Pharmedico Publishers
International Journal of Pharmaceutical Science and Medicine
Volume 3, Issue 2 (2025): 59-69
DOI: 10.70199/IJPSM.3.2.59-69

REVIEW ARTICLE

ISSN: 2584-1610 (Online)

INNOVATIVE NANOGEL DRUG DELIVERY SYSTEMS FOR ARTHRITIS THERAPY *IN VITRO* EVALUATION AND CLINICAL TRANSLATION CHALLENGES

Shahina Rukhsar*, Ram Babu Sharma, Sakshi Tomar

Himalayan Institute of Pharmacy, Kala-Amb, Sirmour - 173030, Himachal Pradesh, India.

Article History
Received: 08 February 2025
Revised: 17 March 2025
Accepted: 07 June 2025
Published: 25 June 2025

Correspondence should be addressed to
Shahina Rukhsar,
Himalayan Institute of Pharmacy,
Kala-Amb, Sirmour - 173030,
Himachal Pradesh, India.

Email- shahirukhsar35@gmail.com

ABSTRACT: Background: Arthritis, a collective term for debilitating joint disorders such as rheumatoid arthritis (RA) and osteoarthritis (OA), continues to outpace therapeutic advancements, leaving millions with pain, disability, and limited options. Traditional treatments suffer from non-specific distribution, systemic side effects, and frequent dosing. In this landscape, nanogels—intelligent, stimuli-responsive drug carriers-are redefining the possibilities of precision medicine. By mimicking the body's soft tissue environment and responding to pathological cues, nanogels hold the promise of delivering drugs exactly where and when they are needed. **Methods:** This review synthesizes findings across materials science, cellular biology, and pharmaceutical engineering. Recent innovations in nanogel synthesis (*e.g.,* click chemistry, ionic gelation) and drug encapsulation strategies were analyzed alongside *in vitro* studies using chondrocytes, macrophages, and fibroblast-like synoviocytes. Evaluation metrics included cytotoxicity, cellular uptake, drug release kinetics, and inflammatory cytokine suppression. Key bottlenecks in regulatory translation and manufacturing were critically assessed. **Results:** Nanogels showcased high biocompatibility, targeted delivery to inflamed tissues, and controlled release triggered by pH, enzymes, or redox gradients within arthritic joints. *In vitro,* they significantly suppressed pro-inflammatory markers such as TNF-α and IL-6 while maintaining cellular viability. Yet, clinical translation is hindered by scale-up complexity, reproducibility challenges, and limited human data. **Conclusion:** Nanogels are not merely carriers-they are adaptive, bioinspired systems poised to revolutionize arthritis therapy. With smart design and strategic collaboration across disciplines, these nanostructures could move from lab bench to clinic, ushering in a new era of joint-specific, patient-personalized drug delivery.

Keywords: Nanogels, Arthritis Therapy, Targeted Drug Delivery, *In Vitro* Evaluation, Clinical Translation

I. INTRODUCTION

Musculoskeletal diseases (such as arthritis, a group of over a hundred conditions affecting the connective tissues and joints) are a primary cause of pain, disability and inability to move in every part of the world. As well as the disease of rheumatoid arthritis (RA), the problem of osteoarthritis (OA) is exceptionally widespread in society and has a disastrous effect on the lives of the population. Rheumatoid Arthritis (RA) is an inflammatory condition whose symptoms include chronic pains, cartilage degeneration, and erosion of the bones, mostly pertaining the synovial joints [1]. Osteoarthritis (OA) is most of the time characterized by joint deformity and reduced locomotion yet it is framed by a biochemical and mechanical wearing down of cartilage. The World Health Organization (WHO) claims that the global community has more than 350 million people living with arthritis and as such, cases are estimated to grow exponentially due to certain factors like being aged, reduced physical activity, and even the obesity epidemic [2]. There are conventional and biological disease-modifying antirheumatic drugs (DMARDs), analgesics, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and other pharmacological remedies; unfortunately, those therapies are regularly associated with the low bioavailability, systemic toxicity, and unspecificity. Most drugs lack sufficient build-up in the inflamed joints and produce undesirable side effects on normal tissues because of systemic administration of such medication and general distribution in the body. There are reduced compliance and efficacy of treatment over time due to daily frequency and drug resistance [3].

