal route or by transfollicular route. Transepidermal pathway can be described as diffusion across the skin. Stratum corneum is the major resistance encountered along this pathway. Transepidermal permeation pathway first involves partitioning into the stratum corneum followed by diffusion across this tissue. Most of the drugs and substances diffuse across the stratum corneum via the intercellular lipoidal route. Transfollicular absorption takes place through skin appendages. Hair follicle and associated sebaceous gland present in skin collectively referred to as skin appendages. This is a secondary route of absorption.

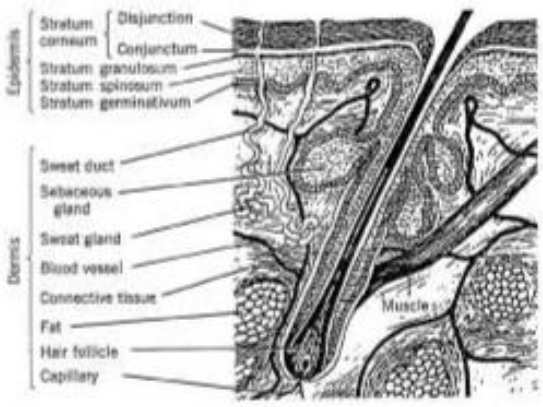

Fig.1. Structure of human skin

After getting insight into skin and its barrier function it is imperative to develop drug delivery systems instead of applying drug molecules alone in a conventional manner to overcome the epidermal barrier for effective topical drug delivery. Drug delivery systems with modifications at both physical and chemical level can be effective against barrier function of the skin.

With an eye on improving the topical delivery of drugs with drug delivery systems certain chemical enhancement methods has been applied such as

(1) Occlusion: to prevent trans-epidermal water loss from stratum corneum by the use of hydrogels, ointment bases 7, 8,

(2) Increasing the hydration of stratum corneum by high water content in the formulation,

(3) Addition of chemical enhances in the formulation to disrupt the lipid organization in the stratum corneum such as azone, terpenes, fatty acids, dimethylsulphoxide (DMSO) and alcohols,

(4) Addition of compounds in the formulation that are able to alter the protein organization in the stratum corneum, such as DMSO or urea,

(5) Use of penetration enhancers in the formulations such as Transcutol P10,

(6) Modifying the thermodynamic activity of the drug in the formulation at the moment of the application, e.g. ethanol11,

(7) For poorly soluble substances, solubilization of the drugs in the donor e.g. surfactants.

Common skin changes in psoriasis

Skin lesions covered with scales having thickened inflammation. Dry skin due to deficient natural moisturizing factor Imbalanced skin lipids Skin having tethered hair Skin sensitivity Corneocytes have excessive growth and aberrant differentiation Topical delivery into the psoriatic skin have lately been proposed to be addressed by the colloidal carrier systems, such as liposomes, niosomes and mixed miceller system, silica aerogel and ethosomes, lipid micro emulsion. The application of lipids in particular in these formulations resolves the problem of lipid imbalance and lack of moisture content. Thus, these lipoidal and allied carriers can result in an effective delivery of drugs across psoriatic skin.

7. Pharmacology

Tacrolimus inhibits dephosphorylation of the transcription factor nuclear factor of activated T-cells by calcineurin, and therefore there is suppressed activity of the genes that code for interleukin 2 (IL-2) in the nucleus. Tacrolimus also causes decreased transcription and release of other T-cell-derived cytokines including IL-3, IL-4, IL-8, TNF-α, INF-γ, and granulocyte macrophage colony-stimulating factor; it has also been found that exocytosis of in cytotoxic T-cells is inhibited by tacrolimus.8 In vitro research has indicated that p53 levels in psoriatic skin are diminished; Lemster et al8 describe augmentation of p53 gene expression by tacrolimus treatment, resulting in a reduced rate of epidermal hyperproliferation. Orally administered ciclosporin is an effective treatment for psoriasis; however, topical application of the drug is ineffective due to inadequate skin penetrance. In light of this, topical pimecrolimus and tacrolimus preparations were developed. Topical tacrolimus penetrates the skin at 0.03% and 0.1% strength; however, topical corticosteroids have a superior skin penetrance than topical calcineurin inhibitors. Due to a more selective mechanism of action that does not alter collagen synthesis, topical calcineurin inhibitors can be utilized as corticosteroid-sparing agents as they are not associated with agenesis of the skin; this has been found to be of particular usefulness in facial, genital, and intertriginous areas. Pimecrolimus is a structurally similar molecule to tacrolimus; however, pimecrolimus has greater lipophilicity. The implication of this is that there is a high level of pimecrolimus retained within the skin following application and thus systemic absorption is minimal. Systemic absorption of topical tacrolimus is reported to be highest through skin that has compromised barrier function and it is not absorbed systemically through intact skin. No systemic side effects have been reported following topical tacrolimus treatment; however, there is a lack of evidence about long-term usage.

