





Recent Advancements and Trends of Topical Drug Delivery Systems in Psoriasis: A Review and Bibliometric Analysis

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Abstract: Psoriasis is an immune-mediated inflammatory skin disease where topical therapy is crucial. While various dosage forms have enhanced the efficacy of current treatments, their limited permeability and lack of targeted delivery to the dermis and epidermis remain challenges. We reviewed the evolution of topical therapies for psoriasis and conducted a bibliometric analysis from 1993 to 2023 using a predictive linear regression model. This included a comprehensive statistical and visual evaluation of each model's validity, literature profiles, citation patterns, and collaborations, assessing R variance and mean squared error (MSE). Furthermore, we detailed the structural features and penetration pathways of emerging drug delivery systems for topical treatment, such as lipid-based, polymer-based, metallic nanocarriers, and nanocrystals, highlighting their advantages. This systematic overview indicates that future research should focus on developing novel drug delivery systems characterized by enhanced stability, biocompatibility, and drug-carrying capacity.

Keywords: psoriasis, bibliometric, drug delivery, topical treatment, nanoparticle, nanocarriers

Introduction

Psoriasis, a persistent and relapsing inflammatory autoimmune skin disease, impacts approximately 2%–5% of the global population, manifesting clinically as psoriasis vulgaris, psoriasis arthropathica, psoriasis erythrodermic and psoriasis pustulosa. Predominantly, psoriasis vulgaris represents the most common form, characterized by erythematous, scaly skin lesions with distinct borders.¹ The pathogenesis involves a genetic predisposition (eg, HLA-C*06:02 risk allele), environmental triggers (such as streptococcal infections, stress, obesity, alcohol consumption, and smoking), and immune response abnormalities (eg, overactivation of the adaptive immune system). Psoriasis exhibits three major interconnected inflammatory loops: T helper (Th)17 cells and interleukin 17 (IL-17)-producing CD8⁺ T (Tc17) cells responses driven by IL-17, IL-23, and C-C motif chemokine ligand 20 (CCL20) feedback loops; type I and type II interferon (IFN) loops driven by plasmacytoid dendritic cells (pDCs) and IFN- γ -secreting T-cells (Th1 and Tc1); and IFN- γ -secreting T-cells (Th1 and Tc1) driven by IL-36. Treatment-induced remission is characterized by resolving psoriatic plaques containing tissue-resident memory cells (TRM), typically CD8⁺ IL-17-positive or CD8⁺ IFN- γ -positive cells. Concurrently, psoriasis is associated with multiple comorbidities, including cardiometabolic diseases, psoriatic arthritis, and depression.^{1,2}

Topical treatments are commonly regarded as the initial choice for managing mild to moderate plaque psoriasis, and for patients with moderate to severe psoriasis, maintenance topical treatments exhibit the capacity to defer relapse.³ Anthralin (also referred to as hydroxyanthrone dithranol) was initially characterized in 1916 by Galewski and Unna, and served as a clinical agent for topically treating psoriatic skin lesions until the 1980s.⁴ Goeckerman demonstrated the

scientific use of coal tar with ultraviolet radiation for treating psoriasis in 1925.⁵ In 1952, topical application of adrenocortical steroids was introduced, and in 1955, an emollient (liquid petrolatum, sodium chloride, and phenol) was first mentioned in the literature for treating scalp psoriasis.^{6,7} The exploration of novel drug delivery systems in dermatology dates back to the 1980s. Hermann RC et al prepared liposomes of cyclosporine and conducted in vitro tests in 1988.⁸ Although the results indicated that topical application of cyclosporine could not improve psoriasis symptoms, various drug delivery systems, including liposomes, have been progressively studied in psoriasis. Vitamin D analogues received approval for treating psoriasis in 1991 in the U.K.⁹ Tazarotene initiated clinical trials for psoriasis treatment in 1996, and in 1998, topical 0.3% tacrolimus (FK506) demonstrated efficacy in a clinical trial.^{10,11} The introduction of topical calcineurin inhibitors marked a significant non-steroidal advance in psoriasis treatment. In 2001, a mouse monoclonal antibody against human interleukin-8 cream was approved for psoriasis treatment in China.¹² Tofacitinib began phase IIa clinical trials in 2013 but awaits formal approval for psoriasis treatment.¹³ Tapinarof, a natural aryl hydrocarbon receptor (AhR) agonist, exhibited a favorable anti-psoriasis effect in vivo and in vitro trials that commenced in 2017, leading to its approval in 2022.^{14,15} The PDE4 inhibitor 0.3% roflumilast completed phase IIb clinical trials in 2020 and is currently FDA-approved for use in patients with moderate-to-severe plaque psoriasis aged 12 years and older.¹⁶ Brepocitinib, a topical TYK2/JAK1 inhibitor, demonstrated good tolerability in phase IIb clinical trials in 2022.¹⁷ Tirbanibulin (KX01), a new Src kinase inhibitor that inhibits keratinocyte proliferation, is currently approved for treating actinic keratosis and has recently initiated a phase I clinical trial for psoriasis treatment.¹⁸ A timeline chart on the emergence of topicals is shown in Figure 1. As our understanding of psoriasis pathogenesis deepens, Figure 2 illustrates a diverse array of drug delivery systems emerging. Notably, new nano-delivery systems, encompassing lipid-based carriers, polymer-based carriers, metallic nanocarriers, and nanocrystals (NCs), offer advantages such as enhanced skin permeability, targeted accumulation at the site of interest, controlled drug release, favorable solubility, high encapsulation efficiency, diminished off-target effects, enhanced drug stability, and biocompatibility.^{19–21} These attributes collectively lead to a reduction in dosage and frequency of administration, consequently elevating therapeutic efficacy and fostering patient compliance.

In recent decades, there has been a progressive exploration of drug delivery systems in the context of psoriasis. However, there is a dearth of literature systematically summarizing and consolidating these findings. Bibliometrics, a widely employed research analysis method, operates at a macro level within databases.²² This approach enables the

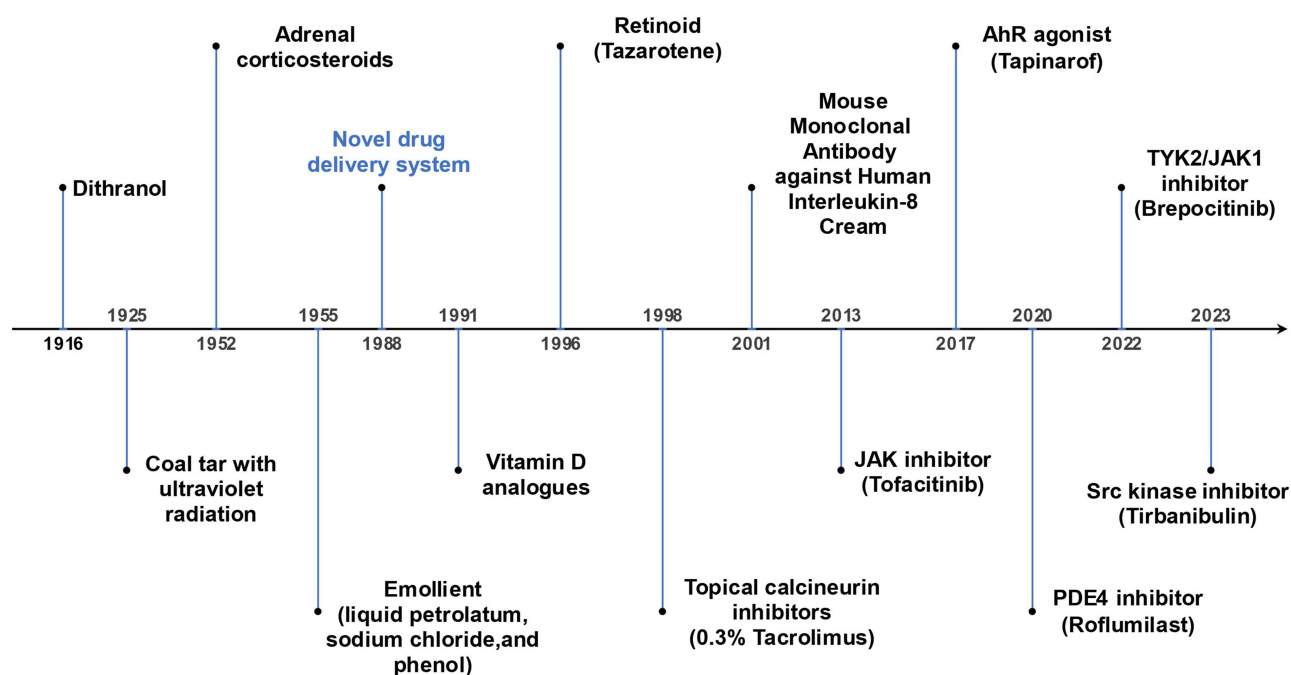


Figure 1 Timeline of topical therapies in psoriasis. The color text highlights the initial time of studies of novel drug delivery systems in psoriasis.

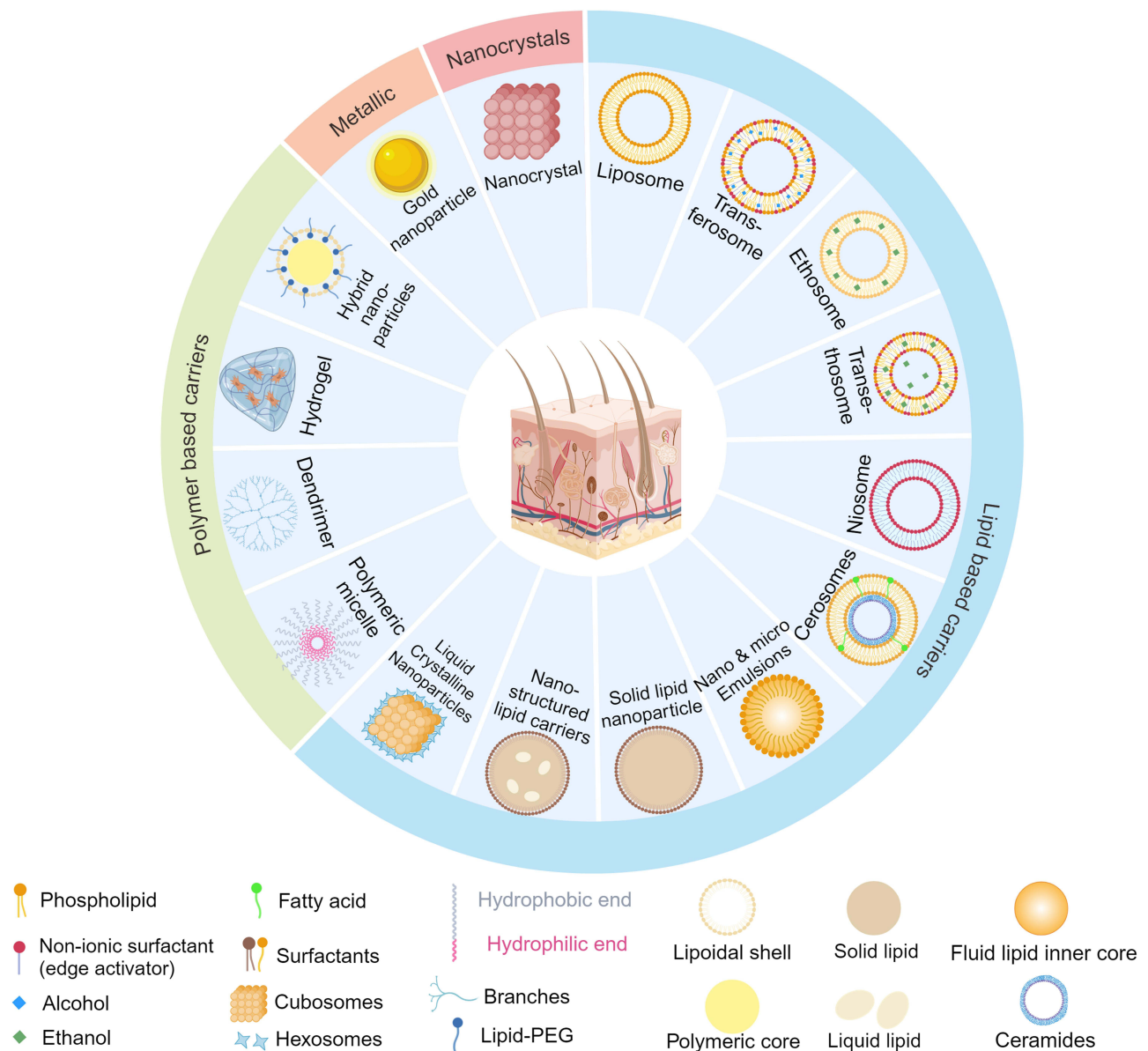


Figure 2 Schematic illustration of anatomical structure of the human skin and representative novel drug delivery system for the topical treatment of psoriasis. Created with BioRender.com.

examination of literature across various dimensions, unveiling the information network of publications. It offers researchers a comprehensive understanding of the field on a larger scale, facilitating grasping the knowledge structure within the research domain.^{23,24}

Materials and Methods

Data Collection and Search Strategies

We conducted an advanced search in the Science Citation Index Expanded (SCI-EXPANDED) in the Web of Science Core Collection (WoSCC) database on 28 December 2022. We used the following search terms to identify publications primarily concerning psoriasis and drug delivery: TS= (“drug deliver*” OR “drug-delivery” OR “drug release*” OR “drug carr*” OR “pulsatile releas*” OR “transdermal deliver*” OR “drug delivery system*” OR “topical delivery” OR “skin delivery ”) AND TS= (psoriasis). Then, the document types were limited to articles and review articles, while the publication language was limited to English. Ultimately, 688 articles met the criteria

for inclusion in this study, comprising 523 articles and 165 review articles. Publications meeting the inclusion criteria were exported as plain text files, adhering to the “Full Record and Cited References” format.

Data Analysis and Visualization

In this study, we employed five bibliometric analysis and visualization tools, ie, CiteSpace (6.2.R4), VOSviewer (version 1.6.19), the bibliometrix package in R software (10.1016/j.joi.2017.08.007), Scimago Graphica and Pajek 5.18 to focus on publications, citations, countries/regions and institutions, authors, journals, references, and keywords. Pajek can make the clustering distributions obtained in VOSviewer more rational and arranged. Scimago Graphica is used to map research collaborations between countries. Bibliometrix in conjunction with RStudio will be used to conduct statistics on impact indicators in bibliometrics. In addition to the common bibliometric data such as publication count, citation and co-citation frequency, and the impact factor (IF), our inquiry also introduces the betweenness centrality and the Hirsch index (h-index) has been introduced to provide a more comprehensive evaluation. Betweenness centrality can be used to identify potentially important nodes in a visualization network.²⁵ The h-index is a quantitative measure used to assess an author’s scholarly output and its corresponding impact on citations within the scholarly community. Characterized by the apex value of h, the h-index signifies that an author has disseminated a minimum of h publications, each garnering no less than h citations.^{26–28} The application of the h-index examines the productivity and impact of an author, thus helping readers to identify more promising researchers. The detailed process of this study is outlined in [Figure 3](#).

Statistical Methods and Data Processing

Our analysis includes data up to October 2023, covering trends from 1993 to 2022 in annual publication volume and cumulative citations. Given the non-linear patterns in the raw data, we applied a log transformation to both metrics to stabilize variance and align more closely with the normality assumption of linear regression. We then fitted linear regression models using the year as the independent variable and the logarithms of annual publications and cumulative citations as dependent variables, respectively. Using ordinary least squares (OLS), we estimated positive coefficients indicating increasing trends: the publication model had a slope of 0.234 and an intercept of -463.96 , while the citation model showed a slope of 0.238 with an intercept of -470.27 ([Figure 4](#)). Furthermore, we evaluated model efficacy using R-squared and Mean Squared Error (MSE). The R-squared values were 0.858 for publications and 0.9921 for citations, suggesting the models account for the most variability in the data. Additionally, the extremely low p-values for the year coefficients confirm the significant influence of time on the trends, reinforcing the robustness and credibility of our interpretations.

Results

Analysis of the Trend of Publications and Citations

The annual volume of publications and citation frequency can serve as indicators reflecting a research field’s developmental trajectory and prospects. Illustrated in [Figure 4](#), the cumulative annual count of articles and citation frequency in this field has exhibited exponential growth since 1993. Although the annual publication count showed minor fluctuations until 2019, a discernible upward trend emerged thereafter, peaking in 2022 at 100 publications. Concurrently, the citation frequency has consistently risen from 1993 to 2022, signifying an increasing output of high-quality literature and breakthroughs in drug delivery systems research for psoriasis. In the statistical methods and data processing section, constructing predictive models for annual publications and cumulative citations suggests that psoriasis drug delivery systems represent significant research potential and are emerging academic hotspots warranting deeper investigation. The substantial research potential in drug delivery systems for psoriasis warrants the attention of the academic community, meriting further exploration.