The recent revolution in the pharmaceutical industry is the nanotechnology, which enables researchers to develop nanoscale carriers that have enhanced drug solubility, circular time, and site-specific release, or say, to have some other advantages. Among these platforms, nanogels have their particular interest as nanosized, soft and cross-linked networks of the hydrophilic polymers. They are able to coordinate when and how drugs are released in the space and time according to the local environmental cues such as temperature, redox, enzyme levels and pH. Unique characteristics of nanogels include, high water content (such as real tissues) modifiable elasticity, large surface area to coat drugs onto and they are fairly biocompatible [4].

The purpose of the review is to have an extensive study of the innovative potential of nanogel-based drugs delivery systems

regarding arthritis. It concentrates on the structural and functional properties of them and emphasizes recent *in vitro* experiments that confirmed the successfulness of them, and thoroughly discusses obstacles that impede their clinical translation. This article offers excitement toward the field of nanogels through a glimpse of what is ahead in the treatment of arthritis due to a combination of knowledge in nanomedicine, pharmacology, and rheumatology [5].

2. Nanogels: Structure, Composition, and Properties

Recently it has been brought to our notice that nanogels a highly versatile hydrogel system in a nanoscale has a high potential as a drug delivery system to inflammatory diseases in the long run such as arthritis. Their three-dimensional and cross-linked polymeric networks retain much water or biological fluids with little effect on their mechanical strengths [6]. They can freely circulate in the bloodstream, gather within a target tissue, and interact with cells with the range of sizes of 20 200 nm. They can achieve high biocompatibility, as well as incorporate wet and fat molecules, which makes them appropriate choices whenever the local or systemic promulgation of anti-arthritic drugs is concerned. Exploring structural characteristics, polymeric contents, physicochemical characteristics, and biological safety features of nanogels is essential in grasping the enormous therapeutic possibilities of the nanogels in managing arthritis [7].

2.1 Structural Features and Network Morphology

Nanogels can be of a wide morphological range including basic homogenous spheres up to complex core-shell structures with numerous functionalities. The core-shell architecture is used with a shell being a polymer coat around a core that is charged with a drug and thus, may stabilise, protect, and respond to the environment. In response to alterations in pH, redox conditions, or enzyme activity, medicinal agents at certain locations can be adjustably released in this structure [8]. The internal polymeric network of the nanogel is dictated by the nature and extent of the cross-linking, which can be of physical type (e.g. hydrogen bonds or ionic interactions) and chemical type (e.g. covalent bonds). This network shape influences such important factors as mechanical strength, the possibility to swell, rates of diffusion of medication, and the ability to react to biological environments. The nanogels applied in the treatment of arthritis should be flexible and strong as well because the diseased tissue is mechanically and enzymatically active [9].

2.2 Composition: Natural and Synthetic Polymer Sources

Nanogels come from a variety of sources, including natural, synthetic, or hybrid materials, and their polymeric composition determines their functionality and bio-compatibility [10].

Natural polymers offer distinct advantages in terms of biocompatibility, biodegradability, and intrinsic bioactivity. Common natural polymers include:

- Chitosan, derived from chitin, possesses cationic properties that allow it to interact with negatively charged cell membranes and mucosal surfaces, offering enhanced adhesion and controlled drug release. It also exhibits mild antimicrobial and anti-inflammatory properties beneficial for arthritis treatment [11].

- Hyaluronic acid (HA) is particularly relevant to joint diseases due to its presence in synovial fluid and cartilage. It binds to CD44 receptors, which are overexpressed in inflamed tissues, allowing for active targeting of nanogels [12].

- Alginate, gelatin, and dextran provide soft, biocompatible matrices with customizable degradation profiles and are often used in enzyme- or pH-responsive systems [13].

