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Formulation Strategies in Psoriasis: Journey from Traditional Preparations to Advanced Drug Delivery Systems

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ABSTRACT

Psoriasis (PSO) is an immune-mediated dermatological disorder marked by thick, erythematous, scaly plaques resulting from rapid, excessive cellular growth. Anti-inflammatory agents, immunosuppressants, and additional pharmaceuticals serve as the principal therapeutic strategy for psoriasis to alleviate symptoms, diminish inflammation, and inhibit the proliferation and division of epidermal cells. Nevertheless, these drugs generally include disadvantages that impose significant physiological and pathological burdens on patients, including inadequate targeting, brief half-lives, limited absorption rates, and severe toxic side effects. Researchers have recently concentrated significant effort on employing delivery systems for the topical administration of drugs to affected psoriatic skin regions. These systems increase pharmacological efficacy, stability, and penetration. More therapeutic concepts for the treatment of PSO are made possible by the ongoing development of numerous multifunctional topical delivery technologies. This publication reviews various delivery strategies, including hydrogels, nanoparticles, microneedles, micelles, dendrimers, liposomes, nanoemulsions, and vesicles, for topical therapy of PSO and delineates their current developmental status in clinical treatment. It is expected to facilitate the progression of PSO treatment methodologies and provide a benchmark for the development of novel topical delivery systems.

Keywords: Psoriasis, pathophysiology, nanomedicine, topical delivery, novel drug delivery system

INTRODUCTION

Psoriasis (PSO) is a chronic, inflammatory, immune-mediated systemic disorder that impacts 2% to 5% of the population. The features that are considered definitive consist of plaques or erythema that are covered with scales, which may be localized or widespread in nature. There are numerous varieties of psoriasis, such as erythrodermic PSO, drip PSO, pustular PSO, and plaque PSO (vulgaris). Patients frequently suffer a number of complications, including depression, diabetes, angiocardiopathy, hypertension, and arthritis. PSO has a complicated etiology that may include T cell differentiation, inflammatory cell infiltration, and keratinocyte growth [1]. Genetics, infections, metabolic illnesses, endocrine abnormalities, and other related variables such as drinking, smoking, stress, tiredness, and mental health difficulties may also cause or make PSO worse.

As a result, PSO treatment is challenging and prone to recurrence, which negatively impacts patients' quality of life. Reducing inflammation, reducing the frequency of flare-ups, and effectively controlling symptoms are the ultimate goals of various treatments [2]. The kind of PSO, the course of the disease, and other personal variables

are the primary determinants of treatment decisions. Topical medicine is the most common treatment for PSO that is mild for age and general health. By lowering inflammatory cytokines or immunological activation, medications such as glucocorticosteroids, vitamin D, and keratolytics can decrease the proliferation of skin cells and lessen symptoms. Long-term use, however, may have adverse consequences like skin thinning and hyperpigmentation, among other things [3]. Moderate to severe PSO may be treated with systemic treatments. Methotrexate and cyclosporine are examples of immunosuppressants that can successfully stop cell proliferation and quickly treat the condition, but their usage is restricted due to their severe nephrotoxicity. Moreover, a number of biological agents, such as TNF-α inhibitors (etanercept, infliximab, and adalimumab), IL-17A inhibitors (secukinumab and ixekizumab), IL-23 inhibitors (guselchizumab), IL-12/23 inhibitors (ustekinumab), and IL-36R inhibitors (pesolizumab), have been approved for use in the treatment of psoriasis on a national and international level. They are able to specifically target and eliminate inflammatory mediators linked to psoriasis, and the majority of rashes usually go away quickly, usually within a month. Their limited clinical use necessitates, however, further evaluation of their long-term safety and effectiveness. Because it is not intrusive and has a high percentage of patient compliance, topical treatment is the best delivery technique. Increased keratinocyte proliferation and differentiation, inflammation-induced vasodilation, and increased vascular permeability all contribute to a compromised epidermal barrier function in PSO patients. These features greatly improve drug permeability and provide an ideal "use environment" for the localized application of topical medications [4] . Nonetheless, numerous topical drugs sometimes possess limitations that hinder the achievement of the desired therapeutic effect, including brief half-lives, inadequate targeting, low absorption, and significant toxic side effects. The development of pharmaceutical delivery systems has become a feasible resolution to this problem. They can be engineered to minimize side effects, attain regulated or extended release, and deliver drugs specifically to PSO lesions. They can enhance bioavailability, prolong drug circulation length, and alter pharmacokinetics [5]. Researchers have leveraged the distinctive attributes of PSO treatment to develop novel formulations. Therefore, the most recent developments in delivery systems, including nanoparticles (NPs), hydrogels, microneedles (MNs), micelles, dendrimers, liposomes, nanoemulsions, and vesicles for the treatment of PSO, have been reviewed based on the advantages and disadvantages of various medications for PSO therapy as shown in Figure 1.

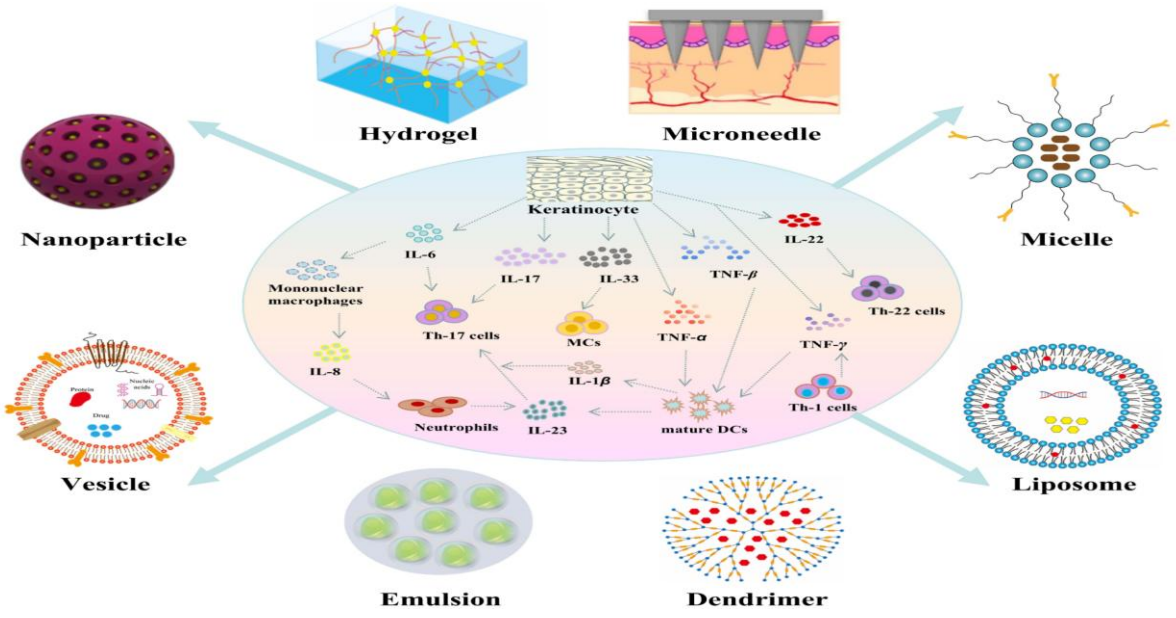

Figure 1. An overview of the several psoriasis topical therapy drug delivery techniques [6]

1. Pathogenesis of Psoriasis

In many of the early phases of the disease, dendritic cells (DCs) play a crucial role as proficient antigen-presenting cells. But DCs aren't always right when it comes to psoriasis [7]. One such method is the detection of antimicrobial peptides (AMPs) produced by keratinocytes in reaction to injury; these AMPs are often

overexpressed in psoriatic skin. Important AMPs associated with psoriasis include LL37, S100 proteins, and β-defensins, which are secreted by injured keratinocytes. There are two types of complexes that LL-37 may form: LL-37-DNA and LL-37-RNA [8]. The LL-37-DNA complex stimulates plasmacytoid dendritic cell through toll-like receptor-9, leading to the release of interferon-α and interferon-β. As a consequence, the myeloid dendritic cells phenotype develops, which in turn triggers the differentiation of Th1 and Th17 and the subsequent function. In order to promote keratinocyte growth in the epidermis, Th17 cells release interleukins (IL)-17, IL-21, and IL-22. The aforementioned nodes are intermediate stops on the path to plasmacytoid dendritic cells, which complex LL-37-RNA initiates via the TLR-7 route. The TLR-8 pathway activates myeloid dendritic cells, which secrete tumour necrosis factor (TNF)-α, IL-23, and IL-12. These cytokines initiate the differentiation and functions of Th1 and Th17. In order to stimulate the proliferation of keratinocytes in the epidermis, Th17 cells secrete IL-17, IL-21, and IL-22 [9]. The pathomechanism of the disease is presented in figure 2.

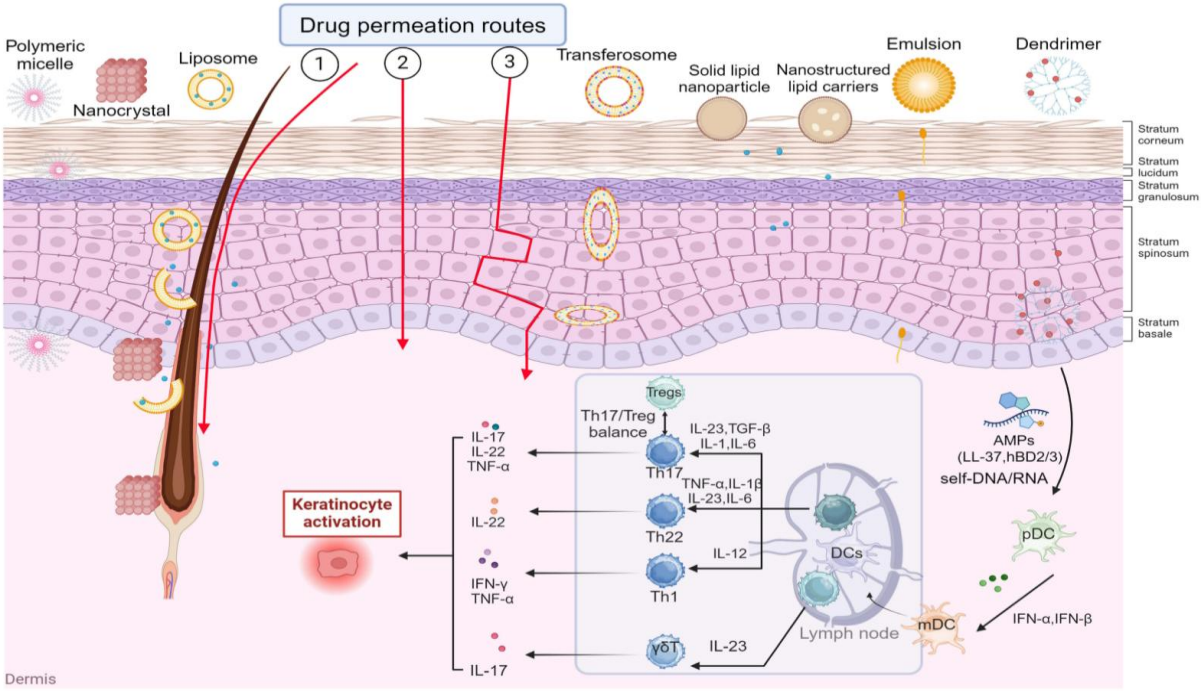

Figure 2. Shows the pathophysiology of psoriasis and three skin penetration paths of new medication delivery technologies [10]

Additionally, genetic variables have a primitive function in the pathophysiology of psoriasis. Genetic epidemiology's main components are pedigree analysis, susceptibility analysis, heritability, twin studies, and familial aggregation [11].The extremely distinctive psoriasis pattern known as "family aggregation" varies each population. A family history of psoriasis affects about 31.26% of Chinese people; among them, 47% have secondary relatives and 67% have direct forebears with the disorder. The pathophysiology of psoriasis has been linked to more than 80 susceptible loci as a result of research into genetic predisposition [12]. In order to give more accurate and sensitive genetic markers that biologics can target for better disease treatment, several next-generation sequencing techniques are being used. Additionally, the associated study of gene activity is well underway. The genetic findings have led to suggestions on the disease's aetiology. The creation of advanced, effective biologic therapies has been focused on managing and preventing disease as a result. Psoriasis can be caused by the LCE cluster, AIM2, LRRC7, MTHFR, MGAT5, PSORS6, and other susceptible genes [13].

