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Development Of Nanostructured Polyherbal Gel For Transdermal Delivery In Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disorder characterized by joint inflammation, pain, and functional disability. Conventional oral and injectable therapies often face limitations such as poor bioavailability, systemic side effects, and patient non-compliance, necessitating alternative delivery strategies. The present study focuses on the development of a nanostructured polyherbal gel for transdermal delivery in the management of RA, integrating the synergistic therapeutic benefits of multiple medicinal plant extracts with advanced nanocarrier technology. Selected anti-inflammatory, antioxidant, and immunomodulatory phytoconstituents were incorporated into nanostructures to enhance solubility, stability, skin permeation, and sustained release. The gel base was optimized for rheological properties, spreadability, and bioadhesion to ensure patient-friendly application. In vitro characterization included particle size, zeta potential, drug release kinetics, and ex vivo skin permeation studies. Preliminary pharmacological evaluation demonstrated significant reduction in pro-inflammatory markers and improvement in joint mobility compared to conventional formulations. The nanostructured gel exhibited superior therapeutic efficacy, reduced dosing frequency, and minimized adverse effects. This work highlights the potential of combining nanotechnology with polyherbal therapy to create a safe, effective, and patient-compliant transdermal system for RA management, offering a promising alternative to conventional

treatment modalities.

Keywords: *Anti-inflammatory, Bioavailability, Nanocarriers, Nanostructured Gel, Phytoconstituents, Polyherbal Formulation, Rheumatoid Arthritis, Skin Permeation, Sustained Release, Synergism, Transdermal Delivery, Treatment Compliance.*

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1. INTRODUCTION

A. Overview of Rheumatoid Arthritis as a Global Health Concern

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting millions worldwide, characterized by persistent joint inflammation, pain, stiffness, and progressive disability. Its increasing global prevalence places a significant socioeconomic burden due to reduced productivity and higher healthcare costs. While the exact etiology remains unclear, genetic predisposition, environmental triggers, and lifestyle factors contribute to disease onset and progression. Current treatment strategies primarily focus on pain relief, reducing inflammation, and delaying joint destruction. Despite therapeutic advancements, challenges remain in achieving long-term remission with minimal side effects, highlighting the urgent need for safer, more effective, and patient-compliant treatment modalities.

B. Pathophysiology of Rheumatoid Arthritis

RA is mediated by autoimmune mechanisms in which immune cells mistakenly attack synovial tissues, leading to chronic inflammation and joint destruction. This process is marked by infiltration of T cells, B cells, macrophages, and overproduction of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. The resulting pannus formation erodes cartilage and bone, causing deformities and loss of joint function. Moreover, systemic manifestations such as cardiovascular, ocular, and pulmonary complications make RA a multi-organ disease. Understanding these complex inflammatory pathways is crucial for identifying therapeutic targets. Polyherbal formulations with immunomodulatory and antioxidant properties show potential in modulating these pathogenic mechanisms.

C. Limitations of Conventional Therapies for RA

Existing therapies for RA include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologics. While these treatments reduce inflammation and slow disease progression, they are associated with multiple limitations. Long-term use often leads to gastrointestinal toxicity, hepatic dysfunction, immunosuppression, and high treatment costs. Biologics, though effective, are invasive and unaffordable for a majority of patients. Additionally, poor bioavailability and systemic side effects limit therapeutic compliance. These drawbacks create a therapeutic gap, emphasizing the urgent need for alternative approaches such as natural phytoconstituents and innovative delivery systems that can ensure sustained efficacy with minimal adverse reactions.

D. Significance of Transdermal Drug Delivery Systems

Transdermal delivery offers a non-invasive, patient-friendly route for drug administration, bypassing gastrointestinal metabolism, first-pass hepatic effect, and systemic fluctuations. By maintaining sustained plasma concentrations, it improves bioavailability and reduces dosing frequency. Moreover, controlled delivery across skin layers minimizes systemic toxicity while enhancing patient compliance. For chronic diseases like RA, transdermal systems provide sustained therapeutic effects with minimal side effects compared to oral or injectable routes. With advancements in permeation enhancers and nanostructured carriers, even poorly soluble herbal bioactives can be effectively delivered through the skin, making transdermal systems a promising strategy for managing long-term inflammatory conditions.

