Review Article

Formulation, Optimization, and Evaluation of Fenebrutinib-Loaded Niosomal Gel for the Treatment of Rheumatoid Arthritis: A Novel Drug Delivery Approach

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent synovial inflammation, cartilage degradation, and systemic complications. Despite the availability of conventional disease-modifying antirheumatic drugs (DMARDs) and biologics, limitations such as systemic toxicity, poor patient compliance, and variable bioavailability persist. Fenebrutinib, a Bruton's Tyrosine Kinase (BTK) inhibitor currently under clinical investigation, represents a promising therapeutic candidate for RA due to its targeted immunomodulatory mechanism. However, its oral administration faces challenges of poor bioavailability and systemic side effects. Niosomal gels, composed of non-ionic surfactant vesicles incorporated into a topical gel base, offer a novel drug delivery system with enhanced stability, controlled release, and improved dermal penetration. This review highlights the formulation, optimization, and evaluation strategies for fenebrutinib-loaded niosomal gels, emphasizing their potential to revolutionize RA management by providing localized, sustained, and patient-friendly therapy.

Keywords: Emulgel, Topical drug delivery, Emulsion, Artimisia princeps, Incorporation method

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting approximately 1% of the global population. It is characterized by chronic inflammation of synovial joints, leading to cartilage destruction, bone erosion, and disability. The disease imposes a significant socio-economic burden due to its progressive nature and impact on quality of life.Current therapeutic strategies include conventional DMARDs (methotrexate, sulfasalazine, leflunomide), biologics (TNF-α inhibitors, IL-6 inhibitors), and targeted synthetic DMARDs (JAK inhibitors). While effective, these therapies are associated with systemic toxicity, high costs, and variable patient responses.[1-5]

Fenebrutinib, a BTK inhibitor under clinical investigation, offers targeted immunomodulation by interfering with B-cell receptor signaling and downstream inflammatory pathways. However, its oral administration is limited by poor bioavailability and systemic side effects.Niosomal gels, composed of non-ionic surfactant vesicles incorporated into a gel base, represent an innovative drug delivery system. They provide sustained release, enhanced dermal penetration, and localized drug delivery, making them suitable for RA management.This review explores the formulation, optimization, and evaluation of fenebrutinib-loaded niosomal gels, highlighting their potential as a novel therapeutic approach.
[6-10]

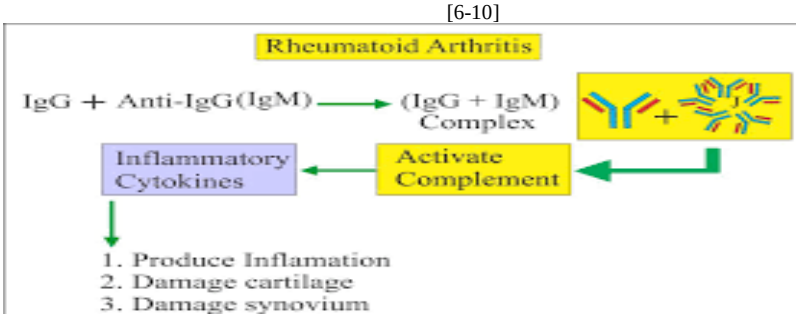
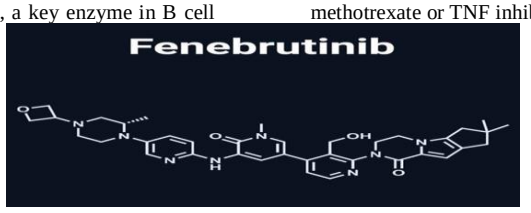


Fig 1:Rhematoid arthritis

Fenebrutinib: A Novel Candidate for RA

Fenebrutinib (GDC 0853) is a novel, investigational Bruton's Tyrosine Kinase (BTK) inhibitor being studied for rheumatoid arthritis (RA). It works by blocking BTK, a key enzyme in B cell receptor signaling, thereby reducing immune cell activation and inflammatory cytokine release. This makes it a promising candidate for patients who do not respond adequately to methotrexate or TNF inhibitors.