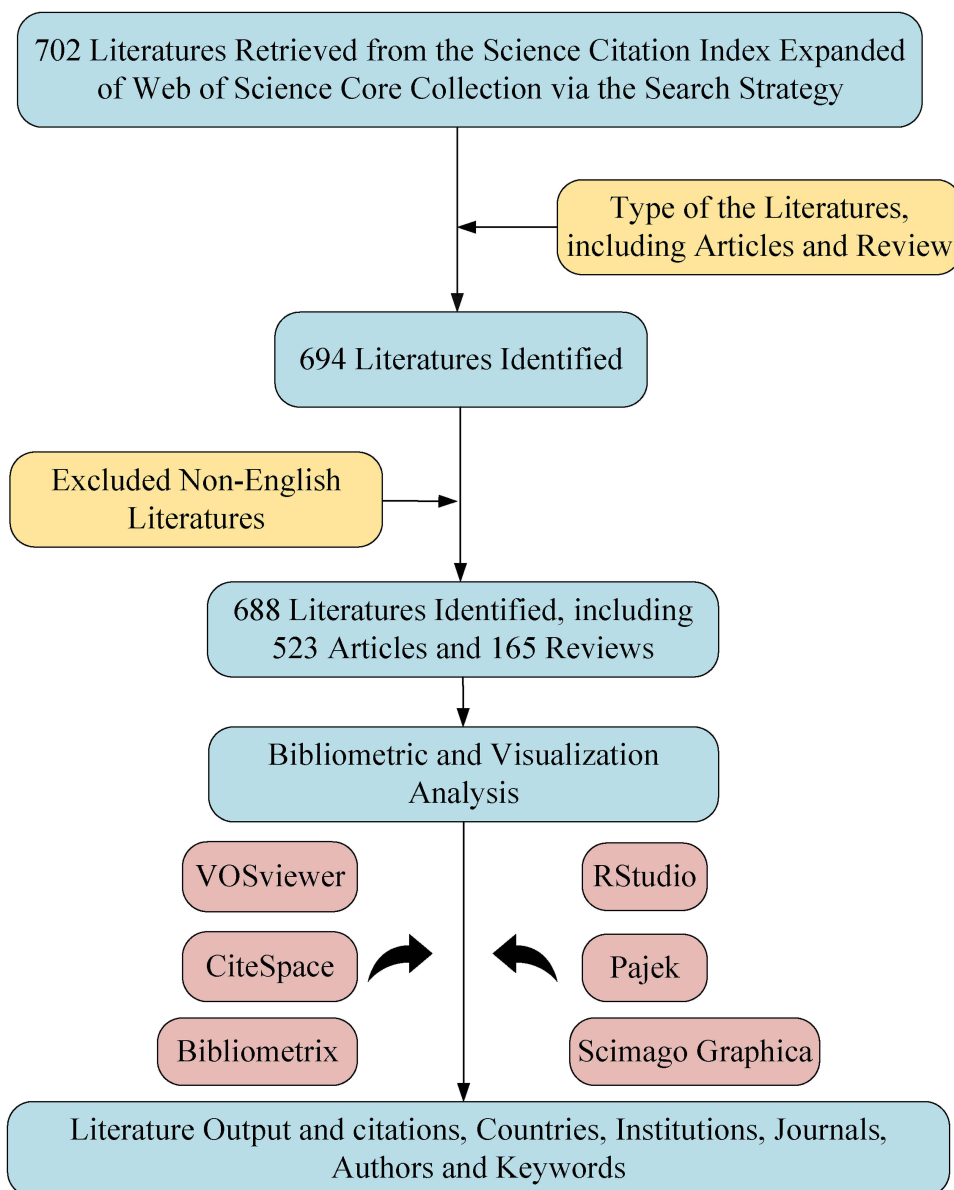


Figure 3 Schematic depiction outlining the literature search, screening, and analytical procedures employed in this investigation.

Distribution of Countries/Regions and Institutions

This study encompasses 1871 institutions across 189 countries and regions. [Table S1](#) details the leading ten countries and institutions in scholarly output. India ranks highest with 198 publications, surpassing most nations globally in citation frequency (5468), average citation frequency (27.62), and h-index (40). Jamia Hamdard University emerges as the most prolific research institution, with a citation frequency of 394. Notably, four Indian institutions feature among the top ten in academic output, underscoring India's profound scientific prowess in the realm of drug delivery systems for psoriasis. [Figure 5A](#) illustrates the cooperation network diagram among the top 20 countries based on publication numbers. The dot size reflects the number of publications; the redder the dot, the stronger the collaboration with other nations. Connecting lines indicate the strength of cooperation between countries. Notably, while the United States exhibits a lower publication count than India and China, it demonstrates the closest collaboration with other countries, suggesting a broader future development outlook in this field. In [Figure 5B](#), the top 20 countries are categorized by the extent of multi-country (red) and single-country (blue) publications. [Figure 5C](#) depicts the institutional cooperation network, where nodes of the same

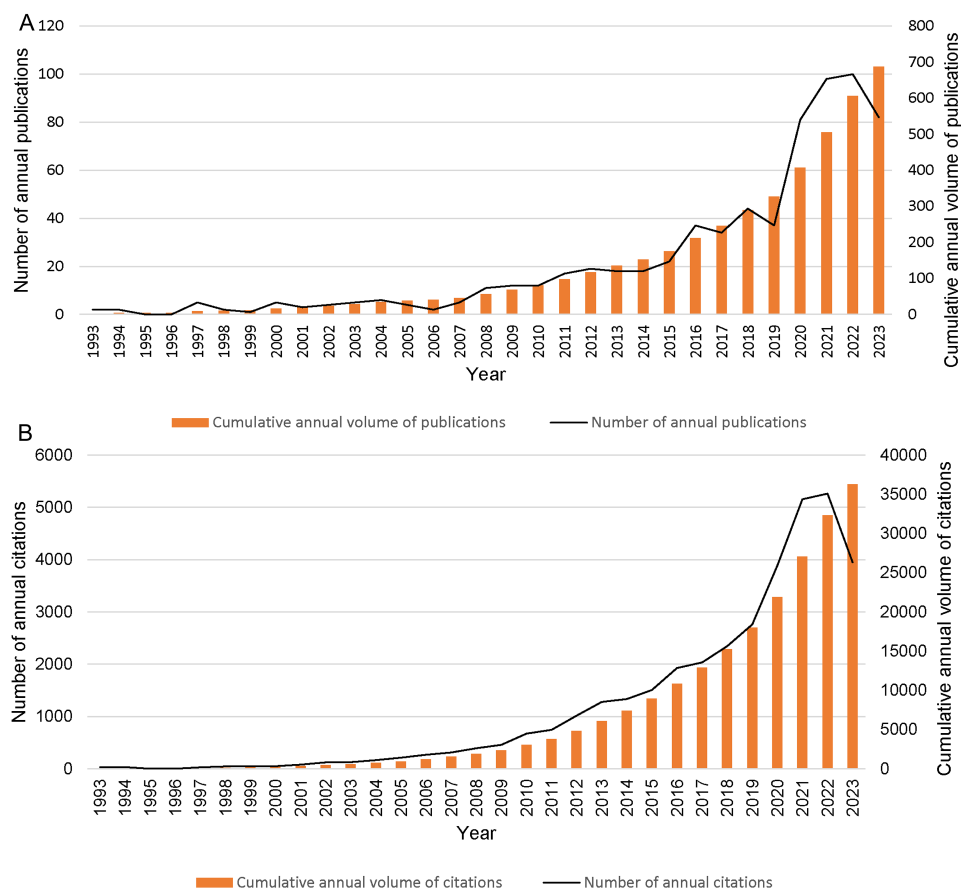


Figure 4 Visualization of annual publication trends and aggregate citation counts for articles related to research on topical drug delivery systems for psoriasis. The yellow bar graph indicates annual publications (**A**) and citations (**B**), while the black line graph depicts the cumulative annual volumes of publications (**A**) and citations (**B**).

color represent a common cluster, emphasizing close collaborative relationships. The strength of the connecting line between nodes indicates the strength of cooperation between institutions. Chang Gung University stands out with the highest cooperation strength in this field. [Figure 5D](#) portrays a map of country publication numbers. Nodes of distinct colors correspond to different countries, with the size of each node reflecting the quantity of articles contributed by that specific country. The intensity of connections between nodes signifies the strength of collaboration among nations. Analyzing article publication and collaboration status provides a comprehensive understanding of drug delivery system research progress in psoriasis, facilitating deeper exploration in this domain. Meanwhile, this analysis lays the foundation for more detailed research. The factors contributing to the success of these high-yield regions and institutions warrant further investigation. Researchers may benefit from visiting and exchanging information with these entities, drawing on the strengths of their research models and policies. Additionally, synthesizing and analyzing data from various countries and institutions alongside other data in the text may yield valuable insights.

Analysis of Authors and Co-Cited Authors

In the realm of drug delivery in psoriasis, we scrutinized 3180 authors. [Table S2](#) lists the top 10 authors based on publication count and co-citation frequency within drug delivery systems research for psoriasis. A higher co-citation frequency signifies closer collaboration with peers and underscores the significance of the author's research contributions to field development.²⁹ [Figure S1A](#) depicts the co-citation network of authors, with node size indicating co-citation frequency. Nodes with purple borders signify higher betweenness centrality (exceeding 0.1). Notably, Madhulika Pradhan from India holds the highest co-citation frequency. [Figure S1B](#) portrays an author co-occurrence network, showcasing collaborations among authors in the field. Gautam Singhvi from Birla Institute of Technology and Science leads in the

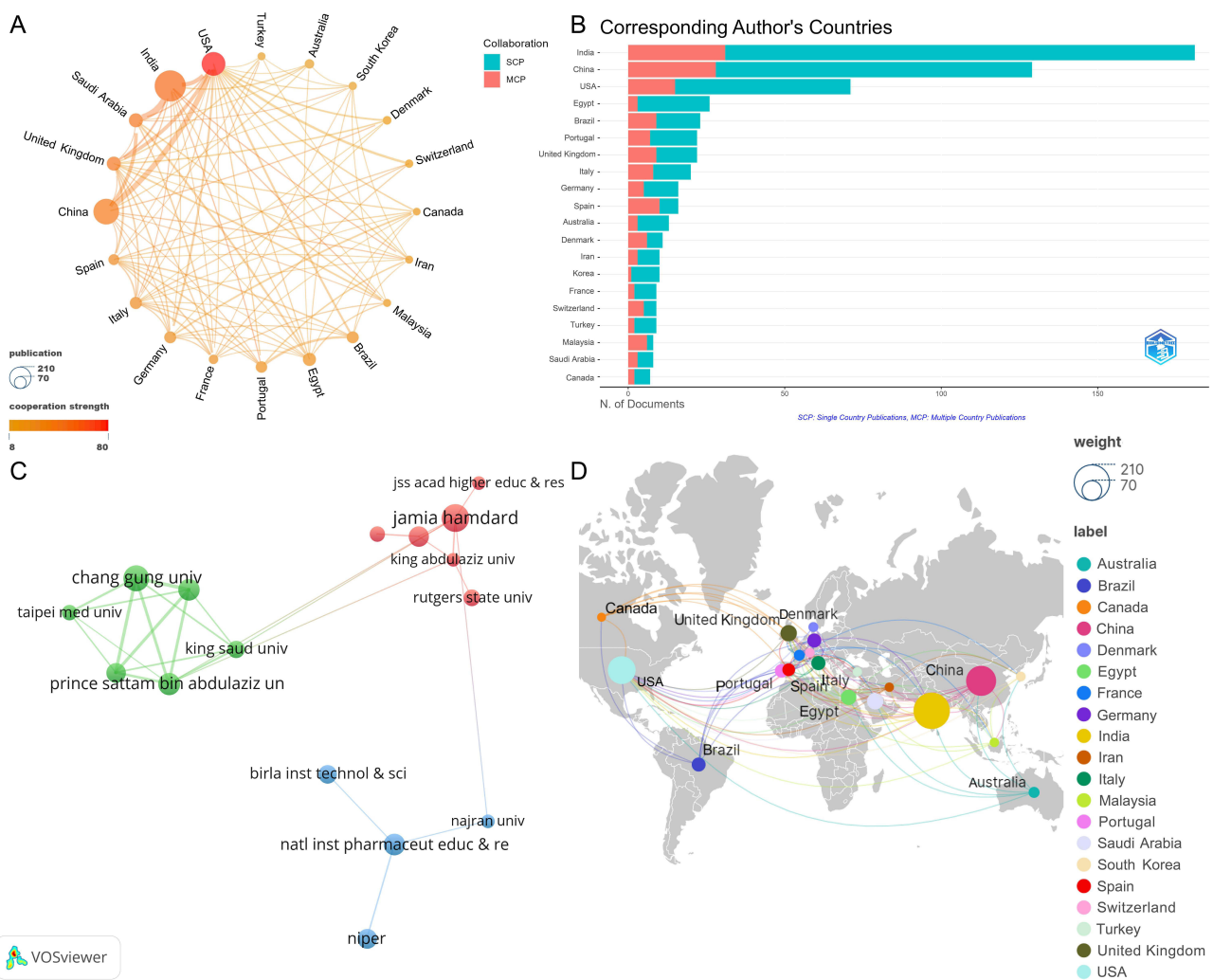


Figure 5 Analysis of collaborative efforts among countries/regions and institutions in topical drug delivery systems research for psoriasis. **(A)** National cooperation networks: node size signifies the number of publications, and node color intensity indicates the strength of cooperation. **(B)** Top 20 countries by publication count, distinguishing between single country publications (SCP) and multiple country publications (MCP). **(C)** Collaboration network: Circle sizes in the figure denote each institution's publishing volume, and connecting lines between nodes represent institutional collaboration. **(D)** A geographical distribution map illustrating the quantity of publications across countries/regions.

number of publications, while Jia-You Fang from Chang Gung University stands out with the highest citation frequency and h-index. Through meticulous statistical analysis of scholarly publications and co-citations, we gain a more accurate understanding of the knowledge landscape in drug delivery systems for psoriasis, enabling the inference of research hotspots.

Analysis of Journals and Co-Cited Journals

To comprehensively explore the foundational and cutting-edge advancements in drug delivery systems for psoriasis, we conducted rigorous statistical and analytical evaluations of historical and co-cited journals. [Table S3](#) enumerates the top ten journals based on both publication count and co-citation frequency. [Figure 6A](#) visualizes the co-citation network of journals, elucidating the types of journals serving as primary sources of knowledge in the field. [Figure 6B](#) illustrates the network of cited journals, encompassing 223 journal types. The top ten journals in [Table S2](#) boast the highest publication volume and co-citation frequency. Notably, the *International Journal of Pharmaceutics* leads in publication volume and co-citation frequency, and all ten journals are recognized by the Journal Citation Reports (JCR). Furthermore, these journals, classified as Q1 in the JCR, underscore the growing academic attention towards studying drug delivery systems



Figure 6 Analysis of journals in research on topical drug delivery systems for psoriasis. **(A)** Visualization of the co-cited journal network. **(B)** Visualization of the cited journal network, with circle size denoting the total link strength (TLS) of the documents represented by the nodes.

in psoriasis. Nine of the ten journals have an IF exceeding 5, signifying the increasing prominence of this research area and its potential as a future research hotspot.

