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Nanotechnology Based Alternative for the Topical Delivery of Psoriasis

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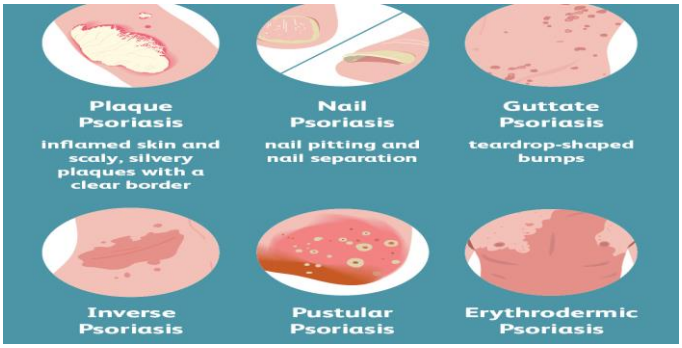
Abstract
Psoriasis, a chronic autoimmune disease, is characterized by patches of abnormal skin that are red, pink, or purple, dry, itchy, and scaly. It affects people of all ages, with peak onset between 32 and 52 years old. Psoriasis is classified into three main types: vulgaris, pustular, and inverse.
Novel Drug Delivery Systems (NDDS) offer innovative approaches to deliver pharmaceutical substances to the body more effectively and safely. These systems aim to increase bioavailability, maintain therapeutic drug concentrations, and minimize toxicity.
Several NDDS are being used for psoriasis treatment, including:

- **Topical nanoparticles:** These offer enhanced skin penetration, controlled release, and reduced side effects.
- **Liposomes:** Spherical vesicles that can encapsulate drugs and deliver them to targeted areas.
- **Microneedle systems:** Create microchannels in the skin for improved drug penetration and localized delivery.
- **Transdermal patches:** Provide non-invasive, sustained drug delivery.
- **Smart drug delivery systems:** Respond to specific stimuli, enabling targeted and controlled drug release

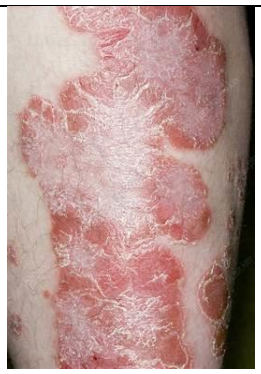
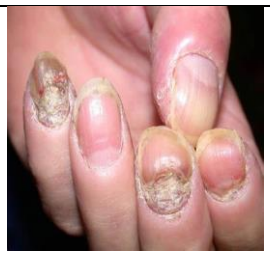
Keywords: Psoriasis, Mechanisms psoriasis, Treatment, Nanotechnology

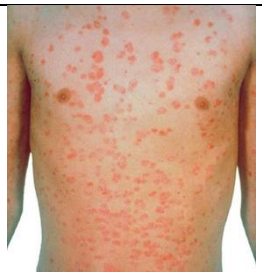
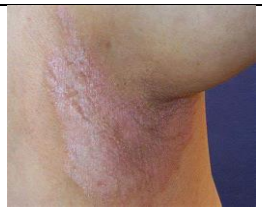
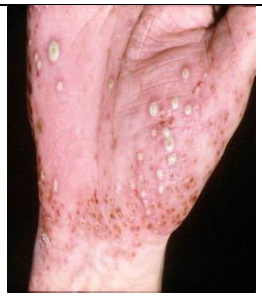
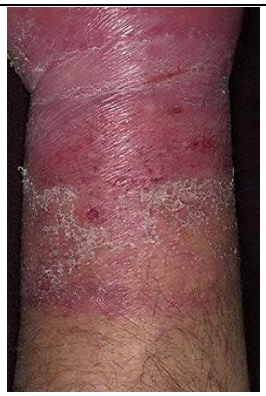
1. Introduction

Psoriasis is disease that affects on the skin, is a long-lasting, disease and characterized by patches of abnormal skin. These areas are showing the red, pink, or purple, dry, itchy, and scaly [1] this type of proliferation and differentiation of impaired. Psoriasis is occur in young child to an old man but occur in age 32 to 52 years.[2]A genetic basis and is characterized by inflammation, resulting from alterations of mechanisms influencing epidermal biology include antigen presentation, cell signaling, and transcriptional control.
The psoriasis is classified at three class
a) Psoriasis Vulgaris, the most prevalent type (80 %);
b) Psoriasis Pustular, a complication of bacterial infection;
c) Psoriasis Inverse
Another classification of severity of the case, mild, moderate, or severe [3]

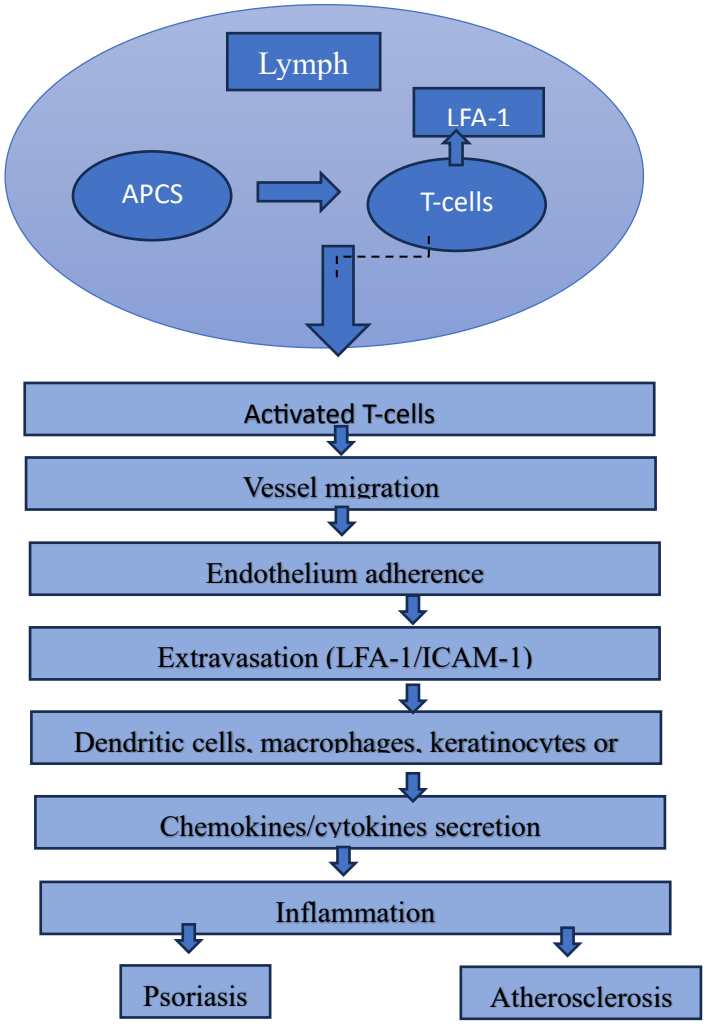


This figure show such as plaque psoriasis, guttate psoriasis, nail psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis) and their characteristic features. "Image created with verywellhealth.com".[4]