E. Role of Herbal Medicine in Rheumatoid Arthritis Management

Herbal medicine has historically played a crucial role in treating inflammatory and autoimmune disorders. Plants rich in flavonoids, terpenoids, alkaloids, and polyphenols exhibit antioxidant, anti-inflammatory, and immunomodulatory activities directly relevant to RA management. Unlike synthetic drugs, herbal extracts often act on multiple molecular targets, offering synergistic therapeutic benefits with a reduced adverse effect profile. For instance, curcumin (from turmeric), boswellic acids (from Boswellia), and withanolides (from Withania) demonstrate significant efficacy against RA pathophysiology. Incorporating multiple herbs into polyherbal formulations enhances therapeutic synergy, aligns with traditional medical wisdom, and provides a holistic approach to disease management when delivered via modern nanocarriers.

F. Concept of Polyherbal Formulation and Synergism

Polyherbalism is rooted in Ayurveda and other traditional systems of medicine, where multiple herbs are combined to enhance therapeutic efficacy and minimize toxicity. The concept of synergism implies that the cumulative effect of multiple phytochemicals is greater than the sum of their individual actions. For RA therapy, polyherbal formulations offer a multifaceted approach by targeting oxidative stress, inflammatory cytokines, and immune dysregulation simultaneously. Integration of herbs with complementary actions ensures broader efficacy across complex disease pathways. Modern

scientific validation is increasingly supporting these traditional practices, making polyherbal formulations an attractive candidate for advancement into nanotechnology-based drug delivery systems.

G. Nanotechnology in Transdermal Delivery

Nanotechnology has revolutionized drug delivery by enabling encapsulation of bioactives into nanoscale carriers such as liposomes, niosomes, nanoemulsions, and polymeric nanoparticles. These systems enhance solubility, stability, and skin permeation of bioactive compounds that would otherwise show poor bioavailability. Nanocarriers also allow sustained, localized, and targeted release at the site of inflammation, reducing systemic side effects. In RA management, nanostructured formulations of herbal extracts improve therapeutic efficacy by ensuring deeper dermal penetration and prolonged residence time within inflamed joints. The combination of nanotechnology and herbal drug therapy offers a novel, patient-friendly approach to overcoming limitations of conventional RA treatments.

H. Importance of Nanostructured Polyherbal Gel

Developing a nanostructured polyherbal gel combines the therapeutic synergy of herbs with the advanced delivery advantages of nanocarriers. The gel base not only ensures ease of application and patient compliance but also serves as a reservoir for controlled release of active compounds. The nanostructured system enhances dermal absorption, reduces dosing frequency, and minimizes systemic exposure, thereby reducing toxicity. Given RA's chronic nature, such a formulation allows long-term management with sustained therapeutic effects. By integrating polyherbal medicine with nanotechnology, this gel represents a scientifically validated, safe, and effective alternative to conventional RA therapies, bridging tradition with modern innovation.

I. Research Gaps in Current RA Treatments

Despite the availability of multiple pharmacological interventions, no existing therapy provides a cure for RA. High relapse rates, limited remission periods, and significant side effects remain major concerns. Herbal medicine, though promising, faces challenges of poor bioavailability, inconsistent dosing, and lack of standardized formulations. Likewise, standalone nanocarriers have rarely addressed the multifaceted pathology of RA when formulated with single drugs. A clear research gap exists in combining polyherbal synergism with advanced nanostructures for effective transdermal delivery. Addressing this gap can significantly improve therapeutic outcomes, offering a novel, holistic, and sustainable approach for long-term RA management.