Synthetic polymers provide superior control over molecular weight, structure, and physicochemical behavior. Widely used examples include:

- Polyethylene glycol (PEG), a non-toxic, hydrophilic polymer that enhances solubility, reduces immunogenicity, and prolongs circulation time [14].

- Poly(N-isopropylacrylamide) (PNIPAM), known for its thermoresponsive behavior, undergoes volume changes near physiological temperatures, making it suitable for temperature-triggered drug release [15].

- Polyacrylic acid (PAA) and poly(lactic-co-glycolic acid) (PLGA) offer structural stability and controlled biodegradation [16].

To achieve a synergy between bioactivity and functional precision, researchers are delving deeper into hybrid nanogels that combine natural and synthetic polymers. For example, chitosan-PLGA systems and HA-PEG conjugates both offer biocompatibility and mechanical strength [17].

2.3 Key Physicochemical and Functional Properties

Nanogels have a number of important physicochemical features that set them apart from other arthritis treatments. Their ability to encapsulate both small molecules and large biologics, such as proteins and nucleic acids, is facilitated by their high water content, which also gives them a soft, tissue-like texture [18].

Another vital feature is their stimuli-responsive behavior, enabling precise and intelligent drug release in response to specific triggers. In the context of arthritis:

- pH-responsive nanogels exploit the acidic environment of inflamed synovial joints to release drugs selectively at the diseased site.

- Redox-responsive nanogels take advantage of elevated glutathione levels within inflammatory cells, leading to triggered disassembly and drug unloading.

- Enzyme-responsive systems can release their payload in the presence of overexpressed enzymes like matrix metalloproteinases (MMPs), which are abundant in degenerative cartilage [19].

Nanogels have adjustable particle size, which has been used to increase therapeutic efficacy. The 50-150 nm nanogels can passively accumulate in developing lesion owing to the increased permeability and retention (EPR) effect, evade clearance by the renal system and prevent phagocytosis. Active targeting can be enhanced further by surface modification (such as PEGylation or conjugation to targeting ligands e.g. antibodies or folic acid) to reduce off-target action [20].

2.4 Biodegradability, Biocompatibility, and Safety Considerations

The chronic illnesses, like arthritis, largely depend on the long-time safety of the distribution system. Nanogels are perfect in this regard since they are biodegradable because they can disintegrate into harmless, urinary metabolites. Degradation pathways can also be altered through insertion of lable bonds reacting to a redox, hydrolysis or enzyme cleavage. As an example, in the presence of intracellular thiols, disulfide-crosslinked nanogels degrade, ensuring drug release to cytosol that causes minimal cell toxicity to any other region of the cell [21].

Nanogels are usually highly biocompatible when composed of natural materials or other materials accepted by FDA. They exhibit this tendency in the lab and in living animals as they exhibit low degrees of cytotoxicity and tend to trigger minimal immunological responses. Surface functionalization, conjugation with stealth polymers, e.g. PEG, a reduction in mononuclear phagocyte system identification and opsonization help enhance systemic circulation and delay clearance [22].

Another factor that renders nanogel appealing to clinicians is its versatility as far as routes of administration are concerned. These are intravenous, oral and intra-articular. They are easily injectable and can be cured with ease in order to release the anti-inflammatory or disease-modifying drugs directly into the joint cavities, where they are allowed to act with precision as well as over a long period [23].

Table 1: Classification of Nanogels by Polymer Type, Cross-Linking Method, and Responsiveness [24]