Types	Figer	Description	Sign and Symptoms	Causes	Ref
Plaque psoriasis		Plaque psoriasis (psoriasis vulgaris) is a long-lasting (chronic) autoimmune disease	-Raised, discolored plaques with a white or silvery -surface -Cracks -Bleeding -Irritation or pain	-stress -alcohol -infection -injury	5(a)
Nail Psoriasis		This affects the fingernails and toenails of roughly 80% of psoriasis sufferers and causes pitting and ridges in the nails.	-Discoloration -Pitting -Changes in nail structure	Psoriatic inflammation Abnormal rapid growth of skin cells Genetics-Environmental factors Immunological problems Trauma to the nail	5(b)

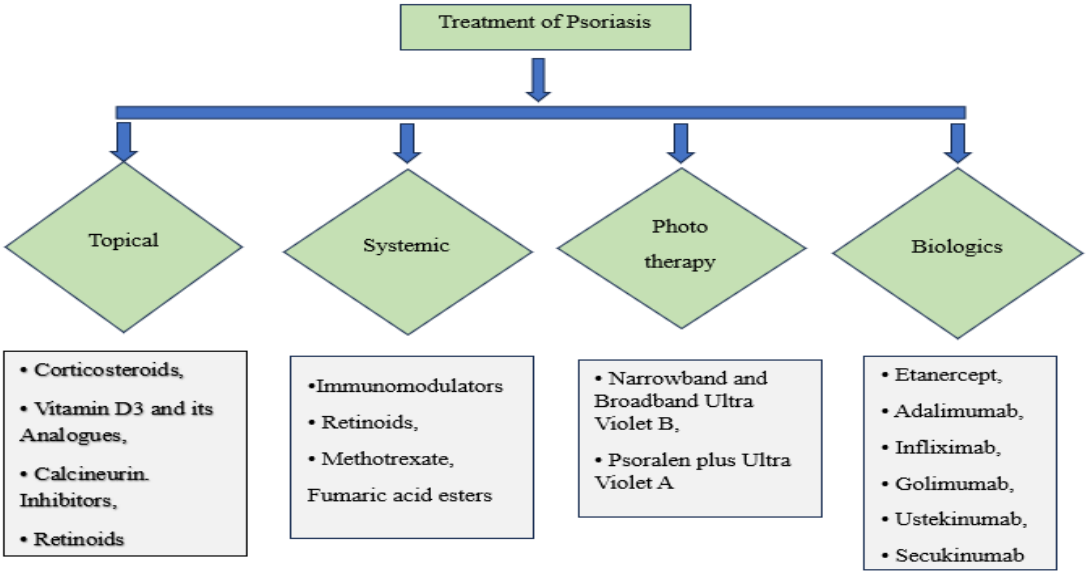
Guttate Psoriasis		which is more prevalent in children and young people and is caused by bacterial infections like strep throat	Round or teardrop-shaped pink or red patches of skin	Infections caused by Group A Streptococcus HIV Autoimmune disorders	5(c)
Inverse Psoriasis		Appear in the groins, beneath the breast, under the arms, and in natal clefts; also known as Flexural psoriasis.	shiny, smooth, discolored Itchiness Moist patch of skin Cracks (fissures) in your skin creases	Abnormal immune system	5(d)
Pustular Psoriasis		Non-follicular sterile pustules, that are characteristic of the hand, foot, or fingertip, can arise in these small locations.	A patch of thick, discolored, flaky and scaly skin (plaque), Skin patch covered in fluid-filled bumps (pustules) or blisters, Mild pain or itchiness.	A patch of thick discolored flaky and scaly skin (plaque)	5 (e)
Erythrodermic psoriasis		A prevalent cause of erythroderma, rare and severe type affects 1-2.25% of psoriatic individuals and is potentially fatal.	pain and redness of skin Body temperature increase Heart rate increase & decrease	Allergic reaction to a medication. Illness or infection. Severe sunburn.	5 (f)

2) Mechanisms psoriasis



(6)

3) Treatment



(7) This figure show the treatment basically such as plaque psoriasis, for the guttate psoriasis, nail psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis

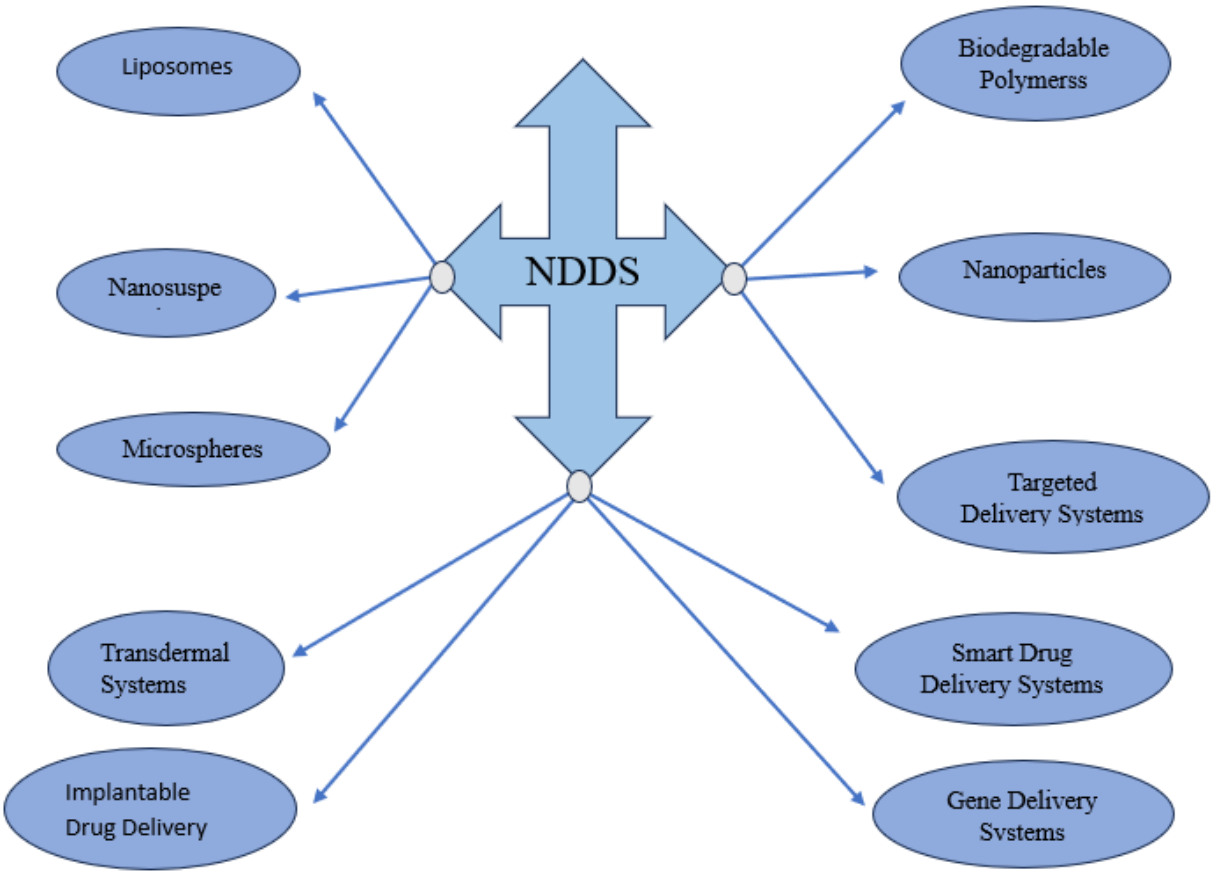
4) **Need for novel drug delivery systems**

A Novel Drug Delivery System (NDDS) is a new way combining creative creation, formulations, new technology, fresh approaches for distributing pharmaceutical substances in the body as needed to safely achieve its targeted pharmacological effects.

