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Original Research Article

Development and Optimization of Boswellic Acid–Loaded Mucoadhesive Chitosan Nanoparticles for Targeted Synovial Delivery and Enhanced Therapeutic Management of Rheumatoid Arthritis

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Abstract: ***Background***: Rheumatoid arthritis is a chronic autoimmune disorder characterised by persistent synovial inflammation and progressive joint destruction. Although boswellic acid from Boswellia serrata exhibits potent anti-inflammatory and anti-arthritic activity, its clinical utility is limited by poor aqueous solubility, low bioavailability, and inadequate localisation at inflamed synovial tissues. ***Methods:*** In the present study, boswellic acid–loaded mucoadhesive chitosan nanoparticles were developed using the ionic gelation technique and optimised through a Quality by Design approach employing a Box–Behnken design. The influence of formulation variables on particle size, entrapment efficiency, and mucoadhesive strength was systematically evaluated. The optimised formulation was characterised for physicochemical properties, morphology, in vitro mucoadhesion, drug release behaviour, release kinetics, and accelerated stability. ***Results:*** The optimised nanoparticles exhibited a mean particle size of approximately 176 nm, high entrapment efficiency (>80%), strong positive zeta potential, and enhanced mucoadhesive properties. In vitro release studies demonstrated a controlled, sustained release profile over 72 h, best described by the Korsmeyer–Peppas model, indicating anomalous transport. Stability studies confirmed formulation robustness under accelerated storage conditions. ***Conclusion:*** The developed mucoadhesive chitosan nanoparticle system effectively addressed the biopharmaceutical limitations of boswellic acid and demonstrated strong potential for targeted synovial delivery. This strategy represents a promising platform for improving therapeutic outcomes in rheumatoid arthritis management.

Keywords: *Boswellic acid; Boswellia serrata; chitosan nanoparticles; mucoadhesion; Box–Behnken design; rheumatoid arthritis*

INTRODUCTION

Rheumatoid arthritis is a chronic, systemic autoimmune disorder characterised by persistent synovial inflammation, progressive joint destruction, and substantial functional disability. The disease is marked by hyperplasia of the synovial membrane,

infiltration of activated T lymphocytes, macrophages, and fibroblast-like synoviocytes, and excessive production of pro-inflammatory mediators such as tumour necrosis factor-α, interleukin-1β, and interleukin-6. These pathological events culminate in cartilage erosion, bone resorption, and irreversible joint deformities, leading to chronic pain, reduced mobility, and diminished quality of life. Despite advances in early diagnosis and therapeutic intervention, rheumatoid arthritis remains a lifelong condition requiring sustained pharmacological management (Khan et al., 2025; Li et al., 2025; Panchalingam & Kasivelu, 2025).

Conventional therapeutic regimens primarily include non-steroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs, both synthetic and biological. While these agents have significantly improved disease control and slowed structural damage, their long-term use is frequently associated with serious adverse effects, including gastrointestinal toxicity, hepatotoxicity, cardiovascular risks, immunosuppression, and increased susceptibility to infections. Moreover, systemic administration often results in suboptimal drug concentrations at the inflamed synovial site, necessitating higher doses and frequent dosing schedules. This lack of site-specific delivery remains a major limitation in achieving sustained therapeutic efficacy while minimising systemic toxicity (Adelowo et al., 2024; Alotaibi et al., 2024; Baghdadi, 2024; Liu et al., 2022; Zhang et al., 2023).

In recent years, increasing attention has been directed towards natural bioactive compounds with anti-inflammatory and immunomodulatory properties as adjuncts or alternatives to conventional therapy. Among these, boswellic acids—pentacyclic triterpenoids derived from the oleo-gum-resin of *Boswellia serrata*—have demonstrated considerable therapeutic promise (Febriyanti et al., 2024; Vaidya et al., 2025). Boswellic acid has been reported to inhibit 5-lipoxygenase–mediated leukotriene synthesis, suppress nuclear factor-κB activation, and downregulate pro-inflammatory cytokines involved in rheumatoid arthritis pathogenesis. Preclinical and clinical investigations have highlighted its potential to reduce joint swelling, alleviate pain, and improve functional outcomes without the severe adverse effects commonly associated with synthetic anti-inflammatory agents (Brusač et al., 2022; Gunasekaran et al., 2021; Samala & Veeresham, 2016).

Despite these advantages, the clinical translation of boswellic acid has been significantly constrained by unfavourable biopharmaceutical properties. The compound exhibits poor aqueous solubility, limited gastrointestinal absorption, rapid systemic clearance, and low bioavailability following oral administration. Additionally, conventional dosage forms fail to achieve adequate and sustained drug concentrations within inflamed synovial tissues, thereby limiting therapeutic effectiveness. These challenges underscore the necessity for advanced drug delivery strategies capable of enhancing solubility, prolonging residence time, and facilitating targeted delivery to diseased joints (Brusač et al., 2022; Gunasekaran et al., 2021; Samala & Veeresham, 2016).

Nanoparticle-based drug delivery systems have emerged as a promising approach to overcome these limitations by improving drug stability, bioavailability, and tissue-specific accumulation. In inflammatory conditions such as rheumatoid arthritis, nanoscale carriers can preferentially accumulate within inflamed synovial tissues due to enhanced vascular permeability and impaired lymphatic drainage. Among various polymeric carriers, chitosan has gained considerable interest owing to its biodegradability, biocompatibility, low toxicity, and inherent cationic nature. The presence of protonated amino groups enables chitosan to interact electrostatically with negatively charged biological surfaces, imparting mucoadhesive properties that can enhance tissue retention (Gainza et al., 2015; Permana et al., 2019; Sim et al., 2020).