2. Etiology and classifications of Psoriasis

Stress and psoriasis are intrinsically connected. Acute stress reduces cortisol levels, which regulate skin inflammation, resulting in the exacerbation of psoriasis. Psoriasis may be generated by trauma-related skin damage and ultraviolet exposure [14]. Various causes, including irritants, burns, skin testing, abrasions, and electrodesiccation, may exacerbate skin injuries. This disease is defined as a squamous cell condition marked by plaques that are red, inflammatory, and silvery-white elevated lesions measuring one centimeter in diameter. The lesions in psoriasis patients located on the scalp are symmetrically distributed. Psoriasis typically manifests on the skin, scalp, elbows, sacral area, knees, tongue, or oral mucosa (figure 3) [15]. Yellow-white patches are observed on the tongue, proliferating more rapidly than typical lesions and undergoing daily alterations. A geographic tongue describes this phenomenon. Scalp seborrheic dermatitis, caused by an invasion of bacteria such as Malassezia furfur, often appears after puberty. Every area of the psoriatic patient's skin is vulnerable to more lesions because of the psoriatic lesions. Cellular enlargement and mononuclear cell infiltration are idiopathic traits seen in the unaffected skin [14]. Table 1 presents the distinctive characteristics of many psoriasis varieties, including plaque, guttate, pustular, erythrodermic, nail, and scalp psoriasis.

Table 1. Classification of different types of psoriasis [16]

Psoriasis Classification (Involved Region)	**Distinctive Attributes**
Guttate psoriasis(affecting the head and extremities)	The lesions are characterized by their homogeneity and mostly affect young people; often, a streptococcal infection follows an illness of the upper respiratory tract.
Psoriasis vulgaris (plaques affecting the entire body, commonly located on the elbows, knees, and scalp)	These unusual lesions resemble erythematous macules that develop into plaques; they are oval in shape, dry, and pointed.
Pustular psoriasis (palmar and plantar)	Blepharitis of the palms and soles with chronic acrodermatitis of the Hallopeau are two distinct forms of psoriasis characterized by localized pustulosis, wherein pustules proliferate and spread across the feet. Pustular lesions in generalized psoriasis may occur during pregnancy or as a consequence of specific treatments.
Erythrodermic psoriasis (affecting the entire body)	This is unstable psoriasis, which can be brought on by a number of conditions, such as heart failure, excessive heat, or vitamin deficiencies.
Nail psoriasis (fingernails, toenails)	Oil spots are small depressions located in the proximal area of the nail, characterized by an orange-yellow zone beneath the nail plate.
Psoriasis of the scalp (hairline)	Selecting the appropriate therapy for the scalp might be difficult.

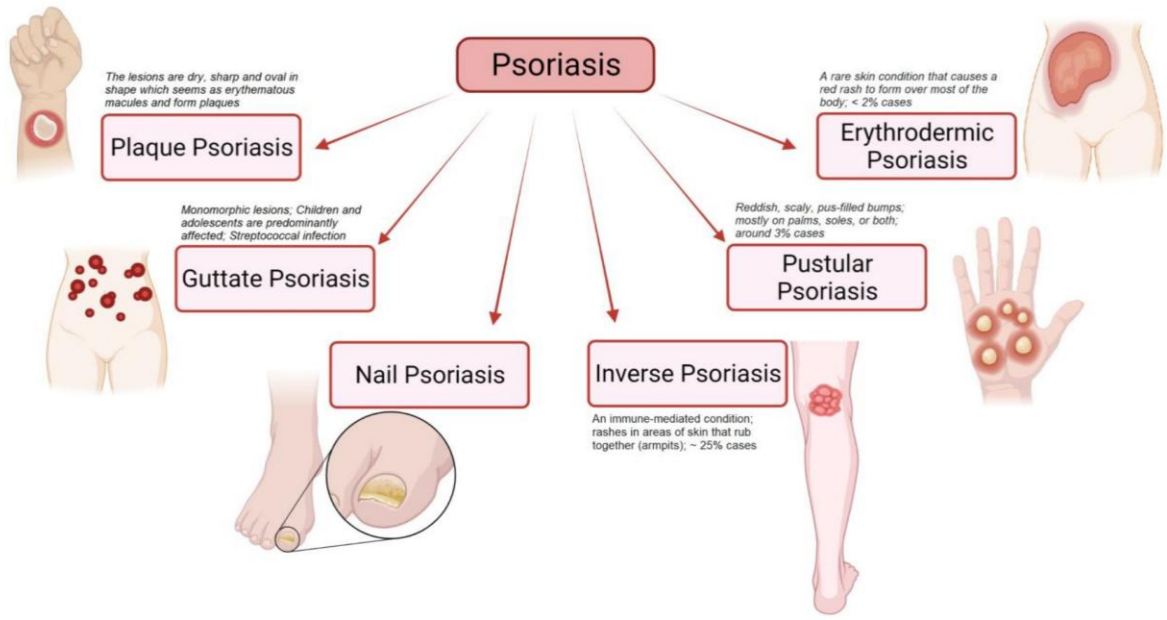

Figure 3. Types of psoriasis [15]

3.Current approaches to psoriasis treatment

Anti-psoriatic therapy has been categorized into two groups based on the severity of the illness: first-line therapy and second-line therapy. Topical therapies, such corticosteroids, coal tar, or calcipotriene, constitute the primary approach for managing psoriasis. These medicines typically shown efficacy in managing mild to moderate psoriasis patients [17]. Topical medications are generally administered to no more than 10% of the body's surface area when addressing localized psoriasis. These therapies are intended to impact the skin externally. Popular examples of traditional formulations for topical application include ointments, creams, and lotions. Second-line therapy may be required in instances with heightened severity. Methotrexate (MTX), cyclosporine, and biologics are instances of systemic medications that may be incorporated. The selection of treatment is contingent upon the specific circumstances and the severity of the condition [18]. A schematic representation of a typical psoriasis therapy is shown in Figure 4.

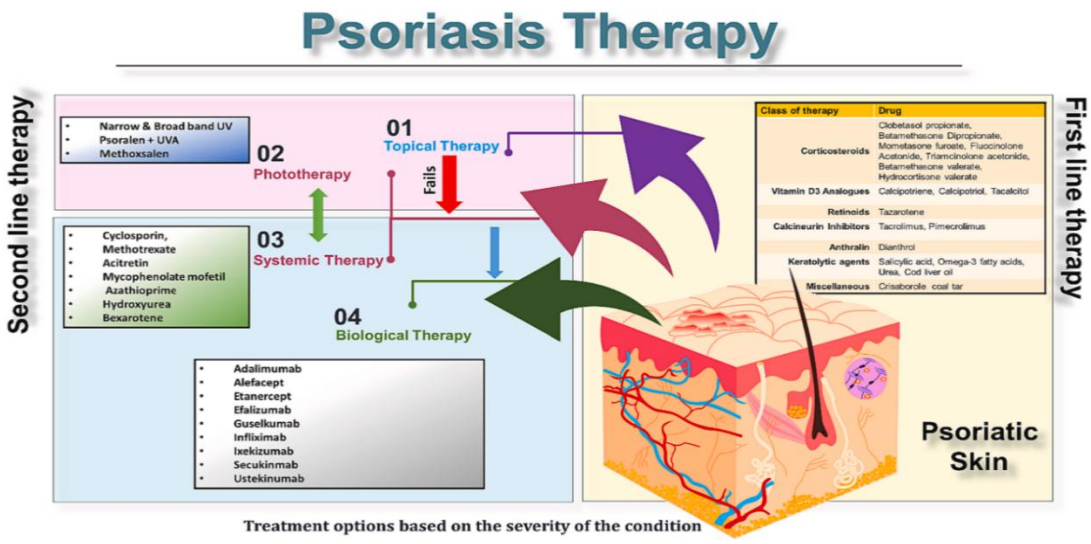

Figure 4. Standard therapeutic options for Psoriasis [19]

3.1. First-line therapy

At first, the most common forms of treatment are topical formulations. Traditional recipes may have unpleasant textures like grease, tackiness, or strong smells. For mild psoriasis, which does not cover more than 10% of the body's surface area, this is the therapy of choice. Individualized effects on affected body parts are necessary for patients with moderate to severe psoriasis. There is a wide variety of dose forms used in topical therapy, such as oils, foams, gels, bath solutions, lotions, tapes, ointments, sprays, and foams. The growth of keratinocytes and skin irritation can both be alleviated with topical treatment. When applied topically, a combination of medications can lessen the likelihood of side effects and increase the efficacy of treatment [20].

3.2. Second-line therapy

When topical treatments are ineffective, second-line therapy choices are frequently used. Phototherapy, systemic therapy, and biologics therapy are some of these alternate method [21].

3.2.1.Phototherapy

Phototherapy, utilizing ultraviolet radiation, is effective in treating psoriasis. Ultraviolet rays have a wavelength range of 100 to 400 nm, with 290 to 400 nm being the most efficacious for therapeutic applications. The predominant forms of phototherapy are psoralen plus ultraviolet-A radiation (PUVA), ultraviolet-B (UV-B), excimer/laser, and ultraviolet-A1 (UV-A1). PUVA is no longer commonly utilized due to its correlation with skin cancer. Individuals with psoriasis generally undergo UV-B phototherapy at a wavelength of 311 nm. Phototherapy inhibits cutaneous immunity, eliminates lymphocytes, and influences cytokine expression. Phototherapy necessitates regular commitment, generally two to three times weekly during the cleaning phase. Although UV-B therapy is deemed safe for pregnant individuals, PUVA treatment is contraindicated due to the carcinogenic properties of psoralen [22].

