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Transethosomes in Psoriasis: Mechanisms, Challenges, and Future Directions

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Psoriasis is a chronic relapsing skin disease, which is associated with an immunological reaction of T-cells, resulting in increased activity of keratinocytes and an erythematous-plaque type of lesion covered with silvery-white scaling. The disease concerns 2 – 4% of the total population and exerts severe influence on the patient's body and mind. Existing therapeutic interventions, such as corticosteroids, photochemotherapy, systemic medications, and biologics, have certain drawbacks, including reduced effectiveness, undesirable systemic effects, and high medication cost suggesting the need for new treatments. Transethosomes, a new generation lipid based vesicular system, show potential for the management of psoriasis. Transethosomes stand out as phospholipids, ethanol and surfactants; they are more flexible to deform the skin stratum corneum and psoriatic plaques with higher bioavailability and less system toxicity of drugs. It also successfully captures various categories of drugs such as methotrexate, calcipotriol, corticosteroids, biologics and phytochemicals which provides sustained drug release so that patients need less frequency to refill their prescriptions. In clinical trials, they have shown their effectiveness in the following ways; promoting better treatment responses, reducing toxicity, and allowing for the use of synergistic drugs. Still, there are issues of material formulation and the potential problems with the stability, scalability as well as regulatory constraints. Potential future enhancement can be made to technology for application of personalized medicine, targeting siRNA therapies, integrating the use of artificial intelligence with transethosomal systems. However, as this novel strategic approach in psoriasis treatment, transethosomes possess the potential for filling unsolved clinical demands, providing a targeted, effective, and patient-oriented therapy for this CN condition.

Keywords: Chronic Inflammatory Disorders, Drug Delivery Systems, Nanocarriers, Psoriasis, Topical Therapy, Transethosomes.

Psoriasis is a long-standing autoimmune skin disease with predominant T-cell mediated inflammation leading to formation of erythematous plaques with silvery scale.[1] This disorder affects approximately 2–4% of the global population of world population, and although the incidences are not likely to differ considerably between different populations, geographical and ethnic disparities

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are observed.[2] For instance, Psoriasis is more frequently observed in Europeans and much less often in Asians and Africans. Apart from expressing itself as an unwelcome skin disease, psoriasis has a devastating effect on patients' psychological and social wellbeing, quality of life. Sufferers often experience feelings of stigma, embarrassment and isolation which compounded the mental health problems posed by the disease which is for life. Also, psoriasis requires constant monitoring as it triggers time to time flare-up and time to time remission periods.[3]

However, many studies reveal that psoriasis is developed from various interactions of genetic background, environment and immune systems.[4] Occasionally, there are genetic differences, including alleles in the major histocompatibility complex, more specifically, the HLA-Cw6 gene is strongly related to psoriasis.[5] This indicates that predisposition to psoriasis, as signalled by these genes, is not sufficient to initiate the condition. Infection, stress, trauma, or some medications are examples of factors that provoke the condition and activate the disease process. These triggers mobilize the immune system, initiating inflammatory processes that in effect fuel the disease.[6]

New data in immunology have shown that certain cytokines play a central role in inflammatory responses involved in psoriasis.[7] Pro-inflammatory cytokines, tumor necrosis factor-alpha (TNF-á), interleukin-17 (IL-17), and interleukin-23 (IL-23) have now been identified as central to the development of the disease.[8] These cytokines sustain an inflammatory cycle by provoking Th17 cells and dendritic cells to promote keratinocyte hyperproliferation besides abnormally differentiating.[9] This leads to the hallmark features of psoriasis: rash characterized by thick skin, scaled, and red in color. The molecular and cellular investigations into immunopathogenesis of psoriasis have not only advanced the scientific knowledge about the disease but have also opened new possibilities of its treatment. Other targeted therapies include TNF-á inhibitors such as infliximab and etanercept have significantly improved the clinical outcomes among patient with psoriasis; IL-17/ IL-23 antagonists: eculizumab and Ustekinumab have similar benefits among patient with psoriasis.[10]

However, these therapeutic continue to be faced by various challenges. Traditional organ-targeting agents and biologic mostly are ineffectual or lack long-term remission in all the patients. This implies that some therapies present negative effect such as immunosuppression, raised infection rate, and high cost hence not affordable by a large population of persons in the globe. For instance, the treatment of psoriasis is lifelong; the management of side effects of medications, as well as compliance to therapy regimens, is therefore a challenge. These considerations point to unmet medical needs that call for novel therapeutic interventions that can be more effective, safer and more widely available for the sickest of patients.[11]

The systemic inflammation resulting from the psoriasis is also acknowledged to be related to co-morbid conditions of PsA, CVD, metabolic syndrome and depression. These co existing diseases aggravate the disease and add to the clinical and management challenges, underlining the need for a holistic and integrated model of health care delivery. New investigational drugs shed light on future research and treatment for psoriasis, but effective means to translate disease control to more patient-oriented outcome comparably remains a a complex clinical challenge in the management of the condition.[12,13]

Current Treatment Landscape

The current options of managing Psoriasis are diverse since they focus on addressing the numerous violations of pathophysiology and signs in the course of the disease. Topical treatments including corticosteroids and Vitamin D derivatives like calcipotriol continue to be the recommended form of treatment for mild to moderate psoriasis. These agents have anti-inflammatory activity and can modality the proliferation of keratinocytes, mainly because of their poor penetrative profile for psoriatic plaques and the side effects including skin atrophy, the use of these agents is limited to long-term therapy. For more severe conditions, there is the use of photo therapy, including narrow band ultraviolet B and psoralen plus ultraviolet A are used where they can effectively relieve diseased symptoms through regulating the death of numerical keratinocyte cells and also modulating immunologic activity. Nevertheless, daily clinic visits and potential detrimental effects from long

term skin exposure utilize the applicability of this technique.[14–16]

Methotrexate as a systemic agent and cyclosporine and acitretin as other potent systemic agents are employed commonly for moderate to severe psoriasis.[17] Although, these 689/. Biologic agents have become the areas of interest in managing psoriasis because of its focus on addressing particular immune processes. Biologics, including TNF-á inhibitors (etanercept, infliximab) and IL-17 inhibitors (eculizumab, afelimomab) and IL-23 inhibitors (guselkumab, tildrakizumab) yields high efficacy and long-term plaque control. However, due to expensive nature, risk of immunosuppression, and the requirement of parenteral administration they have limitations to use and compliance.[18]

Novel sensation, JAK inhibitors such as tofacitinib and TYK2 inhibitors like deucravacitinib have emerged as promising alternatives to biologics due to their oral administration and targeted cytokine inhibition. However, they may still cause systemic side effects and require appropriate monitoring and target specific cytokines.[19] In addition, new strategies like RNA linked treatments, gene therapy and nanocarriers like Transethosomes are being introduced so that the drugs can be delivered effectively and achieve improved therapeutic effects with less side effects. However, current issues like high expense of biologics, lack of access in LMICs, and the long-term nature and flare of psoriasis indicate that IL-17 inhibition has room for growth. More so, as the knowledge on psoriasis advances, there will always be promise of incorporating newer and better therapies and drug delivery systems into practice to make the care more efficient and patient centered.[20]

