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Bioadhesive nanogels for joint-specific drug delivery in osteoarthritis and rheumatoid arthritis

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Abstract
Osteoarthritis and rheumatoid arthritis are both chronic debilitating joint diseases that have a significant impact on mobility, quality of life and healthcare systems worldwide. Traditional systemic treatments such as NSAIDs, corticosteroids, DMARDs and biologics are usually characterized by rapid clearance, lack of specificity to joints and severe systemic side effects. To address these drawbacks, nanogels have come up as superior drug delivery systems with the advantageous factors of high biocompatibility, controllable structure and the ability to release drugs in a controlled and sustained release. Particularly, bioadhesive nanogels offer better retention in the synovial cavity, tissue penetration, and drug delivery, which is both passive and active. The results of these systems have shown promising outcomes in encapsulating a broad variety of therapeutics including NSAIDs, corticosteroids, DMARDs and biologics which have improved anti-inflammatory effects, cartilage protection and lowered dosing rate in arthritic preclinical models. In spite of scalability, stability, and regulatory approval-related issues, the continued development of stimuli-responsive polymers, multi-drug loading, and customized nanomedicine has indicated that nanogel-based therapies have a great future as the next-generation treatments of osteoarthritis and rheumatoid arthritis.

Keywords: Nanogels, bioadhesive nanogels, osteoarthritis, rheumatoid arthritis, intra-articular delivery

Introduction

Arthritis, especially osteoarthritis (OA) and rheumatoid arthritis (RA) is one of the most prevalent chronic disability causes globally, with millions of people of all ages having the disease [1]. OA is mainly a degenerative joint disease with gradual cartilages loss, inflammation of the synovial membrane, and loss of the joint range of movement whereas RA is an autoimmune systemic disease which is characterized by the permanent synovial inflammation, the occurrence of pannus and the destruction of the joints. Global epidemiological reports indicate that OA is on the increase as a result of the age factor and lifestyle choices, whereas RA plays a major part in long-term morbidity and poor life quality. Combined, OA and RA represent a significant socioeconomic cost because they raise costs related to healthcare, decrease working efficiency, and deteriorate everyday activities [2].

Although there are a number of therapeutic options, including non-steroid anti-inflammatory drugs (NSAIDs), corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologic, their clinical efficacy is not effective. The traditional approaches to systemic therapy have a limited half-life, lack of localization to the joint, rapid clearance by the systemic system, and severe dose-dependent adverse effects such as gastrointestinal irritation, hepatotoxicity, immunosuppression and cardiovascular risks [3]. In addition, oral and parenteral preparations are not able to sustain therapeutic levels in the joint affected and consequent disease control is inadequate, leading to an incidence of relapse. These shortcomings underscore the urgent demand to have a safe, effective, and localized therapeutic approach that can be used to deliver drugs straight to the area of inflammatory activity [4].

Localized, joint-specific drug delivery concept has been a very popular and promising concept in recent years, as a way of improving the therapeutic outcomes in arthritis. Local intra-articular drug administration has the benefits of reduced systemic exposure, increased time of residence of the drug in the synovial space, enhanced tissue penetration, and long-term therapeutic concentrations. Yet the appearance of traditional intra-articular preparations such as simple solutions or suspensions are quickly washed out of the joint through lymphatic drain and repeated injections are required thus lowering compliance in patients [5].

Nanogels have been developed as a new and versatile drug delivery platform so as to overcome these challenges. Nanogels are high-water content, cross-linked polymeric networks of nanoscale with high biocompatibility, tuneable mechanical properties, and a wide range of therapeutic encapsulation capabilities. These structural features allow them to penetrate the joint environment when needed, release drugs steadily and in controlled amounts, and increase the retention of the drugs. Furthermore, the functionality of bioadhesive polymer or stimuli-responsive components is added to increase the propensity to localize and remain in inflamed synovial tissues. Consequently, nanogels are a future strategy of targeted arthritis therapy as it overcomes the flaws of systemic and traditional intra-articular therapy [6].

