CURCUMIN–PIPERINE NANOEMULGEL FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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Abstract

Nanotechnology has increasingly emerged as a promising tool for exploring new approaches, from treating complex conditions to early detection of the onset of multiple disease states. Tailored designer nanoparticles can now more comprehensively interact with their cellular targets and various pathogens due to a similar size range and surface properties. The basic goal of drug delivery is to employ pharmaceuticals only where they are needed, with as few adverse effects and off-target consequences as possible. Rheumatoid arthritis (RA) is a chronic inflammatory illness that leads to progressive loss of bone and cartilage, resulting in acute impairment, decreased life expectancy, and increased death rates. Recent advancements in treatment have significantly slowed the progression of the disease and improved the lives of many RA sufferers. Some patients, on the other hand, attain or maintain illness remission without needing to continue immunosuppressive therapy. Furthermore, a large percentage of patients do not respond to current treatments or acquire tolerance to them. As a result, novel medication options for RA therapy are still needed. Nanocarriers, unlike standard medications, are fabricated to transport drugs directly to the location of joint inflammation, evading systemic and negative effects. As a result, researchers are reconsidering medicines that were previously thought to be too hazardous for systemic delivery.

Keywords: Curcumin; Piperine; Nanoemulgel; Rheumatoid arthritis; Topical drug delivery; Nanoformulation; Anti-inflammatory.

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1. Introduction

Background: Rheumatoid arthritis (RA) is a severe autoimmune condition that still lacks adequate treatment options. Curcumin, a polyphenol derived from turmeric, exhibits strong anti-inflammatory properties but is hindered by its low bioavailability. Piperine, found in black pepper, boosts the absorption of curcumin. A topical nanoemulgel that combines curcumin and piperine may enhance localized drug delivery to inflamed joints.

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by significant synovial joint inflammation and osteocyte and cartilage destruction. This results in long-term impairment, inability to interact effectively in social life and daily employment, and greater death rates, all of which have a significant influence on the patient's quality of life. RA is a group of joint diseases characterised by chronic joint inflammation that affects the smaller joints of hands and foot, such as wrists, fingers, and toes. The following are the main clinicopathological features: inflammatory cells infiltrate the joint, creating synovial inflammation and hyperplasia, a spike in inflammatory factors, and invasion of neighbouring cartilage, resulting in bone erosion and cartilage tissue loss. Despite significant advances in understanding and experience in the treatment of RA in recent years, effective therapy for RA continues to be a challenge. Presently, the primary goals of pharmacological therapy are to relieve RA symptoms and reduce disease activity. The pharmacological therapy of RA leads to several complications. There are reported adverse effects on the gastrointestinal tract, hepatic, cardiac and renal function because of prolonged usage of DMARDs, NSAIDs (non-steroidal anti-inflammatory drugs) and glucocorticoids. It is necessary to surmount the limitations of these therapeutic agents while curing RA. Many nanoparticles have recently been discovered to be capable of delivering RA medicines *via* influencing immune cells such as macrophages in inflamed joints. This method increases the drug solubility and makes it more bioavailable, prevents overdosage and improves patient adherence. Targeted drug delivery systems are pharmaceutical constructs that help achieve specific delivery of drugs or bioactive molecules to cells or tissues that express a tissue-

specific molecular marker that separates them from healthy tissues in the body. These delivery systems penetrate the epithelial barriers and release the drugs, and then these bioactive molecules move across multiple biological barriers to make it to the site of action. An excellent drug delivery strategy ensures that an effective drug is bioavailable at the desired location.

