INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Paper

Revolutionizing Rheumatoid Arthritis Therapy:The Potential of Lipid Nanocarriers for Topical Drug Delivery Systems a Comprehensive Review

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ARTICLE INFO

Published: 28 June 2026
Keywords:
Rheumatoid arthritis; nanostructured lipid carriers; topical drug delivery; transdermal delivery; lipid nanoparticles; targeted therapy; anti-inflammatory agents; nanotechnology.
DOI:
10.5281/zenodo.20990895

ABSTRACT

Rheumatoid arthritis (RA) represents a chronic inflammatory autoimmune condition impacting roughly 1% of the global population, marked by progressive joint tissue injury, persistent discomfort, and structural deformities.1Existing therapeutic options—comprising nonsteroidal anti-inflammatory agents, corticosteroid preparations, and disease-altering antirheumatic medications—demonstrate constraints regarding drug bioavailability, widespread systemic reactions, and suboptimal accumulation in damaged joint regions.2,3Lipid-based nanoscale carriers, particularly nanostructured lipid carriers (NLCs), have surfaced as revolutionary delivery mechanisms for topical RA management.5 This examination surveys how NLCs and associated lipid nanoparticles can modify RA treatment by enabling deeper skin permeation, prolonged and controlled medication discharge, elevated drug effectiveness, and site-specific targeting of injured joints. The investigation addresses RA underlying mechanisms, conventional therapy constraints, compositional and functional merits of NLCs, manufacturing protocols, delivery mechanisms, animal and laboratory studies, harmful substance concerns, and prospective directions. Contemporary investigations confirm that NLC-formulated topical remedies achieve substantial clinical outcomes with restricted whole-body medication exposure, representing a fundamental shift in RA management toward patient-convenient, region-specific healing methods.

INTRODUCTION

RA constitutes among the most serious persistent inflammatory illnesses globally, producing considerable impacts on patient standard of living and resource demands within medical systems. Affecting roughly half to one percent of the adult demographic internationally, with elevated percentages in wealthier countries, the illness correlates with heightened dangers of heart-related

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

mortality, bodily impairment, and untimely passing.[1,3,7]

The origin of RA entails complicated cooperative interactions among genetic inclination, external influences, and unbalanced immune processes, producing synovial membrane enlargement, destructive tissue formation, and irreversible skeletal deterioration.[7]

Customary RA interventions depend substantially on full-body drug administration by mouth or injection. This strategy, however, experiences multiple significant obstacles: digestive metabolism diminishing therapeutic concentration, universal organ exposure producing undesired consequences, dose-related harmful reactions impacting intestinal, hepatic, cardiovascular, and kidney functions, and diminished medication adherence from demanding application schedules and unfavorable reactions.[2,15,16] This situation has driven urgent scientific exploration toward supplementary administration methods achieving greatest regional effectiveness while limiting whole-organism toxins.

Topical medication application for RA presents an encouraging option, guaranteeing targeted therapy directly at the inflammation region, evading metabolic transformation in the gut, diminishing body-wide negative responses, and enhancing medication convenience.[5,6] Nevertheless, integumentary tissue's powerful protective mechanism—principally the dead skin stratum—presents substantial hurdles for medication passage into deeper tissues. Customary skin therapies including emulsified preparations, fatty preparations, and hydrogel remedies show insufficient medication movement toward underlying joint tissues.

Advancement in minute-sized drug delivery has reformed pharmaceutical administration through creation of transporters overcoming physiologic hindrances, governing medication liberation timing, and localizing action at particular sites.[9,10] Within varied microscopic transporter categories, lipid-based microscopic fragments receive heightened recognition due to their tissue-friendly qualities, biodegradable nature, capacity to encapsulate both water-repelling and water-loving compounds, and capability for strengthened skin entry.[10,11] NLCs, representing evolved lipid nanoparticles, demonstrate significant superiority relative to initial generation compact lipid microscopic spheres via incorporation of flowing lipids into the compact lipid structure, generating imperfect crystal framework allowing greater medication holding and improved sustained effectiveness.

