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NOVEL DRUG DELIVERY SYSTEMS FOR THE EFFECTIVE TREATMENT OF PSORIASIS- A REVIEW

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Abstract:

Psoriasis is a chronic inflammatory skin disease affecting 1–3% of the total population worldwide. These conditions may adversely influence the patient's quality of life and prompt psychosocial stretch. Various therapeutic agents are available for the treatment of psoriasis but none of them are entirely secure and effective to treat the disease without compromising patient compliance. Furthermore, already existing drugs are supposed to restrain the ailment and alleviate the sign and symptoms with no complete cure. However, they focus on restraining the disease and alleviating the symptoms without providing an absolute cure. Therefore there remains a vital challenge, to explore a new drug moiety or delivery system which could safely and effectively manage psoriasis without compromising patient compliance. Furthermore, conventional formulations offer reduced benefit/risk ratio of anti-psoriatic drugs, which limits the use of existing conventional formulations.

Novel formulations based on nanocarriers are a promising prospect to overcome the limitation of conventional formulations by offering a reduction in dose, dosing frequency, dose-dependent, side effects with enhanced efficacy. Presently nano-formulations have gained widespread application for effective and safe treatment of psoriasis. The present review primarily focuses on conventional therapeutic strategy and recent advances in lipid-based, polymer-based and metallic nano-formulations of a variety of anti-psoriatic drugs. The practicability of various nanocarrier systems including liposomes, nanostructured lipid carriers, ethosomes, solid lipid nanoparticles, nanocapsules, micelles, dendrimers, gold nanoparticles and silver nanoparticles have been discussed in detail. The review also traces related patents to exemplify the role of various nanoparticles in psoriasis treatment. In a nutshell, nano-formulations remain established as a promising modality for treating psoriasis treatment as they propose better penetration, targeted delivery, enhanced safety, and efficacy.

Key Words: *Psoriasis, Types, Pathogenesis of disease, Topical treatments, Novel drug delivery systems.*

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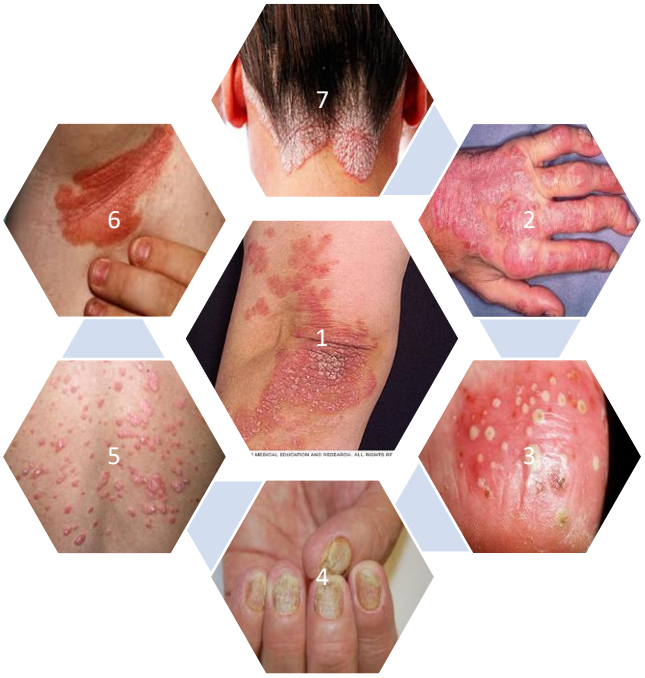
INTRODUCTION:

Psoriasis is a chronic inflammatory skin disease that affects approximately 0.5%–1% of children and 2%–3% of the world's population. It is a long-lasting autoimmune disease characterized by patches of abnormal skin. These skin patches are typically red, itchy, and scaly. It varies in severity from small, localized patches to complete body coverage. [1] Pathophysiology of the disease includes mainly the activation and migration of T cells to the dermis triggering the release of cytokines which lead to the inflammation and the rapid production of skin cells. Psoriasis can be triggered by factors like emotional stress, skin injury, systemic infections, certain medications and intestinal upsets. [2] Various types of psoriasis have been reported which can be diagnosed by clinical findings such as skin biopsies. Therapeutic agents that either modulate the immune system or normalize the differentiation program of psoriatic keratinocytes are suggested for treating psoriasis. Based on the type of psoriasis, its location, extent and severity there are various treatment regimens available such as topical agents, phototherapy and systemic approach which can help to control the symptoms. This review aims to cover each and every aspect of the disorder psoriasis and details of particularly plaque psoriasis as about 80% of people who develop psoriasis have plaque psoriasis. [3]