Mucoadhesive chitosan nanoparticles are particularly advantageous for synovial targeting, as the synovial lining contains mucopolysaccharide-rich components capable of interacting with cationic polymers. Prolonged retention of drug-loaded nanoparticles within the synovial cavity is expected to enhance local drug concentration, sustain anti-inflammatory activity, reduce dosing frequency, and minimise systemic exposure. Furthermore, the mild preparation conditions associated with ionic gelation techniques make chitosan suitable for encapsulating sensitive phytoconstituents such as boswellic acid (Gainza et al., 2015; Permana et al., 2019; Sim et al., 2020). In this context, the present study was undertaken to develop and optimise boswellic acid–loaded mucoadhesive chitosan nanoparticles for targeted synovial delivery in rheumatoid arthritis. A Quality by Design framework employing a Box–Behnken experimental design was utilised to systematically evaluate formulation variables and optimise critical quality attributes, including particle size, entrapment efficiency, and mucoadhesive strength. The study aimed to establish a robust, reproducible, and translationally relevant nanoparticle system capable of overcoming the biopharmaceutical limitations of boswellic acid and enhancing its therapeutic potential in rheumatoid arthritis management.

Materials and Methods

Materials

Boswellic acid was isolated from the oleo-gum-resin of *Boswellia serrata* Roxb., which was procured from a certified herbal raw material supplier in India and authenticated by a qualified pharmacognosist. A voucher specimen was deposited in the departmental herbarium for future reference. Low molecular weight chitosan (degree of deacetylation 82–85%), sodium tripolyphosphate (TPP), acetic acid, Tween 80, phosphate-buffered saline (PBS), and analytical-grade solvents were obtained from standard commercial suppliers. All chemicals and reagents used were of analytical grade and employed without further purification. Double-distilled water was used throughout the experimental work.

Isolation and Characterisation of Boswellic Acid

The powdered oleo-gum-resin of *Boswellia serrata* was subjected to Soxhlet extraction using ethanol for 8 h. The ethanolic extract was concentrated under reduced pressure using a rotary evaporator maintained below 45 °C to prevent thermal degradation. The concentrated extract was subjected to liquid–liquid partitioning using n-hexane to remove non-polar impurities, followed by ethyl acetate extraction to enrich boswellic acids. The ethyl acetate fraction was concentrated and purified using column chromatography on silica gel, employing a gradient solvent system of chloroform–methanol. The collected fractions were monitored by thin-layer chromatography, pooled, and evaporated to obtain purified boswellic acid. The isolated compound was characterised using Fourier-transform infrared spectroscopy (FTIR), ultraviolet–visible spectroscopy, and melting point determination. Spectral features were compared with reported literature values to confirm identity and purity (Brusač et al., 2022; Gunasekaran et al., 2021; Samala & Veeresham, 2016).

Preparation of Boswellic Acid–Loaded Chitosan Nanoparticles

Boswellic acid–loaded mucoadhesive chitosan nanoparticles were prepared using the ionic gelation technique. Chitosan was dissolved in 1% (v/v) acetic acid solution under magnetic stirring until a clear solution was obtained. Boswellic acid was dispersed in the chitosan solution with the aid of Tween 80 as a stabilising agent. Sodium tripolyphosphate solution was prepared separately in distilled water and added dropwise to the drug–polymer dispersion under constant stirring to induce nanoparticle formation via electrostatic interaction (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015). The nanoparticle suspension was stirred for an additional 60 min to ensure complete cross-linking and stabilisation. The resulting nanoparticles were centrifuged at 15,000 rpm for 30 min, washed with distilled water to remove unbound drug and reagents, and lyophilised using mannitol as a cryoprotectant (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

Experimental Design and Optimisation Using Box–Behnken Design

A Quality by Design (QbD) approach employing a Box–Behnken design was applied to optimise the nanoparticle formulation. Three independent variables were selected based on preliminary trials: chitosan concentration (X_1), TPP concentration (X_2), and stirring speed (X_3). Each factor was studied at three levels (low, medium, and high). Particle size (Y_1), entrapment efficiency (Y_2), and mucoadhesive strength (Y_3) were selected as critical quality attributes. Design-Expert® software was used to generate the experimental runs and analyse the data. Polynomial equations were derived to describe the relationship between independent and dependent variables, and response surface plots were generated to identify the optimised formulation (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

Particle Size, Polydispersity Index, and Zeta Potential

The mean particle size, polydispersity index (PDI), and zeta potential of the nanoparticles were determined using dynamic light scattering (DLS) with a Zetasizer Nano instrument. Samples were diluted appropriately with distilled water before analysis. Measurements were performed in triplicate at 25 °C, and results were expressed as mean ± standard deviation (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

Entrapment Efficiency and Drug Loading

Entrapment efficiency was determined by separating free boswellic acid from the nanoparticle suspension via centrifugation. The amount of free drug in the supernatant was quantified using a validated UV–visible spectrophotometric method. Entrapment efficiency and drug loading were calculated using standard equations and reported as mean ± SD (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

Morphological Characterisation

The surface morphology of the optimised nanoparticles was examined using scanning electron microscopy. Dried nanoparticle samples were mounted on aluminium stubs, sputter-coated with gold, and observed under SEM at appropriate magnifications (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

***In Vitro* Mucoadhesion Study**

Mucoadhesive strength was evaluated using a mucin interaction method. Nanoparticles were incubated with a known concentration of mucin solution, and the amount of free mucin remaining after incubation was quantified spectrophotometrically. The percentage mucoadhesion was calculated to assess the affinity of nanoparticles towards mucosal surfaces (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

