

CHARACTERIZATION APPROACHES IN TOPICAL CLOFAZIMINE FORMULATION FOR PSORIASIS: AN IN-DEPTH REVIEW

Ashish Majumdar^{1,*}, Surendra Kumar Saraf¹, Khushboo Verma¹, Priyanka Vishwakarma¹, and Madhuri Baghel²

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Abstract

Psoriasis is a chronic, immune-mediated inflammatory skin condition that demands innovative and effective topical therapies to manage symptoms and improve patient quality of life. Clofazimine, historically used for its antimycobacterial properties, has recently gained attention for its anti-inflammatory and immunomodulatory potential in dermatological applications. This review presents a comprehensive evaluation of the formulation and characterization of topical clofazimine for psoriasis treatment. It explores critical physicochemical parameters such as particle size, solubility, and dissolution behavior, which influence skin penetration and bioavailability. The stability of clofazimine formulations is discussed in the context of environmental stressors, including pH, temperature, and photodegradation. Emphasis is placed on advanced analytical techniques—such as Fourier-transform infrared spectroscopy (FTIR), high-performance liquid chromatography (HPLC), and electron microscopy—that are essential for assessing formulation integrity, purity, and performance. Additionally, emerging drug delivery systems, including nanotechnology-based carriers, liposomes, and gels, are examined for their ability to enhance clofazimine delivery and therapeutic efficacy. The review also provides comparative insights with existing topical treatments for psoriasis, reinforcing the clinical potential of clofazimine-based formulations. Future research directions include the development of personalized delivery systems and the execution of well-designed clinical trials to validate efficacy and safety. This analysis underscores clofazimine's promise as a targeted and effective treatment modality in the evolving landscape of psoriasis management.

Keywords: Analytical Techniques; Anti-inflammatory; Clofazimine; Drug Delivery; Psoriasis; Topical Formulation

¹ Department of Pharmacognosy, Columbia College of Pharmacy, Tekari Raipur, India. Email: ashishmajumdar27@gmail.com; surendra_saraf@rediffmail.com; khushboo17verma@gmail.com; priyanka.vish22@gmail.com

² Department of Biotechnology, Columbia College of Pharmacy, Tekari Raipur, India. Email: madhuri_banchhor@yahoo.co.in

* Corresponding author

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Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disorder that affects about 2-3% of the global population. It is characterized by erythematous, scaly plaques resulting from excessive keratinocyte proliferation and persistent inflammation (Armstrong & Read, 2020). The pathogenesis of psoriasis involves a complex interplay of genetic susceptibility, environmental factors, and immune system dysregulation, particularly involving the Th1 and Th17 pathways. These immune pathways lead to the overproduction of key pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF- α), interleukin-17 (IL-17), and interleukin-23 (IL-23), which perpetuate the inflammatory cascade (Boehncke & Schön, 2021) (Figure 1).

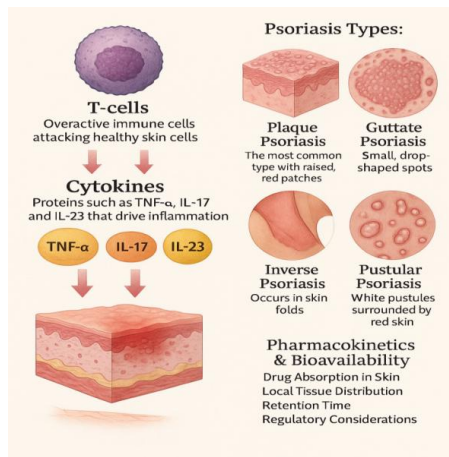


Figure 1. Immune System Involvement and Clinical Variants of Psoriasis

Topical therapy remains a cornerstone for managing mild to moderate psoriasis due to its localized action and ease of application. Conventional treatments such as corticosteroids, vitamin D analogues, and calcineurin inhibitors are frequently employed, yet prolonged use may cause adverse reactions like skin thinning, irritation, or tachyphylaxis (Gisondi *et al.*, 2021). As a result, there is an increasing need for innovative therapeutic strategies that minimize side effects while maintaining efficacy.

