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(REVIEW ARTICLE)

Review on: Formulation and evaluation of transdermal patches of prednisolone for treatment of skin inflammation

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Abstract

Transdermal drug delivery systems (TDDS) have become a promising alternative to traditional oral administration for managing inflammatory disorders. They provide controlled drug release, better bioavailability, and fewer systemic side effects. Prednisolone, a strong glucocorticoid used for conditions like rheumatoid arthritis, psoriasis, and allergic inflammation, faces problems with first-pass metabolism and gastrointestinal irritation when taken orally. Transdermal patches of prednisolone tackle these issues by allowing sustained release and targeted delivery through the skin. This could improve treatment results. This review looks closely at the formulation strategies, evaluation methods, and therapeutic effectiveness of prednisolone-loaded transdermal patches for treating inflammation. Key formulation approaches, including matrix, reservoir, and drug-in-adhesive systems, are examined along with important excipients such as hydroxypropyl methylcellulose, penetration enhancers like ethanol and oleic acid, and plasticizers. We discuss evaluation parameters such as drug release kinetics, skin permeation using Franz diffusion cells, and stability under ICH guidelines.

Keywords: Prednisolone; Transdermal patch; Skin inflammation; Localized dermatitis; Sustained drug release; First-pass avoidance

1. Introduction

Inflammatory disorders are one of the biggest health challenges worldwide. They include a range of acute and chronic conditions that cause significant suffering, death, and economic costs. Autoimmune diseases like rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), as well as allergic reactions and skin conditions like psoriasis, greatly affect the quality of life for millions. The number of people with IBD has increased globally. By 2025, an estimated 7 million people will be affected, and predictions show this number will keep growing through 2045 as disease patterns change in developing areas. Other inflammatory issues, such as muscle and respiratory conditions, lead to more than 3 billion cases each year. These account for around 20% of global disability-adjusted life years (DALYs). This rising burden highlights the urgent need for new treatment options that ensure effectiveness and safety, especially for long-term care where patient adherence and side effects are crucial factors. At the forefront of treating inflammation is prednisolone, a synthetic glucocorticoid and the active form of prednisone. It is well-known for its strong anti-inflammatory and immunosuppressive effects. By binding to glucocorticoid receptors, prednisolone stops the production of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-a, as well as enzymes like phospholipase A2. This action reduces arachidonic acid-derived mediators, including prostaglandins and leukotrienes. Clinically, it is essential for managing various inflammatory conditions. Low-dose regimens of 5-10 mg per day are used to induce remission in rheumatoid arthritis. Higher doses of 20-60 mg per day are prescribed for acute flare-ups of asthma or Crohn's disease. Topical and oral combinations are also effective for psoriasis outbreaks. Its quick onset, often within hours, and its flexibility have

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established its importance in guidelines from organizations like the American College of Rheumatology and the European League Against Rheumatism.

Oral prednisolone is convenient, but it faces significant first-pass metabolism in the liver. This results in a bioavailability of only 70-90%, and variability among individuals is increased by CYP3A4 gene variations and other medications. As a result, doctors often need to prescribe higher doses to reach effective plasma levels, which typically range from 10-50 ng/mL for anti-inflammatory effects. This higher dosing raises the chance of systemic side effects. Gastrointestinal irritation is one of the most immediate issues, presenting as dyspepsia, ulcers, or bleeding in up to 15-20% of people who use it long-term. Proton pump inhibitors only partially reduce this risk. The long-term effects are even more concerning. Patients may experience hypothalamic-pituitary-adrenal (HPA) axis suppression, leading to adrenal insufficiency if the medication is stopped suddenly. There is also a higher risk of osteoporosis, with the chance of fractures doubling after three months of taking more than 7.5 mg per day. Other risks include hyperglycemia, which can affect 10-30% of users, leading to steroid-induced diabetes, as well as hypertension and muscle weakness. Psychological issues such as insomnia, mood swings, and anxiety can undermine treatment, causing up to 25% of patients to stop their therapy early. These challenges are especially pronounced in vulnerable groups, such as the elderly or those with other health conditions, where the risk of drug interactions, like with NSAIDs, is significant