Analysis of References and Co-Cited References

Visualization and statistical analysis of co-cited relationships in the literature enable the identification of influential publications in the domain of drug delivery systems for psoriasis. These publications exhibit temporal fluctuations that mirror the progress and shifts in the research frontiers of the field.³⁰ [Table S4](#) presents the top ten cited publications, with “Overcoming the Achilles’ heel of photodynamic therapy”, authored by Wenpei Fan et al and published in *Chemical Society Reviews* in 2016, emerging as the most frequently cited article. [Figure 7A](#) illustrates the co-citation network of the literature, while [Figure 7B](#) showcases the top 100 articles according to citation frequency. [Figure 7C](#) provides a visual network of co-cited literature clustered based on thematic directions, including novel colloidal carriers, skin disease treatment, transdermal drug delivery, clobetasol propionate, treatment modalities, psoriasis management, psoriasis treatment, topical therapy, and topical microRNA-directed therapy. [Figure 7D](#) displays co-cited reference clustering on a timeline diagram, offering insights into the evolution of the knowledge base in the field of drug delivery systems for psoriasis through changes in nodes over time. The initial cluster, denoted as #0 novel colloidal carrier, represents the embryonic research stage into drug delivery systems for psoriasis. It marks the inception of targeted and extensive investigations in this domain, initiated by Jia-You Fang’s 2004 contribution to the *British Journal of Dermatology*. This seminal work delineates and contrasts two resurfacing techniques—laser and microdermabrasion—that optimize the in vitro skin permeation of 5-aminolaevulinic acid (ALA).³¹ Recent research has identified #1 skin disease treatment and #2 transdermal drug delivery as pivotal areas of inquiry. In the #1 cluster, Xue Zhou’s 2022 article in *Cell Death & Disease*, succinctly outlines the pivotal role of keratinocytes as target cells in psoriasis therapy.³² In the #2 cluster, the latest contribution comes from Ruijie Chen and colleagues in 2022. It demonstrates the application of Alantolactone (ALT)-loaded chitosan/hyaluronic acid (HA) nanoparticles (CHALT) for psoriasis treatment. The study reveals the suppression of psoriasis through the deactivation of STAT3 hyperactivity within keratinocytes and the restriction of immune cell recruitment, offering a promising avenue for improving psoriasis symptoms.³³

Analysis of Keywords

Following the exclusion of redundant keywords sharing search terms or demonstrating low relevance to the study, [Table S5](#) presents the top 20 keywords arranged in descending order based on their frequency in titles and abstracts. Notably, “nanoparticles (NPs)” is the most frequently occurring keyword. In [Figure 8A](#), the top 14 keywords are depicted over time, with a reddish period indicating concentrated bursts, reflective of hotspots in the research field during specific periods. The study identifies 14 influential terms in drug delivery systems for psoriasis, including percutaneous absorption, psoriasis,

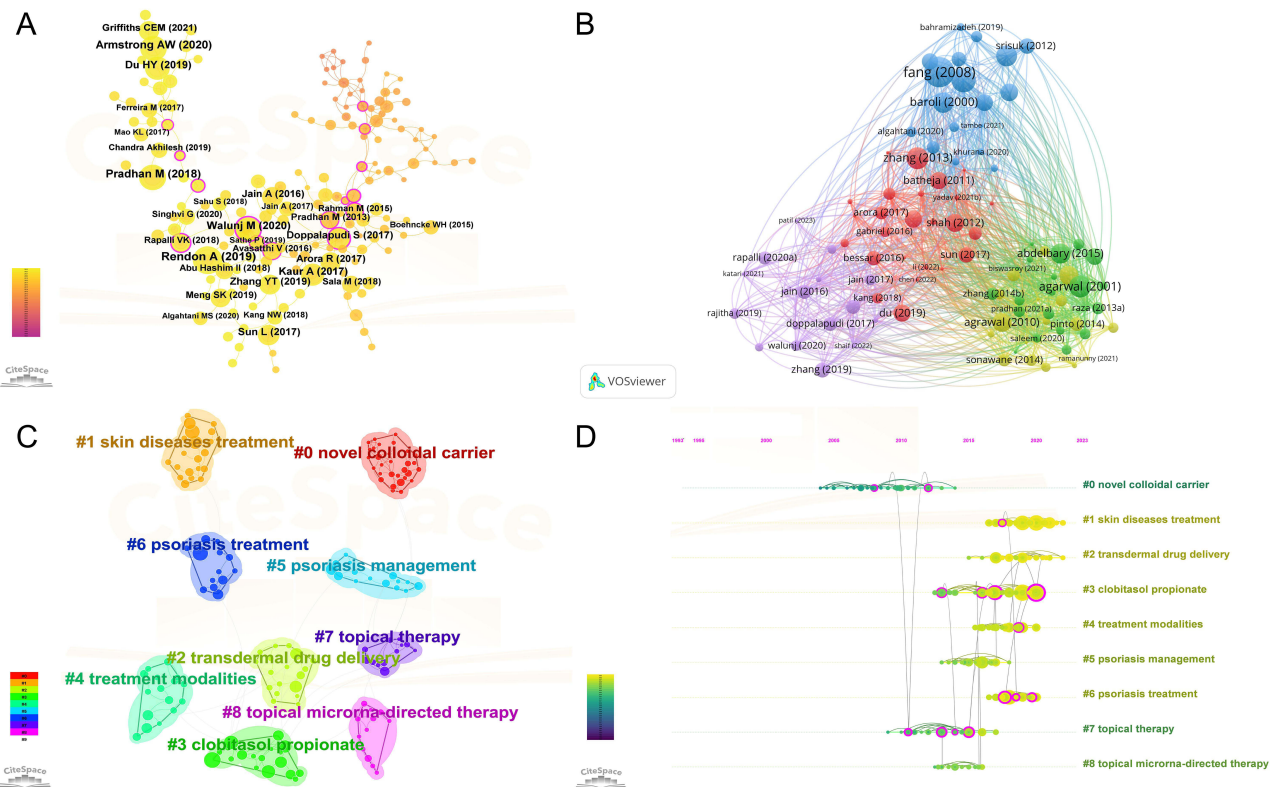


Figure 7 Analysis of references in research on topical drug delivery systems for psoriasis. **(A)** Visualization of the co-cited reference network. **(B)** Top 100 co-cited references, with circle size indicating the total link strength of the documents represented by the nodes. **(C)** Cluster diagrams representing co-cited references. **(D)** Timeline view of the co-cited reference cluster analysis. Connecting lines indicate co-citation relationships between publications, and changes in node color represent temporal shifts.

absorption, in vivo, liposomes, vesicles, mechanisms, stability, transdermal drug delivery, imiquimod-induced psoriasis, Box-Behnken design, inflammation, oxidative stress, and drug delivery system. Figure 8B illustrates the keyword co-occurrence network within the research area, while Figure 8C employs cluster visualization to categorize drug delivery system research in psoriasis into 12 directions. These encompass #0 topical transdermal delivery, #1 psoriasis physiopathology, #2 drug nail permeability, #3 using micellar nanocarrier, #4 in vivo microdialysis, #5 using electroporation, #6 passive diffusion, #7 cutaneous penetration studies, #8 human keratinocyte, #9 5-aminolaevulinic acid, #10 sampling technique, and #11 effective management. Further enhancing clarity, Figure 8D integrates a timeline analysis atop the clustering, providing a clearer depiction of directional changes over time. This approach also facilitates the observation of inter-cluster connections through node connectivity.³⁴ The timeline analysis reveals that the current research frontiers encompass #0 topical transdermal delivery, #3 using micellar nanocarriers, #4 in vivo microdialysis, and #5 using electroporation.

Discussion

This study presents the inaugural bibliometric analysis of hotspots and trends within drug delivery systems in psoriasis research. Our investigation reveals a consistent, albeit fluctuating, increase in publications and annual citation frequency in this field since the close of the twentieth century. This trend signifies a growing scholarly emphasis and attention on studying drug delivery systems in psoriasis. An examination of countries, regions, and institutions identifies India as having the highest publication count, the United States boasts the highest average citation frequency and exhibits the closest collaboration with other nations. Notably, Jamia Hamdard University records the highest publication count, and Chang Gung University achieves the highest citation frequency. Among individual contributors, Gautam Singhvi claims the highest publication count, Madhulika Pradhan leads in co-citation frequency, and Jia-You Fang secures the highest citation frequency. The articles by Singhvi and Pradhan warrant meticulous examination. At the same time, Fang's high citation frequency reflects scholarly recognition of the content and direction of their research—areas deserving of focused

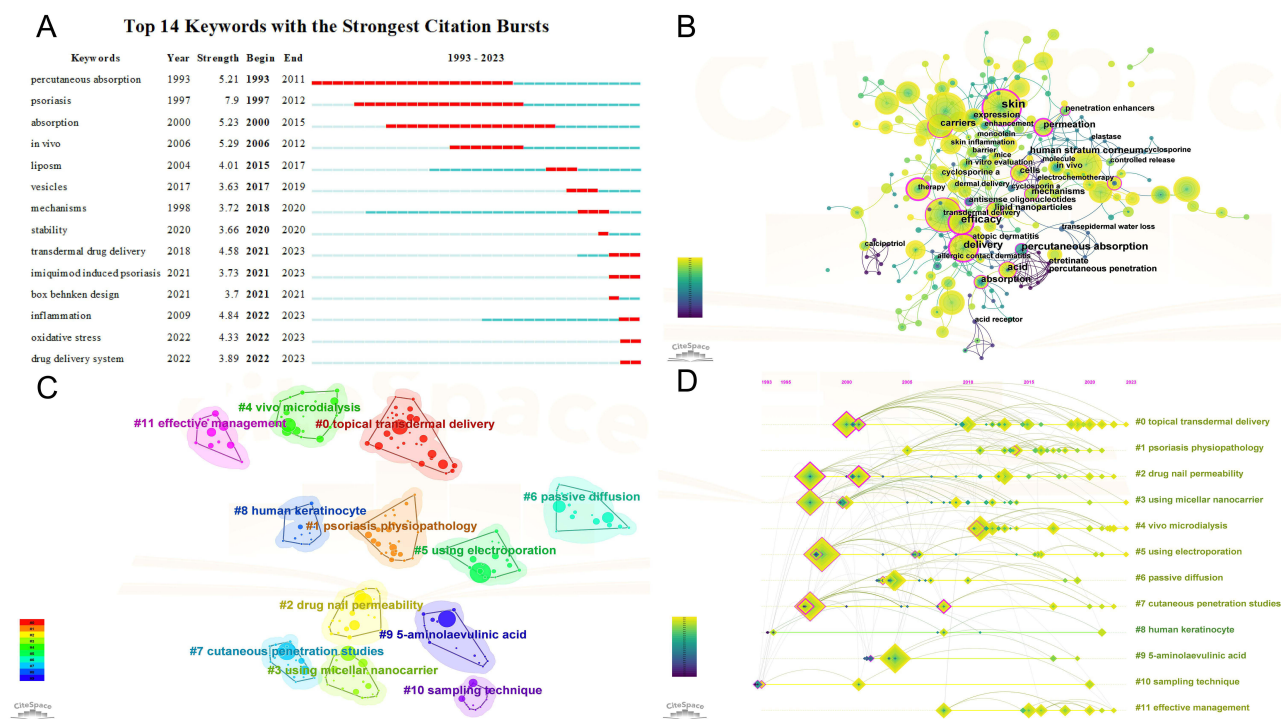


Figure 8 Analysis of keywords in topical drug delivery systems for psoriasis research. (A) The 14 most significant keywords displaying substantial citation bursts within T-cell research in psoriasis. (B) Keyword co-occurrence network. (C) Cluster diagrams of keywords. (D) Timeline view of keyword cluster analysis.

attention in future studies. Journal analysis underscores the *International Journal of Pharmaceutics* as the most prolific in terms of article count, with the *European Journal of Pharmaceutics and Biopharmaceutics* ranking highest in citation frequency. The *International Journal of Pharmaceutics* claims the top spot in co-citation frequency. Researchers are encouraged to prioritize literature within these journals for further study.

Topical treatments are the primary choice for mild to moderate plaque psoriasis.³⁵ Maintenance topical therapy may delay relapse in patients with moderate to severe psoriasis. Noteworthy advantages of topical therapy encompass: 1. reduction of systemic side effects; 2. targeted concentration of the drug in the affected tissue; and 3. circumvention of first-pass metabolism. Commonly employed topical therapeutic agents in clinical practice comprise anthralin, coal tar, salicylic acid (SA), glucocorticoids, emollients, retinoic acid, vitamin D3 derivatives, calcium-modulated phosphatase inhibitors, and herbal medications.³

Over the past decades, nanotechnology has captivated the interest of researchers across diverse fields. Its application in topical therapy has proliferated, marking significant progress in drug delivery systems.¹⁹ Applications of nanocarriers in topical drug delivery systems for psoriasis are shown in Table 1. Nanocarriers confer several advantages: (1) heightened skin permeability; (2) optimal retention of active ingredients with subsequent sustained drug release; (3) binding of hydrophobic and hydrophilic active ingredients;³⁶ (4) targeted delivery with high bioavailability; and (5) increased stability and protection of active ingredients from degradation.³⁷ The skin's hydrophobic nature and tightly packed stratum corneum (SC) are barriers against the penetration of toxic substances and active agents. Therefore, the efficacy of dermal therapy relies on a drug's ability to overcome this skin barrier and penetrate the epidermis. Despite the effectiveness of current topical treatments for psoriasis in various forms (including gels, ointments, tinctures, emulsions, and applications), their limited penetration and lack of targeted enrichment within the dermis and epidermis restrict their application. Consequently, there is a pressing need to develop novel drug delivery systems that enhance topical drugs' skin permeability and targeting capabilities, thereby improving their therapeutic efficacy.³⁸ Figure 9 illustrates the mechanism of the novel drug delivery systems and their association with the pathogenesis of psoriasis.

Table 1 Applications of Nanocarriers in Topical Drug Delivery Systems for Psoriasis

S. No.	Delivery Systems	Composition	Particle Size	Preparation Technique	Drug	In-vivo Model	Result	Ref.
1	Liposomes	Carbomer 940, glycerin, ethylparaben, soybean lecithin, tween 80	70 nm	Film dispersion method	All-trans retinoic acid, TPP-modified CeO ₂	BALB/c mice	The intervention can diminish inflammation levels, mitigate oxidative stress within HaCaT cells, and significantly ameliorate symptoms associated with psoriasis.	[39]
		Carbomer 940, propylene glycol	194 nm	Thin-film hydration method	Quercetin	BALB/c mice, SD rats	It increased skin permeability, downregulated pro-inflammatory cytokines such as TNF- α , IL-17A, and IL-1 β , and mitigated symptoms associated with skin thickening.	[40]
		Cholesterol, carbopol 934	111.00 \pm 1.62 nm	Ethanol injection method	Cyclosporine	BALB/c mice	It reduces the levels of key psoriatic cytokines, including tumor necrosis factor- α , IL-17, and IL-22, thereby alleviating associated symptoms.	[41]
		Briefly, lecithin, tween 80, mannose-PEG2000-DSPE	85.5 \pm 0.7 nm	Thin-film dispersion method	Celastrol	C57/BL6 mice	It enhances DC uptake and induces DC tolerance, thereby alleviating symptoms and inflammation associated with psoriasis.	[42]
		Lecithin, DSPE-PEG-NHS, TD, Tween-80	94–100 nm	Lipid hydration method	Curcumin	SD rats, BALB/c mice	It enhances curcumin delivery through the skin, augments the inhibition of HaCaT cells, and improves the efficiency of antipsoriasis treatment.	[43]
		Cholesterol, carbopol 934, carbopol 940	-	Thin film hydration method	Bexarotene	BALB/c mice	The treatment effectively reversed psoriasis by normalizing affected skin, demonstrating an improved safety profile in skin compatibility studies.	[44]
		Phospholipid, cholesterol, span 80	420–740 nm	Thin-film hydration method	Fusidic acid	LACA mice	The liposomal formulation of FA demonstrated improved penetration and markedly increased anti-psoriatic efficacy.	[45]
		DC-cholesterol/egg lecithin, cholesterol, tetramyristoyl cardiolipin	95–110 nm/95–115 nm	Thin-film hydration method	Psoralen	BALB/c mice	It exhibits enhanced skin permeation, lowering the levels of pivotal psoriatic cytokines, including tumor necrosis factor- α , IL-17, and IL-22, consequently alleviating psoriasis symptoms.	[46]

(Continued)

Table I (Continued).

S. No.	Delivery Systems	Composition	Particle Size	Preparation Technique	Drug	In-vivo Model	Result	Ref.
2	Transferosomes	PEG2000-DSPE, sodium cholate	93.1–95.4 nm	Thin film method	Calcipotriol	-	It maintains superior stability without compromising its favorable skin-accumulation properties.	[47]
		Cholesterol, carbopol 940	257.41 ± 7.58 nm	Ethanol injection method	Zedoary turmeric oil and tretinoin	Kunming strain mice	It surpasses the efficacy of conventional gel formulations and exhibits a notable dose-dependent impact on psoriasis.	[48]
		Cholesterol, carbopol 934, carbopol 940, acetone, mannitol, tween 80	128.53 ± 1.18 nm	Solvent injection technique	Ibrutinib and curcumin	BALB/c mice	It led to a reduction in the levels of proinflammatory cytokines, including IL-17, IL-22, and TNF- α , and alleviated associated symptoms.	[49]
		Phospholipon 90G, cholesterol, tween 20, tween 80, D-Limonene	196 ± 1 nm	Film-hydration method	Cyclosporine A	-	It efficiently transports CyA in vitro to the skin, mitigating systemic side effects.	[50]
		Lecithin, tween-80, carbomer 940, glycerin, ethylparaben	~ 70 nm	Thin-film hydration method	All-trans retinoic acid, betamethasone	BALB/c mice	It improved both skin permeation and retention, exhibiting enhanced efficacy in the treatment of psoriasis.	[51]
3	Ethosomes	Cholesterol, oleic acid, vitamin E	100 nm	Fusion method	Methotrexate	BALB/c mice	It led to a notable dose-dependent reduction in the thickness score in IMQP with reduced toxicity.	[52]
		Hyaluronic acid, propylene glycol, soya lecithin 30, acetonitrile, methanol, ethanol, carbopol 934	315.7 ± 2.2 nm	Ethanol injection method	Tacrolimus	Wistar rats	It confirmed a reduction in symptoms such as erythema, edema, and thickness in the psoriasis model, demonstrating its safety and efficacy in vivo studies.	[53]
		DSPE-PEG2000, hyaluronic acid	-	-	Curcumin	C57BL/6 mice	It facilitates the targeted delivery of drugs, enhancing curcumin accumulation in inflamed skin to improve therapeutic efficacy.	[54]
		Polycarbonate, cholesterol	-	Ethanol injection method	Curcumin	Sprague-Dawley rats	It mitigates skin cell toxicity, improves transdermal drug penetration, and enhances vesicle stability.	[55]
		Lipoid S 100, ethanol	-	-	Psoralen	-	It has the potential to enhance transdermal drug delivery and exhibit superior biocompatibility with human embryonic skin fibroblasts.	[56]

4	Transethosomes	Phospholipids, ethanol, water	146–381 nm	Cold method	Anthralin	Wistar rats	It reduces drug side effects and improves patients' Psoriasis Area and Severity Index (PASI).	[57]
		Polyoxyethylene sorbitan monooleate	111–277 nm	Cold method	Cholecalciferol (vitamin D3)	-	It has been demonstrated as a biocompatible and efficient nanocarrier, presenting a highly promising prospect for transdermal VD3 delivery.	[58]
		Cholesterol, ethanol, carbopol 940	200 nm	Thin-film hydration method	Rosmarinic acid	BALB/c mice	It induces a significant reduction in punch edema, TNF- α , and IL-6, serving as an effective formulation for the skin delivery of rosmarinic acid.	[59]
5	Niosomes	Cholesterol, span 59, carbopol 940	132 nm	Thin-film hydration method	Cyclosporine	Swiss albino mice	It can improve the permeation and deposition of medicine for the effective treatment of psoriasis.	[60]
		Cholesterol, span 60	<500 nm	-	Desoximetasone	-	It can sustain drug penetration and retention in human skin and offers the potential to diminish drug concentration, consequently reducing the required dosing frequency.	[61]
		Span 20, span 60, cholesterol	147.4 \pm 5.6 nm	Thin film hydration method, probe sonication	Celastrol	C57/BL6 mice	It enhances the water-solubility and skin permeation of medication, leading to a significant improvement in its anti-psoriasis efficacy.	[62]
		Cholesterol, span 60, propyl paraben, methyl paraben	369.73 \pm 45.45 nm	Thin-film hydration method	Acitretin	Wistar albino rats, Swiss albino mice	It has significantly improved skin permeation, facilitating enhanced drug deposition in deeper layers while reducing systemic absorption.	[63]
		Span 60, cholesterol	477.8 nm	Thin-film hydration method	Diacerein	Albino rats	It achieves precise drug delivery for improved psoriasis treatment, potentially eliminating adverse side effects linked to systemic exposure.	[64]
6	Cerosomes	Ceramide, phospholipids	-	Thin film hydration method	Tazarotene	Albino rats	It heightened medication entrapment, reduced its release, and concurrently improved its deposition in the skin, correlating with enhanced clinical therapeutic outcomes.	[65]

(Continued)

Table I (Continued).