TYPES OF PSORIASIS [4]:



1. **Plaque psoriasis**
   Plaque psoriasis is the most common form that affects large number of people with psoriasis. It typically appears as raised areas of inflamed skin covered with silvery-white scaly skin. These areas are called plaques and are most commonly found on the elbows, knees, scalp, and back. It may be accompanied by severe itching, swelling, and pain. It is often the result of an exacerbation of unstable plaque psoriasis, particularly following the abrupt withdrawal of systemic glucocorticoids. This form of psoriasis can be fatal as the extreme inflammation and exfoliation disrupt the body's ability to regulate temperature and perform barrier functions.

2. **Psoriatic arthritis**
   Psoriatic arthritis is a form of chronic inflammatory arthritis that has a highly variable clinical presentation and frequently occurs in association with skin and nail psoriasis. It typically involves painful inflammation of the joints and surrounding connective tissue and most commonly affects the joints of the fingers and toes. This can result in a sausage-shaped swelling of the fingers and toes known as dactylitis. About 30% of individuals with psoriasis will develop psoriatic arthritis. Skin manifestations of psoriasis tend to occur before arthritic manifestations in about 75% of cases.

3. **Pustular psoriasis**
   It is characterized by raised bumps filled with non-infectious pus or pustules. These pustules can be localized commonly on the hands and feet, or it can be generalized with random widespread patches on any part of the body.

4. **Nail psoriasis**
   It affects the nails and produces a variety of changes in the appearance of finger and toe nails. Nail psoriasis occurs in 40–45% of people with psoriasis affecting the skin and has a lifetime incidence of 80–90% in those with psoriatic arthritis. These changes include pitting of the nails (pinhead-sized depressions in the nail is seen in 70% with nail psoriasis), whitening of the nail, small areas of bleeding from capillaries under the nail, yellow-reddish discoloration of the nails known as the oil drop or salmon spot, thickening of the skin under the nail loosening and separation of the nail and crumbling of the nail.

5. **Guttate psoriasis**
   It is characterized by numerous small, scaly, red or pink, droplet-like lesions (papules). These numerous spots of psoriasis appear over large areas of the body, primarily the trunk, but also the limbs and scalp. Guttate psoriasis is often triggered by a streptococcal infection, typically streptococcal pharyngitis.

6. **Flexural psoriasis**
   It often appears in skinfolds, such as under the breasts or in the armpits or groin area. This type of psoriasis is red, and often shiny and smooth. The sweat and moisture from skinfolds keeps this form of psoriasis from shedding skin scales. Sometimes it's misdiagnosed as a fungal or bacterial infection. The skin-on-skin contact can make inverse psoriasis very uncomfortable. Most people with inverse psoriasis also have a different form of psoriasis in other places on the body.

7. **Scalp psoriasis**
   It is common in people with plaque psoriasis. For some people, it may cause severe dandruff. For others, it can be painful, itchy, and very noticeable at the hairline. Scalp psoriasis can extend to the neck, face, and ears in one large patch or many smaller patches. In some cases, scalp psoriasis can complicate regular hair hygiene. Excessive scratching can cause hair loss and scalp infections. The condition may also cause feelings of social stress.

PATHOGENESIS OF PSORIASIS:

Psoriasis is a disease known to be caused by multitude of both genetic and environmental factors such as trauma, drugs, infection, alcohol, smoking and stress but its accurate origin is still not known. Unlike normal skin, pathological progression of psoriasis is supposed to rely on multitude of coherent events involving the activation of circulating immune cells and their secreted signaling molecules like cytokines, chemokines and growth factors. These all events further progress to mark hyperkeratosis, congealing of epidermis and neovascularization of circulating immune cells and their secreted signaling molecules as shown in figure given below. Cytokines play an important role in progression of psoriasis. Major cytokines include tumor necrosis factor alpha (TNF-α), Interleukin-23 (IL-23) and IL-17 which aids in the production of other pro-inflammatory cytokines and psoriasis lesions formation. Several of these pro-inflammatory cytokines e.g. TNFα, IL-12 and IL-23 rely on nuclear factor kappa B (NF-kB) as a downstream mediator of their effects on a transcriptional level. Accordingly, increased levels of activated NF-κB are found in psoriasis skin compared with healthy skin. The main factors responsible for psoriasis therefore include the angiogenic factors, over-expression of VEGF in the psoriatic epidermis, transfer in bone marrow transplants from affected individuals, reduced TNF concentrations and increased concentrations of natural killer (NKT) cells. [5]

