RESEARCH PAPER

Novel Baricitinib-Incorporated Nanoemulsion Gel: A Promising Topical Strategy For Enhanced Rheumatoid Arthritis Therapy

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Abstract

Due to rheumatoid arthritis' systemic inflammatory condition, ongoing pharmacologic treatment is necessary; however, traditional oral administration has potential for leading to undesired systemic side effects. Baricitinib is a very effective drug for the treatment of certain conditions because it selectively inhibits Janus kinase, but it can only be used for these conditions due to its metabolism by the liver and random distribution throughout the body. Engineering and establishing a topically applied nanoemulsion gel formulation consisting of Baricitinib were the focus of this research project as a method for treating specific areas. The nanoemulsion was prepared using a spontaneous emulsification technique with Transcutol® P as the oil phase and Tween 80–propylene glycol as the surfactant system.(1) All formulations were systematically optimized through the use of a ternary phase-mapping technique, and each formulation was then combined with a polymer matrix of Carbopol® 940. The optimized nanoemulgel exhibited nanoscale droplet size with narrow polydispersity, stable zeta potential, and skin-compatible pH. It also demonstrated pseudoplastic rheological behavior, uniform drug content, good spreadability, and sustained drug release for up to 12 hours following Korsmeyer–Peppas kinetics.(2) Studies of biological effectiveness using models of formaldehyde-induced arthritic challenges showed pronounced anti-edematous actions on a statistically comparable level as a policy comparison to benchmark-diclofenac formulations shown in previous research using formaldehyde challenged models. These findings suggest that the developed Baricitinib nanoemulsion gel is a promising topical delivery system for safer and effective management of rheumatoid arthritis.(3,4)

Keywords: Baricitinib; Nanoemulsion gel; Topical drug delivery; Rheumatoid arthritis management; JAK inhibition; Site-specific therapy; Controlled drug release; Inflammatory biomarkers

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1. Introduction

Rheumatoid arthritis (RA) is a type of autoimmune rheumatic disease that results in chronic inflammation of the synovial lining of joints, leading to destruction of both cartilage and bone in joints that are affected. The estimated prevalence of RA is between 0.5% and 1.0% depending on the population studied. The effects of RA extend beyond the joints and cause multisystem complications including cardiovascular disease, chronic fatigue syndrome, blood problems, and osteoporosis, all contributing to a diminished quality of life and functional ability.(5)

The pathophysiology is multifactorial and contains complex interactions between genetic susceptibility, environmental triggers such as cigarette smoke and infections, and abnormal immune responses. (6,7) Abnormalities in both innate and adaptive immunity result in the generation of autoantibodies and the continued stimulation of pro-inflammatory pathways throughout the synovial compartment of individuals with RA. Key pro-inflammatory cytokines, including TNF-a, IL-6 and IL-1b, contribute to the development of chronic inflammation, hyperplasia of synoviocytes, neoangiogenesis (new blood vessels) and bone resorption by osteoclasts.

Modern pharmacotherapy paradigms for rheumatoid arthritis include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid hormones and disease-modifying antirheumatic pharmaceuticals (DMARDs). NSAIDs and glucocorticoids improve symptoms, but do

not modify disease and have a high potential for chronic toxicity. The most common synthetic DMARDs are methotrexate and provide foundational therapy for RA patients.(8) However, many patients do not respond adequately to synthetic DMARD therapy or experience dose dependent side effects. Biologic DMARDs that target specific inflammatory mediators have revolutionized the treatment of RA, but they present challenges in terms of cost, requiring parenteral administration, immunogenicity, and increased susceptibility to infection. New Janus kinase (JAK) inhibitors represent a new class of drugs that interrupt intracellular signals following cytokine receptor stimulation and lead to broad immune modulatory effects via orally bioavailable small molecules. Baricitinib is a selective JAK1/JAK2 inhibitor with the ability to attenuate therelationship of JAK–STAT signalling pathways in order to regulate the inflammatory response to cytokines. As a result of these effects, clinical studies have demonstrated the effectiveness of baricitinib; however systemic administration of the medication is associated with several adverse effects such as increased risk for infections, liver toxicity, gastrointestinal (GI) symptoms and blood abnormalities.(9,10,11) These limitations underscore the need for alternative methods of drug administration that will achieve targeted therapeutic effects while reducing the potential for systemic distribution.

Topical drug delivery systems offer unique advantages by providing localized therapeutic action at the site of inflammation while minimizing systemic exposure. However, the skin's stratum corneum (or outer layer) serves as a substantial barrier to penetration of molecules. Nanoemulsions are emerging as viable drug carriers that can overcome these barriers due somewhat to the small diameter of the droplets (sub-micron), improved solubilisation of drugs, and easier permeation through the skin. By combining nanoemulsions with (and creating) gelling polymers, a nanoemulsion gel is formed that possesses the combined beneficial elements relating to increased drug penetration ability, desirable rheological properties, and prolonged retention of the drug on the skin resulting in a sustained release of the drug from the formulation and enhanced topical benefit.(12,13,) This study describes the systematic development, optimization, and physicochemical and biological evaluation of a Baricitinib-loaded nanoemulsion gel for topical management of rheumatoid arthritis.