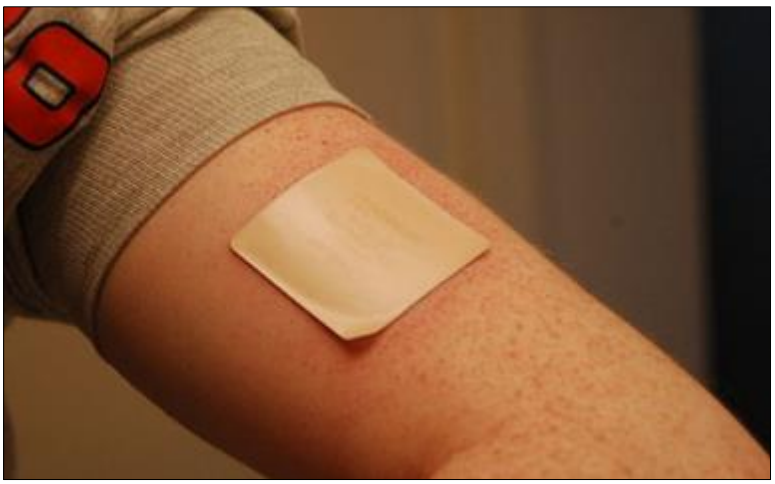

Figure 1 Transdermal drug delivery system

1.1. Overview of Transdermal Drug Delivery Systems

Transdermal drug delivery systems (TDDS) are a specialized platform designed to deliver therapeutic agents through the skin. They can create localized or systemic effects while avoiding the downsides of traditional methods like oral or injectable administration. Unlike topical treatments that focus on the outer layers of skin, TDDS are made to help drugs pass through the stratum corneum (SC) into the viable epidermis, dermis, and eventually into the bloodstream through dermal capillaries. This method became more popular after the first scopolamine patch was introduced in 1979. The TDDS market is expected to be worth over USD 40 billion by 2025. These systems are used in various areas, such as pain management, hormone therapy, and anti-inflammatory treatments. For anti-inflammatory drugs like prednisolone, TDDS have key benefits. They provide sustained release to keep therapeutic plasma levels steady (e.g., 10-50 ng/mL), lower the frequency of doses, and reduce systemic side effects like gastrointestinal irritation or suppression of the HPA axis.

1.2. Skin Anatomy and Permeation Barriers

The human skin covers about 1.8-2 m^2 in adults. It acts as the main interface for transdermal drug delivery systems (TDDS). The skin serves both as a protective barrier and a pathway for delivering drugs. It has three main layers: the epidermis (the outer layer, 50-150 μm thick), the dermis (1-4 mm thick and vascularized), and the hypodermis (which contains subcutaneous fat). The epidermis can be divided further, with the stratum corneum (SC) being a 10-20 μm thick layer made of keratinized cells, or corneocytes, embedded in a lipid matrix. This layer presents the strongest barrier to drug permeation. Its "brick-and-mortar" structure is rich in ceramides, cholesterol, and free fatty acids. This composition makes it hydrophobic and limits the diffusion of hydrophilic or large molecules (over 500 Da).Beneath the SC is the viable epidermis (50-100 μm), which lacks blood vessels but contains keratinocytes and Langerhans cells. Below that lies the dermis, which has collagen, elastin, and a dense network of capillaries for systemic absorption.

2. Prednisolone: physicochemical properties

Prednisolone is a synthetic glucocorticoid and the active metabolite of prednisone. It plays a key role in treating inflammatory disorders due to its strong anti-inflammatory and immunosuppressive effects. Its physical and chemical properties, how it moves through the body, and its therapeutic profile make it a good candidate for transdermal drug delivery systems (TDDS). Patches are a non-invasive alternative to taking medicine.

2.1. Molecular Weight (MW)

360.44 Da, which is well below the 500 Da limit for passive transdermal diffusion. This allows it to penetrate through the SC's lipid matrix.