S. No.	*Polymer Type*	*Polymer Source*	*Cross-linking Method*	*Stimuli Responsiveness*	*Key Applications*
1	Chitosan	Natural	Ionic/Covalent	pH-responsive	Anti-inflammatory drug delivery
2	Hyaluronic Acid (HA)	Natural	Enzymatic/Covalent	Enzyme-responsive	Targeting inflamed joints
3	PEG	Synthetic	Covalent	Non-responsive/Stealth	Stealth nanocarriers
4	PNIPAM	Synthetic	Thermal gelation	Temperature-responsive	Thermo-sensitive release
5	Dextran	Natural	Oxidative/Covalent	Redox-responsive	Macrophage-targeted delivery
6	Alginate	Natural	Ionic (Ca^{2+})	pH-responsive	Oral and local delivery
7	PLGA–PEG	Hybrid	Covalent	Dual pH and enzyme	Controlled systemic delivery
8	Gelatin	Natural	Thermal/Chemical	Temperature-responsive	Cartilage regeneration
9	Polyacrylic Acid (PAA)	Synthetic	Chemical	pH-responsive	NSAID release in joints
10	HA–PEG	Hybrid	Click chemistry	Enzyme and pH-responsive	Targeted arthritis therapy
11	Poly(β-amino esters)	Synthetic	Self-cross-linking	pH and redox	Gene delivery to synovium
12	Carrageenan	Natural	Ionic	pH-responsive	Anti-rheumatic herbal delivery
13	Silated Hydroxypropyl Methylcellulose (Si-HPMC)	Semi-synthetic	Covalent	Shear-responsive	Injectable nanogels for joints
14	Cellulose Nanofibers	Natural	UV/Chemical	Mechanical and pH	Bioadhesive hydrogel systems
15	Zwitterionic Polymers	Synthetic	Covalent	Dual stimuli	Anti-fouling and anti-inflammatory delivery

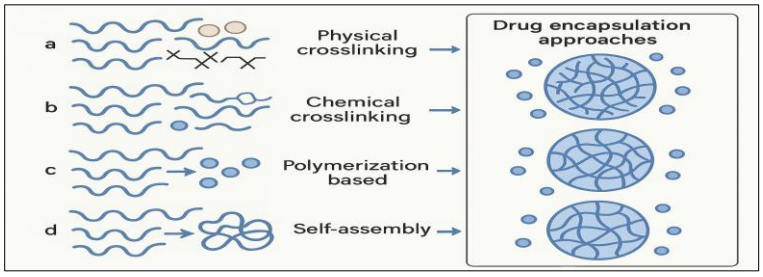

Fig. 1: Schematic of nanogel synthesis techniques and drug encapsulation approaches [25]

3. Drug Loading and Release Kinetics

3.1 Mechanisms of Drug Encapsulation

Nanogels can effectively entrap a wide range of medicinal compounds through two fundamental ways which are likely to include physical entrapment and covalent bonding. Hydrogels may passively entrap pharmaceuticals into their matrix via non-covalent interactions such as a hydrogen bond van der Waals forces, hydrophobic effects, or ionic interactions. It is suitable in cases where the medication or the small size compound to be gathered could be hydrophilic and be able to find its way through the porous structure of the nanogel [26]. However, in covalent bonding drug molecules are instead linked to the polymer backbone using cleavable linkers. Engineering such linkers makes possible the controlled and prompted release of drugs in response to some stimulus, including pH or redox changes or enzyme activity. Covalent conjugation yields better stability and selective activation within the environment of the inflamed tissue hence covalent conjugation is most effective in biologics or drugs which are lowly soluble [27].

Table 2: Summary of Drug Release Studies in Arthritis-Relevant Nanogels [33]