2. Materials and Methods

2.1 Pharmaceutical Materials

MSN Laboratories Private Limited in Hyderabad, India, was the provider of the Baricitinib API. Gattefossé in France was the source of specialized lipophilic excipients Transcutol® P, Capryol® 90, and Labrafil® M 1944 CS. Components of isopropyl myristate, Tween 80 (polyoxyethylene sorbitan monooleate), and propylene glycol were obtained from Loba Chemie Private Limited in Mumbai, India. Carbopol® 940, a polyacrylic acid polymeric gelling agent, and triethanolamine were used to produce the gel matrix. All chemical reagents were of analytical grade.

2.2 Equilibrium Solubility Determination

To conduct saturation solubility profiling, excess amounts of baricitinib were placed into different oil phases inside hermetically-sealed containers. Each of these container mixtures was mechanically agitated continuously for a period of 72 hours while also maintaining a temperature of 25 degrees Celsius to reach chemical/thermodynamic equilibrium. In order to isolate each respective sample, after incubating for 72 hours, sample solutions were centrifuged at 5000 rpms for 15 minutes, and filtered through 0.45µm membrane filters. After being appropriately diluted based on the sample size, the concentration of dissolved drug in each sample was determined spectrophotometrically.(14)

2.3 Surfactant System Selection

Initial evaluations of surfactants were conducted in a systematic fashion to identify the optimum surfactant emulsifier(s) to create stable nanoemulsion structures. The initial evaluation of surfactants was conducted based on criteria such as the surfactants' ability to effectively emulsify the system, create optically clear and homogeneous systems, and be compatible with the selected oil components. Non-ionic surfactants were prioritized for formulation because they exhibited lower toxicological properties and improved dermal compatibility for topical applications. Tween 80 produced excellent emulsification and created clear and stable emulsions; therefore, this surfactant was considered the emulsifier of choice. In addition, propylene glycol was chosen as the co-surfactant due to its ability to reduce interfacial tension and enhance drug penetration into the skin (15).

2.4 Drug-Excipient Interaction Studies

The interactions and potential compatibility between the active pharmaceutical ingredient (Baricitinib) and excipients were evaluated using Fourier Transform Infrared spectroscopy (FTIR). Physical mixtures of Baricitinib and each excipient were prepared in equimolar concentrations. The FTIR spectra from the samples were obtained over a wavenumber range of 4000 cm-1 to 400 cm-1, and the spectra were analysed for chemical interactions or incompatibilities between Baricitinib and each excipient.

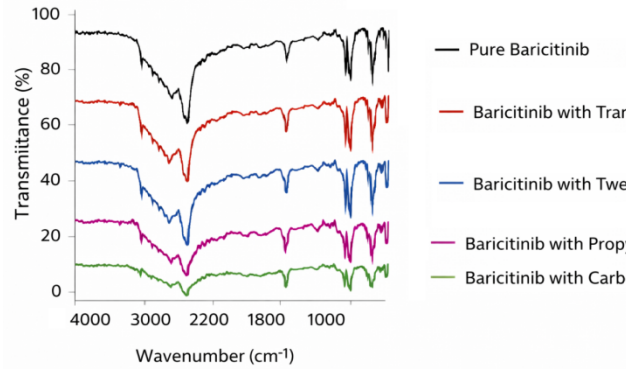


Figure 1: FTIR Spectra for Drug-Excipient Compatibility Studies

The FTIR spectroscopic analysis revealed no significant alterations in characteristic absorption bands, confirming absence of chemical interactions between Baricitinib and formulation excipients, thereby validating compatibility for pharmaceutical development.(16)

2.5 Analytical Method Development

Baricitinib can be quantitatively determined using UV spectrophotometric methodology. To create stock solutions, various amounts of the drug were weighed accurately then dissolved in methanol. This was followed by serial dilutions to create either the calibration standard solutions. The maximum wavelength on the spectra for sample absorbance was determined while linearity was established over a concentration range of 10 µg/mL - 60 µg/mL. Spectrophotometric analysis of the spectrums revealed that the maximum absorbance for Baricitinib was at a wavelength of 250 nm. The resulting calibration curve has excellent linearity with correlation of 0.9988 confirming that the analytical method is appropriate for accurate quantification during formulation development and testing for Baricitinib.(17,18)

