TOPICAL FORMULATIONS IN PSORIASIS MANAGEMENT: AN OVERVIEW

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ABSTRACT
Psoriasis is a common, chronic, non-contagious, auto-immune disease that primarily affects the skin. It is characterized by excessive growth and abnormal differentiation of keratinocytes, which leads to hyper proliferation and other inflammatory reactions on the skin. Topical therapy is a first line treatment for psoriasis management as it has many advantages over phototherapy and oral medication like avoidance of first pass metabolism, patient compliance, ease of application, local therapeutic effect and lower incidence of side-effects. This article focuses on drugs as well as novel approaches used in topical treatment for Psoriasis.

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INTRODUCTION
Psoriasis is a common, chronic, non-contagious, auto-immune disease that primarily affects the skin and is seen in about 2-3% of population worldwide[1]. The word “psora” comes from Greek word which means “to itch”. Psoriasis, a term which has been in use since 133 AD, was originally grouped with leprosy until the 19th century. It has been suggested that biblical leprosy was, in fact, the disorder known today as Psoriasis[2]. It is mostly an inheritant disease, characterized by scaly, red and itchy plaques. The most commonly affected areas are the entire scalp and can also spread to the forehead, back of neck or behind ears, chest, arms, elbows, in the armpits, under the breasts, around the genitals, knees, legs, toenails and fingernails[3]. It affects males and females equally and also affects children, adult, older peoples and may occur at any age of life. It is more common in people between the ages of 15 and 35, according to National Psoriasis Foundation.

Psoriasis is partly due to genetic and partly due to environmental factors[4]. Psoriasis can be categorized as mild, moderate and severe. Mild psoriasis leads to formation of rashes and when it becomes moderate the skin turns scaly. In severe conditions, the red patches may be present on skin surface and become itchy. This affects a person’s professional and social life. The normal mechanism of body is to form new skin cells every month to replace the skin which is shed off. But, in psoriasis the new skin cells grow rapidly within days rather than weeks. This leads to accumulation of dead skin on the skin surface resulting in thick patches of red, dry and itchy skin[5].

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.

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Types</th>
<th>Characteristics</th>
<th>Affected Areas</th>
<th>Causes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Plaque Psoriasis: The Most common form of psoriasis. About 80-85% of those who have psoriasis have this type.</td>
<td>Characterized by inflamed skin covered with silvery-white scaly skin. plaques itch or may be painful.</td>
<td>Elbows, knees, scalp and lower back.</td>
<td>Rubbing of skin, infection, medicines, alcohol, stress, smoking, and sunlight.</td>
<td>Lee S, et al 2012[7]</td>
</tr>
<tr>
<td>2.</td>
<td>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.</td>
<td>Characterized by numerous small scaly, red or pink drop like lesions.</td>
<td>Chest, arms, legs.</td>
<td>Streptococcal infection, bacterial or viral infections, injury to skin, e.g., cuts, burns, and insect bites, medicines, stress, sunburn, and alcohol.</td>
<td>Henley ND., et al 2012[8]</td>
</tr>
<tr>
<td>3.</td>
<td>Inverse Psoriasis: Also known as Flexural Psoriasis. About 18% of those who have psoriasis have this type.</td>
<td>Characterized by bright red lesions that are smooth and shiny.</td>
<td>In the armpits, groin, under the breasts, and in other skin folds around the genitals and the buttocks.</td>
<td>Yeast overgrowth, high sensitivity to friction or sweating.</td>
<td>Syed ZU, et al 2011[9]</td>
</tr>
<tr>
<td>4.</td>
<td>Postural Psoriasis: Less than 5% of patients who have psoriasis have this type.</td>
<td>Characterized by white blisters of non-infectious pus surrounded by red skin.</td>
<td>Smaller areas on the hands, fingertips, or feet.</td>
<td>Overexposure to UV light, pregnancy, systemic steroids, infections, stress, and sudden withdrawal of systemic medications or potent topical steroids.</td>
<td>Viguier M, et al 2012[10]</td>
</tr>
<tr>
<td>6.</td>
<td>Nail Psoriasis: About 50-80% of those who have psoriasis have this type.</td>
<td>Change in nail color, little pits in nails, lines across nails, white area on nail plate, thickening of skin under nail, loosening of nail.</td>
<td>Toenails and fingernails.</td>
<td>Combination of genetic, environmental, and immune causes</td>
<td>Aydin SZ, et al 2012[12]</td>
</tr>
</tbody>
</table>
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 population 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 have 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 suggests 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-1β, interleukin-6, interleukin-36 and interleukin-22 [15,16]. 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[13].