3.2.2. Systemic therapies

Systemic therapies are advised when topical treatments, including creams and lotions, and light therapies, such as phototherapy, fail to alleviate symptoms adequately. Patients undergoing this treatment must have routine liver function and blood testing due to the toxic properties of the administered medications. Immune suppression is the primary mechanism underlying systemic therapy. When alternative therapies are ineffective and the dermatological condition impacts over 5-10% of the body, they may be deemed appropriate. Psoriasis is managed with systemic therapies including acitretin, methotrexate, and cyclosporine [23].

A. Methotrexate

A folic acid derivative called methotrexate prevents DNA synthesis by preventing purine and thymidine synthesis. The first suggested dosage is 7.5–10 mg per week, with a maximum rise to 25 mg per week. Even though methotrexate is frequently used in clinical practice, there is a dearth of significant, well-organized clinical research to assess its safety and effectiveness [24]. Nearly 40% of patients on methotrexate saw a 75% improvement in their Psoriasis area and Severity Index score after 16 weeks, compared to just 18.9% for patients receiving placebo treatment, according to a placebo-controlled, randomized, double-blind research. Methotrexate has not been authorized for the treatment of pediatric psoriasis. Diarrhoea, vomiting, and a feeling of fatigue and nausea are common side effects. Hepatotoxicity is a more severe adverse impact [25].

B. Cyclosporine

Cyclosporine is used to treat moderate to severe psoriatic patients. It is an immunosuppressant of calcineurin inhibitor that suppresses T cells. Additionally, it has been demonstrated to be successful in treating psoriatic arthritis. Cyclosporine has a lot of side effects and drug interactions, which limit its long-term use even if it can

quickly cure symptoms. Nephrotoxicity, non-melanoma skin cancer, and hypertension are clear possible adverse effects [26].

C. Vitamin A

An oral retinoid called acitretin is used to treat moderate to severe psoriasis. Acitretin has been shown to increase efficacy, decrease dosage, and lessen the incidence of side effects when used as an adjuvant therapy in conjunction with other systemic medicines. However, because acitretin is teratogenic, it is recommended that women wait three years after stopping the medicine before getting pregnant. Common adverse effects of acitretin include mucocutaneous dryness, photosensitivity, gastrointestinal issues, and arthralgia; occasionally, it can even cause transaminitis and high triglyceride levels [27].

3.2.3. Biological therapies

Biologics are proteins with many molecules. Biologics are rapidly advancing in their ability to target the immune system in comparison to the standard portion of medical care. It consists of antisense oligonucleotides, kinase inhibitors, cytokines, RNA, and monoclonal antibodies (Ab). Psoriasis is typically treated with fusion proteins and MAb. The USFDA has approved four TNF-α inhibitors, known as MAb, to treat severe psoriasis. They are ustekinumab, adalimumab, infliximab, and etanercept [28]. Compared to the small molecules used for topical and systemic use, biologics are composed of larger molecules. Compared to others, their objectives are more obvious. However, it requires specialized techniques like biotechnology and bioengineering to be produced. The majority of biologics are created by engineering live or altered cells. These techniques are expensive, time-consuming, and difficult. On the other hand, simpler chemical procedures are used to create other small molecules. It is also difficult to pass through biological membranes due to its size. Every biological therapy is superior to every other one and is highly effective. This therapy has significantly altered the way psoriasis is treated [29].

4. Conventional topical treatment for Psoriasis

For mild to moderate psoriasis, topical therapy is typically regarded as the first line of treatment. For moderate to severe psoriasis, anti-psoriatic active agent-containing creams, gels, and ointments are also used; however, they are typically used in conjunction with other therapies like systemic therapy or phototherapy. Corticosteroids are a widely utilized and effective class of medications for alleviating psoriasis symptoms due to their ability to diminish inflammation and immune responses in the skin [30]. The main method for corticosteroid therapy in psoriasis involves the direct application of topical corticosteroids to the skin. Table 2 delineates various potencies, categorized from Class 1 (most potent) to Class 7 (least potent). To prevent potential long-term negative outcomes, including dermal thinning, skin atrophy, striae, and telangiectasia, short-term use is generally advised, usually for several weeks, succeeded by a break or the application of a milder formulation [31]. Based on what we know so far, the vehicle has the potential to alter the therapeutic and unfavorable effects of an active drug via changing its pharmacokinetics and dermal architecture. The creation of a suitable carrier for corticosteroids is a primary focus of pharmacological and dermatological research. Compared to other approaches, Bhutani and her colleagues found that spray formulations containing clobetasol were the most effective. Potentially enhanced effectiveness might result from improved patient adherence to an odorless and easily applied formulation [32].

Table 2. Classification of corticosteroids [33].

The Potency Group		Corticosteroid	Vehicle Type
Class 1	Super-high potency	Betamethasone dipropionate Clobetasol propionate	Ointment, Gel, Lotion Cream, Gel, Lotion, Shampoo, Foam, Aerosol, Ointment, Solution
Class 2	High potency	Desoximetasone Diflorasone diacetate	Cream, Ointment, Gel Ointment, Cream
Class 3	High potency	Fluticasone propionate Mometasone furoate	Ointment Ointment
Class 4	Medium potency	Fluticasone propionate Hydrocortisone valerate	Cream Ointment
Class 5	Lower-mid potency	Fluticasone propionate Hydrocortisone butyrate	Lotion Cream, ointment
Class 6	Low potency	Alclometasone dipropionate Betamethasone valerate Desonide	Cream, ointment Lotion Cream, Lotion, Foam
Class 7	Least potent	Hydrocortisone (base, ≥2%) Hydrocortisone acetate	Cream, Ointment, Lotion, Solution Cream, Lotion

Topical retinoids regulate keratinocyte turnover because they have the potential to affect differentiation and proliferation, which in turn helps to maintain a steady supply of new epidermal cells. Acitretin and tazarotene are two examples. Weinstein et al. found that the intensity of PSO was considerably reduced by using tazarotene creams at doses of 0.1% and 0.05% [34] . Moreover, they found that elevating the concentration of the active component enhanced effectiveness while also amplifying negative effects. Topical retinoids have several adverse effects, such as skin irritation, photosensitivity, erythema, and desquamation, potentially restricting their application in psoriasis. Topical calcineurin inhibitors has anti-inflammatory and immune-modulating characteristics, making them essential in the management of psoriasis. Their main use is in treating atopic dermatitis, more commonly known as eczema. However, they can also be used for psoriasis in specific cases, especially on sensitive areas where other treatments have a higher risk of side effects and have better percutaneous absorption, like the face and genital psoriasis [35]. Dermatologists primarily employ pimecrolimus and tacrolimus,

two calcineurin inhibitors. They work by inhibiting the activity of the enzyme calcineurin, which is involved in the activation of T cells. These drugs alleviate inflammation and the aberrant immune response that defines PSO by blocking the activation of T cells. Nonetheless, a number of clinical studies have shown that topical calcineurin inhibitors are just as effective as topical corticosteroids, with fewer side effects. When it came to treating inverse PSO, Kreuter and his colleagues found that the 0.1% betamethasone formulation worked better than the 1% pimecrolimus formulation [36]. Another potential therapeutic option for people with inverse psoriasis is intermittent therapy, which involves short-term topical corticosteroids and then maintenance treatment with a less effective medicine, such as pimecrolimus or calcipotriol (CPT). Vitamin D analogs, such calcipotriene, are also often used to treat PSO. Becocalcidiol, paricalcitol, and maxacalcitol are some of the new vitamin D analogs that are being studied for the treatment of PSO [37]. By regulating keratinocyte differentiation and preventing epidermal hyperproliferation, they influence the afflicted skin and aid in reversing the aberrant development seen in PSO plaques. Due to their separate but complementary mechanisms of action, they are often used in conjunction with other topical treatments, including corticosteroids, to increase their efficacy. Furthermore, vitamin D may help repair the epidermal barrier after corticosteroid use and reduce the risk of steroid-induced skin shrinking.

Therefore, a more comprehensive and long-term solution for PSO control might be a topical medication that combines corticosteroids with a vitamin D analog [38]. Furthermore, dithranol, or anthralin (1,8-dihydroxy-9anthrone), when applied topically, suppresses skin cell growth. This active component was initially developed in Brazil over a hundred years ago as a chrysarobin derivative derived from the araroba tree. Its ability to stop the overproduction of keratinocytes has made it a go-to remedy for psoriasis for a long time. The stinging and discoloring effects severely limit its use, yet it works particularly effectively to thin down psoriasis plaques because of this. While some research suggests that dithranol may enhance the body's reaction to PSO when used in combination with other topical therapies or UVB phototherapy, other studies suggest that short skin contact with high concentrations of dithranol may be helpful [39]. Salicylic acid is useful in the treatment of psoriasis because it is both an exfoliant and an anti-inflammatory. In addition to reducing redness, irritation, scaling, and inflammation, it promotes scale shedding. Additional anti-psoriatics, such as corticosteroids or vitamin D analogs, may have better penetration and bioavailability through skin thinning [40]. To improve the absorption of topical medicines and soften psoriatic plaques, try using nonmedical emollients and moisturizers before applying the meds. They alleviate dryness, irritation, and flare-ups while also moisturizing the skin. The inflammation caused by PSO may not be immediately alleviated by these, but they may improve skin health overall and complement other treatments to aid [41]. While traditional topical treatment for PSO has its uses, it also has certain drawbacks that need to be considered. For severe cases of PSO, topical therapies may not be helpful, while they can help with mild to moderate symptoms.Redness, itching, or burning are some of the side effects that may occur on the skin as a result of using topical drugs. This is something that those with sensitive skin or open wounds may find especially troublesome. Examples of medications that might irritate the skin on or surrounding psoriasis plaques include calcineurin inhibitors and vitamin D analogs, such as calcipotriene, tazarotene, and dithranol. These active compounds also have a limited permeability, which is a major issue. For this reason, novel medication delivery systems are in high demand [42]. Conventional topical drug that used for the treatment of Psoriasis are given in Table 3.

Table 3. Conventional topical drugs for the treatment of psoriasis [43].