The paper presents the most recent developments, therapeutic opportunities and future prospects of bioadhesive and injectable nanogels to deliver joint specific drugs in osteoarthritis and rheumatoid arthritis.

Pathophysiology of Osteoarthritis and Rheumatoid Arthritis

The two most common types of arthritic disorders are osteoarthritis (OA) and rheumatoid arthritis (RA), which is the difference in their pathology. OA is an autoimmune and inflammatory JDRA unlike OA which is a degenerative and mechanically-induced condition. Their unique pathophysiology needs to be known to develop specific drug delivery vehicles like bioadhesive nanogels [7].

1. Osteoarthritis

Osteoarthritis is said to have progressive destruction of the cartilage surrounding the joints as well as alteration of the whole joint. OA is no longer viewed as a mere wear-and-tear disorder as it is now considered to be a complex disease with biochemical, mechanical and inflammatory elements [8].

Cartilage Degradation: The characteristic of OA is the degradation of the articular cartilage. The sole resident cells of cartilage, which are chondrocytes, change their phenotype to produce more catabolic enzymes (matrix metalloproteinases (MMP-1, MMP-3, MMP-13), aggrecanse (ADAMTS)). Such enzymes degrade collagen type II and aggrecan leading to thinning, fissuring and eventual cartilage destruction. Vascularity of cartilage is also not available further restricting intrinsic repair processes [9].

Synovial Inflammation: Though not as severe as RA, the synovial inflammation in OA also plays a major role in the development of an illness. Pro-inflammatory mediators are released by the inflamed synoviocytes such as IL-1β, TNF-2 and prostaglandins which enhance cartilage matrix degradation. Even in the presence of pain, synovitis enhances the rate of degeneration of a joint via persistent inflammatory transmission [10].

Oxidative Stress and Chondrocyte Apoptosis: Oxidative stress is a significant OA causative agent. Overproduction of reactive oxygen species (ROS) leads to dysfunction of mitochondria and lipid peroxidation and DNA damage in chondrocytes. The persistent oxidative stress leads to apoptosis, which makes the chondrocytes less dense and the extracellular matrix unable to synthesize. This cartilage breakdown to repair disproportion leads to accelerated degeneration of joints and disability [11].

2. Rheumatoid Arthritis

Rheumatoid arthritis is a chronic, autoimmune disorder that is systemic and which is associated with chronic inflammation of the synovium and progressive destruction of the joints. RA also includes local joint pathology as well as systemic immune dysregulation in contrast to OA [12].

Autoimmune Inflammation: RA starts with the activation of immune system provoked by the genetic and environmental factors. T cells and B cells are stimulated by antigen-presenting cells, which results in the generation of autoantibodies e.g. rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). The presence of activated immune cells in the synovium alters it into a hyperplastic aggressive tissue called pannus. This pannus invades cartilage and bone resulting in severe joint damage [13].

Cytokine Storm (TNF-α, IL-1β, IL-6): RA is marked by an excessive amount of release of pro-inflammatory cytokines, commonly referred to as a cytokine storm.

- TNF-α drives chronic inflammation, angiogenesis, and leukocyte recruitment.
- IL-1β stimulates MMP production and cartilage degradation.
- IL-6 contributes to systemic inflammation, autoantibody production, and bone resorption [14].

Joint Erosion and Systemic Complications: The chronological process is perpetuated through the activation of osteoclasts via RANKL-dependent mechanisms which causes bone erosion and deformity in the joint. Concomitant destruction of cartilage is through proteolytic enzyme and invading tissue pannus. RA also has a systemic presentation with anemia, cardiovascular diseases, osteoporosis, fatigue and vasculitis. Such complications make RA a systemic autoimmune disease, and not just a localized disease on the joints [15].