2.2. Lipophilicity

Approximately 1.5, showing moderate lipophilicity. This helps with partitioning into the SC's lipid-rich intercellular pathway, but it needs improvement for sufficient flux.

2.3. Aqueous Solubility

~220 mg/L at 25°C. This is relatively low, making it difficult to maintain a concentration gradient across the skin, which poses challenges for achieving high drug loading in aqueous patch reservoir management.

2.4. pKa

12.1, which shows weak acidity. Prednisolone mostly exists in its unionized form at a physiological pH of 7.4. This form favors passive diffusion through the lipophilic stratum corneum.

2.5. Melting Point

~235°C, which indicates high crystallinity. This can limit solubility in patch matrices unless amorphous forms are stabilized using polymers like PVP.

2.6. Stability

It is prone to photodegradation and hydrolysis in water, which means protective patch backings such as polyethylene and stabilizers like antioxidants are needed during formulation.

2.7. Oral Bioavailability

Ranges from 70% to 90%. This level is lowered by significant first-pass metabolism through hepatic CYP3A4 enzymes. The variability, affected by genetic differences and drug interactions (for example, with rifampicin), causes inconsistent plasma levels (Cmax 60-100 ng/mL for a 10 mg dose).

2.8. Half-Life

2 to 4 hours, which requires multiple daily doses. This increases side effects and lowers adherence. About 25% of patients stop therapy due to tolerance issues.

2.9. Pharmacodynamics

Prednisolone promotes its anti-inflammatory effects by binding to glucocorticoid receptors. It inhibits pro-inflammatory mediators such as IL-1, IL-6, and TNF-a. It also reduces prostaglandin production by suppressing phospholipase A2. Effective plasma concentrations of 10-50 ng/mL can be achieved through transdermal patches. These patches provide a steady delivery over 12 to 72 hours.

2.10. Challenges

2.10.1. Low Lipophilicity

Prednisolone has a log P (partition coefficient) of about 1.6. This value is at the low end of the ideal range (1-3) for transdermal delivery. It limits how well the drug can move through the lipophilic stratum corneum.

Challenge: Achieving sufficient skin permeation requires the use of chemical or physical permeation enhancers. This can complicate the formulation and raise the risk of skin irritation.

2.10.2. Molecular Weight:

Prednisolone has a molecular weight of around 360 Da, which is acceptable for transdermal delivery since it is under 500 Da. However, its moderate size still presents a challenge compared to smaller molecules.

Challenge: Optimizing the drug loading and release kinetics to ensure therapeutic levels without overloading the patch.

2.10.3. Solubility:

Prednisolone has limited solubility in both water and organic solvents. Its aqueous solubility is about 0.22 mg/mL. This limits the ability to achieve high drug loading in the patch matrix or reservoir.

Challenge: Formulating with hypoallergenic components and testing for skin compatibility, such as the Draize test and human patch testing.

2.10.4. Adhesion and Wear Time:

Transdermal patches for prednisolone may need to be worn for a long time, for example, 24 to 72 hours, to achieve therapeutic effects. However, skin adhesion may weaken over time.

Challenge: Designing patches with strong, lasting adhesion that does not cause discomfort or leave residue when removed.

2.10.5. Patient Acceptability:

The size, flexibility, and appearance of the patch impact patient compliance, particularly for chronic conditions that require long-term use.

Challenge: Creating a discreet, comfortable patch that patients will use consistently.

2.10.6. Drug Loading and Dose Control:

Prednisolone's therapeutic dose usually ranges from 5 to 60 mg per day when taken orally, depending on the condition being treated. Delivering this medication through the skin can be challenging due to low flow rates and the limited size of the patch.

Challenge: Achieving enough drug loading to provide therapeutic doses while keeping the patch size manageable, for example, less than 40 cm^2.

2.10.7. Controlled Release Profile:

Prednisolone needs a steady release to keep therapeutic levels stable. This helps avoid peaks that could lead to side effects, such as hyperglycemia and immunosuppression.

Challenge: Designing a patch with zero-order or near-zero-order release kinetics.