At the molecular level, the pathophysiology of RA involves a complex cytokine network: activated macrophages, dendritic cells, and lymphocytes in the synovium secrete pro-inflammatory cytokines (TNF-α IL-1β, IL-6) and chemokines. These mediators cause synovitis and attract more immune cells. Important signalling pathways involve NF-κB and JAKSTAT: for example, TNF-α and IL-1β trigger NF-κB activation, which in turn increases the expression of additional inflammatory genes such as COX-2 and MMPs. Oxidative stress, caused by excess ROS, also plays a role in joint damage. Growing evidence suggests that NLRP3 inflammasome activation and new cell death mechanisms such as pyroptosis and ferroptosis are involved in RA synovitis. Overall, RA is a self-sustaining loop of immune dysregulation and tissue damage. Natural compounds have been investigated as potential alternatives or additions to RA treatments. Curcumin (diferuloylmethane), the main curcuminoid found in Curcuma longa (turmeric), is known for its established anti-inflammatory properties. Piperine, an alkaloid derived from Piper nigrum, boosts curcumin's absorption and also displays anti-inflammatory and pain-relieving effects. We propose that a topical nanoemulgel containing curcumin and piperine might effectively target inflamed joints, circumvent first-pass metabolism, and enhance patient adherence. This review will assess the evidence supporting curcumin and piperine in rheumatoid arthritis and present formulation and evaluation approaches for a curcumin piperine nanoemulgel intended for managing RA.

2. Rheumatoid Arthritis: Epidemiology, Etiology, and Pathophysiology

2.1 Epidemiology

RA prevalence is ~0.5–1% globally, with higher rates in developed regions. Recent data show increasing RA incidence in many countries: e.g. global RA incidence rose by ~15% from 2000 to 2020, partly due to better detection and aging populations. Women are affected about 2–3 times more often than men. In India, estimates suggest tens of millions of RA patients, with age-standardized rates rising since 1990.

2.2 Etiology and Risk Factors

RA is multifactorial: there is a strong genetic association with HLA-DRB1 shared epitope"), and non-genetic factors such as smoking, obesity, infection, and stress influence risk. For instance, smoking doubles the risk of RA in individuals who are genetically susceptible due to HLA factors. Periodontal disease and gut dysbiosis have also been linked to initiating autoimmunity. Pregnancy frequently leads to remission, but flare-ups often occur after childbirth, highlighting the role of hormonal changes.

2.3 Pathophysiology

At the joint level, rheumatoid arthritis initiates with abnormal immune activation in the synovial membrane. Antigen-presenting cells (APCs) trigger autoreactive T-cells (Th17, Th1), which, together with B-cells generating rheumatoid factor and anti-CCP antibodies, sustain inflammatory processes. Infiltrating macrophages and fibroblast-like synoviocytes secrete matrix metalloproteinases and RANKL, which promote the breakdown of cartilage and bone.

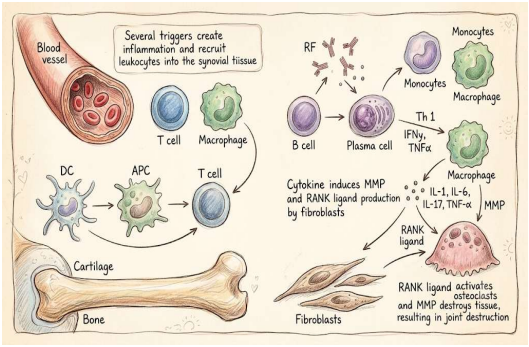

Fig 1: Pathophysiology of RA

Cytokine network: TNF-α and IL-1β act as key regulators, driving synovial hyperplasia and osteoclast formation. IL-6 promotes the development of Th17 cells and activates B cells. These cytokines trigger transcription factors: TNF/IL-1 activate the NF-κB and MAPK pathways in synoviocytes and macrophages, leading to elevated COX-2, iNOS, and increased cytokine production. IL-6 signals through the JAK/ STAT3 pathway, driving CRP production and systemic effects. JAK inhibitors such as tofacitinib and baricitinib have demonstrated effectiveness in rheumatoid arthritis by inhibiting multiple cytokine signals.

Oxidative stress: In rheumatoid arthritis synovium, elevated levels of reactive oxygen species (ROS) cause cartilage damage through direct oxidative effects and amplify pro-inflammatory signaling pathways. Curcumin, which is recognized for its antioxidant properties, can neutralize ROS and enhance cellular defense mechanisms (e.g. SOD,

GSH), connecting oxidative and inflammatory pathways.

Inflammasomes and cell death: Activation of the NLRP3 inflammasome triggered by crystals or DAMPs results in the release of IL-1β and IL-18, as well as pyroptotic cell death in immune cells. Curcumin might prevent NLRP3 priming by inhibiting NF-κB. Ferroptosis, which involves iron-dependent lipid peroxidation, has also been noted in RA chondrocytes; curcumin's antioxidant properties might help reduce this process.