Nanogels: Structure, Properties and Mechanisms

1. Definition and Nanoscopic Structure

Nanogels are hydrogel particles of nanoscale (formed out of cross-linked networks of polymer) that can retain a substantial portion of water at the same time being structurally sound. Nanogels are usually between 20 and 500 nm; thus, combining the properties of hydrogels of high-water content and elasticity with the properties of nanoparticulate systems, including high mobility, enhanced diffusion and deep tissue penetration. The porous internal structure enables simple loading of therapeutic agents and the soft and deformable nature allows the interaction of biological tissues with the cartilage and synovial membranes. The above properties render nanogels good delivery vehicles in osteoarthritis and rheumatoid arthritis [16].

2. Cross-Linked Polymeric Network and High-Water Content

Nanogels are either physically (ionic, hydrogen bonding, hydrophobic) or chemically (covalent) cross-linked polymers, which form a stable but flexible three-dimensional network. Such cross-linked structure defines critical qualities such as particle size, porosity, swelling characteristics, and mechanical strength. The primary characteristic of nanogels is that it has a very high content of water usually more than 8090 percent which makes them highly biocompatible, less irritating to the tissues, and highly solubilizes drugs. This hydrated condition of the nanogel matrix is very similar to natural biological tissues in the body hence it is quite compatible when introduced into the body intra-articularly [17].

3. Mechanisms of Drug Loading: Physical, Electrostatic, and Covalent

Nanogels have several procedures to entrap drugs, based on the character of the therapeutic molecule as well as the polymer system. The physical entrapment enables the drugs to be retained in the porous structure of the gel by hydrophobic type of interactions and polymer entanglement. Interactions The electrostatic interactions play a crucial role when the charged drugs connect to the oppositely charged polymer chains and this way, loading is significantly increased and the drug is stabilized within the nanogel. To release the drug molecules onto the polymer backbone by cleavable linkers, covalent conjugation is recommended to enable long-term release or stimuli-responsive release. The technique is particularly useful with weak biologics like peptides and proteins which need to be preserved against enzyme degradation [18].

4. Controlled and Stimuli-Responsive Drug Release

Among the most important benefits of nanogels, it is possible to mention the controlled, sustained, and stimuli-responsive drug delivery. It is possible to modify nanogels to react to a particular physiological stimulus found in arthritic joints. Nanogels can be thermo-responsive, pH-responsive, and trigger release by changes in temperature and pH, respectively, thereby allowing the use of temperature-dependent release profiles, and specifically drop their cargo at the disease site, respectively. ROS-sensitive systems are specifically applicable in rheumatoid arthritis, which can be characterized by an increase in the concentrations of ROS that destroy particular chemical bonds, releasing drugs in inflamed tissues. Besides, nanogels responsive to enzymes can be degraded by matrix metalloproteinases (MMPs), which are expressed in OA and RA, making sure that the target population is delivered to diseased cartilage [19].

5. Advantages Over Hydrogels, Nanoparticles, and Liposomes

Nanogels have a unique biocompatibility, loading capacity, and flexibility relative to other delivery systems. They can be penetrated into the cartilage and the synovial tissue at a deeper level unlike the traditional hydrogels because they have a much smaller nanoscale size and do not need surgical implantation. Nanogels are soft and hydrated compared to rigid nanoparticles and thus they do not aggregate, trigger the immune system minimally, and stick better to the synovial surfaces. Nanogels are more structurally stable, have greater drug-loading capabilities, and a broader range of surface modification capabilities than liposomes. These special properties make nanogels the best platforms to treat arthritis, which can provide localized therapy with precision and a sustained therapeutic effect [20].

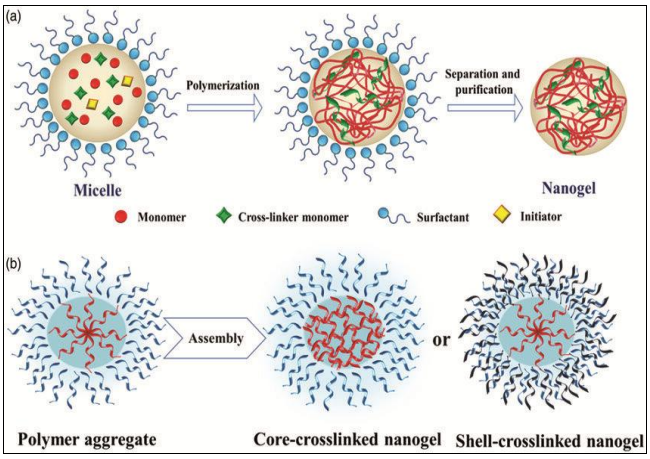

Fig 1: Schematic representation of nanogel structure, drug loading, and release mechanism [21]