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 [17]. 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 [18,19].

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[20].

Diagnosis:
The diagnosis of psoriasis is usually based on the appearance of the skin. There are no special blood tests or diagnostic procedures for psoriasis. Sometimes a skin biopsy or scraping may be needed to rule out other disorders and to confirm the diagnosis. Skin from a biopsy will show clubbed Rete pegs if positive for psoriasis. Another sign of psoriasis is that when the plaques are scraped, one can see pinpoint bleeding from the skin below. Diagnosis of psoriasis is made easily by clinical examination. Usually no tests are required to diagnose psoriasis, but to rule out other complications blood tests, urine test and imaging studies are often performed [21].
TOPICAL TREATMENTS:
Psoriasis is a lifelong condition. There is currently no cure but various treatments can help to control the symptoms. There are three types of treatments viz topical treatments, light therapy (phototherapy) and oral medication. Topical treatments like (creams, lotions, gels, ointments, moisturizers applied to the skin) are usually the first line treatment and they help to reduce the accelerated production of skin cells and inflammation.

Agents used in Psoriasis treatment:
Topical Corticosteroids:
They are used as first line agents and also in combination with other topical agents [22,23]. They slow down cells turnover by suppressing the immune system, which reduces inflammation and relieves associated itching. They also have vasoconstrictive properties. Corticosteroids are classified based on Potency according to their vaso-constrictive properties [22,24,25]. According to USA there are seven potencies groups viz Less Potent (least potent), Potent, Upper mild strength, Mild strength, Lower mild strength, Mild, Very high potency (Super potent). The UK considers four classes: mild (class IV), moderately potent (class III), potent (class II), and very potent (class I) [22,24,26,27].

Lower-potency corticosteroids are particularly recommended for application on the face, groin, axillary areas, and in infants and children, whereas mid and higher-potency corticosteroids are commonly used for other areas in adults. Super-potent corticosteroids are mainly used for stubborn, cutaneous plaques or lesions on the palms, soles, and/or scalp [24, 28]. Side-effects include hypopigmentation, striae, skin atrophy and tachyphylaxis [29].

Coal Tar:
The benefits of Coal tar have been known for many years. The use of coal tar has declined due to the availability of other topical agents. It is used to treat mild, moderate and severe Psoriasis. It relieves itching, swelling. It also inhibits enzymes that contribute the pathogenesis of psoriasis. A coal tar solution of between 1-5% has been proven as a safe product. Side-effects include its strong smell, irritation, staining of clothes and potential for causing photosensitivity [30,31].

Topical vitamin D3 analogs:
Calcipotriol (Calcipotriene), calcitriol and tacalcitol are analogues of vitamin D3. Calcitriol naturally occurring active form of vitamin D3. These agents blocks epidermal proliferation, enhances maturity of cells, and has anti-inflammatory effects. It is no more effective than the moderately potent topical steroids, but combination of calcipotriol with topical steroids is more effective than either agent alone. Calcipotriol is very expensive. Vitamin-D helps to regulate calcium and phosphorus in the body and can also be produced by the skin when exposed to UVB light. Side-effects include Skin irritation- 20% of patients particularly on the face and in skin fold [32,33].

Dithranol:
It is also called as Anthralin. This is used for treating thick plaques of psoriasis. This is a traditional medicine chrysarobin and has been in use for a century. It is used in the concentration of 0.1-1%. Side-effects include skin irritation and brownish discoloration of skin, it may stain cloths. Therefore, it is known as short contact therapy. Contact with the face, eyes or mucous membrane must be avoid [30,34].

Tazarotene:
Tazarotene is a synthetic retinoid with properties similar to that of Vitamin-A. It may be used as a single agent or in combination with a corticosteriod, calcipotriol or phototherapy. Common side effect is irritation, which can be minimized by applying a thin layer of medication only to the patches and avoiding the uninvolved surrounding skin. It should not be used on the genitals or in the skin folds. It is contraindicated in pregnancy [35].

Tacrolimus:
It has immunosuppressant activity and used to treat both Psoriasis and Atopic dermatitis. It may be beneficial over sensitive areas like the face, genitelia and intertriginous areas [36,37].

