RESEARCH ARTICLE

Formulation and In-Vitro Evaluation of Sheep Milk-Derived Microbeads as a Novel Drug Delivery System for Anti-Arthritic Therapy

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Abstract

Arthritis represents a persistent inflammatory joint disease driven by complex immune-mediated processes, including protein denaturation, that collectively contribute to progressive tissue injury and functional decline. While conventional non-steroidal anti-inflammatory drugs (NSAIDs) such as Diclofenac Sodium remain a cornerstone of symptomatic management, their long-term use raises significant safety concerns. Despite established osteoprotective effects, the anti-arthritic potential of sheep milk remains underreported, supporting the rationale of this study. Sheep milk is rich in bioactive constituents, including casein and whey proteins (lactoferrin and immunoglobulins), bioactive peptides, essential fatty acids such as conjugated linoleic acid and omega-3 and omega-6 fatty acids, along with vitamins (A, D, E, and B-complex) and minerals (calcium, phosphorus, zinc, and magnesium), which collectively contribute to its observed anti-inflammatory and therapeutic potential.The present work aimed to develop and characterize a

sheep milk-based microbead formulation as a naturally derived, biocompatible drug delivery platform and to investigate its in-vitro anti-arthritic properties. Microbeads were fabricated via the ionic gelation method, utilizing Sodium Alginate as the matrix-forming polymer and Calcium Chloride as the ionic cross-linking agent. The resulting microbeads were subjected to comprehensive physicochemical evaluation, encompassing microbead weight analysis, particle size measurement by optical micrometry, swelling behaviour assessment at different pH values, and wet/dry weight comparison. Anti-arthritic efficacy was examined using an in-vitro protein denaturation inhibition assay employing egg albumin as the model protein. The formulated sheep milk microbeads demonstrated a clear dose-dependent inhibitory effect, yielding inhibition values of 47.1%, 64.4%, and 65.3% at concentrations of 100, 200, and 400 µg/mL, respectively. The reference standard Diclofenac Sodium produced comparatively higher inhibition of 70%, 80%, and 85% at the same concentrations. These outcomes indicate that sheep milk microbeads hold meaningful anti-arthritic potential and represent a viable natural, biocompatible alternative for anti-inflammatory drug delivery. Hence, the developed sheep milk microbeads demonstrate significant potential as a safe and effective alternative for anti-arthritic drug delivery and require further detailed studies.

Keywords: *Sheep milk, microbeads, anti-arthritic activity, sodium alginate, protein denaturation assay, Novel Drug Delivery System*

1. Introduction

Arthritis is among the most widely prevalent chronic musculoskeletal disorders globally, characterized by persistent joint inflammation, pain, swelling, stiffness, and incremental cartilage deterioration that ultimately compromises mobility and overall well-being (1). Rheumatoid arthritis and osteoarthritis constitute the two most clinically significant subtypes, both of which involve sustained inflammation and progressive structural disruption to joint architecture and adjacent tissues (2).

The worldwide burden of arthritic disease has emerged as a major public health challenge, disproportionately affecting older populations. Pathogenesis involves intricate biochemical and immunological cascades, including excessive production of inflammatory mediators and aberrant alterations in protein conformation. Protein denaturation — the loss of a protein's functional three-dimensional structure in response to physical or chemical stressors — is one key molecular event implicated in inflammatory diseases (3). Such structurally altered proteins can behave as neoantigens, eliciting immune reactions that further perpetuate and intensify the inflammatory milieu.

The pharmacological management of arthritis predominantly depends on NSAIDs such as Diclofenac Sodium and Ibuprofen, which attenuate inflammation and alleviate pain through inhibition of cyclooxygenase enzymes and consequent reduction in prostaglandin biosynthesis (4). Although these agents effectively manage symptoms, sustained use is frequently accompanied by adverse outcomes including gastrointestinal mucosal injury, peptic ulceration, nephrotoxicity, and cardiovascular risks, underscoring the necessity for safer therapeutic modalities.

In recent years, interest in novel drug delivery systems has grown considerably, driven by their ability to improve active ingredient stability, enhance bioavailability, and enable controlled or sustained release profiles (5). Microbeads, as microparticulate polymeric carriers, have attracted particular attention for their capacity to encapsulate biologically active substances and release them in a regulated and predictable manner, while simultaneously shielding these substances from environmental degradation (6).