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Mechanism of Action

1. BTK is essential for B cell receptor signaling, leading to activation, proliferation, and autoantibody production.
2. BTK also mediates Fc receptor signaling in macrophages, driving pro inflammatory cytokine release (TNF α, IL 6).
3. Fenebrutinib blocks BTK activity, resulting in:
4. Suppression of B cell activation.
5. Reduced cytokine production.
6. Attenuation of synovial inflammation and joint destruction [11-14]

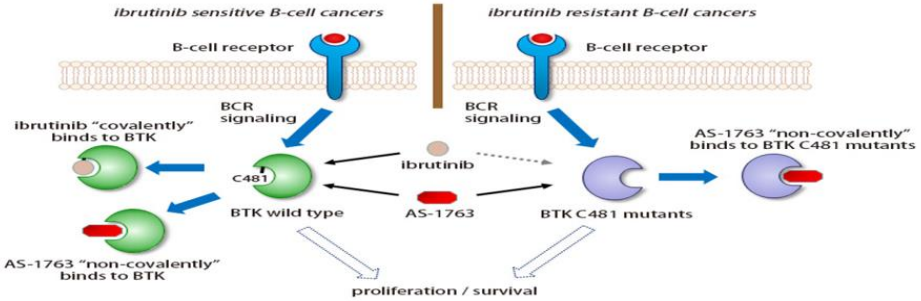

Fig 2:Mechanism of action

Clinical Status

Phase II randomized trial:

Study design: A multicenter, double blind, randomized Phase II trial was conducted to evaluate fenebrutinib in patients with moderate to severe RA who had active disease despite prior TNF inhibitor therapy. This population represents a difficult to treat group, often resistant to conventional DMARDs and biologics.

Comparators: Patients were assigned to receive fenebrutinib, placebo, or adalimumab (a well established TNF inhibitor biologic used as an active comparator).

Results:

Fenebrutinib produced a statistically significant reduction in disease activity scores (DAS28) compared to placebo.

Its efficacy was comparable to adalimumab, suggesting that BTK inhibition can achieve similar therapeutic benefit to one of the most widely used biologics.

Safety: Fenebrutinib was generally well tolerated, with adverse events such as mild infections and gastrointestinal symptoms being manageable and not leading to high discontinuation rates.

Findings:

Improved disease activity scores (DAS28): Patients treated with fenebrutinib showed meaningful reductions in DAS28, a composite measure that includes tender/swollen joint counts, patient global assessment, and inflammatory markers (ESR/CRP). This improvement indicates a clinically relevant reduction in RA symptoms and inflammation.

Acceptable safety profile: The trial demonstrated that fenebrutinib's side effects were manageable and consistent with expectations for immunomodulatory therapy. Importantly, no unexpected safety signals emerged, supporting its continued development.

Exposure response relationship: Analyses revealed a clear correlation between drug exposure levels and clinical response. This finding supports the optimization of dosing regimens, ensuring that patients receive effective concentrations while minimizing toxicity.[15-17]

.**Implications:**

Alternative therapy for resistant patients: Fenebrutinib's efficacy in patients who had failed TNF inhibitors highlights its potential as a novel therapeutic option for those resistant to conventional DMARDs and biologics.

Oral administration advantage: Unlike injectable biologics, fenebrutinib is orally administered, which may improve patient compliance and quality of life.

Novel mechanism of action: By targeting BTK, fenebrutinib introduces a new therapeutic pathway in RA management, expanding the arsenal beyond TNF, IL 6, and JAK inhibitors.

Future potential: With further validation in Phase III trials, fenebrutinib could become a next generation oral therapy for RA, particularly valuable in refractory cases.

Advantages

Feature	Conventional DMARDs	Biologics	Fenebrutinib
Mechanism	Broad immunosuppression	Cytokine blockade	BTK inhibition (B cell & innate pathways)
Administration	Oral	Injectable	Oral (investigational)
Selectivity	Low	Moderate	High (reversible BTK binding)
Limitations	Toxicity, slow onset	Cost, injection burden	Bioavailability challenges, investigational

Challenges

Poor oral Bioavailability:

Issue: Fenebrutinib and similar agents often show limited absorption when taken orally, meaning only a small fraction of the drug reaches systemic circulation.