Classification	Drug Name	Active Pharmaceutical Ingredient	Dosage Form
Topical vitamin D analogs	Calcipotriol Ointment	Calcipotriol	Greasy-based ointment
	Calcitriol Ointment	Calcitriol	Greasy-based ointment

	Maxacalcitol (Oxarol Ointment)	Maxacalcitol	
Calcineurin inhibitors	.03% or 0.1%, Tacrolimus Ointment 1%, Pimecrolimus Cream	Tacrolimus Pimecrolimus	Greasy-based ointment O/W Cream
AhR-modulating agents	1%, (Vtama) Tapinalof Cream	Tapinalof	O/W Cream
RA drugs	Tretinoin Cream 0.05% or 0.1%, Tazarotene Gel	Tretinoin Tazarotene	O/W Cream Gel
PDE-4 inhibitors	0.3% Zoryve (Roflumilast) Cream	Roflumilast	O/W Cream
Other	Dithranol Ointment	Dithranol	Greasy-based ointment

5. Challenges in the Topical Delivery of Anti-Psoriatics

Anti-psoriatic topical delivery faces a number of difficulties that affect treatment efficacy and patient compliance. These difficulties include problems with drug formulation, skin properties, and patient-specific variables. As a barrier, the stratum corneum, the skin's outermost layer, restricts how quickly the active ingredients can penetrate the skin. Because thickened and hyperkeratotic plaques are common in psoriasis, drug penetration is further hampered, making conventional treatments less effective. For topical medications, it is challenging to penetrate the skin's outermost layer using the traditional medication formulation approach [42]. Extreme disease-related conditions like hyperkeratosis and irritation make this issue even more difficult. The skin features of psoriasis, such as elevated cholesterol and decreased ceramide content, can make it more difficult for the active ingredients to penetrate the skin's deeper layers. Furthermore, hydrating stimuli like skin water are insufficient, which restricts the drug's ability to enter in comparatively high concentrations. However, ,usually, the skin is not sufficiently hydrated, which restricts how much anti-psoriatic medication can penetrate the skin [44]. Furthermore, the degree of skin permeability varies across various anatomical regions. One example is how much more porous the skin is on the face and genitalia than it is on the soles and palms of the hand. Consideration of the affected area's specific characteristics is essential when choosing a distribution mechanism. Some anti-psoriatic drugs, such as tacrolimus, dithranol, and calcipotriene, are classified as Class II in the Biopharmaceutical Classification System (BCS). This means that they are not very water-soluble, which might affect how well they are absorbed and how much of them reaches the bloodstream. Because of this, formulations that improve the solubility of medications are often necessary. Chronic, long-term administration of a topical therapy is usually necessary for psoriasis. Potential side effects, treatment duration, and the hassle of regular administration are just a few of the reasons why patients may struggle to follow their treatment programs [32]. As mentioned before, skin irritation, dryness, or itching may occur with long-term use of antipsoriatics, especially potent corticosteroids. This has the potential to decrease the rate of treatment adherence and attrition. It is also possible for drugs to enter

the circulation when administered topically to huge portions of the body or to those with impaired skin integrity. The likelihood of systemic side effects may increase [45].

6. Novel delivery approaches to address limitations of traditional treatments

Researchers have explored alternative distribution methods to address limitations in traditional formulations. Some issues with conventional psoriasis treatments include hyperpigmentation, first-pass metabolism, inadequate medication penetration into the skin, and a burning sensation on both healthy and diseased skin[46]. Thus, novel drug delivery technologies have been used to improve patient safety and efficacy while avoiding the drawbacks of traditional psoriasis treatment methods. Improved drug diffusion and penetration have been demonstrated by innovative drug delivery methods, which results in a greater and longer accumulation of the drug in the skin. Furthermore, it is possible to target drugs to the dermal and epidermal areas, which lowers dosage. Additionally, the innovative formulations lessen some medications' systemic toxicity, burning, irritation, and necrotizing effects. Compared to traditional therapies, a novel medication delivery is safer , more tolerable, quicker follicular and intercellular penetration pathway since it reduces the need for repeated administrations and boosts therapeutic effectiveness [47].

6.1. Emulsion Drug Delivery System Applications in Psoriasis

Drug delivery techniques utilizing emulsions for psoriasis therapy encompass multiple emulsions, microemulsions, and nanoemulsions (Figure 5).

6.1.1. Multiple Emulsions

Various drug delivery technologies, including multiple emulsion, microemulsion, and submicron emulsion, are available for the treatment of psoriasis. Water-in-oil-in-water (w/o/w) or oil-in-water-in-oil (o/w/o) Dispersed systems stabilized by lipophilic or hydrophilic surfactants exemplify numerous emulsions. These emulsions show great promise for improved therapeutic efficacy, less side effects, enhanced patient compliance, and extended skin retention without improving transdermal penetration. Formulated several topical hydrocortisone emulsions displaying a sustained release of medication and 1.5 times more hydrocortisone permeation through the epidermis compared to a conventional emulsion [7].

6.1.2. Microemulsion

An isotropic mixture of water, oil, and a co-surfactant with globule diameters ranging from 10 to 100 nm is known as a microemulsion. It is a transparent and stable solution. Since the droplet width of microemulsions is less than a fourth of the visible light wavelength, they are transparent or translucent [48]. Skin penetration, drug release from the vehicle, and movement all influence the microemulsion action. Changes in the stratum corneum and a variety of permeation enhancers, such as isopropyl myristate and short-chain fatty acids, affect the permeation factor [49]. Salicylic microemulsions were studied by Badawi et al. for improved solubility for effective topical keratolytic and antibacterial activities. In order to treat a hyperproliferative skin condition, Barolia et al. created a microemulsion of 8-methoxsalen and 5-methoxy psoralen that increased drug accretion in the skin and had no negative side effects [50].

6.1.3. Nano-emulsions

Nanoemulsions are transparent, stable dispersion systems of an insoluble oil phase and a water phase, with surfactant-stabilized droplet sizes varying from 5 to 200 nm. In PSO treatment, nanoemulsions provide a number of benefits over traditional emulsions, including improved drug permeability and loading capacity, which

increases therapeutic effectiveness, and the absence of stability issues, including flaking, delamination, deposition, and coarsening [51]. Through careful formulation and component screening, nanoemulsions enhance the skin penetration and therapeutic effectiveness of anti-PSO medicines, including tacrolimus, methotrexate, and glucocorticoid analogs, by providing a safer and more efficient mode of delivery [52]. Rai et al. developed an innovative nanoemulsion called ATNEG that increases the absorption and effectiveness of the local medication tacrolimus against PSO. The nanoemulsion is made with soy lecithin and vitamin E oil. We adjusted the droplet size, assured uniform dispersion, and regulated viscosity to increase the availability and efficacy of the topical medication. Its pH is similar to that of the skin, making it an ideal candidate for topical use. Additionally, the emulsion showed a controlled pattern of drug release with penetration lasting longer than 24 hours. This feature is designed to ensure that drugs may be absorbed via the skin without interruption. In contrast to tacrolimus ointment sold in stores, this emulsion allowed for greater and more sustained medication absorption by the skin [53]. To improve fluticasone propionate's skin permeability, Jain and colleagues created a nanoemulsion gel. The nanoemulsion gel, which included fluticasone propionate, negentropic gel, and aloe vera gel, proved to be very effective in providing long-term relief from PSO [54]. According to these results, it also made the skin more permeable. The quantity of fluticasone propionate that was found to be maintained in deep skin was about quadrupled by its use [55]. In in vivo investigations for anti-PSO action, the nanoemulsion gel outperformed a commercially available treatment. In addition, Rashid et al. successfully developed a nanoemulsion based on MTX and olive oil (MTX NEG) for the PSO therapy. A foamed nanoemulsion containing the photosensitizer Ce6 (Ce6 FM) was recently produced by Ma et al. Ce6 may cross the epidermal barrier and stay in the epithelial layer after topical application, allowing for targeted administration to the aberrantly growing keratinocytes [56]. Emulsion drug delivery System applications in psoriasis treatment are given in Table 4.

Table 4. Recent research has focused on emulsion medication delivery systems for the treatment of psoriasis [7]

Drug	Delivery system	Excipients	Preparation Method	Results and Clinical Significance
Hydrocortisone	Multiple emulsion	Glycerol sorbitan fatty acid ester, Liquid paraffin	Oil-water-oil emulsification	Extended topical delivery of hydrocortisone in the dermis and epidermis.
Salicylic acid	Micro-emulsion	Tween20,Polyethylene glycol, Isopropyl myristate	O/W emulsification	After six months, ME with 10% SA exhibits no change in storage stability.
8-Methoxsalen	Micro-emulsion	Octanediol, Span 80, Isopropyl myristate, Tween 80, Water	O/W emulsification	The cutaneous deposition of 8-Methoxsalen augmented by 1.5 to 4.5-fold.
Methotrexate	Nano- emulsion	Chaulmoogra oil, Tween 80, Water	Self-emulsification	Displayed heightened skin penetration and little skin irritation.

6.2. Vesicular Drug Delivery System Applications in Psoriasis

Liposomes, ethosomes, niosomes, pharmacosomes, phytosomes, and transferosomes are vesicular drug delivery systems that may be helpful in the treatment of psoriasis (figure 5).

6.2.1. Liposomes

Liposomes are small, spherical vesicles that contain cholesterol and natural, non-toxic phospholipids. Because they have hydrophilic and hydrophobic ends, these compounds are considered amphiphilic. Their bilayer composition gives liposome molecules their rigidity and flexibility; saturated phospholipids provide a rigid bilayer structure, while unsaturated phosphatidylcholine allows permeability [57]. The two main shapes of liposomes are multi-lamellar vesicles, which resemble onions, and unilamellar vesicles, which are spherical structures composed of a single phospholipid bilayer. They have found extensive usage as nanocarriers for hydrophilic and lipophilic drugs due to their excellent biocompatibility, biodegradability, and lack of toxicity or immunogenicity. By enhancing drug solubility, controlling drug distribution, and offering surface modification flexibility, liposomes may achieve target-specific sustained release [58]. They are generally utilized for drug encapsulation, with sizes ranging from 50 to 150 nm, rendering them appropriate for drug delivery via many routes. Liposomal formulations have been studied in the context of psoriasis to improve the targeted distribution of medicinal drugs to the skin, perhaps enhancing efficacy and minimizing side effects. Jain et al. developed tacrolimus and curcumin-loaded synergistic liposphere gels, which exhibited enhanced antipsoriatic action alongside higher inhibition of interleukin-22, interleukin-17, and tumor necrosis factor-alpha. Walunj et al. developed and evaluated the enhanced efficacy of a topical gel incorporating cyclosporine-loaded cationic liposomes in an imiquimod-induced psoriatic plaque model [59].

6.2.2. Ethosomes

Nanovesicles called ethosomes contain phospholipids and a high concentration of ethanol (20-45%). When incorporated into vesicular systems, ethanol produces flexible nanosheets, which are known to have improved permeability. Improved lipid fluidity and cell membrane permeability may result from its capacity to interact with the polar head group area of lipid molecules, which lowers the melting point of the stratum corneum's lipids. The flexible vesicles may pass through spaces that are less than their diameter because of the very elastic ethanol-derived vesicle membranes [60]. When compared to hydroalcoholic solutions and traditional liposomes, ethosome systems are superior in skin delivery. Citrin, a second-generation retinoid, is used to treat severe PSO. Its systemic adverse effects and low water solubility make it difficult to dose effectively [61]. Peram and colleagues set out to develop and evaluate a nanogel for the treatment of localized psoriasis that included ethosomes loaded with acitretin. According to the findings of the fluorescence microscopy analysis, the rate of acitretin penetration from the gel without ethosomes is lower than the rate of ethosomes into the deeper layers of skin [62]. An in vivo investigation showed a significant increase in the therapeutic response, while ex vivo testing showed that the generated ethosomal gel significantly enhanced skin permeability and deposition. Dadwal and colleagues developed ethosomal formulations of tacrolimus and hyaluronic acid using soy lecithin, ethanol, and propylene glycol to address the significant adverse effects that may arise with frequent use of the medicine. The research demonstrated that the tacrolimus ethosome based on hyaluronic acid increased dermal flow, had a greater enhancement rate after skin penetration, and extended drug release. Adding hyaluronic acid to the ethosome gel enhanced its efficacy in in vivo trials treating PSO with tacrolimus [63].

