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Molecular Analysis, Pathophysiology, and Drug Delivery Mechanism with Reference to Psoriasis: (A Mini Review)

JYOTI SHARMA[1] and RIPU DAMAN[2]

[1,2]Chandigarh University, UIPS, NH-95 Gharuan Chandigarh-Ludhiana Highway, Mohali, Punjab 140413, India.
*Corresponding author E-mail: Info@bionome.in

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ABSTRACT

Psoriasis is a dermal condition caused by an immunological response. Interrelations among the innate and adaptive immunological responses are the fundamental cause to trigger the pathogenesis of the psoriatic plague. The study of psoriasis pathophysiology has greatly advanced our understanding of epidermal physiology. Advancements in psoriasis etiology have paved the way for effective tailored and specialized drugs, revealing invaluable discernment into the pathophysiology of the chronic inflammatory dermal condition. In this review, we discuss the clinical classification, identification, and management of psoriasis. Further, we will briefly discuss the hurdles in the conventional treatment and how various nano-based carriers used in the drug delivery are able to overcome them. The clinical categorization, detection, and management of psoriasis are discussed in this review. Further, we'll discuss the limitations of conventional treatment and the advantages of nan-drugs over them.

Keywords: Psoriasis, Nanocarriers, Drug delivery, Topical treatment, Pustular psoriasis.

INTRODUCTION

Psoriasis is a common dermal condition defined as a persistent autoimmune dermal inflammation that exacerbates symptoms like skin itchiness, and sore regions of coarse, red skin surrounded by white markings[1]. Though the pathophysiology is highly attributed to the active members of the immunological system the underlying mechanism that dictates the disease progression is the highly intricate involving proliferation of epidermal cells and differentiation of the keratinocytes. The psoriasis disease will strike people of all ages, it is more prevalent among people aged 15-25 years[2]. The disease further progresses to a condition termed psoriatic arthritis which is frequent among middle-aged people (30-50 years). When differentiating the disease based on ethnic diversity, it is more ubiquitous among Caucasians and high latitude dwellers[3].

While the actual cause of the condition has been elusive, it has been associated with a number of hereditary and environmental variables, including climatic excruciates, plagues, intense emotional distress, certain drugs, and pathogenic infections. The

disease occurs in 1-2 percent of the global population and is characterized by quick recurrence, unusual appearance, appalling presentation, and recurrence, which will altogether affect the social life of the individuals resulting in considerable comorbidities[4,5].

The major insights about the clinical manifestation of the disease and the disease progression are majorly acquired by the clinical trials as these psoriasis research lack animal model experimentation and validation and hence common drugs like methotrexate and arsenic were utilized to address the hyperproliferation of the epidermal layers[6,7]. Though psoriasis is an auto-immune disease, the specific autoantigens that trigger the pathogenesis are not identified, therefore, the common hypothesis that is predominantly accepted is the active mobilization of autoreactive T-cells in the skin[8-10].

The patient-reported outcome for the prescribed topical applicators formulated as gels or cream has been unfavorable. do not like the currently available local and systemic therapy, which includes drugs like salicylic acid, retinoic acid, and vitamin D analogs[11,12]. Salicylates, Vitamin A& D-based therapies fall in first-line management and their prolonged application can trigger burning, itching, scaling, and advance towards skin peeling and erythema. Oral and parenteral drugs could be used as an adjunct to the topical applicators, but the major constraint will be the drug exposure to non-targeted organs. As a result, developing a solution that might circumvent the limitations of oral and parenteral approaches has been a priority in treating psoriasis[13,14,15,16].

The nanosized particles in nano-delivery system displays advantageous properties from the larger sized particles and hence presents better opportunities in drug delivery. The enhanced delivery can be accredited to their unique physicochemical properties, permeation amplifying roles of the surfactants employed which allows the translocation of the drug through transdermal layers, etc[17].

