**ANTIPSORIATIC GEL FORMULATIONS: AN UPDATED WRITE UP**

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**INTRODUCTION**

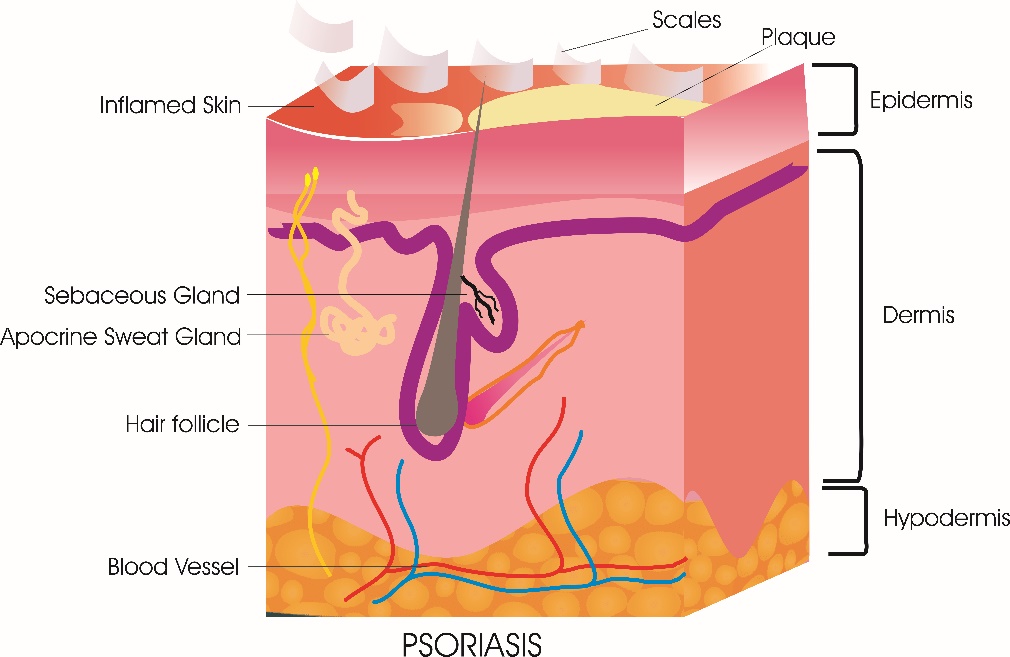
Psoriasis is very common and chronic inflammatory immune mediated skin disorder of papulosquamous type consisting of reddish papules with scales. Its occurrence is worldwide and found at any age, moreover, this disease has a negative effect on the physical, emotional, and psychosocial well-being of affected patients. It requires long term therapy and Methotreaxate, Cyclosporin, Acitretin, Fumarate and some traditional medicines are being used for the treatment of Psoriasis (1-3). Topical treatment is the first line treatment for psoriasis and gel formulations one of the most important topical treatments. The skin disease like acne, rosacea or psoriasis requires slow absorption, and gel formulation fulfils the criteria therefore, considered as most effective treatment (4). The present review targets the different gel formulations, their active ingredients with mechanism used for the treatment of psoriasis.

**METHODOLOGY**

The literature survey has been successfully completed by searching terminologies of “Psoriasis”, “Psoriasis and Treatment”, “Gel Formulations and Skin”, “Gel Formulations and Psoriasis”, “Corticosteroids and Psoriasis”, “First line drugs of Psoriasis” in online databases as well as search engines like Scopus, Google Scholar, PubMed, Publons, Elsevier, Springer and so on. Authors searched and reviewed more than 80 research articles, review papers, magazines, and newspapers. Then, they included 52 articles after reviewing the full-text, and the remaining 28 were excluded because of unauthentic, less reliable information.