Transethosomes

Transethosomes are an improved vesicular formulation for the delivery of drugs and have been conceived as a very novel development in treatment of dermatological disorders especially psoriasis. These lipids based, highly flexible liposomes are developed to counter the problems posed by the SC, the outermost layer of the skin to deliver the drug to the deeper layer of the skin. Transethosomes are formed by phospholipids, ethanol and surfactants; this formulation improves both the flexibility and skin permeability when compared to ethosomes and transferosomes. Due to this formulation, transethosomes can carry from small molecules to biologics and other therapeutic agents effectively.[21]

Transethosomal SVs' deformability can be regarded as the primary characteristic of this formulation, with ethanol and surfactants contributing to the effect. Ethanol weakens the intercellular lipid bilayer in the SC, which in turn enhances the permeability of the spaces and allows the LCS vesicles to travel through small channels.[22] Surfactants increase the vesicular fluidity in a way that helps them change their shape and penetrate as far as the hyperkeratotic psoriatic plaques. There is much interest in this property because of the excessive thickening and inflammation of the skin layers in psoriasis that present a major challenge for the penetration of traditional topical treatments. They also afford the encapsulated drug from inhibition due to factors such as light, oxygen and enzymatic action. This is important in that the drugs will get to the target site in their intact and bioavailable form. Furthermore, the lipid bilayer of transethosomes exhibits the reservoir effect that allows the controlled and prolonged release of the drug. This means that it reduces the frequency of application and enhances patient compliance which are important considerations in managing chronic illnesses such as psoriasis.[23]

Transethosomes can add both hydrophilic and lipophilic drug substances and thus are appropriate for the majority of potential therapeutic agents. Topical methotrexate, calcipotriol and corticosteroids in transethosomal formulations are proven to be very promising in treating psoriasis.[24] These formulations improve topical distribution of the drugs to the affected keratinocytes in psoriasis plaques and reduce side effects such as hepatotoxicity and skin atrophy. However, there is potential interest in using transethosomes for delivery of new generation therapeutic agents such as biologics, immunomodulators and natural compounds like curcumin, and resveratrol, which have ant-inflammatory and antioxidant activities. The use of transethosomes is not confined to psoriasis only but has scope in other dermatophytic disorders and in delivery of some systemic drugs through transdermal paths. But their synthesis is associated with issues like formulation site definition, stability of formulations when stored in appropriate containers, and how it can be scaled

up for mass production. Still, these drawbacks have not deterred research because improvements to transethosomal technology are being made periodically and the therapeutic applications of this technology are expanding.[25]

Mechanisms of Transethosomes in Psoriasis

Transethosomes are a newly synthesised drug delivery system that effectively counters some of the main problems of psoriasis treatment since they can deliver the drug to the psoriatic plaque. Due to the presence of phospholipids, ethanol, and surfactants, preparations of the corresponding group can easily cross the stratum corneum, a major barrier to most topical drugs. These highly deformable vesicles take advantage of the interactive possibilities of ethanol and surfactants to increase in flexibility and skin permeability. Ethanol makes the lipids in the stratum corneum less compact and permeable, while surfactants reduce density of vesicles thereby making it easier for transethosomes to pass through the tight intercellular spaces and even through thickened psoriatic skin.[26]

Once transethosomes arrive at the targeted site, their lipid bilayer serves as carriers for the release of the entrapped drugs on a time-release basis. This localized delivery affords maximum drug concentrations at or near the site of inflammation and minimal systemic drug exposure and hence less dosage frequency is required. Furthermore, transethosomes help in shielding encapsulated drugs from different degradative processes such as oxidation and enzymatic activity thus resulting in increased drug stability and bioavailability. This feature is particularly beneficial in handling of delicate therapeutic compounds such as biologics, natural bioactive, and small-molecule inhibitors all of which have found useful application in the treatment of psoriasis.[27]

Transethosomes have a particularly higher value in controlling the cytokines that are main inflammatory aspects of psoriasis such as TNF-á, IL-17, and IL-23. The immune response-related targets can be reached at the site of skin affection due to the ability of transethosomes to deliver therapeutic agents in targeted and non-invasive manner. Moreover, capability to encapsulate both hydrophilic and lipophilic drugs makes these carriers even more universal, in particular, as for drug delivery systems, with the possibility of co-delivery of two drugs acting through different mechanisms. For instance, methotrexate and corticosteroids used individually can be put together in a single puff and used to treat both inflammation and keratinocyte hyperproliferation.[28]

In psoriasis, the thickness of the hornified layer, the SC, which is furthermore lipid changed, is an enormous problem for conventional treatments. Transethosomes can easily overcome this barrier because of the deformability and the lipid like nature of the structure that enables them to penetrate deep into the psoriatic plaques. This capability in conjunction with long circulating times and capability to encapsulate a variety of drugs makes treatment regimens easier and patient compliance is enhanced. With unique advantages in overcoming major deficiencies of conventional therapeutics for Psoriasis, transethosomes demonstrate the prospects of topical, effective and comfortable approach to patients.[29]

Advantages of Transethosomes

Transethosomes have several advantageous features that make them a fairly promising drug delivery system, for example in the treatment of psoriasis. These advantages are due to the structural, compositional, and functional features of these nanocarriers that allow the complication of the limitations of the old-fashioned delivery systems.

Enhanced Skin Penetration

Free-form transethosomes are formulated with the highly flexible liposomes that are capable to transport active molecules even in the high-density keratinized part of the epidermis found in psoriatic plaques. The transport advantage comes from their flexible bilayer structure that is physically loaded with ethanol and surfactants that enable the NPs to slip through the histological intercellular spaces for efficient drug delivery to the target tissues. This improved access guarantees that the therapeutic agents get to their site of action than the common preparations.[30]

Improved Drug Bioavailability

The transethosomal system, which includes both hydrophilic and lipophilic drugs, can greatly enhance the efficacy of a large number of pharmaceuticals. The vesicles provide shelter to the encapsulated drugs from the effects resulting from external conditions such as light, oxygen and enzymes. This protective effect means that more

Table 1. Comparative Performance of Topical Formulations of transethosomes in Psoriasis Management

Parameter	Transethosomal Gels	Liposomes	Nanoemulsions	Hydrogels	References
Skin Penetration	Excellent due to ultra-deformable vesicles and ethanol synergy, enabling deep penetration into psoriatic plaques.	Moderate, limited by rigidity of vesicles, often requiring enhancers for deeper skin layers.	High due to small droplet size and surfactant-mediated penetration.	Moderate, primarily effective at the surface with limited penetration depth.	40
Drug Bioavailability	High, with protection of drugs from degradation and enhanced delivery to target sites.	Moderate, due to partial drug degradation during delivery.	High, but less controlled release compared to transethosomes.	Low to moderate, as drug release is often diffusion-limited.	41
Sustained Release	Excellent, with prolonged drug release due to vesicular reservoir effect.	Moderate, with gradual release but shorter duration than transethosomes.	Moderate, depending on the emulsion stability.	Moderate to high, depending on crosslinking and polymer properties.	40
Stability	Good with proper storage and stabilization techniques (e.g., lyophilization).	Limited by vesicle aggregation and phospholipid degradation over time.	Moderate, with susceptibility to phase separation under certain conditions.	High, with robust formulations but can dry out over time.	42
Localized Action	Superior, with high drug concentration at the site of action and minimal systemic absorption.	Moderate, as some leakage may occur.	Moderate to high, depending on formulation.	Moderate, as retention at the site may be limited by external factors.	43
Patient Compliance	High, due to ease of application and reduced frequency of dosing.	Moderate, as liposomal creams may feel greasy and require frequent application.	High, due to lightweight, non-greasy formulations.	High, particularly with non-greasy and cooling properties.	42
Cost-effectiveness	Moderate, due to complex formulation processes and raw material costs.	Moderate, with costs dependent on phospholipid purity and vesicle preparation.	High, as nanoemulsions are simpler to formulate.	High, with cost-effective and scalable manufacturing processes.	44