1) Properties of NDDS

a) Novel Drug Delivery System show the site of action
b) This system increase the bioavailability
c) Its maintain the concentration of drug therapeutic effect
d) Minimize the toxicity
e) Enhanced Bioavailability
f) Targeted Delivery
g) Controlled Release
h) Reduced Toxicity
i) Versatility in Formulation
j) Improved Stability
k) Enhanced Permeation and Retention (EPR)
l) Size and Surface Modifiability
m) Biocompatibility
n) Ability to Cross Biological Barriers (e.g., blood-brain barrier) [8,9]

2) Terminology of NDDS



(8,9,10,74-82)

This figure show the treatments of Novel Drug Delivery System for varies disease., but mostly. Used in psoriasis disease. As follow

A. Topical Nanoparticles
B. Liposomes
C. Microneedle Systems
D. Transdermal Patches
E. Smart Drug Delivery Systems
F. Biologics Delivery System

(A) Topical nanoparticles

Topical nanoparticles have emerged as a significant advancement in dermatological drug delivery, offering improved skin penetration, enhanced drug stability, and controlled release of active ingredients. Nanoparticles, generally sized between 1 and 100 nm, are being used to address limitations in conventional topical therapies for various skin conditions such as psoriasis, acne, and skin cancers.

- **Advantages of Using Topical Nanoparticles:**

1. **Enhanced Skin Penetration:** Nanoparticles enhance the penetration of drugs through the stratum corneum, the outermost layer of the skin, which serves as a formidable barrier to most conventional formulations. The nanoscale size of these particles allows for more effective delivery of active ingredients into the deeper skin layers (11)
2. **Controlled and Sustained Release:** Nanoparticles allow for the controlled release of drugs, ensuring that therapeutic levels are maintained for extended periods, reducing the frequency of application. This feature is particularly useful in chronic skin conditions like psoriasis that require long-term management (12)
3. **Improved Drug Solubility and Stability:** Many topical drugs, such as corticosteroids, curcumin, and retinoids, have poor water solubility or are unstable when exposed to environmental factors. Nanoparticles improve the solubility of these drugs and protect them from degradation by encapsulating them within protective matrices. (13)
4. **Targeted Delivery**: Nanoparticles can be designed to specifically target inflamed or diseased skin tissues. By attaching targeting ligands to their surface, they can bind to specific receptors on the skin, ensuring that the drug is delivered primarily to the affected area, reducing off-target effects. (14)
5. **Reduced Side Effects**: Nanoparticles provide localized drug delivery, minimizing systemic absorption. This is especially important for drugs like corticosteroids and immunosuppressants, where systemic exposure can lead to significant side effects(15)

- **Mechanism of Action of Topical Nanoparticles in Psoriasis**
- **Enhanced Penetration through the Skin Barrier**:
  - Psoriatic skin, characterized by hyperkeratosis and scaling, poses a significant challenge for drug delivery. The stratum corneum, the outermost layer of the skin, is often thickened in psoriasis, hindering drug absorption. Nanoparticles, due to their nano-size, can penetrate this barrier more efficiently than larger particles.
  - Nanoparticles, particularly lipid-based nanoparticles (e.g., solid lipid nanoparticles, nanostructured lipid carriers) and polymeric nanoparticles, can bypass the stratum corneum and deliver drugs deeper into the epidermis and dermis where the disease pathology is located. (11)

- **Controlled and Sustained Drug Release**:
  - One of the most significant benefits of nanoparticles is their ability to provide controlled drug release. Nanoparticles can encapsulate drugs and release them over a prolonged period, maintaining therapeutic drug concentrations for extended durations. This reduces the frequency of application, which is beneficial for patient adherence, especially for chronic conditions like psoriasis.
  - This controlled release minimizes the peaks and troughs of drug concentration that can lead to inefficacy or toxicity. (12)
- **Targeted Delivery to Inflamed Areas**:
  - Nanoparticles can be functionalized with ligands or surface modifiers that allow them to selectively target inflamed psoriatic lesions. This allows the drug to concentrate at the site of disease, improving efficacy while reducing systemic absorption and side effects.
  - For example, methotrexate encapsulated in nanoparticles can be delivered directly to inflamed keratinocytes, reducing systemic exposure and side effects. (13)
- **Modulation of Immune Responses**:
  - Nanoparticles can be designed to deliver immunomodulatory agents (such as corticosteroids or biologics) directly to immune cells involved in psoriasis (e.g., T cells, dendritic cells). This can help downregulate the immune-mediated inflammation characteristic of psoriasis without widespread systemic immunosuppression. (14)
- **Factors Affecting the Performance of Topical Nanoparticles in Psoriasis Treatment**

1. **Particle Size and Surface Properties**:
   - The size and surface charge of nanoparticles significantly influence their ability to penetrate the skin. Smaller particles (usually less than 100 nm) can penetrate the skin barrier more efficiently. Additionally, surface charge affects their interaction with the skin's lipids and proteins. Cationic nanoparticles tend to adhere better to the negatively charged skin surface, enhancing drug retention. (16)
2. **Drug Encapsulation Efficiency**:
   - The efficiency with which nanoparticles encapsulate the drug affects the overall drug delivery process. High encapsulation efficiency ensures that a significant amount of the drug reaches the target area. This is influenced by the type of nanoparticle (lipid-based, polymeric, etc.) and the physicochemical properties of the drug. (17)
3. **Release Kinetics**:
   - Nanoparticles can be engineered to control the rate at which the encapsulated drug is released. Factors such as particle composition, degradation rate, and the matrix structure affect how quickly the drug is released. In psoriasis, sustained release over time ensures continuous drug action, minimizing the need for frequent application.(18).
4. **Stability of the Nanoparticles**:
   - Stability of the nanoparticles is critical for their efficacy. External factors like pH, temperature, and exposure to light can affect nanoparticle stability. Nanoparticles should maintain their integrity to ensure proper delivery of the drug to the target tissue in psoriasis. (19)
5. **Skin Condition (Psoriatic Skin)**:
   - The altered skin morphology in psoriatic patients (thickened epidermis, disrupted skin barrier, etc.) affects the penetration and distribution of nanoparticles. Nanoparticles must be designed to accommodate the unique features of psoriatic skin to ensure effective delivery. (20)