Standard formulations accumulate on the epidermis owing to their bigger particle size, conversely, nanostructures can infiltrate into the skin layers and pass the natural dermal barriers. The precedence of nanodrugs over conventional therapies is its propensity to modify the solubility of hydrophobic drugs. Thus, these properties ensure controlled release of the drugs to the targets, improved efficacy, low toxicity and side effects[18,19].

This review briefly circumscribes various aspects of psoriasis pathogenesis, its types, approved clinical interventions, ongoing clinical trials, herbal based treatment approaches, limitations of the conventional drugs and various drug delivery routes and carriers[20-23].

Types of psoriasis

Psoriasis can be triggered by a multitude of variables such as climate shifts, stress, skin breakdown, or the intake of Lithium, Quinidine, Inderal, or antimalarial medication, or it might be induced by allergies or an inappropriate diet. Although the majority of patients will have one form prevalent at a time, the activity of one of these variables can encourage the appearance of another of psoriasis. Depending on the location of incidence and clinical manifestations, psoriasis is divided into the following subtypes[24].

Plague psoriasis

The most prevalent form of psoriasis is plague psoriasis also called as psoriasis vulgaris, which is marked by rash, skin rash, erythema, inflammation covered with silver scale around the elbows, knee, skin, and lower back. Steroids to alleviate inflammation or phototherapy are frequently used to address the illness. For patients who are unresponsive to first line treatment are administered with oral medications or IV treatments[25-27]. The common medications administered for the management of plague psoriasis is enlisted in Table 1.

Table 1: Commonly employed drugs in the management of Plague Psoriasis

Drug name	Type	Application
Shyrizi	Subcutaneous injection	Antagonist for IL-23
Otezla	Oral pills	PDE4 inhibitor
Humira	Subcutaneous inject	Blocks TNF
Enbrel	Subcutaneous inject	Blocks TNF
Deucravacitinib	Oral	Inhibits TYK2

Guttate psoriasis

Children and teenagers are more likely to get the second most common form of psoriasis. It is characterised by the presence of small round scaly spots designated as papules which are the resultant of streptococcal infection, perspirations or friction.

The papules usually react to topical applicators and phototherapy, while combined therapy will be implemented based on the progression. Tonsillitis, bronchial inflammations, sinusitis, skin damage, and stress are the variables that trigger the pathogenesis of guttate psoriasis. Guttate psoriasis is localized in trunk, thighs, scalp and upper arm regions[28-32]. The common medications administered for the management of Guttate psoriasis is document in Table 2.

Table 2: Commonly employed drugs in the management of Guttate Psoriasis

Drug name	Type	Application
Corticosteroids	Topical application (creams/ointment)	Anti-inflammatory
Salicylic acid	Topical application	Reduces itching
Coal tar	Topical application	Reduces itching
Antibiotics	Pills	Antimicrobial
Occlusive moisturisers	Creams or lotion	Reduces dermal dehydration and dryness
Humectants (Glycerine)	Topical application	Increases water holding capacity

Inverse psoriasis

Skins folds like arm pits, groins, genitals, buttocks and breast are the targeted region for inverse psoriasis. It is also termed as intertriginous psoriasis and is implicated by the presence of red shiny lesions. Overweight, obesity, sweat is friction greatly favors the occurrence of inverse psoriasis and their diagnosis is often challenging due to their undeniable similarity with other skin conditions. In the infant it can lead to a condition termed as napkin psoriasis. The unique whitish scales of psoriasis are generally absent in inverse psoriasis and the lesion appears smooth and often leads to the misdiagnosis of the condition. Inverse psoriasis is greatly triggered by Candida spp, fungal infection, inflammatory diseases or by other bacterial infections. Dermoscopy, reflectance confocal microscopy and histopathological examinations are employed to diagnose the condition. topical corticosteroids and vitamin D analogues are administered as first line treatment while emollients and topical tar-based products are employed as second line of medications[33-37]. The common medications administered for the management of Inverse psoriasis is listed in Table 3.