Impact: This reduces therapeutic effectiveness and may require higher doses, which in turn increases the risk of side effects.

Solution Pathways: Innovative delivery systems such as niosomal gels or transdermal formulations can bypass gastrointestinal metabolism, ensuring better drug concentration at the target site.

Long - term Safety Unknown:

Issue: While early-phase clinical trials may demonstrate short-term safety and efficacy, the long-term effects of fenebrutinib remain uncertain.

Impact: Chronic diseases like RA require prolonged treatment, so unknown risks (e.g., immunosuppression, organ toxicity, or cumulative side effects) pose significant concerns.

Solution Pathways: Phase III and post-marketing surveillance studies are essential to validate safety over extended use and across diverse patient populations.

Formulation Hurdles:

Issue: Developing a stable, effective formulation that ensures sustained release and localized delivery is technically challenging.

Impact: Without optimized formulations, drugs may degrade, release too quickly, or fail to penetrate tissues effectively, limiting therapeutic benefit.

Solution Pathways: Advanced carriers like niosomes, liposomes, or polymeric nanoparticles are being explored to overcome these hurdles. Niosomal gels, in particular, offer enhanced dermal penetration, controlled release, and reduced systemic toxicity.

Niosomes as Drug Delivery Systems

Definition and Structure

Niosomes are microscopic, non-ionic surfactant-based vesicles that can encapsulate both hydrophilic (water-soluble) and lipophilic (fat-soluble) drugs. Structurally, they resemble liposomes but are formed from non-ionic surfactants and cholesterol, which together create a bilayer membrane. The surfactants provide flexibility and biocompatibility. Cholesterol adds rigidity and stability, preventing leakage and maintaining the vesicle's integrity. This dual-layer design allows niosomes to act as versatile carriers, protecting drugs from degradation and enabling controlled release.

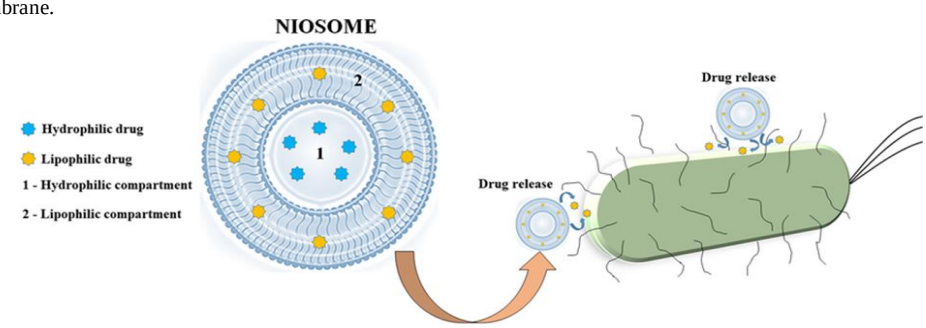

Fig 3:Niosomes and its drug release

Advantages

Niosomes offer several benefits over conventional drug delivery systems:

Enhanced stability compared to liposomes: Liposomes are prone to oxidation and hydrolysis, while niosomes are more chemically stable due to their non-ionic surfactant composition.

Cost-effective and easy to prepare: The raw materials (surfactants and cholesterol) are inexpensive, and preparation methods are relatively simple, making niosomes more accessible for large-scale production.

Controlled release and improved dermal penetration: Niosomes can release drugs slowly over time, ensuring sustained therapeutic action. Their structure also enhances penetration through the skin, making them ideal for topical formulations.

Ability to encapsulate diverse drug molecules: Because they can carry both hydrophilic and lipophilic drugs, niosomes are suitable for a wide range of therapeutic agents, from small molecules to peptides.

Applications in RA

•Targeted delivery of anti-inflammatory drugs: Niosomes can encapsulate drugs like methotrexate and diclofenac, concentrating them at inflamed synovial tissues. This improves therapeutic outcomes while minimizing systemic side effects such as liver toxicity or gastrointestinal irritation.