S. No.	Delivery Systems	Composition	Particle Size	Preparation Technique	Drug	In-vivo Model	Result	Ref.
7	Emulsion Drug Delivery Systems	Cholesterol, ceramide-3, tween 80	181.27 ± 1.44 nm	Ethanol injection method	Methotrexate, nicotinamide	SD rats, BALB/c mice	It minimises the systemic toxicity of medication and enhances its efficacy in treating psoriasis.	[66]
		Ceramide, hyaluronic acid, edge activator	222.36 ± 0.36 nm	Thin film hydration method	Cyclosporine-A, dithranol	C57BL/6 mice	Cyclosporine-A and dithranol, which have limited oral bioavailability, were encapsulated in ceramide/phospholipid composite cerosomes to enhance skin penetration and exert antiproliferative effects.	[67]
		Fish oil, linseed oil, tween 80, transcuto-P	<130 nm	Spontaneous emulsification method, high pressure homogenization technique	Tacrolimus	Albino mice	The intervention enhances medication efficacy by minimizing irritation and promoting greater patient compliance.	[68]
		Span 80, tween 80	16.46 ± 0.07 nm	-	Tacrolimus	SD rats, BALB/c mice	It enhances medication solubility and permeability, acting as an adjuvant in anti-psoriasis treatment.	[69]
		Kalonji oil, cremophor RH 40, polyethylene glycol 400	93.37 ± 2.59 nm	Spontaneous emulsification method	Tacrolimus	BALB/c mice	The intervention significantly diminishes serum cytokine levels, resulting in an amelioration of the psoriatic condition.	[70]
		Oleic acid, tween 20	76.20 ± 1.67 nm	Aqueous titration method	Curcumin, resveratrol, thymoquinone	BALB/c mice	The formulation improves drug retention in the skin and is safe for topical applications, exhibiting non-irritating properties. Consequently, this suggests the potential for long-term therapeutic use.	[71]
		Carbopol 934, labrafac PG, tween20, solutol-HS15	10.57 nm	Low-energy emulsification method	Curcumin	BALB/c mice	The formulation demonstrated accelerated and early healing in a psoriatic mouse model, accompanied by increased permeation.	[72]
Oleic acid, tween 80/ vitamin E, transcuto/ propylene glycol/1,3 propanediol	-	Water titration method	Cyclosporine	-	These drug delivery systems can optimize topical therapy for psoriasis.	[73]		

8	Solid lipid nanoparticles	Carbopol 940, isopropyl myristate	< 50 nm	Water titration method	Cyclosporine	-	It enhances the penetration of cyclosporine, providing a sustained depot effect for the effective treatment of psoriasis.	[74]
		Light mineral oil, diethyl sebacate	-	Polymeric emulsion technology	Halobetasol propionate, tazarotene	-	It showcased superior delivery of active ingredients, resulting in rapid and sustained efficacy post-treatment.	[75]
		Ethyl oleate, transcutool, capryol 90	30.25 ± 4.8 nm	-	Oleuropein	Albino mice	It exhibited a small nanometer size, maintained stability during storage, and effectively penetrated various skin layers to alleviate psoriatic manifestations in patients.	[76]
		Olive oil, tween 80	202.6 ± 11.59 nm	High shear homogenization technique	Methotrexate	Sprague Dawley rats	It exhibits superior anti-psoriatic effectiveness with reduced serum accumulation and mitigates systemic toxicity.	[77]
		Silicon oil AR200, squalene, tween 80, PEG 400	696.2 ± 188.3 nm	Water titration method	Salvanolic Acid B	BALB/c mice	It achieves high therapeutic efficacy while ensuring ample hydration for dry skin.	[78]
		Compritol® 888 ATO, precirol® ATO 5, tween® 80	245.66 ± 17 nm	High-shear homogenization method, ultrasound method	Noscapine	BALB/c mice	It diminishes IL-17-producing T cells at the site, mitigating psoriasis-induced skin inflammation.	[79]
		Tween 80, compritol® 888 ATO, phospholipon® G90	273.1 nm	Microemulsion technique	Leflunomide	-	It enhances the photostability and safety of LEF while minimizing drug irritation.	[80]
		Precirol ATO 5, compritol 888 ATO, stearic acid, glyceryl monostearate, oleic acid	167.70 ± 1.5 nm	Hot emulsification method, probe sonication	Apremilast	-	It exhibited enhanced permeation, increased skin deposition, prolonged release, and effectively treated psoriasis by targeting specific skin layers.	[81]
		Transcutol® P, compritol 888 ATO	120–133 nm	Hot homogenization technique, ultrasonication	8-methoxypsoralen	-	It enhances the cellular uptake of nanoparticles without concurrent increases in cytotoxicity.	[82]
		Compritol® 888 ATO, precirol® ATO 5	114.5 ± 1.32 nm	Emulsification–ultrasonication method	Triamcinolone acetonide	-	It selectively accumulates in the epidermis, mitigating undesirable side effects of systemic absorption.	[83]
Compritol 888 ATO, precirol ATO 5, GMS, tristearin, stearic acid	~ 200 nm	Hot melt high shear homogenization technique	Betamethasone dipropionate, calcipotriol	BALB/c mice	It can impede the rapid proliferation of keratinocytes, reduce epidermal thickness, and enhance melanocyte count.	[84]		
Lipocire DM, pluronic F-127, oleic acid	200 nm	Hot homogenization method	Cyclosporine A	-	It enhanced the topical bioavailability of the medication while demonstrating reduced cytotoxicity and lower transdermal permeation.	[85]		

(Continued)

Table I (Continued).

S. No.	Delivery Systems	Composition	Particle Size	Preparation Technique	Drug	In-vivo Model	Result	Ref.
9	Nanostructured lipid carriers	Softisan [®] 649, tween 80 [®]	200 nm	Hot ultrasonication method	Cyclosporine A	-	It can mitigate the systemic side effects of the medication.	[86]
		Naringenin, linolenic acid	470 nm	Microemulsion technique	Cyclosporine A	-	It exhibited robust in vitro anti-inflammatory activity, proving beneficial in mitigating the inflammatory processes involved in the pathogenesis of psoriasis.	[87]
		Glyceryl monostearate, egg lecithin	-	Microemulsion technique	Methotrexate	Swiss albino mice	It demonstrated slow, sustained, and targeted activity, avoiding accumulation in various body parts, thus showing promise in managing psoriasis.	[88]
		Cocoglyceride, stearic acid, poloxamer 188, PEG-40 stearate, brij [®] 58, PEG-1000	152.9 ± 4.09 nm	Emulsification and low-temperature solidification method	Tacrolimus	New Zealand white rabbits	Thermosensitive TCR-SLNs, crafted based on the thermodynamic properties dictated by the surfactant, promise to enhance drug delivery to the skin.	[89]
		Melted cetyl palmitate, polysorbate 80, cetyl palmitate	356 ± 2 nm	Hot ultrasonication method	Methotrexate, etanercept	-	It delivers therapeutic quantities of methotrexate to psoriatic human skin while minimizing transdermal permeation.	[90]
		Precirol [®] ATO 5, geranium oil, tea tree oil, lavender oil, tween 80	202–538 nm	High shear homogenization, solvent diffusion approach	luteolin	Albino rats	It demonstrates a substantial enhancement in anti-psoriatic efficacy and increased skin deposition.	[91]
		Glyceryl monostearate, capryol 90 (oil), tween 80, Span 20	144.95 ± 2.80 nm	Emulsification-solvent-evaporation technique	Tacrolimus, thymoquinone	-	It exhibits significantly higher dose-dependent toxicity against HaCaT cell lines and enhanced skin permeation depth.	[92]
		Beeswax, peppermint oil, lavender oil, tween [®] 80	<200 nm	Hot-pressure homogenization method	Riluzole	-	It can deliver medicine in a sustained manner and inhibit keratinocyte cell proliferation without being angiogenic.	[93]
		Compritol 888ATO, oleic acid, tween 80, span 20, transcutoil P	758 nm	Cold homogenization technique	Apremilast	-	It exhibits a slow and sustained release profile, ensuring prolonged maintenance of drug concentration on the skin.	[94]
Precirol ATO 5, compritol 888 ATO, stearic acid, glyceryl monostearate, oleic acid, dynasan 114, polysorbate 80	157.91 ± 1.267 nm	Hot emulsification technique	Apremilast	Swiss albino mice	It exhibits increased skin retention and reduces TNF- α mRNA expression without inducing toxicity or irritation.	[95]		

10	Liquid Crystalline Nanoparticles	Compritol 888, capmul MCM C8, trehalose dehydrate, carbopol 934P	253.00 ± 8.65 nm	Solvent diffusion technique	Methotrexate	BALB/c mice	It exhibits superior anti-psoriatic activity and demonstrates a prolonged and sustained release effect.	[96]
		Polysorbate 80, cetyl palmitate	292 ± 4 nm	Hot ultrasonication technique	Methotrexate, etanercept	-	It improved the deposition of medication within the skin while minimizing transdermal permeation.	[90]
		Carbopol® 934	-	Microemulsion technique	Fluocinolone acetonide	Sprague Dawley rats, BALB/c mice	It enhances both phenotypic and histopathological characteristics of psoriatic skin, reducing levels of critical cytokines implicated in its pathogenesis.	[97]
		Compritol® 888 ATO, miglyol® 812, poloxamer 188	139.32 ± 2.14 nm	Emulsification-ultrasonication method	Triamcinolone acetonide	-	It demonstrated improved drug solubility, facilitating preferential drug deposition in the epidermis.	[98]
		Glycerol distearate, oleic acid, polyethylenimine, poloxamer 407, phosphate buffer	230 nm	Hot homogenization technique	Tacrolimus	Hairless mice	It effectively prevents the formation of psoriatic plaques and reduces TNF- α expression.	[99]
		Glyceryl monostearate, stearic acid, oleic acid, precirol ATO 5, compritol 888 ATO	96.2 ± 0.9 nm	Hot emulsification followed by probe sonication method	Curcumin	Albino mice	It enhances the targeted medication delivery to the skin layers, ensuring prolonged retention.	[100]
		Tripalmitin, tricaprin, trimyristin, glyceryl monostearate, precirolVR ATO 5	<300 nm	Hot melt homogenization method	Dithranol	BALB/c mice	It demonstrates a marked decrease in disease severity and levels of cytokines such as Interleukins-17, 22, 23, and tumor necrosis factor- α .	[101]
		Labrafil® M 2125 CS, poloxamer 407	173.25 ± 2.192 nm	Hot emulsification technique	Apremilast	Swiss albino mice	It demonstrates increased drug retention in the stratum corneum and viable epidermis, enhancing skin permeation and retention.	[102]
		Monoolein, oleic acid, poloxamer 407	150 nm	-	Triptolide	-	It exhibits favorable compatibility with rapid internalization and enhances drug distribution across the porcine epidermis and dermis.	[103]
		Phytantriol, pluronic F128, ethanol, water	221 ± 14 nm	Solvent shifting method	Rapamycin	-	It exhibits antiproliferative activity in vitro against natural killer cells.	[104]

(Continued)

Table I (Continued).

S. No.	Delivery Systems	Composition	Particle Size	Preparation Technique	Drug	In-vivo Model	Result	Ref.
11	Dendrimers	Monoolein, poloxamer 407	204.3 nm	-	Tacrolimus	BALB/c mice	It exhibits a notable increase in drug permeation and retention, proving more effective in treating psoriasis-like skin inflammation.	[105]
		Sodium oleate, glyceryl monooleate, hydroxypropyl methylcellulose, poloxamer-407	137 ± 3.7 nm	Hydrotrope method	Berberine	Wistar albino rats, BALB/c mice	It demonstrates elevated drug accumulation and enhanced permeation, mitigates symptoms of psoriasis, and diminishes levels of inflammatory cytokines associated with psoriatic conditions.	[106]
		PAMAM dendrimer, triton X-100, diethyl pyro carbonate water, ethidium bromide, phosphate buffer saline	99.80 ± 1.80 nm	-	siRNA against TNF- α	BALB/c mice	It enhanced phenotypic and histopathological characteristics while decreasing the levels of IL-6, TNF- α , IL-17, and IL-22.	[107]
		PAMAM G-4 dendrimer with surface amino groups	28 ± 1.12 μ m - 130 ± 1.01 μ m	Quasi-emulsion solvent diffusion method	Dithranol	Wister rats	It can achieve sustained efficacy without inducing skin toxicities.	[108]
		Ethylenediamine, acrylonitrile	8.00 ± 0.04 nm	-	Dithranol	Albino rats	It enhances the controlled topical bioavailability of molecules, promoting the targeted accumulation of drugs within the skin.	[109]
12	Micelle	1,2,3,4 butane tetracarboxylic acid, PEG methacrylate, gallic acid, polyethylene oxide	2.45–8.24 nm	-	Methotrexate	-	It enhanced drug loading and exhibited slow-release characteristics.	[110]
		Kolliphor [®] 407, N-Hydroxysuccinimide	25.08 ± 0.24 nm	-	Mycophenolic acid	-	Due to its enhanced aqueous solubility and increased biological activity, there is potential for further development of this compound for the treatment of psoriasis.	[111]
		Novel amphiphilic MPEG-dihexPLA copolymer, 4-vinylbenzylamine	25–52 nm	-	Ciclosporin A	-	It enhanced the water solubility and cutaneous bioavailability of the drug.	[112]
		Fmoc-lys(Fmoc)-OH, N, N'-Diisopropylcarbodiimide, N-hydroxybenzotriazole	20–30 nm	Thin-film formation/ dispersion method, reverse micelle method	Methotrexate	BALB/c mice	It enhanced the targeting precision of psoriasis treatment, demonstrating superior and enduring efficacy in alleviating skin inflammation.	[113]

13	Hydrogel	Methoxy-poly(ethylene glycol)-dihexyl substituted polylactide (MPEG-dihexPLA) diblock copolymer	10–50 nm	Solvent evaporation method	Tacrolimus	-	It enhanced the bioavailability of the drug on the skin, improving clinical efficacy without elevating the risk of systemic exposure.	[114]
		Cholesterol, lecithin, oleic acid, poloxamer, PEG	18.3 ± 2.1 nm	-	Silibinin	BALB/c mice	It can enhance drug efficacy by facilitating targeted localization within psoriatic plaques.	[115]
		Hyaluronic acid, poloxamer 188	229.6 ± 3.0 nm	Wet media milling technique	Indirubin	BALB/c mice	It has the potential to enhance the delivery of topical drugs to inflamed tissues in psoriatic conditions.	[116]
		Sodium dodecyl sulfate, 12-O-Tetradecanoylphorbol 13-acetate	-	Compound 1 :2Br was dissolved in ethanol using a sonicator before adding water as the anti-solvent.	Methotrexate/ tacrolimus/ gemcitabine/ betamethasone/ triamcinolone	Swiss CD-1 mice	This supramolecular hydrogel exhibits viscoelastic properties ideal for localized drug delivery, enhances drug concentration in skin tissues while reducing side effects, and is straightforward to prepare.	[117]
		Acetonitrile, acetic acid, dimethyl sulfoxide, sodium lauryl sulfate, and xylol	100 nm	Gels without CCMoids were prepared by dissolving 1 :2Br in EtOH using sonication.	Curcumin	Sprague–Dawley rats	The supramolecular hydrogel enhances curcumin's skin penetration, decreases its side effects, and effectively reduces skin inflammation.	[118]
		Tween 20, choline, geranic acid ionic liquid, isopropylacrylamide, silk fibroin	ca. 20 nm	-	Methotrexate	BALB/c mice	It effectively mitigates IMQ-induced skin inflammation without adverse effects.	[119]
		Pluronic F127, choline chloride	-	-	Kaempferol	BALB/c mice	It reduces both the Psoriasis Area and Severity Index (PASI) score and downregulates the expression of specific pro-inflammatory cytokines.	[120]
		Polyvinylpyrrolidone (PVA/PVP) K-90 polymeric blend	252.31 ± 35.50 nm	Electrospinning technique, solvent casting method	Tazarotene, calcipotriol	Wistar rats	It exhibited a prolonged release pattern over an extended period and demonstrated potential antipsoriatic activity by promoting the regeneration of the epithelial layer.	[121]
		Polysorbate 80, isopropyl myristate, water, alkylated carbomer	-	Aqueous titration	Methotrexate	Swiss mice	It is indicated for localized psoriasis treatment.	[122]

(Continued)

Table I (Continued).