Table 2: Commonly employed drugs in the management of Inverse Psoriasis

Drug name	Type	Application
Corticosteroids	Topical applicators	Reduces inflammation
Pimercrolimus	Cream or gel	Targets eczema
Castederm	Topical (act like skin paint)	Reduces moisture and controls fungal or bacterial infections
Humira	IV (biologics)	Relieves pain
Dovonex	Cream	Vitamin D based. It impedes the cell growth
Soriatane	Oral pill	Second generation retinoid to address severe psoriasis
Taltz	Auto-injector	Binds to interleukin 17a and reduces inflammation

Pustular psoriasis

The hyperactivity of the immune of the immune system results in the formation of sore and painful pus-filled sterile pustules which aggregate over time and causes redness and scaling. Pustular psoriasis is rare among other forms and is frequent among middle aged Asian population. Based on the affected area Pustular psoriasis is further divided into 3 subtypes[38].

Generalized Pustular Psoriasis (GPP)

Affecting the larger areas of the body is the Generalized Pustular Psoriasis (GPP) that spreads rapidly and inflicts chills, pyrexia, fatigue, itching etc. Von Zumbusch psoriasis is a subtype of GPP which can be fatal. It develops extensive lesions throughout the body. Nausea, uneasiness, tiredness, pyrexia and joint discomfort are all significant manifestations of the condition[39]. Diffused blisters and sores are also a characteristic of Exanthematic psoriasis. This subtype, on the other hand, is not accompanied by systemic symptoms. Sores usually fade away after a few days. Impetigo herpetiformis, often known as Pregnancy Pustular Psoriasis (PPP), is a type of GPP that develops during pregnancy[40]. It commonly begins during the 3rd trimester of pregnancy and can lead to systemic clinical complications. Ulcerating red patches distinguish Annular psoriasis from other subtypes of GPP.

Localized Pustular Psoriasis (LPP)

Palmoplantar Pustular Psoriasis (PPPP) is a subtype of LPP affecting palms and soles while Acrodermatitis Continua of Hallopeau (ACH) affects finger and toe tips particularly nails[41,42]. The

common medications employed in the treatment and management of all types and subtypes of Pustular Psoriasis is listed in Table 4 and specific drugs are documented in Table 5.

Table 4: Medications used for the treatment of Pustular Psoriasis

Psoriasis Type	Drug Class
GPP	Oral Retinoids, Biologics, Phototherapy
PPP	Corticosteroids, Phototherapy, Vitamin D analogues, Cyclosporine, Biologics
PPPP	Corticosteroids, Phototherapy, Vitamin D analogues, Cyclosporine, Biologics, Salicylic acid, Oral Retinoids
ACH	Vitamin D analogues, corticosteroids, phototherapy

Erythrodermic Psoriasis (EP)

This is an uncommon kind of psoriasis that is particularly harmful. The illness is attributed by severe reddish skin, painful itchy scaly skin, and pustules. EP was shown to be more common in Asian population particularly among Chinese and Taiwanese. Episodes of elevated body temperature, oedema in ankles and feet, exfoliation and increased heart rate are the characteristics of the condition. Allergens, steroid medication, alcohol use, infections, and severe sunburns often exaggerates the condition. Oral medications, topical treatments and biologics are generally employed in the management of the condition[43,44].

Table 5: General Treatment for Pustular Psoriasis

Drug Type	Applications	Examples
Topicals	Slows cell reproduction	Corticosteroids, Non steroids like Vitamin D3 and A, moisturizers, Jojoba oil
Phototherapy	Slows the growth of affected cells	Ultraviolet B Therapy Excimer laser Psoralen with Ultraviolet A (PUVA) Sunlight
Oral Drugs	Reduces inflammation Relieves pain Act as antibiotics	Cyclosporine Methotrexate Soriatane

Drug delivery system in psoriasis treatment

Nanotechnology functions by altering the physicochemical and biological characteristics to generate applications that yields enhanced results due to nano-sized particle size. These strategies render a numerous of advantages over conventional therapies, including higher potency, and capacity to deliver drug in dose dependent manner to the target region[45]. Nanodrugs are gaining significance importance owing to their applications in diagnosis and diseases management[46]. The reduced toxicity and adverse effects of nanodrugs makes them better than the conventional carriers. The drugs addressing the dermatological conditions must penetrate through the transdermal layer and should cross the natural barriers of the skin including stratum corneum, which is successfully achieved by the nanosized particles[47].