**PSORIASIS**

Psoriasis is categorised as common and chronic inflammatory dermatoses that found in all ages. It is characterised by well-demarcated, pink to light pink coloured (salmon coloured) plaque and covered by loosely adherent scale of silver-white in colour. It mostly affects the part of skin of elbows, knees, scalp and intergluteal cleft. The different types of psoriasis mentioned in the literature are *Psoriasis Vulgaris, Inverse Psoriasis, Guttate Psoriasis* and *Pustular psoriasis*. Histologically, the presence of marked epidermal hyperpalasia (acanthosis), parakareotic scale, dermal dendritic cells, macrophages, T cells and neutrophils within the superfacial epidermal layers are mentioned in the text (5). Though the causes, detailed pathogenesis and activation of psoriasis are not clearly understood, but one of the important findings as per previous literature is the recognition of antimicrobial peptides (AMPs). In the response to skin injury keratinocytes secrets AMPs that results in Psoriasis. For the development of this disease autoantigen-specific T cells contribute more and it shows auto-immune type of mechanism. In psoriasis LL37 is one of 2 well-studied T cell autoantigens (6-7). Fig. 1 represents the structure of psoriasis skin.

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**Fig.1: Psoriasis: Skin structure**

**OVERVIEW OF GEL FORMULATIONS**

Gel is a solid or semisolid dosage forms intended for the topical use which can be applied on skin or mucus membrane. It is a two-phase interpenetrating system and elastic colloidal material which consists of dispersed liquid incorporated in the solid phase. The colloidal particles (gelator or gallant) are uniformly distributed in the dispersed liquid or dispersion medium (8-12). Gel formulations have several advantages and dis-advantages over other topical formulations (13-14). Some of the advantages are-

1. Easy to formulate
2. Non-greasy formulations
3. Optimum spreadibility
4. Can be easily washed
5. Achieve optimal cutaneous and percutaneous drug delivery
6. Biodegradable and biocompatible
7. Used as controlled drug delivery formulations
8. Optimum adherence property
9. Avoiding of GIT absorption and enzymatic activity
10. Higher retention time
11. Can form a protective layer over the affected area

Some of the dis-advantages are-

1. May cause allergic reaction or irritability
2. Slower sustained effect
3. May cause the growth of microbial growth
4. Upon long time storage gels may shrink and loose the entire liquid present inside (Syneresis)
5. Ingredients having large particle size, less permeability are the limitation
6. Flocculation can cause unstable gel
7. Degradation of drugs may occur

Gels, as we mentioned, achieve both cutaneous and percutaneous drug delivery. In percutaneous drug delivery, drugs diffuse through vehicle into the skin and choose both trans-follicular route and trans-epidermal route. Via, trans-follicular route the drugs partitions into sebaceous glands whereas, through trans-epidermal route, the drugs partitions into stratum corneum and finally partitions into viable epidermis. Drug diffuses through viable epidermis followed by upper epidermis and is finally uptaken (resorption) into the vascular system.

**TREATMENT OF PSORIASIS AND GEL FORMULATIONS**

There are plenty of topical and systemic therapies that are approached for the treatment of the cutaneous management of psoriasis and gel is one of them as it avoids gastrointestinal drug absorption difficulties caused by gastrointestinal pH and enzymatic activity (15). In the topical therapies, ointments, creams, solutions, gels, or foams are generally used though the patients’ acceptability of these formulations are not uniform due to their altered effectiveness. As per the previous literature (16), patient having skin diseases prefer to use gels and creams, and between them gel is more acceptable because it can be applied to the skin of both the body and the scalp. Some of the drugs used in the treatment of psoriasis and their mechanism are discussed below-

***Corticosteroids***

Corticosteroids are lipophilic in nature and they easily migrate through the cell membrane to bind the glucocorticoid receptors within the cell. As a result, the receptor complex form dimmers that reaches to nucleus to bind with the DNA molecule. This exerts the pharmacological action by inhibiting genes transcription process from the bind location. This results in hastening vascular permeability followed by decrease in dermal edema and leukocyte penetration. This effect is recognized as anti-inflammatory effect (17).

***Vitamin D 3 analog, Calcitriol***

Calcitriol acts on psoriasis (Fig.2) via following ways (18)-

* Increment in cellular specialization/ morphological and biochemical differentiation of cultured keratinocytes
* Decrease in cellular proliferation
* As an immune-modulator

**Fig.2: Mechanism of Calcitriol**

***Dithranol***

Dithranol, also known as, anthralin is an anthracene derivative used in the treatment of psoriasis. It acts by mitochondrial dysfunction to produce its therapeutic effects by causing the following cascades (19).