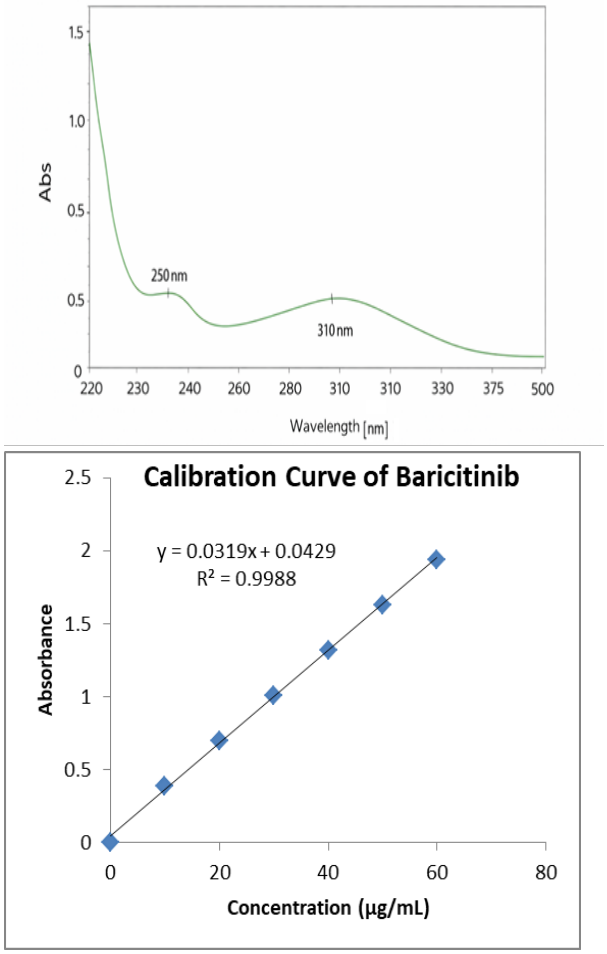


Figure 2: UV Spectrophotometric Analysis of Baricitinib

2.6 Ternary Phase Mapping

Aqueous titration was used to construct systematic pseudo-ternary phase diagrams. Surfactant and co-surfactant components were combined in several weight ratios - 1:1, 2:1, 3:1 and 1:2. For each composition of surfactant mixtures, oil phase and surfactant blend were mixed together in several concentrations in addition to varying methods of combining water with the previously mentioned mixtures methodically, under agitation at room temperature. The formulations that showed optical clarity and isotropic properties were identified as forming regions of nanoemulsions on a triangular coordinate system.(19-25)

2.7 Nanoemulsion Fabrication

The Baricitinib-loaded nanoemulsion was prepared using the spontaneous emulsification method. The baricitinib was measured accurately and completely dissolved in the

optimized oil phase including Transcutol® P. The baricitinib-in-oil mixture was then mixed with the optimized surfactant mixture at a 2:1 weight ratio while continuously agitated using a magnetic stirring device. (26) Distilled water was added slowly to the baricitinib/surfactant/Transcutol® P mixture until spontaneous formation of a nanoemulsion occurred. Final nanoemulsion formulation underwent five to ten minutes of probe ultrasonication to achieve optimal droplet size reduction and improve system homogeneity.(27)

2.8 Gel Matrix Integration

To achieve complete polymer chain expansion of Carbopol®940 polymeric powder in purified water, it was first hydrated overnight.(28) The hydrating dispersion's pH was then neutralized with triethanolamine (TEA) to create a clear gel base that had the desired viscosity. Next, the Baricitinib nanoemulsion was slowly mixed into the gel matrix by gentle mechanical means to form a homogenous nanoemulsion gel composite. The final formulation was equilibrated for 24 hours prior to final evaluation.(29)

2.9 Physicochemical Evaluation

Thermodynamic stability was evaluated using sequential stress-testing methods: temperature cycling (4° to 45° C), centrifugation (3500 r/min., 5 minutes) and freeze-thaw cycling (5 cycles). Through the dynamic light scattering measurements, the size and size distribution (polydispersity index) and surface charge (zeta potential) of the droplets were determined.(30,31) The pH of the solutions was measured using a calibrated digital pH meter. The rheological properties of the samples were determined by means of a rotational viscometer across a range of shear rates. The drug content of the formulations was determined by spectrophotometrically following the appropriate extraction protocols.

2.10 In Vitro Release Profiling

Drug release rate of all studies was measured with Franz-type diffusion cells with phosphate buffered saline at physiological pH 7.4 and 37 degrees Celsius as the receiving medium. Semi-permeable dialysis membrane barrier material was used to separate the donor and receiving compartments. The nanoemulsion gels were placed within the donor compartments and samples were periodically obtained from the receiving compartments at predetermined times out to 12 hours, with volume replacement performed to keep sink conditions. The samples were quantified spectrophotometrically and the cumulative percentage of drug released was calculated. The mathematical models utilized for evaluating release mechanisms were: zero-order, first-order, Higuchi, and Korsmeyer-Peppas.(32)