6.2.3. Niosomes

The niosome structure allows for controlled, targeted, and sustained pharmaceutical delivery by localizing the hydrophilic medicine within the core aqueous compartment and the hydrophobic moiety within the bilayer matrix. The systems are built upon nonionic surfactants and have various benefits, such as accommodating hydrophilic and hydrophobic drugs, reducing toxicity, improving compatibility, and promoting biodegradation.

Phospholipids are being preferred over liposomes because of their specific drawbacks, such as their susceptibility to oxidation, high cost, and chemical instability [64]. To tackle the several drawbacks of existing psoriasis treatments—withdrawal rebound, expensive costs, and various side effects—Meng et al. developed niosomes containing celastrol. Research on animal models of psoriasis found that cerastrol niosomes reduced redness and scaling on the skin's surface, and in vitro investigations showed that they were more permeable than the crude medication. Cilossome encapsulation of celastrol improved its water solubility and skin penetration, which in turn increased its anti-inflammatory effectiveness in mice, according to the research [65]. To improve the local penetration and deposition of cyclosporine for the effective treatment of psoriasis, Pandey et al. created a niosome gel. It has been shown that pentoxifylline may reduce the side effects of cyclosporine, making it a potential therapy option for psoriasis. Using the thin-film hydration approach, Bhardwaj et al. optimized niosomes that contained pentoxifylline and cyclosporine. Since only a small percentage of the medications could cross the epidermis and a large portion stayed within the stratum corneum, the niosomes had a significant impact on the penetration of both medications. Niosomes encapsulating pentoxifylline and cyclosporine considerably increased histological abnormalities and the Psoriasis Area and Severity Index compared to solutions containing each active ingredient individually, according to in vivo research performed on IMQ-induced psoriasis in mice [66].

6.2.4. Cerosomes

Cerosomes are unique vesicular structures that rely on ceramide lipids to form a lipid bilayer. Ceramide sphingolipids found naturally in the skin promote medication penetration by altering the skin's intercellular lipid structure. Ceramides improved the encapsulation rate of tazarotene in tubulated vesicles called "cerosomes," decreasing its release and increasing its skin deposition. Twenty patients with plaque psoriasis participated in a clinical trial, and the results showed that this delivery mechanism significantly reduced PASI scores compared to tazarotene gel [67]. Cerosomes modified by Yang et al. are capable of transporting nicotinamide (NIC) in addition to MTX. Through the formation of hydrogen bonds, NIC effectively dissolves MTX. Cerosomes improve the uptake and maintenance of drugs in rat skin. Strong antiproliferative, apoptotic, and HaCaT cell- resistant MTX/NIC cerosomes [68].

6.2.5. Transfersomes

Transfersomes possess significant deformability, enabling them to navigate through minuscule gaps due to their supramolecularly organized structures. They are analogous to liposomes in morphology, although they possess the functional ability to conform to significantly smaller apertures. Transfersomes are vesicular particles characterized by at least one internal aqueous compartment and ultradeformable lipid bilayers, relative to their size. In order to build transfersomes that contained tamoxifen, Bhatia et al. used phospholipids and the surfactant Span 80. They were then mixed with a Carbopol hydrogel. We compared orthokeratosis in a mouse tail model to determine the anti-psoriatic effectiveness of the tamoxifen-transfersome-loaded gel. After four weeks of daily dosing, the gel containing tamoxifen transfersome caused a greater amount of orthokeratosis compared to a free tamoxifen gel. The efficacy of phospholipid-rich transfersomes can be attributed to their advantageous interactions with epidermal lipids.Todke et al. developed transfersomes incorporating both cyclosporine and clobetasol propionate. The thin-layer hydration method was employed to produce the transferosomes.They developed tiny transferosomes (under 150 nm) with an exceptional encapsulation efficiency of cyclosporine (>86%). These transfersomes were able to successfully deliver cyclosporine and clobetasol propionate to the dermis, according to ex vivo data. The enhanced formulation reduced TNF-α and IL-1 levels, as indicated by RT-PCR tests [69]. Vesicular drug delivery system applications in psoriasis treatment are given in Table 5.

Table 5. Recent research in vesicular drug delivery system for psoriasis treatment [7].

Drug	Delivery system	Excipients	Preparation method	Results and Clinical Significance
Methotrexate	Ethosome	Soya phosphatidyl-choline, methanol, hydro-ethanolic solution,chloroform	Mechanical dispersion Cast film	Enhanced transdermal flow and decreased lag time of 0.9 hours across the skin of a human cadaver.
Dithranol	Liposome, Niosome	Phosphatidyl choline, cholesterol, chloroform, span 60	Thin-film hydration	The findings showed that leakage increased at higher temperatures and that there was improved vesicle permeability, as indicated by the dithranol flow.
Tacrolimus	Transferosome	Lipoid E80, Tween 80, dehydrated alcohol, Span 80	Thin film hydration	Comparing TFs-gel to commercial ointment, the in vitro drug release was greater after 24 hours, and the cumulative drug release from TFs-gel after 12 hours was 37.6%.
Betamethasone dipropionate	Transferosome	Soya phosphatidyl-choline, Sodium deoxycholate, Tween 80, chloroform	Film hydration technique	Significant improvements in safety and tolerability.

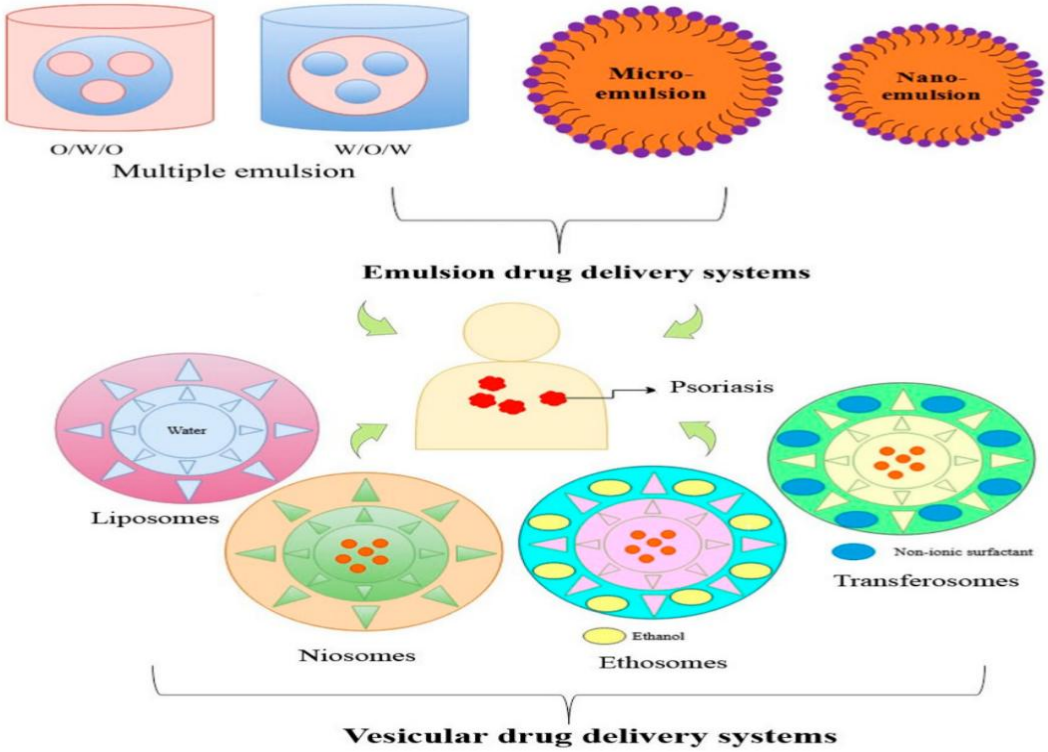

Figure 5. Fundamental vesicular drug delivery and emulsion structures [7]

6.3. Particulate Drug Delivery System Applications in Psoriasis

Solid lipid nanoparticles (SLNs), solid lipid microparticles (SLMs), dendrimers, aquasomes, nanocrystals, polymeric nanoparticles, nanospong and gold nanoparticles are examples of particulate drug delivery systems (Figure 6).

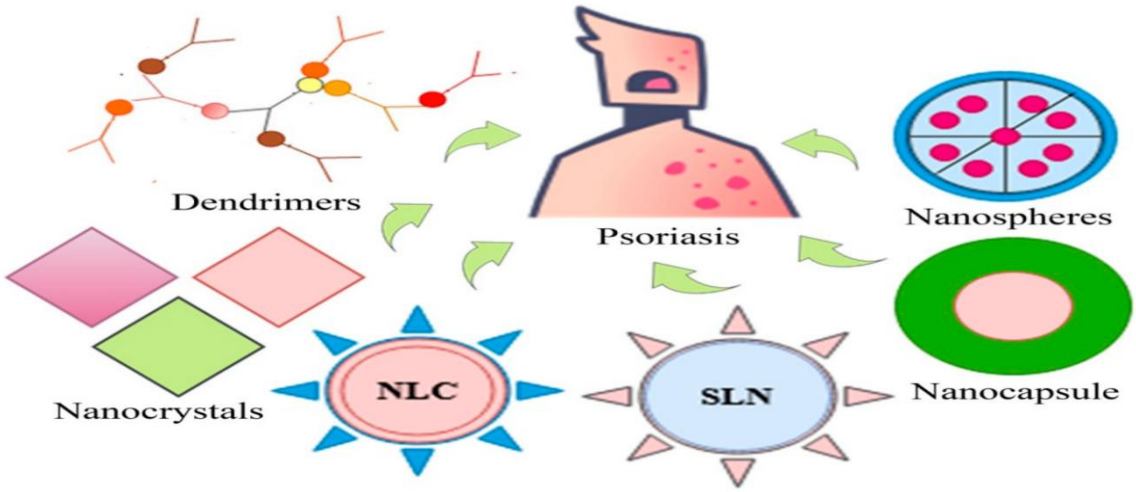

Figure 6. Particulate drug delivery systems' fundamental structures [7]

6.3.1. Microparticles of solid lipids (SLMs) and solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) and solid lipid microparticles (SLMs) are aqueous, colloidal, biodegradable, and biocompatible systems that do not necessitate organic solvents. They consist of lipids dispersed in surfactant and water solutions. SLNs exhibit exceptional biocompatibility and the ability to deliver both lipophilic and

hydrophilic drugs, while also facilitating drug release regulation, enhancing drug stability, and enabling targeted delivery. Due to the non-toxic and non-irritating nature of lipids, SLNs are effective in treating dermatological conditions such as psoriasis and alleviating inflammation, rendering them suitable for topical applications. Ferreira et al. concluded that the topical co-administration of SLNs containing etanercept and methotrexate may represent a targeted approach for psoriasis management [70].