Ionic gelation represents a preferred fabrication strategy for microbead development owing to its procedural simplicity, economic feasibility, and compatibility with biopolymers (7). Sodium alginate, a natural anionic polysaccharide, is routinely employed in this method because of its well-established ability to undergo instantaneous cross-linking upon exposure to divalent calcium ions. The ensuing interaction between alginate and calcium chloride generates mechanically stable gel microbeads that are biodegradable and exhibits excellent biological compatibility (8).

Naturally derived biomaterials are increasingly being explored in pharmaceutical development given their inherent safety profiles and potential therapeutic activity. Sheep milk is a nutritionally dense bioresource, rich in proteins, bioactive peptides, essential amino acids, vitamins, and trace minerals. These constituents have been associated with antioxidant, anti-inflammatory, and immunomodulatory properties, suggesting their potential utility in managing inflammatory conditions. Despite this, the integration of sheep milk into alginate-based microbead systems for anti-arthritic applications remains underexplored.

Accordingly, the principal aim of this study was to develop sheep milk-encapsulated microbeads using sodium alginate through ionic gelation and to characterize both their physicochemical properties and in-vitro anti-arthritic activity via protein denaturation inhibition assay. Such a naturally derived delivery platform may improve therapeutic outcomes while mitigating the adverse effects characteristic of synthetic anti-inflammatory agents (9).

2. Materials and Methods

2.1 Formulation of Sheep Milk Microbeads by Ionic Gelation

Sheep milk microbeads were prepared through the ionic gelation technique. A precisely weighed quantity of sodium alginate was dispersed incrementally into a measured volume of distilled water under continuous magnetic stirring until a clear, homogeneous polymeric solution was achieved (10). A predetermined amount of sheep milk powder was then added to this solution with ongoing agitation to yield a smooth, uniform dispersion that facilitated thorough distribution of the milk constituents throughout the polymeric matrix.

A calcium chloride solution of defined concentration was prepared independently as the cross-linking medium (11). The sodium alginate–sheep milk dispersion was loaded into a syringe and extruded dropwise into the calcium chloride solution from a fixed height under gentle stirring (12). Immediate ionic cross-linking occurred as the alginate droplets contacted the calcium ion-rich medium, giving rise to discrete spherical microbeads (13). The microbeads were maintained in the cross-linking bath for a defined curing interval to permit complete gelation and structural consolidation (14).

After the curing period, the microbeads were separated by filtration and rinsed thoroughly with distilled water to remove residual calcium chloride and unreacted material. The washed

microbeads were subsequently air-dried at ambient temperature to constant weight and stored in sealed containers pending further characterization and biological evaluation.

Table 1: Composition of Sheep Milk Microbead Formulation

Ingredient	Quantity
Sheep Milk Powder	1 g
Sodium Alginate	0.2 g
Calcium Chloride	1 g
Distilled Water	q.s.

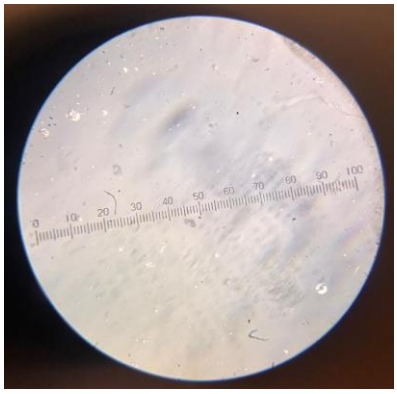
2.2 Physicochemical Evaluation of Microbeads

a. Microbead Weight Determination

The weights of freshly prepared and dried microbeads were recorded using a calibrated analytical balance. Wet weight was determined immediately after preparation, while dry weight was obtained following air-drying at room temperature to constant mass. The values obtained were used to estimate moisture content and drying efficiency.

b. Particle Size Determination

Figure 1: Microscopic image of sheep milk-based microbeads



Particle dimensions were assessed using an optical microscope fitted with an eyepiece micrometer that had been calibrated against a stage micrometer. Ten microbeads were randomly selected, and their diameters were individually measured. Mean particle size was derived by multiplying the average eyepiece divisions by the applicable calibration factor.

c. Effect of pH on Swelling Index

Swelling characteristics were examined in two pH environments: 0.1 N hydrochloric acid (acidic) and 0.1 N sodium hydroxide (alkaline). A known dry weight of microbeads was immersed in each medium for a defined time interval. The swollen microbeads were carefully

removed, surface moisture was blotted, and they were reweighted to determine the extent of swelling at each pH condition.

d. Wet and Dry Weight Difference

Figure 2.1: Freshly prepared wet sheep milk-based microbeads

Figure 2.2: Dried sheep milk microbeads showing variation in size and morphology after drying