This investigation furnishes exhaustive investigation of lipid-based microscopic carriers, emphasizing NLCs, in addressing RA via topical treatment. We examine supporting rationale for regional treatment in RA, compositional and operational characteristics of NLCs, synthesis and quality assessment methodologies, preclinical information substantiating their usefulness, and forthcoming development options for transition into patient management.

2. Rheumatoid Arthritis: Pathophysiology and Current Therapeutic Landscape

2.1 Etiology and Pathogenesis

RA represents an enduring, body-wide immunological ailment principally impacting articulated joints.[3,7] The pathogenic cascade includes intricate immune activities preceding clinical presentation by prolonged intervals, typically commencing at epithelial barriers including respiratory passages, mouth surfaces, and digestive regions.

Genetic Factors

The strongest hereditary linkage with RA manifests within HLA class II loci, most notably HLA-DRB1 genotypes expressing the "distributed

protein" (SE) arrangement.[13] This arrangement raises RA vulnerability through exhibiting inflammatory-causing protein fragments to T-cells, stimulating resistant reactions. Supplementary hereditary variables comprise PTPN22, STAT4, TRAF1-C5, and CTLA4, found through comprehensive hereditary investigations. Altogether, heritable components constitute roughly sixty percent of illness family inheritance.

Environmental Triggers

Smoking stands as the most recognized extraneous danger element for antibody-positive RA.[4,13] Supplementary prospective environmental factors encompass mouth infection involving Porphyromonas gingivalis, digestive tract microbial imbalance, silica mineral contact, and reproductive hormone impacts. Environmental circumstances could stimulate protein modification (post-translational citrullination), a chemical procedure catalyzed by PAD compounds, resulting in creation of self-attacking molecular targets acknowledged by anti-citrullinated protein immune factors.

Immunological Mechanisms

Significant immune messengers propelling RA evolution comprise cancer necrosis substance-alpha (TNF-α), interleukin-first (IL-1), interleukin-sixth (IL-6), and interleukin-seventeenth (IL-17).[7,14] Such compounds activate inflammatory responses, bone-destroying cell generation, protein deterioration, and protective cell gathering. Persistent irritation gets perpetuated via constant engagement of numerous message transmission routes, comprising atomic transcription regulator-κB (NF-κB), kinase cascade components (MAPKs), and cellular signal integration/transcription activators (JAK/STAT) machinery.

2.2 Current Therapeutic Approaches

RA treatment has significantly transformed, progressing from singular medication use toward prompt, strong, and precisely targeted intervention methods. Contemporaneous guidance from the US Arthritis Association and European Rheumatism Organization emphasize target-directed treatment philosophy, pursuing disease elimination or minimum inflammatory response.[15,16]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory agents supply symptom reduction via inhibiting COX catalyst activity and suppressing prostaglandin compound generation.[8] Though efficient for distress and inflammation decrease, they do not change sickness development and demonstrate substantial stomach, heart, and renal dangers with extended application.

Conventional Synthetic DMARDs (csDMARDs)

Methotrexate (MTX) continues functioning as the foundation drug in RA management.[17] Further csDMARDs comprise leflunomide, sulfasalazine, and hydroxychloroquine. Though advantageous, such compounds necessitate continuous surveillance for liver harm, marrow problems, plus supplementary unfavorable reactions.

Biologic DMARDs (bDMARDs)

TNF-α antagonists, IL-6 channel antagonists, T-lymphocyte assistance suppressors, plus anti-CD20 compounds revolutionized RA management.[2,3] Regardless of remarkable advantage, biotherapies demonstrate substantial expense, mandate injection application, plus involve infection danger.

Targeted Synthetic DMARDs (tsDMARDs)

JAK antagonists present mouth consumption and fast activity advantage yet include dangers regarding cardiac incidents, malignant conditions, plus vein clotting.