6.3.2. Nano-Structured Lipid Carriers (NLCs)

To get around the limitations of SLNs and SLMs, NLCs increase drug loading capacity and reduce drug ejection. NLCs are made up of solid fatty acids and trace amounts of liquid lipids. Fluocinolone acetonide loaded with nanostructured lipid carriers was created by Pradhan et al. for the prospective and successful treatment of psoriasis [71]. Methotrexate-loaded nanostructured lipid carriers were created by Pinto et al. in order to potentially treat psoriasis topically with less systemic toxicity [72].

6.3.3. Polymer-based nanocarriers

A. Polymeric nanoparticles

Excellent biodegradability and biocompatibility allow polymeric nanoparticles (NPs) to encapsulate both hydrophilic and hydrophobic medications and prevent drug degradation. Khalid et al. showed that improving the apremilast-loaded PLGA nanoparticles' bioavailability and long-term retention could support a once-daily regimen. Tomo-da et al. used the emulsion solvent evaporation approach to create spherical, indomethacin-loaded PLGA nanoparticles, which they then used for transdermal distribution. Shah et al. used PLGA and chitosan to create surface-modified bilayered nanoparticles containing oleic acid [73].

B. Polymeric nanocapsules

In recent years, polymeric nanocapsules have been thoroughly investigated as a possible medication delivery method.The therapeutic potential of nanocapsules for the safe and effective administration of medications used in various conditions, including psoriasis, has been extensively studied. Eudragit RS 100 polymers were used to create cationic nanocapsules containing dexamethasone, and the in vitro drug release and skin permeability were evaluated. These nanocapsules have drawn a lot of attention due to their exceptional capacity to penetrate skin and control drug release throughout. Numerous medications are found in the viable epidermis, which is the main target region for dexamethasone to work against psoriasis, according to studies on skin penetration using pig skin. Because the negatively charged skin surface speeds up the penetration of the positively charged particles when applied topically, this result suggests that cationic nanocarriers are suitable for targeting the epidermis in psoriatic skin. Additionally, Beber et al. created hydrogel-formulated cationic polymeric nanocapsules that contained dexamethasone. They proposed that it is anticipated that dexamethasone will be delivered using nanocapsules [74].

C. Polymeric nanospheres

Nanospheres are synthetic, polymer-based nanocompounds that are biodegradable and biocompatible. Pharmaceuticals have been successfully administered to the dermis using nanospheres (TyroSpheres). Nanospheres offer enhanced solubility, physicochemical preservation of the therapeutic agent, better absorption, and regulated medication release. Batheja et al. loaded tyrosine-derived nanospheres into lipophilic medications for topical application, finding that TyroSphere exhibited enhanced drug penetration compared to aqueous nanosphere formulations. TyroSphere serves as an effective delivery mechanism for lipophilic drugs in the treatment of dermatological conditions such as psoriasis and acne [6].

6.3.4. The nanocrystals

Nanocrystals are crystalline structures that measure between 20 and 100 nanometres and consist solely of unmodified medicines without any polymer conjugation. Nanocrystals enhance solubility and dissolve by increasing the dissolving pressure, surface area, and curvature of particles, thereby largely improving the drug's oral bioavailability. The accelerated follicular and intercellular penetration pathway of nanocrystals enhances absorption, which is highly advantageous. They have prolonged the medication's duration of action and obviated the necessity for multiple administrations. Döge et al. developed a nanocrystal encapsulating dexamethasone, which they found enhanced the drug's transdermal absorption [75].

6.3.5. Gold nanoparticles

Fereig et al.'s study demonstrated that gold nanoparticles linked with tacrolimus-infused lecithin–chitosan hybrid nanoparticles showed markedly enhanced effectiveness in the treatment of psoriasis compared to unaltered hybrid nanoparticles without gold [7]. A lower spleen-to-body weight ratio and better histological skin condition were further indicators that these gold conjugates had anti-inflammatory action compared to the other formulations that were tested [10]. The study conducted by Özcan et al. showed that MTX with gold nanoparticles effectively reduced inflammation more than MTX alone. No lymphocytes, CD4+ T cells, or neutrophils were detected after the combination treatment. On top of that, it was well-received worldwide and in certain areas. Results showed that MTX-AuNPs significantly affected skin immunology and stroma, reducing psoriasis etiology in preclinical models. Researchers Fratoddi et al. found that in a mouse model of imiquimod-induced psoriasis, methotrexate-loaded gold nanoparticles reduced keratinocyte count and epidermal thickness in vivo [7].

6.3.6. The nanosponges (NSs)

Nanosponges are hyper-crosslinked cyclodextrin polymers that combine with crosslinker-like carbonyl diimidazole to form nanostructured three-dimensional networks. Several polymer chains can form unique microdomains within their crystal structure that are suitable for encasing medications with various chemical compositions. Nanosponges are renowned for their ability to dissolve medications with low water solubility and promote extended release. Because of their exterior hydrophilic branches and inside hydrophobic cavities, they can load both hydrophilic and hydrophobic medication molecules successfully [76]. On top of that, they have the potential to improve drug delivery in a variety of therapeutic contexts. Topical corticosteroids like clobetasol propionate show promise in psoriasis treatment, however there are side effects to be aware of when using steroids on the skin, including hyperpigmentation, acne, and allergic contact dermatitis. Kumar et al. created a hydrogel with nanosponges, made of β-cyclodextrin and diphenyl carbonate, to counteract these adverse effects. The formulation resulted in an 86% drug release value and a 45-fold increase in the solubility of pure clobetasol propionate in water. Furthermore, the biocompatibility of nanosponges containing clobetasol propionate was demonstrated using in vitro cell viability experiments utilising a human monocyte cell line (THP-1). Compared to the control group of mice that did not receive treatment, the in vivo examination demonstrated a significant decrease in the severity of orthokeratosis. In addition, the study found that the medicine was highly effective and that the epidermal thickness decreased [77]. Particulate drug delivery System applications in Psoriasis treatment are given in Table 6.

Table 6. Recent research on the use of particulate drug delivery system for the treatment of psoriasis.

Drug	Delivery system	Excipients	Preparation method	Results and Clinical Significance
Methotrexate	SLN	Polysorbate 80, Cetyl palmitate,	Ultra-sonication	In vitro findings demonstrated improved skin deposition and an 8-hour sustained release for psoriasis treatment [7].
Dexamethasone	Nano-crystal	Sodium lauryl sulphate, Polyvinyl alcohol	Wet bead milling	Better medication distribution and penetration into the skin at a lower dosage [7].
Methotrexate	Gold nano-particle	tetrachloroauric (III) acid, sodium borohydride, 3-mercapto-1-propansulfonate, Diethylaminoethanethiol hydrochloride,	Bioconjugation and functionalization	There was a reduction in keratinocytes, hyperproliferation, epidermal thickness, and inflammatory infiltration in a mouse model of imiquimod-induced psoriasis [75].
Apremilast	Polymeric nano-particle	Polyvinyl Alcohol, Poly (D, L-lactide co-glycolide),	Single emulsion solvent evaporation	Long-term retention of nanoparticles to offer a once-daily regimen is achieved by improving half-life and mean residence time and increasing bioavailability by 2.25 times compared to standard APM solution [7].
Clobetasol propionate	Nanospong	β-cyclodextrin, Acetone, Carbopol 934,Diphenyl carbonate, Methanol, Double-distilled water	Hot-melt method	Enhanced anti-psoriatic effectiveness and reduced epidermal thickness [32].

6.4. Self- assembled based drug delivery system

6.4.1. Dendrimers

Dendrimers are polymers that have a reactive, spherical, three-dimensional structure and several peripheral functions that can be controlled. The creation of drug-dendrimer conjugates is facilitated by the covalent bonding or physical trapping of drug molecules with functional groups. Dendrimers come in several types, including glycocondrimers, peptide dendrimers, and lysine core dendrimers [78]. An external sugar unit is present in glycoldendrimers due to the presence of a carbohydrate integrated into the dendrimer structure. Peptide dendrimers have lysine embedded into their central structure. When compared to conventional treatment, Tripathi et al. discovered that a dendrimer loaded with dithranol decreased skin irritation and burning. Improved drug accumulation in the skin and improved targeting of dermal and epidermal areas were among the encouraging outcomes of psoriasis therapy using dithranol-loaded polypropylene imine dendrimers, according to research by Agrawal et al. [79].

6.4.2. Micelle

Incorporate reverse micelles, mixed micelles, and polymeric micelles (see figure 7). These drug delivery devices possess a diameter ranging from 10 to 100 nm and consist of hydrophilic surfaces and hydrophobic cores. While hydrophobic micelles may alter the pharmacological characteristics and kinetics, hydrophilic surfaces allow drugs to linger in the bloodstream for longer periods of time undetected by the reticuloendothelial system. Polymeric micelles improve the rate of pharmaceutical absorption into the bloodstream and their accumulation in lymph nodes. When compared to a conventional commercial formulation, tacrolimus-loaded polymeric micelles produced by Lapteva et al. resulted in a twofold increase in skin penetration [80].

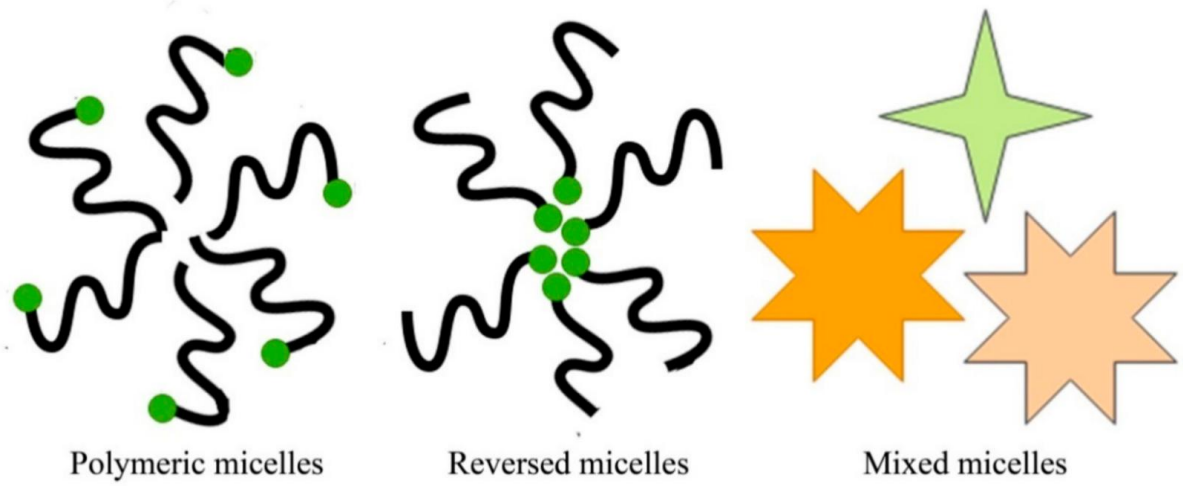

Figure 7. Micelle drug delivery systems' fundamental structures [7]

6.4.3. Hydrogels

These intelligent polymer materials possess three-dimensional cross-linked network architectures; they may facilitate the construction of a multidrug co-delivery system via physical and chemical interactions with biologically active molecules (such as siRNA or antibody fragments) and hydrophilic or hydrophobic pharmaceuticals. By combining gene silencing with immunomodulation and tailored medication release, this integrated strategy is able to circumvent the drawbacks of individual therapies. Furthermore, the dynamic network structure offers two benefits: first, it can be cross-linked to create an adhesive protective film that extends the

drug's skin permeability; second, it can respond to changes in the microenvironment (pH, enzyme concentration) by solubilizing, allowing for controlled release. Since this sustained administration strategy greatly decreases the dosage frequency and is appropriate for PSO with chronic recurrence, it has garnered a lot of interest from the therapeutic community. The creation of a highly permeable and viscous preparation that can enhance the level of medication retention on the skin surface is crucial for overcoming the current limitation of PSO treatment [81]. The first water-responsive hydrogel (WRG) was created by Yao et al.47 using glyceryl dioleate (GDO) and phosphatidyl choline (PC). This hydrogel exhibited the distinct properties of a water-induced sol-gel transition. The substance changed from its solution state to a hydrogel as soon as water was added. The immunomodulatory, anti-inflammatory, and antibacterial medication curcumin (Cur), which is effective against PSO, was loaded into WRG and achieved sustained drug release [82]. A new CUR-WRG gel as shown in Figure 8.