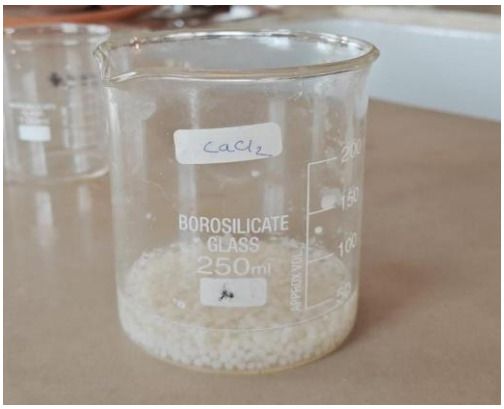


Figure 2.1

Figure 2.2

Freshly prepared microbeads were weighed to record wet mass, then dried at ambient conditions until constant weight was achieved. The difference between the initial wet weight and the final dry weight was calculated to quantify the water-holding capacity and moisture content of the hydrogel matrix.

e. Protein Denaturation Inhibition Assay

Anti-arthritic activity was determined through an in-vitro protein denaturation inhibition assay using egg albumin as the substrate protein. Reaction mixtures comprising egg albumin, sodium chloride solution, and graded concentrations of the test samples were incubated under standardized conditions (15). Absorbance was measured spectrophotometrically at 660 nm, and the percentage inhibition of denaturation was calculated with reference to Diclofenac Sodium as the positive control (16).

3. Results

3.1 Eyepiece Micrometer Calibration

Prior to particle size analysis, the eyepiece micrometer was systematically calibrated against a stage micrometer to establish a reliable conversion factor. During calibration, it was determined that four divisions on the eyepiece micrometer corresponded precisely to five divisions on the stage micrometer. Given that each stage micrometer division represents a known distance of 0.01 mm, five such divisions collectively span 0.05 mm. Dividing this distance equally across the four corresponding eyepiece divisions yielded a calibration factor of 0.0125 mm per eyepiece division. This value was subsequently applied as a uniform conversion constant throughout all particle size measurements, ensuring consistency and dimensional accuracy across the dataset.

3.2 Particle Size Measurement

To determine the mean diameter of the prepared sheep milk micro-beads, ten individual micro-beads were randomly selected and measured using the calibrated eyepiece micrometer. The recorded eyepiece division readings were 4, 3, 3, 4, 4, 2, 3, 3, 2, and 3, with a cumulative sum of 31 divisions. Dividing this total by the number of measured micro-beads yielded an arithmetic mean of 3.1 eyepiece divisions per particle. Upon applying the established calibration factor, the mean particle diameter was calculated as follows: 3.1 × 0.0125 mm = 0.03875 mm, which corresponds to approximately 38.75 µm. This result indicates that the micro-beads were produced within a size range consistent with that reported for ionically cross-linked alginate-based micro-particulate systems, and is considered appropriate for facilitating controlled drug release and effective tissue distribution.

3.3 Anti-Arthritic Activity — Protein Denaturation Inhibition Assay

Absorbance measurements were recorded at 660 nm for all test and reference samples. The control absorbance was 0.30. Percentage inhibition was computed using:

% Inhibition = [(Control Absorbance − Test Absorbance) / Control Absorbance] × 100

Table 2: Comparative In-Vitro Protein Denaturation Inhibition Activity by sheep milk microbeads and Diclofenac Sodium across tested concentrations.

Conc. of Microbeads (µg/mL)	Absorbance (Microbeads)	% Inhibition (Microbeads)	Conc. of Diclofenac Na (µg/mL)	Absorbance (Diclofenac Na)	% Inhibition (Diclofenac Na)
100	0.1587	47.1	100	0.090	70
200	0.1067	64.4	200	0.055	80
400	0.1041	65.3	400	0.030	85

A progressive, concentration-dependent increase in protein denaturation inhibition was observed for the sheep milk microbeads. This dose-response relationship suggests that the bioactive components of sheep milk retained within the alginate matrix contribute meaningfully to the

anti-inflammatory activity recorded. Although Diclofenac Sodium demonstrated superior inhibitory capacity, the microbeads exhibited appreciable inhibition across all concentrations, supporting their anti-arthritic potential.