2.3 Limitations of Systemic Therapy

Regardless of medical innovations, meaningful restrictions endure. Mediocre mouth bioavailability impacts numerous RA compounds resulting from weak dissolvability, stomach break-down, or substantial digestive metabolism; methotrexate bioavailability, for instance, depends upon quantity and demonstrates considerable variation (thirty to seventy percent).[18] Organism-wide distribution affects all structures with restorative compounds, generating well-recognized dangerous consequences encompassing stomach-related NSAID harm, methotrexate liver damage, biological medicine contamination danger, and heart dangers. Minimal quantities of supplied compounds reach inflammatory joints, demanding increased whole-body dosage worsening poisoning. Long-lasting medication requiring repeated application, needle injection, plus clinical monitoring contributes to suboptimal patient dedication, undermining extended success.

3. Rationale for Topical Drug Delivery in Rheumatoid Arthritis

3.1 Advantages of Topical Administration

Integumentary medication application toward damaged joints provides numerous theoretical merits: concentrated medication delivery at main sickness location; prevention of digestive compound transformation; decreased organ-particular poisoning; raised consumer ease and adherence; plus sustained regional medication concentrations via regulated-release preparations.[5,6]

3.2 Skin Barrier Challenges

The stratum corneum (SC), a five to twenty micrometer superficial skin component comprising ten to twenty-five strata of deceased skin cellular elements within a fatty multi-layered substrate, establishes the primary rate-governing obstacle for medicinal movement.[6,10] This "brick construction" design consists primarily of fat-similar substances (forty to fifty percent), steroid-alcohol molecules (twenty-five percent), plus unmodified lipid substances (ten to fifteen percent), offering remarkable barrier capabilities.

Compounds can penetrate the SC through three pathways: (one) straight-line passage via dead cells and lipid zones; (two) peripheral passage via constant lipid films separating dead cells, representing the predominant mechanism for lipid-scaled carriers; (three) follicle passageway via oil glands plus hair roots, comprising merely roughly zero-point-one percent of epidermis yet constituting essential substance repositories.

3.3 Enhancing Topical Delivery with Nanocarriers

Microscale transporters provide numerous cooperative procedures overcoming SC resistance, encompassing elevated chemical tendency promoting compound partitioning, water-sealing improving SC moisture, fatty substance modification via inserted lipids into SC lipid frameworks, plus follicle targeting delivering durational liberation repositories.[10,11,12]

4. Nanostructured Lipid Carriers: Structure, Composition, and Properties

4.1 Evolution from Solid Lipid Nanoparticles to NLCs

Compact lipid microscopic capsules emerged as alternatives to polyester nanoparticles, liquid emulsions, plus membranous sacs, merging physiologic tolerance, medication discharge regulation, plus mechanical endurance.[9,10] However, compact lipid microscopic capsules present restricted medication holding capability owing to medication displacement throughout fat reorganization, medication liberation danger throughout conservation, plus solidification inclination.

NLCs appeared as evolved lipid microscopic capsules tackling these constraints. Merging flowing fats (oils) inside compact fat frameworks, NLCs manufacture less-arranged fat frameworks with voids lodging greater medication quantities plus preventing medication loss throughout conservation.[11,12]

4.2 Structural Architecture of NLCs

Multiple NLC configurations have been categorized according to lipid arrangement:

• Imperfect Type: Flowing fat interrupts the highly-arranged compact fat structures, generating gaps for medicine lodging. This stands as the prevalent variety utilized in pharmaceutical application.

• Amorphous Type: Non-crystalline compact fats hinder crystallization plus medicine ejection, accomplished via merging particular lipids with flowing oils.

• Multiple Type (Oil-in-Solid-in-Water): Oil portions distributed inside compact lipid substrate, notably appropriate for highly lard-soluble compounds requiring substantial loading.

4.3 Advantages of NLCs for Topical RA Therapy

NLCs give multiple notable merits relative to customary medicines and introductory generation compact lipid microscopic capsules for integumentary RA treatments.[5,10,11]

Parameter	Conventional	SLNs	NLCs
Drug load	Low	Moderate	High
Stability	Variable	Limited	Excellent
Controlled release	Poor	Moderate	Excellent
Skin entry	Low	Moderate	High

5. Formulation Strategies and Characterisation

5.1 Preparation Methods for NLCs

Strong-pressure distribution represents the most widespread approach for experimental plus market-scale NLC generation, delivering scalable manufacturing plus steady outcome.[10] Heated strong-pressure distribution requires melting fats, merging therapeutic substance, dispersing in heated water-based surfactant option, plus homogenizing at raised heats preceding cooling. Refrigerated strong-pressure distribution matches heat-sensitive compounds.