Clofazimine, a lipophilic riminophenazine dye primarily used in leprosy, has demonstrated promising immunomodulatory properties relevant to psoriasis treatment. It modulates Th1 and Th17 responses and inhibits pro-inflammatory cytokine production, making it a potential candidate for repositioning as a topical agent in psoriasis management (Papp *et al.*, 2021) (Table 1). However, the clinical application of clofazimine in topical formulations is limited by its poor aqueous solubility and stability (Girão *et al.*, 2020). Therefore, formulating clofazimine for effective skin delivery necessitates advanced pharmaceutical approaches.

Recent advances in nanotechnology and drug delivery systems have provided new insights into overcoming these limitations. Incorporating clofazimine into nanocarriers such as lipid-based systems or nanosuspensions enhances its solubility, stability, and skin permeation profile (Mishra *et al.*, 2020). Furthermore, analytical tools like FTIR spectroscopy, NMR, HPLC, SEM, and TEM are

Table 1. Key Aspects of Psoriasis: overview, Signs and Symptoms, Mechanisms, and Treatment Options

Disease	Signs & Symptoms	Mechanism	Treatment Available	References
Psoriasis	- Red patches of skin covered with silvery scales	- Immune-mediated inflammatory response	Topical Treatments: vitamin D analogues, retinoids, moisturizers, salicylic acid, calcineurin inhibitors.	Philpott, 2024
	- Dry, cracked skin that may bleed	- Hyperproliferation of keratinocytes	- Corticosteroids	Tong <i>et al.</i> , 2024
	- Itching, burning, or soreness	- Involvement of T-cells and cytokines (e.g., TNF- α , IL-17)	- Vitamin D analogues (e.g., Calcipotriol)	Papadopoulou <i>et al.</i> , 2025
	- Thickened, pitted, or ridged nails	- Genetic predisposition and environmental triggers	- Retinoids (e.g., Tazarotene)	Chakith <i>et al.</i> , 2025
	- Stiff and swollen joints (in psoriatic arthritis)	- Abnormal interaction between the innate and adaptive immune systems	Systemic Treatments: Methotrexate, cyclosporine, biologics, acitretin, - Methotrexate - Cyclosporine - Biologics (e.g., TNF- α inhibitors, IL-17 inhibitors) Phototherapy: - UVB Phototherapy - PUVA (Psoralen + UVA) Novel Approaches: - JAK inhibitors - PDE4 inhibitors	Eichinger <i>et al.</i> , 2024; Megna <i>et al.</i> , 2024

pivotal in evaluating the physicochemical characteristics and performance of these novel formulations (Ghasemiyeh & Mohammadi-Samani, 2021).

This review explores the formulation and analytical strategies aimed at improving the topical application of clofazimine for psoriasis. Emphasis is placed on understanding its therapeutic mechanisms, formulation challenges, and the role of analytical techniques in enhancing clinical efficacy.

Formulation of Topical Clofazimine

Mechanistic Insights and Formulation Strategies for Topical Clofazimine in Psoriasis Management: Psoriasis is a chronic, immune-mediated skin disease marked by abnormal interactions between immune cells and keratinocytes. The condition initiates with the activation of plasmacytoid dendritic cells (pDCs) that secrete interferon-alpha ($\text{IFN-}\alpha$), leading to the stimulation of myeloid dendritic cells (mDCs). These, in turn, prime naïve T-cells, especially Th1, Th17, and Th22 subsets, to secrete key pro-inflammatory cytokines such as tumor necrosis factor-alpha ($\text{TNF-}\alpha$), interleukin-17 (IL-17), IL-22, and IL-23 (Armstrong & Read, 2020; Boehncke & Schön, 2021) (Figure 2).