- **Example: Curcumin Nanoparticles for Psoriasis Treatment**
- **Curcumin**, a natural anti-inflammatory agent, has shown promise in treating psoriasis due to its ability to modulate inflammatory pathways. However, its poor solubility and rapid degradation in the body have limited its effectiveness. Nanoparticle formulations of curcumin overcome these challenges by enhancing skin penetration, improving stability, and providing sustained release.
  - **Mechanism of Action**: Curcumin nanoparticles can reduce the expression of pro-inflammatory cytokines like TNF-α and IL-6 in psoriatic lesions, reducing inflammation and keratinocyte proliferation.
  - **Effectiveness**: Studies have shown that curcumin nanoparticles applied topically lead to significant improvements in the severity of psoriatic plaques compared to traditional formulations. (21)

(B) Liposomes

Liposomes are spherical vesicles composed of one or more phospholipid bilayers, which can encapsulate hydrophilic and hydrophobic drugs. They are widely used in topical drug delivery due to their biocompatibility, ability to carry diverse drugs, and capacity to enhance drug penetration into the skin. In psoriasis, liposomal formulations are emerging as effective tools for enhancing drug delivery to the affected skin layers, minimizing systemic side effects, and providing controlled release of therapeutic agents.

Mechanism of Action of Liposomes in Psoriasis

1. **Enhanced Drug Penetration**:
   - Liposomes have the ability to merge with the lipid layers of the stratum corneum, the outermost skin barrier, due to their phospholipid composition, which is similar to the skin's natural lipids. This enhances the penetration of the encapsulated drug into deeper layers of the skin, including the epidermis and dermis.
   - Liposomes can encapsulate both hydrophobic (lipid-soluble) and hydrophilic (water-soluble) drugs, allowing for versatile drug delivery. In psoriasis, liposomal encapsulation can enhance the effectiveness of drugs such as corticosteroids, methotrexate, and retinoids. (22)
2. **Targeted Delivery to Psoriatic Lesions**:
   - Liposomes can be engineered to target specific receptors or molecules present in inflamed psoriatic lesions. Surface modifications such as ligands or antibodies can be added to the liposome surface, enabling targeted delivery to the overactive keratinocytes or T cells involved in psoriasis.
   - This targeted approach reduces systemic drug exposure, minimizing adverse effects while maximizing drug concentration at the site of inflammation. (23)
3. **Sustained and Controlled Drug Release**:
   - Liposomes can provide sustained release of encapsulated drugs, ensuring prolonged therapeutic effects. This is particularly beneficial for treating chronic conditions like psoriasis, where long-term drug delivery can reduce the need for frequent application.
   - Liposomes with multiple bilayers (multilamellar vesicles) can release drugs over a more extended period than unilamellar vesicles (single-bilayer liposomes).(24)
4. **Reduction of Drug Toxicity**:
   - By encapsulating drugs like methotrexate or corticosteroids in liposomes, the systemic absorption of the drug can be significantly reduced, limiting potential toxicities such as immunosuppression or organ

damage. This is critical for potent drugs that can cause significant adverse effects when absorbed systemically. (25)

Factors Affecting the Performance of Liposomes in Psoriasis Treatment

1. **Size and Structure of Liposomes**:
   - Liposomes come in different sizes, from small unilamellar vesicles (SUVs) to large multilamellar vesicles (MLVs). Smaller liposomes (below 100 nm) can penetrate the skin more effectively, whereas larger ones may remain on the surface for longer periods, which could be useful for local action.
   - Multilamellar liposomes provide a slower and more controlled release of the drug compared to unilamellar liposomes, which release the drug more rapidly. (26)
2. **Liposome Composition**:
   - The choice of phospholipids (such as phosphatidylcholine, cholesterol, or sphingomyelin) significantly influences liposome stability, skin penetration, and drug release profile. Phospholipids with long-chain fatty acids can improve the rigidity of the liposomal bilayer, prolonging drug retention in the skin.
   - The inclusion of cholesterol in the liposomal bilayer can further stabilize the structure and control drug release by reducing the permeability of the lipid bilayer.(27)
3. **Surface Charge and Modifications**:
   - The surface charge of liposomes can affect their interaction with the skin and cellular uptake. Cationic liposomes (positively charged) tend to interact more effectively with the negatively charged skin and keratinocytes, enhancing adhesion and penetration.
   - Liposomes can also be surface-modified with ligands or peptides to target specific receptors on the skin or immune cells involved in psoriasis. (28)
4. **Drug Encapsulation Efficiency**:
   - The efficiency with which a drug is encapsulated within a liposome influences the overall therapeutic efficacy. Hydrophilic drugs are encapsulated within the aqueous core, while lipophilic drugs are embedded in the phospholipid bilayer. High encapsulation efficiency ensures that a substantial amount of the drug reaches the target site. (29)
5. **Stability of Liposomes**:
   - Stability is a crucial factor in the effectiveness of liposomes. Unstable liposomes may release their contents prematurely or degrade before reaching their target. The stability of liposomes can be influenced by environmental factors such as pH, temperature, and light exposure.
   - Liposomes containing antioxidants or preservatives can help improve stability and extend the shelf life of the formulation. (30)

Example: Liposomal Methotrexate for Psoriasis Treatment

- Methotrexate, an immunosuppressive agent used to treat severe psoriasis, has significant side effects when administered systemically. Liposomal formulations of methotrexate have been developed to enhance topical delivery, targeting the skin while reducing systemic exposure.
  - Mechanism of Action: Methotrexate-loaded liposomes can penetrate the thickened psoriatic skin, delivering the drug directly to inflamed keratinocytes and immune cells (such as T cells). This targeted delivery helps reduce inflammation and keratinocyte proliferation.
  - Effectiveness: Studies have shown that liposomal methotrexate reduces the severity of psoriatic plaques more effectively than conventional formulations, with fewer systemic side effects (31).

(C) Microneedle system

Microneedle systems represent an innovative approach for delivering therapeutic agents through the skin in the treatment of psoriasis, a chronic inflammatory skin disease characterized by thickened plaques, scaling, and immune dysregulation. These devices consist of small, minimally invasive needles that create microchannels in the skin, enhancing drug penetration, bypassing the stratum corneum (skin's outer barrier), and facilitating targeted and controlled drug delivery.