In case of psoriasis dermal drug delivery, the major hurdle will be the keratinized epidermal barrier which is highly dense due the hyperproliferation events and therefore impede the infiltration of the drugs. The nanodrugs potentially establishes a contact to improve the physicochemical properties of the therapeutic agents and to improve their skin retention time. Nanocomposites have the ability to infiltrate the skin via intercellular spaces, and hair follicles[48,49]. Treatment compounds are incorporated within the nanocarriers either by encapsulation or by carrier conjugation. Nanocarriers are advantageous as they help to overcome the limitations of the conventional drugs. For example, nanocarriers prevents drug aggregation as a thin film, enhances the skin retention time of the drug, prolongs drug half-life and facilitates diffusion. This section entails a brief account on various nanocarriers (Fig. 1) employed in psoriasis treatment[50].

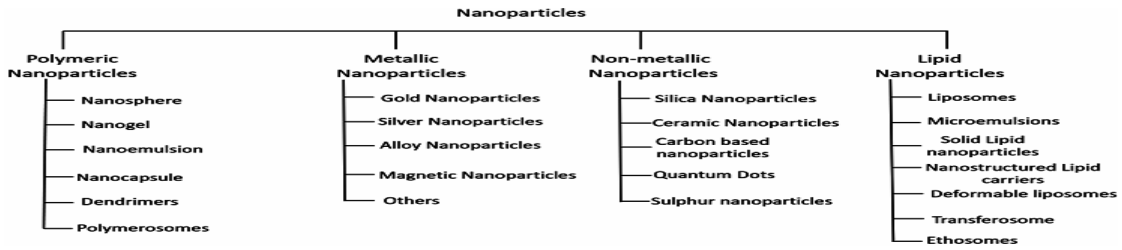

Fig. 1. Classifiaction of various nanaparticles employed as drug carriers in treating psoriasis

Polymeric nanoparticles (PNPS)

The colloidal structures of PNPs are of 10-1000nm in size and highly preferred for drug delivery. Their greater advantage is their flexibility which allows various modifications and formulations[51,52]. The matrix based nanospheres, shell based nano capsules highly branched dendrimers, and the gel emulsifiers are different form PNPs. Enhanced circulation in the body, longer adherence, reduced side effects, non-allergic formulations, biocompatibility, bioavailabilty and biodegradability properties makes them suitable for topical application[53-55].

The PNPs are efficient in carrying both hydrophobic and hydrophilic medicaments. Some of the common PNPs used in drug delivery are polylactic glycolic acid, polyethylene-glycol, chitosan, gelatin dextran, polyplexes, poloxamer, albumin, polyethyleneimine, silk fibrins, polyalkylcyanoacrylates, polyamidoamine, polyhydroxylpropylmethacrylamide, etc. Among the PNPs nanocapsules and nanospheres have better drug accumulation in the dermal layer and they sediment on the dermis, indicating that they are the most suitable candidates to be implemented as topical applicators. PNPs can be modified chemically to develop charged PNPs which are suitable to address skin inflammation[56-58].

As discussed earlier the natural barriers of the skin is the greater obstacle for PNPs, therefore the PNPs undergoes chemical modification to enhance their penetration across the natural skin barriers. The skin penetration properties can be achieved either by active or passive methods[59]. Wherein, the former method implements the usage of electrical, mechanical and other methods. Iontophoresis and electrophoresis are majorly employed in the electrical method while microarray needle technique, abrasion method, suction, stretching and needleless injection methods are used to increase skin permeation in machinal methods. Other miscellaneous methods are the utilisation of ultrasound, magnetophoresis, radio frequency temperature, laser, photomechanical waves, etc. to improve skin permeation. Similarly in the passive methods either the stratum corneum is manipulated or the drug delivery methodology is optimised to achieve improved skin permeation[60]. Chemical enhancers and hydration techniques are best suited to manipulate stratum corneum whereas, ion pairs, supersaturation methods, eutectic systems, nanocarriers, etc optimize the drug delivery system. Increasing the drug diffusion and solubility also aids in better distribution and permeation across the skin. Managing psoriasis with topical applicators has resulted in better patient outcome as these topicals directly addresses the epidermal basal layer it gives better results[61,62].