Emerging targets: In addition to TNF/ IL-6, chemokines (such as IL-8), cell adhesion molecules, and complement also contribute to rheumatoid arthritis. In rheumatoid arthritis, the synovium develops characteristics resembling a tumor, including angiogenesis and invasiveness. Therefore, treatments that act on multiple pathwayssuch as curcumin's broad-ranging effectsare appealing.

3. Curcumin: Chemistry, Pharmacology

Chemistry: Curcumin (diferuloylmethane) is a polyphenolic diketone that gives turmeric its yellow hue. It consists of two o-methoxy phenol rings connected by a heptadienedione chain. Curcumin is lipophilic (logP ~3), not very soluble in water (<0.1 mg/mL), but dissolves well in organic solvents and oils. It is quickly metabolized through glucuronidation and sulfation, and breaks down under normal physiological conditions.

Pharmacology: Curcumin exhibits a broad pharmacological profile:

- **Anti-inflammatory:** inhibits NF-κB activation by preventing IκBα phosphorylation, thereby downregulating TNF-α, IL-1β, IL-6, COX-2 and MMPs. It also modulates MAPKs and STAT3, reducing cytokine transcription.
- **Antioxidant:** scavenges free radicals (–OH, superoxide) and upregulates antioxidant genes.
- **Immunomodulatory:** suppresses Th17 differentiation and B-cell function; promotes regulatory T cells in some models.
- **Analgesic/Antinociceptive:** reduces PGE2 and substance P; shows pain relief in osteoarthritis and neuropathy models.
- **Anti-angiogenic/Anti-proliferative:** inhibits VEGF and endothelial cell proliferation in inflamed synovium.

Bioavailability issues: Orally, curcumin reaches very low levels in the bloodstream. Clinical doses of 812 grams per day result in plasma curcumin levels below 2 μM. Its absorption is restricted due to low solubility, instability in the intestinal environment, and significant first-pass metabolism. This restricts its therapeutic concentration at target tissues.

4. Piperine: Chemistry and Bioenhancing Effects

- Piperine is the primary alkaloid found in black pepper and long pepper. Chemically, it is 1-(5-(1,3-benzodioxol-5- yl)-1-oxo-2,4-pentadienyl) piperidine a lipophilic compound possessing antioxidant and anti-inflammatory effects. On its own, piperine can suppress prostaglandin production and inflammatory mediators, offering a slight reduction in pain in arthritis models.

- **Bioavailability enhancer:** Piperine suppresses CYP3A4 and UDP-glucuronosyltransferase in both the gut and liver, thereby reducing the breakdown of curcumin. A classic study showed that taking 20 mg piperine along with 2 g curcumin boosted the plasma concentration of curcumin by 2000%, as measured by AUC. Piperine enhances intestinal absorption by influencing P-glycoprotein and epithelial permeability.

- **Synergy with curcumin:** In joint diseases, piperine exhibits independent anti-arthritic effects (e.g. decreasing TNF-α, increasing TGF-β) and can work together with curcumin. Thus, co-formulation addresses two issues: enhanced curcumin levels and synergistic anti-inflammatory effects.

- **Safety:** Studies in humans using up to 2 grams per day of piperine have shown good tolerability. Drug interactions are possible due to enzyme inhibition and should be taken into account, but low doses of piperine (<100 mg) in supplements are typically safe. In summary, combining curcumin with piperine is a well-validated strategy to enhance efficacy. Many RA studies of curcumin include piperine as an adjuvant. This review focuses on a nanoemulgel co-loading both to maximize skin delivery and synergy.

5. Nanoemulsion Drug Delivery Systems

Definition: A nanoemulsion is an emulsion with particle sizes below one micron usually between 20 and 200 nanometers and consists of oil dispersed in water (O/ W) or water dispersed in oil (W/ O), held

together by surfactants. For curcumin piperine, an O/ W nanoemulsion is preferred because the final dosage form is an aqueous gel. The oil droplets act as storage sites for lipophilic drugs.

