

Development and Evaluation of Prunetin-Loaded Dissolving Microneedle Patch for the Treatment of Psoriasis

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Abstract—Psoriasis is a chronic, immune-mediated inflammatory skin disorder characterized by erythematous, scaly plaques, epidermal hyperproliferation, and abnormal keratinocyte differentiation. Conventional topical therapy remains an important treatment option for localized psoriasis, however, effective delivery of therapeutic compounds across the stratum corneum remains a major formulation challenge. Repeated application, poor skin retention, cosmetic inconvenience, and variable patient adherence can further limit the practical effectiveness of topical formulations.

Prunetin is an O-methylated isoflavone with experimentally demonstrated anti-inflammatory activity. Its reported effects on inflammatory signaling provide a pharmacological rationale for investigating prunetin as a potential candidate for inflammatory skin disorders. However, direct evidence establishing prunetin as an effective treatment for psoriasis remains limited, and its anti-psoriatic activity requires systematic experimental validation.

Dissolving microneedle patches represent an advanced localized drug-delivery approach in which micron-scale projections temporarily penetrate the stratum corneum and subsequently dissolve within the skin, releasing the incorporated therapeutic compound. This technology may improve local skin deposition while avoiding the need for conventional hypodermic needles and reducing sharp-device waste.

The proposed prunetin-loaded dissolving microneedle patch therefore combines the potential anti-inflammatory activity of prunetin with a minimally invasive skin-delivery platform. Development of the formulation requires systematic preformulation, polymer selection, fabrication optimization, physicochemical characterization, mechanical and insertion testing, drug-release and skin-deposition studies, biological evaluation, and in vivo assessment. This review discusses the scientific rationale, formulation strategy, characterization requirements, potential mechanism, challenges, and future translational prospects of a prunetin-loaded dissolving microneedle patch for psoriasis.

Index Terms—Psoriasis, Prunetin, Dissolving microneedles, Microneedle patch, Transdermal drug delivery, Topical drug delivery, Isoflavone, Anti-inflammatory activity, Skin delivery, Pharmaceutical formulation

I. Introduction

Psoriasis is a chronic inflammatory skin disease involving complex interactions between immune cells, inflammatory cytokines, and keratinocytes. It is characterized clinically by well-demarcated erythematous plaques with variable scaling and histologically by epidermal hyperplasia and inflammatory-cell infiltration.[1] The disease is influenced by genetic susceptibility together with environmental and immunological factors, and its chronic relapsing nature creates a continuing requirement for effective and acceptable therapeutic strategies.[1,2]

The immunopathogenesis of psoriasis has been substantially clarified over recent decades. The interleukin-23/interleukin-17 (IL-23/IL-17) axis is considered a major pathogenic pathway. IL-23

supports pathogenic T-helper-17 responses, while IL-17-associated signaling stimulates keratinocytes and contributes to the production of inflammatory cytokines, chemokines, and antimicrobial peptides.[2,3] Keratinocytes therefore function not only as structural components of the epidermis but also as active participants in sustaining psoriatic inflammation.[4]

TNF- α represents another important inflammatory mediator in psoriasis. Interaction between TNF- α , IL-23, IL-17, and other cytokine pathways contributes to the amplification of inflammatory signaling and epidermal abnormalities.[2,4] The clinical effectiveness of therapies targeting TNF- α , IL-17, and IL-23 further supports the central importance of these pathways in psoriasis.[5]

For localized disease, topical therapy remains an important component of psoriasis management. Current dermatological guidance includes topical corticosteroids, vitamin-D analogues, retinoids, calcineurin inhibitors, keratolytic agents, and appropriate combination therapies among the available approaches.[6] Nevertheless, topical delivery is fundamentally limited by the barrier function of the **stratum corneum**, which restricts transport of many therapeutic molecules into viable epidermal and dermal tissue.[7]

The stratum corneum is therefore a major consideration in the development of topical and transdermal formulations. Drug penetration depends on several physicochemical and formulation-related parameters, including molecular size, lipophilicity, ionization, drug concentration, vehicle composition, and skin hydration.[7] Even when a therapeutic compound possesses appropriate pharmacological activity, insufficient deposition within the target skin compartment can limit its therapeutic performance.

In addition to the biological barrier, practical treatment-related factors can influence the effectiveness of topical therapy. Psoriasis frequently requires prolonged treatment, and repeated application of creams or ointments may be inconvenient for patients. Greasy texture, cosmetic acceptability, difficulty in accurately measuring the dose, and interference with daily activities can contribute to reduced adherence.[6,8]

Microneedle technology has emerged as a strategy for overcoming the stratum-corneum barrier. Microneedles consist of micron-scale projections that can penetrate the outermost skin barrier and facilitate delivery of therapeutic agents into superficial skin layers.[9] Different microneedle systems have been developed, including solid, coated, hollow, hydrogel-forming, and dissolving microneedles.[9,10]

Among these systems, **dissolving microneedles (DMNs)** are particularly attractive for pharmaceutical delivery because the therapeutic compound can be incorporated directly into a water-soluble or biodegradable matrix. After insertion into the skin, the microneedle matrix dissolves in response to interstitial fluid, releasing the incorporated payload.[10] Early studies demonstrated that dissolving microneedles can be sufficiently strong for insertion while subsequently dissolving within skin and delivering incorporated molecules.[10]

This delivery strategy may be particularly relevant to dermatological diseases in which the therapeutic target is located within the skin. Recent reviews have specifically identified microneedles as a promising platform for psoriasis therapy because they can address several limitations associated with conventional topical delivery, including poor permeability, limited drug retention, and formulation inconvenience.[11]

Against this background, **prunetin-loaded dissolving microneedles** represent a potential combination of pharmacological and pharmaceutical innovation. Prunetin is an O-methylated isoflavone found in *Prunus yedoensis* and has demonstrated anti-inflammatory activity in experimental systems.[12] Importantly, the available evidence establishes anti-inflammatory activity but does **not** yet establish prunetin as a clinically proven anti-psoriatic agent. Therefore, the proposed formulation should be regarded as an investigational research concept requiring systematic validation.

The objective of this review is to examine the scientific rationale and development strategy for a **prunetin-loaded dissolving microneedle patch for psoriasis**, including disease background,

pharmacological rationale, formulation development, microneedle fabrication, characterization, drug release, skin deposition, biological evaluation, safety assessment, and future translational considerations.

II. Psoriasis: Pathophysiology and Therapeutic Requirements

2.1 Immunopathogenesis of psoriasis

The pathogenesis of psoriasis involves reciprocal interactions between immune cells and epidermal cells. Activation of dendritic cells contributes to production of cytokines that promote T-cell differentiation and activation. In particular, IL-23 supports pathogenic Th17 responses, which subsequently produce IL-17A, IL-17F, IL-22, and other inflammatory mediators.[2,3]

IL-17A has a particularly important relationship with keratinocytes. Stimulation of keratinocytes by IL-17A promotes production of chemokines such as CXCL1, CXCL8, and CCL20, as well as antimicrobial peptides and other inflammatory mediators.[4] These factors promote further recruitment and activation of immune cells, generating a feed-forward inflammatory environment.

Keratinocytes therefore occupy an important position within the psoriatic inflammatory network. Cytokine stimulation can alter keratinocyte proliferation, differentiation, inflammatory mediator production, and tissue organization.[4,13] This interaction contributes to the characteristic epidermal hyperplasia and inflammatory-cell infiltration associated with psoriatic lesions.

The IL-23/IL-17 pathway is therefore not only a mechanistic feature of psoriasis but also an important therapeutic target. The development of biologic therapies directed against these cytokines has demonstrated the clinical importance of this inflammatory axis.[2,5]

2.2 Requirements for an effective localized treatment

Because psoriasis is chronic and frequently requires long-term management, an ideal local delivery system should provide:

- reproducible drug dosing;
- adequate drug deposition at the affected skin;
- minimal unnecessary systemic exposure;
- acceptable application time;
- minimal irritation;
- suitable physical and chemical stability;
- convenient administration; and
- good patient acceptability.