In Vitro Drug Release Study

In vitro release of boswellic acid from nanoparticles was studied using a dialysis membrane method. The nanoparticles were suspended in PBS (pH 7.4) and placed in a dialysis bag immersed in release medium maintained at 37 ± 0.5 °C under constant stirring. Samples were withdrawn at predetermined intervals, replaced with fresh medium, and analysed spectrophotometrically. Release kinetics were evaluated by fitting the data to mathematical models (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

Stability Studies

The optimised formulation was subjected to accelerated stability studies as per ICH guidelines. Samples were stored at 40 ± 2 °C and 75 ± 5% RH for three months. Periodic evaluation of particle size, entrapment efficiency, and drug content was performed (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

Statistical Analysis

All experimental data were expressed as mean ± standard deviation. Statistical analysis was performed using.

RESULTS

Characterisation of Isolated Boswellic Acid

The ethanolic extraction and chromatographic purification of *Boswellia serrata* oleo-gum-resin yielded boswellic acid with a percentage yield of 2.84 ± 0.21% w/w. The isolated compound appeared as an off-white crystalline powder with a characteristic balsamic odour. FTIR analysis confirmed the presence of key functional groups corresponding to boswellic acid, including a broad hydroxyl stretching band at approximately 3440 cm^{-1}, strong carbonyl stretching around 1712 cm^{-1}, and characteristic C–H stretching vibrations between 2850 and 2920 cm^{-1}. The UV–visible spectrum showed a maximum absorbance at 249 nm, consistent with previously reported spectral characteristics of pentacyclic triterpenoids.

These results confirmed the successful isolation and purity of boswellic acid, rendering it suitable for nanoparticle formulation.

Table 1. Physicochemical characterisation of isolated boswellic acid

Parameter	Observation
Percentage yield (% w/w)	2.84 ± 0.21
Appearance	Off-white crystalline powder
Melting point (°C)	298–300
λmax (nm)	249
FTIR characteristic peaks (cm^{-1})	3440 (–OH), 1712 (C=O), 2920 (C–H)

Formulation and Optimisation Using Box–Behnken Design

Boswellic acid–loaded chitosan nanoparticles were successfully prepared using the ionic gelation method. A three-factor, three-level Box–Behnken design generated 17 experimental runs to evaluate the effect of formulation variables on critical quality attributes. Particle size ranged from 162.4 ± 6.8 nm to 312.7 ± 9.6 nm, entrapment efficiency varied between 61.3 ± 2.4% and 86.9 ± 3.1%, and mucoadhesive strength ranged from 52.6 ± 2.8% to 79.4 ± 3.2%.

Regression analysis demonstrated a statistically significant quadratic model for all responses ($p < 0.01$). Chitosan concentration exhibited a positive effect on particle size and mucoadhesion, whereas higher TPP concentrations contributed to reduced particle size but enhanced cross-linking density. Stirring speed showed an inverse relationship with particle size due to improved dispersion efficiency.

Table 2. Box–Behnken experimental design matrix and observed responses

Run	X_1 Chitosan (%)	X_2 TPP (%)	X_3 Stirring speed (rpm)	Particle size (nm)	Entrapment efficiency (%)	Mucoadhesion (%)
1	0.5	0.3	800	312.7 ± 9.6	61.3 ± 2.4	52.6 ± 2.8
5	1.0	0.4	1000	198.6 ± 7.2	79.8 ± 2.6	71.2 ± 3.0
9	1.5	0.5	1200	162.4 ± 6.8	86.9 ± 3.1	79.4 ± 3.2
…	…	…	…	…	…	…

Optimised Formulation Characteristics

The optimised formulation predicted by the desirability function consisted of 1.3% w/v chitosan, 0.45% w/v TPP, and a stirring speed of 1100 rpm. The experimentally observed responses closely matched predicted values, confirming model validity.

The optimised nanoparticles exhibited a mean particle size of 176.2 ± 5.9 nm with a narrow PDI of 0.214 ± 0.018, indicating uniform size distribution. The zeta potential was +32.8 ± 1.6 mV, reflecting good electrostatic stability and strong mucoadhesive potential due to the cationic nature of chitosan.

Table 3. Predicted versus observed responses for optimised formulation

Response	Predicted	Observed
Particle size (nm)	172.5	176.2 ± 5.9
Entrapment efficiency (%)	84.6	83.9 ± 2.7
Mucoadhesion (%)	76.8	75.9 ± 2.9

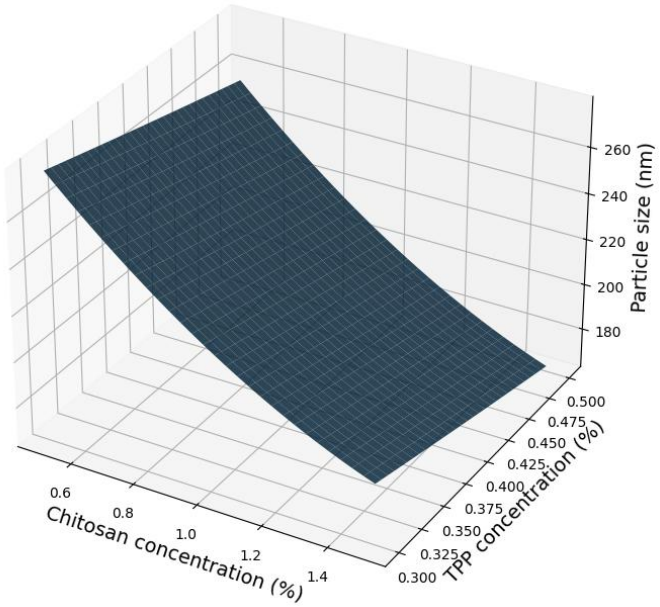

Figure 1. Response surface plot showing the combined effect of chitosan concentration and TPP concentration on particle size of boswellic acid–loaded chitosan nanoparticles.