S. No.	*Polymer Type*	*Drug Encapsulated*	*Stimuli Responsiveness*	*Key Findings*
1	Chitosan-PEG	Methotrexate	pH-responsive	Enhanced release in acidic joint environment; improved anti-inflammatory effect.
2	Hyaluronic acid-based	Dexamethasone	Enzyme-responsive (MMPs)	Targeted degradation in inflamed joints; reduced systemic toxicity.
3	PNIPAM-co-acrylic acid	Celecoxib	Temperature and pH	Dual-responsive system showed precise release and joint accumulation.
4	Gelatin–dextran	Tocilizumab	Enzyme (collagenase)	Sustained release over 7 days; effective in reducing joint swelling.
5	PEGylated poly(lactic-co-glycolic acid)	Etanercept	Redox-sensitive (GSH)	Selective intracellular release in macrophages.
6	Poly(N-vinylcaprolactam)	Curcumin	Thermoresponsive	Improved solubility and joint retention of curcumin.
7	Alginate-chitosan	Indomethacin	pH-sensitive	pH-triggered release in synovial fluid; minimized gastric irritation.
8	HA–PLGA	TNF-α siRNA	Enzyme and pH dual-responsive	Gene silencing in synovial fibroblasts; reduced cartilage damage.
9	Poly(acrylic acid)-grafted dextran	Prednisolone	ROS-sensitive	ROS-mediated burst release in inflamed tissues.
10	Hydroxyethylcellulose-PEG	Naproxen	Sustained release (non-triggered)	Extended drug release over 48 hours; reduced dosing frequency.
11	Poly(L-glutamic acid)	Tocilizumab	pH and enzymatic	Improved synovial uptake; suppressed IL-6 levels.
12	Silk fibroin–PEG	Leflunomide	Biodegradable	Enhanced bioavailability; joint-targeted distribution observed.
13	Dextran-spermine	siRNA against TNF-α	pH and redox dual-responsive	Protected siRNA delivery to inflamed joints; potent anti-inflammatory response.
14	Collagen hydrogel + chitosan	NSAIDs (mixed)	Enzymatic	Tuned degradation via MMP levels; personalized dosing potential.
15	Hyaluronic acid–PEI	IL-1Ra gene plasmid	pH-responsive	Efficient transfection in synoviocytes; sustained IL-1 blockade *in vivo*.

3.2 Controlled and Sustained Drug Release

The ability of nanogels to establish regulated and sustained medication delivery is a necessary characteristic that makes them valuable in the control of chronic conditions like arthritis. Release profile can be customized by a variety of parameters, such as determination of cross-linking density, rate of polymer breakdown, hydrophilicity, network mesh size, and so forth. Nanogels can be designed to exhibit two different kinds of drug release regimes zero-order (constant-rate) release and biphasic release, and the former can be used to achieve rapid therapeutic efficiencies and the latter can be used to achieve a protracted treatment period. Consequently, frequency of dose is reduced, patient compliance is improved and the concentration of the drug at the target site is maintained and therefore chances of occurrence of adverse effects which are as a result of changes in drug concentration are minimized [28].

3.3 Stimuli-Responsive Drug Release

The ability of nanogels to respond to specified physiological or pathological stimuli enables them to release medication in specific sites and upon demand which is one of the most unique attributes. The condition of arthritis can be used to improve therapeutic precision using various stimuli. Inflammatory joints have an acidic environment, which can be used to faster drug release programs *via* pH responsive

nanogels. The enzyme-responsive systems are activated by overexpression of some enzymes in the synovial tissue (such as matrix metalloproteinases (MMPs)) and cartilage of people with arthritis [29]. Temperature-sensitive nanogels, like those made using polymers, such as PNIPAM, are ideal in conditions of local inflammation-activated release since they can undergo sol-gel transition at or within the body range of temperatures.

Redox-sensitive nanogels can deliver drugs in activated synoviocytes and macrophages when the redox-sensitive nanogels become activated upon sensing a rise of glutathione and reactive oxygen species (ROS) in the inflammatory cells. These smart delivery mechanisms minimize the systemic exposure and increase the specificity of therapy to a large extent [30].

3.4 Targeted *vs.* Systemic Delivery Approaches

Depending on the medicinal property, and clinical need, targeted or systemic nanogel delivery can be achieved. Surface alterations (e.g. PEGylation) are commonly required to enhance the circulation time and reduce immune clearance when delivered systemically, such as intravenous injection. It is possible to specifically bind receptors overexpressed in arthritic tissue (e.g. hyaluronic acid or folic acid) onto nanogels. This improves the therapeutic depositions within the inflamed joints [31]. Local delivery or rather intra-articular injection has also emerged as another alternative, and this method could be used to introduce nanogels into target joints.

The method minimizes the systemic side effects and maximizes local concentration of medication at site of disease. It gives improved inflammatory control and prolonged joint retention of biologics, corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs) [32].