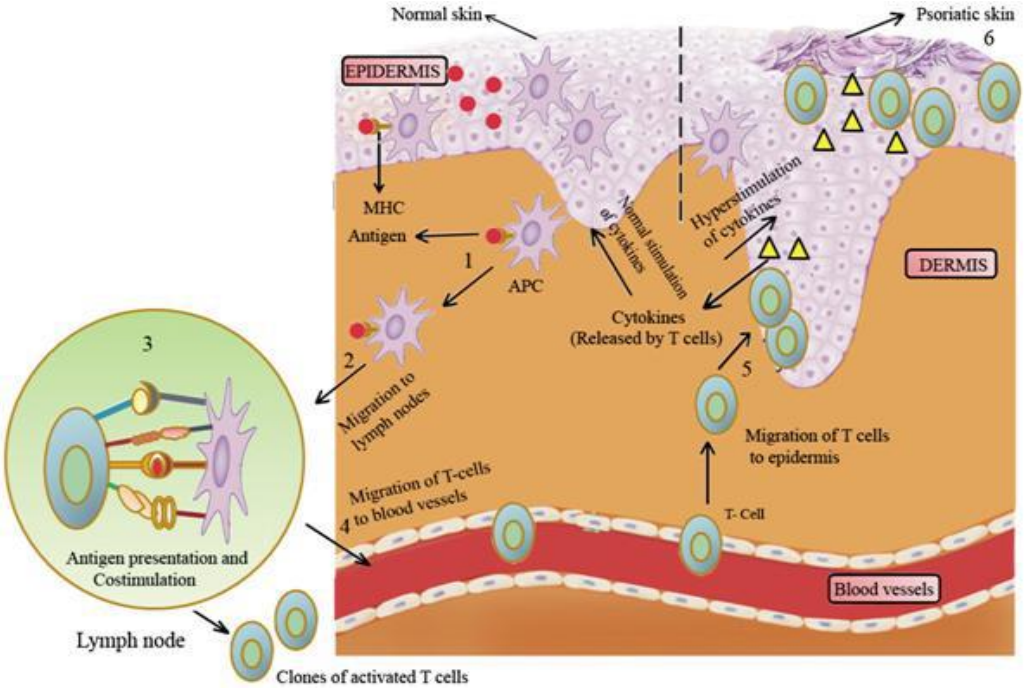


Fig: Different events in pathogenesis of psoriasis.

TOPICAL TREATMENTS [6]:

1. **Topical corticosteroids:** These drugs are the most frequently prescribed medications for treating mild to moderate psoriasis. They reduce inflammation and relieve itching and may be used with other treatments. Mild corticosteroid ointments are usually recommended for sensitive areas, such as your face or skin folds, and for treating widespread patches of damaged skin. Clobestol propionate (Temovate) and Halobestol propionate (Ultravate) are available as creams and ointments.

2. **Vitamin D analogues:** These synthetic forms of vitamin D slow skin cell growth. Calcipotriene (Dovonex) is a prescription cream or solution containing a vitamin D analogue that treats mild to moderate psoriasis along with other treatments.

3. **Anthralin:** This medication helps slow skin cell growth. Anthralin (Dritho-Scalp) can also remove scales and make skin smoother.

4. **Topical retinoids:** These are vitamin A derivatives that may decrease inflammation. The most common side effect is skin irritation.

5. **Calcineurin inhibitors:** Calcineurin inhibitors like Tacrolimus and Pimecrolimus reduce inflammation and plaque buildup. They may be especially helpful in areas of thin skin, such as around the eyes, where steroid creams and retinoids are too irritating or may cause harmful effects.

6. **Salicylic acid:** Available over-the-counter and by prescription, it promotes sloughing of dead skin cells and reduces scaling. Sometimes it's combined with other medications, such as topical corticosteroids or coal tar, to increase its effectiveness.

7. **Coal tar:** Derived from coal, coal tar reduces scaling, itching and inflammation.

8. **Moisturizers:** Moisturizing creams alone won't heal psoriasis, but they can reduce itching, scaling and dryness. Moisturizers in an ointment base are usually more effective than are lighter creams and lotions.