Bioadhesive Nanogels for Arthritis Therapy

1. Concept of Bioadhesion and Interaction with Synovial Tissues

Bioadhesive nanogels are specifically designed to adhere to biological tissues, including the surfaces of the synovial membrane and cartilage. Bioadhesion occurs through different intermolecular interactions such as hydrogen bonding, electrostatic attraction, van der Waals forces, and hydrophobic interactions between nanogel polymers and extracellular matrix components. In inflamed joints, synovial tissues generally carry a net negative charge, which enhances the electrostatic attraction toward positively charged polymers like chitosan. Once adhered, nanogels are not rapidly cleared by lymphatic drainage, allowing them to remain at the inflammation site for prolonged periods. This sustained localization significantly improves therapeutic performance, as high drug concentration is maintained exactly where it is needed, while minimizing systemic side effects [22].

2. Injectable In-Situ Gelling Nanogels

Intra-articular nanogels can be administered as low-viscosity liquids that transform into a gel depot once inside the joint cavity. This in-situ gel formation occurs in response to physiological triggers such as temperature changes, pH variations, or enzyme activity commonly observed in arthritic tissues. Thermo-responsive nanogels containing polymers like PNIPAM or Pluronic F127 undergo sol–gel transition at body temperature, whereas pH-responsive nanogels gel under the mildly acidic conditions of inflamed synovium. Enzyme-responsive systems utilize elevated levels of matrix metalloproteinases (MMPs) in OA and RA to achieve controlled gelation and degradation. These gel-forming nanogels provide continuous drug release, enhanced joint retention, and reduced dosing frequency [23].

3. Key Polymers Used in Bioadhesive and Injectable Nanogels

A wide range of natural and synthetic polymers is used to formulate bioadhesive and in-situ forming nanogels. Chitosan, a cationic biopolymer, exhibits excellent mucoadhesion due to its strong affinity for negatively charged synovial tissues. Hyaluronic acid (HA), an endogenous component of synovial fluid, offers high biocompatibility and supports active targeting via CD44 receptors overexpressed in inflamed synoviocytes. Carbopol, a high-viscosity polyacrylic acid derivative, contributes strong hydrogen bonding and network stability. Synthetic polymers such as PEG improve hydrophilicity and stability, while PNIPAM enables temperature-triggered sol–gel transitions. Together, these polymers allow fine control over nanogel structure, adhesion properties, release behavior, and overall tissue compatibility [24].

4. Therapeutic Advantages: Retention, Controlled Release, and Penetration

Bioadhesive and in-situ forming nanogels offer multiple therapeutic advantages compared to traditional arthritis formulations. Their strong adherence and gel-depot formation significantly extend intra-articular retention, minimizing the need for frequent administration. The cross-linked network provides sustained and regulated drug release, maintaining therapeutic levels over longer durations. Due to their hydrated, flexible nanostructure, nanogels are capable of penetrating deeply into synovial layers and cartilage tissues. These combined properties enhance drug bioavailability at disease sites, improve therapeutic response, and reduce systemic toxicity—making them highly effective carriers for arthritis therapy [25].

5. Targeting Strategies: Passive and Active Approaches

Nanogels enhance targeted drug delivery in arthritic joints through both passive and active targeting mechanisms.

Passive targeting occurs naturally because inflamed synovial tissues possess enhanced permeability and retention-like characteristics, allowing nanogels to accumulate preferentially. Active targeting is achieved by decorating nanogel surfaces with ligands specific to receptors overexpressed in OA and RA tissues, such as hyaluronic acid for CD44 receptors, RGD peptides for integrins, or antibody fragments and aptamers for disease-specific markers. These strategies improve cellular uptake, optimize drug release at the site of inflammation, and increase therapeutic precision [26].