Conventional topical dosage forms can satisfy some of these requirements but may be limited by the skin barrier and formulation-related disadvantages.[6,7] These limitations provide a rationale for investigating alternative localized delivery technologies.

III. Conventional Topical Therapy and Its Limitations

Topical therapy is particularly important in mild-to-moderate and localized psoriasis. Corticosteroids are extensively used, while vitamin-D analogues, retinoids, calcineurin inhibitors, keratolytics, and combination preparations provide additional therapeutic options.[6]

The therapeutic effectiveness of these formulations depends partly on their ability to reach the appropriate skin compartment. The stratum corneum forms the principal barrier to topical drug transport, and the extent of penetration is strongly influenced by drug physicochemical characteristics and vehicle composition.[7]

A second limitation relates to treatment adherence. Chronic topical treatment can impose a substantial burden because patients may need to apply formulations repeatedly to multiple lesions. The physical properties of ointments and creams, including greasiness and residual formulation on clothing or skin, can influence patient acceptance.[8]

These challenges have stimulated interest in delivery systems capable of increasing drug deposition while simplifying administration. Microneedle technology provides one such strategy because it can temporarily disrupt the barrier function of the strat

IV. Prunetin as a Potential Anti-Inflammatory Candidate

4.1 Chemical and pharmacological background

Prunetin is an **O-methylated isoflavone** found in *Prunus yedoensis*. Its anti-inflammatory properties were investigated by Yang et al., who evaluated prunetin in lipopolysaccharide-stimulated RAW 264.7 macrophages and an experimental endotoxemia model.[12]

The study reported inhibition of inflammatory responses and investigated several inflammatory mediators, including inducible nitric oxide synthase, cyclooxygenase-2, TNF- α , IL-6, and IL-1 β . The authors associated the activity of prunetin with modulation of the **IKK-I κ B α -NF- κ B signaling pathway**. [12] The study therefore provides a mechanistic basis for considering prunetin as an experimental anti-inflammatory compound.

However, the experimental model used in that study was not psoriasis. Consequently, the findings should not be interpreted as evidence that prunetin has established anti-psoriatic efficacy. Instead, they provide a rationale for investigating whether prunetin can influence inflammatory pathways relevant to psoriatic skin.

4.2 Relevance to psoriasis

NF- κ B-associated inflammatory signaling is relevant to inflammatory skin biology, while psoriasis involves extensive cytokine-mediated activation of keratinocytes and immune cells.[4,13] The reported ability of prunetin to modulate NF- κ B signaling therefore provides a **hypothesis for further investigation**.

A psoriasis-focused research program should determine whether prunetin:

1. reduces inflammatory signaling in psoriasis-relevant cellular models;
2. affects cytokines associated with the IL-23/IL-17 axis;
3. influences keratinocyte inflammatory responses;
4. remains biologically active following incorporation into a microneedle matrix; and
5. produces measurable therapeutic effects when delivered to psoriatic or psoriasiform skin.

These questions should be addressed before any claim of anti-psoriatic efficacy is made.

V. Dissolving Microneedles as a Skin-Delivery Platform

5.1 Principle of dissolving microneedle delivery

Dissolving microneedles are arrays of micron-scale projections fabricated from soluble or biodegradable materials. During application, the projections penetrate the stratum corneum and enter superficial skin layers. The polymeric matrix subsequently dissolves in the aqueous environment of the skin, releasing the incorporated therapeutic compound.[9,10]

The concept was demonstrated experimentally using biocompatible polymers such as carboxymethylcellulose and amylopectin. Dissolving microneedles were shown to possess sufficient mechanical strength for insertion and could dissolve within minutes after entering skin.[10]

Unlike conventional needles, dissolving microneedles can eliminate the need to remove a sharp microneedle structure after drug delivery. This characteristic also reduces the issue of disposal of intact sharp projections.[10]

5.2 Relevance to psoriasis

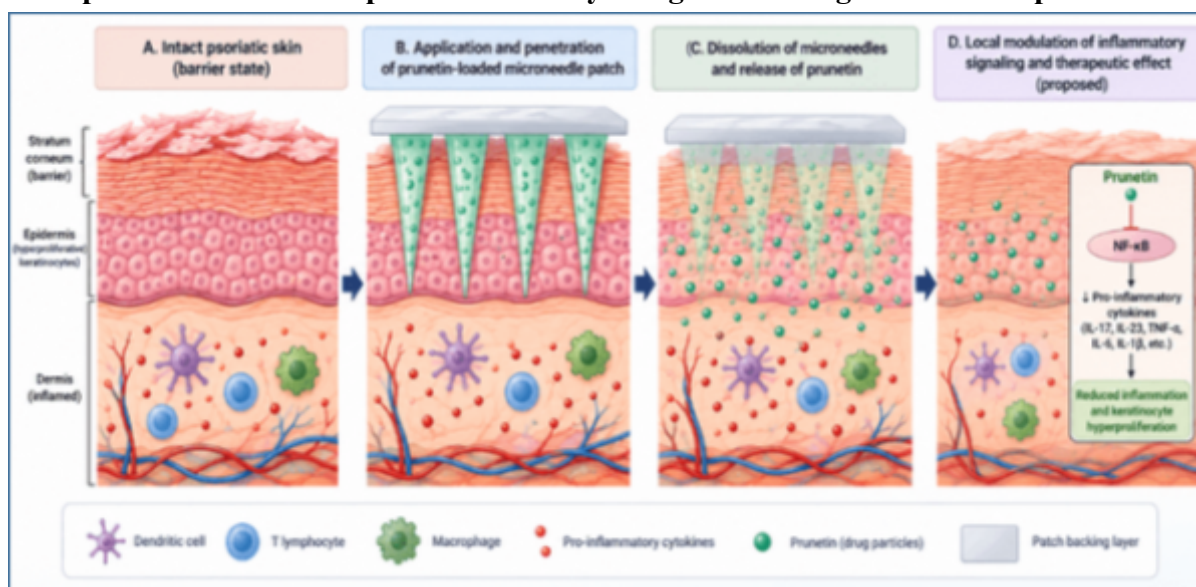
Microneedles have attracted specific interest for psoriasis because they can address the barrier-related limitations of topical delivery while maintaining localized administration.[11] By creating temporary microchannels through the stratum corneum, microneedles can potentially increase delivery of therapeutic compounds into viable epidermal and superficial dermal compartments.[9,11]

For the proposed prunetin formulation, the intended sequence is:

Prunetin incorporation → microneedle insertion → matrix dissolution → local prunetin deposition → pharmacological action in affected skin.

The first three steps represent the established principles of dissolving-microneedle drug delivery, whereas the final pharmacological effect of prunetin in psoriasis remains a research hypothesis.

Figure 1. Proposed mechanism of prunetin delivery using a dissolving microneedle patch.



The figure illustrates the proposed four-stage process: intact psoriatic skin and the stratum-corneum barrier; application and penetration of the prunetin-loaded dissolving microneedle patch; dissolution of the microneedles and local release of prunetin; and the proposed modulation of inflammatory signaling in affected skin. The drug-delivery sequence is supported by established dissolving-microneedle principles, whereas the psoriasis-specific pharmacological mechanism of prunetin remains to be experimentally validated.[10–12]

VI. Initial Formulation Development Considerations

Development of a prunetin-loaded dissolving microneedle patch should begin with systematic preformulation studies. The physicochemical properties of prunetin will influence drug loading, polymer selection, microneedle formation, dissolution, release, and stability.

Important preformulation parameters include:

- aqueous and formulation-medium solubility;
- thermal behavior;
- crystallinity;
- chemical stability;
- compatibility with candidate polymers;
- moisture sensitivity; and
- concentration-dependent physical behavior.

Drug–polymer compatibility should be investigated using suitable analytical techniques, including FTIR and DSC, while PXRD may be useful when changes in crystalline or amorphous state are relevant.