3.4 Microbead Weight Determination

The yield and water-retention characteristics of the prepared micro-beads were assessed through gravimetric analysis. Freshly prepared micro-beads exhibited an initial wet weight of 5 g. Following air-drying at ambient room temperature to a constant mass, the dry weight was recorded at 1 g, representing a four-fold reduction in total mass. This substantial decrease in weight is primarily attributable to the loss of water molecules entrapped within the three-dimensional cross-linked alginate network during the gelation process. The magnitude of this weight reduction is characteristic of hydrogel-based delivery systems, wherein the polymer matrix retains large quantities of water during the aqueous preparation stage. These findings confirm the successful formation of a hydrophilic micro-bead system and are consistent with the established water-absorption and retention properties of ionically cross-linked sodium alginate matrices.

3.5 Swelling Behaviour under Different pH Conditions

The swelling behaviour of the prepared micro-beads was investigated under both acidic and alkaline conditions to assess their sensitivity to physiological pH variation. When subjected to acidic medium (0.1 N HCl), the microbeads exhibited comparatively restricted swelling, attributable to the protonation of the carboxylate functional groups ($–COO^-$) present along the sodium alginate polymer chains. Under acidic conditions, these groups exist predominantly in their protonated form (–COOH), which diminishes electrostatic repulsion between polymer chains and consequently limits water uptake and matrix expansion. Conversely, exposure to alkaline medium (0.1 N NaOH) resulted in markedly enhanced hydration and volumetric expansion. At elevated pH values, the carboxylate groups undergo progressive deprotonation, acquiring a net negative charge that intensifies inter-chain repulsion, promotes polymer chain relaxation, and facilitates significant water absorption into the matrix. This pH-dependent ionization behaviour is a well-recognised property of alginate-based hydrogel systems. The differential swelling profile observed across the two pH environments demonstrates the pH-responsive nature of the micro-bead formulation and implies a capacity for site-specific, environment-triggered drug release — particularly relevant in the context of gastrointestinal drug delivery, where pH transitions between gastric (acidic) and intestinal (alkaline) environments are physiologically significant.

4. Discussion

The current investigation was carried out to develop sheep milk–based microbeads using the ionic gelation technique and to evaluate their possible anti-arthritic potential through an in vitro protein denaturation inhibition assay. The ionic gelation method was chosen for preparing the microbeads due to its operational simplicity, good reproducibility, and compatibility with drug delivery systems utilizing natural polymers. (17) The anti-arthritic activity was selected as the primary focus of this study due to the increasing prevalence of inflammatory joint disorders and the need for safer, naturally derived therapeutic alternatives. Since the osteoprotective potential of sheep milk has already been extensively explored, the present study was specifically focused on investigating its anti-arthritic activity to explore its therapeutic potential in inflammatory joint conditions.(18) Since protein denaturation is a key mechanism involved in the pathogenesis of arthritis, evaluating the inhibitory effect of the formulation on protein denaturation provides a relevant and reliable approach to assess its anti-inflammatory potential. The successful production of microbeads in this study confirms the effective ionic interaction occurring between sodium alginate and the divalent calcium ions supplied by calcium chloride.(19) The interaction between alginate polymer chains and calcium ions promotes the formation of a stable three-dimensional hydrogel structure that traps the incorporated constituents and leads to the formation of spherical microbeads.(20) Polymeric systems of this nature are well known for their high biocompatibility, biodegradability, and minimal toxicity, which makes them highly suitable for pharmaceutical as well as biomedical applications.(21) Therefore, the utilization of the ionic gelation technique in the present work provided a convenient and efficient strategy for the development of microbead-based drug delivery systems.

The physicochemical evaluation of the formulated microbeads indicated satisfactory formulation characteristics. Particle size determination performed using optical microscopy showed that the microbeads exhibited comparatively uniform dimensions with an acceptable distribution of particle sizes. Particle size represents a critical parameter that influences the efficiency of microbead formulations because it directly impacts surface area, water absorption ability, and release characteristics of the encapsulated materials.(22) Achieving a uniform particle size distribution is considered advantageous in drug delivery systems as it ensures predictable swelling behavior and consistent drug release patterns.(23) Microbeads possessing an appropriate size range may also enhance interaction with biological fluids and may consequently improve the bioavailability of incorporated bioactive constituents.