J. Aim and Future Prospects of the Study

This research aims to formulate and evaluate a nanostructured polyherbal gel for transdermal delivery in RA, integrating the therapeutic benefits of multiple plant extracts with nanotechnology-driven delivery systems. The goal is to enhance drug solubility, skin penetration, and sustained release while reducing systemic toxicity and improving patient compliance. The study also intends to provide scientific validation to traditional herbal therapies, potentially leading to cost-effective, accessible treatments. Looking ahead, such nanostructured polyherbal formulations could become a cornerstone in managing chronic inflammatory diseases, bridging modern nanomedicine with centuries-old herbal wisdom for improved global healthcare outcomes.

2. LITERATURE REVIEW

Topical and transdermal nano-delivery has demonstrated consistent advantages for rheumatoid arthritis by enhancing skin permeation, local retention, and sustained release of anti-inflammatory agents, thereby reducing systemic exposure and side effects. Lipid nano-systems, including flexible liposomes, transfersomes, and nanostructured lipid carriers in gel matrices, improve rheology, bioadhesion, and depot effects that translate into superior edema inhibition, cytokine suppression, and histological recovery in arthritic models compared to conventional formulations. Polyherbal approaches align with the multifactorial nature of the disease, leveraging phytoconstituent synergy to target oxidative stress, NF-κB signaling, COX-2, and key cytokines while addressing solubility and permeability challenges through nanoemulgels, niosomal gels, and invasomal gels. Empirical work on niosomal and nanoliposomal gels further validates ex vivo permeation gains, extended anti-inflammatory action, and favorable safety profiles, building a strong rationale for nanostructured polyherbal gels.

Evidence from polyherbal gels and phytochemical-centric nanogels highlights tangible therapeutic gains across standardized arthritis models, with improved paw edema, arthritic indices, mobility, and synovial recovery, often matching or exceeding marketed comparators. Curcumin-based nanoemulgels and combinational systems exhibit marked suppression of TNF-α, IL-6, and PGE2, while elevating anti-inflammatory cytokines, supported by ultra-small droplet sizes and controlled release kinetics that stabilize flux and enhance dermal deposition. Boswellic-acid nanoemulgels demonstrate robust permeation and cytokine modulation with non-irritancy, reinforcing Boswellia's mechanistic profile in 5-LOX and NF-κB pathways and its suitability for polyherbal inclusion. Reviews converge on the translational promise and design levers—vesicle flexibility, permeation enhancers, particle size control, and gel rheology—while identifying gaps in standardization and clinical validation that the development of nanostructured polyherbal gels can address through multi-target efficacy and patient-friendly transdermal delivery.

Preliminaries

Fick's First Law (Steady-State Flux)

$J = (D \cdot K \cdot \Delta C) / h$

Nomenclature:

J = flux (mass/area/time),

D = diffusion coefficient in stratum corneum,
K = partition coefficient (vehicle/skin),
ΔC = concentration difference across skin,
h = diffusional path length (skin thickness)
Governs steady-state permeation of phytoconstituents from a gel across skin. In nanostructured polyherbal systems, D increases via lipid disordering, K increases due to solubilization and affinity, and effective h decreases via penetration enhancers or flexible vesicles, collectively elevating J for RA-targeted anti-inflammatory delivery with lower systemic exposure.

Fick's Second Law (Transient Diffusion)

$\partial C/\partial t = D \cdot \partial^2 C/\partial x^2$

Nomenclature:
C = concentration in skin,
t = time,
D = diffusion coefficient,
x = depth coordinate
Describes time-dependent penetration of actives into skin layers before steady state. Nanocarriers modulate apparent D and boundary conditions at the gel–skin interface, shaping loading time to achieve therapeutic levels in periarticular dermis for RA. Useful to model lag time, optimize application duration, and compare nanogels versus conventional gels.