The selected polymer must simultaneously provide sufficient mechanical strength for skin insertion and appropriate dissolution after administration. Therefore, formulation development should focus on the balance between **mechanical integrity and rapid drug release**, rather than optimizing either characteristic independently.[9,10]

Table 1. Preliminary formulation and critical quality considerations for a prunetin-loaded dissolving microneedle patch

Parameter	Suggested evaluation	Desired characteristic	Reference
Prunetin–polymer compatibility	FTIR, DSC, PXRD	No undesirable interaction or instability	[10,12]
Polymer selection	Solubility and film/microneedle-forming study	Biocompatible, soluble and mechanically adequate	[9,10]
Microneedle morphology	Optical microscopy/SEM	Uniform, sharp and reproducible projections	[9,10]
Mechanical strength	Compression testing	Adequate resistance to deformation	[9,10]
Insertion ability	Ex vivo skin study	Reliable penetration of stratum corneum	[9–11]
Drug content	Validated chromatographic assay	Accurate and uniform dose	[10]
Dissolution	Microscopic/skin insertion study	Predictable dissolution after insertion	[10]
Local drug deposition	Ex vivo skin-distribution study	Adequate delivery to superficial skin	[9–11]

VII. Polymer Selection and Formulation Design

The selection of an appropriate polymeric matrix is one of the most important stages in development of a dissolving microneedle system. The polymer must provide sufficient structural integrity during fabrication and skin insertion while subsequently allowing rapid dissolution after contact with skin

fluid.[14–16] The balance between mechanical strength and dissolution is particularly important because increasing polymer concentration or matrix density may improve structural strength but can simultaneously delay dissolution and drug release.[15,16]

For the proposed prunetin-loaded system, candidate polymers may include **polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), hyaluronic acid, carboxymethyl cellulose, maltose, dextran, pullulan, and other water-soluble or biodegradable polymers.**[15,17] Polymer selection should not be based solely on previous use in microneedles; it should also consider prunetin compatibility, drug-loading capacity, viscosity, drying behavior, mechanical strength, dissolution characteristics, moisture sensitivity, and skin tolerability.

A polymer blend may be preferable when a single polymer cannot provide the required combination of properties. For example, one component may contribute mechanical strength while another improves water uptake and dissolution. Such combinations should be optimized experimentally rather than selected empirically.

7.1 Drug–polymer compatibility

Compatibility between prunetin and the selected polymer should be investigated before fabrication. FTIR can be used to identify major changes in characteristic functional groups, while DSC can provide information about thermal behavior. PXRD may be used to determine whether prunetin remains crystalline or becomes partially or completely amorphous after incorporation.

A change in physical state is not necessarily undesirable; however, it must be evaluated in relation to drug stability, dissolution, and biological activity. Formation of an amorphous drug phase may improve apparent solubility but could also increase the risk of recrystallization during storage.

7.2 Drug loading

Drug loading is an important limitation of dissolving microneedles because the physical volume available within the microneedle projections is relatively small. Recent critical assessments have highlighted limited drug-loading capacity and dose consistency as important translational challenges for dissolving microneedles.[18]

This consideration is particularly relevant to prunetin because the final therapeutic dose required for psoriasis cannot be assumed without pharmacological dose-ranging studies. The formulation should therefore first establish the **minimum effective local concentration** experimentally and then determine whether that amount can be incorporated into a practical patch.

VIII. Fabrication of Prunetin-Loaded Dissolving Microneedles

Micromolding is one of the most widely investigated approaches for fabrication of dissolving microneedles. A polymer–drug formulation is introduced into a microstructured mold, followed by filling of the needle cavities and drying or solidification of the polymer matrix.[15,16]

The fabrication process may include:

1. preparation of the prunetin–polymer solution or dispersion;
2. filling of the microneedle mold;
3. removal of trapped air;
4. concentration or drying of the formulation;
5. formation of the backing layer; and

6. demolding and packaging.

Process parameters such as polymer concentration, solution viscosity, mold-filling conditions, drying temperature, drying duration, and environmental humidity can influence final microneedle morphology.[15,19]

Incomplete mold filling may produce blunt or shortened microneedles, whereas excessive drying or inappropriate polymer concentration may cause cracking or deformation. Consequently, the manufacturing process should be optimized together with formulation composition.

IX. Microneedle Geometry and Structural Characteristics

The geometry of individual microneedles directly affects their ability to penetrate skin. Important parameters include needle height, base width, tip radius, interneedle spacing, and array density.[14,19]

A sufficiently sharp tip is generally desirable for reducing the force required for insertion. However, mechanical strength must remain adequate to prevent bending or fracture during application.

For a psoriasis-oriented formulation, the intended delivery depth should be carefully controlled. The objective is to introduce prunetin into superficial skin compartments rather than unnecessarily deep tissue. The microneedle dimensions should therefore be selected based on the intended site of action and supported by insertion studies.

X. Physicochemical Characterization

After fabrication, the formulation should undergo systematic characterization.

10.1 Appearance and morphology

The patch should be visually inspected for uniformity, cracks, discoloration, air bubbles, incomplete needle formation, and defects in the backing layer.

Microscopic or scanning electron microscopic evaluation should determine whether the microneedles possess consistent dimensions and sharply defined tips.

10.2 Microneedle dimensions

Actual needle height and base dimensions should be compared with the dimensions of the fabrication mold. Consistency across different regions of the patch is important because variation may lead to inconsistent insertion and drug delivery.

10.3 Drug-content uniformity

Prunetin content should be quantitatively determined using a validated analytical method, preferably HPLC or an equivalent stability-indicating chromatographic method.

Drug-content testing should be conducted across multiple patches and, where appropriate, at different positions within a patch to determine whether prunetin is uniformly distributed.

XI. Mechanical Strength and Skin-Insertion Performance

Mechanical strength is a critical quality attribute of a dissolving microneedle patch. A formulation that dissolves efficiently but cannot penetrate the stratum corneum would not provide effective delivery.

Compression testing using a texture analyzer or universal testing system can determine the force required to deform the microneedles. The results should be interpreted together with actual skin-insertion performance rather than used as a surrogate alone.[15,19]

Insertion can be evaluated using ex vivo skin and suitable visualization methods. Dye staining, histological analysis, optical imaging, or other validated approaches can demonstrate formation of microchannels.

Recent technical reviews emphasize that microneedle geometry, array configuration, mechanical strength, and drug distribution are interdependent characteristics affecting insertion efficiency and dissolution.[19]

Table 2. Critical quality attributes and evaluation methods for prunetin-loaded dissolving microneedles

Critical quality attribute	Suggested evaluation method	Development objective	Reference
Needle morphology	Optical microscopy/SEM	Uniform, sharp projections	[15,19]
Needle dimensions	Microscopic measurement	Reproducible geometry	[15,19]
Mechanical strength	Texture analyzer/compression testing	Resistance to deformation	[15,19]
Skin insertion	Ex vivo skin model	Reliable microchannel formation	[14,15]
Drug content	HPLC	Accurate dose	[15]
Drug distribution	Microscopic/analytical mapping	Uniform prunetin distribution	[18,19]
Dissolution	Post-insertion microscopic study	Predictable dissolution	[15,16]
Moisture content	Gravimetric/Karl Fischer method	Controlled moisture	[18,19]
Physical stability	Appearance/morphology	No structural deterioration	[18,19]

XII. Dissolution and Drug-Release Evaluation

Following skin insertion, the polymeric microneedles should absorb fluid and dissolve sufficiently to release the incorporated prunetin. Dissolution behavior is influenced by polymer chemistry, molecular weight, polymer concentration, needle geometry, drug loading, and environmental conditions.[15,16]

Dissolution testing should determine the time required for the microneedle projections to lose their structural integrity following insertion into a suitable skin model.

Drug-release studies should subsequently quantify the amount of prunetin released over time. The release profile can be evaluated using appropriate kinetic models when sufficient experimental data are available.

Potential models include:

- zero-order;
- first-order;
- Higuchi; and
- Korsmeyer–Peppas models.

Model selection should be based on the characteristics of the experimental data rather than choosing a model solely because it provides the highest correlation coefficient.