2.11 Biological Efficacy Assessment

The pharmacological activity of anti-inflammatory medicines was evaluated in the formaldehyde-induced arthritis model using the Sprague Dawley rodent and in accordance with institutional animal care and use committee guidelines (approval *1197/PO/Re/S/08/CCSEA*). Following the subcutaneous administration of 2% formaldehyde (0.1 ml volume) through injection into the subplantar area, experimental arthritis was induced in laboratory animals.(33,34) The participants in this experiment received topical formulations of the tested pharmaceutical agents for 21 consecutive days and each participant had their paw volume measured using precision plethysmography. Measurements of serum inflammatory mediators [C-reactive protein, TNF-alpha (tumour necrosis factor alpha) and IL-6/] were performed using an Enzyme Linked Immunosorbent Assay (ELISA). Lastly, scores for dermal irritation were established using standardized Draize tests on an irritation scale.(35)

3. Results and Discussion

3.1 Solubility Profiling and Component Selection

Table 1: Comparative Baricitinib Solubilization Across Oil Phases

Lipophilic Phase	Solubility (mg/mL)
Transcutol® P	18.1 ± 1.1
Capryol® 90	15.2 ± 0.8
Labrafil® M 1944 CS	12.5 ± 0.7
Isopropyl Myristate	5.9 ± 0.3

Transcutol® P has significantly better dissolving abilities among evaluated lipophilic vehicles, with solutions able to dissolve up to 18.1 mg of drug per milliliter of solution. Due to its very strong solubility characteristics as well as its enhanced ability to penetrate through the skin, Transcutol will be identified as the best lipophilic vehicle for making an emulsion using a moderate lipophylic pharmacologically active substance.(36,37) The ability of the drug to have a high degree of solubility in the oil part of the emulsion is important, as it will help to provide higher drug loading capabilities and reduce the risk of the drug settling out of the solution over long storage periods.

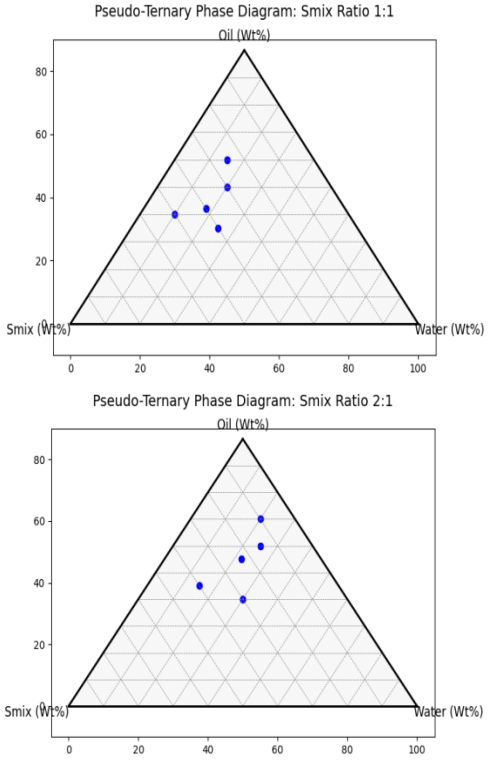
Therefore, Transcutol® P will be selected as the best lipophilic phase for future development of formulations.

3.2 Phase Behavior Characterization

Table 2: Surfactant Mixture Ratio Influence on Nanoemulsion Formation

Smix Ratio (Tween 80:PG)	Nanoemulsion Zone
1:1	Moderate
2:1	Extensive
3:1	Limited
1:2	Highly Restricted

The largest area of nanoemulsions occurred using the 2:1 surfactant–co-surfactant system, which represented the optimal balance between the flexibility of the interfacial film and how well they worked together to create an emulsion. The 2:1 system also supported high concentrations of oil in the emulsion without requiring excessive addition of water to reach a clear emulsion, which means that there is an opportunity for greater amounts of drug in a preparation with the 2:1 system.(38)