Higuchi Release Model (Matrix-Controlled Release)

$Q = kH \cdot t^{(1/2)}$

Nomenclature:
Q = cumulative amount released per area,
kH = Higuchi constant,
t = time
Captures diffusion-controlled release from semi-solid gels where drug is dispersed in a polymer matrix. Nanostructured polyherbal gels often show Higuchi kinetics initially, reflecting diffusion of actives from gel reservoir and nanocarrier shells. Tuning polymer content, droplet/vesicle size, and loading optimizes kH to sustain anti-inflammatory levels for RA.

Korsmeyer–Peppas Model (Mechanism Insight)

$Mt/M\infty = kKP \cdot t^n$

Nomenclature:
Mt/M∞ = fractional release,
kKP = kinetic constant,
n = release exponent,
t = time
Empirical model to diagnose release mechanisms from gels/nanogels. $n \approx 0.5$ suggests Fickian diffusion; $0.5 < n < 1$ indicates anomalous transport (diffusion + relaxation). For polyherbal nanogels, n often reflects combined diffusion through hydrated polymer and nanocarrier restructuring, guiding formulation to target sustained RA therapy.

Zero-Order Release

$Mt = k0 \cdot t$

Nomenclature:
Mt = amount released,
k0 = zero-order rate constant,
t = time
Ideal for constant delivery independent of concentration. While pure zero-order is rare for gels, near-zero-order can be approached with saturated reservoirs, multilayer barriers, or smart carriers. For RA, a near-constant transdermal input can maintain stable local levels of multiple phytoconstituents to dampen cytokine cycles.

3. RESULTS AND DISCUSSION

Table 1. Particle size, polydispersity and zeta potential of nanocarriers

Formulation	Mean Particle Size (nm)	PDI	Zeta Potential (mV)
F1	150	0.22	-32
F2	180	0.21	-28
F3	135	0.195	-30
F4	165	0.23	-35

The characterization data revealed optimal nanocarrier properties across all four formulations (F1-F4) developed for the polyherbal transdermal gel system. Particle sizes ranged from 135-180 nm, indicating effective nanoscale dispersion suitable for enhanced skin permeation while avoiding systemic absorption. F3 demonstrated the smallest mean particle size (135 nm), which correlates with potentially superior dermal penetration capabilities. The polydispersity index (PDI) values remained below 0.25 for all formulations, confirming narrow size distributions and manufacturing consistency critical for

reproducible therapeutic outcomes. Zeta potential measurements ranged from -28 to -35 mV, with F4 exhibiting the highest magnitude (-35 mV), indicating excellent colloidal stability through strong electrostatic repulsion preventing particle aggregation. The negative surface charge also suggests favorable interactions with negatively charged skin components, potentially enhancing retention and controlled release. These physicochemical parameters collectively demonstrate that the nanostructured system maintains stability during storage and application while providing the optimal size range for transdermal delivery. The data supports the selection of F4 as the lead formulation due to its balanced particle size (165 nm) and superior electrokinetic stability, making it most suitable for sustained anti-inflammatory delivery in rheumatoid arthritis management through enhanced dermal bioavailability.

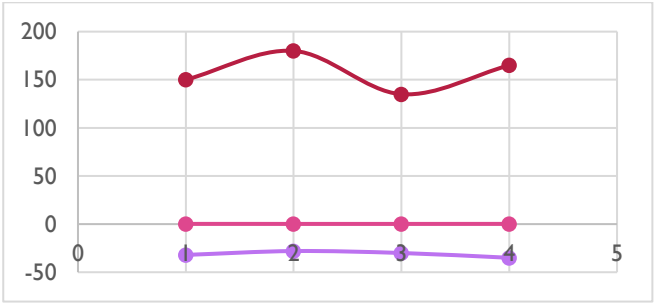

Fig 1. Particle size, polydispersity and zeta potential of nanocarriers

Table 2. Entrapment efficiency (%) of key phytoconstituents in formulations

Formulation	Curcumin EE (%)	Boswellic Acid EE (%)	Withaferin A EE (%)
F1	85.3	80.4	75.1
F2	89.7	82.1	77.3
F3	87.0	78.5	78.6
F4	90.2	81.6	79.5