Mechanism of Action of Microneedle Systems in Psoriasis

1. **Enhanced Skin Permeation**:
   - Microneedles pierce the outermost layer of the skin (stratum corneum) without reaching nerve endings, making the process relatively painless while creating channels that allow drugs to penetrate deeper into the skin. This enhanced permeability enables the delivery of both hydrophilic and hydrophobic drugs to the dermis and epidermis, where psoriasis-related inflammation occurs.
   - For psoriasis, drugs such as methotrexate, corticosteroids, and biologics are often poorly absorbed through the thickened psoriatic skin. Microneedles overcome this barrier by creating microconduits for drug delivery, allowing these medications to reach their target tissues effectively. (32)
2. **Targeted and Localized Drug Delivery**:
   - By delivering drugs directly into the skin, microneedles offer localized treatment at psoriatic lesions, reducing the risk of systemic absorption and related side effects. This targeted delivery ensures that therapeutic concentrations of drugs are maintained in the affected area without being distributed throughout the body.
   - Microneedles can also deliver biologics (e.g., TNF-α inhibitors, IL-17 inhibitors) directly to the immune cells responsible for the inflammation in psoriasis, offering a localized treatment that would otherwise require systemic injection or intravenous infusion. (33)
3. **Controlled Drug Release**:
   - Dissolvable microneedles can encapsulate drugs that are gradually released into the skin as the microneedles dissolve. This allows for controlled and sustained release of therapeutic agents, which is particularly beneficial in chronic diseases like psoriasis that require long-term management.
   - This sustained drug release ensures consistent therapeutic effects over time, reducing the need for frequent application and improving patient compliance. (34)
4. **Immune Modulation**:
   - Psoriasis is driven by immune dysregulation, primarily involving T cells and cytokines like TNF-α, IL-17, and IL-23. Microneedles can deliver immunomodulatory agents directly to immune cells in the dermis, helping to downregulate the overactive immune response in psoriatic lesions. This local immune modulation can minimize the systemic side effects commonly associated with oral or injected immunosuppressants. (35)

Factors Affecting the Performance of Microneedle Systems in Psoriasis

1. **Microneedle Type and Design**:
   - Microneedles can be made of different materials (metal, silicon, polymers, or dissolvable materials), each impacting how the drug is delivered. Solid microneedles can create channels through which topical drugs are applied, while dissolvable microneedles can encapsulate drugs within the needles, releasing them as they dissolve in the skin.
   - The length, shape, and sharpness of microneedles affect how deeply they penetrate the skin and how efficiently they deliver the drug. Shorter microneedles (around 150-600 μm) are typically used to avoid

pain and injury, targeting the upper dermal layers where psoriatic inflammation occurs. (36)

2. **Skin Thickness and Psoriatic Skin Condition**:
   - Psoriatic skin is often thickened due to hyperproliferation of keratinocytes, which can influence the performance of microneedles. Longer microneedles may be needed to effectively penetrate the thicker plaques in severe cases, while milder forms of psoriasis may require shorter microneedles.
   - Additionally, the inflammatory state of psoriatic skin (redness, scaling, and irritation) may impact the sensitivity of the skin to microneedle penetration, potentially requiring adjustments in needle length or pressure applied during use. (37)
3. **Drug Encapsulation and Release Kinetics**:
   - The encapsulation efficiency of drugs in dissolvable microneedles is a critical factor affecting their therapeutic effectiveness. Microneedles must encapsulate sufficient quantities of drugs to deliver the required therapeutic dose. Factors like drug solubility, pH, and the nature of the microneedle material influence how well the drug is loaded and released.
   - The rate of drug release is also influenced by the microneedle material—rapidly dissolving microneedles may release the drug in minutes, while more stable formulations can provide sustained release over hours or days. (38)
4. **Pain and Tolerability**:
   - While microneedles are generally considered painless, their tolerability can depend on factors like needle length, sharpness, and the number of microneedles in the array. Most patients report minimal discomfort, but in sensitive or inflamed psoriatic lesions, some may experience mild irritation or itching during or after microneedle application.
   - Microneedle systems need to be designed in a way that maximizes patient comfort while ensuring effective drug delivery to the affected skin layers. (39)

Example: Dissolvable Microneedles for Dimethyl Fumarate Delivery in Psoriasis

- Dimethyl fumarate (DMF) is an anti-inflammatory agent often used in psoriasis treatment. However, its use is limited by systemic side effects, particularly gastrointestinal discomfort. To overcome this, dissolvable microneedles have been developed to deliver DMF directly to psoriatic lesions, reducing systemic exposure.
  - **Mechanism of Action**: The microneedles are composed of biocompatible polymers that dissolve upon contact with the skin, releasing DMF into the dermis. This localized release modulates the immune response in psoriatic lesions by reducing the activity of pro-inflammatory cytokines like TNF-α and IL-17.
  - **Effectiveness**: Studies have shown that microneedle-mediated delivery of DMF significantly reduces the severity of psoriatic plaques with fewer systemic side effects compared to oral DMF administration. The localized delivery enhances drug efficacy at the site of inflammation and avoids the first-pass metabolism associated with oral delivery. (38)

(D) Transdermal Patches

Transdermal patches offer a non-invasive and convenient way to deliver drugs through the skin, making them an attractive option for treating **psoriasis**. Psoriasis is characterized by immune dysregulation, keratinocyte hyperproliferation, and skin inflammation, and requires long-term drug management. Transdermal patches provide controlled, sustained delivery of therapeutic agents, which can help manage the chronic symptoms of psoriasis while minimizing systemic side effects.

Mechanism of Action of Transdermal Patches in Psoriasis

1. **Drug Penetration Through the Skin**:
   - Transdermal patches deliver drugs through the skin in a controlled manner. They are designed to bypass the stratum corneum, the outermost skin layer that serves as a barrier to most drugs, by either chemically enhancing drug permeability or using formulations that facilitate penetration.
   - In psoriasis, drugs like corticosteroids, vitamin D analogs, or biologics can be delivered via transdermal patches to reduce inflammation and abnormal keratinocyte proliferation. (36)
2. **Sustained and Controlled Drug Release**:
   - Transdermal patches allow for sustained release of drugs over a long period, ensuring a steady therapeutic concentration at the site of application. This is particularly beneficial for psoriasis patients who require continuous exposure to drugs to manage symptoms.
   - Matrix patches and reservoir patches are commonly used. Matrix patches incorporate the drug into a polymer matrix, allowing it to diffuse slowly, while reservoir patches contain a liquid or gel reservoir, offering controlled release through a rate-controlling membrane. (40)
3. **Localized Action at Psoriatic Lesions**:
   - Transdermal patches can be applied directly to psoriatic plaques, delivering high concentrations of drugs precisely where they are needed, while avoiding systemic exposure. This localized delivery reduces the risk of systemic side effects commonly seen with oral or injectable drugs.
   - For example, corticosteroid patches can be used to reduce inflammation at the site of psoriatic plaques, helping to reduce redness, scaling, and thickness of the lesions.(42)
4. **Minimization of Systemic Side Effects**:
   - By delivering drugs locally and avoiding first-pass metabolism (as seen in oral administration), transdermal patches can reduce drug toxicity and systemic side effects. This is particularly important in psoriasis treatment, where many drugs (e.g., methotrexate, immunosuppressants) carry risks of adverse effects when absorbed systemically.
   - Vitamin D analog patches have been developed to treat psoriasis with minimal systemic absorption, reducing the risk of hypercalcemia, a common side effect of oral vitamin D treatments. (43)