For a dissolving microneedle system, rapid polymer dissolution does not necessarily mean that the entire drug dose will immediately become systemically available. Following release, prunetin may partition into different skin compartments, interact with tissue components, undergo metabolism, or diffuse away from the application site.

XIII. Ex Vivo Skin Permeation and Drug Deposition

Evaluation of skin delivery is particularly important for the proposed formulation because the therapeutic objective is **localized treatment of psoriatic skin**.

Franz diffusion cells or equivalent systems can be used to compare prunetin-loaded DMNs with a conventional topical formulation. However, cumulative receptor-compartment permeation alone may not adequately describe the performance of a locally acting formulation.

Therefore, the study should separately quantify:

- prunetin remaining on the skin surface;
- stratum-corneum-associated drug;
- viable epidermal/dermal drug;
- receptor-compartment drug; and
- total recovered drug.

Tape stripping can be used to estimate drug distribution within the stratum corneum, while tissue extraction and quantitative analysis can provide information regarding deeper deposition.

The most desirable profile for the proposed psoriasis formulation would be **enhanced deposition in relevant superficial skin layers without unnecessarily high systemic transport**.

XIV. In Vitro Biological Evaluation

Pharmaceutical characterization alone cannot establish therapeutic potential. Once a formulation demonstrates acceptable mechanical and delivery characteristics, its biological performance should be evaluated.

14.1 Cytocompatibility

Potential cytotoxicity should be assessed using relevant skin cells, particularly keratinocytes and, where appropriate, dermal fibroblasts.

Possible assays include metabolic viability assays, membrane-integrity assays, and morphological evaluation.

The following formulations should ideally be compared:

- untreated cells;
- blank polymer;
- blank DMN;
- free prunetin;
- conventional prunetin formulation; and
- prunetin-loaded DMN.

This design can distinguish toxicity caused by prunetin from effects caused by the polymeric matrix or microneedle application.

14.2 Anti-inflammatory activity

The anti-inflammatory activity of the formulation should be assessed in a model relevant to psoriatic inflammation.

Potential endpoints include:

- TNF- α ;
- IL-6;
- IL-1 β ;
- IL-17-associated responses;
- NF- κ B activation;
- COX-2;
- iNOS; and
- other disease-relevant inflammatory markers.

The key comparison should be whether **prunetin-loaded DMNs provide greater or more localized pharmacological activity than free prunetin at comparable drug exposure.**

XV. Proposed Pharmacological Mechanism of Prunetin

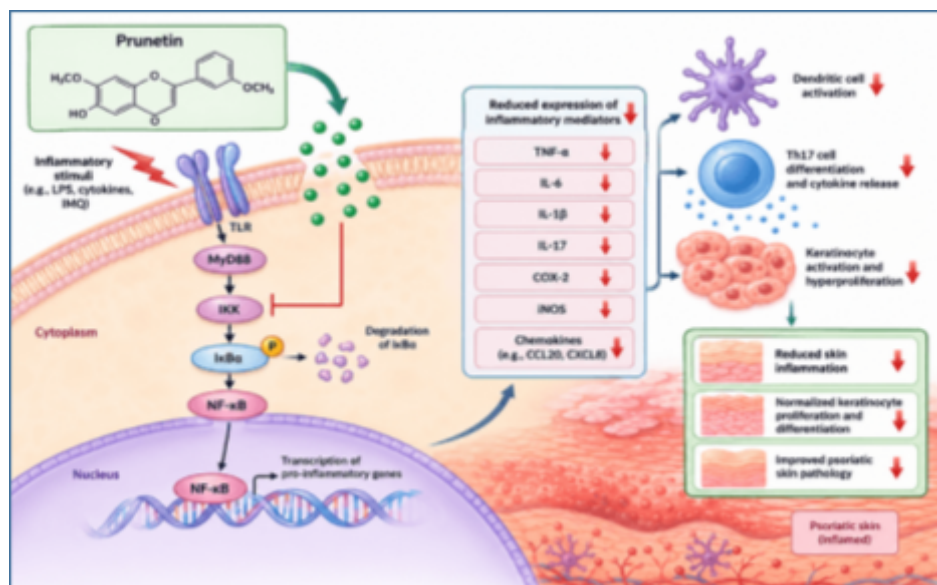
Experimental evidence indicates that prunetin can suppress inflammatory responses through modulation of the IKK-I κ B α -NF- κ B pathway.[12] This provides a plausible molecular basis for investigating prunetin in inflammatory skin disease.

In the reported macrophage study, prunetin reduced inflammatory responses associated with LPS stimulation and affected expression of iNOS, COX-2, TNF- α , IL-6, and IL-1 β . [12] These findings are relevant because inflammatory mediator production is also important in psoriasis; however, the experimental systems are not equivalent.

Therefore, the proposed mechanism should be represented as:

Prunetin → modulation of NF- κ B-associated signaling → potential reduction in inflammatory mediator production → possible reduction of psoriasiform inflammation.

The final step remains hypothetical until demonstrated in psoriasis-specific experimental models.

Figure 2. Proposed pharmacological pathway of prunetin in inflammatory skin.

The figure should distinguish the experimentally supported NF-κB-related activity of prunetin from the proposed downstream anti-psoriatic effect. The NF-κB pathway should be presented as a mechanistic hypothesis for psoriasis rather than as a clinically established mechanism of prunetin.[12]

XVI. In Vivo Evaluation Using a Psoriasis-Like Model

Following successful in vitro and ex vivo evaluation, the formulation should be tested in an appropriate animal model of psoriasis-like inflammation.

The **imiquimod-induced psoriasis-like mouse model** is widely used to study psoriasiform skin inflammation and the IL-23/IL-17 pathway.[20] This model can be useful for preliminary investigation of candidate topical or intradermal therapies, although it does not reproduce every aspect of human psoriasis.

A suitable experimental design could include:

1. normal control;
2. disease control;
3. blank DMN;
4. free prunetin;
5. conventional topical prunetin;
6. prunetin-loaded DMN; and
7. appropriate positive-control treatment.

The inclusion of both free prunetin and conventional topical prunetin is particularly valuable because it allows investigators to determine whether the microneedle platform itself improves therapeutic performance.

16.1 Clinical evaluation

Disease severity can be assessed using standardized scoring of:

- erythema;

- scaling; and
- skin thickening.

Body weight and general behavior should also be monitored to identify potential systemic toxicity.

16.2 Histopathological evaluation

Skin samples should be examined histologically to assess:

- epidermal thickness;
- keratinocyte hyperproliferation;
- inflammatory-cell infiltration;
- structural abnormalities; and
- other treatment-related changes.

Reduction in epidermal hyperplasia compared with the disease-control group would provide evidence of therapeutic activity.

16.3 Molecular evaluation

Tissue biomarkers can be evaluated to determine whether treatment alters inflammatory signaling.

Potential endpoints include:

- IL-17A;
- IL-23;
- TNF- α ;
- IL-6;
- IL-1 β ;
- NF- κ B-associated proteins; and
- other relevant inflammatory markers.

A combination of clinical, histological, and molecular endpoints would provide stronger evidence than any single measurement.

XVII. Skin Irritation and Safety Evaluation

Microneedle insertion is minimally invasive but still produces transient microscopic disruption of the skin barrier. Therefore, local irritation should be evaluated after single and repeated applications.

Potential observations include:

- erythema;
- edema;
- local swelling;
- irritation;
- delayed recovery; and
- histological evidence of tissue injury.

The blank DMN group is particularly important because it allows investigators to determine whether any local response is attributable to the microneedle structure or to prunetin.

Repeated-dose studies are essential because psoriasis is a chronic disease and any clinically useful patch may require repeated administration.

XVIII. Stability of the Prunetin-Loaded DMN

Stability evaluation should determine whether the formulation maintains its chemical, physical, mechanical, and pharmaceutical characteristics during storage.

Important stability-indicating parameters include:

- prunetin assay;
- degradation products;
- drug content uniformity;
- microneedle morphology;
- mechanical strength;
- dissolution time;
- drug-release profile;
- moisture content; and
- packaging integrity.