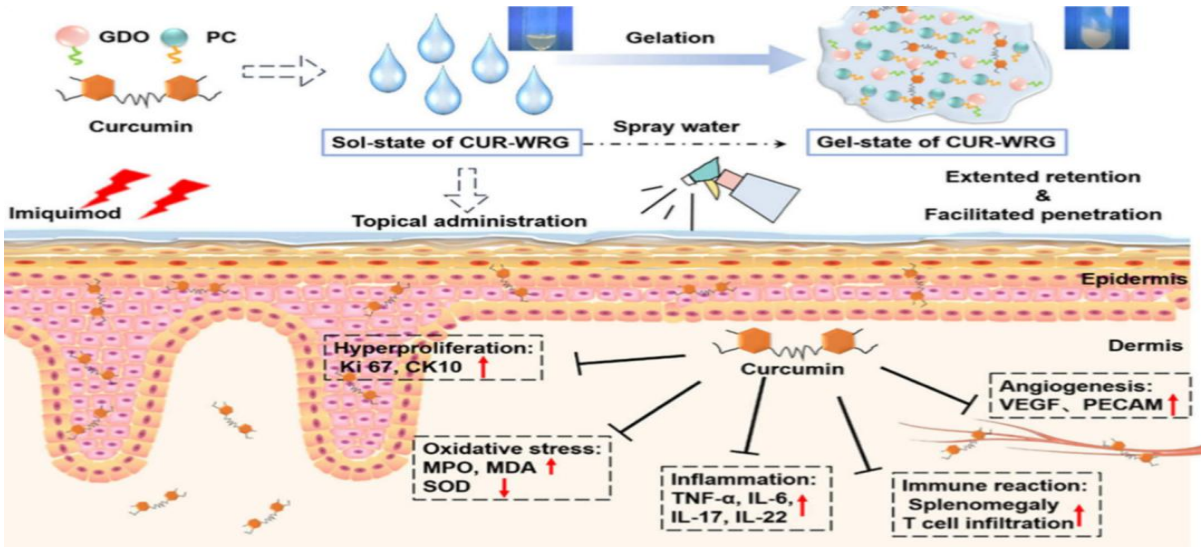

Figure 8. The schematic of the topical administration of curcumin for PSO therapy using a new CUR-WRG gel [82]

6.4.4.Nanogel

Nanoparticles mixed with hydrogel make up nanogel. Synthetic polymers or biopolymers that have been chemically or physically crosslinked form the crosslinked hydrophilic polymer network that makes up hydrogels. Nanogels were created by Singka et al. to deliver methotrexate topically [5]. Nanogel particles ranged in size from 100 nm to 1 μm.13. One of the factors contributing to this delivery's widespread use was the colloidal particles' tendency to swell in a variety of solvents. Depending on a number of factors, including temperature, solvent type, and ionic strength, the monomers utilized in nanogels were crucial to the volume phase transition. Nanogels could be made from methyl methacrylate, styrene divinyl benzene, etc. N-isopropylacrylamide is the most commonly utilized monomer because it can collapse at low temperatures (32°C–34°C). The study used a copolymer of N-isopropylacrylamide and the nonionic monomer butacrylate to create the nanogel. Baboota et al. investigated the topical administration of betamethasone dipropionate for psoriasis treatment using nanocarrier hydrogels. Salicylic acid was added to this system to improve skin descaling and formulation stability. On the skin utilized for permeation investigations, researchers conducted histological analyses. Significant alterations in the structure of the epidermal membrane were shown by preliminary investigations. Additionally, the carrageenan-induced hind edema approach was used to conduct anti-inflammatory research on Wistar rats. The microemulsion-based hydrogel containing betamethasone dipropionate and salicylic acid had approximately 72% anti-inflammatory activity, while the commercial preparation showed approximately 44% activity [53]. Self-assembled based drug delivery system applications are given in Table 7.

Table 7. Recent research on the use of Self assembled based drug delivery system for the treatment of psoriasis.

Drug	Delivery system	Excipients	Preparation method	Results and Clinical Significance
Methotrexate	Micelle	N-hydroxybenzotriazole ,Fmoc-lys(Fmoc)-OH, N,N-Diisopropylcarbodiimide	Thin-film formation/ dispersion method, reverse micelle method	It improved the targeting accuracy of psoriasis treatment, exhibiting greater and long-lasting effectiveness in reducing inflammation of the skin [10].
Indirubin	Hydrogel	Hyaluronic acid, poloxamer 188	Wet media milling technique	has the potential to improve topical medication distribution to inflammatory regions in psoriatic conditions [10].
Dithranol	Dendrimer	Polyvinyl alcohol, Poly (amido) amine, ethyl cellulose, carbopol 934	Quasi-emulsion solvent diffusion	The results showed that the formulation produced extended efficacy without generating skin toxicities [7].
Tapinarof	Nanogel	Surfactants: Labrafil M, Triacetin, Tween 80, Kolliphor EL, PEG 400, Transcutol HP, Oleic acid , Gelling Agent: Carbopol 940/934 Humectant: Glycerin Neutralizer: Triethanolamine Solvents: Ethanol, Purified Water	Emulsion-based nanogel preparation using the Self-Nanoemulsifying Drug Delivery System (SNEDDS) incorporated into Carbopol gel.	Drug release, skin compatibility, and wound-healing activity were all enhanced by the tapinarof nanogels, indicating that nanoformulation improves local efficacy and safety for psoriasis therapy [83].

6.5. Transdermal physical systems

Microneedles

Microneedles (MNs) are a kind of composite delivery system that uses an array of tiny needle points, with lengths varying from 25 to 1000 μm, as shown in Figure 9. The MN array may contain the active ingredient, and the internal and external concentration gradients can be used to trigger its release. In order to participate in microcirculation and produce pharmacological reactions, it is able to selectively infiltrate the stratum corneum without crossing it. The transdermal absorption rate of medicine supplied by MN is constant, it is easy to use, and the patient may self-administer the drug. Through physical and chemical interactions with biologically active

molecules (such as siRNA or antibody fragments) and hydrophilic or hydrophobic medicines, these smart polymer materials with three-dimensional cross-linked network topologies may be used to construct a multidrug co-delivery system. [84]. Everyone knows that PSO patients have relatively thick skin lesions, which makes drug delivery a challenge. However, MN therapy can penetrate the stratum corneum, avoiding the step of penetration needed for topical drugs, and achieve the goal of long-term, precise, and sustained symptom relief. In addition, MN may be able to use its imaging, diagnostic, and therapeutic capabilities to determine the extent of PSO and direct therapy accordingly. Transdermal medication delivery using MNs has recently shown great promise in dermatologic treatment. Improving their structure, function, and components for smart medicine delivery has been the subject of research. [85]. The combination of soluble microneedles with methotrexate sodium (MTX Na) nanocrystals was recently described by Tekko et al. Due to its hydrophilicity, MTX Na cannot be effectively delivered subcutaneously. Because of its high clearance rate, MTX Na must be administered more often to keep the dosage intensity constant, which might impact patient compliance. After skin simulations, the MTX Na microneedles showed great mechanical strength and penetration; they dissolved completely 20 minutes after being applied to pig skin and delivered about 25% of the MTX to skin with psoriasis. While reducing systemic exposure to MTX, significantly higher quantities of MTX Na were deposited compared to oral MTX. [29].

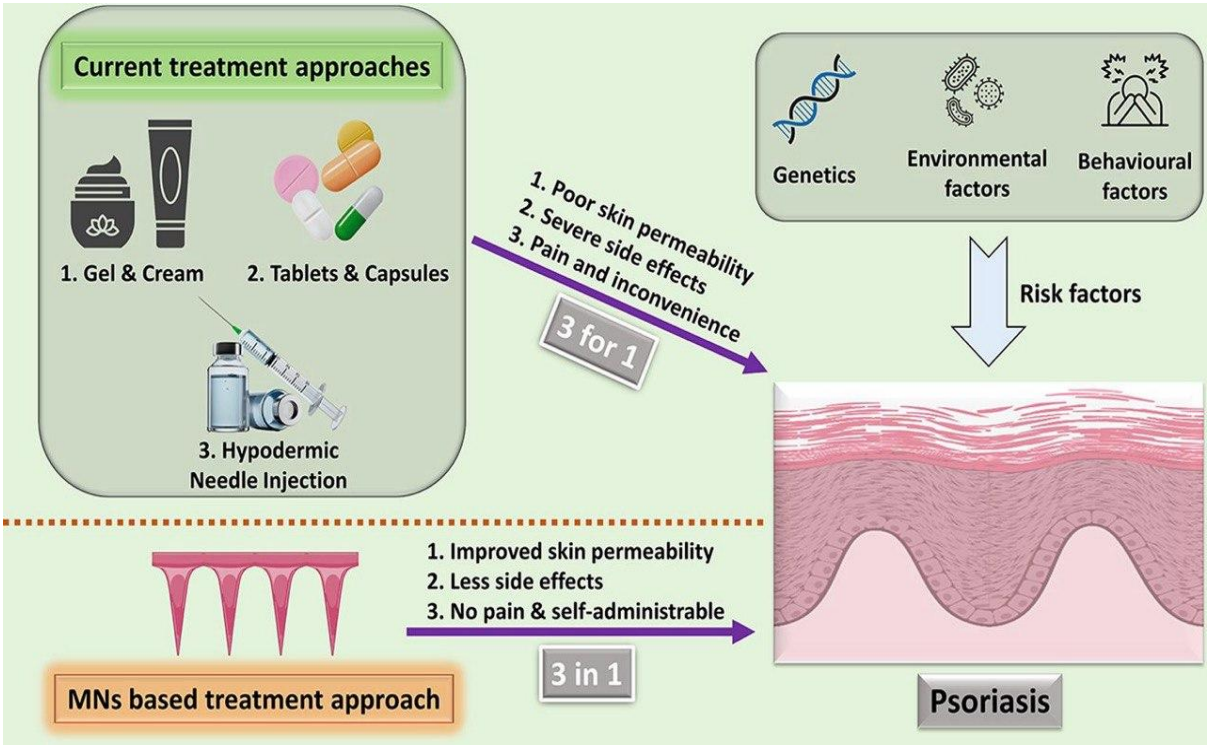

Figure 9. Microneedles - based drug delivery for the treatment of psoriasis [84]