Substitute approaches encompass emulsion-microemulsion methods (yielding lesser fragments though necessitating great surfactant volumes), solvent breaking-dissolution, solvent movement, plus intense vibration. Selection relates to compound chemical attributes, measure specifications, plus sought particles.

5.2 Quality by Design and Optimisation

Quality engineering approaches leveraging trial organizing methods grow commonly implemented toward NLC progress.[9,11] Graphing strategies—encompassing field testing designs, midpoint composition designs, plus element designs—facilitate organized evaluation of mixture characteristics plus their interactions.

5.3 Characterisation Parameters

Thorough assessment verifies NLC excellence, capability, plus endurance.[9,12] Fragment scale plus distribution breadth get evaluated via dynamic dispersion distinction; adequate integumentary consumption needs fragments below 300 nanometers plus distribution breadth below zero-point-three. Exterior electrical charge exceeding plus/negative thirty thousandths generally suggests excellent mechanical endurance via electric deflection. Great medication addition (over ninety percent) demonstrates powerful medication incorporation.

5.4 Gel Formulation for Topical Application

Useful usage demands combining NLC suspensions into viscous bases delivering suitable features for integumentary contact. Standard gelling compounds encompass carbomers, cellulose substances, plant-based polymers, plus polyethers.[5,12] Component attributes encompass pH, stiffness, distributing capability, removability, uniformity, plus compound amount evenness.

6. Mechanisms of Transdermal Delivery by NLCs

Multiple coordinating processes underpin NLC capability toward surpassing SC obstacles.[10,11,12]

• Sealing Impact: NLCs generate steady movie on epidermis, decreasing moisture release, raising SC moisture, subsequently diminishing resistance toward medicine distribution.

• Lipid Fluidity: Exterior fats integrate inside SC lipid frameworks, boosting cellular porousness plus minimizing protective operation.

• Adhesion: Microscale magnitude plus great face vigor encourage firm touch, lengthening residency plus medicine vigor.

• Follicular Targeting: Hair-producing systems offer uninterrupted passageways via SC, with subdivisions under three-hundred to four-hundred-nanometer measurements encouraging follicular entry plus storage formation.

• Thermodynamic Action: Substantial fixation yields a super-full remedy upon epidermis usage, propelling medicine movement inside SC plus sustaining super-full circumstances via extended durations.

• Enhancement Components: Particular surfactants plus unsaturated fats demonstrate organic penetration-advancing qualities, producing cooperative impacts when merged in NLC preparations.

7. Preclinical Evidence for NLC-Based Topical RA Therapy

7.1 Rofecoxib-Loaded NLCs

The most detailed contemporary research examined rofecoxib (ROX)-filled NLCs for topical RA medicine.[2] Rofecoxib, a potent COX-2 focus chemical, withdrew from international markets in two-thousand-four because of raised cardiac danger with mouth consumption. Its remarkable chemical strength creates it appropriate for localized treatment if complete organism intake gets reduced.

Scientists examined therapeutic worth in a rodent rheumatism model, using topical ROX-NLC compound once per twenty-four hours for twenty-one intervals.[2] Main findings demonstrated: inflammation decrease of seventy-eight point four percent with ROX-NLC compound versus forty-two point seven percent for plain ROX compound plus forty-eight point three percent for mouth rofecoxib; illness rating decline from three point eight to one point two with ROX-NLC compound; preservation of bone design; plus standard tissue appearance without swelling, tissue creation, plus bone degeneration in healed pets.

Notably, heart tissue assessment showed zero irregularities in ROX-NLC treated creatures, whereas mouth rofecoxib triggered heart tissue swelling plus scar formation.[2] Bloodstream substance amounts stayed under recognition restriction following topical NLC consumption, verifying minimal organism distribution, whereas mouth rofecoxib accomplished top concentrations of one point twenty-four microgram/milliliter. This investigation immediately substantiates that topical NLC consumption can restore a compound previously taken out because of harmful organism reactions.