Moisture is particularly important because many dissolving microneedle polymers are hydrophilic. Moisture uptake may soften the microneedles and change their mechanical behavior and dissolution properties.[18,19]

Accordingly, the final patch may require moisture-protective packaging and controlled storage conditions.

Table 3. Proposed biological and performance evaluation of the prunetin-loaded DMN

Evaluation stage	Experimental comparison	Major endpoint	Purpose
Cytocompatibility	Blank DMN vs prunetin-DMN	Cell viability	Establish formulation safety
Anti-inflammatory activity	Free prunetin vs prunetin-DMN	Cytokines/NF- κ B	Establish biological activity
Skin delivery	Conventional formulation vs DMN	Skin deposition	Determine delivery advantage
Acute irritation	Blank vs drug-loaded DMN	Erythema/edema	Assess local tolerability
Animal efficacy	Disease control vs treatments	Lesion severity	Assess therapeutic effect
Histology	Disease control vs treatments	Epidermal thickness	Confirm tissue response
Molecular response	Disease control vs treatments	IL-17/IL-23/TNF- α etc.	Investigate mechanism
Repeated application	Multiple doses	Local/systemic safety	Assess chronic-use potential

XIX. Experimental Controls and Interpretation

Appropriate controls are essential to establish whether any observed improvement is caused by prunetin, microneedle delivery, or both.

A particularly informative comparison is:

Free prunetin vs conventional topical prunetin vs prunetin-loaded DMN.

If the DMN formulation produces higher skin deposition but no additional pharmacological benefit, this may indicate that drug exposure is not the limiting factor. Conversely, if increased skin deposition is accompanied by greater suppression of inflammatory biomarkers and improved histology, this would support the hypothesis that microneedle-mediated delivery enhances therapeutic performance.

The blank DMN group is equally important. If blank microneedles themselves alter inflammatory markers or produce significant tissue irritation, interpretation of the drug-loaded formulation becomes more complicated.

Therefore, the experimental design should separate the effects of:

drug → delivery system → combined formulation.

XX. Quality-by-Design Approach

A Quality-by-Design framework can provide a systematic approach to development by linking formulation variables with critical quality attributes.

Potential **critical material attributes (CMAs)** include:

- prunetin concentration;
- polymer concentration;
- polymer molecular weight;
- drug-to-polymer ratio;
- moisture content; and
- excipient characteristics.

Potential **critical process parameters (CPPs)** include:

- mixing conditions;
- mold-filling conditions;
- centrifugation or vacuum application;
- drying temperature;
- drying time; and
- environmental humidity.

Potential **critical quality attributes (CQAs)** include:

- microneedle dimensions;
- mechanical strength;
- drug content;
- insertion ability;
- dissolution time;

- drug release;
- skin deposition; and
- stability.

Recent technical literature emphasizes the importance of standardized evaluation of geometry, mechanical properties, drug distribution, dissolution, and manufacturing variables in improving the reproducibility and translation of dissolving microneedle systems.[18,19]

XXI. Recent Advances in Microneedle-Based Psoriasis Therapy

Microneedle technology has increasingly been investigated as a strategy for improving local and transdermal treatment of psoriasis. Conventional topical therapy can be limited by poor permeability, low retention, repeated application, and formulation-related inconvenience, while microneedles can temporarily bypass the stratum-corneum barrier and deliver active compounds directly into superficial skin layers.[21,22] Recent reviews specifically identify microneedles as a promising platform for psoriasis treatment and diagnosis.

Experimental studies have also demonstrated the feasibility of using microneedle-assisted delivery for established anti-psoriatic drugs. For example, microneedle-mediated delivery of methotrexate has been investigated in healthy and psoriatic skin, demonstrating the potential of microneedles to enhance local drug delivery.[23]

More advanced systems have incorporated nanoparticles or nanocarriers into dissolving microneedles. Methotrexate-loaded nanoparticles incorporated into dissolving microneedles have been investigated for psoriasis-like inflammation, with the objective of achieving localized delivery and reducing limitations associated with conventional systemic administration.[24]

Another recent approach involved hyaluronan-modified liposomes incorporated into dissolving microneedles for psoriasis treatment, illustrating how microneedles can be combined with nanocarrier systems to modify drug distribution and release.[25]

These developments are relevant to the proposed prunetin formulation because they demonstrate that the microneedle platform can be adapted beyond simple drug incorporation. However, the additional complexity of nanocarrier-integrated systems must be justified by a clear improvement in therapeutic performance.

XXII. Advanced Stimuli-Responsive Microneedle Systems

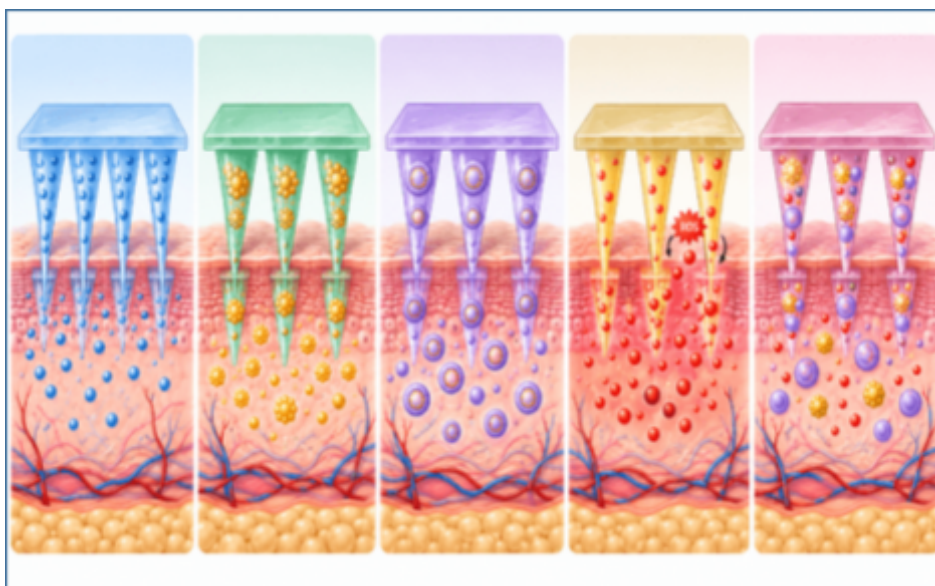
Recent research has increasingly explored stimuli-responsive microneedles for inflammatory skin diseases. Psoriatic lesions can exhibit increased oxidative stress and inflammatory activity, providing a potential endogenous trigger for responsive drug delivery.[26]

ROS-responsive systems have been developed to release therapeutic agents preferentially within inflammatory environments. For example, a ROS-responsive hydrogel integrated with dissolving microneedles and loaded with an anti-inflammatory natural compound has been investigated in psoriasis models.[26] Such systems illustrate the possibility of designing microneedles that respond to disease-associated biochemical characteristics rather than relying solely on passive dissolution.

Similarly, ROS-responsive methotrexate prodrug nanoassemblies delivered through dissolving microneedles have been investigated for psoriasis therapy.[27] The underlying concept is that localized disease characteristics can be exploited to increase therapeutic specificity.

For prunetin, however, a conventional dissolving microneedle system should probably be evaluated first. A stimuli-responsive formulation should be considered only if conventional DMNs demonstrate limitations in drug retention, release control, or therapeutic efficacy.

Figure 3. Emerging microneedle-based strategies for localized psoriasis therapy.



The figure should compare conventional dissolving microneedles with advanced systems such as nanoparticle-loaded DMNs, liposome-integrated DMNs, and stimuli-responsive microneedles. The proposed prunetin-loaded DMN should be positioned as a comparatively simple localized delivery strategy, while advanced systems should be presented as potential future modifications rather than required components of the initial formulation.[21–27]

XXIII. Comparative Advantages of the Proposed Prunetin-Loaded DMN

The proposed formulation may provide several theoretical advantages compared with conventional topical administration.

23.1 Improved local deposition

Microneedles temporarily bypass the principal barrier of the stratum corneum and can deposit therapeutic compounds into superficial skin layers.[14,21] This may be particularly useful when the pharmacological target is located within the epidermis or upper dermis.