* proliferation of keratinocytes
* decreases the action of T-cells,
* enhance cell differentiation
* production of free radicals

***Retinoids***

Retinoids exhibits the desired pharmacological activity via binding and activation with nuclear retinoid receptors (having α, β, and γ subtypes) of both the RAR (retinoic acid receptor; Tazarotene binds with RAR) and RXR (retinoid X receptor) receptors. These result in the activation of transcription process, reduction of epidermal hyperproliferation, normalization of keratinocyte differentiation, reducing inflammation and apoptosis (20).

***Keratolytics***

The main advantages of using keratolytic agents in psoriasis are it hydrates, and softens the stratum corneum. It also exfoliates thick plaques hyperkeratotic skin (21, 22). Keratolytic agents such as salicylic acid, glycolic acid, and retinoic acid are used to control psoriasis (23). The exact mechanisms of these agents are still unknown. Salicylic acid is used in the treatment of psoriasis as an adjuvant with urea. Salicylic acid improves the skin penetration while used with other topical corticosteroids (24).

***Methotrexate***

It is a folic acid antagonist which at lower doses exhibits immunosuppressant effects adjuvant with anti-inflammatory activity. Studies reveal that MTX exerts its action on epidermal psoriatic cells by selectively inhibiting DNA synthesis and therefore seizing mitotic activity (25).

**Table No 1: Types of carrier, advantages and limitations of different antipsoriatic gel formulations**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| S.  No | Drug | Type of carrier for gel formulation | Advantage | Limitations |
|  | Dithranol/Anthralin | Liposomal gels | Localised drug delivery and improved availability at the site of action | Dermal irritation and staining |
|  | Betamethasone | Hydrogel-thickened nanoemulsion | Enhancement and sustaining of drug delivery | Poor permeability,  Cutaneous atrophy,  Rebound Psoriasis |
|  | Betamethasone-Calcipotriol | Nano-emulsions  Solid – Lipid Nanoparticles | Protection against chemical/enzymatic degradation of drugs | Dermal irritation |
|  | Mometasone | Aspasomal gel  Solid – Lipid Nanoparticles | Reduced risk of skin pigmentation  Enhanced permeation | Dermal irritation |
|  | Fluocinolone | Nanostructured Lipid Carriers | Minimised dose dependent side effects | Burning sensation  Dermal acne |
|  | Acitretin | Nanostructured Lipid Carriers | Selective drug delivery to dermal layers | Poor Photostability,  Low water solubility |
|  | Tacrolimus | Liposphere gel  Liposomal gel | Reduced systemic toxicity | Low dermal penetration |
|  | Methotrexate | Ethosomes  NLCs  SLNs & NLCs | Increased drug loading | Poor dermal penetration |

**DISCUSSION**

Dithranol, 1,8-dihydroxy-9-anthrone, has been in the elementary topical treatment of psoriasis (26). Over the years it has been used as one of the most rudimentary topical treatments of stable plaque psoriasis yet dermal irritation and staining properties have been its major drawbacks. Dithranol is an unstable molecule and so, its standardization as a topical formulation is difficult. However, in subsequent researches on Dithranol containing novel carriers over the decade has claimed increased skin penetration in treatment of psoriasis. Broadly, the treatment regimen for dithranol is divided into two: a short contact therapy where dithranol in 1% concentration is directly applied to skin lesions for an exposure of 5-10 minutes and then slowly rinsed with luke-warm water. Whereas the classical 24-hour therapy utilizes 0.1% Dithranol applied twice daily without rinsing off. Several literatures support efficacy of gel formulation of the drug in psoriatic skin. In a 2-week study, A. Saraswat et al. showed that 0.5 % liposomal entrapped dithranol in an aqueous gel base demonstrated significant efficacy than 1.15 % dithranol ointment. They also reported that the dithranol lipo-gel resulted in significantly lighter skin staining compared to any conventional dithranol cream or gel pertaining to a greater cosmetic acceptability and patient compliance. Moreover, the lipo-gel type drug delivery was observed with a reduction in prevalent perilesional erythema (27). The efficacy of lipo-gel systems can be attributed to the strategic development of the aforementioned formulation since membrane properties of liposomes restrict dermal irritation and staining.