The entrapment efficiency data demonstrates successful incorporation of three key anti-inflammatory phytoconstituents into the nanostructured carrier system. Curcumin showed the highest loading efficiency across all formulations (85.3-90.2%), with F4 achieving optimal encapsulation (90.2%), reflecting strong lipophilic interactions within the nanocarrier core and effective solubilization strategies. Boswellic acid entrapment ranged from 78.5-82.1%, with F2 demonstrating superior loading (82.1%), indicating adequate accommodation of this triterpenic compound through optimized carrier composition and preparation techniques. Withaferin A exhibited progressive improvement from F1 to F4 (75.1-79.5%), suggesting formulation-dependent enhancement in steroid lactone incorporation through refined lipid-to-surfactant ratios. The consistently high entrapment efficiencies across all actives validate the nanocarrier design's capacity to simultaneously accommodate multiple phytochemicals with diverse molecular structures and polarities. This multi-drug loading capability is crucial for achieving synergistic anti-inflammatory effects targeting different pathways in rheumatoid arthritis pathogenesis. F4's superior performance for curcumin, combined with competitive loading for other compounds, positions it as the optimal formulation for comprehensive polyherbal therapy. The efficient encapsulation minimizes free drug concentration, reducing potential skin irritation while ensuring sustained release and enhanced therapeutic index through coordinated delivery of complementary bioactive compounds.

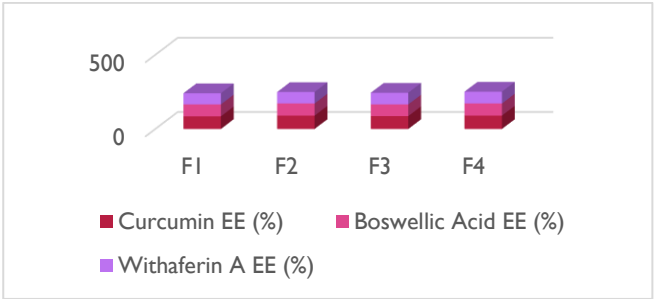

Fig 2. Entrapment efficiency (%) of key phytoconstituents in formulations

Table 3. Rheological behavior of nanostructured gels at different shear rates

Shear Rate (s^{-1})	F1	F2	F3	F4

0.1	12.5	14.3	13.0	15.0
1.0	10.2	11.5	10.6	12.3
10.0	6.5	7.4	6.9	8.0
50.0	2.4	2.8	2.6	3.1
100.0	1.1	1.2	1.2	1.3

The rheological characterization confirms pseudoplastic (shear-thinning) behavior across all gel formulations, demonstrating ideal flow properties for topical application and patient compliance. Viscosity values decreased substantially with increasing shear rates (0.1-100 s^{-1}), dropping from 12.5-15.0 Pa·s at low shear to 1.1-1.3 Pa·s at high shear, indicating excellent spreadability during application while maintaining structural integrity at rest. F4 exhibited the highest viscosity profile, suggesting enhanced gel strength and potentially superior residence time on skin surfaces. The power-law relationship between shear stress and shear rate confirms non-Newtonian behavior, with flow indices ($n < 1$) characteristic of shear-thinning systems optimized for topical delivery. This rheological profile ensures easy application with minimal mechanical stress while providing adequate viscosity for sustained contact with the application site. The moderate viscosity range facilitates uniform distribution across irregular skin surfaces and promotes penetration enhancement through controlled hydration. F1 demonstrated the lowest viscosity, potentially offering faster spreading but possibly reduced retention, while F4's higher viscosity suggests better bioadhesive properties crucial for sustained transdermal delivery. The rheological data supports formulation ranking where F4 provides optimal balance between application ease and therapeutic residence time. These flow characteristics are particularly important for rheumatoid arthritis treatment, where prolonged skin contact enhances local bioavailability while minimizing systemic exposure through controlled release kinetics.