S. No.	Delivery Systems	Composition	Particle Size	Preparation Technique	Drug	In-vivo Model	Result	Ref.
		Chitosan, acetic acid, triethanolamine, dimethyl sulfoxide	256.4 ± 2.17 nm	O/w emulsion solvent evaporation method	Methotrexate	BALB/c mice	It sustains drug release and effectively treats psoriasis in murine models.	[123]
		Tin (II) 2-ethylhexanoate, polyethylene glycol, ε-Caprolactone, lipopolysaccharide, carbopol 934, eucalyptus oil	ca. 200 nm	-	Methotrexate	C57BL/6 J mice	It demonstrates superior transdermal delivery and enhanced efficacy through the synergy of intrinsic nanoparticles and extrinsic MTX.	[124]
		Glycine-glycine dipeptide, hydrophilic cholic acid	-	-	Betamethasone	C57BL/6j mice	It mediates the reduction of IL-1β, IL-17, and K16, contributing to the alleviation of psoriasis.	[125]
		β-cyclodextrin, diphenyl carbonate	194.27 ± 49.24 nm	-	Clobetasol propionate	Swiss albino mice	It mitigated drug side effects, enhancing therapeutic efficacy by modulating antioxidant enzymes and oxidative stress.	[126]
		Methoxy poly- (ethylene glycol) hexyl substituted poly-(lactic acid)	50 nm	-	Tacrolimus	C57BL/6 mice	It was crafted to possess advanced pharmaceutical formulation properties, delivery efficiency, and localized bioavailability.	[127]
		Epichlorohydrin-β-CD, pluronic® F-127/ hyaluronate hydrogel	-	-	Curcumin	-	It exhibited notable solubility and a substantial decrease in IL-6 levels.	[128]
		Choline-calixarene I	46 nm	-	Curcumin	BALB/c mice	It displayed negligible toxicity while demonstrating an anti-psoriatic effect in a psoriasis model, achieved by mitigating the pro-inflammatory process.	[129]
		Cholesterol, span 20, span 60, carbopol powder	133 nm	Thin-film hydration, sonication	Celastrol	C57/BL6 mice	It attained its anti-psoriatic effect by inhibiting inflammation and hyperproliferation of keratinocytes in the skin while further suppressing systemic inflammation.	[130]
		Cetyltrimethylammonium chloride solution, triethanolamine, 1-octadecene, tetraethyl orthosilicate	3.5 nm (DMSN1), 4.6 nm (DMSN2)	-	Erianin	-	It exhibits increased drug retention while minimizing penetration into the skin.	[131]

14	Hybrid nanoparticles	Lecithin, low molecular weight chitosan, acetic acid, tween	170.5 ± 0.087 nm	Ionic-gelation method	Gallic Acid	BALB/c mice	It demonstrates improved penetration, substantial retention, fewer side effects, and heightened efficacy against IMQ-induced psoriasis.	[132]
		Cholecalciferol, methoxy poly, DL-lactide, stannous octanoate, tween 80, carbopol 974P	123.1 nm	Hot homogenization method	Vitamin D3	Swiss albino mice	It enhances the anti-psoriatic activity of vitamin D3, resulting in an improved Psoriasis Area and Severity Index (PASI) score.	[133]
		Carbopol 974P, cholesterol, cholic acid, DL-lactide, stannous 2-ethyl hexanoate	94.8 nm	-	Clobetasol propionate	Swiss albino mice	It exhibits improved cellular uptake, heightened skin penetration, and enhanced skin retention.	[134]
		Compritol® 888 ATO, poloxamer 188, allylamine hydrochloride	142 nm	Hot homogenization method	TNF α siRNA	Hairless mice	It resulted in reduced TNF α levels, leading to a corresponding alleviation of redness and scaling in the mouse skin.	[135]
		Chitosan, tween 80, lecithin, acetic acid	118.7 ± 13.3 nm	Ethanol injection technique	Tacrolimus	C57BL/6 mice	It demonstrates superior efficacy in the treatment of psoriasis, coupled with enhanced skin deposition.	[136]
15	Metallic nanocarriers	Cetyltrimethylammonium bromide, HAuCl ₄ , poly (vinyl alcohol)	180 nm	Seed-mediated growth method	Isatin	BALB/c mice	It effectively addresses psoriasis through hyperthermia-induced apoptosis triggered by near-infrared irradiation.	[137]
		HAuCl ₄ 3H ₂ O, thiol 3MPS	5 nm	Wet reduction method	Methotrexate	C57BL/6 mice	It induces a decrease in keratinocyte hyperproliferation, epidermal thickness, and inflammatory infiltrate in mice.	[138]
		Carbopol® 934, potassium bromide, tetrachloroauric acid III	10–20 nm	-	Myricetin, Quercetin, Ellagic acid	Swiss albino mice	It reduces the mean DAI score, serum cytokine levels, epidermal thickness, and parakeratosis, and significantly diminishes the hyperproliferation of keratinocytes.	[139]
16	Nanocrystals	Hydroxypropyl methylcellulose, methyl cellulose, poloxamer 407	276.9 ± 16.49 nm	Anti-solvent precipitation technique	Diosmin	Sprague–Dawley rats	It maintains the equilibrium between Th17 and Treg cells, modulates TLR7/8/NF- κ B, miRNA-31, AKT/mTOR/P70S6K pathways, and upregulates TNFAIP3/A20 expression in psoriatic skin tissues.	[140]
		Lutrol® F127, plantacare® 2000, carbopol® Ultrez 10 NF, kollicream® 3C, tween® 60	200 nm	Wet media milling technique	Apremilast	-	It selectively delivers drugs to viable skin layers by crossing the stratum corneum barrier.	[141]
		Poly(vinylalcohol), poly(vinylpyrrolidone)	678 ± 15 nm	Acid-base neutralisation precipitation method with sonication	Methotrexate	Sprague-Dawley rats	It presents a promising approach for effective, localized, and sustained intradermal delivery, offering potential enhancements for psoriasis treatment.	[142]

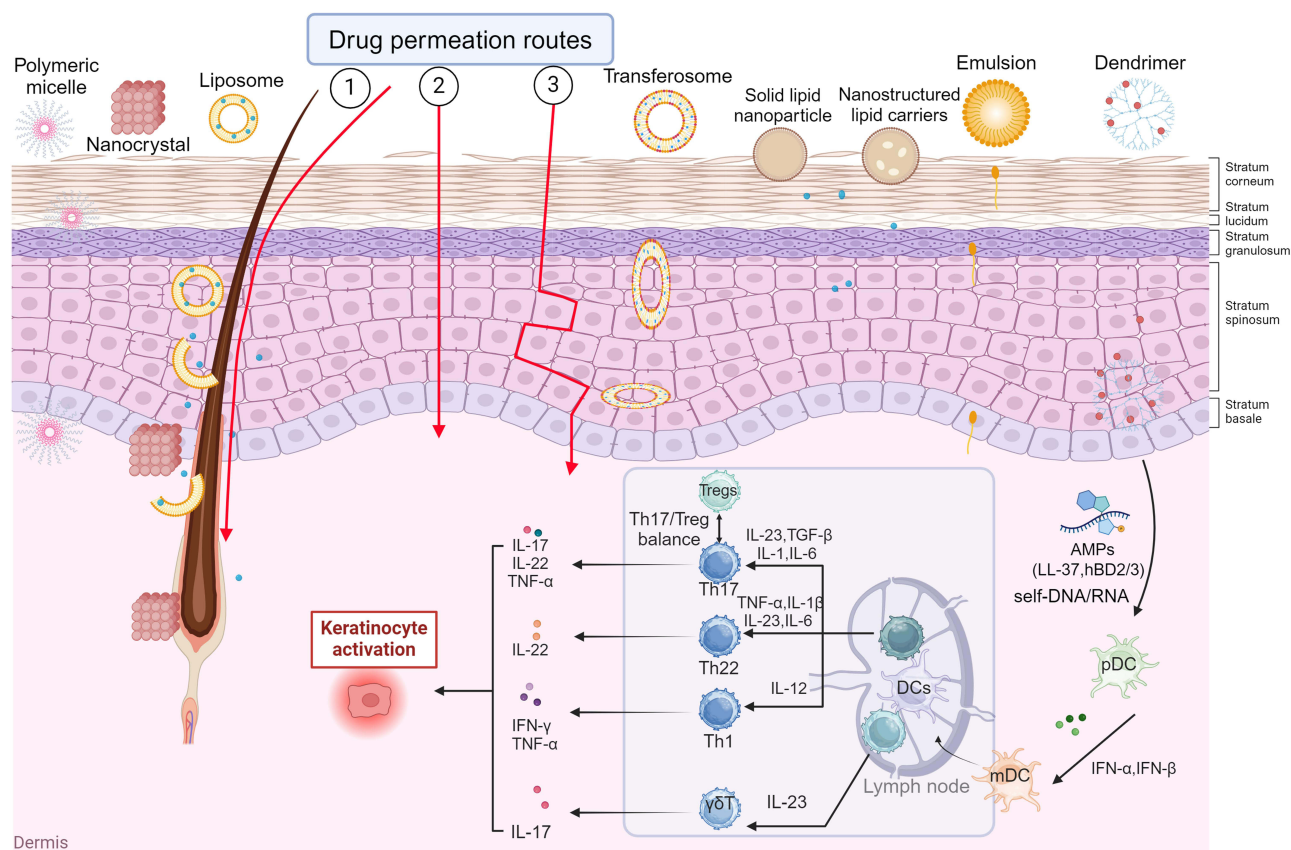


Figure 9 Illustration of three skin penetration pathways of novel drug delivery systems and pathogenesis of psoriasis. Elastic nanoparticles, including micelles, nanocrystals, liposomes, transfersomes, emulsions, and dendrimers, efficiently traverse skin layers, penetrating into deeper regions via hair follicles or intercellular spaces. Solid particles (Solid lipid nanoparticles and nanostructured lipid particles) generate a thin film that integrates into the stratum corneum. This occlusive effect amplifies the intercellular spaces among corneocytes, consequently augmenting skin permeation. 1:Transfollicular route; 2:Transcellular route; 3:Intercellular route. Created with BioRender.com.

Lipid-Based Carriers

Lipids are crucial in preserving skin hydration, integrity, and overall health. Lipid-based carriers encompass epidermal lipid-like components such as fatty acids, oils, polymers, and lipid derivatives, coupled with stabilizers (emulsifiers, surfactants, and cosurfactants). These carriers exhibit a notable ability to penetrate the deeper layers of the skin and demonstrate favorable biocompatibility as delivery systems.¹⁴³ Simultaneously, they offer several advantages, including straightforward preparation, self-assembly capabilities, high bioavailability, the capacity to carry substantial payloads, and controllability.^{144–146} Lipid-based carriers primarily fall into four categories: emulsion systems (comprising multiple emulsions, microemulsions (MEs), and nanoemulsions (NEs)), particulate systems (including solid lipid nanoparticles (SLNs), solid lipid microparticles, and Nanostructured lipid carriers (NLCs)), and NP systems (specifically liposomes, ethosomes (ETH), niosomes, transfersomes (TFs), and transmethylated liposomes), along with transmolecular systems (involving multiple emulsions, MEs, and NEs).¹⁴⁴

Vesicular Systems

Liposomes

Liposomes, composed of phospholipids forming monolayer or multilayer vesicle structures, offer substantial pharmacokinetic advantages.^{147,148} They exhibit the capacity to transport and deliver hydrophilic, hydrophobic, and lipophilic drugs, as well as encapsulate both hydrophilic and lipophilic compounds within the same system.^{144,149} Modulations in NP size, surface charge, lipid composition, number of phospholipid layers, and surface modifications (with ligands or polymers) can influence the stability of liposomes.^{144,145,150} Combining many drugs with liposomes can enhance their

physicochemical properties and facilitate drug absorption and retention in the skin, thereby demonstrating improved efficacy in psoriasis treatment.

Previously, the use of certain drugs in topical psoriasis treatments was constrained by poor water solubility, among other factors. However, liposome-related studies have enhanced drug solubility and penetration. Raju Saka et al optimized liposomes (67.8 ± 7.15 nm, PDI 0.26 ± 0.02) with an entrapment efficiency of over 90%, incorporating them into a gel loaded with bexarotene.⁴⁴ In another study, quercetin-loaded liposomes were stabilized by hydroxypropyl- β -cyclodextrin (HPCD), which forms a stabilizing layer through hydrogen bonding with the liposome interface, enhancing stability.⁴⁰ Additionally, Fan Yu developed peptide-modified liposomes, while Harsha Jain et al created formulations loaded with ibrutinib and co-loaded with curcumin, significantly improving transdermal curcumin efficiency.^{43,49}

Liposome research on drugs commonly used for topical therapy is advancing rapidly. Sindhu Doppalapudi's team investigated two liposomal formulations: cationic liposomes (DC-Chol and cholesterol) and anionic liposomes (egg lecithin, cholesterol, and tetramyristoyl cardiolipin), recording zeta potentials of +25.8mV and -28.5mV, and entrapment efficiencies of 75.12% and 60.08%, respectively. These studies demonstrated a fivefold increase in psoralen permeation using liposomal carriers, potentially enhancing the efficacy of topical PUVA treatments for psoriasis.⁴⁶ Similarly, Manoj Walunj's team developed cationic liposomes (DOTAP and cholesterol) loaded with cyclosporine.⁴¹ Fei Qu et al enhanced skin retention times to 132 hours and improved cellular internalization in vivo by integrating microneedles with 250 nm cationic liposomes. They found that dexamethasone-loaded cationic liposomes integrated with microneedles outperformed their anionic counterparts in a psoriasis-like animal model. Long Xi et al combined celastrol-loaded mannosylated liposomes with microneedles, inhibiting DC maturation markers (CD80, CD86, MHC-II).⁴² Wei Wang et al developed a nanotransdermal system (TCeO2-TRA-FNL-Gel) combining all-trans retinoic acid, triphenylphosphine-modified cerium oxide nanoparticles, and flexible nanoliposomes, showing enhanced skin retention and superior mitochondrial targeting related to scavenging reactive oxygen species (ROS) over free TRA.³⁹ Lastly, formulations including liposomal fusidic acid and calcipotriol-loaded liposomes with one mol% PEG-DSPE, as well as a liposomal gel containing zedoary turmeric oil and tretinoin, have demonstrated superior efficacy compared to direct topical applications.^{45,47,48}

Transferosomes

TFs, also known as transfersomes, are elastic liposomes primarily composed of phospholipids (eg, soya PC, egg PC, dipalmityl PC, etc) and surfactants (eg, Span[®]80, Tween[®]80, sodium cholate, etc). serving as edge activators.^{151–153} Their high deformability enables penetration into the skin through the self-extrusion of intracellular closed lipids along the SC.¹⁵⁴ TFs exhibit a burst release effect during the initial 4 hours post-administration, followed by a gradual release. The bursting effect is linked to minor breaks in the lipid bilayer, and the drug within the nucleus is also partially released due to vesicle deformation during penetration.¹⁵⁵

Recent studies have demonstrated the enhanced efficiency of TFs loaded with cyclosporine A (CyA/CsA) through membrane extrusion, in vitro skin diffusion studies revealed that the maximal flux ($\mu\text{g}/\text{cm}^2/\text{h}$) of extruded transfersomes was twice as high as that of sonicated transfersomes. Additionally, extruded transfersomes exhibited a higher CyA concentration, reaching 445 ± 39 $\mu\text{g}/\text{mL}$.⁵⁰ Wei Wang et al prepared TRA and BT dual-loaded flexible liposomes with an average particle diameter of ~ 70 nm and high drug encapsulation efficiency exceeding 98%. Compared to free drugs, these liposomes significantly enhanced drug penetration and retention in the skin. In vivo experiments showed optimal reduction in epidermal thickness and cytokine levels (TNF- α and IL-6).⁵¹ Mahdiyeh Bahramzadeh et al prepared methotrexate-entrapped TFs with a particle size of approximately 100 nm and an average zeta potential of -72.87 mV. These TFs exhibited an encapsulation efficiency greater than 85%, achieved 50% skin penetration, and resulted in a more significant reduction in skin thickness scores in mice compared to the group receiving injected methotrexate (MTX) in the in vivo experiments.⁵² Nilanchala Sahu et al formulated nanotransfersomes (NTF) using Phospholipon 90G, cholesterol, and sodium cholate for delivering Solanum xanthocarpum extract (SXE-NTF). The vesicles had an average diameter of 146.3 nm, a PDI of 0.2594, an EE of $82.24 \pm 2.64\%$, a drug loading of $8.367 \pm 0.07\%$, and a release rate of $78.86 \pm 5.24\%$. Ex vivo permeation tests demonstrated that SXE-NTF gel significantly outperformed SXE gel, achieving a permeability of $82.86 \pm 2.38\%$ compared to $35.28 \pm 1.62\%$.¹⁵⁶ These findings substantiate the efficacy of the TFs delivery system.¹⁵⁷