Corticosteroids with high potency are generally applied for the treatment of persistent psoriatic plaques. Betamethasone (BD), a class III corticosteroid, has been acquainted with methodical topical delivery approach for the treatment of mild to moderate psoriasis (28). Betamethasone dipropionate is a potent glucocorticoid steroidal moiety possessing anti-inflammatory, immunosuppressive and antiproliferative abilities is reported to present significant improvement (40-50%) in an average duration of 4 weeks. In an anti-inflammatory study, the betamethasone dipropionate nano emulsion gel formulation (0.05%) manifested inhibition of edema by 77.83% within 24 hours when compared to marketed preparations which resulted in edema inhibition by only 40.97% (29).Nano-emulsions prove to be one among the most promising techniques for topical drug delivery due to high drug loading capacity, lower risk of skin irritation and significantly augmented permeation power through skin. Nano-gel formulation of BD not only proves to enhanced anti-inflammatory activity but also reduced dosing frequencies and sustained release of drug for desired period of time leading to better anti-psoriatic activity. To commensurate with anti-psoriatic activity of BD, using vehicles with same therapeutic effect such as Babchi oil which contains psoralen, a photoactive furocoumarin anti-psoriatic compound which exerts by subsiding cell proliferation. For nano-gel formulations babchi oil acts as an excellent oil phase for a stable emulsion system (30).Literature (31-32) mentions other potent combinatorial approach via distinct mechanism of actions for anti-psoriatic effect aiming at synergistic responses viz Betamethasone dipropionate (BD), an anti-proliferative agent, combined with Calcipotriol (CT), a synthetic vitamin D derivative. Calcipotriol is seen effective in short as well as long term therapy. The rationale behind this combination is probably suppression of vitamin D induced dermal irritation by corticosteroid and thereby reducing the overall concentration of corticosteroid in the gel formulation. Sonawane R et al. (31) demonstrated the anti-psoriatic activity of the formulation of CT-BD-SLN (0.005% and 0.05% respectively) loaded gel using mouse tail model as a function of thickness of epidermal layer and total melanocyte count. A subsequent decrease in the epidermal thickness and increase in the melanocyte function was clearly observed. They reported that CT-BD SLNs followed the shunt pathway or appendageal pathway encompassing drug permeation through trans-follicular route (via hair follicles) or sweat gland ducts. Some extent of passive permeation through intercellular route is also reported. The major advantage of formulating submicron sized colloidal particles like SLNs as gels is that they accumulate in hair follicles in deeper layers of the skin and therefore act as reservoir for drugs applied topically for the treatment regimen. Furthermore, in an interim analysis of 8 weeks study performed on a large patient population confirmed high patient acceptability for the fixed combination of once daily CT-BD topical gel as compared to their previous monotherapies (32). The emerged combination-therapy paved its way due to strong discouragement of monotherapy of BD gels which often resulted into risks of cutaneous atrophy and rebound psoriasis (33). The CT-BD gel formulation being cosmetically acceptable may be used for long term therapy.

Corticosteroids prove to be highly potent substrates for local allergic reactions to severe chronic inflammation. Topical corticosteroids are augmented with reducing the thickness of the dermal layer which is favorable in psoriasis. Penetration of drug is correlated inversely with the thickness of the Stratum corneum. In accordance to this several vesicular systems have been designed to not only contain the pharmacological effect of the drug within the skin but also to reduce the associated systemic toxicities. Due to hyper-proliferation of keratinocytes, a topical treatment ensuring higher deposition of drug in the epidermal layer and minimal penetration is desirable to which mometasone, a medium potent topical glucocorticoid, containing SLN gel were reported to lay greater skin deposition than marketed cream formulation, releasing the drug for a longer period of time post application (34).

A hydrocortisone derivative, Fluocinolone acetonide portrays its anti-psoriatic activity through anti-inflammatory, anti-proliferative and immune-suppressive activity. However, in a conventional topical drug delivery system it shows dose dependent side effects such as skin irritation, skin burning sensation and steroid associated acne (35). In the literature (36), in-vivo efficacy of Fluocinolone acetonide-salicylic acid integrated NLC gel was evaluated and compared with a conventional gel formulation in imiquimod induced psoriasis model presented significantly higher efficacy of the former.While screening the choice of corticosteroids and its vehicle for delivery, parameters like site of action, severity of the disease, age group of the patient as well as patient preference must be taken under consideration. For instance, infants and children at young age are exposed to higher chances of risk of adverse effect and/or side effect due to higher skin surface to body ratio.