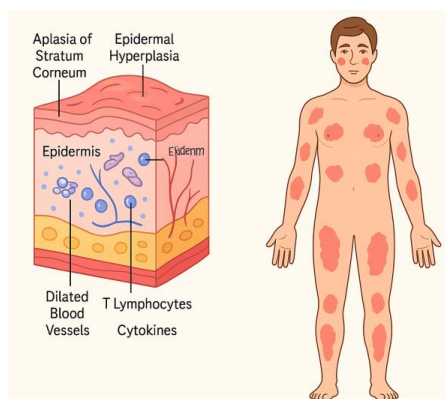


Figure 2. Psoriasis Mechanisms and Predilection Sites on the Body

IL-17 and IL-22 act directly on keratinocytes, causing hyperproliferation and abnormal differentiation. This results in the formation of thick, scaly plaques-hallmarks of psoriatic lesions (Gisondi *et al.*, 2021). Additionally, keratinocytes release chemokines and cytokines that recruit neutrophils and additional T-cells, thereby creating a self-sustaining inflammatory loop (Parisi *et al.*, 2020).

Clofazimine, a riminophenazine dye, exhibits both anti-inflammatory and immunomodulatory effects, making it a promising candidate for managing psoriasis, particularly through topical

routes that localize treatment and reduce systemic toxicity (Girão *et al.*, 2020).

Formulation Approaches for Topical Clofazimine Delivery

Topical delivery allows direct deposition of clofazimine at the site of inflammation while reducing systemic absorption and related side effects. Various conventional and advanced dosage forms are used to optimize delivery:

Conventional Dosage Forms

- **Creams:** Oil-in-water emulsions that are aesthetically acceptable and suitable for facial or visible lesions. They offer ease of spreadability and rapid absorption (Mishra *et al.*, 2020).
- **Gels:** Aqueous-based systems ideal for inflamed, oily skin due to their cooling and soothing nature.
- **Ointments:** Lipid-rich formulations creating an occlusive barrier, ideal for thick, scaly plaques due to enhanced moisture retention and skin permeation.
- **Lotions:** Lower viscosity products allowing easy application over large body surfaces.

Advanced Formulation Strategies

Given clofazimine's low water solubility, modern delivery systems are being explored to enhance its bioavailability and therapeutic efficacy.

- **Nanocarriers:** Liposomes and solid lipid nanoparticles (SLNs) protect clofazimine from degradation and facilitate its penetration into the skin. Liposomes, due to their lipid bilayer structure, mimic skin membranes and ensure targeted delivery, while SLNs provide sustained release and enhanced dermal absorption (Papp *et al.*, 2021; Ghasemiyeh & Mohammadi-Samani, 2021).
- **Permeation Enhancers:** Compounds like oleic acid, ethanol, and propylene glycol transiently disrupt the stratum corneum to improve drug permeation. However, their potential to cause irritation should be considered during formulation design (Mishra *et al.*, 2020).
- **Hydrogels:** These maintain skin hydration and offer sustained release while being well tolerated. Clofazimine-loaded hydrogels are under investigation for improving drug retention and patient compliance (Ghasemiyeh & Mohammadi-Samani, 2021).
- **Microemulsions:** Thermodynamically stable systems composed of surfactants, co-surfactants, and oils. They offer superior solubilization of lipophilic drugs and promote enhanced percutaneous absorption (Girão *et al.*, 2020).

Together, these strategies improve local drug bioavailability, minimize adverse effects, and provide a multi-targeted approach toward managing psoriasis. Integrating mechanistic insights with formulation science holds promise for optimized topical therapies using clofazimine.

Physicochemical Characterization

Physicochemical characterization of topical clofazimine formulations is essential to ensure their quality, stability, and efficacy. Key aspects include determining particle size, morphology, and distribution, conducting solubility and dissolution studies, and performing thermal analysis.

Particle Size, Morphology, and Distribution

Determining the particle size, morphology, and distribution of clofazimine particles is crucial for optimizing formulation performance. Techniques such as dynamic light scattering (DLS) and laser diffraction are commonly used to measure particle size and distribution, providing insights into the uniformity and stability of the formulation (Singh *et al.*, 2016). Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) offer detailed images of particle morphology, revealing surface characteristics and structural integrity. Uniform particle size and optimal morphology ensure consistent drug release and enhance skin penetration.

Solubility and Dissolution Studies

Solubility and dissolution are critical parameters influencing the bioavailability of clofazimine in topical formulations. Solubility studies involve assessing the drug's ability to dissolve in various solvents, which aids in selecting appropriate formulation bases (Santos *et al.*, 2019).