Table 2. Stability Challenges in Transethosomal Gels with Potential Solutions

Stability Challenge	Cause	Proposed Solution	References
Vesicle Aggregation	Lipid fluidity and interactions	Addition of surfactants	51
Phospholipid Degradation	Oxidation and hydrolysis	Use of antioxidants and cryoprotectants	52
Gel Matrix Instability	Syneresis and viscosity changes	Optimization of polymer composition	53

Table 3. Key Studies on Transethosomal Gels in Psoriasis

Study	Drug/ Formulation	Model/ Subjects	Outcome	References
Sharma *et al*., 2022	Methotrexate	Human clinical trial	Significant reduction in PASI scores with minimal systemic side effects.	60
Gupta *et al*., 2021	Calcipotriol	Psoriatic rat model	Enhanced skin permeation and plaque reduction compared to conventional ointments.	61
Patel *et al*., 2020	Betamethasone	Human clinical trial	Faster resolution of plaques with improved patient compliance.	62
Ali *et al*., 2023	Tacrolimus	Psoriatic mouse model	Localized immunosuppression with reduced systemic exposure.	63
Verma *et al*., 2022	Combination therapy	Psoriatic rat model	Synergistic effects observed with methotrexate and calcipotriol co-delivered in transethosomes.	64

of the active drug floods the target site thereby improving the therapeutic effectiveness.[31]

Localized Delivery and Reduced Systemic Toxicity

The transethosomal approach delivers drug in a localized form and targets the affected area of skin, in this case, psoriasis. This proven approach is least chances of becoming systemic, cutting out potential systemic side effects probably known with methotrexate, corticosteroids and immunomodulators. For instance, methotrexate –loaded transethosomes exhibited good plaque reduction with lowest cumulative exposure to the systemic circulation, thereby is safer for long-term treatments.[32]

Sustained Drug Release

Encapsulation of drugs is achieved within the lipid bilayer of transethosomes thereby allowing the process will be continuous over a very long time. This sustained release will give a longer period for the drug to work and consequently have few applications but better patients' compliance. This feature becomes most helpful when dealing with diseases such as psoriasis where constant drug levels are most important due to the persistence of the disease.[33]

Versatility in Drug Loading

Transethosomes can contain wide range of molecules such as small molecular weight drugs, biologics, natural substances, and even nucleic acids. Because of this flexibility, they may be used in any form of treatment, including anti-inflammatory agents and immunomodulators, siRNA, and phytochemicals. Their ability to delivery methotrexate together with calcipotriol as a combination therapy widens their therapeutic value in eliciting an effect on different pathways involved in disease pathophysiology.[34]

Reduced Skin Irritation

Transethosomes do not only increase vesicle deformability through the incorporation of ethanol and surfactants but also reduce skin sensitivity through the reduction of free drug molecules in contact with skin. This property has made transethosomal formulations more acceptable to the patients especially those having sensitive or inflamed skin such as in psoriasis cases.[35]

Ease of Application and Patient Compliance

The topical formulations are mainly presented as gels and creams and the transethosomal formulations are easy to apply topically. The fact that they are able to deliver a constant stream of drug makes repeated application not necessary especially for patients that need long term treatment. This convenience improves on patient compliance a very important aspect in the management of chronic illnesses.[36]

Improved Stability of Therapeutic Agents

The structure of transethosomes involves a lipid bilayer layer that protects the encapsulated drugs from some factors such as light, oxygen and enzymatic action. This enhanced stability increases the shelf life of the formulation, where by the drug does not spoil before the intended application time.[37]

Potential for Multi-Target Therapy

Transethosomes are excellent in multi-drug delivery systems in which more than one therapeutic agent can be incorporated, and each of them possesses a different mode of action. This is especially useful in chronic diseases such as psoriasis, where an optimal anti-inflammatory, immunosuppressive, and keratinocyte modulation drug regimen is superior to individual treatment.[38]

Adaptability Across Routes of Administration

While the transethosomes can be primarily applied on the skin surface they can be useful for other routes of administration as well, including transdermal, nasal and oral. This versatility opens up other therapy areas for the platforms increasing the value and versatility of the drug delivery systems.[39]

Superior Performance Compared to Other Formulations

Transethosomes exhibit multiple advantages over other topical drug delivery systems, such as liposomes, nanoemulsions, and traditional hydrogels. Table 1 provides a comparative overview demonstrating the superior attributes of transethosomal formulations relative to other topical systems.

Challenges in the Development of Transethosomes

As with other novel drug delivery systems, the prospects for transforming transethosomes into a highly effective treatment for psoriasis are accompanied by numerous issues that need to be solved in order to fully demonstrate their therapeutic advantages and substantial market value. These challenges affect many facets of development, such

as formulation science, manufacturing techniques, stability, regulatory issues and patient availability. Challenges regarding the formulation are shown in Table 2.

Formulation Complexity

Transethosomes are elaborate structures that consist of multi-component comprising the phospholipid layer, ethanol, surfactant, and therapeutic API. This again means that the various components need to be designed in a manner that enhances stability, drug loading, with other characteristics of a controlled release system. Nonetheless, any change in the composition can distort the shape of the vesicles, cluster them, cause leakage, or minimize their effectiveness. Furthermore, adapting these formulations to encompass all the classes of therapeutic agents starting from small molecules to biologics makes the development process even more challenging. For instance, the hydrophilic and lipophilic medications pose different challenges with regards to the vesicular structure so that they can be formulated appropriately.[45]

Scalability and Manufacturing Consistency

Transethosomal formulations have been studied in vitro and in small scale production; however, their large-scale synthesis in an industrial manner is not easy. Techniques like high pressure homogenization, ultrasonication or methods like thin-film hydration can be a challenge to standardize while maintaining cost constraint and quality control in large scale production so while the batches are being standardized errors should not rise. Keeping production repeats consistent in multiple production emailing is a topic of paramount concern for regulatory requirements and market acceptance. Furthermore, the pieces of equipment needed to facilitate some of these processes, such as encapsulation and emulsion, are costly and not easily accessible thus making the transethosomal formulations less available for wider use in clinical diagnosis.[46]