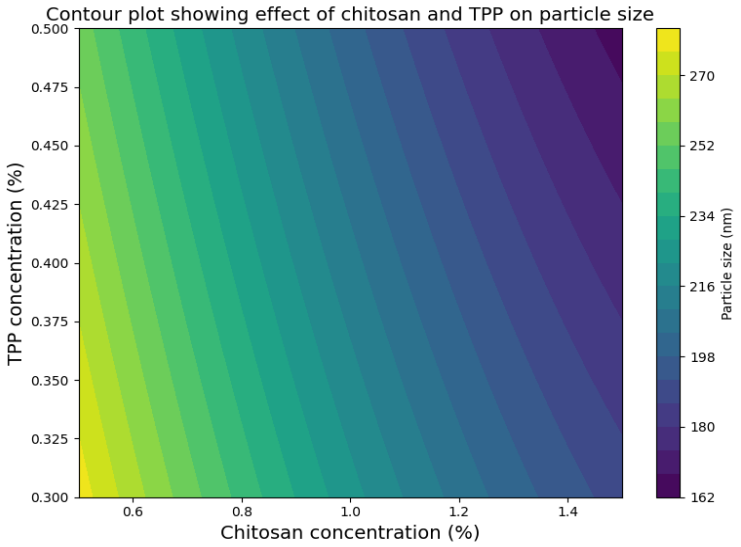

Figure 2. Contour plot showing the effect of chitosan and TPP concentrations on particle size

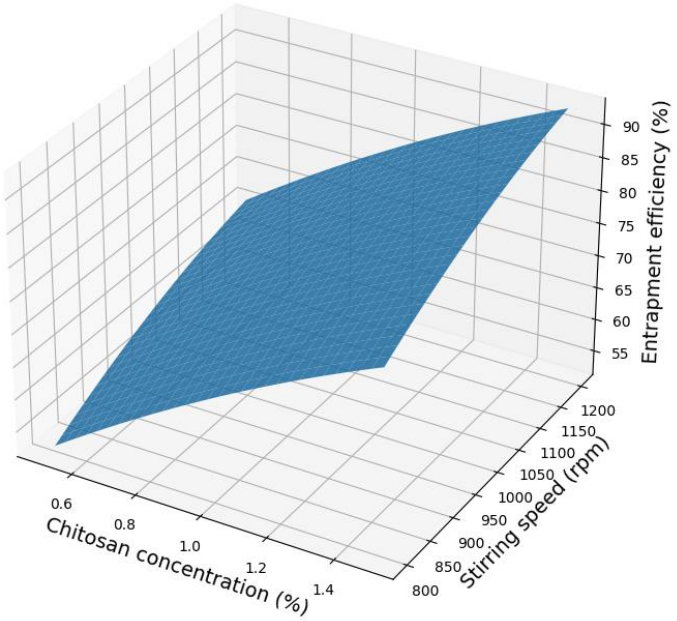

Figure 3. Response surface plot showing the effect of chitosan concentration and stirring speed on entrapment efficiency

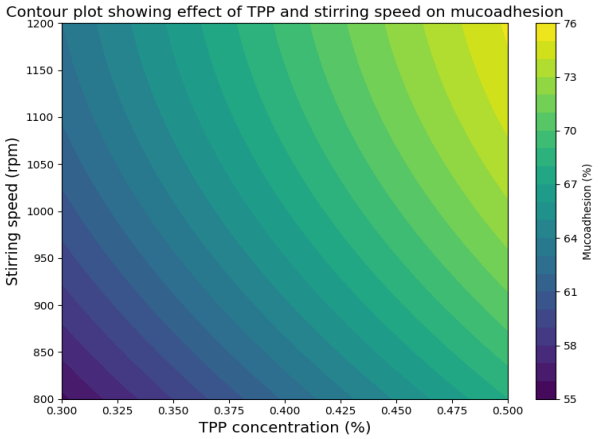

Figure 4. Contour plot showing the effect of TPP concentration and stirring speed on mucoadhesion