Factors Affecting the Performance of Transdermal Patches in Psoriasis

1. **Skin Permeability**:
   - The permeability of the skin is a critical factor in the effectiveness of transdermal patches. In psoriatic skin, the stratum corneum is often thicker due to hyperkeratosis, which can impede drug penetration. To enhance drug permeation, chemical enhancers like ethanol, dimethyl sulfoxide (DMSO), or lipophilic carriers are often incorporated into the patch.
   - Patches may also use microneedles or iontophoresis (using electrical current to enhance drug delivery) to overcome the barrier posed by the thickened psoriatic skin. (42)
2. **Patch Adhesion and Skin Hydration**:
   - Patch adhesion is essential for maintaining drug contact with the skin. In psoriasis, the scaly and inflamed skin can affect how well a patch adheres, reducing drug delivery. Hydrogels and polymer-based adhesives can improve patch adherence to psoriatic plaques.
   - Skin hydration also plays a role in patch performance. Dry or thickened psoriatic skin may reduce the hydration needed for optimal drug diffusion. Moisturizers or occlusive dressings can be applied before patch use to enhance skin hydration and improve drug penetration. (40)

3. **Drug Solubility and Stability**:
   - The solubility of the drug in the transdermal patch matrix is a key factor in determining how effectively the drug can be delivered through the skin. Hydrophobic drugs generally penetrate the skin more easily, but hydrophilic drugs may require additional formulation strategies, such as the use of liposomes or nanoemulsions, to improve their solubility and enhance absorption.
   - Stability of the drug in the patch is also critical, especially for biologics like TNF-α inhibitors or interleukin blockers, which can degrade when exposed to air or light. Proper formulation and storage are necessary to maintain the efficacy of these sensitive drugs. (36)
4. **Patch Size and Application Duration**:
   - The size of the patch affects how much drug can be delivered and how long the patch remains effective. Larger patches can deliver more drugs, but may be uncomfortable for patients, especially when applied to sensitive areas affected by psoriasis.
   - The duration of patch application (typically 12-24 hours) also affects the release kinetics. Some patches are designed for extended wear, while others may require more frequent replacement, depending on the drug's release profile and stability. (42)

Example: Betamethasone Transdermal Patch for Psoriasis

- Betamethasone, a potent corticosteroid, is commonly used to treat psoriasis due to its anti-inflammatory and immunosuppressive properties. However, prolonged use of topical creams or ointments can lead to skin atrophy and systemic absorption. To address these issues, betamethasone transdermal patches have been developed.
  - **Mechanism of Action**: The transdermal patch delivers betamethasone directly to psoriatic plaques, reducing inflammation and keratinocyte proliferation. By maintaining a steady drug release over 24 hours, the patch minimizes the need for frequent application while ensuring localized treatment at the site of inflammation.
  - **Effectiveness**: Clinical studies have shown that betamethasone patches reduce plaque thickness and scaling in patients with mild-to-moderate psoriasis, with fewer systemic side effects compared to traditional topical formulations. The patch also improves patient adherence, as it requires less frequent application. (43)

(E) Smart Drug Delivery Systems

Smart drug delivery systems (SDDS) for psoriasis represent an advanced approach to delivering therapeutic agents with high precision, targeting specific areas of the skin, and responding to local stimuli such as inflammation, pH, or temperature. Psoriasis is a chronic inflammatory skin disease characterized by immune dysregulation and excessive keratinocyte proliferation. Traditional treatments can have systemic side effects or poor patient compliance, but SDDS aim to overcome these challenges by providing controlled, localized, and efficient drug release.

Mechanism of Action of Smart Drug Delivery Systems in Psoriasis

1. **Targeted Delivery to Psoriatic Lesions**:
   - Smart drug delivery systems can be designed to target inflamed psoriatic tissues by utilizing specific markers of the disease, such as overexpressed cytokines (TNF-α, IL-17), or changes in the microenvironment, like altered pH or temperature.

- Nanoparticles, liposomes, and polymeric micelles can be functionalized with ligands that specifically bind to receptors on the inflamed psoriatic cells, ensuring the drug is released primarily at the site of inflammation, reducing systemic side effects.(44)

2. **Stimuli-Responsive Systems**:

- Smart drug delivery systems often employ stimuli-responsive mechanisms where the drug is released in response to external (e.g., light, heat) or internal (e.g., pH, enzymes) stimuli. Psoriatic skin has a slightly more acidic pH and higher levels of reactive oxygen species (ROS) compared to normal skin, and SDDS can be designed to release the drug under these conditions.
- pH-responsive nanoparticles are engineered to remain stable in neutral conditions but degrade or swell in acidic environments, releasing their payload specifically at psoriatic lesions.
- ROS-sensitive systems trigger drug release in response to the oxidative stress present in inflamed psoriatic tissues. (45)

3. **Controlled and Sustained Release**:

- One of the advantages of smart drug delivery systems is the ability to provide controlled release of the drug over time. Hydrogel-based systems or nano-based carriers can encapsulate drugs and release them slowly over days or weeks, providing long-term management of psoriasis without the need for frequent application or systemic exposure.
- Temperature-sensitive hydrogels can release drugs in response to the increased heat associated with inflamed psoriatic lesions, offering on-demand drug delivery at specific sites. (46)

4. **Minimization of Side Effects**:

- By using smart drug delivery systems, it is possible to reduce the systemic absorption of drugs that can lead to adverse effects. For example, drugs like methotrexate or biologics (e.g., TNF-α inhibitors) have potent effects but carry significant risks when absorbed systemically. SDDS help localize these drugs at the site of psoriatic plaques, reducing overall body exposure and minimizing side effects such as liver toxicity or immunosuppression.
- In some cases, biodegradable nanoparticles release anti-inflammatory agents in a controlled manner, which helps maintain drug levels within the therapeutic window without causing systemic overload. (47)

Factors Affecting the Performance of Smart Drug Delivery Systems in Psoriasis

1. **Drug Encapsulation and Loading Efficiency**:

- The effectiveness of smart drug delivery systems depends heavily on the encapsulation efficiency and loading capacity of the carrier system. Poor encapsulation may lead to insufficient drug delivery at the target site. The physical properties of the drug (e.g., solubility, molecular weight) also affect how well it can be encapsulated in liposomes, micelles, or polymer matrices.
- Hydrophobic drugs typically show better encapsulation efficiency in lipid-based systems, while hydrophilic drugs may require more complex formulations like dual-layer nanoparticles or multi-functional polymers. (48)

2. **Stability and Release Kinetics**:

- The stability of the smart delivery system in the skin environment is a critical factor. Nanoparticles or micelles must remain stable long enough to deliver their payload, especially in the harsh environment of psoriatic plaques, which often feature an excess of proteolytic enzymes and inflammatory mediators.