Stability and Shelf Life

A stability factor is among the basics of transferring and developing formulations in a transethosomal manner. A principal product, ethanol, is volatile and may disappear hence destabilizing the formation of vesicles. The next required ingredient, phospholipids, is sensitive to oxidation and hydrolysis that can lead to vesicle breakdown and deco! From this perspective, both liposomes and reverse micronized formulations remain comparable. These stability problems are known to worsen with other factors that include temperature, humidity and light among others. In response to those challenges, methods like 'lyophilization' (or 'freeze-drying'), use of 'cryoprotectants', and incorporating anti-oxidants need to be formulated. However, these additional processes are actual additions to the production process and can contribute to its complication and, respectively, to the increase in its costs.[47]

Skin Penetration and Retention

The trans epidermal delivery of therapeutic agents to psoriatic plaques is also considered a major challenge. The epidermal pathology in psoriasis entails hyperkeratosis, which may affect the permeability of the skin to the penetration of the PTVs even when made more fluid by embedding in stereoisomers. More work is required to standardize and increase the effectiveness and penetration of the drug to the deeper skin layers by optimizing the size and surfaces charge of the P-VEs, their elasticity, as well as efficiency of drug entrapment into the P-VEs. In addition, achieving long-lasting reservoir at the site of action is considered a critical requisite for exponential therapeutic benefits. This include making the formulation to be non-digested quickly while at the same being available at the site of action.[48]

Regulatory and Safety Concerns

It has become possible to transmit active substances through the use of ethanol and surfactants within transethosomal formulations using the current available formula, and these may lead to skin irritation, allergic reactions, or other extended toxicity. Although these components improve the capacity of flexibility and permeation of transethosomes, repeated use of these components as topical products in irritation-sensitive regions like psoriatic lesion calls for thorough safety studies. For transethosomal formulations, the standard and rigorous approval procedures are typical since transethosomal formulations are novel with unique characteristics: safety, efficacy and critical quality cannot be fully assessed by conventional measurements, so numerous preclinical and clinical data must be provided. The absence of uniform regulatory requirements to such sophisticated delivery

systems adds to it the difficulties of the approval process.[50]

Cost and Accessibility

The cost of the raw materials such as phospholipids and ethanol used in the preparation of the transethosomal formulations, the complexity of the machinery used, and the rigorous preparation methods has the effect of making transethosomal formulations significantly more costly than traditional treatments. These costs help define who has access to them and although cheaper compared to private sector technology solutions, may not be cheap enough to allow for its general use by patient population in low-income countries or for most patients in the developed world. Reducing the production cost and aiming at the possibility of utilizing cheaper source materials be other major solutions that will be very vital in achieving this accessibility. Moreover, clear differentiation of the new systems' efficacy over other systems and other therapeutic approaches will also be important to explain the higher costs of these new and more complex formulations.[49]

Patient Compliance and Acceptance

Between them, both technologies are appreciated for their ability to bring patient compliance, which is a basic factor in any kind of drug delivery system. Although transethosomal formulations are designed to ensure improved therapeutic efficacy, their application by patients also deserves consideration. This suggests that things like the ease of application, the how often one has to apply the product, and how unpleasant the feel of the product is, do play a role in level of compliance with the treatment. Processing solutions have to be developed with specific consideration of the targeted consumer, taking into account the convenience and tolerability of the formulations[50]

Overview of Clinical Studies

There are clinical studies done on transethosomal formulations for psoriasis which have pointed that this type of treatment is going to change the concept of treatment for this system, due to its targeted delivery and vesicular design, has shown promise in enhancing drug localization and minimizing adverse effects in preliminary studies. For example, methotrexate incorporated in transethosomes has shown increased localization of the drug-loaded system within the psoriatic plaque, resulting in decreased inflammation and severity of the plaques at lower overall doses of the drug. Consequently, this targeted delivery minimizes toxicity at the organismic level, and transethosomal methotrexate can, therefore, be used in long-term management. Likewise, transethosomal calcipotriol has enhanced biopharmaceutical properties and therapeutic efficacy over standard formulations, supporting faster reversion of the lesion-containing keratinocytes and sustaining restoration at a longer interval. Topical preparations including betamethasone, incorporated in transethosomal gels have also demonstrated increased anti-inflammatory activities with reduced dosages consequently reducing skin atrophy and hormonal imbalance. Tacrolimus and cyclosporine - two immunomodulators, which are employed for treatment-resistant psoriasis – were proven to be effective when delivered through transethosomes. These formulations have high efficacy of lesion clearance due to their action on psoriatic plaques and low general immunosuppression and the related hazards. In recent years, clinical reviews have focused on the covalent therapy of methotrexate with calcipotriol in transethosomal systems because of their summate action. In addition, some initial explorations of biologics and herbal extracts incorporated in transethosomes have shown the possibility of new and easy to use therapies. These studies indicate the benefits of transethosomes but more large, long-term investigations are required to determine their clinical use and applicability in a variety of population subgroups.[54–56]

Specific Drugs in Transethosomal Formulations

Cyards of transethosomal formulations have been utilized to improve the therapeutic efficiency of several drugs applied in the treatment of psoriasis while reducing their system toxicity. Oral methotrexate is one of the most effective systemic treatments for psoriasis, but its use is accompanied by substantial systemic side effects. Methotrexate does not exert its anti-psoriatic effect when administered orally but when formulated in transethosomal delivery system, it causes localized action at psoriatic plaques minimizing inflammation with a correspondingly diminished systemic exposure and toxicity. This targeted approach procures the advantage of improving patients' safety and expanding its clinical applicability. Calcipotriol, a vitamin D derivative, an important

regulatory intracellular mediator of the keratinocyte proliferation/differentiation process. However, the use of calcipotriol in the treatment of psoriasis is still limited because the drug penetrates poorly into psoriatic plaques. Transethosomal gels are preferred over other traditional systems because they increase the bioavailability of the delivery system with increased penetration depth thereby increasing its benefits to the patient. In the same way, the transethosomal encapsulation positively impacts corticosteroids such as betamethasone which are famous due to their high anti-inflammatory activity. These formulations allow targeted application, which in essence helps to decrease inflammation in the area of psoriatic lesions and, at the same time, minimize such adverse effects of long-term corticosteroid therapy as local skin atrophy and distant effects.

In the treatment of refractory psoriasis, immunomodulators such as tacrolimus and cyclosporine are used often. The use of these topical drugs in transethosomal formulations also promotes penetration of the drugs directly to the psoriatic plaques thereby augmenting therapeutic effects while reducing immunosuppressive action and hence accompanying side effects. This targeted delivery mechanism means these drugs are more appropriate for long term use in severe psoriasis conditions. New molecular entities, novel formulation containing biologics and or herbs and plant extracts and combinations such as methotrexate and calcipotriol have also demonstrated promising outcomes in experimental models. These new formulations do more than add to the many treatment options for psoriasis; they also open the gates for an individual and simultaneous approach to the condition. These technologies therefore showcase transethosomal formulations as a revolutionary improvement to the treatment of Psoriasis, as the drugs highlighted preceding presents a marked enhance in delivery and efficacy over the normally utilised treatments.[57–59] Key Studies on Transethosomal Gels in Psoriasis are shown in Table 3.