Table 1: Polymers used in bioadhesive nanogels [27]

Polymer	Type	Key Function	Relevance in Arthritis Therapy
Chitosan	Natural	Bioadhesion, positive charge	Strong synovial adhesion & enhanced retention
Hyaluronic Acid	Natural	CD44-mediated active targeting	High biocompatibility & joint specificity
Carbopol	Synthetic	High viscosity, strong hydrogen bonding	Prolonged residence & gel robustness
PEG	Synthetic	Hydrophilicity, stability	Extended circulation & reduced aggregation
PNIPAM	Synthetic	Thermo-responsive sol–gel transition	In-situ gelation at body temperature

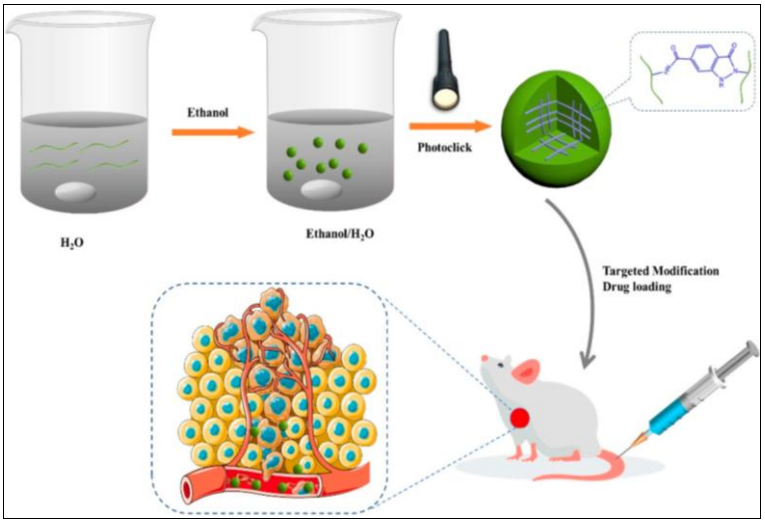

Fig 2: Mechanism of nanogel delivery and in-situ gel formation inside the joint [28]

Drugs Delivered via Nanogels and Therapeutic Outcomes

1. NSAIDs Encapsulated in Nanogels

The most widely used drugs in the treatment of osteoarthritis and rheumatoid arthritis are non-steroidal anti-inflammatory drugs (NSAIDs), which have adverse side effects on the GIT and cardiovascular systems when administered systemically. Nanogels offer a very effective way of delivering NSAIDs like Flurbiprofen and Diclofenac to the inflamed joints. Their solubility is improved in encapsulation, their retention in the synovial cavity is increased, their release is controlled and hence their therapeutic levels are available in the organism over a long period of time. This local action minimizes systemic toxicity and enhances anti-inflammatory activity [29].

2. Corticosteroid-Loaded Nanogels

Strong anti-inflammatory drugs like Betamethasone and Dexamethasone are common corticosteroids that are administered into the joint in intra-articular therapy. Nevertheless, the simple injections are easily evacuated out of the joint space. This drawback is overcome by nanogels that create depots that release the corticosteroid gradually, in days or even weeks. Nanogels are adhesive and injectable to enhance joint residence time and prolonged inhibition of cytokines, which leads to greater reduction of swelling, pain, and inflammation of the tissue [30].

3. DMARDs Incorporated into Nanogels

The most important treatments of RA are disease-modifying antirheumatic drugs (DMARDs), particularly Methotrexate and Leflunomide. Systemic delivery can result in hepatotoxicity and immunosuppression. Their therapeutic index is boosted by nanogel encapsulation by increasing their localization to inflamed synovium and reducing systemic exposure. *In vivo* and *in vitro* studies of methotrexate-loaded nanogels have demonstrated greater penetration in cartilages and greater inhibition of inflammatory mediators [31].