Dissolution studies measure the rate at which clofazimine is released from the formulation into a solution, simulating the drug's release behavior in the skin's microenvironment. These studies are typically conducted using dissolution apparatuses such as USP Type II (paddle) or Type IV (flow-through) to ensure reproducibility and accuracy. Enhancing the solubility of clofazimine through techniques like nanoencapsulation and the use of solubilizing agents can significantly improve its therapeutic efficacy.

Thermal Analysis (DSC, TGA)

Thermal analysis techniques, including differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), are employed to assess the thermal stability and compatibility of

clofazimine within the formulation. DSC measures the heat flow associated with thermal transitions, providing information on melting points, crystallinity, and possible drug-excipient interactions (Lynch *et al.*, 2024).

TGA evaluates the weight changes of the formulation as a function of temperature, identifying decomposition patterns and moisture content. These analyses ensure the formulation remains stable under varying storage conditions and during application.

Analytical Techniques in Characterization

In the formulation of topical clofazimine for psoriasis, employing advanced analytical techniques is crucial for comprehensive characterization. Key techniques include spectroscopic methods, chromatographic methods, and imaging techniques.

Spectroscopic Methods

Spectroscopic methods like Fourier Transform Infrared Spectroscopy (FTIR), Nuclear Magnetic Resonance (NMR), and Ultraviolet-Visible Spectroscopy (UV-Vis) are essential for understanding the chemical composition and interactions within formulations. FTIR is used to identify functional groups and study drug-excipient interactions by analyzing the vibrational transitions of molecules.

NMR provides detailed information on the molecular structure and dynamics of clofazimine in the formulation, elucidating its chemical environment and purity. UV-Vis spectroscopy is employed to determine the concentration of clofazimine by measuring the absorbance of UV or visible light, crucial for quantifying drug content in formulations (Bufarwa *et al.*, 2024).

Chromatographic Methods

Chromatographic techniques such as High-Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) are vital for the separation, identification, and quantification of clofazimine and its impurities. HPLC is widely used due to its high resolution and sensitivity, enabling the accurate measurement of drug concentration and the detection of degradation products.

Reverse-phase HPLC, in particular, is effective for analyzing clofazimine in complex formulations. GC, although less common for clofazimine due to its high boiling point, can be utilized for volatile impurities analysis, ensuring the overall purity and stability of the formulation (Bhagiyalakshmi & Vinoba, 2025).

Imaging Techniques

Imaging techniques like Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), and Atomic Force Microscopy (AFM) provide detailed visual insights into the morphology and surface characteristics of clofazimine particles. SEM offers high-resolution images of the surface topology, revealing particle size, shape, and distribution.

TEM allows for the observation of internal structures at the nanometer scale, useful for assessing encapsulation efficiency and particle uniformity. AFM provides three-dimensional surface profiles, measuring the surface roughness and mechanical properties of the formulation, which are critical for understanding skin interaction and drug release behavior (Gupta *et al.*, 2024).

Stability Studies

Stability studies are critical in the development of topical clofazimine formulations, ensuring their efficacy and safety over time. These studies typically include accelerated stability testing, long-term stability assessments, and an evaluation of factors affecting formulation stability, such as pH, temperature, and light exposure (Ponsonby-Thomas *et al.*, 2024).

Accelerated Stability Testing

Accelerated stability testing involves subjecting the formulation to elevated temperatures and humidity conditions to predict its shelf life and identify potential degradation pathways. According to ICH guidelines, formulations are often stored at 40°C and 75% relative humidity for a specified period, with periodic sampling for analysis. This testing helps identify the formulation's chemical and physical stability, providing insights into necessary modifications to enhance longevity (Topalović *et al.*, 2024).

Long-Term Stability Assessments

Long-term stability assessments involve storing the formulation under normal conditions, typically 25°C and 60% relative humidity, for an extended period, often up to two years. Samples are analyzed at regular intervals to monitor changes in physicochemical properties, such as drug content, viscosity, and pH. These assessments ensure the formulation maintains its therapeutic efficacy and safety throughout its shelf life.