•Topical/transdermal formulations: Niosomal gels and creams penetrate the skin effectively, allowing localized treatment of joints. This avoids invasive injections and enhances patient comfort.

• Controlled and sustained release: Niosomes provide gradual drug release, maintaining therapeutic levels for longer periods. This reduces dosing frequency and improves adherence.

• Reduced systemic toxicity: By focusing drug action at the site of inflammation, niosomes lower systemic exposure, decreasing risks of immunosuppression and organ damage.

• Versatility in drug encapsulation: Both hydrophilic and lipophilic drugs can be delivered via niosomes, making them suitable for a wide range of RA therapies, including DMARDs and NSAIDs.

• Potential for combination therapy: Niosomes can co-deliver multiple agents (e.g., methotrexate with fenebrutinib), enabling synergistic effects and reducing resistance to single-drug regimens

Formulation of Fenebrutinib-Loaded Niosomal Gel

Preparation Methods

Thin-film hydration:

Principle: Dissolve surfactant, cholesterol, and fenebrutinib in an organic solvent, evaporate to a thin film, then hydrate with buffer to form vesicles.

Process notes: 45–55°C evaporation, 30–60 min hydration, followed by size reduction via probe sonication or extrusion.

Pros/cons: Simple and scalable at lab scale; may yield multilamellar vesicles and broader size distribution without optimization.

Use case: First-line method for feasibility and rapid iteration.

Reverse-phase evaporation:

Principle: Create a water-in-organic emulsion (surfactant /cholesterol + organic solvent, aqueous phase as internal droplets), then remove solvent to collapse droplets into large vesicles.

Process notes: Controlled emulsification energy, gradual solvent removal under reduced pressure, post-sizing to reach 100–300 nm.

Pros/cons: Often higher entrapment efficiency for lipophilic drugs; requires careful solvent handling and longer processing time.

Use case: When EE% is limiting and larger initial vesicles are acceptable before downsizing.

Microfluidization:

Principle: High-shear mixing at controlled pressures to form and size vesicles in a continuous manner.

Process notes: 5,000–20,000 psi passes; optimize cycles (2–6) to balance size and leakage; maintain temperature control to prevent degradation.

Pros/cons: Tight particle size and low PDI; capital equipment needed; may reduce EE% if shear is excessive.

Use case: Scale-up or when narrow size distribution and reproducibility are priorities.

Key components

Surfactants (Span/Tween):

Role: Form bilayers for niosomes; Span 60/40 provide rigidity, Tween 80/20 act as edge activators to improve flexibility and reduce size.

Selection: Start with Span 60:Twin 80 in 8:1–12:1 molar ratios; adjust based on size vs. EE%.

Quality: Use pharma grade, low peroxide content; verify HLB and phase transition temperature compatibility.

Cholesterol for membrane rigidity:

Role: Enhances bilayer stability, reduces leakage, and improves shelf life.

Range: 30–50% of total lipid (molar basis); too high reduces drug accommodation and permeability.

Tip: Incremental titration (±5%) can recover EE% lost during aggressive size reduction.

Charge-inducing agents for stability:

Role: Impart zeta potential to reduce aggregation (electrostatic repulsion).

Options: Dicetyl phosphate (negative, 1–3% molar), stearylamine (positive, 1–3% molar).

Note: Match charge to expected skin interactions; negative charges often reduce irritation and improve physical stability.