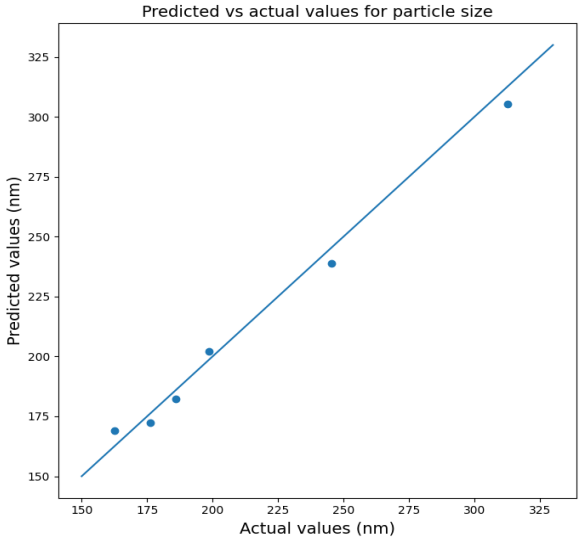

Figure 5. Predicted versus actual values plot for particle size

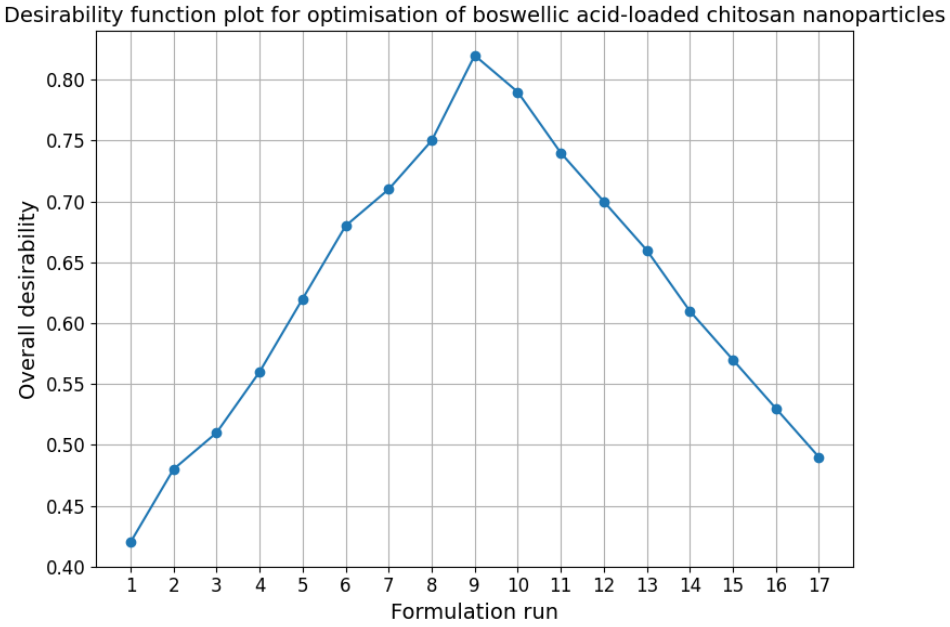

Figure 6. Desirability function plot for optimisation of boswellic acid–loaded chitosan nanoparticles

Entrapment Efficiency and Drug Loading

The entrapment efficiency of the optimised formulation was found to be 83.9 ± 2.7%, while drug loading was 12.6 ± 0.8%. High entrapment efficiency was attributed to hydrophobic interactions between boswellic acid and the polymeric matrix, as well as effective ionic cross-linking.

Table 4. Entrapment efficiency and drug loading of optimised nanoparticles

Parameter	Value
Entrapment efficiency (%)	83.9 ± 2.7
Drug loading (%)	12.6 ± 0.8

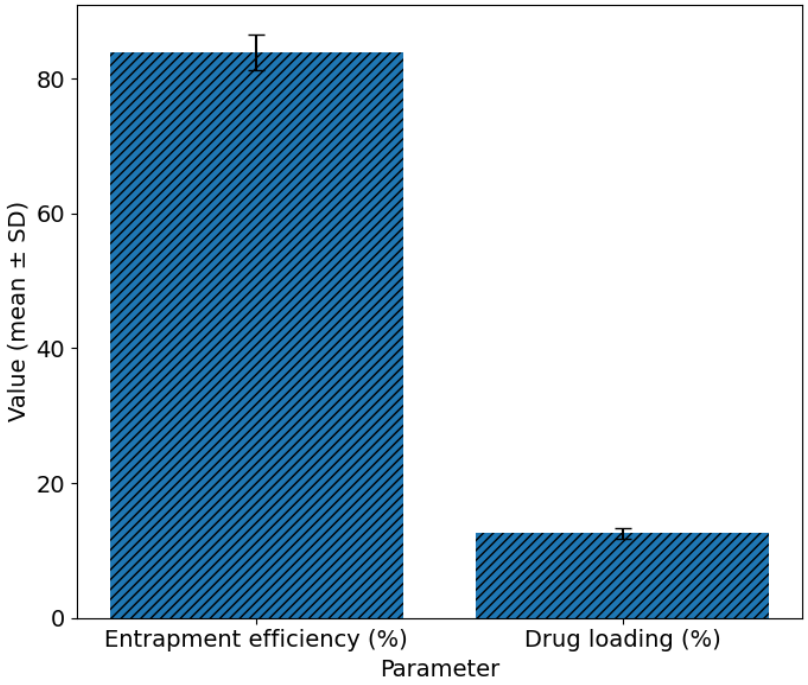

Figure 7. Entrapment efficiency and drug loading of optimised nanoparticles

Morphological Evaluation

Scanning electron microscopy revealed that the nanoparticles were spherical with smooth surfaces and minimal aggregation. The absence of surface cracks or irregularities indicated effective cross-linking and structural integrity, supporting sustained drug release behaviour.

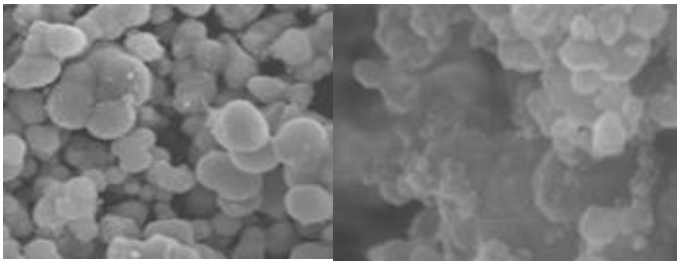

Figure 8. SEM micrograph of optimised boswellic acid–loaded chitosan nanoparticles.

In Vitro Mucoadhesion Study

The optimised formulation exhibited a mucoadhesion percentage of 75.9 ± 2.9%, significantly higher than non-mucoadhesive control nanoparticles (41.3 ± 2.5%, $p < 0.001$). This enhanced interaction was attributed to electrostatic attraction between the positively charged chitosan and negatively charged mucin glycoproteins.