8. Utility for face and flexural skin

In numerous case studies, topical tacrolimus has shown promise for the treatment of facial psoriasis. Subsequently, 10 long-term psoriasis sufferers were included in a trial to examine the efficacy of tacrolimus 0.1% ointment used on anogenital and facial lesions. Tacrolimus 0.1% ointment was applied twice daily for 10 days, and follow-up continued for 12 weeks in total. There was notable improvement in all subjects by the end of the first week, and no adverse effects were reported.20 Following this, a multicenter randomized double-blind placebo-controlled trail investigated the utility of tacrolimus 0.1% ointment in 167 patients with inverse psoriasis. The participants were instructed to apply the ointment twice daily to areas of facial or intertriginous psoriasis for 8 weeks. Observers noted that from day 8 of the trial, more patients in the active treatment arm had completely cleared or achieved marked improvement than in the vehicle group. By the end of the trail, 65.2% of patients treated with tacrolimus 0.1% ointment were clear or almost clear of their psoriasis, compared to 31.5% treated with placebo ($p<0.0001$). Then an open-label single-arm clinical trial was conducted that included 21 patients who had psoriasis affectingthe face or intertriginous areas, or both. The participantsapplied tacrolimus 0.1% ointment twice daily for 8 weeks.Two participants reported mild pruritus at the applicationsite on the first day of treatment, and a transient warm sensation was also reported, lasting for 1 hour after

applicationfor the initial few days of treatment. Seventeen (out of 21)participants achieved complete skin clearance by the endof the study – supporting the use of topical tacrolimus ininverse psoriasis.

9. Treatment of pediatric psoriasis

Steele et al published a promising retrospective case study of 13 pediatric patients, aged from 22 months to 16 years. Twelve of the participants achieved complete clearance of psoriatic skin lesions affecting the face and intertriginous areas within 2 weeks. These participants were treated with Tacrolimus 0.1% ointment twice daily and were instructed to stop application of the ointment once their psoriasis had cleared. Patients were followed up for 2 years after the start of the study and instructed to apply the ointment if there was any recurrence of skin lesions.26 More recently, a pilot study of 11 pediatric patients between the age of 6 and 15 years demonstrated the efficacy of tacrolimus 0.1% ointment for treatment of facial and inverse psoriasis. All patients had either complete clearance or had excellent improvement of psoriasis after 30 days of treatment, and there was an unacceptable degree of pruritus experienced by only one patient when using the ointment in the genital region. Several participants experienced a relapse of their condition following cessation of treatment, but after recommencing treatment adequate control was regained within 7 days. When surveyed at the end of trial, caregivers rated the treatment regimen as easy or very easy for them to use and all but one caregiver stated that the treatment provided complete control of the disease.

10. Treatment of nail and pustular psoriasis

Tacrolimus 0.1% ointment also produced promising treatmentresults when used in a randomized controlled open-labelstudy, involving 21 patients with nail psoriasis. Participantswere randomized to either the treatment or placebo groupand were instructed to apply the ointment to their nails oncedaily at bedtime and to avoid washing their hands until themorning. Severity of nail psoriasis was measured using theNail Psoriasis Severity Index (NAPSI). NAPSI score canrange from 0 in a nail with normal matrix and bed, to a scoreof 8 when nails signs are present in all four quadrants on thenail in both the matrix and the bed. At the end of the 12-weektrial, the participants who received treatment had a meansignificant reduction in NAPSI score of 13, compared with amean reduction of 3 points in the placebo group ($p<0.001$). A number of case reports and small case series havesuggested that topical tacrolimus treatment is effective forgeneralized pustular psoriasis,29,30 palmoplantar pustularpsoriasis,31 and oral psoriasis.32,33 Topical tacrolimus andexcimer laser treatment was effective for a patient with inversepsoriasis; it was postulated that the laser therapy decreasedthe thickness of the epidermis and thus facilitated penetrationof the topical preparation, which lead to a reduction in thenumber of cutaneous nerve fibers and diminished pruritus. Tacrolimus ointment 0.1% has also been reported as effectivewhen used as part of a combined topical treatment regimen ina patient with psoriasis lesions affecting the lips.

11. Conclusion

Psoriasis is a topical disorder with unknown etiology and still after advancement in medical science complete cure of this disease is not yet established. Thus quality of life after disease identification is definitely compromised in a big way and requires a conscious efforts and protocols as disease management is an important tool to keep this disease under control. Topical therapy whether it is conventional or novel is always choice of delivery system for pharmaceutical technocrats. Psoriatic skin pose a stiff challenge in designing a viable topical delivery system for delivery of antipsoriatic drugs and combining advantages of novel drug delivery system precisely colloidal drug delivery approaches provides a better drug delivery regime to the psoriasis treatment.

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