Topical retinoid, tazarotene is a derivative of vitamin A. It is the first synthetic compound indicated to be used in the topical treatment regimen of psoriasis. The anti-psoriatic activity of tazarotene pertains to its anti-inflammatory action, reduction in epidermal hyper-proliferation and normalized keratinocyte differentiation. In a study it was revealed that 0.1% and 0.05% tazarotene gel was as effective as 0.05% fluocinonide cream with reduced incidence of dermal irritation (37). The most common side effect associated with tazarotene gel is dermal irritation, erythema and burning sensation, pruritus and desquamation (38). However, it has been studied that use of topical corticosteroids in conjunction with tazarotene results in suppression of skin irritation significantly. Also, the FDA has issued a cautionary warning regarding use of tazarotene gel while exposure to sunlight and therefore psoriasis patients undergoing tazarotene therapy are advised to use sunscreens. Being a category X drug, it is contraindicated in pregnancy. In another clinical study, a new retinoid, bexarotene in 1% gel formulation is also find effective in treatment of mild to moderate psoriasis (39).

Calcineurin inhibitors are commonly prescribed in the treatment of atopic dermatitis. Nevertheless, their role in treatment of psoriasis can be significantly addressed. Tacrolimus, a II generation macrolide immunosuppressant obtained from *Streptomyces tsukubaensis* is mostly useful in treatment of facial psoriasis. When applied in its conventional cream formulation, it does not show significant efficacy in treating plaque type psoriasis. The first reason being high molecular weight of drug and secondly, dermal plaques in psoriatic skin are thick. Notable penetration can however be achieved by occlusion (40) and tacrolimus gel formulation in combination with keratolytic agents such as salicylic acid (41).

Methotrexate (MTX), a folic acid analogue and antagonist, is indicated in the treatment moderate to severe psoriasis (42) which works by blocking epidermal mitosis (43). Nevertheless, its use had been limited due to incidences of dose related side effects such as decrease in RBC, WBC and platelet count, hepatotoxicity and stomach damage (44-46). Topical MTX formulations are therefore aimed to diminish such side effects. The major challenge in aforesaid was the high molecular weight and hydrophilic nature of MTX which limited its permeation through stratum corneum (47). Over years of exhaustive researches, several permeation enhancers and novel carrier were introduced assuming particulate carrier systems may mean a better option to enhance drug penetration. In a 2 weeks clinical study, it was reported that 1% MTX topical gel illustrated improvement in erythema, psoriatic scales with significant infiltration in dermal layers (48). Avasatthi et al. reported MTX loaded nano structured lipid carriers in gel formulation displayed mild keratosis and enhanced penetration of drug through dermal layers compared to conventional formulations (49). In the literature (50), it has been reported that along with phospholipid vesicular systems(liposomes), solid lipid nano carriers and nano-structured lipid carriers loaded with MTX as gel formulation are efficient techniques for sustained effect in psoriasis. However, the concept of MTX loaded carrier systems are reported to suffer low drug entrapment (51). Chandra et al. reported remarkably high entrapment efficiency in ethosomal gel containing methotrexate in combination with salicylic acid (52).

**FUTURE ASPECTS**

Topical treatments prove to be useful in psoriasis in varying degrees viz, mild to moderate and severe; either as monotherapy (for mild psoriasis) or combined with systemic therapy (for moderate to severe psoriasis). Majorly, the occurrence of mild psoriasis is common wherein topical agents play standard first line treatment regimen. Among topical treatments, gels unlike lotions, creams and ointments, have rendered better impact in enhancing drug penetration in dermal layers and drug retention in the skin. Gel formulations not only help in maintaining optimum skin hydration but also may be optimized to minimize the use of penetration enhancers or promoters which ultimately decreases the risk of skin burning and irritation. Furthermore, gels occupy more advantage of being easily applicable to both skin and scalp rather than sticky ointments or lotions. The recent advances show development of various nano carriers as gels towards treatment of psoriasis with cosmetic elegance and ease of application to ensure better patient acceptability which in turn ameliorate the life quality of the patient. The possibility of obtaining a fair standard of gel formulation to gear unwanted effects and promoting higher patient satisfaction is the need of the hour to achieve even better outcomes. With findings of newer compounds, a wide repository of innovative topical gel formulations is under investigation.

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