7. New Developments in the Use of Herbal Nano-Carriers to Treat Psoriasis

Because most herbal medications are insoluble, they have a low bioavailability and increased systemic clearance, requiring frequent administration or higher dosages. Consequently, the creation of a colloidal delivery system offers phytoconstituents better permeability, decreased toxicity, increased pharmacological strength, strengthened stability, and sustained release, among other advantages. Therefore, the delivery systems of colloidal drugs containing herbal ingredients hold potential for enhancing the effects of herbal medicines and resolving issues associated with them [86]. The Mangifera indica tree is a source of mangiferin, which is extracted from its bark and leaves. After isolating it, the researchers set out to transform it into a nano-emulsion. This would improve its ability to penetrate the skin and enhance its overall effectiveness. The formulation was made using Lipoid® S75, hyaluronic acid, and polysorbate 80. The emulsion is stabilized and spread out with the help of these ingredients. The next step was to use ultrasonication to break the mixture down into tiny particles, which were then transformed into a homogenous nanosized emulsion. This nanoscale system's ability to combat inflammation

was significantly enhanced upon the addition of mangiferin. The nano-emulsion significantly decreased leukocyte infiltration and edema compared to the drug-free, empty nano-emulsion by a factor of nearly twenty. According to these findings, mangiferin can be improved in terms of efficacy and bioavailability by transforming it into a nano-emulsion [7].

8. Psoriasis preclinical and clinical assessment of advanced topical delivery systems in psoriasis.

8.1. Preclinical Research Developments

Before evaluating new medicines on humans, preclinical research on psoriasis treatment evaluates them using lab and animal models (Table 9). These studies, which often concentrate on immunological pathways like IL-17 and IL-23, help ascertain the safety, efficacy, and mechanism of action of a medication. Researchers use models such as imiquimod-induced rats or 3D human skin cultures to assess tissue response and inflammation control. At this point, the scientific foundation required to move promising medications into clinical trials is supplied [87].

Table 8. Preclinical Trial Progress of Drug Delivery Systems for Psoriasis Therapy.

Carrier	Drug	In Vitro/In Vivo Model	Outcomes
Liposome(2017)	Psoralen	Imiquimod-induced psoriatic plaque model.	Decreased psoriatic symptoms and decreased levels of TNF-α, IL-17, and IL-22 [88].
Niosomes(2016)	Tazarotene	Rat skin	Increased skin retention within the layers of skin; improved local bioavailability [89].
SLN(2014)	Betamethasone dipropionate Calcipotriol	Mouse -HaCaT cells.	-Reduced thickness of the epidermis. -A higher number of melanocytes. -Minimal skin irritation. -Improved skin tolerance. -Delayed abrupt keratinocyte growth[90].
NLC(2020)	Tacrolimus	Guinea pig	Better skin deposition and less irritation [91].
Polymeric NPs(2017)	Curcumin	Imiquimod-induced psoriatic mice	-More therapeutic impact. -A stronger capacity to penetrate the skin. -A decrease in TNF-α,

			NF-κB, and IL-6 expression [92].
Hybrid polymer-lipid NPs (PLNs)	siRNA	Imiquimod-induced psoriatic mouse model.	Created a useful approach that combines photochemical internalization and silencing gene therapy for topical psoriasis treatment [93].

8.2. Clinical Research Developments

Recent technical breakthroughs have yielded several anti-PSO pharmaceutical delivery methods that have considerable promise in laboratory settings, with some progressing to clinical trials, hence indicating their potential for PSO therapy [32]. Clinical studies of anti-PSO medication delivery systems are given in Table 10.

Table 9. Clinical Trial Progress of Drug Delivery Systems for Psoriasis Therapy.

Formulation	**Stage**	**Patient Population**	**Intervention**	**Measures of Results**
Cyclosporine- loaded liposome(2016)	Single center randomized clinical trial	Patients with mild to moderate chronic plaque PSO (N = 38)	Treated for 8 weeks	The DSS score was dropped and 41% of lesions could be totally removed [94].
MTX based Nanoemulsion (2018)	A randomized experiment	Patients with plaque PSO (N = 30)	Continuous treatment for 8 weeks	There was a notable decrease in the plaques' TES scores (thickness,erythema,scaling) [95] .
Nanoemulsion containing Rosa damascena extract in Cur-loaded vesicles (2022)	A randomized experiment	PSO Patients (N = 20)	Continuous treatment for 6 weeks	Patients' quality of life has much improved, and their erythema and scales have decreased [96].
Once-daily roflumilast 0.3% cream(2022).	Two Phase III, randomized, double-blind	plaque PSO (trial 1, n = 439; trial 2;	Treated for 8 weeks	PSO improved quickly, and more patients were successful with IGA [97].

		n = 442)		
Acitretin loaded nanostructured lipid carriers(2010)	double-blind clinical studies in psoriatic patients	PSO Patients N=18	Treated for 4 weeks	Clinical research showed that ActNLCs-loaded gel significantly improved therapeutic response and reduced local side effects [98].
liposomal and ethosomal gels containing dithranol(2020)	Randomized clinical trial conducted by Fathalla et al	Patients with plaque PSO N=20	Treated for 6 weeks	Their findings indicated that dithranol ethosomes were markedly more effective than liposomes. Their mixture demonstrated minor irritation and negligible discoloration of the skin [32].
curcumin-containing niosomes(2023)	A Pilot Randomized Controlled Trial	Five patients with mild-to-moderate psoriasis, aged between 18 and 60 years old	Treated for 4 weeks	The therapy markedly diminished erythema and exfoliation, resulting in a comprehensive enhancement. The gene expression analysis demonstrated significant decreases in IL-17, IL-23, IL-22, and TNF-α in the lesions. [99].
Use of Hyaluronic Acid-Based Dissolving Microneedle Patches(2025)	A Randomized Controlled Trial	N= 22 patients	Treated for 2 weeks	Histopathological examination showed that hyaluronic acid-based DMN patches successfully formed channels and improved drug transport [100].

9. Current and Future Developments

Problems with current psoriasis treatments include skin discoloration, burning, and insufficient drug penetration. Systemic therapies have uneven pharmacokinetics, poor absorption, and limited water solubility; topical therapy possibilities include both healthy and diseased regions. However, as this article explains, colloidal systems have been created recently for a number of medications. For currently available medications, creating a novel drug delivery system could enhance drug transport, diffusion, and targeting, perhaps leading to quicker and longer skin deposition. Additionally, these colloidal compositions might lessen the dosages and harmful side effects of current drugs, such as burning, itching, and necrosis. In the forthcoming decades, considerable study may be conducted on colloidal drug carrier-based pharmaceutical formulations as effective therapeutic agents with tailored drug release capabilities, potentially relevant for the successful treatment of many skin disorders.

Conclusions

Finally, optimizing skin permeability and drug accumulation with minimal systemic absorption are the primary goals of topical administration strategies for the treatment of psoriasis. The combination of specific medicinal components with rational delivery technologies may achieve this aim. Nanoparticles, hydrogels, microneedles, micelles, dendrimers, liposomes, nanoemulsions, and vesicles are only a few of the topical delivery modalities included in this study of PSO treatment. Through material innovation and dosage form improvement, they have shown significant improvements in penetrating the skin barrier, achieving accurate localization, extending residence time, and minimizing systemic exposure. This study lays the theoretical and technological groundwork for future PSO therapy strategies. Some of the challenges that modern topical administration approaches face include the need to synchronize the breakdown rate of drug carriers with the kinetics of drug release and the protracted bioaccumulation of carriers, which may induce immunogenicity. The manufacturing costs and scalability are both affected by the complexity of the procedures used, such as hydrogel crosslinking and constant vesicle size. Passive targeting relies on considerable permeability at the site of inflammation, putting normal tissues at risk of medication exposure. Unfortunately, macromolecular medicines are still unable to fully permeate the stratum corneum, which acts as a barrier to their penetration. The fact that PSO incorporates several pathogenic pathways further complicates achieving complete control with the current single-target therapeutic technique. Potentially, in the future, drug delivery systems will be able to detect inflammatory microenvironments by analyzing factors like pH and susceptibility to reactive oxygen species and then set off a chain reaction of drug releases. Patients with PSO may benefit from innovative, precisely administered, and safely tolerated pharmaceuticals due to comprehensive evaluations of the delivery system and technological advancements that yield safer and more effective treatment options. With the hope of finding a therapeutic solution, researchers are working to create drug delivery techniques that can treat psoriasis in several ways.

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استراتيجيات التحضير في الصدفية: رحلة من التحضيرات التقليدية إلى أنظمة توصيل الأدوية المتقدمة

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الخلاصة

الصدفية حالة جلدية مرتبطة بالجهاز المناعي تتميز بقشور جلدية حمراء سميكة وقشور ناتجة عن تكاثر سريع ومفرط للخلايا. تُستخدم الأدوية المضادة للالتهابات، والمثبطات المناعية، وأدوية أخرى كنهج علاجي رئيسي لمرض الصدفية بهدف تقليل الأعراض، وتقليل الالتهاب، وإبطاء تكاثر وانقسام خلايا الجلد. ومع ذلك، فإن هذه الأدوية عادة ما تكون لها عيوب تضع عبئًا فيزيولوجيًا ومرضيًا ثقيلًا على المرضى، مثل ضعف الاستهداف، والأمد القصير، وانخفاض الامتصاص، والآثار الجانبية السامة الخطيرة. ركز الباحثون مؤخرًا الكثير من الاهتمام على استخدام أجهزة التوصيل لإعطاء الأدوية موضعيًا للمناطق المتضررة من الجلد الصدفي. هذه الأنظمة تزيد من الفعالية الدوائية، والاستقرار، والاختراق. تُحسن هذه الأنظمة فعالية الدواء، واختراقه، واستقراره. تتيح التطورات المستمرة للعديد من تقنيات التوصيل الموضعي متعددة الوظائف مفاهيم علاجية جديدة لعلاج مرض الصدفية. في ضوء ذلك، يتم استعراض الأبحاث حول استراتيجيات توصيل متعددة في هذا المنشور. (مثل الهلام المائي، الجسيمات النانوية، الإبر الدقيقة، الميسيلات، الدندريمرات، الحويصلات الدهنية، المستحلبات النانوية، الحويصلات، إلخ) لعلاج الصدفية الموضعي ويستعرض حالتها الحالية في العلاج السريري. من المتوقع أن يدعم تقدم تقنيات العلاج الموضعي لمرض الصدفية ويكون مرجعًا لإنشاء أنظمة توصيل موضعية مبتكرة .

الكلمات المفتاحية: الصدفية، الفيزيولوجيا المرضية، النانوميديسين، التسليم الموضعي، نظام توصيل الأدوية الجديد