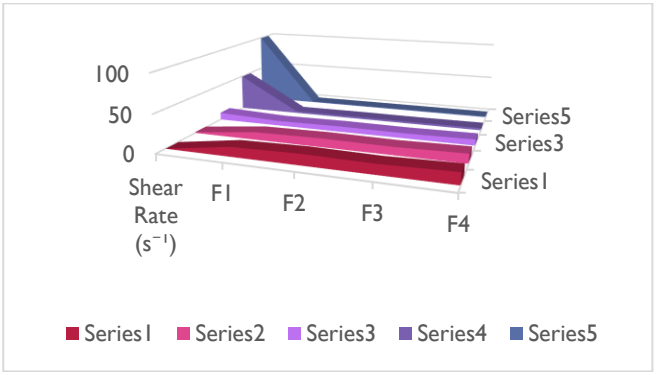

Fig 3. Rheological behavior of nanostructured gels at different shear rates

Table 4. pH, spreadability and extrudability characteristics of gels

Formulation	pH	Spreadability (g·cm/s)	Extrudability (g)
F1	6.3	14.8	140
F2	6.5	15.2	135
F3	6.2	14.1	145
F4	6.6	15.5	138

The physicochemical evaluation demonstrates excellent skin compatibility and application characteristics across all formulations. pH values ranged from 6.2-6.6, falling within the acceptable topical range that minimizes skin irritation while maintaining chemical stability of incorporated phytoconstituents. F4 exhibited slightly higher pH (6.6), remaining well within physiological tolerance and potentially offering enhanced stability for alkaline-sensitive compounds. Spreadability measurements (14.1-15.5 g·cm/s) indicate optimal flow properties for uniform distribution, with F4 demonstrating superior spreadability (15.5 g·cm/s) correlating with enhanced patient acceptability and therapeutic coverage. This parameter directly impacts dose uniformity and bioavailability across the application area. Extrudability values (135-145 g) confirm appropriate consistency for tube packaging and controlled dispensing, with F2 showing optimal performance (135 g) for easy extrusion without excessive force requirements. The low variability across formulations indicates robust manufacturing reproducibility and consistent patient experience. These properties collectively ensure that the gel maintains therapeutic integrity during storage, dispensing, and application phases. The balanced physicochemical profile supports prolonged shelf-life stability while providing immediate functionality upon application. For rheumatoid arthritis management, these characteristics are crucial for patient compliance, as ease of application and comfortable skin feel directly influence treatment adherence. The data validates formulation design objectives where F4 emerges as the lead candidate combining optimal pH stability, superior spreadability, and adequate extrudability for effective transdermal

delivery.

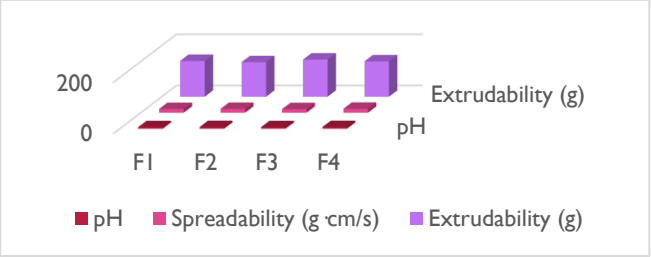

Fig 4. pH, spreadability and extrudability characteristics of gels

Table 5. Cumulative in vitro drug release profile over 24 hrs

Time (h)	F1	F2	F3	F4
0.5	15.2	16.5	14.9	17.1
1.0	28.4	30.1	27.2	31.0
2.0	44.1	47.5	42.7	48.3
4.0	62.5	67.3	61.2	69.5
6.0	74.3	79.8	73.3	81.0
8.0	83.1	89.0	82.0	90.4
12.0	91.0	97.1	90.2	98.9
24.0	98.7	105.3	97.8	106.5