Ethosomes

ETHs consist of phospholipids, typically 2%–5% phosphatidylcholine (PC), along with 20%–45% ethanol and water (to 100%, ω/w).¹⁵⁸ The vesicle size is adjustable within the nanometer to micrometer range, and vesicles can have single or multiple layers.^{159,160} The first stage in the penetration of ETH through the skin is termed the “ethanol effect”, wherein ethanol disrupts the conformation of SC lipids. Increased lipid mobility reduces the density of lipid multilayers, facilitating deeper vesicle penetration into the skin. This is followed by the “ETH effect”, during which the phospholipids within the SC fuse with ETH vesicles, enhancing drug delivery.^{161,162}

In previous investigations, 30% alcohol plasmids loaded with tacrolimus (TAC) exhibited significantly heightened permeability in the epidermis and superior epidermal accumulation compared to traditional formulations.¹⁶³ In recent research, hyaluronic acid-based tacrolimus ETH (HA-TAC-ETH) demonstrated nanometric vesicle sizes (315.7 ± 2.2 nm), a polydispersity index (PDI) of 0.472 ± 0.07 , and high entrapment efficiency ($88.3 \pm 2.52\%$). These ETHs exhibited increased dermal flux and an enhancement ratio alongside sustained drug release. In a psoriasis mouse model, the HA-TAC-ETH gel effectively reduced erythema, edema, and skin thickness, offering a favorable safety profile compared to systemic drug administration.⁵³ Yongtai Zhang et al developed a novel topical drug delivery system by covalently linking hyaluronic acid (HA) to propylene glycol-based ETHs (HA-ES). HA-ES significantly enhanced transdermal curcumin delivery compared to plain ethosomes (ES) and a curcumin propylene glycol solution (PGS). Specifically, the cumulative transdermal delivery and retention in the skin after 8 hours were 1.6 and 1.4 times greater with HA-ES than with ES and 3.1 and 3.3 times greater than with PGS, respectively. Furthermore, *in vivo* studies showed that the psoriatic skin retention of curcumin using HA-ES was 2.3 and 4.0 times higher than with ES and PGS, respectively.⁵⁴ Yu Li et al developed curcumin-loaded composite phospholipid ETHs composed of a 1:1 ratio of unsaturated phosphatidylcholine (PC) to saturated hydrogenated phosphatidylcholine (HPC). These ETHs demonstrated optimal vesicle stability and flexibility compared to free curcumin. Additionally, their low uptake by HaCaT cells suggests reduced toxicity and enhanced penetration into deeper skin layers via the hair follicle pathway.⁵⁵ In a comparative study, ETHs significantly outperformed liposomes in delivering psoralen, with transdermal flux and skin deposition rates of 38.89 ± 0.32 $\mu\text{g}/\text{cm}^2/\text{h}$ and 3.87 ± 1.74 $\mu\text{g}/\text{cm}^2$, respectively. These rates were 3.50 and 2.15 times higher than those achieved with liposomes.⁵⁶ Liposomal and ethosomal gels designed for the topical delivery of anthralin demonstrated high drug encapsulation efficiencies, achieving $\geq 97.2\%$ for liposomes and $\geq 77\%$ for ETHs. Post-treatment, the mean PASI changes were -68.66% for liposomes and -81.84% for ETHs, indicating a statistically significant superior efficacy of ETHs.⁵⁷

Transethosomes

Transethosomes (TEs) possess a structure comprising the fundamental constituents of ETH (20%–45% ethanol and phospholipids) and single-chain surfactants serving as edge activators (Tween[®]80, sodium taurocholate, oleic acid, or decyl methyl sulfoxide, etc).¹⁶⁴ This surfactant amalgamates the features of TFs and ETHs, synergizing sudden release with robust permeability. Costanzo et al demonstrated that TEs, comprising polysorbate 80 (T80) loaded with cholecalciferol (vitamin D3), exhibited no adverse effects on keratinocyte survival. Within 2 hours of administration, these TEs penetrated keratinocytes, undergoing complete degradation and release within 24 hours. Hence, this vector emerges as a promising vehicle for the transdermal administration of vitamin D3.⁵⁸ Rodríguez-Luna et al developed TEs -in-Carbopol[®] loaded with rosmarinic acid, wherein the TE incorporated sodium deoxycholate as a limbic activator. This formulation addressed the challenges of rosmarinic acid, characterized by poor water solubility, low permeability, and chemical instability. In a murine model of IMQ-induced psoriasisform dermatitis, notable improvement in skin edema was observed, accompanied by reduced levels of TNF- α and IL-6 at the skin lesions, affirming the efficacy of this delivery approach.⁵⁹

Non-Ionic Surfactant Vesicles (Niosomes)

Niosomes (Nios), also recognized as nonionic surfactant vesicles, represent microscopic lamellar structures formed through the amalgamation of nonionic surfactants (eg, amino acid compounds, alkyl esters, alkyl amides, fatty acids, and alkyl ethers) followed by hydration.^{153,165,166} Their composition distinguishes Nios from liposomes, as the former contains less toxic nonionic surfactants than phospholipids. This choice imparts superior stability, enhanced antioxidant

properties, and reduced production costs.¹⁶⁷ Nonionic surfactants can modify the SC, rendering it more permeable and lax, consequently amplifying the residence time and local concentration of drugs in the SC and epidermis.¹⁶⁸

Nio gel, laden with cyclosporine, demonstrated superior penetration compared to the suspension. Drug deposition studies and fluorescence microscopy revealed a 59-fold increase in drug deposition in the SC and the vivo epidermis/dermis (VED) layer. Concurrently, intervention using this drug delivery mode significantly reduced histopathological and PASI scores in the IMQ-induced psoriasis model, underscoring the formulation's superiority.⁶⁰ Gel formulations incorporating carbomer 980 into desoximetasone-loaded Nios exhibited a stable slow-release process in vitro skin permeation tests. After 24 hours, the niosomal gel released $9.75 \pm 0.44 \mu\text{g}/\text{cm}^2$ of desoximetasone, compared to $24.22 \pm 4.29 \mu\text{g}/\text{cm}^2$ from the reference gel. Drug deposition studies demonstrated that the Nios achieved superior skin deposition ($30.88 \text{ ng}/\text{mg}$ versus $26.01 \text{ ng}/\text{mg}$) than conventional gels, indicating enhanced drug penetration and retention in human skin.⁶¹ Meng et al synthesized Celestrol Nios using the thin film hydration method followed by probe sonication, utilizing a formulation of Span 20, Span 60, and cholesterol in a 3:1:1 weight ratio. These Nios, with an average particle size of approximately 147 nm, yielded up to 90%. They exhibited significantly enhanced water solubility and permeability alongside improved antipsoriatic activity in mice.^{62,169} Acitretin (Act) -loaded Nios (span 60: cholesterol molar ratio 1:1) demonstrated enhanced stability and reduced irritation. In vitro, skin penetration studies in rats revealed a significantly higher cumulative penetration of Act nio gel compared to Act gel after 30 hours. Moreover, Act nio gel exhibited notable antipsoriasis benefits in a topical application on a mouse tail model.⁶³ Loaded with diacerein, Nios addressed low solubility, low bioavailability, a short half-life, and severe gastrointestinal adverse effects. Niosomes were prepared using 90 mg of Span 60 and 10 mg of cholesterol with a hydration time of 45 minutes. This formulation significantly enhanced the penetration of diacerein into the epidermal and dermal layers of rat skin, improving drug stability and supporting its use in psoriasis treatment.⁶⁴

Cerosomes

Cerosomes represent a distinctive vesicular class, incorporating ceramide lipids as a crucial component in the lipid bilayer. The presence of ceramide sphingolipids, naturally occurring in the skin, imparts the vesicles prepared with ceramide with the capability to enhance drug penetration by disrupting the intercellular lipid organization of the skin.¹⁷⁰

In tubulated vesicles, termed "cerosomes", loaded with tazarotene, ceramides increased the encapsulation rate of tazarotene while reducing its release, concurrently enhancing its deposition in the skin. In a clinical trial involving 20 patients with plaque psoriasis, this delivery system significantly outperformed tazarotene gel, resulting in a more substantial reduction in PASI scores.⁶⁵ Yang et al developed MTX/NIC cerosomes co-delivering MTX and nicotinamide (NIC). NIC effectively solubilizes MTX through the formation of hydrogen bonds. The cerosomes facilitate drug penetration and retention in rat skin. MTX/NIC cerosomes induce apoptosis and exhibit robust resistance to HaCaT cells, displaying potent antiproliferative effects.⁶⁶ Sammar Fathy Elhabal et al developed positively charged cerosomes based on ceramide IIIB to co-deliver CsA and dithranol (DTH). The cerosomes exhibited an average particle size of $222.36 \pm 0.36 \text{ nm}$, a polydispersity index of 0.415 ± 0.04 , an entrapment efficiency of $96.91\% \pm 0.56$, and a zeta potential of $29.36 \pm 0.38 \text{ mV}$. Compared to a CsA/DTH solution, the cerosomes enhanced drug penetration by 66.7% and decreased PASI by 2.73-fold and 42.85%, respectively.⁶⁷

Emulsion Drug Delivery Systems

Emulsions represent biphasic liquid systems, wherein the inner phase (dispersed phase) forms tiny droplets dispersed in the outer phase (continuous phase). The oil phase matrix typically comprises diacylglycerols, monoacylglycerols, triacylglycerols, and free fatty acids bound with loaded drugs and lipophilic surfactants. The aqueous phase consists mainly of water, surfactants, cosurfactants, emollients, and other components.¹⁷¹ Oil-in-water (O/W) emulsions consist of oil droplets dispersed in water, providing a vehicle for loading hydrophobic drugs into the oil core. Conversely, water-in-oil (W/O) emulsions possess the opposite structure, with water droplets dispersed in oil, making them a preferred carrier for hydrophilic drugs.¹⁷² The fundamental structure of W/O/W emulsions involves large oil droplets dispersed in an aqueous phase, containing water droplets as the dispersed phase. In the O/W/O emulsion system, water droplets containing the oil droplets are dispersed in the oil phase.¹⁷¹ These two multiple emulsion systems are suitable for loading hydrophilic and

hydrophobic actives in the aqueous and oil phases. Emulsion Drug Delivery Systems primarily consist of two forms: miniemulsions and NEs.

Nanoemulsion (NE) gels containing TAC and using fish or flax oil as the oil phase with 1% Carbopol 934 significantly enhance penetration and skin retention. Compared to commercially available creams, these nanoemulsions achieve cumulative drug penetration into the skin, which is twice as effective and provides approximately 1.5 times greater penetration depth and skin retention. In IMQ-induced psoriasis mice, treatment with these NE gels resulted in significantly reduced levels of TNF-alpha and IL-6 in the skin, demonstrating superior antipsoriasis efficacy compared to cream administration.⁶⁸ Sahu et al also developed a NE loaded with TAC, utilizing kalonji as the oil phase. In an in vitro mouse skin penetration assay, the NE gel with Caropol 934 displayed sustained release, achieving 4.33 times higher dermal bioavailability than commercially available cream.^{68,70} Wan et al devised and optimized a TAC-loaded microemulsion formulation using a binary surfactant mixture of d- α -tocopheryl polyethylene glycol succinate (TPGS) and Labrasol. The study results indicated complete solubilization of TAC in TPGS-ME, exhibiting significantly increased TPGS-ME uptake. The topical application of TAC-TPGS-ME for psoriasis treatment in a mouse model surpassed the efficacy of existing creams.⁶⁹ Khatoon et al developed a NE gel co-loaded with curcumin (CRC), resveratrol, and thymoquinone. The optimized formulation featured a droplet size of 76.20 ± 1.67 nm, a PDI of 0.12 ± 0.05 , a refractive index (RI) of 1.403 ± 0.007 , and a viscosity of 137.9 ± 4.07 mPa·s. This formulation inhibited the A-431 cell line growth, displayed potent anti-angiogenic activity, and demonstrated therapeutic efficacy in an IMQ-induced mouse model psoriasis.⁷¹ Algahtani et al employed a novel method to optimize a NE loaded with CRC, transforming it into a nanoemulgel by adding Carbopol 934. The study results indicated a 4.87-fold increase in drug penetration in the nanoemulgel.⁷² Benigni et al developed microemulsions (MEs) loaded with cyclosporine, utilizing a high-viscosity system containing TPGS. This formulation showed significantly elevated skin accumulation and rapid absorption, achieving approximately six times the skin accumulation of cyclosporine compared to a control solution in propylene glycol.⁷³ Pandey et al developed a microemulsion (ME) gel loaded with cyclosporine, using isopropyl myristate as the oil phase and Carbopol 940 as the gelling agent. This formulation demonstrated a significantly higher permeation rate than cyclosporine suspensions and exhibited substantial drug retention in skin tissue, achieving a retention rate of 38.92%.⁷⁴ Tanghetti et al developed an O/W emulsion system that co-encapsulates halobetasol propionate and tazarotene within a polymeric matrix, incorporating moisturizing and hydrating ingredients. This formulation enhanced hydration and improved drug release, promoting deeper penetration into the dermis and reducing irritation. The 0.01% halobetasol propionate/0.045% tazarotene lotion, utilizing polymeric emulsion technology, achieved more effective delivery of active ingredients than either 0.05% halobetasol propionate or 0.1% tazarotene creams alone. Moreover, the synergistic effect of the combined drugs significantly increased efficacy in treating psoriasis compared to single-drug applications.⁷⁵ El-Gogary et al formulated an Oleuropein ME formulation. The selected microemulsion formulation displayed a particle size of 30.25 ± 4.8 nm, zeta potential 0.15 ± 0.08 mV and polydispersity index 0.3 ± 0.08 , with storage stability for 1 year in room temperature and total deposition in skin layers amounting to 95.67%. That, in an eight-week clinical trial involving 20 patients with plaque-type psoriasis, exhibited a more pronounced reduction in PASI scores than clobetasol propionate. Dermoscopic symptomatic improvement was more prominent with the Oleuropein ME formulation.⁷⁶ Rashid et al developed a nanoemulsion gel (MTX NEG) containing MTX and olive oil, using sodium alginate as the gelling agent. The optimized MTX NEG displayed a particle size of 202.6 ± 11.59 nm, a PDI of 0.233 ± 0.01 , and an average entrapment efficiency of $76.57 \pm 2.48\%$. Over 24 hours, the gel facilitated the permeation of an average of 70.78 ± 5.8 $\mu\text{g}/\text{cm}^2$ of MTX, with a flux value of 2.078 ± 0.42 $\mu\text{g}/\text{cm}^2/\text{h}$. This formulation achieved higher skin retention than both the MTX solution and the plain MTX gel, particularly in the deeper epidermal and dermal layers. In an IMQ-induced rat model, topical MTX NEG demonstrated superior therapeutic effects compared to oral MTX treatment.⁷⁷ Guo et al designed a ME formulation loaded with salvianolic acid B, significantly improving IMQ-induced psoriasis lesions in mice. The formulation inhibited epidermal hyperplasia, increased skin moisture, and decreased IL-23/IL-17 cytokine expression.⁷⁸

Lipid Nanoparticles

Lipid NPs are non-homogeneous systems comprising an inner lipid phase and an outer aqueous phase stabilized by one or two surfactants. Topically applied lipid NPs encompass SLNs and NLCs.¹⁰³ The surface charge of lipid NPs is typically determined by the lipid headgroups, which exhibit positive, negative, or amphotericly charged characteristics. The surface potential, contingent on the surface charge density, governs inter-particle interactions and counteracts ion adsorption, thereby regulating NP stability.^{104,105,153} Lipid NPs augment drug penetration into the epidermis and mitigate systemic absorption by overcoming the stratum SC barrier through various mechanisms: (1) Forming a thin film on the skin surface enhances skin hydration and decreases water loss,¹⁷³ facilitating improved drug penetration into the SC. (2) Inducing a controlled occlusion effect due to particle size enhances skin hydration in the SC and promotes active substance diffusion into deeper skin layers.¹⁰⁶ (3) Contributing to rearranging SC lipids and aiding active substance penetration. (4) Facilitating the miscibility or mixing of NLC lipid components with SC lipids to enhance penetration. (5) Introducing surfactants to disrupt skin structure and improve absorption. (6) Significantly altering intercellular accumulation, reducing keratinocyte accumulation, and widening the interstitial space between keratinocytes.¹⁷⁴ Moreover, lipid NPs offer additional advantages such as non-toxicity and protection against light-sensitive, oxidizing, and hydrolyzing drugs.¹⁷⁵