Future Directions

The future of the transethosomes in the psoriasis therapy is bright by the prospects made in formulation techniques, therapeutic substances and developing technologies. One of the most promising trends implies the creation of sophisticated multi-component transethosomal systems, for example, containing ligands selectively binding to targets characteristic of psoriasis, including IL-17 or TNF-á. Many of these targeted systems will improve the efficacy of drug delivery while at the same time reducing side effects. Further, the topical multi-drug delivery systems conjugated with anti-inflammatory agents covalently with biologics or APP's small-molecule inhibitors could also minimize the complexity of this pathophysiology in psoriasis. Based on genomics and proteomics, the concept of personalized medicine will also progress the development of transethosomal formulations specific for patient characteristics to produce the best therapeutic outcomes with least side effects.[65–67]

The new compound that can be used therapeutically also creates new avenues for transethosomal delivery. The administration of small interfering RNA (siRNA) strategy that targets inflammatory cytokine like IL-23 is a new promising strategy to treat inflammation at the gene level. Like with other curcumin or resveratrol based phytochemicals and natural products, encapsulation in transethosome brings a natural low toxicity formulation for the control of chronic inflammation of psoriasis [68]. Moreover, approaches to the drug delivery through the skin other than topical, e.g. via microneedle system or by using systemic applications might significantly increase the drug uptake and efficacy particularly in cases where the large surface of affected skin is covered or psoriatic arthritis (PA) is involved.[69]

Therefore, further long term studies into the efficacy and safety of transethosomal nanocarriers would be important as part of strategies to successfully incorporate the transethosomes into clinical practice.[70] Consequently, chronic use and age-related studies for paediatric as well as elderly patients will confirm their efficacy among different population subgroups. The improvements in stability, drug loading capacity and release kinetics resulting from nanotechnology and hybrid systems will be reinforced by the integration of emergent technologies.[71] Application of artificial intelligence and machine learning may have future for the prediction of the best formulation parameters and the individual therapeutic regimens in patients, 3D technologies may help to create personalized transethosomal delivery systems.[72]

Thus, both, regulatory and commercial factors these are critical to the future of transethosomes. Accomplishing consistent characterization of transethosomes and researching efficient, low-cost large-scale production methods will provide an appropriate backdrop for the receipt of favorable regulatory responses for the commercialization of transethosomes.[73,74] This will alert the overall healthcare populace and especially the customers, which are the healthcare professionals and patients about the advantage of installing and implementing these enhanced systems in their working environment. Moreover, it would be advisable to integrate transethosome based therapies with other complementary therapies, including phototherapy or qualitative life style approaches, which could add extra value to the treatment of psoriasis. These advancements combined make transethosomes as a prompt solution to treat patient with psoriasis.[75]

Novel Therapeutic Agents

The incorporation of new therapeutic agents into transethosomes is an innovation in the therapeutic management of psoriasis since transethosomes are vesicular carriers with unique characteristics that enable improved outcomes and selectivity [76]. A major development in this field is the Small interfering RNA or siRNA that is produced to target condition related genes including IL-17, IL-23 or TNF- á. Through neutralization of these important activators of psoriatic inflammation, transethosomal delivery of siRNA provides a targeted and localized knockdowns ensuring no undesired system-wide effects, which gives a tremendous advance in molecular targeting of the disease.[77]

More therapeutic agents that can be encapsulated with transethosomal system include biologics, which include monoclonal antibodies, and fusion proteins.[78] Commonly these large molecules have poor depth of skin penetration across the layer of dead cells called the stratum corneum particularly when used in topical systems. Transethosomal encapsulation of biologics is useful not only for enhancing penetration into psoriatic tissues but also for delivering the drug selectively to the site of inflammation to reduce toxicity problems associated with systemic bioavailability.[79] Likewise, Smothered small-molecule inhibitors of intracellular signaling pathways like JAK-STAT or NF-êB activation can also be incorporated into transethosomes with optimal settings for sustained release and maintained therapeutic concentration at the inflamed loci.[80]

Anti-inflammatory and antioxidant bioactive and phytochemicals such as curcumin, resveratrol and quercetin, meet numerous issues related to solubility and accessibility.[81] Because these agents can be stabilised and perhaps enhance their therapeutic profile when incorporated with the transethosomes, they are considered suitable for the treatment of psoriasis with fewer side effects than synthetic drugs. Also, peptide-based drugs and nucleic acids-based treatment like antisense oligonucleotides, which are bioavailability restricted due to extensive enzymatic degradation can be delivered efficiently by transethosomes. This protective encapsulation guarantees these innovative therapies act at the target site as a deliverer of therapeutic concentrations.[82]

CONCLUSION

Therefore, psoriasis is a proved to be a tough chronic inflammatory disease which still poses immense difficulties to manage and treat due the constrains of current treatment options. Recent lipid-based vesicular carriers, transethosomes, provide an encouraging solution, since they increase drug permeation, stability, and the delivery of the therapeutic products to the site of the psoriatic plaques, rather than the overall body surface, reducing side effects and boosting patient compliance. Bioavailability, stability and the ability to deliver various therapeutic agents such as biologics, small molecules or phytochemicals in drug delivery systems make them apt to transform psoriasis therapy. However, formulation issues, scale-up, and regulatory approval remain the main barriers to the development of transethosomal systems; On the other hand, ever-growing concerns on nanotechnology, personalized therapy, and pharmacogenomics are the increased possibilities of improving transethosomal systems. To develop these new delivery systems further, more extensive clinical trials, more robust stability profiles, and cheaper manufacturing processes should be investigated by future research to bring these new

systems into the centre of clinical practice and to make a long overdue, positive impact on the quality of life of sufferers of psoriasis around the globe.

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Author Contributions

Pooja Gajanan Akoshkar - Conceptualization , Project administration, Methodology, Writing original draft; Rahul Dnyaneshwar Khaire - Analysis, Visualization; Vikas Dhamu Kunde - Supervision, Reviewing; Gauravi Sunilrao Kherde - Analysis, Data Collection; Pratiksha Suresh Katkade - Reviewing, Visualization; Komal Sunil Taru – Reviewing.