- The rate of drug release depends on the material used for the delivery system. For example, PEGylated nanoparticles often provide a slow and controlled release due to the shielding effect of PEG (polyethylene glycol), while pH-sensitive systems release their payload more rapidly in the acidic conditions of inflamed skin. (45)

3. **Penetration Through Psoriatic Skin**:

- Psoriatic skin is characterized by thickening of the stratum corneum and hyperkeratosis, which can impede drug penetration. Smart systems must either be small enough to pass through the altered barrier or be designed to penetrate more effectively, such as through the use of penetration enhancers or microneedles that can bypass the stratum corneum.
- Nanocarriers smaller than 100 nm in size generally penetrate the skin more effectively, but larger systems may require additional strategies such as chemical penetration enhancers or physical methods like ultrasound to improve skin absorption. (49)

4. **Biocompatibility and Toxicity**:

- The materials used in smart drug delivery systems must be biocompatible and non-toxic to avoid triggering unwanted immune responses or local irritation. For example, polymeric nanoparticles made from PLGA (polylactic-co-glycolic acid)) are biodegradable and approved for medical use. These materials slowly degrade into non-toxic byproducts (e.g., lactic acid) that the body can easily metabolize.
- Any chemical enhancers or stimuli-responsive materials must also be safe for long-term use, especially in chronic conditions like psoriasis, where repeated application is necessary. (42)

Example: Nanoparticle-Based Methotrexate Delivery System for Psoriasis

- Methotrexate, a well-known systemic treatment for psoriasis, often causes significant side effects such as liver toxicity when administered orally or intravenously. To improve the safety and efficacy of methotrexate, nanoparticle-based delivery systems have been developed to provide localized and controlled drug release.
- **Mechanism of Action**: Nanoparticles encapsulating methotrexate are functionalized with ligands that target inflamed psoriatic skin, releasing the drug in response to pH changes or increased ROS levels in the skin microenvironment. The nanoparticles allow for localized delivery to psoriatic plaques, minimizing systemic absorption and reducing side effects.
- **Effectiveness**: Studies have demonstrated that methotrexate-loaded nanoparticles can significantly reduce psoriatic plaque size and inflammation with fewer side effects compared to traditional systemic methotrexate administration. The nanoparticle formulation enhances drug penetration through the thickened psoriatic skin and ensures sustained release over time. (48)

(F) Biologics Delivery System

Biologics are advanced therapeutic agents used for the treatment of moderate-to-severe psoriasis, targeting specific components of the immune system involved in the disease's pathogenesis. These agents include TNF-α inhibitors, IL-17 inhibitors, IL-23 inhibitors, and IL-12 inhibitors. While biologics have transformed psoriasis treatment, the challenges in their delivery—such as their large molecular size, sensitivity to degradation, and need for targeted action—have driven the development of specialized delivery systems.

Mechanism of Action of Biologics in Psoriasis

1. **Inhibition of Key Immune Pathways**:

- Psoriasis is driven by overactivation of the immune system, particularly through TNF-α, interleukin-17 (IL-17), and interleukin-23 (IL-23) pathways. Biologics are designed to selectively bind to these cytokines or their receptors, preventing them from triggering inflammation in the skin.
- For example:
  - Adalimumab and etanercept are TNF-α inhibitors that block the interaction between TNF-α and its receptor, reducing the inflammatory response that drives psoriasis symptoms.
  - Secukinumab and ixekizumab are IL-17 inhibitors that bind to IL-17, preventing it from activating immune cells and keratinocytes.
  - Ustekinumab is an IL-12/IL-23 inhibitor that blocks both cytokines, interfering with the differentiation of Th1 and Th17 immune cells, which are key drivers of inflammation in psoriasis. (50)

2. **Monoclonal Antibodies (mAbs)**:

- Biologics are often monoclonal antibodies (mAbs) designed to target specific cytokines or immune receptors. These antibodies are engineered to recognize and bind to these immune system proteins with high specificity, neutralizing their activity.
- The large size of mAbs, typically around 150 kDa, limits their ability to penetrate the skin when applied topically, necessitating systemic routes of administration (subcutaneous or intravenous injection). (51)

3. **Reduction of Inflammatory Cascade**:

- By blocking specific cytokines like TNF-α, IL-17, or IL-23, biologics reduce the hyperactivation of immune cells (like Th17 cells) and subsequent keratinocyte proliferation, which are hallmarks of psoriasis.
- This leads to a reduction in skin inflammation, scaling, and the formation of psoriatic plaques. (52)

Biologics Delivery Systems: Challenges and Strategies

Given the large size and delicate nature of biologics, their delivery requires specialized systems to ensure stability, proper targeting, and efficacy.

1. **Stability and Protection from Degradation**:

- Biologics are proteins that are susceptible to degradation by proteolytic enzymes in the bloodstream and tissues. Delivery systems like nanoparticles, liposomes, or polymeric carriers protect these fragile molecules until they reach their target.
- Encapsulation of biologics in carriers like PLGA nanoparticles (poly-lactic-co-glycolic acid) can prevent premature degradation and allow for controlled, sustained release of the biologic at the target site. (53)

2. **Targeted Delivery to Inflammatory Sites**:

- Targeted delivery systems are designed to increase the concentration of biologics at inflamed psoriatic lesions while minimizing systemic exposure. Nanoparticles can be functionalized with ligands that bind to specific markers overexpressed in psoriatic plaques, such as integrins or cytokine receptors.
- PEGylation (the addition of polyethylene glycol chains) of biologics can also prolong circulation time and reduce immune clearance, enabling sustained activity at the target site. This approach has been used with biologics like certolizumab pegol.(54)

3. **Penetration and Bioavailability**:

- Due to their large size, biologics are usually administered via subcutaneous or intravenous injections to bypass the skin barrier. However, microneedle patches or transdermal systems are being explored

as potential ways to deliver biologics through the skin, offering a less invasive method of administration.

- These systems create microchannels in the skin, allowing biologics to penetrate into the dermis and exert their effects directly at the site of inflammation. (55)

4. **Controlled and Sustained Release**:

- To reduce the frequency of biologic administration, sustained-release systems are being developed. Hydrogels and polymer-based systems can encapsulate biologics and release them slowly over time, providing consistent therapeutic levels without frequent injections.
- For example, PLGA microspheres have been explored for delivering biologics like etanercept, allowing for a more controlled release over extended periods. (56)

Factors Affecting Biologics Delivery

1. **Size and Molecular Weight**:

- The large size of biologics (typically 150 kDa for monoclonal antibodies) affects their ability to penetrate biological barriers like the skin. Thus, most biologics are administered via injection rather than topically.
- Additionally, the large molecular size makes biologics more prone to clearance by the immune system and necessitates protective delivery systems to maintain efficacy. (57)

2. **Immunogenicity**:

- Biologics can be recognized as foreign proteins by the immune system, which may lead to the development of anti-drug antibodies (ADAs) that neutralize the biologic's activity. This can reduce the efficacy of treatment and lead to treatment failure.
- Strategies such as PEGylation and the use of biocompatible delivery systems help reduce immunogenicity by hiding the biologic from the immune system or modifying its structure to reduce immune recognition. (58)

3. **Half-Life Extension**:

- Extending the half-life of biologics is crucial to reduce the frequency of dosing. Fusion proteins, Fc modifications, and PEGylation are common strategies used to prolong the half-life of biologics, allowing for dosing intervals of several weeks or months.
- For example, ustekinumab (an IL-12/IL-23 inhibitor) has a long half-life, allowing for maintenance dosing every 12 weeks. (51)

Examples of Biologics Delivery Systems for Psoriasis

1. **PEGylated Certolizumab Pegol**:

- Certolizumab pegol is a PEGylated TNF-α inhibitor that has been designed to extend its half-life and improve its pharmacokinetic profile. The PEGylation process reduces immune clearance and allows for less frequent dosing (every 2-4 weeks).
- Mechanism of Action: Certolizumab binds to TNF-α, preventing it from interacting with its receptor and reducing inflammation in psoriatic skin.
- Effectiveness: Certolizumab pegol is effective in reducing psoriasis symptoms, with a favorable safety profile and minimal immunogenicity due to PEGylation. (51)

2. **Microneedle Patch for Adalimumab**:

- Researchers are exploring microneedle patches for delivering biologics like adalimumab directly through the skin. The microneedles create microchannels in the skin, allowing the biologic to bypass the stratum corneum and reach the dermis.