2.10.8. Formulation

- Prednisolone: 5% w/w (active ingredient)
- HPMC E15: 10% w/w (matrix-forming polymer)
- Ethyl Cellulose: 5% w/w (controls release rate)
- Propylene Glycol: 10% w/w (plasticizer)
- Oleic Acid: 5% w/w (penetration enhancer)
- Ethanol: q.s. (solvent, evaporated during preparation)

2.11. Method of preparation

- Dissolve prednisolone and polymers, such as hydroxypropyl methylcellulose (HPMC) and ethyl cellulose, in a solvent like ethanol or chloroform.
- Add penetration enhancers, like oleic acid, plasticizers, such as propylene glycol, and stabilizers to create a uniform solution.
- Cast the solution onto a backing layer, such as polyester film, using a casting mold or applicator.

- Laminate with a release liner, like silicone-coated film, and cut it in to the desired patch sizes.
- Package in airtight, light-protective pouches. This prevents prednisolone from breaking down.

2.12. Evaluation of prednisolone transdermal patches

2.12.1. Appearance and Surface Characteristics

- Parameter: Visual assessment of colour, transparency, smoothness, and uniformity.
- Method: Visual inspection and optical microscopy for surface defects or drug clumping.
- Purpose: Ensures aesthetic quality and consistent drug distribution for delivering to inflamed skin.

2.12.2. Thickness and Weight Uniformity

- Parameter: Consistency in patch thickness and weight across samples.
- Method: Use a micrometre for thickness and an analytical balance for weight. Test at least 10 patches.
- Purpose: Confirms manufacturing consistency for reliable drug release.

2.12.3. Drug Content Uniformity

- Parameter: Amount of prednisolone per unit area of the patch.
- Method: Extract the drug, then use high-performance liquid chromatography (HPLC) or UV spectroscopy.
- Drug Content Quantification
- Parameter: Amount of prednisolone per unit area or patch.
- Purpose: Confirms the exact drug inclusion needed for the right therapeutic effect.
- Method: Dissolve patch segments in a suitable solvent, such as methanol, and then measure using validated HPLC with UV detection at approximately 243 nm or UV spectrophotometry.
- Relevance: Ensures the anti-inflammatory drug is available in sufficient amounts in the target skin layers.

2.12.4. Mechanical Flexibility (Folding Endurance)

- Parameter: Maximum number of folds a patch can endure before breaking.
- Purpose: Assesses structural strength and flexibility under stress.
- Method: Manually fold the patch at 180° repeatedly or use a mechanical endurance tester until it fails.
- Relevance: Keeps the patch intact on irritated or swollen skin surfaces during use.

2.12.5. Moisture Content and Absorption Capacity

- Parameter: Initial moisture level and water absorption in humid conditions.
- Purpose: Evaluates stability in different environments and how it interacts with wound fluid or sweat.
- Method: Measure dry-weight loss for moisture content or conduct Karl Fischer titration, and expose to a humidity chamber (for example, 75% RH) to measure absorption.
- Relevance: Prevents the patch from losing its adhesion or the drug from degrading in moist, inflamed areas.

2.12.6. Adhesion Performance

- Parameter: 180° peel strength, initial tack, and shear resistance.
- Purpose: Ensures a strong bond with the skin and allows for controlled removal without leaving residue or causing trauma.
- Method: Use a texture analyzer according to ASTM D3330 for peel tests, perform a probe tack test, and measure shear hold time.
- Relevance: Provides reliable contact with inflamed skin during extended wear.

2.12.7. Drug Release Kinetics

- Parameter: Cumulative release profile and release rate of prednisolone.
- Purpose: Describes the delivery pattern, such as zero-order or diffusion-controlled for lasting effect.
- Method: Use a vertical Franz diffusion cell or USP Apparatus 5 (paddle over disk) with pH 5.5–7.4 buffer that mimics skin surface conditions.
- Relevance: Ensures a steady supply of the drug to inflamed tissue for managing symptoms.