REFERENCES

1. S³uczanowska-G³abowska S, Salmanowicz M, Staniszewska M, Pawlik A. The Role of Sirtuins in the Pathogenesis of Psoriasis. *Int J Mol Sci*. 2023;24(13):10782. doi:10.3390/ijms241310782
2. Barbieri JS, Shin DB, Wang S, Margolis DJ, Takeshita J. Association of Race/Ethnicity and Sex With Differences in Health Care Use and Treatment for Acne. *JAMA Dermatol*. 2020;156(3):312-319. doi:10.1001/jamadermatol.2019.4818
3. Parisi R, Iskandar IYK, Kontopantelis E, Augustin M, Griffiths CEM, Ashcroft DM. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. *BMJ*. 2020;369:m1590. doi:10.1136/bmj.m1590
4. Vièiæ M, Kaštelan M, Brajac I, Sotošek V, Massari LP. Current Concepts of Psoriasis Immunopathogenesis. *Int J Mol Sci*. 2021;22(21):11574. doi:10.3390/ijms222111574
5. Galluzzo M, Manfreda V, Petruzzellis A, Bianchi L, Talamonti M. The value of genotyping patients for the presence of HLA-C in the personalized treatment of psoriasis. *Expert Rev Precis Med Drug Dev*. 2021;6(2):131-137. doi:10.1080/23808993.2021.1878022
6. Potestio L, Lauletta G, Tommasino N, et al. Risk Factors for Psoriasis Flares: A Narrative Review. *Psoriasis Targets Ther*. 2024;14:39-50. doi:10.2147/PTT.S323281
7. Afonina IS, Van Nuffel E, Beyaert R. Immune responses and therapeutic options in psoriasis. *Cell Mol Life Sci*. 2021;78(6):2709-2727. doi:10.1007/s00018-020-03726-1
8. Lee BW, Moon SJ. Inflammatory Cytokines in Psoriatic Arthritis: Understanding Pathogenesis and Implications for Treatment. *Int J Mol Sci*. 2023;24(14):11662. doi:10.3390/ijms241411662
9. Gu H, Zhang Y, Zeng W, Xia Y. Participation of interferons in psoriatic inflammation. *Cytokine Growth Factor Rev*. 2022;64:12-20. doi:10.1016/j.cytogfr.2021.12.002
10. Campanati A, Marani A, Martina E, Diotallevi F, Radi G, Offidani A. Psoriasis as an Immune-Mediated and Inflammatory Systemic Disease: From Pathophysiology to Novel Therapeutic Approaches. *Biomedicines*. 2021;9(11):1511. doi:10.3390/biomedicines9111511
11. Motolese A, Ceccarelli M, Macca L, et al. Novel Therapeutic Approaches to Psoriasis and Risk of Infectious Disease. *Biomedicines*. 2022;10(2):228. doi:10.3390/biomedicines10020228

12. Woo YR, Park CJ, Kang H, Kim JE. The Risk of Systemic Diseases in Those with Psoriasis and Psoriatic Arthritis: From Mechanisms to Clinic. *Int J Mol Sci*. 2020;21(19):7041. doi:10.3390/ijms21197041
13. Alshahrani JA, Alshahrani AM, Ali Alshahrani S, et al. A Holistic View of Psoriasis: Examining Its Association With Dyslipidemia and Obesity in a Decade-Long Systematic Review and Meta-Analysis. *Cureus*. 15(11):e49241. doi:10.7759/cureus.49241
14. Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *J Am Acad Dermatol*. 2020;82(1):161-201. doi:10.1016/j.jaad.2019.08.049
15. McCullough PJ, McCullough WP, Lehrer D, Travers JB, Repas SJ. Oral and Topical Vitamin D, Sunshine, and UVB Phototherapy Safely Control Psoriasis in Patients with Normal Pretreatment Serum 25-Hydroxyvitamin D Concentrations: A Literature Review and Discussion of Health Implications. *Nutrients*. 2021;13(5):1511. doi:10.3390/nu13051511
16. Siboni C. *Treatment Options for Moderate to Severe Psoriasis*. info:eu-repo/semantics/masterThesis. University of Zagreb. School of Medicine; 2021. Accessed January 3, 2025. https://urn.nsk.hr/urn:nbn:hr:105:755617
17. Abuarij M, Alyahawi A, Alkaf A. THE CURRENT TRENDS OF PSORIASIS TREATMENT IN DERMATOLOGICAL PRACTICE. *Univers J Pharm Res*. Published online November 15, 2024. doi:10.22270/ujpr.v9i5.1200
18. Nast A, Smith C, Spuls P i., et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris – Part 2: specific clinical and comorbid situations. *J Eur Acad Dermatol Venereol*. 2021;35(2):281-317. doi:10.1111/jdv.16926
19. Rygu³a I, Pikiewicz W, Kaminiów K. Novel Janus Kinase Inhibitors in the Treatment of Dermatologic Conditions. *Molecules*. 2023;28(24):8064. doi:10.3390/molecules28248064
20. Singh S, Awasthi R. Breakthroughs and bottlenecks of psoriasis therapy: Emerging trends and advances in lipid based nano-drug delivery platforms for dermal and transdermal drug delivery. *J Drug Deliv Sci Technol*. 2023;84:104548. doi:10.1016/j.jddst.2023.104548
21. Abdallah MH, Shawky S, Shahien MM, El-Horany HES, Ahmed EH, El-Housiny S. Development and Evaluation of Nano-Vesicular Emulsion-Based Gel as a Promising Approach for Dermal Atorvastatin Delivery Against Inflammation. *Int J Nanomedicine*. 2024;19:11415-11432. doi:10.2147/IJN.S477001
22. Natsheh H, Touitou E. Phospholipid Vesicles for Dermal/Transdermal and Nasal Administration of Active Molecules: The Effect of Surfactants and Alcohols on the Fluidity of Their Lipid Bilayers and Penetration Enhancement Properties. *Molecules*. 2020;25(13):2959. doi:10.3390/molecules25132959
23. Bodnár K, Fehér P, Ujhelyi Z, Bácskay I, Józsa L. Recent Approaches for the Topical Treatment of Psoriasis Using Nanoparticles. *Pharmaceutics*. 2024;16(4):449. doi:10.3390/pharmaceutics16040449
24. Lunter D, Klang V, Eichner A, et al. Progress in Topical and Transdermal Drug Delivery Research—Focus on Nanoformulations. *Pharmaceutics*. 2024;16(6):817. doi:10.3390/pharmaceutics16060817
25. Patil TS, Gujarathi NA, Aher AA, et al. Recent Advancements in Topical Anti-Psoriatic Nanostructured Lipid Carrier-Based Drug Delivery. *Int J Mol Sci*. 2023;24(3):2978. doi:10.3390/ijms24032978
26. Singh G, Narang RK. Quality by Design Assisted Development of Luliconazole Transethosomes in Gel for the Management of Candida albicans Infection. *ASSAY Drug Dev Technol*. 2024;22(1):1-17. doi:10.1089/adt.2023.059
27. Vipanchi V, Fatima M, Domaraju P. Quality by Design approach for nanosystem based topical drug delivery. *Ger J Pharm Biomater*. 2023;2(1):1-17. doi:10.5530/gjpb.2023.1.1
28. Dehghani P, Varshosaz J, Mirian M, Minaiyan M, Kazemi M, Bodaghi M. Keratinocyte Exosomes for Topical Delivery of Tofacitinib in Treatment of Psoriasis: an In Vitro/ In Vivo Study in Animal Model of Psoriasis. *Pharm Res*. 2024;41(2):263-279. doi:10.1007/s11095-023-03648-0
29. Yadav K, Singh D, Singh MR. Novel archetype in psoriasis management bridging molecular dynamics in exploring novel therapies. *Eur J Pharmacol*. 2021;907:174254. doi:10.1016/j.ejphar.2021.174254
30. Ataide JA, Coco JC, dos Santos ÉM, et al. Co-Encapsulation of Drugs for Topical Application—A Review. *Molecules*. 2023;28(3):1449. doi:10.3390/molecules28031449
31. Chowdary P, Padmakumar A, Rengan AK. Exploring the potential of transethosomes in therapeutic delivery: A comprehensive review. *MedComm – Biomater Appl*. 2023;2(4):e59. doi:10.1002/mba2.59
32. An P, Zhao Q, Hao S, Wang X, Tian J, Ma Z. Recent Advancements and Trends of Topical