4. Biologics and Peptide Drug Delivery

Some of the challenges associated with biologics are enzymatic degradation and short half-lives, which are common in TNF- 2 and IL-6 blockers, as well as anti-inflammatory peptides. The low-energy gel of nanogels is hydrated, thus offers high protective properties to the delicate biomacromolecules, which leads to preserving stability and guaranteeing their release. The conjugation of hyaluronic acid or peptide-specific conjugation in specific nanogel systems is further improved to increase the uptake by inflamed synovial cells, leading to better treatment in RA [32].

5. Evidence from *In Vitro* Evaluation

In vitro experiments have continuously shown that nanogels offer controlled, sustained release of drugs, which can be up to 24 96 hours depending on polymer composition and method of drug loading. The Mucoadhesion tests indicate that the nanogels interact with models of the synovial tissue and swelling studies prove that nanogels are sensitive to changes in the pH and the temperature in the body. These

findings support their appropriateness when it comes to long-term therapeutic concentrations of joint tissues [33].

6. Evidence from *In Vivo* Arthritis Models

Nanogel preparations are widely tested *in vivo* and on models of carrageenan induced paw edema, complete Freunds adjuvant (CFA) induced arthritis, and collagen induced arthritis (CIA). In all these models, nanogels have been shown to have a lesser paw swelling, decreased levels of inflammatory cytokines, enhanced mobility, and inhibited cartilage erosion. The long-time retention of nanogels in the joint cavity also increases its levels of therapeutic efficacy and decreases the dosage frequency, which is a significant advantage compared to traditional formulations [34].

7. Overall Therapeutic Outcomes

Across preclinical studies, nanogel-based drug delivery systems show remarkable benefits [35]:

- Significant reduction in inflammation and edema,
- Superior cartilage preservation,
- Longer intra-articular retention,
- Enhanced suppression of inflammatory cytokines,
- Lower systemic toxicity, and
- Improved functional recovery.

Table 2: Drugs incorporated in nanogels and their key therapeutic advantages [36]

Drug Class	Example Drugs	Benefits of Nanogel Delivery
NSAIDs	Flurbiprofen, Diclofenac	Sustained release, deeper tissue penetration, reduced systemic toxicity
Corticosteroids	Betamethasone, Dexamethasone	Prolonged joint retention, strong cytokine suppression
DMARDs	Methotrexate, Leflunomide	Improved targeting, reduced hepatotoxicity, enhanced anti-inflammatory effect
Biologics/Peptides	TNF inhibitors, IL-6 blockers	Stability protection, controlled release, receptor-specific targeting

Current Challenges and Future Perspectives

Nanogels possess a number of challenges that reduce their implementation into clinical practice despite their potential in therapy. Mass production is still a challenging task because it is hard to maintain stability, there is a difference between batches, and cross-linking in polymers is a complicated process. There is also the lack of long-term safety data and lack of standard evaluation guidelines in order to achieve regulatory approval. Nevertheless, new developments like smart stimuli-responsive nanogels (pH-, ROS-, and enzyme-sensitive), dual-, or multi-drug delivery systems, and personalized preparations, which are being optimized by artificial intelligence, are promising new avenues of improving therapeutic specificity. Through further development of innovation and clinical trials, the nanogel-based systems have great potential of becoming the next-generation osteoarthritis and rheumatoid arthritis treatment [37].

Conclusion

Nanogels are a revolutionary platform of localized therapy of osteoarthritis and rheumatoid arthritis. Their extraordinary characteristics such as high-water content, tunable structure, strong bioadhesion and release stimuli allow accurate and controlled delivery of a variety of therapeutic agents. Nanogels improve the retention of the joint, increase the availability of drugs, and decrease systemic exposure, overcoming the significant shortcomings of traditional therapies. Nanogels have a great potential to transform the management of arthritis in the future and become a part of safer, more effective and long-term treatment methods due to the ongoing technological evolution, such as smarter polymer design, multi-drug loading, and AI-driven optimization.

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