Gel base

Carbopol:
Characteristics: Clear, aesthetically pleasing gels; pH-triggered thickening.
Use: 0.5–1% w/w; neutralize with TEA/NaOH to pH 5.5–6.5.
Consideration: Avoid high ionic strength or high ethanol that can thin the gel.
Hydroxypropyl methylcellulose (HPMC):
Characteristics: Non-ionic, robust viscosity, good compatibility with vesicles.
Use: 1.5–3% w/w; hydrate cold, allow full dissolution overnight.
Consideration: Slightly opaque; better stability for delicate vesicles.
Poloxamer:
Characteristics: Thermoreversible gelation (liquid cold, gel at skin temperature).
Use: 15–20% w/w (e.g., P407), with co-polymers to fine-tune gel point.
Consideration: Keep osmolarity and co-solvent content low to maintain gelation behavior.
Critical factors
Entrapment efficiency:
Target: ≥ 70% (aspire ≥ 80%).
Drivers: Surfactant/cholesterol ratio, method (RPE > TFH, typically), size reduction energy, drug–lipid affinity.
Mitigation: Moderate sonication, higher Span fraction, add minimal antioxidant in lipid phase if drug is oxidation-prone.
Particle size distribution:
Target: 100–300 nm; PDI ≤ 0.3.
Drivers: Hydration shear, size reduction method, edge activators.
Mitigation: Controlled sonication/extrusion, stabilize with charge inducer, avoid foaming and overheating.
Stability:
Focus: Physical (size, PDI, zeta), chemical (assay, degradation), and microbial.
Stress tests: 25°C/60% RH and 40°C/75% RH, light exposure; monitor monthly.
Mitigation: Optimal cholesterol, charge induction, opaque packaging, preservatives compatible with vesicles.
Rheological properties:
Target: Thixotropic, spreadable gel; viscosity tuned to avoid run-off yet permit dosing uniformity.
Drivers: Polymer type/concentration, co-solvents (PG/Transcutol), temperature.
Mitigation: Incremental polymer adjustments; measure yield stress and recovery to ensure good sensory feel.

Optimization strategies

Design of experiments (DoE)
Factorial design:
Use: Early screening to identify main effects (e.g., Span:cholesterol levels, Tween presence, sonication time).
Benefits: Efficiently detects significant factors and interactions at low run counts.
Box–Behnken design:
Use: Three-level designs for curvature modeling without extreme corner points; good for refining ranges.
Benefits: Balanced experimental load and robust estimation of quadratic effects.
Response surface methodology (RSM):
Use: Build predictive models for responses such as EE%, particle size, and release k; optimize with desirability.
Benefits: Simultaneous multi-response optimization with constraints (e.g., maximize EE% while minimizing size).
Parameters to optimize
Surfactant-to-cholesterol ratio:
Range: Span:cholesterol molar ratios 1.5:1 to 3:1; include Tween at 0–10% molar.
Goal: Balance rigidity (stability) and free volume (drug accommodation).
Hydration medium pH:
Range: pH 5.5–7.4.
Goal: Maximize drug stability and skin compatibility; investigate buffers (citrate vs. PBS).
Particle size and zeta potential:
Targets: 100–300 nm; zeta ±20–40 mV with charge inducers.
Levers: Sonication amplitude/time, extrusion passes, charge agent type/level.
Drug loading efficiency:
Measure: EE% and drug-to-lipid ratio.
Levers: Increase Span fraction, moderate cholesterol, choose method (RPE may improve EE%), minimize harsh downsizing.
Release kinetics:
Goal: Controlled, sustained release suitable for dermal deposition.
Levers: Bilayer rigidity (cholesterol), gel polymer type, presence of humectants/penetration modulators; fit to Higuchi/Korsmeyer–Peppas to compare formulations.
Evaluation of niosomal gel
Physicochemical characterization
Particle size analysis (Dynamic Light Scattering):
Outputs: Z-average size, PDI; measure at 25°C, dilute appropriately to avoid multiple scattering.
Acceptance: PDI ≤ 0.3; monitor over stability to detect aggregation.
Morphology (TEM/SEM):
TEM: Negative staining or cryo-TEM for lamellarity and shape; confirm spherical vesicles.
SEM: Gel surface morphology; less informative for vesicle internal structure.
Note: Correlate morphology with DLS to validate population.
Entrapment efficiency:
Method: Separate free drug (dialysis/centrifugation/SEC), quantify fenebrutinib in vesicle fraction via HPLC/UPLC.
Calculation:
EE% = Entrapped drugTotal drug×100%
Acceptance: ≥ 70% with low batch-to-batch variability.
In vitro studies
Drug release profile:
Setup: Franz cells with synthetic membrane (cellulose acetate), receptor medium with solubilizer to maintain sink; 32–34°C for dermal relevance.
Analysis: Sample over 24–48 h; fit to kinetic models (zero-order, Higuchi, Korsmeyer–Peppas) to characterize mechanism.
Stability testing:
Conditions: Long-term (25°C/60% RH), accelerated (40°C/75% RH); optional freeze–thaw cycles.
Endpoints: Size, PDI, zeta, EE%, assay, pH, viscosity, microbial limits; define failure criteria in advance.