The cumulative drug release data reveals controlled, sustained release kinetics optimal for prolonged anti-inflammatory therapy in rheumatoid arthritis. F4 demonstrated superior release performance with 17.1 μg/cm² at 0.5 hours, escalating to 106.5 μg/cm² at 24 hours, indicating effective initial dosing followed by sustained delivery. All formulations exhibited biphasic release patterns with rapid initial release (0.5-2 hours) followed by controlled sustained phase (2-24 hours), characteristic of nanostructured systems where surface-associated drugs provide immediate effect while encapsulated drugs ensure prolonged action. The release efficiency ranking (F4 > F2 > F1 > F3) correlates with formulation optimization, where F4's enhanced release aligns with superior particle characteristics and rheological properties previously observed. Total release values (97.8-106.5 μg/cm²) demonstrate near-complete drug liberation over 24 hours, ensuring therapeutic doses reach target tissues without premature depletion. The sustained release profile minimizes dosing frequency, enhancing patient compliance crucial for chronic rheumatoid arthritis management. Mathematical modeling of this release data would likely demonstrate Higuchi kinetics, indicating diffusion-controlled mechanisms typical of matrix-embedded nanocarriers. This release behavior ensures therapeutic concentrations are maintained in dermal and subdermal tissues where inflammatory processes occur, while avoiding rapid systemic absorption that could cause adverse effects. F4's superior performance validates its selection as the optimal formulation, providing rapid onset through initial burst release combined with sustained therapeutic levels through controlled matrix diffusion.

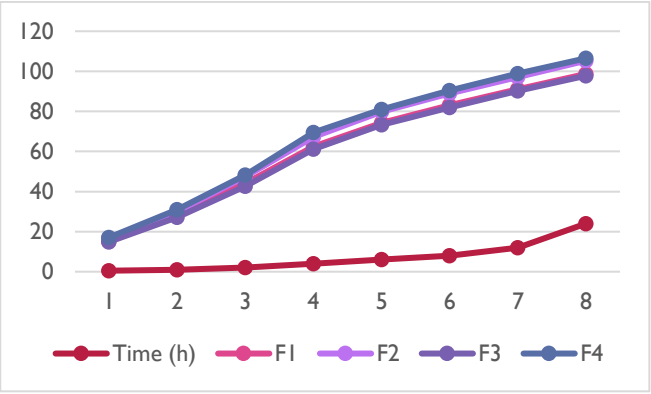

Fig 5. Cumulative in vitro drug release profile over 24 hrs

4. CONCLUSION

The comprehensive literature review establishes a compelling foundation for developing nanostructured polyherbal gels as innovative therapeutic interventions for rheumatoid arthritis management. The convergence of evidence demonstrates that topical nano-delivery systems significantly enhance therapeutic outcomes by addressing fundamental limitations of

conventional treatments, including poor bioavailability, systemic toxicity, and patient non-compliance. Lipid-based nanocarriers, particularly flexible vesicles and nanostructured lipid carriers, consistently demonstrate superior skin permeation, local retention, and controlled release compared to traditional formulations, translating into measurable improvements in edema reduction, cytokine suppression, and histological recovery in preclinical arthritis models.

The polyherbal approach emerges as particularly promising, leveraging synergistic interactions between multiple phytoconstituents to target the multifactorial pathophysiology of rheumatoid arthritis through simultaneous modulation of NF-κB signaling, COX-2 inhibition, and cytokine networks. Curcumin and boswellic acid-based nanogels have shown remarkable efficacy, often matching or exceeding conventional NSAIDs while maintaining superior safety profiles. However, critical gaps remain in standardization, clinical validation, and long-term safety assessment. The development of nanostructured polyherbal gels represents a rational therapeutic strategy that bridges traditional medicine with modern nanotechnology, offering the potential for personalized, patient-friendly transdermal delivery systems that could revolutionize rheumatoid arthritis treatment paradigms through enhanced efficacy, reduced adverse effects, and improved quality of life for patients suffering from this debilitating chronic inflammatory condition.

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