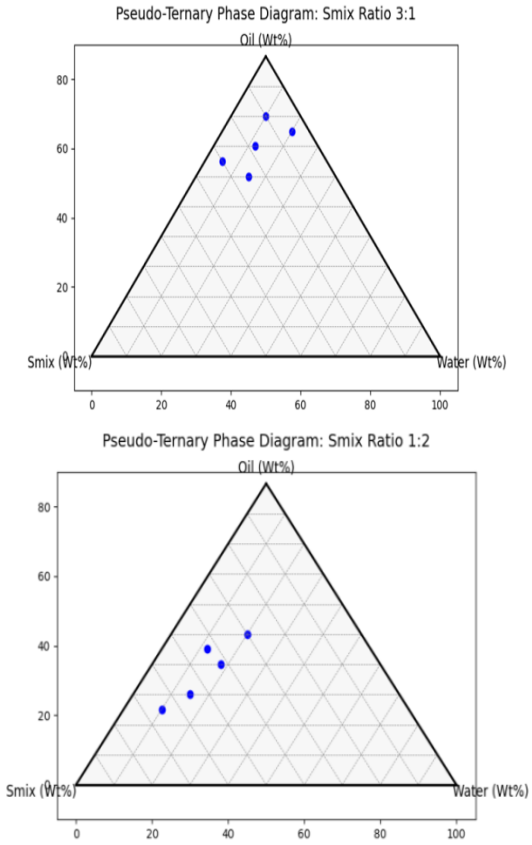


Figure 3: Pseudo-Ternary Phase Diagrams at Different Smix Ratios

Distinct regions of nanoemulsification exist across surfactant/co-surfactant ratios using pseudo-ternary phase diagrams, as evidenced by the widened blue points for nanoemulsion regions in the 2:1 surfactant/co-surfactant ratio, thereby supporting its selection as the most appropriate ratio for formulation design, due to the highest level of oil incorporation with least amount of water needed to produce a concurrent composition.(39)

3.3 Formulation Refinement

Table 3: Physicochemical Attributes of Nanoemulsion Formulations

Batch	Oil (%)	Smix (%)	Diameter (nm)	PDI	ζ-potential (mV)
F1	15	40	>250	>0.35	−18.6
F4	30	55	186.4 ± 4.2	0.241	−31.4

Formulation F4 exhibited a small droplet size, low polydispersity index, and high negative zeta potential,

indicating good homogeneity and physical stability. (40-45)

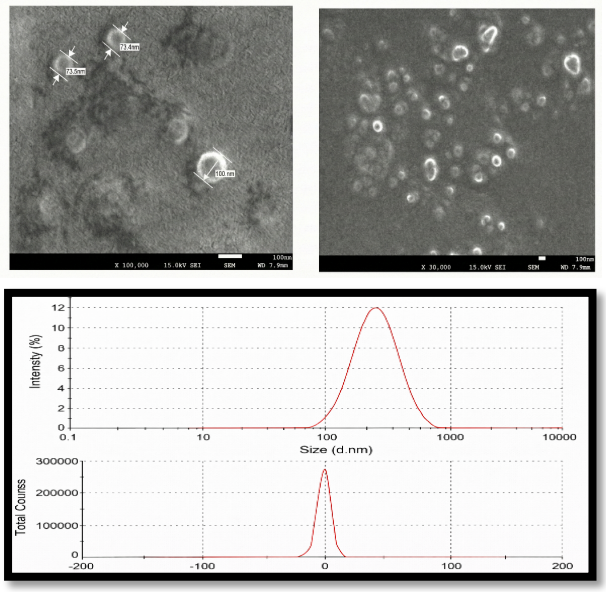


Figure 4: Nanoemulsion Characterization

Dynamic light scattering results demonstrated that formulation F4 had a consistent particle size with a mean size of 186.4 nm and a zeta potential of −31.4 mV which indicates adequate colloidal stability.. Scanning electron micrographs showed that the nanoemulsion droplets were spherical in shape and had a uniform size distribution providing further evidence of a successful formulation. (47)

3.4 Nanoemulsion Gel Characterization

Table 4: Critical Quality Attributes of Optimized Nanoemulsion Gel

Parameter	Observed Value
Hydrogen Ion Concentration (pH)	6.18 ± 0.04
Apparent Viscosity at 5 rpm (cP)	21,860
Spreadability Coefficient (g·cm/sec)	19.6 ± 0.8
Drug Content Uniformity (%)	98.2 ± 1.4

The nanoemulsion gel that we produced appeared to have physiologically compatible pH values close to neutrality, as well as pseudoplastic flow characteristics that resulted in a decrease in viscosity with increasing shearing forces (i.e., shear thinning).(48,49) In addition to these properties, the gel also demonstrated positive spreadability and uniform distribution of drugs throughout the matrix. Together, these characteristics support the use of the gel for dermally compatible, easy-to-apply, stable (e.g., on the shelf) products with predictable therapeutic effects.

3.5 Drug Liberation Kinetics

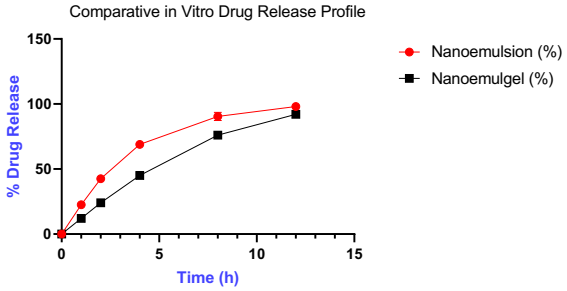


Figure 5: Comparative in Vitro Drug Release Profile

Table 5: Mathematical Release Modeling Analysis

Mathematical Model	Correlation Coefficient (R^2)
Zero-Order Kinetics	0.921
First-Order Kinetics	0.904
Higuchi Square Root Model	0.963
Korsmeyer–Peppas Power Law	0.991 (n = 0.62)