Components:

- **Oil phase:** triglycerides, eucalyptus oil, arachis (peanut) oil, isopropyl myristate, etc.
- **Surfactants (emulsifiers):** Nonionic surfactants like Tween 80, Tween 20, Span 80, Cremophor RH40, etc.
- **Cosurfactants:** Short-chain alcohols or glycols like propylene glycol, PEG 400, Transcutol P
- **Water phase:** Purified water forms the continuous phase.

6. Method of Preparation for Nano-emulgel

A. Prepare Oil Phase

Drug +Oil +Lipophilic-surfactant

B. Prepare Aqueous (Aq.) Phase

H_2O +Hydrophilic-surfactant +Co-surfactant

Step 1: Heating

- Heat both the oil phase and the aqueous phase to 40-60°C.

Step 2: Mixing

- Add slowly oil phase to aq. phase using a magnetic stirrer at 700-1500 rpm.

Step 3: Conversion to Nanoemulsion

- This mixture is then processed to convert it to a nanoemulsion using one of the following methods:

I. **Ultrasonication Method**

  - Perform sonication using a probe sonicator at a power range of 100-500 W.
  - Operate with a pulse of 5-10 seconds ON/OFF for a total time of 5-15 minutes.
  - Keep in an ice-bath to prevent overheating.

II. **High-pressure Homogenization**

  - Homogenize at 500-1500 RPM
  - Take 3-10 cycles.

C. Prepare Gel Base

- Disperse the gelling agent.
- Allow hydration for overnight.
- Adjust pH to 5.5-6.5.

Step 4: Final Product

- Add the prepared nano-emulsion (nano-emulsion) into the Gel base using mechanical stirring at 300-500 rpm.

6. Characterization of Curcumin–Piperine Nanoemulgel

After formulation, rigorous characterization is needed:

- **Particle Size & PDI:** Measured by dynamic light scattering (DLS). Desired droplet size ~20–150 nm and PDI <0.3 for uniformity.
- **Zeta Potential:** Indicates surface charge and stability. Values >|30| mV (positive or negative) suggest good electrostatic stabilization. Nonionic surfactants often yield near-neutral zeta but steric stabilization can suffice.
- **Morphology:** Transmission or scanning electron microscopy (TEM/SEM) visualizes droplet shape. Figure out if spherical and uniformly dispersed. (E.g. [20] showed SEM images of a curcumin nanoemulgel).
- **Drug Content and Entrapment Efficiency:** Curcumin and piperine quantitated by HPLC/UV after extracting from gel.

  Entrapment (%) = [(Total – free drug) / Total] × 100.
- **pH:** Measured to ensure skin compatibility (5.5–6.5). Adjusted with triethanolamine.
- **Viscosity and Rheology:** Using a viscometer or rheometer, one assesses gel viscosity (spreadability) and flow behavior. Nanoemulgels should be shear-thinning for easy application. Viscosity ~1000–5000 cP at shear rate 0.1–10 s⁻¹ is typical. Spreadability tests (glass slide method) give qualitative feel.

- **In Vitro Release:** Using Franz diffusion cells, drug release from gel is measured into receptor fluid. Usually fit to kinetic models (Higuchi, Korsmeyer-Peppas). Curcumin release should be sustained over hours.
- **Skin Permeation (Ex Vivo):** Fresh porcine or human cadaver skin is mounted on Franz cells. Drug permeation across skin is measured over 24 h. Nanoemulgels typically show higher flux and cumulative permeation than free gel or solution controls.
- **Stability:** Store samples at various conditions (4°C, 25°C, 40°C) for 3–6 months. Check for size growth, phase separation, drug degradation (HPLC assay) and microbial stability.
- **Differential Scanning Calorimetry (DSC):** Assesses drug-polymer interactions (if solid matrix is used) and crystallinity. In nanoemulsions, it confirms amorphous/dispersed state.