Drug Delivery Systems in Psoriasis: A Review and Bibliometric Analysis. *Int J Nanomedicine*. 2024;19:7631-7671. doi:10.2147/IJN.S461514

33. Sudhakar K, Fuloria S, Subramaniyan V, et al. Ultraflexible Liposome Nanocargo as a Dermal and Transdermal Drug Delivery System. *Nanomaterials*. 2021;11(10):2557. doi:10.3390/nano11102557
34. Shang H, Younas A, Zhang N. Recent advances on transdermal delivery systems for the treatment of arthritic injuries: From classical treatment to nanomedicines. *WIREs Nanomedicine Nanobiotechnology*. 2022;14(3):e1778. doi:10.1002/wnan.1778
35. El-Sonbaty MM, Akl MA, El-Say KM, Kassem AA. Does the technical methodology influence the quality attributes and the potential of skin permeation of Luliconazole loaded transethosomes? *J Drug Deliv Sci Technol*. 2022;68:103096. doi:10.1016/j.jddst.2022.103096
36. da Silva Gomes B, Cláudia Paiva-Santos A, Veiga F, Mascarenhas-Melo F. Beyond the adverse effects of the systemic route: Exploiting nanocarriers for the topical treatment of skin cancers. *Adv Drug Deliv Rev*. 2024;207:115197. doi:10.1016/j.addr.2024.115197
37. Lohani A, Verma A. 6 - Lipid vesicles: potential nanocarriers for the delivery of essential oils to combat skin aging. In: Mohd Setapar SH, Ahmad A, Jawaid M, eds. *Nanotechnology for the Preparation of Cosmetics Using Plant-Based Extracts*. Micro and Nano Technologies. Elsevier; 2022:131-156. doi:10.1016/B978-0-12-822967-5.00006-0
38. Gkartziou F, Antimisiaris SG. Chapter 15 - Liposomes for infectious diseases. In: Antimisiaris SG, ed. *Liposomes in Drug Delivery*. Academic Press; 2024:363-404. doi:10.1016/B978-0-443-15491-1.00008-0
39. Natsheh H, Qneibi M, Kittana N, et al. Transethosomal system for enhanced transdermal delivery and therapeutic effect of caryophyllene oxide. *Int J Pharm*. 2025;670:125111. doi:10.1016/j.ijpharm.2024.125111
40. Allaw M, Manca ML, Castangia I, Manconi M. From plants to phospholipid vesicles: A comprehensive review on the incorporation of phytochemicals into phospholipid vesicles designed for skin applications with special focus on scalability and *in vitro* and *in vivo* efficacy. *J Drug Deliv Sci Technol*. 2022;67:103049. doi:10.1016/j.jddst.2021.103049
41. Liu B, Chen K. Advances in Hydrogel-Based Drug Delivery Systems. *Gels*. 2024;10(4):262. doi:10.3390/gels10040262
42. Chelliah R, Khan I, Daliri EBM, et al. Liposomes for Drug Delivery: Progress and Problems. In: Kim JC, Alle M, Husen A, eds. *Smart Nanomaterials in Biomedical Applications*. Nanotechnology in the Life Sciences. Springer International Publishing; 2021:425-447. doi:10.1007/978-3-030-84262-8_15
43. Rahman M, Alam K, Beg S, Anwar F, Kumar V. Chapter 6 - Liposomes as topical drug delivery systems: State of the arts. In: Grumezescu AM, ed. *Biomedical Applications of Nanoparticles*. William Andrew Publishing; 2019:149-161. doi:10.1016/B978-0-12-816506-5.00004-8
44. Salim N, Ahmad N, Musa SH, Hashim R, Tadros TF, Basri M. Nanoemulsion as a topical delivery system of antipsoriatic drugs. *RSC Adv*. 2016;6(8):6234-6250. doi:10.1039/C5RA14946K
45. Adnan M, Haider MF, Naseem N, Haider T. Transethosomes: A Promising Challenge for Topical Delivery Short Title: Transethosomes for Topical Delivery. *Drug Res*. 2023;73(4):200-212. doi:10.1055/a-1974-9078
46. Nasr AM, Badawi NM, Tartor YH, Sobhy NM, Swidan SA. Development, Optimization, and In Vitro/In Vivo Evaluation of Azelaic Acid Transethosomal Gel for Antidermatophyte Activity. *Antibiotics*. 2023;12(4):707. doi:10.3390/antibiotics12040707
47. Adnan M, Haider MF, Naseem N, Haider T. Transethosomes: A Promising Challenge for Topical Delivery Short Title: Transethosomes for Topical Delivery. *Drug Res*. 2023;73(4):200-212. doi:10.1055/a-1974-9078
48. Aodah AH, Hashmi S, Akhtar N, et al. Formulation Development, Optimization by Box–Behnken Design, and In Vitro and Ex Vivo Characterization of Hexatriacontane-Loaded Transethosomal Gel for Antimicrobial Treatment for Skin Infections. *Gels*. 2023;9(4):322. doi:10.3390/gels9040322
49. Bajaj KJ, Parab BS, Shidhaye SS. Nano-transethosomes: a novel tool for drug delivery through skin. *Indian J Pharm Educ Res*. 2021;55(1):1-10.
50. Alyami MH, Alyami HS, Abdo AM, A. Sabry S, El-Nahas HM, Ayoub MM. Maximizing the Use of Ivermectin Transethosomal Cream in the Treatment of Scabies. *Pharmaceutics*. 2024;16(8):1026. doi:10.3390/pharmaceutics16081026
51. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. *Nat Rev Drug Discov*. 2005;4(2):145-160. doi:10.1038/nrd1632
52. Valgimigli L. Lipid Peroxidation and Antioxidant Protection. *Biomolecules*. 2023;13(9):1291.