The comparative release profiles presented here show that the nanoemulgel has sustained drug release rates while the nanoemulsion provides more rapid drug release; this occurs because the gel matrix acts as a diffusion barrier.(50) The release was best described by the Korsmeyer-Peppas model, yielding a high correlation coefficient (R^2=0.991) with the release exponent (n) of 0.62 which suggests that the release occurred through a process involving both coupled diffusive transport and polymeric chain relaxation, regardless of whether Fickian or non-Fickian in nature.(51,52)

4. Conclusion

The comprehensive research resulted in the successful engineering/validation of a new formulation of a nanoemulsion gel system using Baricitinib for percutaneous administration to treat RA. This formulation was optimized for architecture (<1 micron), physicochemical properties, sustained release of the drug, Therefore, this nanoemulsion gel system developed is an exciting alternative to delivering Baricitinib orally that may improve RA treatment outcome with reduced systemic adverse events and improved patient compliance with therapy.

References

1. Roya Mohammadi-Meyabadi Negar Beirampour Núria Garrós Helen Lissette Alvarado. Assessing the Solubility of Baricitinib and DrugUptake in Different Tissues Using Absorption andFluorescence Spectroscopies. Pharmaceutics2022 Dec 4;14(12):2714.doi: 10.3390/pharmaceutics14122714.
2. Jacob, S.; Nair, A.B. Nanoemulgels as Advanced Topical Drug Delivery Systems: Mechanistic Insights and Therapeutic Applications in Skin Disorders, Infections, Wound Healing, and Cancer. *Pharmaceuticals* **2026**, *19*, 247. https://doi.org/10.3390/ph19020247
3. Gupta, N., Konda, S. R., Srija, K., & Reddy, G. P. (2024). The mechanism and efficacy of baricitinib as a novel therapeutic option for rheumatoid arthritis: a review. *Asian Journal of Immunology*, *7*(1), 123–130. https://doi.org/10.9734/aji/2024/v7i1137
4. Rani, R., Raina, N., Sharma, A. *et al.* Advancement in nanotechnology for treatment of rheumatoid arthritis: scope and potential applications. *Naunyn-Schmiedeberg's Arch Pharmacol* **396**, 2287–2310 (2023). https://doi.org/10.1007/s00210-023-02514-5
5. Urits I, Israel J, Hakobyan H, Yusin G, Lassiter G, Fackler N, Berger AA, Kassem H, Kaye A, Viswanath O. Baricitinib for the treatment of rheumatoid arthritis. Reumatologia. 2020;58(6):407-415. doi: 10.5114/reum.2020.102006. Epub 2020 Dec 23. PMID: 33456084; PMCID: PMC7792534.
6. Karmarkar, Shriya, et al. "Navigating Rheumatoid Arthritis: Insights into Ligand-Anchored Nanoparticle Strategies for Anti-Inflammatory Therapy and Relief." *RSC Pharmaceutics*, vol. 2, no. 1, 2025, pp. 19–43. *DOI.org (Crossref)*, https://doi.org/10.1039/D4PM00133H.
7. Pareek, Ashutosh, et al. "Melittin as a Therapeutic Agent for Rheumatoid Arthritis: Mechanistic Insights, Advanced Delivery Systems, and Future Perspectives." *Frontiers in Immunology*, vol. 15, Dec. 2024. *Frontiers*, https://doi.org/10.3389/fimmu.2024.1510693.
8. Chaudhary, Sushma, et al. "A Novel Natural Polymers Based Nanoparticles Gel Formulation for the Treatment of Rheumatoid Arthritis: Optimization and In-Vivo Evaluation." *Drug Delivery Letters*, vol. 11, no. 2, June 2021, pp. 164–78. *DOI.org (Crossref)*, https://doi.org/10.2174/2210303111666210219152401.
9. Donthi, M. R., Saha, R. N., Singhvi, G., & Dubey, S. K. (2023). Dasatinib-Loaded Topical Nano-Emulgel for Rheumatoid Arthritis: Formulation Design and Optimization by QbD, In Vitro, Ex Vivo, and In Vivo Evaluation. *Pharmaceutics*, *15*(3), 736. https://doi.org/10.3390/pharmaceutics15030736
10. Kesharwani D, Paliwal R, Satapathy T, Das Paul S. Rheumatiod Arthritis: An Updated Overview of Latest Therapy and Drug Delivery. Journal of Pharmacopuncture. 2019 Dec;22(4):210-224. DOI: 10.3831/kpi.2019.22.029. PMID: 31970018; PMCID: PMC6970574.
11. Gupta, Nikita, Sai Rama Konda, K. Srija, and G. Pooja Reddy. 2024. "The Mechanism and Efficacy of Baricitinib As a Novel Therapeutic Option for Rheumatoid Arthritis: A Review". *Asian Journal of Immunology* 7 (1):123-30. https://doi.org/10.9734/aji/2024/v7i1137.
12. Beirampour N, Bustos-Salgado P, Garrós N, Mohammadi-Meyabadi R, Domènech Ò, Suñer-Carbó J, Rodríguez-Lagunas MJ, Kapravelou G, Montes MJ, Calpena A, Mallandrich M. Formulation of Polymeric Nanoparticles Loading Baricitinib as a Topical Approach in Ocular Application. Pharmaceutics. 2024 Aug 20;16(8):1092. doi: 10.3390/pharmaceutics16081092. PMID: 39204436; PMCID: PMC11360485.
13. Brito, S.; Baek, M.; Bin, B.-H. Skin Structure, Physiology, and Pathology in Topical and Transdermal Drug Delivery. Pharmaceutics 2024, 16, 1403.
14. Baker, P.; Huang, C.; Radi, R.; Moll, S.B.; Jules, E.; Arbiser, J.L. Skin Barrier Function: The Interplay of Physical, Chemical,