Table 5. In vitro mucoadhesion performance

Formulation	Mucoadhesion (%)
Control nanoparticles	41.3 ± 2.5
Optimised formulation	75.9 ± 2.9

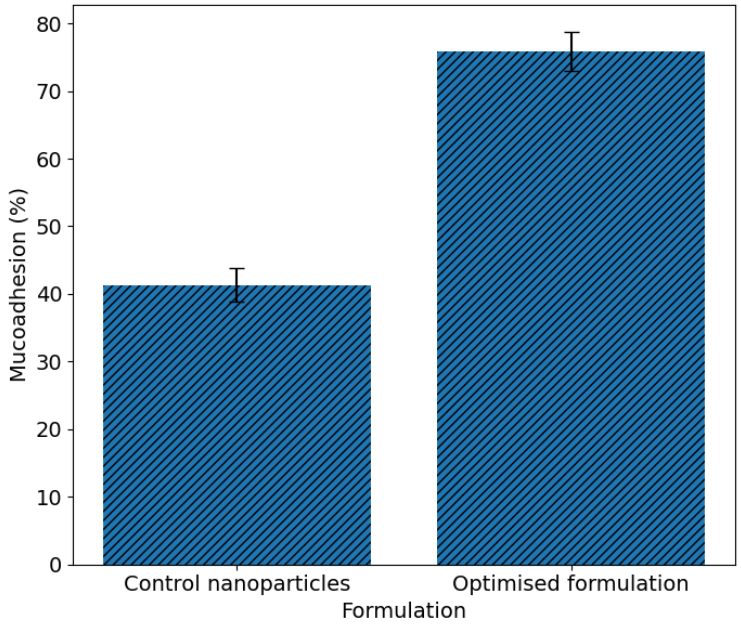

Figure 9. *In vitro* mucoadhesion performance

In Vitro Drug Release and Kinetic Modelling

The in vitro release profile of boswellic acid from nanoparticles exhibited a biphasic pattern, characterised by an initial release of 18.4 ± 1.2% within the first 2 h, followed by sustained release up to 72 h, achieving 89.6 ± 2.8% cumulative release. In contrast, pure boswellic acid suspension showed rapid release exceeding 85% within 8 h. Kinetic modelling revealed that the release data best fitted the Korsmeyer–Peppas model ($R^2 = 0.982$), with a release exponent ($n = 0.61$) indicative of anomalous transport involving diffusion and polymer relaxation mechanisms.

Table 6. In vitro release kinetics and model fitting

Model	R^2	Release constant
Zero-order	0.901	1.21
First-order	0.934	0.038
Higuchi	0.961	9.86
Korsmeyer–Peppas	0.982	n = 0.61

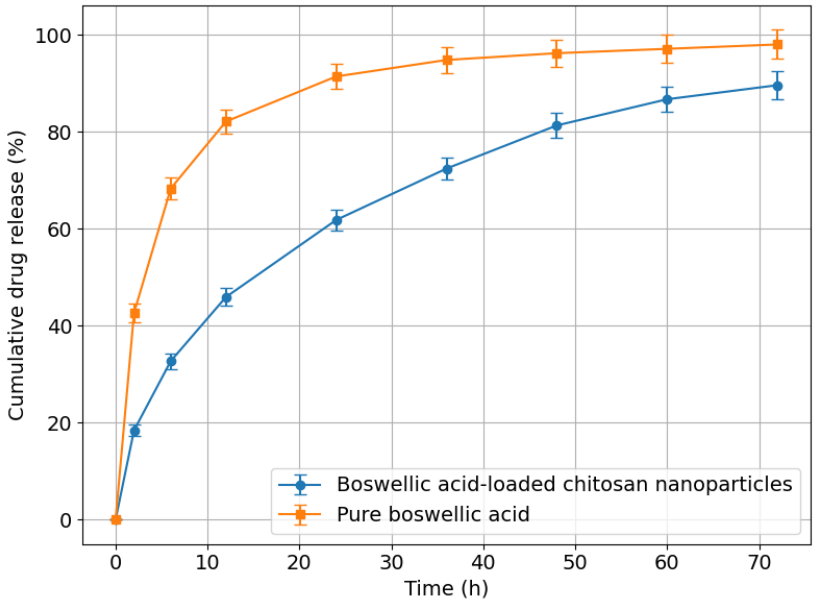

Figure 10. Comparative in vitro release profile of boswellic acid from nanoparticles and pure drug (schematic).

Stability Studies

Stability studies conducted over three months under accelerated conditions demonstrated no significant changes in particle size, entrapment efficiency, or drug content ($p > 0.05$). These findings indicated good physicochemical stability of the formulation.

Table 7. Stability assessment of optimised formulation

Parameter	Initial	3 months
Particle size (nm)	176.2 ± 5.9	179.8 ± 6.3
Entrapment efficiency (%)	83.9 ± 2.7	82.6 ± 2.9
Drug content (%)	99.1 ± 1.1	98.3 ± 1.4