7.2 Methotrexate and Combination Delivery

Methotrexate continues representing principal RA treatment, yet mouth consumption suffers from unpredictable bioavailability plus stomach plus liver dangers.[17,19] One investigation created MTX-

containing fat-polyester crossbreed microscopic capsules alongside aceclofenac-containing NLCs for integrated delivery. This combined method demonstrated heightened aceclofenac movement via integumentary levels, modulation of irritation mechanisms, programmed cellular passing initiation, restoration of foot design, plus healing results equaling marketed options with greater protection.

7.3 Safety and Toxicity Considerations

Fat-foundation microscale transporters demonstrate general tolerability owing to regular foundation components.[5,6] Employed fatty ingredients plus flowing fats (unsaturated fats, heavy-weighted triglycerides) pass regulatory permit plus experience cellular metabolic breakdown, reducing accumulation dangers. Non-ionic surfactants demonstrate reduced skin problems than ion-foundation varieties.

Primary safety merit originates from limiting organism publicity. Biodistribution investigations substantiate undetectable drug concentrations, offering confidence in decreased organism dangers. Still, thorough investigation via suitable creatures plus humans requires completion for full safety profile establishment.

8. Clinical Translation: Challenges and Opportunities

8.1 Scale-Up and Manufacturing

Drug manufacturing requires steady, expandable procedures.[5,6] Strong-pressure distribution provides expandability yet demands stringent regulation. Challenges involve batch-to-batch homogeneity, germicidal technique suitability, extended storage reliability, plus expense efficiency relative to present medicines.

8.2 Regulatory Pathway

Permission wants thorough evaluation per worldwide specifications for fine medications.[5,6] Particular issues cover particle attributes, specification management, preservation research, IVIVC creation, plus safety grading. FDA plus EMA guidance continues developing, plus initial authorization council interaction proves strongly suggested.

8.3 Clinical Trial Design

Well-constructed scientific investigations prove vital for confirming advantage plus protection.[15,16] Suggested designs encompass: preliminary security assessment in regular persons calculating organism intake plus skin problems; dose-scaling research in RA sufferers utilizing clinical effectiveness metrics (remedial reply measurements, sickness extent markers, pain rating, patient evaluation); plus substantial randomized, double-treatment, dummy comparison, plus substitute comparison investigations.

9. FUTURE PERSPECTIVES

Succeeding NLC iterations joining responsive components, focused goal delivery, plus combined compound loading give encouraging capabilities for raising exactness in managing this chronic inflammatory illness.[1,5,6] Development concerning actual scientific validation plus more substantial patient research information constitute essential next phases in establishing this ground-breaking therapy choice for rheumatoid joint sufferers internationally.

CONCLUSION

NLCs constitute a progressive system for integumentary medicine application in RA, providing possibility to convert this lasting inflammatory condition administration. Merging lipid-substance compatibility with nano-scale advancement perks, NLCs tackle numerous limits

of customary integumentary preparations plus organism-broad medicines.[1,2,5]

Contemporary research, particularly comprehensive rofecoxib-NLC examination, verifies greater healing advantage versus customary topical plus mouth kinds, plus minimal organism interaction with maintained cardiac safety—straight confirming integumentary NLC application as recuperating formerly withdrawn substances.[2]

Substantial obstacles persist ahead of NLC topical RA therapy accomplishes scientific implementation. Manufacturing scalability, extended stability, authorization routes, plus vigorous investigative approval represent vital difficulties requiring organized fixing. Potential expansion incorporating focused goal action, responsive components, plus incorporated treatment capacities assure greater clinical exactness for RA control.

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HOW TO CITE: Shreya Pathak, Pankaj Kumar, Ritesh Jain, Revolutionizing Rheumatoid Arthritis Therapy:The Potential of Lipid Nanocarriers for Topical Drug Delivery Systems a Comprehensive Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 6, 7087-7095, https://doi.org/10.5281/zenodo.20990895