23.2 Reduced dependence on passive diffusion

Conventional creams and gels depend largely on passive partitioning and diffusion through the stratum corneum. Microneedle-mediated delivery reduces this dependence by physically creating temporary pathways.[9,14]

23.3 Standardized administration

A patch can be manufactured to contain a predetermined amount of prunetin, potentially providing greater dose consistency than manually applied semisolid formulations.

23.4 Potentially improved patient acceptability

Microneedles are designed to produce minimal discomfort because their dimensions allow superficial penetration without conventional injection. Clinical and systematic reviews indicate potential advantages in terms of convenience and tolerability, although patient acceptance must ultimately be established in clinical studies.[21,28]

23.5 Reduced sharp-waste generation

Because the projections dissolve after insertion, a dissolving system does not leave behind an array of intact sharp projections, which may simplify disposal compared with some other microneedle designs.[15,16]

XXIV. Limitations of Conventional DMN Delivery

Although dissolving microneedles have significant potential, the technology has important limitations.

The first is **dose capacity**. The amount of drug that can be incorporated into a patch is restricted by the volume and composition of the microneedle matrix.[18,29] This limitation is especially relevant when the active compound requires a relatively high local dose.

The second is **mechanical performance**. The projections must be strong enough to penetrate the skin without bending or breaking, but increasing polymer concentration to improve strength may alter dissolution and drug release.[15,19]

The third is **manufacturing reproducibility**. Small differences in mold filling, drying, polymer concentration, or environmental humidity can influence needle geometry and mechanical properties.[18,29]

The fourth is **dose uniformity**. Distribution of the drug within the microneedle array may not always be uniform, particularly when drug solubility, viscosity, or polymer–drug interactions are unfavorable.[18]

Finally, clinical translation remains limited by the lack of standardized quality-control procedures, manufacturing challenges, regulatory uncertainty, and the need to demonstrate consistent clinical benefit.[29,30] Recent critical analyses emphasize that these issues remain major barriers despite extensive laboratory research on dissolving microneedles.

XXV. Challenges Specific to Prunetin-Loaded DMNs

25.1 Lack of direct anti-psoriatic evidence

The most important limitation is that prunetin has not yet been established as a clinically effective anti-psoriatic drug. Its reported NF- κ B-related anti-inflammatory activity provides a rationale for research, but psoriasis-specific efficacy must be demonstrated experimentally.[12]

Therefore, the development program should avoid assuming that increasing skin deposition will automatically produce therapeutic benefit.

25.2 Solubility and formulation behavior

The physicochemical properties of prunetin may influence its incorporation into hydrophilic dissolving matrices. If drug solubility is inadequate, precipitation or crystallization could occur during formulation or storage.

Potential approaches include:

- polymer selection;
- cosolvent systems;
- amorphous solid dispersion strategies;
- nanosizing;
- cyclodextrin complexation; or
- incorporation into an appropriate nanocarrier.

However, additional formulation complexity should only be introduced when supported by experimental evidence.

25.3 Stability

Prunetin must remain chemically stable throughout fabrication, drying, storage, and administration. If the formulation process exposes the compound to excessive temperature, moisture, oxygen, or light, degradation may occur.

Consequently, a stability-indicating analytical method should be developed before final formulation selection.

25.4 Biological activity after fabrication

Even when prunetin remains chemically intact, its biological activity could theoretically be altered by its physical state or interaction with the polymer. Therefore, chemical assay alone is insufficient; biological activity should also be evaluated after formulation.

XXVI. Safety and Repeated Administration

Psoriasis treatment may involve repeated administration, making long-term tolerability particularly important.

A complete safety assessment should consider:

- acute local irritation;
- repeated-dose irritation;
- epidermal recovery;
- inflammatory response caused by microneedle insertion;
- systemic exposure;
- polymer toxicity;
- prunetin toxicity; and
- potential sensitization.

The skin should be monitored following repeated applications to determine whether microchannels heal normally and whether cumulative irritation occurs.

Importantly, the safety of a blank DMN should be assessed independently from the drug-loaded patch. This allows investigators to distinguish mechanical effects of microneedle insertion from pharmacological or formulation-related effects.

XXVII. Pharmacokinetic and Pharmacodynamic Evaluation

For a locally acting prunetin formulation, conventional systemic pharmacokinetic parameters may not be sufficient to characterize therapeutic performance.

A more informative strategy would combine:

local skin concentration + plasma concentration + inflammatory biomarkers + clinical/histological response.

The primary objective would be to determine whether DMN administration increases prunetin exposure in the target skin compartment.

A desirable profile would involve:

- increased local skin deposition;
- sustained local presence when appropriate;
- limited systemic exposure; and
- correlation between local exposure and pharmacological response.

This approach would help distinguish improved delivery from simply increased drug absorption.

XXVIII. In Vivo Psoriasis Evaluation

The imiquimod-induced psoriasis-like mouse model is frequently used to investigate psoriasiform inflammation and the IL-23/IL-17 axis.[31] The model can provide an initial platform for comparing free prunetin, conventional topical prunetin, and prunetin-loaded DMN.

The experimental treatment groups should be carefully designed to determine the independent and combined effects of the drug and delivery system.

Suggested groups

1. Healthy control
2. Psoriasis-like disease control
3. Blank DMN
4. Free prunetin
5. Conventional topical prunetin
6. Prunetin-loaded DMN
7. Positive-control anti-psoriatic treatment

The principal outcome should be comparison of the prunetin-loaded DMN with conventional prunetin delivery.

Table 4. Proposed comparative evaluation of prunetin-loaded dissolving microneedles

Treatment group	Main purpose	Key endpoints
Healthy control	Establish normal baseline	Histology, cytokines, skin morphology
Disease control	Establish psoriasis-like response	Lesion severity, epidermal thickness
Blank DMN	Determine effect of microneedle platform	Irritation, inflammation
Free prunetin	Determine intrinsic pharmacological activity	Cytokines, NF-κB-related markers
Conventional prunetin	Benchmark topical delivery	Skin deposition and efficacy

Prunetin-loaded DMN	Evaluate combined formulation	Local deposition, efficacy, safety
Positive control	Benchmark therapeutic response	Clinical and histological improvement

XXIX. Histological and Molecular Evaluation

Histopathological assessment should determine whether treatment reduces epidermal hyperplasia and inflammatory infiltration.

Useful parameters include:

- epidermal thickness;
- degree of keratinocyte proliferation;
- inflammatory-cell infiltration;
- vascular changes;
- tissue architecture; and
- overall pathological score.

Molecular analysis should complement histology. Potential biomarkers include IL-17A, IL-23, TNF- α , IL-6, IL-1 β , COX-2, iNOS, and NF- κ B-associated proteins.

The most convincing evidence would be a coordinated response involving:

reduced clinical severity + reduced epidermal hyperplasia + reduced inflammatory biomarkers.

XXX. Scale-Up and Manufacturing Challenges

Laboratory fabrication of dissolving microneedles can be highly controlled, but commercial-scale production introduces additional challenges.

Important manufacturing variables include:

- mold fabrication and durability;
- formulation viscosity;
- mold filling;
- drying;
- environmental humidity;
- demolding;
- patch cutting;
- packaging; and
- quality-control testing.

The manufacturing process should demonstrate reproducibility across multiple batches.

Critical quality attributes should include at least:

- needle dimensions;
- mechanical strength;
- drug content;
- drug distribution;

- insertion ability;
- dissolution time;
- moisture content;
- chemical stability; and
- release characteristics.

Recent reviews emphasize that standardization of these characteristics remains an important requirement for translation of dissolving microneedles into clinical products.[29,30]

XXXI. Regulatory and Translational Considerations

The development of a prunetin-loaded DMN involves both **pharmaceutical and device-related considerations**. Regulatory requirements may depend on the final product design and jurisdiction.