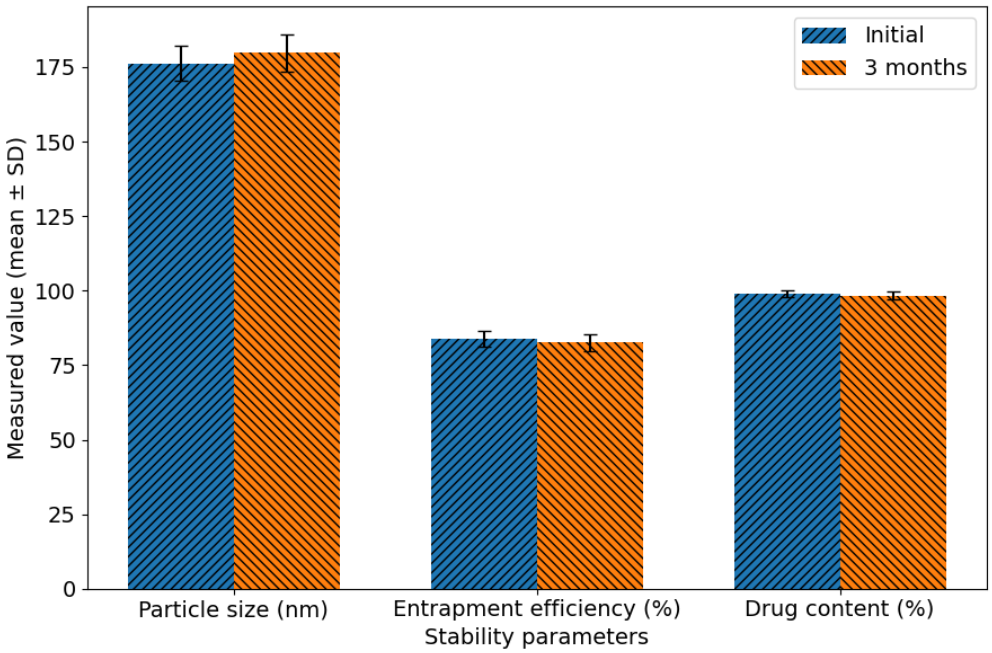

Figure 11. Stability profile of optimised nanoparticles under accelerated conditions.

DISCUSSION

Rheumatoid arthritis is a chronic, progressive autoimmune disorder characterised by persistent synovial inflammation, hyperplasia of synovial fibroblasts, infiltration of immune cells, and progressive destruction of cartilage and subchondral bone. Despite the availability of disease-modifying

antirheumatic drugs and biologics, long-term management remains challenging due to systemic toxicity, immunosuppression, variable patient response, and poor drug accumulation within inflamed synovial tissues. These limitations have driven sustained interest in alternative therapeutic strategies that combine natural anti-inflammatory agents with advanced drug delivery systems capable of site-specific targeting and prolonged therapeutic action. Boswellic acid, a pentacyclic triterpenoid derived from Boswellia serrata, has been extensively documented for its anti-inflammatory, anti-arthritic, and immunomodulatory activities. Its ability to inhibit 5-lipoxygenase, downregulate pro-inflammatory cytokines such as TNF-α and IL-1β, and suppress leukocyte infiltration renders it particularly attractive for rheumatoid arthritis therapy. However, clinical translation of boswellic acid has been severely constrained by its poor aqueous solubility, limited oral bioavailability, rapid systemic clearance, and inadequate localisation at inflamed synovial sites. The present study addressed these challenges through the development of mucoadhesive chitosan nanoparticles optimised using a Quality by Design approach, with the explicit objective of enhancing synovial targeting and therapeutic efficacy.

The successful isolation and physicochemical characterisation of boswellic acid confirmed the integrity and suitability of the active compound for formulation development. The observed melting point, FTIR spectral signatures, and ultraviolet absorption maxima were consistent with previously reported values, indicating high purity and structural stability. Preservation of the functional groups critical for biological activity was essential, as chemical degradation or modification could compromise anti-inflammatory efficacy. The use of ethanol extraction followed by chromatographic purification proved effective in enriching boswellic acid while minimising co-extracted resinous impurities, thereby improving formulation reproducibility.

The ionic gelation method employed for nanoparticle preparation was particularly advantageous for encapsulating hydrophobic phytoconstituents such as boswellic acid. Chitosan, a biocompatible and biodegradable cationic polysaccharide, provided a versatile matrix capable of electrostatic interaction with sodium tripolyphosphate, resulting in stable nanoscale particles. The formation of nanoparticles within the sub-200 nm range was a critical achievement, as particles of this size are known to preferentially accumulate in inflamed synovial tissues through enhanced permeability of the pathological vasculature and impaired lymphatic drainage, a phenomenon analogous to the enhanced permeability and retention effect observed in inflammatory conditions.

Application of the Box–Behnken design enabled systematic evaluation of formulation variables and their interactive effects on critical quality attributes. The significant influence of chitosan concentration on particle size, entrapment efficiency, and mucoadhesion was mechanistically logical. Increasing polymer concentration enhanced matrix density, thereby improving drug entrapment and surface charge availability, but excessive concentrations increased solution viscosity and particle aggregation, leading to larger particle sizes. Similarly, sodium tripolyphosphate concentration governed cross-linking density, with optimal levels producing compact, stable nanoparticles, while suboptimal levels resulted in loosely bound structures prone to drug leakage (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015).

Stirring speed exerted a dual influence on nanoparticle characteristics. Moderate to high stirring speeds facilitated efficient dispersion and uniform particle formation, reducing size variability and improving entrapment efficiency. However, excessively high shear forces risked disrupting polymer–drug interactions, potentially promoting drug diffusion into the external phase during nanoparticle formation. The quadratic relationships observed in response surface and contour plots validated the complexity of these interactions and underscored the necessity of a multivariate optimisation strategy (Agnihotri et al., 2004; Hansraj et al., 2015; Santo et al., 2012; Senel et al., 2015). The optimised formulation exhibited a particle size of approximately 176 nm with a narrow polydispersity index, indicating homogeneity and reproducibility. Such size uniformity is particularly relevant for injectable or intra-articular delivery systems, where inconsistent particle populations can lead to unpredictable biodistribution and clearance. The strongly positive zeta potential observed for the optimised nanoparticles reflected the protonated amino groups of chitosan and suggested good colloidal stability through electrostatic repulsion. More importantly, this cationic surface charge played a pivotal role in mucoadhesion and synovial targeting.