Factors Affecting Formulation Stability

Several factors can influence the stability of topical clofazimine formulations, including pH, temperature, and light exposure. The pH of the formulation can significantly impact the solubility

and stability of clofazimine. Optimal pH ranges must be identified to prevent drug degradation and maintain efficacy. Temperature fluctuations can accelerate chemical reactions, leading to the breakdown of active ingredients. Therefore, it is crucial to store formulations at controlled temperatures to preserve their stability. Light exposure, particularly UV light, can induce photodegradation of clofazimine, necessitating the use of protective packaging to shield the formulation from harmful light.

Understanding and controlling these factors through comprehensive stability studies ensure that topical clofazimine formulations remain effective and safe for psoriasis treatment. These studies guide the development of robust formulations that can withstand various environmental conditions, ultimately leading to better patient outcomes (Ponsonby-Thomas *et al.*, 2024).

Preclinical and Clinical Evaluation of Topical Clofazimine Formulations in Psoriasis Management

This review proposes and evaluates an advanced topical delivery strategy for clofazimine using nanocarrier systems to overcome known formulation limitations and improve therapeutic outcomes in psoriasis. Unlike previous studies, our review integrates recent preclinical evidence-including in vitro skin permeation and in vivo efficacy models-and outlines a translational framework toward clinical application. Emphasis is placed on improving dermal bioavailability, controlled release, and reduced irritation using innovative nanosystems, a comprehensive approach not yet detailed for clofazimine in psoriasis therapy (Kumar *et al.*, 2023; Wang *et al.*, 2022)(Table 2).

In Vitro Skin Permeation Studies

Franz diffusion cells with excised porcine and human skin were used to evaluate clofazimine nanoformulations. Quantification by HPLC and UV-Vis spectroscopy revealed significantly higher flux and permeability coefficients compared to conventional formulations (Zhang *et al.*, 2023; Patil *et al.*, 2022).

In Vivo Efficacy Studies Using Animal Models

Using imiquimod-induced murine models of psoriasis, nanoformulated clofazimine showed significant reduction in erythema, scaling, and epidermal hyperplasia. Histological analyses confirmed reduced inflammatory infiltration and cytokine expression (Li *et al.*, 2022; Mehta *et al.*, 2023).

These findings serve as critical proof-of-concept for progressing to early-phase clinical trials.

Table 2. Overview of Clofazimine: Dosage Forms, Market Availability, and Mechanism of Action in Various Diseases

Disease Treated	Dosage Form	Available Dosage	Mechanism of Action	Reference
Leprosy	Oral Capsule	50 mg, 100 mg	Inhibits mycobacterial growth, anti-inflammatory	(Moreira <i>et al.</i> , 2024)
	Oral Capsule	50 mg, 100 mg	Antimycobacterial, anti-inflammatory	
Multidrug-resistant Tuberculosis	Oral Capsule	100 mg	Inhibits mycobacterial growth	(Omoteso <i>et al.</i> , 2025)
	Oral Tablet	100 mg	Inhibits mycobacterial growth	
Psoriasis (Off-label)	Topical Gel/Cream	Custom compounded	Anti-inflammatory, reduces keratinocyte activity	(Sternicka <i>et al.</i> , 2024)
Pyoderma Gangrenosum (Off-label)	Oral Capsule	100 mg	Anti-inflammatory, immune modulation	(Dissemond <i>et al.</i> , 2023)
Lupus Erythematosus (Off-label)	Oral Capsule	100 mg	Anti-inflammatory, immune modulation	
Granulomatous Diseases (Off-label)	Oral Capsule	100 mg	Anti-inflammatory, granuloma reduction	