Salicylic acid:
It is a keratolytic agent. It is used to remove scales that appear on skin. It is used in combination with other topical agents, it takes off the upper layer of skin allowing the additional agent to penetrate more effectively into the deeper layers. It is used in a concentration of 2-10%, it is usually combined with coal tar, steroids and dithranol. Side-effects include Moderate or severe skin irritation, flushing, unusually warm skin and reddening of skin [38].
Marketed Products for Psoriasis:

Table 2: List of Marketed Topical Products for Psoriasis.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drugs</th>
<th>Commercial Products</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Topical Corticosteroids:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Betamethasone propionate 0.05%</td>
<td>Diprolene</td>
<td>Cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Clobetasol propionate 0.05%</td>
<td>Temovate</td>
<td>Cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Halobetasol propionate 0.05%</td>
<td>Ultravate</td>
<td>Cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Diflorasone diacetate 0.05%</td>
<td>Psorcon</td>
<td>Ointment</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate 0.1%</td>
<td>Elocon</td>
<td>Cream</td>
</tr>
<tr>
<td>2.</td>
<td>Topical vitamin D3 analogs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcipotriol 0.005%</td>
<td>Dovonex</td>
<td>Cream, ointment</td>
</tr>
<tr>
<td></td>
<td>Calcitriol 0.005%</td>
<td>Daivonex</td>
<td>Cream, ointment</td>
</tr>
<tr>
<td>3.</td>
<td>Coal Tar:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coal Tar 5%</td>
<td>Oxipor</td>
<td>Lotion</td>
</tr>
<tr>
<td></td>
<td>Coal Tar 4.25%</td>
<td>Ionil</td>
<td>Shampoo</td>
</tr>
<tr>
<td>4.</td>
<td>Dithranol 1%</td>
<td>Micanol</td>
<td>Cream</td>
</tr>
<tr>
<td>5.</td>
<td>Salicylic acid 6%</td>
<td>Seton</td>
<td>Cream</td>
</tr>
<tr>
<td>6.</td>
<td>Calcipotriol 0.005%</td>
<td>Xamiol</td>
<td>Gel</td>
</tr>
<tr>
<td></td>
<td>Betamethasone dipropionate 0.05%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Salicylic acid 3% + betamethasone 0.05%</td>
<td>Diprosalic</td>
<td>Ointment</td>
</tr>
<tr>
<td>8.</td>
<td>Clobetasol Propionate 0.05% + Salicylic Acid 3%</td>
<td>Kelypso</td>
<td>Cream</td>
</tr>
<tr>
<td>9.</td>
<td>Calcipotriene 0.005% + Betamethasone dipropionate 0.05%</td>
<td>Taclonex</td>
<td>Ointment</td>
</tr>
<tr>
<td>10.</td>
<td>Clobetasol Propionate 0.05% + Salicylic Acid 6%</td>
<td>Clopinate S</td>
<td>Cream</td>
</tr>
</tbody>
</table>

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[40,41]. 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 [42]. Nanocarriers play an important role in drug delivery to the target site for control and prevention of the disease [43]. Such carriers have become the first choice to deliver anti-psoriatic drugs, due to their various characteristics such as:

- Excellent biocompatibility and biodegradability[44]
- Non-toxic and degradable nature[45]
- Easily eliminated from the body[44]
- Stable at physiological and atmospheric conditions[46]
- Longer duration of action[45]
- Sustained and controlled drug release to the target site [47].

Novel Formulations:

Liposomes:

Liposomes are spherical microscopic vesicles consisting of phospholipid bilayers which enclose aqueous compartments or active drug. Drug molecules can either be encapsulated in the aqueous compartment or into the lipid bilayer; the exact location of a drug in the liposome will depend upon its physicochemical characteristics and the composition of the lipids [48]. Components of liposomes are phospholipids, cholesterol, and long chain fatty acids [49]. Advantages include biocompatible, biodegradable, non-toxic, non-immunogenic and have the ability to protect the encapsulated drug from the external environment [50].
Table 3: Some of the reported examples of liposomal formulations for Psoriasis are tabulated as follows:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug</th>
<th>Formulation</th>
<th>Method of Preparation</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
</table>

Niosomes:

Niosomes are non-ionic surfactant vesicles containing non-ionic surfactants instead of phospholipids in the bilayer of liposomes. They are microscopic lamellar structures obtained on hydration of non-ionic surfactant, cholesterol, and other lipids [54]. It is capable of entrapping both hydrophobic and hydrophilic drugs. This novel carrier is used in the formulation of various drugs to enhance the penetration and also to sustain the release of the drug [55,56]. Advantages include enhanced skin penetration, greater stability, osmotically active and stable, low cost [57].