4. Nanogels in Arthritis Therapy

4.1 Applications Across Arthritis Types

A recent concern on the adaptation of nanogels as a delivery vehicle in the management of a variety of forms of arthritic conditions, including gout, osteoarthritis (OA), and rheumatoid arthritis (RA), has become a matter of concern. Nanogels are useful in targeted and longer-term medication release in reducing inflammation and slowing down the progression of rheumatoid arthritis (RA), a disease that is associated with the inflammatory responses and chronic inflammation causing the destruction of the synovial joints [34]. Nanogels can be applied in the case of osteoarthritis (OA), mechanical wear, and cartilage degeneration during which drugs that protect chondrocytes and have anti-inflammatory properties are delivered directly to the area of the pathology. Nanogels would allow the custom administration of anti-gout drugs such as colchicine or uricase, reducing systemic side effects and focusing therapy precisely in case of a burge During off days, they would allow repeated anti-gout doses. Gout is an inflammation caused by the acute crystals of urate [35].

4.2 Encapsulation of Therapeutic Agents

Nanogels have proven to be very effective in encapsulation as well as transportation of a myriad of medications used in treating arthritis. These include various drugs, such as the ones that alter the immune system (DMARDs) such as leflunomide and methotrexate, NSAIDs including naproxen and indo-methacin, corticosteroid medications such as dexamethasone and prednisolone as well as biologic drugs such as interleukin inhibitors and/or anti-TNF alpha antibodies. The soft hydrated nature of nanogels entraps therapeutic molecules to be enzyme resistant, and the hydrated nature permits a high loading dose of drug. Gene therapy using plasmid DNA or short interfering RNA to express anti-inflammatory cytokines is a recent precision-medicine advance and nanogels have been successfully utilised to incorporate this payload [36].

4.3 Site-Specific Delivery: Intra-Articular vs. Systemic

A major attribute of nanogels is the ability to deliver medication at specific sites. Nanogels would allow high local drug concentration and prolonged residence time with low systemic availability by administration intra-articularly into the joint cavity. In the case of biologics and corticosteroids, this is the most ideal approach to the use of these agents when severe arthritis symptoms are in effect. Conversely, to be active systemically it is possible to functionalize nanogels with targeted ligands (e.g., hyaluronic acid, folate, antibodies) and subsequently inject them intravenously at which point they will congregate in the inflammatory joint. When these ligands bind to the overexpressed receptors on synovial cells or inflammatory cells, a more specific delivery to a joint is obtained with a minor off target effect [37].

4.4 Therapeutic Efficacy and Inflammation Reduction

The efficacy of nanogel-based formulations in alleviating joint inflammation, cartilage degradation, and synovial hyperplasia has been proven in a plethora of *in vitro* and *in vivo* investigations. Nanogels provide stimuli-responsive release in inflammatory settings, enhance drug penetration into dense cartilage matrices, and extend the retention duration of medicines [38]. The anti-inflammatory efficacy, dose requirements, and systemic side effects of nanogel-encapsulated therapies are all higher than those of free medicines. Joint edema, inflammatory cytokine levels, and histopathological damage were all significantly reduced in arthritis animal models treated with nanogels containing methotrexate, curcumin, or anti-TNF biologics. These encouraging findings highlight the possibility that nanogels can alter the course of diseases in addition to alleviating their symptoms [39].

5. *In Vitro* Evaluation Strategies

5.1 Cell Models for Arthritis

Preclinical research of nanogel-based arthritis therapeutics relies heavily on *in vitro* evaluation, which allows for the assessment of therapeutic potential, functionality, and safety.

The inflammatory milieu of arthritic joints is mimicked using many cell models that are relevant to arthritis. One such group consists of fibroblast-like synoviocytes (FLS), which are important in mediating joint inflammation and cartilage invasion; they are isolated from individuals with rheumatoid arthritis [40]. Nanogel interactions are also studied using macrophages (*e.g.*, RAW 264.7 cells or THP-1 derived macrophages) because of their important function in immune activation and cytokine generation. In order to determine how well nanogels maintain the cartilage matrix and how well drugs penetrate dense extracellular tissues, researchers employ chondrocytes, which are the cell type naturally found in cartilage [41].