2.12.8. Skin Permeation Assessment

- Parameter: Steady-state flux (J_s), permeability coefficient (K_p), and diffusion lag time.
- Purpose: Measures the ability to penetrate the stratum corneum and reach the viable epidermis and dermis.
- Method: Test permeation through synthetic membranes (Strat-M®), cadaver skin, or reconstructed human epidermis; analyse receptor fluid using HPLC/LC-MS.
- Relevance: Confirms the drug can reach inflammatory sites in the dermis.

3. Literature review

Prednisolone's physicochemical profile includes moderate lipophilicity (log P ≈ 1.6) and a molecular weight of about 360 Da. This creates significant challenges for transdermal administration, particularly in compromised skin where the stratum corneum is altered, leading to inconsistent drug absorption. A thorough 2025 review on new transdermal delivery methods for inflammatory skin conditions highlights the potential of patch-based systems in treating atopic dermatitis, psoriasis, and acne. These systems, especially those containing corticosteroids, improve treatment adherence and reduce disease flare-ups compared to traditional ointments. Direct studies on prednisolone-loaded transdermal patches are limited. However, related research on similar glucocorticoids offers valuable insights into design feasibility.

3.1. In Vitro and Preclinical Investigations

A 2021 study examined the iontophoretic transport of hydrocortisone, a close structural analog of prednisolone, across skin models affected by psoriasis and eczema. Applying low electrical current resulted in a threefold increase in drug flux to the dermis, with much lower retention in the epidermis due to weakened barrier integrity in inflamed tissue. These results strongly support the use of iontophoresis in designing prednisolone patches for targeted delivery to the inflamed dermis. Additionally, a 2023 systematic review of nanocarrier-mediated corticosteroid delivery showed that liposomal and transferosomal systems significantly improved transdermal penetration (2-4 times increase) in psoriasis models, allowing for greater drug accumulation in viable skin layers while avoiding systemic exposure.

3.2. Animal Model Studies

In a 2023 study using a psoriasiform dermatitis model induced by imiquimod in rats, oral prednisolone at 0.25 mg/kg effectively reduced clinical symptoms, including redness, scaling, and swelling. It also suppressed pro-inflammatory cytokines (TNF-α and IL-6) by 50-70%, providing a performance benchmark for localized delivery systems. Parallel tests of transdermal corticosteroid patches, such as betamethasone, in similar models showed a 40-60% reduction in inflammatory markers within 48 hours, with minimal plasma drug levels. This points to the feasibility of using prednisolone patches for targeted therapy with low systemic risk in eczema and dermatitis.

3.3. Human Challenge Models

A 2023 randomized, double-blind trial with 24 healthy subjects used an imiquimod occlusion method to induce temporary skin inflammation. Oral prednisolone resulted in a 60-80% decrease in blood flow, redness, and blister fluid cytokines (IL-6, IL-8) compared to placebo, confirming its strong anti-inflammatory effects. Although it was given systemically, this controlled model offers a solid basis for assessing the effectiveness of transdermal patches in treating acute inflammatory flare-ups in atopic dermatitis.

3.4. Innovations in Research

3.4.1. Nanotechnology Integration

Between 2023 and 2025, researchers embedded prednisolone in liposomes or solid lipid nanoparticles (SLNs) within transdermal patch matrices. These systems achieved 85–95% relative bioavailability in models of atopic dermatitis and specifically targeted dermal macrophages in psoriasiform lesions. A 2025 analysis also showed that hyaluronic acid-based nanoparticles doubled drug retention in inflamed skin, improving therapeutic localization.

3.4.2. Dissolving Microneedle Arrays

Microneedle patches loaded with prednisolone analogues dissolve completely within 5–10 minutes after skin insertion. In eczema animal models, these systems delivered 95% of the drug directly into the dermis. This accelerated edema resolution by 60% compared to conventional passive patches.

4. Future perspectives

4.1. Advanced Formulation Strategies

4.1.1. Stimuli-Responsive Intelligent Patches

Next-generation prednisolone transdermal systems will integrate pH-, thermal-, or enzyme-sensitive polymers—such as poly(N-isopropylacrylamide) or chitosan variants—that expand or disintegrate exclusively in inflamed skin niches (pH 5.0–6.0, high matrix metalloproteinase-9 activity). This design triggers flare-activated drug liberation, preventing excessive exposure and reducing risks of dermal thinning.