- **Mechanism of Action**: The microneedle patch facilitates the localized delivery of adalimumab, reducing systemic side effects and enhancing efficacy by directly targeting psoriatic lesions.
- **Effectiveness**: Studies have shown improved bioavailability and patient compliance with microneedle patches, as they offer a non-invasive alternative to injections. (49)

3. **Hydrogel-Based Etanercept**:

- Etanercept, a TNF-α inhibitor, has been encapsulated in hydrogel-based delivery systems to provide sustained release and improved patient compliance. Hydrogels release the biologic slowly, maintaining therapeutic levels over time.
- **Mechanism of Action**: Etanercept binds to TNF-α, reducing the inflammatory response in psoriasis.
- **Effectiveness**: Hydrogel-based delivery improves the bioavailability of etanercept and prolongs its therapeutic effects, reducing the need for frequent injections. (54)

Examples of Nanotechnology-Based Formulations in Psoriasis Treatment

SR NO	Active Ingredient	Nanoparticle Type	Mechanism of Action	Benefits	Ref
1)	Cyclosporine A	Solid Lipid Nanoparticles (SLNs), Nanocapsules	Inhibits T-cell activation and reduces pro-inflammatory cytokines	Improved skin penetration, reduced systemic toxicity	59
2)	Methotrexate	Polymeric Nanoparticles, SLNs	Inhibits DNA synthesis in proliferating keratinocytes, modulates immune response	Enhanced local delivery, reduced side effects	60
3)	Tacrolimus	Liposomes, SLNs	Inhibits calcineurin, preventing T-cell activation and inflammation	Reduced irritation, improved stability, localized action	61
4)	Clobetasol Propionate	Liposomes, Nanospheres	Suppresses inflammatory cytokine production	Enhanced penetration, localized delivery, fewer side effects	62
5)	Curcumin	Polymeric Nanoparticles, Liposomes	Inhibits NF-κB and pro-inflammatory cytokines, antioxidant properties	Improved solubility and stability, anti-inflammatory effect	60
6)					59

	Dithranol (Anthralin)	SLNs, Nanoemulsions	Reduces keratinocyte proliferation, anti-inflammatory	Improved skin tolerance, reduced irritation	
7)	Tazarotene	Liposomes, SLNs	Modulates keratinocyte differentiation, reduces proliferation	Enhanced skin penetration, reduced irritation	62
8)	Calcipotriol (Vitamin D Analog)	Liposomes, SLNs	Regulates keratinocyte proliferation and differentiation, anti-inflammatory	Enhanced stability, reduced irritation	59
9)	Apremilast	Nanoparticles, Solid Dispersions	Inhibits PDE4, reducing pro-inflammatory cytokine production (TNF-α, IL-17, IL-23)	Improved bioavailability, reduced side effects	63
10)	Psoralen	Liposomes, Nanoparticles	Inhibits DNA synthesis and induces apoptosis when activated by UVA light	Improved phototherapy efficiency, reduced dose	66
11)	Betamethasone	Nanostructured Lipid Carriers (NLCs)	Anti-inflammatory corticosteroid that reduces immune cell activity	Improved penetration, reduced systemic absorption	64
12)	Salicylic Acid	Nano capsules, Nanospheres	Acts as a keratolytic, reducing the thickening of the skin	Enhanced skin absorption, localized effect	67
13)	Resveratrol	Nano capsules, Liposomes	Antioxidant and anti-inflammatory, inhibits NF-κB signaling	Enhanced skin permeation, localized antioxidant effects	68
14)			Anti-inflammatory properties via		69

	Indigo Naturalis (Herbal Extract)	Liposomes, Polymeric Nanoparticles	inhibition of pro-inflammatory cytokines	Improved bioavailability, localized action	
15)	Etanercept (TNF-α Inhibitor)	Hydrogel-Based Nanoparticles	Binds and inhibits TNF-α, reducing inflammation	Sustained release, enhanced bioavailability	70
16)	Adalimumab (Anti-TNF-α)	Microneedle Arrays, Nanoparticles	Blocks TNF-α interaction with its receptor, reducing inflammation	Enhanced delivery, improved patient compliance	71
17)	Hydrocortisone	Nanospheres, Nanocrystals	Anti-inflammatory corticosteroid reducing immune response	Localized delivery, reduced skin irritation	72
18)	CBD (Cannabidiol)	Lipid Nanoparticles, Nano emulsions	Anti-inflammatory, modulates the endocannabinoid system	Improved stability, enhanced anti-inflammatory effect	73

Conclusion:

Smart Drug Delivery Systems (SDDS) hold significant promise for improving the treatment of psoriasis. By addressing the limitations of traditional therapies, SDDS offer targeted, controlled, and localized drug delivery, reducing systemic side effects and enhancing patient compliance.

Key advantages of SDDS in psoriasis include:

- **Targeted delivery:** SDDS can be designed to specifically target inflamed psoriatic lesions, minimizing off-target effects.
- **Controlled release:** SDDS can provide sustained drug release, reducing the frequency of application and improving patient adherence.
- **Reduced side effects:** Localized drug delivery can minimize systemic absorption and associated toxicities.
- **Enhanced drug penetration:** SDDS can overcome the thickened skin barrier in psoriasis, improving drug delivery to affected areas.

While SDDS offer significant potential, challenges and future considerations include:

- **Drug encapsulation and loading efficiency:** Ensuring efficient drug encapsulation and loading within the delivery system.
- **Stability and release kinetics:** Maintaining the stability of SDDS in the skin environment and controlling drug release.
- **Skin condition and interactions:** Addressing the impact of psoriatic skin on SDDS performance.
- **Patient factors:** Considering individual variations in skin characteristics and drug responses.
- **Clinical trials and regulatory approval:** Conducting rigorous studies to evaluate the safety and efficacy of SDDS for psoriasis.

Ongoing research and development are essential to overcome these challenges and translate SDDS into effective clinical therapies for psoriasis**.** By combining the advantages of SDDS with other treatment modalities, we can improve the quality of life for patients with psoriasis and provide more personalized and effective care.

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