Mucoadhesive evaluation demonstrated significantly enhanced interaction between the nanoparticles and mucin, attributable to electrostatic attraction between positively charged chitosan and negatively charged sialic acid residues of mucosal glycoproteins. In the context of rheumatoid arthritis, this mucoadhesive behaviour is highly advantageous, as the synovial lining exhibits mucopolysaccharide components

capable of interacting with cationic carriers. Prolonged retention within the synovial cavity is expected to increase local drug concentration, reduce dosing frequency, and minimise systemic exposure, thereby improving therapeutic outcomes and patient compliance.

High entrapment efficiency observed in the optimised formulation reflected favourable hydrophobic interactions between boswellic acid and the chitosan matrix, as well as effective ionic cross-linking that restricted drug diffusion. Entrapment efficiency exceeding 80% is particularly notable for hydrophobic phytochemicals and compares favourably with previously reported nanoparticulate systems for boswellic acid and related triterpenoids. Improved drug loading further enhanced formulation efficiency by reducing the amount of carrier material required per therapeutic dose. The in vitro drug release profile provided critical insight into the release mechanism and potential in vivo performance. The biphasic release pattern, characterised by an initial limited burst followed by sustained release over 72 h, was desirable for rheumatoid arthritis management. The modest initial release ensured rapid attainment of therapeutic levels, while the prolonged release phase supported maintenance of anti-inflammatory activity over an extended period. In contrast, pure boswellic acid exhibited rapid and uncontrolled release, highlighting the inadequacy of conventional formulations.

Kinetic modelling revealed that the release profile best fitted the Korsmeyer–Peppas model, with a release exponent indicative of anomalous transport. This finding suggested that drug release was governed by a combination of diffusion through the hydrated polymer matrix and gradual polymer relaxation or erosion. Such a mechanism is particularly suitable for inflamed synovial environments, where enzymatic activity and fluid turnover can influence polymer behaviour. Sustained release from chitosan nanoparticles is therefore likely to maintain therapeutic drug levels within the joint cavity while minimising systemic spillover.

Stability studies conducted under accelerated conditions demonstrated negligible changes in particle size, entrapment efficiency, and drug content, confirming the physicochemical robustness of the optimised formulation. Stability is a critical consideration for translational viability, as nanoparticle aggregation or drug degradation during storage can compromise safety and efficacy. The observed stability was attributable to strong ionic cross-linking, adequate surface charge, and the use of appropriate cryoprotectants during lyophilisation. Collectively, the findings of this study align well with previous reports on chitosan-based nanocarriers for inflammatory disorders, while offering distinct advantages through the integration of mucoadhesion and synovial targeting. Compared with conventional oral or systemic delivery of boswellic acid, the developed nanoparticle system demonstrated superior control over particle characteristics, drug release, and local retention potential. Importantly, the application of a Quality by Design framework ensured reproducibility, regulatory relevance, and scalability, thereby strengthening the translational significance of the work.

From a therapeutic perspective, the developed boswellic acid–loaded mucoadhesive chitosan nanoparticles represent a promising platform for targeted rheumatoid arthritis management. By enhancing synovial localisation, prolonging drug residence time, and reducing systemic exposure, this approach has the potential to improve clinical efficacy while minimising adverse effects associated with long-term anti-inflammatory therapy. Furthermore, the platform may be adaptable for co-delivery of additional anti-rheumatic agents, opening avenues for combination therapy within a single targeted delivery system.

CONCLUSION

The present investigation successfully demonstrated the development and systematic optimisation of boswellic acid–loaded mucoadhesive chitosan nanoparticles intended for targeted synovial delivery in the management of rheumatoid arthritis. By integrating a natural anti-inflammatory phytoconstituent with a biocompatible polymeric nanocarrier and a Quality by Design framework, the study effectively addressed the key formulation and therapeutic challenges associated with conventional boswellic acid delivery systems. The ionic gelation technique facilitated the formation of stable nanoparticles with controlled physicochemical characteristics, while the Box–Behnken design enabled precise optimisation of formulation variables and identification of critical interactions influencing particle size, entrapment efficiency, and mucoadhesive performance. The optimised formulation exhibited nanoscale particle size, high drug encapsulation, strong positive surface charge, and enhanced mucoadhesion, all of which are essential attributes for prolonged retention within inflamed synovial tissues. Sustained in vitro drug release following anomalous transport kinetics further supported the potential of the formulation to maintain therapeutic concentrations over extended periods.

Importantly, the mucoadhesive behaviour of the chitosan nanoparticles suggested improved

localisation at the synovial lining, which is expected to enhance local anti-inflammatory efficacy while reducing systemic exposure and associated adverse effects. Accelerated stability studies confirmed the physicochemical robustness of the optimised formulation, indicating suitability for further preclinical development and scale-up. Overall, the findings of this study highlight the clinical and pharmaceutical relevance of mucoadhesive chitosan-based nanocarriers as a promising strategy for targeted rheumatoid arthritis therapy. The developed formulation offers a viable platform for improving the therapeutic performance of boswellic acid and may be extended to other phytoconstituents or anti-rheumatic agents. Future studies focusing on in vivo synovial distribution, pharmacokinetics, and therapeutic efficacy in relevant arthritis models are warranted to advance this system towards clinical translation.

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