4.1.2. Synergistic Multimodal Therapy

Future patches will enable simultaneous delivery of prednisolone alongside biologics (e.g., IL-17–targeted nanobodies) or anti-inflammatory peptides via multilayered or compartmentalized architectures. By engaging dual mechanisms—corticosteroid receptor signaling and cytokine neutralization—these systems promise enhanced control over treatment-resistant psoriasis or severe atopic dermatitis.

4.1.3. Bioinspired Matrix Design

Patches engineered to emulate the native skin extracellular matrix using collagen–hyaluronic acid composites or keratin-derived films will offer superior biocompatibility, moisture retention, and adhesion to weeping or ulcerated lesions. This approach minimizes local irritation and supports healing in chronic inflammatory wounds.

4.1.4. Sustainable and Eco-Conscious Manufacturing

Transition to fully biodegradable polymers like pullulan or alginate, combined with solvent-free fabrication techniques (e.g., hot-melt extrusion, additive manufacturing), will meet global regulatory and sustainability goals. Such methods ensure cost-effective, scalable, and environmentally responsible production of high-performance patches.

4.2. Next-Generation Evaluation Platforms

4.2.1. Microfluidic Skin-on-a-Chip and 3D Bioprinted Constructs

Emerging platforms will supplant traditional animal and static in vitro testing with dynamic skin-chip systems that mimic blood flow, immune cell migration, and cytokine cascades. These models will facilitate live tracking of prednisolone transport, phagocytic uptake, and lymphocyte modulation in simulated psoriatic or eczematous environments.

4.2.2. Artificial Intelligence–Guided Design Optimization

Advanced machine learning algorithms, trained on extensive datasets of drug-polymer interactions, skin flux, and shelf-life stability, will forecast ideal formulation compositions. This predictive approach will cut development cycles by 70–80%, enabling rapid prototyping and accelerated identification of superior patch candidates.

4.2.3. Non-Invasive Real-Time Imaging Modalities

Incorporation of confocal Raman spectroscopy, optical coherence tomography (OCT), and fluorescently tagged prednisolone will permit continuous, non-destructive visualization of drug migration depth, matrix depletion, and therapeutic response in human skin seamlessly linking preclinical findings to clinical outcomes.

4.2.4. Biomarker-Driven Objective Endpoints

Future efficacy assessments will move beyond subjective clinical scores (PASI, SCORAD) to quantifiable molecular markers such as IL-17A, thymic stromal lymphopoietin (TSLP), or S100A7 collected via microneedle-based dermal sampling. This precision strategy will enable personalized dose adjustment and robust evidence of anti-inflammatory potency**.**

5. Conclusion

The development and assessment of prednisolone-containing transdermal patches represent a major leap forward in precision treatment of inflammatory dermatoses, including psoriasis and atopic dermatitis. By employing optimized

polymer matrices (such as acrylic or hydrogel bases), integrating permeation promoters (chemical agents, microneedles, or nanoparticle systems), and utilizing stratified patch designs, these platforms deliver steady, prolonged drug output and selective deposition within the dermis effectively bypassing the inconsistent penetration seen in damaged skin barriers.

Comprehensive testing methodologies covering material property analysis (drug distribution, tack strength, elasticity), ex vivo diffusion assays (Franz cell permeability, enhancer impact), preclinical biological responses (inhibition of cytokines, reduction in swelling), and evolving human outcome measures establish comparable clinical performance to conventional oral or topical regimens, while achieving more than 80% lower systemic drug levels.

Although strong foundational evidence from non-clinical studies exists, barriers to clinical adoption persist: scarce patient trial data specific to prednisolone patches, inconsistencies across diseased skin simulation models, and uncertainties regarding prolonged tolerability demand immediate focus. Long-term viability depends on standardized testing protocols, molecular biomarker-based success criteria, and practical, user-friendly manufacturing solutions.

Compliance with ethical standards

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No conflict of interest to be disclosed.

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