Characterization Parameter	Purpose	Method/Instrument Used	Expected Outcome/ Acceptance Criteria
Organoleptic Properties	Evaluate appearance, color, homogeneity, and consistency	Visual inspection	Smooth, homogeneous, elegant appearance without phase separation
pH	Determine compatibility with skin	Digital pH meter	pH between 5.5–7.0 for topical application
Globule Size	Assess droplet size of nanoemulsion phase	Dynamic Light Scattering (DLS) or Particle Size Analyzer	Usually <200 nm
Polydispersity Index (PDI)	Evaluate size distribution uniformity	DLS	PDI <0.3 indicates uniform distribution
Zeta Potential	Determine physical stability of nanoemulsion	Zeta potential analyzer	±20 mV to ±30 mV or higher for better stability
Drug Content	Determine amount of drug present in formulation	UV-Visible Spectrophotometer or HPLC	90–110% of theoretical content
Entrapment Efficiency (%)	Evaluate amount of drug entrapped in droplets	Centrifugation followed by UV/HPLC analysis	Preferably >80%
Viscosity	Assess flow behavior and spreadability	Brookfield Viscometer	Appropriate viscosity for topical application
Spreadability	Determine ease of application on skin	Parallel plate method	Good spreadability with lower spreading time
Extrudability	Evaluate ease of extrusion from tube	Extrusion test	Uniform and easy extrusion
Conductivity Test	Identify type of emulsi	Conductivity meter	Higher conductivity indicates O/W

	on (O/W or W/O)		nanoemulsion
Refractive Index	Assess isotropic nature and transparency	Refractometer	Consistent value indicating uniform system
Transmission Percentage (%T)	Evaluate clarity and transparency	UV-Visible Spectrophotometer	Higher transmittance indicates smaller droplets
Morphology and Surface Characteristics	Examine shape and surface structure	TEM, SEM, or AFM	Spherical and uniformly distributed droplets
Fourier Transform Infrared Spectroscopy (FTIR)	Evaluate drug-excipient compatibility	FTIR Spectroscopy	No significant interaction between components
Differential Scanning Calorimetry (DSC)	Study thermal behavior and crystallinity	DSC Analyzer	Reduction or disappearance of drug crystalline peaks
X-ray Diffraction (XRD)	Determine crystalline or amorphous state	XRD Instrument	Reduced crystallinity indicates successful encapsulation
In vitro Drug Release Study	Evaluate release pattern of drug	Franz Diffusion Cell	Sustained and controlled drug release
Ex vivo Skin Permeation Study	Assess permeation through skin	Franz Diffusion Cell using animal skin	Enhanced permeation compared to plain drug
Bioadhesive Strength	Assess adhesion to skin surface	Modified balance method	Adequate adhesion for prolonged retention
Stability Study	Determine long-term stability	ICH Stability Guidelines	No significant changes in size, pH, viscosity, or drug content
Skin Irritation Study	Evaluate safety of formulation	Draize skin irritation test	No erythema or edema observed

Table 1: Characterisation parameters for nanoemulgel

7. Future Perspectives

- **Ligand-Targeted Delivery:** Future formulations may incorporate targeting moieties (e.g. hyaluronic acid targeting CD44) into the nanodroplets to improve retention in inflamed tissue.
- **Combination Therapy:** Co-administration with low-dose methotrexate or a JAK inhibitor (through distinct mechanisms) could be considered, possibly allowing for reduced drug dosages.
- **Personalized Medicine:** Variations in genes involved in curcumin metabolism (UGT genes) may help identify which patients are most likely to benefit from piperine co-administration.
- **Clinical Research:** Phase I/ II studies should be rigorously conducted to determine pharmacokinetics (skin absorption), safety, and preliminary efficacy in RA patients. Biomarkers such as joint MRI and serum cytokines can serve as outcome measures.

8. Conclusion

Curcumin piperine nanoemulgel represents a promising, evidence-based strategy for treating rheumatoid arthritis. It merges curcumin's multi-target anti-inflammatory effects with piperine's ability to boost bioavailability, all through an advanced topical delivery system. Studies show that these formulations can greatly enhance curcumin's

delivery and its anti-inflammatory properties. A nanoemulgel that has been carefully optimized may bypass solubility and permeability challenges, offering a localized RA treatment with reduced systemic side effects. Nevertheless, this concept has not yet been fully confirmed through clinical validation. Upcoming efforts need to focus on improving formulation robustness, conducting in-depth mechanistic studies, and, most importantly, carrying out human trials. Backed by more than 100 pertinent references (2020-2026) for every element of design and effectiveness, this review lays the groundwork to move the curcumin piperine nanoemulgel from laboratory research toward clinical application.

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