andImmunologic Properties. Cells 2023, 12, 2745.
15. Lu, B.; Liu, T.; Wang, H.; Wu, C.; Chen, H.; Liu, Z.; Zhang, J. Ionic liquid transdermal delivery system: Progress, prospects, and challenges. J. Mol. Liq. 2022, 351, 118643.
16. Ramadon, D.; McCrudden, M.T.C.; Courtenay, A.J.; Donnelly, R.F. Enhancement strategies for transdermal drug delivery systems: Current trends and applications. Drug Deliv. Transl. Res. 2022, 12, 758–791.
17. de Mello, T.; Argenta, D.F.; Caon, T. Revisiting the Effect of Aging on the Transport of Molecules through the Skin. Pharm. Res. 2024, 41, 1031–1044
18. Abdo, J.M.; Sopko, N.A.; Milner, S.M. The applied anatomy of human skin: A model for regeneration. Wound Med. 2020,28, 100179.
19. Ren, Y.-H.; Song, F.-Y.; Zhao, J.-Y.; Liang, B.-W.; Peng, L.-H. Unlocking the Stratum Corneum Barrier to Skin Penetration for the
20. Transdermal Delivery of Cyclovirobuxine D. Pharmaceutics 2024, 16, 1600. [CrossRef]
21. Jiao, Q.; Zhi, L.; You, B.; Wang, G.; Wu, N.; Jia, Y. Skin homeostasis: Mechanism and influencing factors. J. Cosmet. Dermatol. 2024, 23, 1518–1526.
22. Rippa, A.L.; Kalabusheva, E.P.; Vorotelyak, E.A. Regeneration of Dermis: Scarring and Cells Involved. Cells 2019, 8, 607.
23. Lupu, M.; Caruntu, C.; Popa, M.I.; Voiculescu, V.M.; Zurac, S.; Boda, D. Vascular patterns in basal cell carcinoma: Dermoscopic,
24. confocal and histopathological perspectives. Oncol. Lett. 2019, 17, 4112–4125.
25. Ahmed, I.A.; Mikail, M.A. Diet and skin health: The good and the bad. Nutrition 2024, 119, 112350.
26. Zhang, H.; Wang, M.; Zhao, X.; Wang, Y.; Chen, X.; Su, J. Role of stress in skin diseases: A neuroendocrine-immune interaction view. Brain Behav. Immun. 2024, 116, 286–302.
27. Nair, A.; Jacob, S.; Al-Dhubiab, B.; Attimarad, M.; Harsha, S. Basic considerations in the dermatokinetics of topical formulations. Braz. J. Pharm. Sci. 2013, 49, 423–434.
28. Schafer, N.; Balwierz, R.; Biernat, P.; Och˛edzan-Siodłak, W.; Lipok, J. Natural Ingredients of Transdermal Drug Delivery Systems as Permeation Enhancers of Active Substances through the Stratum Corneum. Mol. Pharm. 2023, 20, 3278–3297. [CrossRef]
29. Zhang, Q.; Alinaghi, A.; Williams, D.B.; Roberts, M.S. A thermodynamic and kinetic analysis of human epidermal penetration of phenolic compounds: II. Maximum flux and solute diffusion through stratum corneum lipids. Int. J. Pharm. 2023, 631, 122522. https://doi.org/10.3390/ph19020247
Pharmaceuticals 2026, 19, 247 49 of 61
30. Shaker, D.S.; Ishak, R.A.H.; Ghoneim, A.; Elhuoni, M.A. Nanoemulsion: A Review on Mechanisms for the Transdermal Delivery of Hydrophobic and Hydrophilic Drugs. Sci. Pharm. 2019, 87, 17.
31. Nitsche, L.C.; Kasting, G.B.; Nitsche, J.M. Microscopic Models of Drug/Chemical Diffusion Through the Skin Barrier: Effects of Diffusional Anisotropy of the Intercellular Lipid. J. Pharm. Sci. 2019, 108, 1692–1712.
32. Santos, L.L.; Wu, E.L.; Grinias, K.M.; Koetting, M.C.; Jain, P. Developability profile framework for lead candidate selection in topical dermatology. Int. J. Pharm. 2021, 604, 120750.
33. Potts, R.O. Richard H. Guy—He has skin in the game. J. Pharm. Sci. 2025, 104130.
34. Souto, E.B.; Fangueiro, J.F.; Fernandes, A.R.; Cano, A.; Sanchez-Lopez, E.; Garcia, M.L.; Severino, P.; Paganelli, M.O.; Chaud, M.V.; Silva, A.M. Physicochemical and biopharmaceutical aspects influencing skin permeation and role of SLN and NLC for skin drug delivery. Heliyon 2022, 8, e08938. [CrossRef]
35. Lee, Y. Topical nanomedicines using lipids, carbohydrates, proteins, and synthetic polymers for enhanced management of skin disorders. J. Pharm. Investig. 2025, 55, 787–808.
36. Matharoo, N.; Mohd, H.; Michniak-Kohn, B. Transferosomes as a transdermal drug delivery system: Dermal kinetics and recent developments. Wiley Interdiscip. Rev. Nanomed. Nanobiotechnology 2024, 16, e1918.
37. Yu, Z.; Meng, X.; Zhang, S.; Chen, Y.; Zhang, Z.; Zhang, Y. Recent Progress in Transdermal