CHALLENGES IN THE TREATMENT OF PSORIASIS:

Presently, many therapeutic options are available for treatment of psoriasis, but finding an effective therapy is still a significant challenge. Topical therapy remains a widely employed option for psoriasis, and about 80% of the psoriasis population depends on topical therapy. However, topical therapy using conventional formulation possesses its limitation of poor drug penetration and absorption due to barrier properties of skin. This barrier results in slow penetration rates and restricted uptake of

therapeutic moiety. Furthermore, in psoriasis, skin becomes very tough and rigid owing to epidermal hyperplasia, hyperkeratosis and lack of common moisturizing elements like water. All these phenotypic changes limit sufficient drug penetration across the psoriatic skin. Thus the therapeutic effectiveness of conventional topical therapy remains a considerable issue. [7]

Novel drug delivery systems (NDDS) is a promising strategy to overcome these side effects and offer many advantages which include increased safety and efficacy, drug targeting specificity and lowering of systemic drug toxicity.[8] Stratum corneum (SC) is the main barrier in percutaneous absorption of topically applied drugs. Small and relatively narrow size distribution with novel carriers permit site specific delivery to the skin with improved drug solublization of hydrophobic drugs and better bioavailability.[9] NDDS play an important role in drug delivery to the target site for control and prevention of the disease. Such carriers have become the first choice to deliver anti-psoriatic drugs, due to their various characteristics such as:

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

NOVEL APPROACHES FOR THE EFFECTIVE TREATMENT OF PSORIASIS [10]:

Nanomedicines, also regarded as nanotherapeutics, act as a versatile carrier owing to their unique features for interaction with the skin and modify its barrier property particularly in psoriasis.

1. **LIPOSOMES:** They are bilayer vesicular carriers mainly composed of phospholipids, cholesterol and stabilizers. The vesicle size can vary from nanometer to several hundred micrometers depending on their structure from unilamellar to multilamellar vesicles. Liposomes can encapsulate both hydrophilic and lipophilic drugs in aqueous core and bilayers, respectively. These have numerous meritorious visages like higher encapsulation efficiency, enhanced biocompatibility and controlled-release rate of drug delivery. Innumerable properties of liposomes like smaller size, elasticity and lammellarity have favored for their higher utility in antipsoriatic drug delivery.
   Rajiv Kumar et al., reviewed and reported that Topical liposomal formulation of cyclosporine, 2.0%w/w, is effective in treatment of limited chronic plaque psoriasis with a satisfactory safety profile. Future clinical trials should assess liposomal cyclosporine in larger study populations.

2. **ETHOSOMES:** These are the soft vesicular nanocarriers, mainly composed of ethanol, phospholipids and stabilizers. Presence of high percentage of ethanol in the vesicles helps in their ease of penetration into the stratum corneum. These are suitable for drug delivery in treatment of various skin maladies such as psoriasis, dermatitis etc.
   Yong-Tai Zhang et al., are characterized by much better percutaneous permeation than conventional vehicles. Enhanced permeation and skin deposition of psoralen delivered by ethosomes may help reduce toxicity and improve the efficacy of long-term psoralen treatment.

3. **AQUASOMES:** Aquasomes are the nanoparticulate carriers composed of three-layered, self-assembled structures. Physiochemical properties of aquasomes provide enhanced protection of labile biological molecules and proven as an efficient carrier over simple nanoparticles.

4. **SOLID LIPID NANOPARTICLES:** These are the lipid-based nanoparticulate carriers with size ranging from 50 to 1000 nm. These are mainly composed of phospholipid dispersed in the aqueous solution of surfactant. Their meticulous properties like enhanced biocompatibility, availability of higher surface area, drug loading capacity, and extended drug release action coupled with high stability make them as versatile carriers over conventional polymeric carriers.
   Jyotsana R Madan et al., developed SLNs were meaningfully utilized for the topical delivery of lipophilic, anti-psoriatic drug, MF. Greater skin deposition and slow drug release was observed with the developed SLN. SLN topical gel containing MF would be advantageous over the marketed cream product. Production of MF loaded SLNs and its formulation as a topical gel could be a new, cost-effective and commercially viable alternative to the marketed product.

5. **NANOSTRUCTURED LIPID CARRIERS:** Like SLNs, nanostructured lipid carriers (NLCs) are composed of solid lipid added with liquid lipids provides excellent biocompatibility and higher surface area, resulting into greater permeation of drug across the skin.
   Navjot Kaur et al., reviewed and reported that the prepared NLC based formulation has proved to be a promising carrier system for the treatment of psoriasis.

6. **MICROEMULSIONS:** Microemulsions are the isotropic dispersions containing lipids, surfactants and co-surfactant and exhibit higher drug permeation due

to their surface area and partitioning property through skin layers. These have been increasingly employed for drug delivery to the skin for management of psoriasis. Microspheres are one of the polymeric carriers with size ranging between 1 and 1000µm. These provide sustained delivery of drugs and reduce dosing frequency with higher patient compliance. Moreover, it also has ability to increase the drug-targeting specificity.