Solid Lipid Nanoparticles

SLNs represent a lipidic nanocarrier system designed to enhance drug penetration and overall efficacy, typically exhibiting a particle size ranging from 10 to 1000 nm, categorizing them as “first-generation lipid nanocarriers”.¹⁷⁶ SLNs consist of solid lipids, forming a crystal structure akin to a “brick wall”, effectively preventing particle coalescence.¹⁷⁷ This unique structure allows drug molecules to stay solubilized or dispersed within the lipid matrix, providing SLNs with superior physical stability compared to liposomes.¹⁷⁸ The central lipid core of SLNs is enveloped by a surfactant (emulsifier) layer, with the selection of an appropriate lipid matrix and surfactant being crucial for the preparation of effective and stable SLNs.¹⁷⁹ When delivered to the skin, SLNs exhibit an initial burst release from the NP surface, followed by a controlled release, enabling the drug to penetrate further into the epidermis and dermis, contingent on its lipophilicity.¹⁵⁷ Furthermore, SLNs offer elevated drug loading, enhanced bioavailability, facile mass production, and obviate the need for organic solvents.¹⁸⁰

In a recent study, Rahmanian-Devin P et al developed SLN encapsulating Noscapiine (SLN-NOS) using a central composite design, modified high-shear homogenization, and ultrasound methods. Precirol® was chosen as the optimal lipid base. Over 72 hours, SLN-NOS released 83.23% of Noscapiine at pH 5.8 and 58.49% at pH 7.4. Franz diffusion cell experiments showed that skin absorption of Noscapiine from SLN was 46.88%, significantly higher than the 13.5% from cream formulations, effectively improving symptoms in a psoriasis mouse model. The formulation also decreased IL-17, TNF- α , and transformed growth factor- β levels while increasing IL-10.⁷⁹ Alhelal HM et al developed leflunomide (LEF)-loaded solid lipid nanoparticles (SLNs) integrated with hydrogels, achieving an entrapment efficiency of $65.25 \pm 0.95\%$ and a total drug content of $93.12 \pm 1.72\%$. These formulations exhibited enhanced stability and anti-inflammatory activity compared to pure drug solutions. Additionally, modifications to the preparation method significantly reduced skin irritation.⁸⁰ For the topical delivery of apremilast (API), Rapalli et al developed SLNs, which achieved delayed release of API over 18 hours. The dispersion of API in these SLNs led to a twofold reduction in TNF- α miRNA expression compared to the free drug. This formulation enhanced API's skin penetration and retention, offering slow release, non-toxicity, reduced systemic absorption, and improved efficacy in treating psoriasis.⁸¹ Pitzanti et al developed SLNs incorporating the penetration enhancer Transcutol® P (TRC) to deliver 8-methoxy psoralen (8-MOP). The study showed that SLNs with 4% TRC enhanced the accumulation of 8-MOP in each skin layer compared to formulations with 2% and 0% TRC. Additionally, including TRC in SLNs increased cellular nanoparticle uptake without increasing cytotoxicity.⁸² Pradhan M et al developed SLNs encapsulating triamcinolone acetonide (TA), which exhibited prolonged drug release, closely following Higuchi release kinetics with an R^2 value of 0.9909. Furthermore, the sustained-release profile of these TA-loaded SLNs and their preferential accumulation in the epidermis significantly reduced undesirable systemic absorption and associated side effects.⁸³ Sonawane, R. et al developed solid lipid nanoparticles (CT-BD-SLNs) loaded with betamethasone dipropionate (BD) and clobetasol propionate (CT), incorporated into a carbopol gel matrix. Compared to Daivobet ointment, this SLN gel formulation reduced the systemic absorption of CT and BD, exhibited non-

irritating properties, and increased dermal bioavailability. This enhanced distribution within skin layers and demonstrated improved anti-psoriatic effects in a mouse psoriasis model.⁸⁴ Essaghraoui, A. et al formulated SLNs based on Softisan[®] 649, a commonly used cosmetic ingredient, for localized CsA delivery. These SLNs exhibit a remarkable 95-fold increase in the local bioavailability of drugs by enhancing their water solubility.⁸⁵ In a parallel approach, Silva et al developed an oleogel nanoformulation incorporating CsA-loaded SLNs, demonstrating improved drug stability and enhanced skin penetration.⁸⁶ Additionally, Trombino, zaS. et al enriched SLN carriers with naringenin and linolenic acid, both possessing potent anti-inflammatory activity, for the topical administration of CsA. The researchers explored SLNs as a vehicle for CsA topical administration, incorporating various lipophilic gelling agents to enhance local drug release.^{87,181} Debarati Maiti et al engineered SLNs loaded with MTX. The results indicated that MTX was gradually released, achieving 80.36% skin permeation and effectively inhibiting keratinocyte growth with reduced cytotoxicity. Furthermore, this formulation's flux and permeation rates surpassed those of existing marketed and standard preparations.⁸⁸ Kang J. et al investigated thermosensitive SLNs encapsulating TAC with various shell surfactants to facilitate rapid drug release into surrounding tissues for enhanced therapeutic effects.⁸⁹ Ferreira, M. et al encapsulated MTX in etanercept-coupled SLNs within carboplatin hydrogels. This formulation significantly increased MTX's dermal bioavailability and allowed for sustained drug release through the carboplatin hydrogel. In vitro studies showed that these SLNs provided a sustained release of methotrexate over 8 hours. The hydrogel's mucosal adhesion properties also extended MTX retention in the skin.⁹⁰

Nanostructured Lipid Carriers

NLCs, recognized as “second-generation lipid nanocarriers” and structurally akin to SLNs, are typically synthesized through various inorganic or organic solvent methods. Their superior loading capacity and long-term stability position them as more favorable nanocarriers than SLNs. NLCs consist of solid and liquid lipids, particularly unsaturated ones, resulting in a minimal crystalline matrix.^{182,183} Moreover, the reduced water content in NLC particle suspensions minimizes drug release during storage compared to SLNs. The irregular structure of NLCs facilitates the creation of distinct compartments in the lipid matrix, enhancing drug loading capacity and preventing premature release during storage.¹⁷⁸ Due to their high skin adhesion, controlled occlusion properties, which enhance skin hydration and bioavailability, and stable drug encapsulation capability, NLCs find extensive use in topical drug delivery.¹⁸³

Recent investigations have leveraged luteolin (Lut) as an anti-psoriasis drug in the formulation of Lut-NLC. The prepared nanoparticles exhibited sustained drug release up to 24h and enhanced the skin deposition of Lut by 3.4-fold higher in stratum corneum, epidermis and dermis compared to Lut suspension with minimum transdermal delivery. This administration mode heightened the anti-psoriasis efficacy of Lut compared to the free drug.⁹¹ A newly developed nanogel based on TAC and thymoquinone-co-loaded NLCs demonstrated sustained drug release over 24 hours, showcasing superior penetration depth in suspension gel with dose-dependent toxicity.⁹² The optimized NLC loaded with riluzole exhibited optimal properties for dermal application, inhibiting keratinocyte proliferation and enabling sustained drug delivery.⁹³ Madan, J.R. et al formulated NLCs by a cold homogenization technique using Compritol 888ATO, oleic acid, Tween 80 and Span 20, and Transcutol P as a solid lipid, liquid lipid, surfactant mixture, and penetration enhancer, respectively. Containing Apremilast (APM) for topical application. ex vivo skin permeation results showed low drug diffusion, sustained drug release, and 60.1% skin deposition.⁹⁴ In a parallel effort, Rapalli, V.K. et al developed APM-loaded NLCs characterized by their lack of cytotoxicity and skin irritation. Notably, these formulations achieved a threefold increase in ear skin retention in vitro compared to conventional gel formulations. In a psoriasis mouse model, the APM-loaded NLC dispersions were more effective than the free drug, particularly in reducing TNF- α levels.⁹⁵ Agrawal, Y.O. et al developed NLCs optimized using 32 full factorial designs loaded with MTX by a solvent diffusion technique. Significantly higher deposition of MTX was found in HCS from MTX NLC gel ($71.52 \pm 1.13\%$) as compared to MTX plain gel ($38.48 \pm 0.96\%$). In a mouse psoriasis model, the application of MTX NLC gel led to a noteworthy reduction in the PASI score and decreased expression of inflammatory cytokines. It mitigated local side effects.⁹⁶ Pradhan, M. et al developed NLCs loaded with fluocinolone acetonide (FA) and successfully integrated them into carbopol 934 gel bases containing salicylic acid (SA), resulting in an FA-loaded NLC + plain SA gel formulation (FSG). These FA-loaded NLCs demonstrated selective localization in the epidermis and deep dermis. In a psoriasis

mouse model, the FSG treatment was more effective than the PFSG (plain FA and SA gel) group.⁹⁷ Pradhan, M., D. Singh, and M.R. Singh developed optimized NLCs loaded with TA, which enhanced drug solubility. In vitro studies demonstrated selective drug deposition in the epidermis and reduced adverse side effects associated with systemic exposure compared to TA suspension.⁹⁸ Viegas, J.S.R. et al designed NLCs to co-deliver TAC and TNF- α siRNA. Experimental results demonstrated slow TAC release over 24 hours, efficient siRNA translocation across the stratum corneum (SC), and enhanced TAC retention in the skin. In a psoriasis mouse model, NLCs loaded with TAC and TNF- α siRNA significantly reduced TNF- α expression in skin tissue compared to controls.⁹⁹ Rapalli, V.K. et al formulated NLCs loaded with CRC exhibiting extended in vitro release for up to 48 hours. The formulation demonstrated a 3.24-fold improvement in penetration and skin retention compared to free CRC gel.¹⁰⁰ Sathe, P. et al prepared NLC, particle size below 300 nm, polydispersity index (PDI) below 0.3 and percentage entrapment efficiency of ~100% gels loaded with dithranol, showcasing extended drug release and protection from oxidation. The NLC gel loaded with dithranol led to a more pronounced reduction in IL-17, IL-22, and IL-23 levels in the skin tissues of IMQ-induced psoriasis mice compared to commercially available creams.¹⁰¹

Liquid Crystalline Nanoparticles

Liquid Crystalline Nanoparticles (LCNs) represent bulk liquid crystalline arrays between liquid and solid crystalline states, deconstructed into NPs characterized by anisotropic structures composed of amphiphilic lipids.¹⁰¹ LCNs, derived from MO, exhibit the capacity to modulate and disrupt lipid phases within the SC barrier. Their bioadhesive properties, resembling biofilm-like structures, and the pro-osmotic effects of related substances facilitate drug uptake.¹⁸⁴

In the most recent investigation, Apremilast-loaded lyotropic LCNs were developed by researchers, incorporating non-toxic excipients in the formulation. The in-vitro drug release showed the prolonged-release for 18h. The ex-vivo studies revealed that LCNs formulation exhibited drug retention up to 3.2 and 11.9-fold higher, in stratum corneum and viable epidermis compared to conventional gel preparation. The dermatokinetic study revealed the AUC₀₋₂₄ of the LCNs loaded gel was 8.4 fold higher in epidermis and 2.06 fold in dermis, respectively compared to plain gel.¹⁰² Furthermore, Silvestrini et al developed triptolide-loaded LCNs coupled with small interfering RNAs (siRNAs) targeting TNF- α and IL-6. In vitro permeation studies revealed an increase of more than 20-fold in the distribution of triptolide (TP) through the porcine epidermis/dermis was achieved after the application of LCN-TP or LCN TP in hydrogel. In cell culture, the formulation showcased good compatibility and rapid internalization.¹⁰³ Rapamycin (RAPA), an immunosuppressant that inhibits the mammalian target of RAPA complex 1 (mTORC1), is proposed for treating psoriasis. RAPA is encapsulated in phytantriol-based liquid crystalline nanoparticles (NPs) stabilized with pluronic F127. This formulation exhibits over 95% encapsulation efficiency, provides sustained drug release for 14 days in vitro, and demonstrates antiproliferative activity against natural killer cells.¹⁰⁴ TAC-loaded LCNs, prepared by Thapa and Yoo, resulted in a six-fold increase in drug penetration into mouse skin after 24 hours of application compared to TAC dissolved in propylene glycol. This application significantly reduced PASI scores and the number of inflammatory cells in skin tissues.¹⁰⁵ Berberine (BBR) is recognized as a highly promising natural plant-derived drug for future psoriasis treatment due to its diverse biological effects, including antiproliferative, anti-inflammatory, and antioxidant properties.¹⁷³ However, BBR needs help with poor solubility in aqueous solutions and low skin permeability. Freag and Torkey's group addressed this issue by preparing monoolein-based BBR-oleate-loaded (BBR-OL) LCNs. The optimized BBR-OL-LCNs functioned as a liquid crystalline nanosuppository, Berberine (Brb)-OL-LCNPs showed a threefold increase in the drug accumulated within rat skin and around tenfold increase in the drug permeation compared with crude Brb. In vivo studies revealed that topical application of Brb-OL-LCNPs hydrogel significantly alleviated psoriasis symptoms and reduced the levels of psoriatic inflammatory cytokines.¹⁰⁶

Polymer-Based Carriers

Polymer-based carriers typically comprise eco-friendly polymers within the 10–1000 nm size range. Therapeutic components can either be internally encapsulated or surface-bound to the nanocarrier.¹⁸⁵ These carriers are effective delivery vehicles due to their tunable size, high stability, surface ligand modification, controlled drug release, ease of

preparation, and targeting capabilities. Drug release can be modulated through adjustments in the drug-to-polymer ratio and the polymer's composition and molecular weight.¹⁸⁴

Dendrimers

Dendrimers, intricate drug delivery systems, comprise highly branched molecules with a precisely controlled, spherical, reactive three-dimensional structure and many controllable peripheral functions. Drug molecules are either physically enveloped or covalently linked to functional groups, giving rise to drug-dendrimer couplings.¹⁸⁶ Various dendrimer types encompass glycodendrimers, peptide dendrimers, and lysine core dendrimers.¹⁷⁴ Different types of dendrimers have the potential to modulate drug solubility, penetration, and retention, offering diverse avenues for achieving effective topical psoriasis therapy.

Jebbawi, R. et al discovered that a poly(phosphorhydrazone) dendrimer, which features anionic aza bisphosphonate groups and is referred to as an ABP dendrimer, demonstrates anti-psoriatic therapeutic potential in a mouse model of psoriasis. RNA interference operates at the genomic level, with siRNA acting post-transcriptionally to down-regulate protein production, a crucial mechanism for managing and mitigating diverse diseases. Furthermore, Pandi P. et al investigated the impact of a poly(amidoamine) dendrimer (PAMAM) on human immune cells *in vitro*. They demonstrated control over clinical and histopathological scores and macrophage infiltration in the skin of treated mice within corresponding mouse models.¹⁷⁵ PAMAM dendrimers and liposomes were utilized for the targeted delivery of anti-TNF- α siRNA in a mouse model of psoriasis. The dendriplex particles displayed a size of 99.80 ± 1.80 nm, a zeta potential of 13.40 ± 4.84 mV, and an entrapment efficiency of $98.72 \pm 2.02\%$. Both treatment groups demonstrated significant improvements in clinical phenotype and histopathology, accompanied by reduced levels of IL-6, TNF- α , IL-17, and IL-22 in the skin lesions.¹⁰⁷ Tripathi, P.K. et al investigated the potential of PAMAM dendrimers loaded with dithranol (DIT) for topical application in a microsphere-based gel. The formulation yielded a 66.28% return, with encapsulation efficiencies ranging from 71.33% to 49.21% and particle sizes varying from 28 ± 1.12 μ m to 130 ± 1.01 μ m. The optimized formulation demonstrated enhanced stability and non-irritation to the skin of experimental animals, increased DIT solubility, improved skin permeability, and reduced the rate of anthralin autoxidation.¹⁰⁸ Agrawal U. et al explored the application of polypropylene imine (PPI) dendrimers for the topical administration of DIT. DIT-PPI demonstrated a significantly enhanced permeation rate constant of 11.61 ± 1.80 μ g/cm²/h and reduced skin irritation, rated at 1.0, compared to the plain DIT solution, which showed a rate of 2.72 ± 0.31 μ g/cm²/h and an irritation score of 2.3. Additionally, DIT-PPI was found to effectively penetrate the sebaceous gland area of hair follicles.¹⁰⁹ Dhanikula, R. S., investigated MTX-loaded polyester-co-polyether dendrimers, noting their enhanced biocompatibility and significant encapsulation capacity, with MTX loading as high as 24.5% w/w. Increases in polyethylene glycol branches and expansions of hydrophobic regions within the dendrimers moderated the rapid drug release, suggesting the formulation's potential as a targeted sustained-release carrier.¹¹⁰

Micelle

A micelle is a self-assembled nanocarrier comprised of amphiphilic compounds, exhibiting a size ranging from 5 to 100 nm.¹⁸⁷ Comprising a hydrophobic core and a hydrophilic shell, the micelle carries lipophilic and hydrophilic drugs in its shell. The modes of drug release vary depending on the loading method and drug location.¹¹¹ Micelles offer advantages such as high bioavailability, substantial drug loading capacity, a low drug degradation rate, minimal side effects, and enhanced skin permeability.¹⁸⁴

Mycophenolic acid (MPA), CsA, and MTX are conventional immunosuppressive drugs employed in psoriasis. However, their limited water solubility significantly hampers their topical application. Supasena et al synthesized poloxamer 407 (P407)-MPA micelles by coupling Kolliphor[®] 407 with MPA, resulting in a conjugate that displayed enhanced micellization properties, achieving over a 12-fold reduction in critical micelle concentration compared to P407 alone. These micelles exhibited a sustained release profile of MPA and demonstrated antiproliferative effects on TNF- α -induced HaCaT cells.¹¹¹ Guo, D. et al designed a hydrophilic nanocarrier for MTX using micelles. This formulation ensured efficient loading of MTX when dispersed in an aqueous solution.¹¹³ Lapteva, M. et al developed TAC polymer micelles using MPEG-dihex-PLA, achieving an optimal 0.1% micelle formulation that remained stable at 4°C for seven

months. This formulation enhanced TAC deposition in the skin, delivering $1.50 \pm 0.59 \mu\text{g}/\text{cm}^2$ compared to $0.47 \pm 0.20 \mu\text{g}/\text{cm}^2$ for Protopic (0.1% w/w TAC ointment).¹¹⁴ Silibinin (SL), the principal component of milk thistle (*Silybum marianum*), exhibits antioxidant and antitumor activities, along with inhibitory effects on STAT3 and cell proliferation.¹⁸⁸ Chavoshy, F. et al synthesized SL-loaded polymeric micelles. The optimized batch exhibited a mean particle size of $18.3 \pm 2.1 \text{ nm}$ and an entrapment efficiency of $75.8 \pm 5.8\%$. These SL-loaded micelles reduced the Psoriasis Area Index by over 78% after 14 days. This suggests topical STAT-3 inhibitors may represent a novel strategy in psoriasis treatment.¹¹⁵

Hydrogel

Hydrogel, a self-assembled supramolecular aggregate, excels at water retention. Its mesh size, degradation rate, and drug interactions make it a potent drug delivery vehicle.¹⁸⁹ Hydrogel offers an alternative to traditional creams and ointments in treating psoriasis. Its high water content and non-greasy texture help maintain skin moisture, minimize transdermal water loss, enhance drug penetration and sustained release, and provide a cooling effect via surface evaporation.