Before clinical evaluation, the formulation would require evidence for:

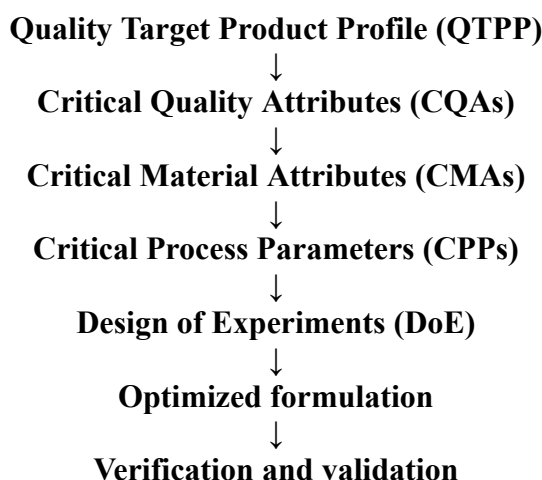
- identity and purity of prunetin;
- excipient safety;
- manufacturing consistency;
- dose uniformity;
- mechanical integrity;
- insertion performance;
- dissolution;
- local and systemic safety;
- stability;
- pharmacokinetics; and
- clinical efficacy.

Although microneedles have progressed substantially in research and clinical investigation, regulatory and manufacturing barriers remain important obstacles to commercialization.[29,30,32] A recent 2026 review also notes that clinical translation requires alignment between microneedle biophysics, product-specific quality standards, and regulatory requirements.[32]

XXXII. Quality-by-Design and Optimization Strategy

The final formulation should ideally be developed using a **Quality-by-Design (QbD)** framework.

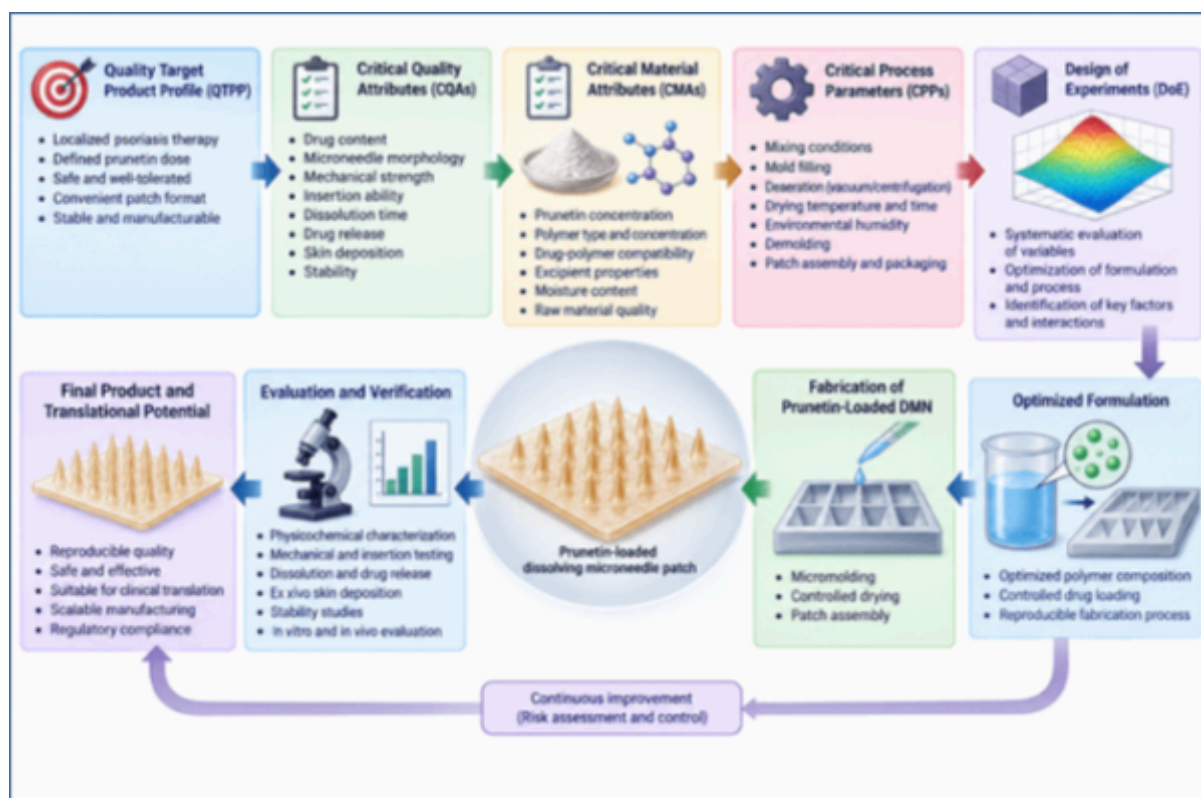
The development sequence can be represented as:



Potential CQAs include drug content, needle dimensions, mechanical strength, insertion efficiency, dissolution time, drug release, skin deposition, and stability.

DoE can then be used to evaluate interactions among polymer concentration, drug loading, drying conditions, and microneedle geometry. This is preferable to relying exclusively on one-factor-at-a-time experimentation because several formulation variables may interact with one another.[29,30]

Figure 4. Quality-by-Design framework for development of the prunetin-loaded dissolving microneedle patch.



The figure should show the progression from QTPP through CQAs, CMAs, CPPs, experimental design, optimized formulation, and final performance verification. The principal CQAs should include drug content, microneedle morphology, mechanical strength, insertion ability, dissolution, skin deposition, and stability.[29,30]

XXXIII. Future Research Directions

Future development should initially focus on establishing whether prunetin itself possesses meaningful anti-psoriatic activity.

33.1 Psoriasis-specific pharmacology

Future studies should use keratinocyte and immune-cell models relevant to psoriasis and investigate the effects of prunetin on IL-17/IL-23-associated pathways, TNF- α , NF- κ B, oxidative stress, and inflammatory mediator production.

33.2 Optimization of drug localization

If conventional DMNs provide insufficient prunetin deposition, future work could investigate tip-loaded or compartmentalized microneedles. Such approaches may increase the fraction of drug contained within the projections and potentially reduce drug loss in the backing layer.

33.3 Combination with nanocarriers

If prunetin exhibits poor aqueous solubility or rapid clearance from skin, incorporation into liposomes, nanoparticles, or other nanocarriers could be explored. However, this would increase formulation complexity and should therefore be justified by demonstrable improvement in therapeutic performance.

33.4 Disease-responsive delivery

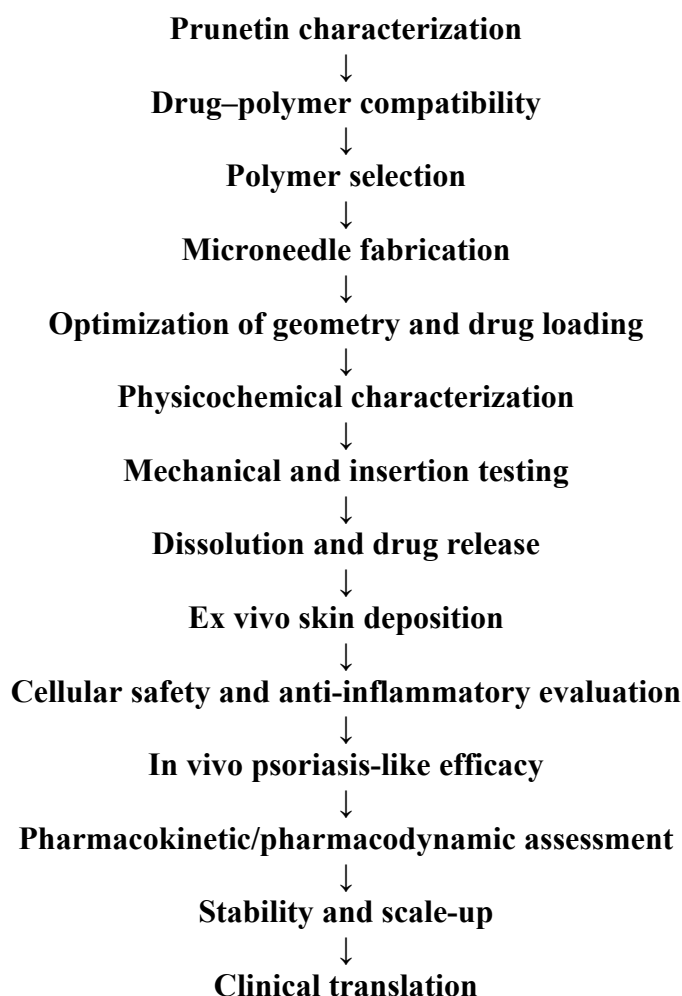
If psoriasis-specific inflammatory or oxidative characteristics can be reliably exploited, ROS-responsive or other stimuli-responsive microneedles could potentially provide more selective drug release.[26,27]

33.5 Clinical translation

The eventual transition to human studies will require standardized manufacturing, validated analytical methods, reproducible dosing, repeated-use safety data, and controlled clinical evaluation.