Mettalic nanoparticles (MNPS)

There are numerous scientific evidence citing the advantage of gold and silver nanoparticles as antimicrobial agents, in the treatment of tumours, renal disorders, hepatic disorders, etc. In recent years MNPs are exploited to be used as dermatological applicators owing to their anti-inflammatory properties[63]. They are practically advantageous in addressing various skin conditions and are therefore used as antibacterial, antifungal, anti-cancerous, skin protectors, radiation filters, anti-inflammatory products, moisturizers etc[64]. The MNPs can be formulated using various metals like Au, Ag, Fe, Cu, Se, PT, Ti,, Se, etc. to develop carriers like nanopores, nanosphere, nanotubes, nanorods, etc.. MNPs are affordable as they can be synthesized from chemical o organic materials[65].

Among the MNPs gold and silver MNPs are the most common as they can be easily synthesized natural materials with the utilization of gold cations, reducing agents and an equilibrator in the reduction medium[66]. The favourable properties of gold nanoparticles like cost effectiveness, alteration in size, anti-inflammatory properties, larger surface area, variable shapes, makes them preferred among other MNPs. On the other hand silver MNPs offers better drug targeting, bioavailability and solubility[67]. MNPs can be toxic to the keratinocytes and follicular stem cells of the epidermis due to the production of free radicals but gold MNPs are not cytotoxic[68].

Lipid nanoparticles (LNPs)

LNPs are best suited to manage psoriatic plagues as they are natural, affordable, diffusible, and nontoxic. The LNPs used to deliver hydrophobic drugs are either solid LNPs or nanostructured LNPs which are comprised of a lipid core and a dispersed particulate lipid system[69-72]. Solid LNPs have a better crystal structure, on the contrary the nanostructures LNPs lack these structures or these structures are rather imperfect in them. This imperfection makes them the best candidate in drug delivery as the imperfection ensure reduced drug leakage and better confinement of the drug.

Hot homogenization, cold homogenization, micro emulsification techniques are mainly deployed in the synthesis of solid and nanostructured LNPs[73-76]. Among the LNPs the liquid crystal system offers double melting points and increases the dispersion of the nanoparticles. The vesicular LNPs are efficient in locating the drug in the lipid core, improves the loading and stability of drugs. Liposomes enclose a aqueous core surrounded by a phospholipid bilayer and are effective as anti-inflammatory drug carriers. The efficacy of the LNPs is greatly dictated by the type of bilayer formulated to surround the core[77-79]. This can be constructed according to the target and delivery requirements. Some of the widely used LNPs are the fluidity modifying liposomes, niosomes, flexible transferosomes, aquasomes with a solid core, spherical colloidosomes, cubical cubosomes, sphingosomes constituting the sphingolipids, ufasomes with unsaturated fatty acid structures, vesicular cryptosomes, disc shaped discomes, photolyase enzyme containing photosome, virosomes with virus extracted proteins, protease enzyme containing proteasmes, genetic material containing genosome, etc.[80-82]

CONCLUSION

Psoriasis is a multifaceted, challenging illness for which several innovative therapeutics have emerged in recent years. Despite advancements in targeted medicines, psoriasis represents a manageable but not preventable condition. The management of psoriasis has altered substantially owing to the new biologics. The eradication of risk factors like life style, obesity, allergies, etc. is critical for preventive measures. Though conventional drug represents the first line of treatment they have poor patient outcome, whereas, nanodrugs are more acceptable due to their anti-inflammatory properties, increased solubility and bioavailability and provide new perspective in the management and treatment of psoriasis.

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Conflict of interest

The authors declare no conflict of interest

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