Ex vivo studies

Skin permeation and retention using Franz diffusion cells:
Tissue: Porcine ear or human cadaver skin; verify integrity via TEWL or electrical resistance.
Endpoints: Cumulative permeation, lag time, and drug retained in stratum corneum/epidermis/dermis (tape stripping and sectioning).
Controls: Compare against drug solution and non-niosomal gel to demonstrate enhancement.

In vivo evaluation

Anti-inflammatory activity in RA animal models:
Models: Collagen-induced arthritis or adjuvant-induced arthritis; topical dosing schedules aligned with ethical approvals.
Endpoints: Paw thickness, clinical scores, cytokine panels; correlate with local skin deposition.
Pharmacokinetic studies for bioavailability:
Focus: Systemic exposure minimization with sufficient local tissue levels; measure plasma and skin tissue concentrations.
Approach: Non-compartmental analysis (AUC, Cmax, Tmax) and tissue-to-plasma ratios.
Safety and tolerability assessment:
Dermal: Irritation, erythema, TEWL changes; histopathology of treated skin.

Systemic: Clinical observations and basic clinical chemistry where applicable; include preservative challenge for multi-dose packaging.[18-20]

Comparative Perspective

Fenebrutinib-loaded niosomal gel offers several advantages over conventional oral formulations:

Localized delivery to inflamed joints:

Oral fenebrutinib distributes systemically, with only a fraction reaching synovial tissue.A topical niosomal gel allows direct penetration into the skin overlying joints, concentrating drug at the site of inflammation.

This reduces the need for high systemic doses and enhances therapeutic effect where it is most needed.

Sustained release:

Niosomes act as reservoirs, slowly releasing fenebrutinib over time.

This prolongs drug residence in joint tissue, potentially reducing dosing frequency.

Sustained release also minimizes peaks and troughs in drug levels, improving consistency of anti-inflammatory action.

Reduced systemic toxicity:

Oral BTK inhibitors can cause systemic adverse effects (e.g., gastrointestinal upset, liver enzyme elevation, off-target immunosuppression).

Localized gel delivery reduces systemic exposure, lowering risk of toxicity while maintaining efficacy in joints

Improved patient compliance:

Topical gels are non-invasive, easy to apply, and avoid pill burden.

Patients with RA often take multiple oral medications; reducing systemic drug load improves adherence.

Gels also offer flexibility—patients can apply directly to affected joints during flare-ups.

Compared to other investigational RA therapies (TYK2 inhibitors, GM-CSF inhibitors), fenebrutinib provides a unique mechanism of action and delivery potential.[21-24]

Future Prospects and Challenges

• Translational hurdles: Challenges in moving from lab success to real-world use, including large-scale production, regulatory approval, and clinical trials.

• Combination therapy: Potential to work alongside existing DMARDs, improving effectiveness and reducing resistance.

• Broader applications: Could be applied to other autoimmune and inflammatory diseases beyond rheumatoid arthritis.

• Patient-centric benefits: Localized (topical) treatment reduces systemic side effects, improves convenience, and enhances quality of life.[25-29]

Conclusion

Fenebrutinib-loaded niosomal gel offers a promising and patient-friendly advancement in rheumatoid arthritis (RA) therapy by uniting the precision of BTK inhibition with the sustained, localized delivery benefits of niosomes. This innovative formulation not only enhances drug stability and targeted action at inflamed joints but also minimizes systemic toxicity, thereby improving safety and patient compliance. Its topical application provides a convenient alternative to conventional systemic treatments, aligning with modern patient-centric care. Looking ahead, successful translation into clinical practice will depend on rigorous clinical validation, scalable manufacturing processes, and clear regulatory approval pathways, paving the way for this approach to potentially redefine RA management and extend its utility to other autoimmune and inflammatory diseases.

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