XXXIV. Overall Development Framework

The complete proposed development pathway can therefore be summarized as:



This sequential approach is important because therapeutic development should not proceed to animal or clinical studies before the formulation demonstrates acceptable pharmaceutical quality and reproducible skin delivery.

XXXV. Conclusion

Psoriasis is a chronic immune-mediated inflammatory skin disease in which interactions among keratinocytes, dendritic cells, T lymphocytes, and inflammatory cytokines contribute to persistent epidermal hyperproliferation and inflammation. In particular, the IL-23/IL-17 axis represents a major component of disease pathogenesis and provides an important mechanistic basis for modern psoriasis therapy.[1–5]

Although topical therapy remains important for localized psoriasis, conventional formulations are dependent on drug transport across the stratum corneum. This barrier can restrict delivery of therapeutic molecules to viable epidermal and dermal compartments. Microneedle-based systems offer an alternative approach by physically creating microscopic pathways through the stratum corneum and enabling localized deposition of therapeutic agents.[9,14,15]

Among different microneedle platforms, dissolving microneedles are particularly attractive because the active compound can be incorporated within a water-soluble or biodegradable matrix. Following insertion, the projections dissolve in skin fluid and release the incorporated payload. Experimental work has demonstrated that appropriately designed dissolving microneedles can possess sufficient mechanical strength for skin insertion and subsequently dissolve within the skin.[15]

Prunetin represents an interesting candidate for incorporation into such a delivery system because of its experimentally reported anti-inflammatory activity. Its ability to modulate NF- κ B-associated inflammatory signaling provides a pharmacological rationale for further investigation.[12] Nevertheless, this rationale should be interpreted cautiously. Direct evidence demonstrating that prunetin is an effective anti-psoriatic treatment remains insufficient, and therefore the proposed formulation should be regarded as an **investigational therapeutic strategy rather than an established psoriasis treatment**.

The development of a prunetin-loaded dissolving microneedle patch should consequently integrate pharmaceutical and pharmacological evaluation. Drug–polymer compatibility, microneedle morphology, mechanical strength, insertion ability, dissolution, drug loading, skin deposition, cytocompatibility, anti-inflammatory activity, local safety, and stability should all be established before therapeutic efficacy is investigated.

The imiquimod-induced psoriasis-like model provides one potential platform for preliminary in vivo evaluation because its inflammatory response involves the IL-23/IL-17 axis.[31] Comparative studies involving blank DMNs, free prunetin, conventional topical prunetin, and prunetin-loaded DMNs would help establish whether the delivery platform provides a genuine pharmacological advantage.

Overall, the proposed prunetin-loaded dissolving microneedle patch represents a scientifically plausible combination of an anti-inflammatory phytoconstituent and an advanced localized drug-delivery platform. Its ultimate therapeutic potential, however, will depend on demonstrating a clear sequence of evidence:

successful formulation → reproducible skin insertion → adequate prunetin deposition → modulation of psoriasis-relevant inflammatory pathways → therapeutic improvement → acceptable safety.

XXXVI. Future Perspectives

Future investigation should initially focus on establishing the **psoriasis-specific pharmacology of prunetin**. Studies in keratinocytes and appropriate immune-cell systems should determine whether prunetin modulates IL-17-, IL-23-, TNF- α -, and NF- κ B-associated inflammatory responses at concentrations that can realistically be achieved in skin.

A second priority is optimization of prunetin loading within the microneedle projections. Dissolving microneedles must simultaneously provide adequate mechanical strength, drug-loading capacity, and

sufficiently rapid dissolution, which can create competing formulation requirements.[16] If conventional incorporation results in substantial drug retention within the backing layer, tip-loaded or compartmentalized microneedles could subsequently be investigated.

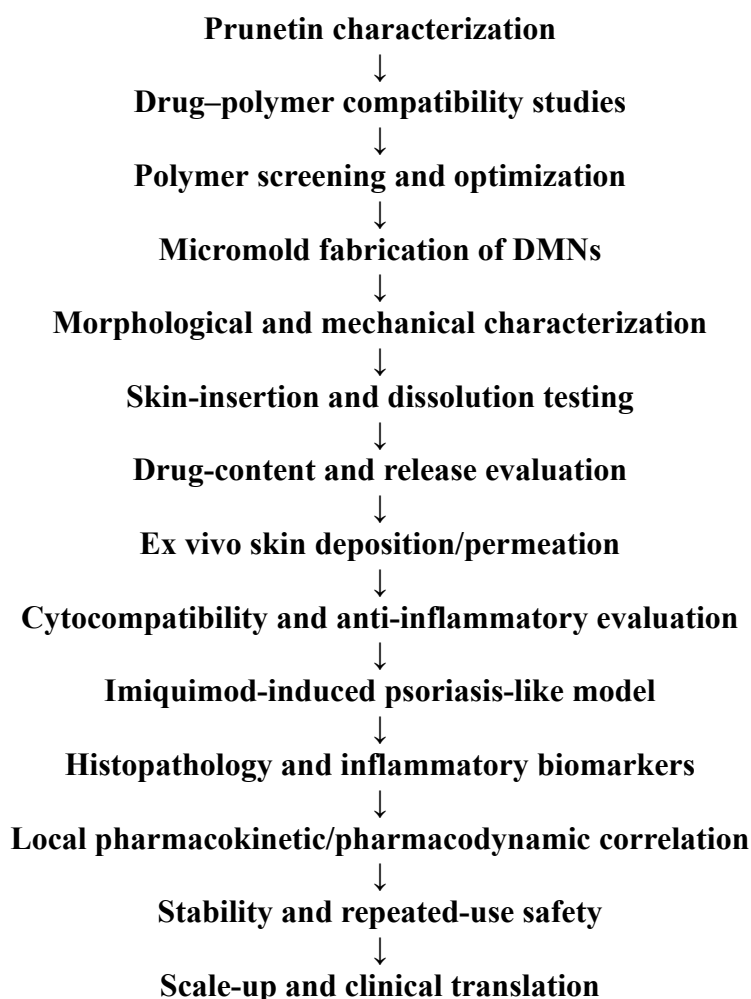
Future studies should also establish the relationship between **local pharmacokinetics and pharmacodynamics**. Measurement of prunetin concentration within the epidermis and dermis should be correlated with inflammatory biomarkers and histopathological improvement. Such studies would establish whether enhanced skin deposition actually translates into improved biological activity.

If the aqueous solubility or skin retention of prunetin becomes a limiting factor, advanced approaches such as cyclodextrin complexation, amorphous formulations, nanoparticles, or liposomal carriers may be investigated. However, increasing formulation complexity should be justified by measurable improvements over a simpler prunetin-loaded DMN.

Long-term development will also require standardized manufacturing, packaging, stability studies, repeated-dose safety assessment, patient acceptability studies, and ultimately controlled clinical evaluation. Dissolving microneedle research has identified mechanical strength, adequate drug dose, and rapid release as important formulation challenges.[16]

Thus, future work should progress systematically from **proof of formulation** to **proof of delivery**, followed by **proof of pharmacological activity** and finally **proof of therapeutic benefit**.

XXXVII. Final Overall Development Pathway



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