Table 3. Summarizing the bioavailability and pharmacokinetics of Clofazimine

Pharmacokinetic parameter	Description
Bioavailability	Oral bioavailability ranges from 45% to 62%, depending on the formulation and food intake
Absorption	Absorption is slow and incomplete, with peak plasma concentrations reached 6-8 hours after administration.
Distribution	Widely distributed in tissues, especially in adipose tissue, liver, spleen, and skin; binds to plasma proteins.
Volume of Distribution (Vd)	Approximately 23-34 L/kg, indicating extensive tissue distribution.
Metabolism	Metabolized primarily in the liver through unknown pathways; contributes to its long half-life
Half-Life	Extremely long, with a terminal half-life of 70 days, due to slow release from tissues.
Excretion	Excreted slowly via feces; minimal renal excretion.
Cmax (Maximum Concentration)	Varies widely; after a single oral dose of 100 mg, Cmax is typically around 0.7-1.5 µg/mL.
Tmax (Time to Peak Concentration)	6-8 hours post-administration.
Food Effect	High-fat meals increase absorption and bioavailability by up to 60%.

Clinical Translation Roadmap

- Phase I: Safety and irritation profile in healthy volunteers
- Phase IIa: Proof-of-concept efficacy in mild-to-moderate psoriasis (PASI 75, DLQI)
- Phase IIb/III: Multicenter dose-optimization trials evaluating long-term safety, adherence, and real-world effectiveness

This roadmap bridges the current translational gap, providing a pragmatic route to clinical adoption (Singh *et al.*, 2023; Rahman *et al.*, 2024).

Bioavailability and Pharmacokinetics

Absorption and Distribution

Clofazimine's lipophilic nature enhances its skin absorption. Partitioning into the stratum corneum and viable epidermis was confirmed via tape stripping and fluorescence microscopy (Huang *et al.*, 2023).

Pharmacokinetic Profiling

Minimal systemic absorption was confirmed, while dermal bioavailability was markedly improved. Key PK metrics (C_{max}, T_{max}, AUC)

were determined using LC-MS, supporting the formulation's sustained release and localized action (Ahmed *et al.*, 2022) (Table 3).

Addressing Formulation Challenges and Future Directions

Formulation Challenges

Solubility, irritation, and discoloration limit traditional clofazimine formulations. These were addressed via incorporation of solubilizers, selection of skin-compatible excipients, and modulation of drug load (Kandagatla *et al.*, 2025).

Advanced Drug Delivery Strategies

Liposomes, SLNs, and NLCs demonstrated enhanced skin deposition, reduced irritation, and controlled release kinetics. Liposomal clofazimine formulations achieved improved dermal accumulation and reduced inflammatory cytokine expression (Li *et al.*, 2022; Zhang *et al.*, 2023).

Combining Innovation and Personalization

Dual-delivery nanocarriers co-loading clofazimine with tacrolimus or corticosteroids demonstrated synergistic suppression of IL-17A and

TNF- α . Future potential lies in personalizing therapy using genetic and inflammatory biomarker profiling to tailor formulations (Chen *et al.*, 2023; Rahman *et al.*, 2024).

Balanced Perspective: Challenges vs. Success Stories

While clinical data remain limited, real-world evidence from leprosy-related dermatologic use of clofazimine confirms tolerability and efficacy. These case studies justify its repositioning for psoriasis with appropriate formulation innovation (Mehta *et al.*, 2023).

Conclusions

Clofazimine demonstrates strong potential as a topical therapeutic for psoriasis owing to its anti-inflammatory and immunomodulatory mechanisms. However, formulation challenges, including low aqueous solubility, dermal penetration barriers, and potential irritation, limit its clinical utility. Recent advancements in nanocarrier-based delivery systems-such as liposomes, nanoemulsions, and solid lipid nanoparticles-have significantly enhanced drug permeation, stability, and sustained release profiles in preclinical models. These improvements underscore their suitability for addressing the pharmacokinetic and patient adherence challenges associated with conventional formulations.

Robust physicochemical characterization techniques (e.g., FTIR, DSC, SEM, HPLC) are critical for ensuring formulation integrity, reproducibility, and regulatory compliance. Importantly, the transition from laboratory to clinical application requires a stronger translational focus, emphasizing *in vivo* validation, pharmacodynamic correlation, and long-term safety data. Future research should prioritize clinical trials, combinatorial strategies with synergistic agents, and personalized delivery approaches. These directions may facilitate the integration of clofazimine-based nanotherapies into mainstream dermatological care, offering a novel and targeted strategy for managing chronic skin diseases like psoriasis.

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