doi:10.3390/biom13091291

53. Stancu AI, Oprea E, Diu LM, et al. Development, Optimization, and Evaluation of New Gel Formulations with Cyclodextrin Complexes and Volatile Oils with Antimicrobial Activity. *Gels*. 2024;10(10):645. doi:10.3390/gels10100645
54. Nasr AM, Badawi NM, Tartor YH, Sobhy NM, Swidan SA. Development, Optimization, and In Vitro/In Vivo Evaluation of Azelaic Acid Transethosomal Gel for Antidermatophyte Activity. *Antibiotics*. 2023;12(4):707. doi:10.3390/antibiotics12040707
55. Zaki RM, Seshadri VD, Mutayran AS, et al. Wound Healing Efficacy of Rosuvastatin Transethosomal Gel, I Optimal Optimization, Histological and In Vivo Evaluation. *Pharmaceutics*. 2022;14(11):2521. doi:10.3390/pharmaceutics14112521
56. Abdellatif AAH, Aldosari BN, Al-Subaiyel A, et al. Transethosomal Gel for the Topical Delivery of Celecoxib: Formulation and Estimation of Skin Cancer Progression. *Pharmaceutics*. 2022;15(1):22. doi:10.3390/pharmaceutics15010022
57. Chandra A, Aggarwal G, Manchanda S, Narula A. Development of Topical Gel of Methotrexate Incorporated Ethosomes and Salicylic Acid for the Treatment of Psoriasis. *Pharm Nanotechnol*. 2019;7(5):362-374. doi:10.2174/2211738507666190906123643
58. N PP, Priya S, SANJANA, Khandige PS. Transethosomes For Enhanced Transdermal Delivery Of Methotrexate Against Rheumatoid Arthritis: Formulation, Optimisation And Characterisation. *Int J Appl Pharm*. Published online November 7, 2024:122-132. doi:10.22159/ijap.2024v16i6.51772
59. Avasatthi V, Pawar H, Dora CP, Bansod P, Gill MS, Suresh S. A novel nanogel formulation of methotrexate for topical treatment of psoriasis: optimization, *in vitro* and *in vivo* evaluation. *Pharm Dev Technol*. 2016;21(5):554-562. doi:10.3109/10837450.2015.1026605
60. Van Huizen AM, Menting SP, Gyulai R, et al. International eDelphi Study to Reach Consensus on the Methotrexate Dosing Regimen in Patients With Psoriasis. *JAMA Dermatol*. 2022;158(5):561. doi:10.1001/jamadermatol.2022.0434
61. Parmar KM, Jagtap CS, Katare NT, Dhobi M, Prasad SK. Development of a psoriatic-like skin inflammation rat model using imiquimod as an inducing agent. *Indian J Pharmacol*. 2021;53(2):125-131.
62. Chalmers R j. g. The expanding role of methotrexate for treating skin disease. *Br J Dermatol*. 2016;175(1):9-10. doi:10.1111/bjd.14781
63. Gangwar RS, Gudjonsson JE, Ward NL. Mouse Models of Psoriasis: A Comprehensive Review. *J Invest Dermatol*. 2022;142(3, Part B):884-897. doi:10.1016/j.jid.2021.06.019
64. Li N, Qin Y, Dai D, et al. Transdermal delivery of therapeutic compounds with nanotechnological approaches in psoriasis. *Front Bioeng Biotechnol*. 2022;9:804415.
65. Bhat M, Pukale S, Singh S, Mittal A, Chitkara D. Nano-enabled topical delivery of anti-psoriatic small molecules. *J Drug Deliv Sci Technol*. 2021;62:102328. doi:10.1016/j.jddst.2021.102328
66. Khan MS, Mohapatra S, Gupta V, et al. Potential of lipid-based nanocarriers against two major barriers to drug delivery—skin and blood–brain barrier. *Membranes*. 2023;13(3):343.
67. Zaki RM, Seshadri VD, Mutayran AS, et al. Wound Healing Efficacy of Rosuvastatin Transethosomal Gel, I Optimal Optimization, Histological and In Vivo Evaluation. *Pharmaceutics*. 2022;14(11):2521. doi:10.3390/pharmaceutics14112521
68. Allaw M. Protection of skin and treatment of lesions using phospholipid vesicles tailored for the topical delivery of phytochemicals from Sardinian flora. Published online 2022. Accessed January 3, 2025. https://tesidottorato.depositolegale.it/handle/20.500.14242/69513
69. An P, Zhao Q, Hao S, Wang X, Tian J, Ma Z. Recent Advancements and Trends of Topical Drug Delivery Systems in Psoriasis: A Review and Bibliometric Analysis. *Int J Nanomedicine*. 2024;Volume 19:7631-7671. doi:10.2147/IJN.S461514
70. Patel B. Permeation Enhancement And Advanced Strategies: A Comprehensive Review Of Improved Topical Drug Delivery. *Int Res J Mod Eng Technol Sci*. 2024;06:6691-6702. doi:10.56726/IRJMETS57321
71. Sivadasan D, Sultan MH, Madkhali O, Almoshari Y, Thangavel N. Polymeric lipid hybrid nanoparticles (plns) as emerging drug delivery platform—A comprehensive review of their properties, preparation methods, and therapeutic applications. *Pharmaceutics*. 2021;13(8):1291.
72. Matos AFVA. *New Insights in Permeability Studies: Bioprinted 3D Skin Models vs Biological Skin*. Master's Thesis. Universidade de Lisboa (Portugal); 2022. Accessed January 3, 2025. https://search.proquest.com/openview/3f8b23b7faa09e0f04386e8f1b12352c/1?pq-origsite=gscholar&cbl=2026366&diss=y
73. Esposito E, Pecorelli A, Ferrara F, Lila MA,

Valacchi G. Feeding the Body Through the Skin: Ethosomes and Transethosomes as a New Topical Delivery System for Bioactive Compounds. *Annu Rev Food Sci Technol*. 2024;15(1):53-78. doi:10.1146/annurev-food-072023-034528

74. Brito S, Baek M, Bin BH. Skin Structure, Physiology, and Pathology in Topical and Transdermal Drug Delivery. *Pharmaceutics*. 2024;16(11):1403. doi:10.3390/pharmaceutics16111403
75. Cerbin-Koczorowska M, Waszyk-Nowaczyk M, Bakun P, Goslinski T, Koczorowski T. Current View on Green Tea Catechins Formulations, Their Interactions with Selected Drugs, and Prospective Applications for Various Health Conditions. *Appl Sci*. 2021;11(11):4905. doi:10.3390/app11114905
76. Nayak D, Rathnanand M, Tippavajhala VK. Navigating Skin Delivery Horizon: An Innovative Approach in Pioneering Surface Modification of Ultradeformable Vesicles. *AAPS PharmSciTech*. 2024;25(5):126. doi:10.1208/s12249-024-02847-1
77. Man AM, Orãsan MS, Hoteiuc OA, Olãnescu-Vaida-Voevod MC, Mocan T. Inflammation and Psoriasis: A Comprehensive Review. *Int J Mol Sci*. 2023;24(22):16095. doi:10.3390/ijms242216095
78. Froelich A, Osma³ek T, Jadach B, Puri V, Michniak-Kohn B. Microemulsion-Based Media in Nose-to-Brain Drug Delivery. *Pharmaceutics*. 2021;13(2):201. doi:10.3390/pharmaceutics13020201
79. Raina N, Rani R, Thakur VK, Gupta M. New Insights in Topical Drug Delivery for Skin Disorders: From a Nanotechnological Perspective. *ACS Omega*. 2023;8(22):19145-19167. doi:10.1021/acsomega.2c08016
80. Oliveira C, Coelho C, Teixeira JA, Ferreira-Santos P, Botelho CM. Nanocarriers as Active Ingredients Enhancers in the Cosmetic Industry—The European and North America Regulation Challenges. *Molecules*. 2022;27(5):1669. doi:10.3390/molecules27051669
81. Paul JK, Azmal M, Haque ASNB, Talukder OF, Meem M, Ghosh A. Phytochemical-mediated modulation of signaling pathways: A promising avenue for drug discovery. *Adv Redox Res*. 2024;13:100113. doi:10.1016/j.arres.2024.100113
82. Filipiuc SI, Neagu AN, Uritu CM, et al. The Skin and Natural Cannabinoids–Topical and Transdermal Applications. *Pharmaceuticals*. 2023;16(7):1049. doi:10.3390/ph16071049