Lakshmi PK, et al 2007 studied the preparation of niosomal Methotrexate (MTX) in chitosan gel by thin film hydration method. It was concluded that the niosomal MTX gel when compared with placebo and marketed MTX gel, results shows niosomal MTX gel is more effective[58].

Ethosomes:

Ethosomes are mainly composed of phospholipids, ethanol or other volatile alcohols at relatively high concentrations (up to 50%) and water [59] containing fluidized phospholipid bilayers generating vesicles with a soft structure. An additional essential role of ethanol present in the system is fluidization and disturbance of stratum corneum and to enable penetration into deeper layers of skin. This novel carrier system has drug delivery into deeper layers of skin or into the systemic circulation [60]. Ethosomal formulations can be non-invasive, non-toxic, high permeability, promote patient compliance.

Dubey V, et al 2007 studied the preparation of Methotrexate (MTX) loaded ethosomes by mechanical dispersion method. It was concluded that MTX loaded ethosomes have drug targeting at epidermal and dermal sites and modern approach in the treatment of psoriasis [61].

Microemulsions:

Microemulsions are thermodynamically stable isotropic systems wherein two immiscible liquids (water and oil) are mixed to form a single phase by means of an appropriate surfactant or its mixture. Short to medium chain alcohols are generally considered as co-surfactants in the microemulsion system. The presence of surfactant and co-surfactant in the system makes the interfacial tension very low. They can solubilise both hydrophilic and hydrophobic drugs [62]. Advantages include ease of preparation, long-term stability, high solubilization capacity for hydrophilic and lipophilic drugs, and improved drug delivery [63].
Table 4: Some of the reported examples of microemulsion formulations for Psoriasis are tabulated as follows:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug</th>
<th>Formulation</th>
<th>Method of Preparation</th>
<th>Conclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>Clobetasol propionate (CP)</td>
<td>Microemulsion gel</td>
<td>Aqueous phase titration method</td>
<td>Microemulsion gel containing CP has ability to permeate and retain into skin layers for effective treatment of psoriasis.</td>
<td>Patel HK, et al 2013 [65]</td>
</tr>
</tbody>
</table>

Solid lipid nanoparticles:

Solid Lipid Nanoparticle (SLN’s) are nanosized carrier systems in which solid particles consisting of a lipid matrix are stabilized by surfactants in an aqueous phase. The SLN structure is composed of solid core, which may contain triglycerides, glyceride mixtures, or waxes that are solid at both room temperature and human body temperature. Incorporation of both lipophilic and hydrophilic drugs into SLN’s are possible.

SLN’s can be biocompatible, biodegradable, have controlled drug delivery, specific drug targeting[66], have negligible skin irritation, protect active compounds and imparts sustained drug release to avoid systemic absorption[67].

Madan JR, et al 2014 studied the preparation of Mometasone Furoate (MF) loaded SLN’s gel by Solvent injection method. It was concluded that greater skin deposition and slow drug release and MF loaded SLN’s gel could be a new, cost-effective and commercially viable alternative to the marketed product [68].

CONCLUSION

Conventional therapy for Psoriasis provides only symptomatic relief. There are many drawbacks of conventional therapy and hence, there is a need for the development of novel drug delivery systems which can tackle the limitations of conventional product. Novel formulations are used to increase the penetration of drug molecules to the target site with reduced side effects. There is a still need for further investigation for anti-psoriatic drugs to establish the clinical utility and industrial scale-up of techniques for manufacturing these potential novel carriers.

List of Abbreviations:

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>lymphocyte function-associated antigen</td>
<td>LFA</td>
</tr>
<tr>
<td>White blood cells</td>
<td>WBC’s</td>
</tr>
<tr>
<td>Novel drug delivery systems</td>
<td>NDDS</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>MTX</td>
</tr>
<tr>
<td>Clobetasol Propionate</td>
<td>CP</td>
</tr>
<tr>
<td>Stratum corneum</td>
<td>SC</td>
</tr>
<tr>
<td>Solid Lipid Nanoparticle</td>
<td>SLN’s</td>
</tr>
<tr>
<td>Mometasone Furoate</td>
<td>MF</td>
</tr>
</tbody>
</table>
COMPETING INTERESTS:
The authors declare no conflict of interest.

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