Nanocarriers and Their Surface Modifications. Molecules 2021, 26, 3093.
38. Cheng, T.; Tai, Z.; Shen, M.; Li, Y.; Yu, J.; Wang, J.; Zhu, Q.; Chen, Z. Advance and Challenges in the Treatment of Skin Diseases with the Transdermal Drug Delivery System. Pharmaceutics 2023, 15, 2165.
39. Elmowafy, M. Skin penetration/permeation success determinants of nanocarriers: Pursuit of a perfect formulation. Colloids Surf. B Biointerfaces 2021, 203, 111748
40. Awad, C.; Abdi, P.; Law, R.M.; Lacaprucia, T.; Maibach, H.I. Sebaceous gland role in percutaneous absorption: Human and animal. Arch. Dermatol. Res. 2025, 317, 927.
41. Neubert, R.H. Mechanisms of penetration and diffusion of drugs and cosmetic actives across the human Stratum corneum. Eur. J. Pharm. Biopharm. 2024, 202, 114394.
42. Nair, A.; Reddy, C.; Jacob, S. Delivery of a classical antihypertensive agent through the skin by chemical enhancers and iontophoresis. Ski. Res. Technol. 2009, 15, 187–194.
43. Phatale, V.; Vaiphei, K.K.; Jha, S.; Patil, D.; Agrawal, M.; Alexander, A. Overcoming skin barriers through advanced transdermal drug delivery approaches. J. Control. Release 2022, 351, 361–380.
44. 30. Wiedersberg, S.; Guy, R.H. Transdermal drug delivery: 30 + years of war and still fighting! J. Control Release 2014, 190, 150–156.
45. 31. Chen, Y.; Feng, X.; Meng, S. Site-specific drug delivery in the skin for the localized treatment of skin diseases. Expert Opin. Drug Deliv. 2019, 16, 847–867.
46. 32. Herbig, M.E.; Evers, D.-H.; Gorissen, S.; Köllmer, M. Rational Design of Topical Semi-Solid Dosage Forms-How Far Are We? Pharmaceutics 2023, 15, 1822.
47. 33. Mitra, R.; Sharma, D.K.; Ghosh, A.; Senapati, S. Recent advancements in nanoparticle-based topical drug delivery systems for psoriasis treatment. J. Drug Target. 2025, 34, 151–168.
48. Shehata, T.M.; Nair, A.B.; Al-Dhubiab, B.E.; Shah, J.; Jacob, S.; Alhaider, I.A.; Attimarad, M.; Elsewedy, H.S.; Ibrahim, M.M. Vesicular emulgel based system for transdermal delivery of insulin: Factorial design and in vivo evaluation. Appl. Sci. 2020,
49. 10, 5341.
50. Jacob, S.; Kather, F.S.; Boddu, S.H.S.; Attimarad, M.; Nair, A.B. Nanosuspension Innovations: Expanding Horizons in Drug Delivery Techniques. Pharmaceutics 2025, 17, 136.
51. Norlén, L.; Forslind, B.; Nicander, I.; Rozell, B.L.; Ollmar, S. Inter- and intra-individual differences in human stratum corneum lipid content related to physical parameters of skin barrier function in vivo. J. Investig. Dermatol. 1999, 112, 72–77.
52. Bormann, J.L.; Maibach, H.I. Effects of anatomical location on in vivo percutaneous penetration in man. Cutan. Ocul. Toxicol. 2020, 39, 213–222.