The swelling behaviour of the prepared microbeads was examined under different pH conditions, specifically in an acidic environment (0.1 N hydrochloric acid) and an alkaline environment (0.1 N sodium hydroxide).(24) The observations revealed that the developed microbeads showed significant swelling in both media, demonstrating the hydrophilic nature of the alginate-based polymer matrix.(25) Swelling occurs when the surrounding aqueous medium penetrates the polymer network, causing expansion of the hydrogel structure.(26) The degree of swelling is influenced by the physicochemical characteristics of the polymer as well as by the pH of the external medium. The pH-dependent swelling pattern observed in this study indicates that the microbeads possess the ability to modulate the release of entrapped substances under varying physiological environments. (27) Such swelling behaviour is particularly beneficial in controlled drug delivery systems where hydration of the polymer matrix regulates the diffusion of active components from the formulation. (28)

Evaluation of the wet and dry weights of the microbeads also provided valuable information regarding their hydration capability and structural integrity. Freshly prepared microbeads exhibited greater weight due to the presence of water molecules retained within the polymeric matrix. Upon drying at room temperature, a gradual decrease in weight was observed as the entrapped moisture evaporated from the microbeads.(29) The variation between the wet and dry weights therefore reflects the water-holding capacity of the polymer network and confirms the formation of a hydrated hydrogel system.(30) Proper drying of the microbeads is necessary to improve their physicochemical stability and to ensure their suitability for storage and further pharmaceutical evaluation.

The anti-arthritic potential of the developed sheep milk microbeads was assessed using the protein denaturation inhibition assay, which is commonly employed as a reliable vitro technique for evaluating anti-inflammatory activity. Denatured proteins may act as autoantigens capable of initiating immune responses and inflammatory pathways in the body. Therefore, compounds capable of preventing or reducing protein denaturation may demonstrate therapeutic potential in the treatment of inflammatory conditions such as arthritis. The findings obtained in the present study showed that sheep milk microbeads produced concentration-dependent inhibition of protein denaturation. As the concentration of the formulation increased, the percentage inhibition also increased, suggesting an enhancement in anti-inflammatory activity. The highest inhibition recorded was 65.3% at a concentration of 400 µg/mL, indicating that the formulated microbeads possess notable anti-arthritic potential.

For comparison, the inhibitory activity of the formulation was evaluated against the standard non-steroidal anti-inflammatory drug Diclofenac Sodium. (31) The standard drug exhibited comparatively higher inhibitory activity, showing a maximum inhibition of 85% at the same concentration level. Although the standard drug demonstrated stronger activity, the sheep milk microbeads still exhibited considerable inhibition of protein denaturation. (32) The observed biological activity may be associated with the presence of naturally occurring bioactive components found in sheep milk. Sheep milk is known to contain numerous nutritionally and pharmacologically important constituents such as high-quality proteins, bioactive peptides, essential fatty acids, vitamins, and minerals. (33) Previous studies have reported that these components possess antioxidant, anti-inflammatory, and immunomodulatory properties, which may contribute to suppression of inflammatory reactions and stabilization of protein structures. (34)

Another important advantage of the present formulation is the incorporation of a natural biomaterial that may possess therapeutic benefits. Conventional anti-inflammatory drugs such as Diclofenac Sodium are frequently used in the management of arthritic conditions; however, prolonged administration of these synthetic drugs is often associated with several adverse effects including gastrointestinal irritation, ulcer formation, renal dysfunction, and cardiovascular complications. In contrast, formulations containing natural bioactive materials may offer improved safety and better tolerability. Incorporating sheep milk constituents within a polymeric microbead delivery system may further improve their stability and enable controlled release, thereby enhancing their therapeutic effectiveness. (35)

The formulation of sheep milk-derived microbeads therefore represents a novel strategy in the development of natural product-based pharmaceutical systems. Additional studies involving

advanced characterization methods as well as in vivo pharmacological investigations may provide deeper understanding regarding the therapeutic efficacy and clinical potential of this formulation for the treatment of arthritis and other inflammatory conditions.

5. Conclusion

Sheep milk microbeads were successfully prepared using the ionic gelation technique with sodium alginate as the matrix polymer and calcium chloride as the cross-linking agent. The formulated microbeads exhibited satisfactory physicochemical characteristics, including a mean particle size of 38.75 µm, pH-sensitive swelling behavior, and appropriate wet/dry weight profiles indicative of a hydrogel system. In-vitro protein denaturation inhibition assay demonstrated that the microbeads possess notable anti-arthritic activity in a concentration-dependent manner, achieving up to 65.3% inhibition at 400 µg/mL. While Diclofenac Sodium displayed greater inhibitory capacity, the sheep milk microbeads represent a promising naturally derived, biocompatible delivery platform. These results encourage further preclinical and clinical exploration of sheep milk-based formulations as safer alternatives for the management of arthritis and related inflammatory disorders.

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