In a recent study, Lin Li et al developed hydrogels loaded with indirubin NCs mixed with HA, improving indirubin delivery and skin accumulation and enhancing efficacy against psoriatic inflammation.¹¹⁶ Su, H. et al formulated a kaempferol hydrogel with controlled-release properties that scavenged over 90% of free radicals at specific concentrations, also inhibiting HaCaT cell proliferation without significant cytotoxicity; in mouse models, it markedly reduced psoriasis symptoms and pro-inflammatory cytokines TNF- α , IL-6, and IL-17A.¹²⁰ Sunita Thakur et al created a tazarotene-CT-loaded nanofiber and carbopol-based hydrogel film that biodegraded within two weeks, achieving nearly 96% drug release in 72 hours with anti-psoriatic solid effects in a mouse model.¹²¹ Rana, K. et al used a cholic acid-dipeptide conjugate for self-assembly in a betamethasone-loaded hydrogel, enhancing the steroid's solubility and release properties.¹²⁵ Kumar, S., M. Prasad, and R. Rao developed a cyclodextrin nanosponge-based hydrogel loaded with clobetasol propionate, which decreased oxidative stress markers and improved anti-psoriatic effects in a mouse tail model.¹²⁶ Gabriel, D. et al employed mPEGhexPLA-based nanocarriers in a carbopol-based hydrogel for enhanced dermal delivery of TAC in a psoriasis mouse model, showing superior efficacy to the commercial cream Protopic.¹²⁷ Finally, Qiu, F. et al demonstrated that their Cel Niosome hydrogel significantly inhibited pro-inflammatory markers and improved histological outcomes compared to topical TAC in skin models.¹³⁰

There is a notable focus on hydrogel studies involving MTX. Shu, Y. et al developed a thermo-responsive hydrogel with an ionic liquid ME for MTX delivery, which exhibits inherent antimicrobial properties and enhances MTX solubility for temperature-controlled release.¹¹⁹ Bernardes, M.T.C.P. et al prepared alkylated carbomer-based hydrogels loaded with MTX, which reduced inflammation, modulated epidermal thickness, and decreased COX-2, myeloperoxidase activity, and TNF- α levels in a psoriasis mouse model.¹²² Asad, M.I. et al optimized chitosan hydrogels loaded with MTX-NPs, retaining most of the drug in the epidermis within 24 hours and demonstrating 73% sustained drug release over 48 hours. This formulation outperformed commercially available TAC cream and free MTX hydrogel in improving psoriasis symptoms, significantly reducing TNF- α and IL-6 levels in the skin.¹²³ Xu, J. et al introduced a multifunctional composite hydrogel modified with nanomicelles and ZnO/Ag NPs, which suppressed pro-inflammatory pathways in macrophages and keratinocytes while optimizing MTX release and enhancing transdermal delivery. This hydrogel demonstrated superior immunomodulatory effects and reduced cytokine expression in a psoriasis mouse model.¹²⁴

Research on curcumin hydrogels is advancing across multiple teams. Fernández-Romero, A. et al created an Epichlorohydrin- β -Cyclodextrin/CRC Binary System embedded in a Pluronic[®]/Hyaluronate Hydrogel, which increased CRC solubility and permeation, showed anti-inflammatory solid effects in HaCaT cells, and notably decreased IL-6 expression.¹²⁸ Similarly, Filippone, A. et al engineered a choline-calix[4]arene-based nanohydrogel loaded with CRC that normalized the distribution of tight junction proteins ZO1 and occludin and effectively reduced TNF- α and inducible nitric oxide synthase levels.¹²⁹

Pérez-García L et al developed supramolecular hydrogels employing low-molecular-weight gelators to explore a range of psoriasis therapeutics, including gemcitabine hydrochloride, MTX sodium salt, TAC, betamethasone 17-valerate, and triamcinolone acetonide. These gelators, typically amphiphilic compounds, self-assemble via diverse supramolecular interactions such as electrostatic, hydrophobic, and π - π interactions. Supramolecular hydrogels combine the properties of traditional hydrogels with those of nanoparticulate systems containing amphiphiles, often incorporating

ethanol to enhance permeation. Consequently, these hydrogels can increase drug penetration and retention in the skin by up to 15 times compared to conventional formulations at equivalent drug concentrations.^{117,118}

Hybrid Nanoparticles

Lipid-polymer hybrid nanoparticles present clear advantages over lipid- or polymer-based systems, encompassing enhanced drug loading, exceptional colloidal stability, sustained release profiles, and heightened cellular uptake.^{190,191}

In a recent study, investigators crafted a self-assembled gallic acid-loaded lecithin-chitosan hybrid nanostructured gel for psoriasis treatment. This formulation exhibits superior drug release and deeper penetration levels compared to standard gel systems. Moreover, it mitigates irritation, reduces PASI scores, and addresses splenomegaly.¹³² Pukale, S.S., A. Mittal, and D. Chitkara formulated monolithic lipid-polymer hybrid nanoparticles (VD3/LPHNPs) loaded with vitamin D3 and developed them into a topical gel containing VD3/LPHNPs. This formulation exhibited marked improvement in histopathology and PASI scores in a psoriasis mouse model, surpassing the antipsoriasis activity of free VD3 gel.¹³³ Pukale, S.S. et al additionally formulated monolithic lipid-polymer hybrid nanoparticles loaded with clobetasol (CP/LPNs) and incorporated carbopol 974P to create hydrogels. This formulation exhibited sustained release and stability, with CP/LPNs demonstrating substantial growth inhibition of HaCaT cells. Compared to commercial creams, the CP/LPNs gel significantly improved PASI scores, reducing skin damage and hyperplasia in rat models of psoriasis.¹³⁴ Suzuki et al developed a siRNA delivery system utilizing hybrid polymer-lipid nanoparticles (PLNs). This system efficiently encapsulates TPPS2a and complexed siRNA to enhance the endosomal escape of TNF α siRNA into the cytoplasm. In murine models, the combination of PLN-TPPS2a and complexed siRNA demonstrated enhanced endosomal escape of TNF α siRNA into the cytoplasm.¹³⁵ Fereig, S.A. et al developed lecithin-chitosan hybrid NPs loaded with TAC. The study showed that particles containing Tween 80 released 79.98% of the drug within 48 hours, faster than those containing olive oil. These hybrid NPs significantly improved PASI scores and skin histopathology in mouse models. Moreover, the skin deposition of these NPs exceeded that of commercially available products.¹³⁶

Metallic Nanocarriers

Metallic nanocarriers, derived from elements like gold, silver, platinum, zirconium, copper, palladium, iron, selenium, and strontium, can assume various arrangements such as nanopores, nanotubes, nanorods, nanoclusters, and nanostars.¹⁹² Nanopores, synthesized through chemical or organic materials in a process known as green synthesis or biosynthesis, offer a cost-effective and environmentally safe approach.¹⁷⁹ These nanocarriers boast advantages such as small size, a relatively large surface area, facile modification of surface functional groups, and inherent anti-inflammatory effects.¹⁸⁵ Gold nanoparticles (AuNPs) within the 1–100 nm size range offer versatile advantages as drug carriers, presenting heightened stability, enhanced transmembrane permeability, and intracellular targeting.

Studies have revealed that localized application of AuNPs enables penetration through the SC and further into the epidermis and dermis, augmenting their efficacy in transdermal drug delivery.¹⁹³ Han et al innovatively designed NPs with a gold core and a 1000 Da polyethylene glycol shell, modified with octadecyl chains. These nanoparticles efficiently penetrated the stratum corneum and selectively targeted keratinocytes when applied to imiquimod-induced psoriasis in mice without an excipient. In a psoriasis mouse model, this formulation demonstrated antipsoriatic activity comparable to that of steroids and vitamin D analogs when used independently.¹⁹⁴ Nirmal GR et al developed a nanoformulation that induces hyperthermia-mediated apoptosis for treating psoriasis, activated by near-infrared (NIR) irradiation. This formulation incorporates gold nanorods (GNRs) and isatin—an anti-inflammatory agent—to enhance antipsoriatic efficacy within a poly(lactic-co-glycolic acid) (PLGA) matrix, creating effective nanocomplexes. Upon NIR exposure, these nanocomplexes penetrate the keratinocyte cytoplasm, reducing keratinocyte viability by approximately 60%, offering a novel therapeutic strategy against psoriasis.¹³⁷ Fratoddi et al synthesized AuNPs functionalized with 3-mercaptopropylsulfonate (AuNPs-3MPS) and loaded them with MTX. Topical application of AuNPs-3MPS@MTX in a mouse model of psoriasis led to reduced epidermal thickness, decreased PASI scores, and alterations in immunohistochemistry, specifically lower Ki67, K6, CD3, and CD8 staining.¹³⁸ HSP70, critical in maintaining homeostasis and exhibiting cytokine-like and immunomodulatory properties, is a vital target in psoriasis pathogenesis. Raghuwanshi et al developed AuNPs loaded with an ethanolic extract of *Woodfordia fruticosa* flowers, encapsulated in a Carbopol[®] 934 gel

to target HSP70-1. In a rat model of psoriasis, this formulation significantly reduced serum cytokine levels, attenuated epidermal thickness, keratotic dyskeratosis, and keratinocyte hyperproliferation.¹³⁹

Nanocrystals

NCs are submicron particles, ranging from 100 to 1000 nm, consisting of 100% drugs in a crystalline state, typically encased by a stabilizing layer.¹⁹⁵ Unlike conventional carriers, NCs lack additional materials, maximizing their drug loading capacity to 100%. Notably, they exhibit prolonged stability with neutral pH and can be produced through solvent-free and easily scalable techniques.¹⁹⁶ NCs significantly improve the concentration gradient between the formulation and the skin. This, in turn, leads to heightened drug skin penetration and increased bioavailability by enhancing poorly soluble drugs' dissolution rate and saturated solubility.¹⁹⁷

Recently, Shahine et al developed a diosmin-loaded NC gel, a formulation that enhances the drug's bioavailability. This gel was demonstrated to preserve the balance between T helper 17 and T regulatory cells. Furthermore, it modulates TLR7/8/NF- κ B, miRNA-31, AKT/mTOR/P70S6K, and upregulates TNFAIP3/A20 expression in psoriatic skin tissues, presenting a promising approach for psoriasis treatment.¹⁴⁰ The saturation solubility of NCs increased twofold compared to micronized apremilast. Skin penetration studies demonstrated superior penetration for nanoformulations compared to standard formulations. Consequently, apremilast NC-based formulations facilitate selective delivery into viable layers by overcoming the SC barrier.¹⁴¹ The researchers utilized NC and dissolving MN technologies to prepare MTX NC. This formulation enables sustained in vitro drug release for over 72 hours, reducing systemic drug exposure. The skin deposition is higher than oral administration, while blood concentration is only 40% of that observed with the oral route. This delivery approach proves effective as a topical method for treating psoriasis.¹⁴² Döge et al prepared NCs loaded with dexamethasone, facilitating rapid drug release and significantly accelerating its penetration. Dex became detectable in eluates after just 6 hours when NCs were applied to intact skin.¹⁹⁸

Limitations

In our bibliometric analysis, we primarily used the Web of Science database. This approach may have omitted some data, prompting manual searches for articles by critical authors to enrich our dataset. Future research will consider employing multiple databases for comparative analyses and engaging industry experts to enhance data accuracy and completeness. Although our annual publication and cumulative citation models appeared robust visually, the Durbin-Watson statistic indicated residual autocorrelation in annual citation frequency models, suggesting incomplete capture of data patterns. Future studies should consider more complex time series models or include additional explanatory variables such as research field activity, financial support, and team size. While the h-index is a prevalent metric for assessing academic impact, it may favor researchers with longer careers and more opportunities to accumulate citations. Moreover, it needs to reflect citation quality.¹⁹⁹ To address this, our paper pairs the h-index with total citation counts for a more comprehensive evaluation.

Conclusion

Currently, topical therapy is the first choice for treating and maintaining mild to moderate psoriasis, and we summarized the timeline of the development of topical therapy. However, problems such as skin permeability and drug targeting affect the therapeutic effect. Novel drug delivery systems were born for this purpose and became a hot research topic. We pioneered the use of bibliometrics to track the research hotspots in this field, and according to the frequency of keywords, solid lipid nanoparticles and nanostructured lipid carriers are the most intensively and extensively researched drug delivery modes in lipid-based carriers. The former has a small particle size and large surface area, and its solid lipid layer can enhance the stability of the loaded drug. At the same time, the nanoscale dimensions can help to change its biodistribution, which is conducive to carrying the drug through the skin barrier and realizing precise delivery.²⁰⁰ As the second generation of lipid nanocarriers to make up for the disadvantages of the former, such as easy aggregation and low loading of certain drugs, NLC has an irregular structure. Its biocompatibility can reduce its toxicity, and the property of no recrystallization after cooling can effectively prolong the drug's release time, thus increasing its efficacy.²⁰¹ The two drugs MTX and CsA are also hot research topics in various carriers. While both drugs are usually taken orally for systemic therapy, more and more scholars have turned their attention to the development of topical delivery of both

drugs, aiming to achieve therapeutic efficacy while reducing the toxic side effects of the drugs. The topical delivery of MTX needs to overcome the unique physicochemical properties, as well as hydrophilicity, which affects the residence time of the drug in the skin.¹⁴² In animal experiments, MTX in TFs, emulsion drug delivery systems, SLNs, NLCs, dendrimers, micelles, hydrogels, metallic nanocarriers, NCs, and other carriers assisted by localized drug delivery has been achieved with good results, among which hydrogels, is one of the more frequently used modalities for MTX. The high molecular weight and lipophilicity of CyA limit the application of topical drug delivery, so our development of its nanocarriers mainly focuses on these two points. SLNs for CyA can be used as the primary vehicle for local drug delivery, which can improve the drug's stability and reduce the drug's systemic absorption through the skin while increasing the dermal delivery of the drug.

In response to the discussion of the current research progress in this field, we can see that lipid-based nanodelivery systems have more substantial skin penetration and drug-carrying capacity, which can achieve targeted drug release and improve local drug action while reducing the side effects of drug therapy. However, lipid nanodelivery systems are less stable and water-soluble, limiting their application. Compared with lipid-based nanodelivery systems, polymer-based carriers, metallic nanocarriers, and nanocrystals have broader application prospects due to their controllable particle size, easy modification, and better drug loading ability. However, compared with the above nanodelivery systems, NCs, due to their strong stability and biocompatibility, can effectively change the permeability of the skin at the treatment site as well as the local drug accumulation capacity, thereby improving the local therapeutic effect of psoriasis.

In the future, for the development of new drug delivery systems in the field of psoriasis treatment, on the one hand, we can choose more suitable drug carriers for the physicochemical properties of commonly used topical therapeutic drugs. This includes using carriers to improve skin permeability, ensure continuous drug release in skin lesions, prolong drug retention time in the skin, protect the drug's structure within the carrier, stabilize the drug's nature, and achieve targeted transport of the drug for effective local treatment. The bioavailability of the drug is improved by using the carrier to realize the targeted transportation of the drug. On the other hand, the choice of new drugs, from the original oral to external application of the drug delivery method of innovation, as well as new ingredients or even new drugs and old drugs, co-carrying the innovation of the drug composition. All will help the development of localized psoriasis treatment, thus reducing the chance of psoriasis recurrence, reducing the adverse effects of treatment, and improving the quality of patients' prognosis and survival.

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Disclosure

The authors report no conflicts of interest in this work.

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