Marta Benigni et al., The data collected in the present paper underline the important role of microemulsion structure on cyclosporine uptake into the skin. These systems could, in principle, contribute to optimizing topical therapy, also in the framework of the new strategies for psoriasis treatment, involving combination, rotational and sequential therapy.

7. **MICROSPHERES:** Microspheres-based topical formulations have demonstrated controlled drug delivery and therapeutic effectiveness for prolonged periods of time. These have been successfully employed for topical treatment of psoriasis.

Ulya Badılla et al., Clobetasol propionate-loaded PLGA microspheres were successfully prepared using oil-in-water emulsion–solvent evaporation technique. Microparticles were formulated in an emulgel base and a topical delivery system was developed for psoriasis treatment.

8. **NIOSOMES:** Unlike liposomes, niosomes are the non-ionic surfactant containing vesicles, having ability to encapsulate both hydrophilic and hydrophobic drugs. These have better stability over liposomes and ethosomes, because of their resistance against oxidation. Niosomes has been widely used in the psoriasis treatment with lesser side effects and better patient compliance.

Lakshmi PK et al., reviewed and reported that the niosomal methotrexate gel is more efficacious than placebo and marketed methotrexate gel.

9. **TRANSFEROSOMES:** Transferosomes are the elastic vesicles, which provide ease of penetration through the stratum corneum of the skin. Literature reports have demonstrated the utility of nanomedicines in treatment several skin ailments. Various nanodrug carriers investigated for targeted drug therapy in psoriasis are illustrated in the figure given below. The present section explicitly describes the application of diverse nanomedicines for active delivery of pharmacotherapeutics for effective treatment of psoriasis.

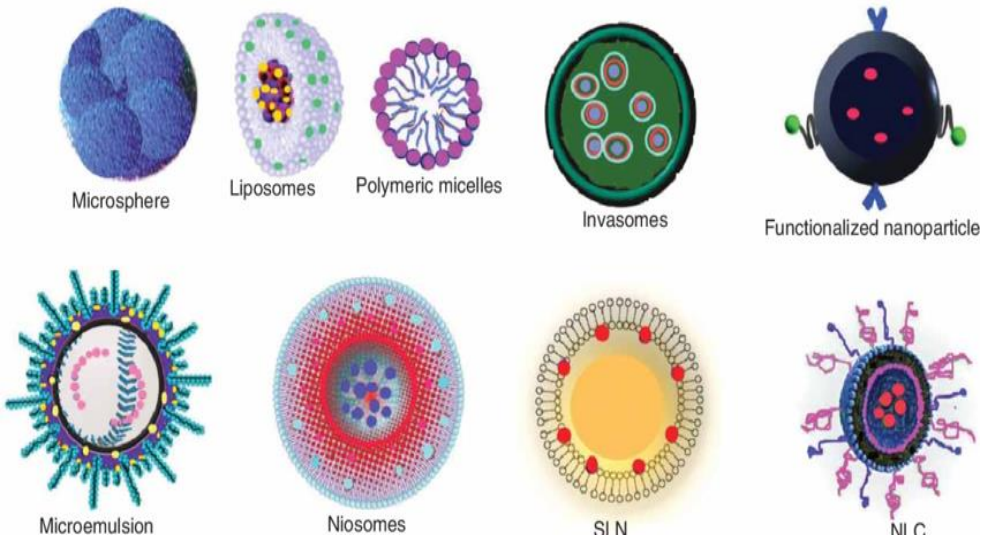


Fig: Different novel drug delivery systems

CONCLUSION:

Psoriasis is a chronic skin disease affecting around 2-3% of the world population and a lot of care should be taken to minimize the severity of this disease. Conventional therapy for Psoriasis provides only symptomatic relief. There are many drawbacks of conventional therapy and hence, there is a need for the development of novel drug delivery systems which can overcome these limitations of conventional drug delivery systems. Novel drug delivery approach could provide an inimitable prospect for the development of highly competent and low toxic treatment modalities. Furthermore, they hold easy entry into the skin and offer deeper penetration to the skin. These are also used for targeted drug delivery with the improved benefit-risk ratio. However, the clinical significance in the treatment of psoriasis remains in its early stage of research. Through an advanced understanding of the pathophysiology of psoriasis, new strategies could be expanded by developing

novel economic, biological agents with high therapeutic value. In future, apart from drug delivery, nano-formulations could also be exploited for delivery of a therapeutic gene to achieve more successful and targeted therapy.

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