5.2 Biocompatibility Testing

It is crucial to ensure that nanogels are biocompatible before they are translated into clinical practice. The MTT assay and live/dead labeling are two standard methods for determining cellular viability; the former uses metabolic activity as a measure and the latter uses membrane integrity to differentiate between healthy and injured cells. It is possible to do extra tests for hemolysis and cytotoxicity, especially if systemic injection is planned. All of the cells tested, both target and non-target, showed no signs of cytotoxicity when exposed to nanogels at therapeutic doses [42].

5.3 Evaluation of Anti-inflammatory Effects

The anti-inflammatory effects of nanogels are usually measured utilizing cytokine assays to confirm their therapeutic efficacy *in vitro*. The amounts of pro-inflammatory markers like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) in the supernatants of treated macrophages or synoviocytes can be measured using enzyme-linked immunosorbent assays (ELISA). An successful inhibition of inflammatory pathways is indicated by a decrease in cytokine release following nanogel treatment, particularly when compared to free medicines. In order to measure the amounts of inflammatory mediators and enzymes like COX-2 and MMPs, several studies additionally use gene expression analysis (qRT-PCR) [43].

5.4 Cellular Uptake and Intracellular Processing

When using nanogels for delivery, it is essential that the cells efficiently absorb the agents and digest them within the cell. This is especially true for intracellular-acting agents like siRNA, proteins, or other substances. Quantification of uptake across several cell lines is made possible by fluorescently labeling nanogels (e.g., with FITC or Rhodamine) and then viewing them using confocal laser scanning microscopy (CLSM) or flow cytometry [44]. The process of endosomal escape, which is crucial for intracellular delivery, is frequently assessed using colocalization experiments using endo/ lysosomal markers, such as LysoTracker. Predicting *in vivo* clearance and sustained release behavior can be achieved by studying nanogel biodegradation within cells. This can be done by employing polymer-specific degradation profiles or by releasing encapsulated fluorescent probes [45].

Table 3: Recent *In Vitro* Studies on Nanogels for Arthritis [47]

S. no.	*Nanogel Formulation*	*Encapsulated Drug*	*Cell Line Used*	*Key In Vitro Findings*
1	Chitosan–hyaluronic acid nanogel	Methotrexate	RA-FLS	Reduced IL-6 and TNF-α secretion; >80% cell viability; effective anti-proliferative action.
2	PEGylated PNIPAM nanogel	Dexamethasone	RAW 264.7	Suppressed NO and cytokine production under LPS stimulation.
3	Alginate–chitosan nanogel	Indomethacin	C28/I2 human chondrocytes	Sustained release for 48 h; no cytotoxicity; maintained chondrocyte viability.
4	PLGA–HA nanogel	TNF-α siRNA	RA-FLS	Efficient siRNA delivery; knockdown of TNF-α expression confirmed via qRT-PCR.
5	PAA–dextran ROS-responsive nanogel	Prednisolone	THP-1 derived macrophages	Enhanced release in ROS-rich environment; significant cytokine reduction.
6	Collagen–chitosan hydrogel nanogel	Celecoxib	SW982 synoviocytes	Prolonged anti-inflammatory effect; no cellular toxicity observed.
7	Dextran–spermine nanogel	TNF-α siRNA	RAW 264.7	High transfection efficiency; potent TNF-α suppression and macrophage deactivation.
8	Silk fibroin-based nanogel	Leflunomide	RA-FLS	High encapsulation efficiency; decreased MMP expression; increased apoptosis in FLS.
9	Hyaluronic acid–PEI nanogel	IL-1Ra gene plasmid	SW982 & primary RA-FLS	Successful gene transfection; IL-1 receptor antagonist expression sustained over 48 h.
10	PNIPAM–acrylic acid nanogel	Naproxen	C20A4 chondrocytes	Thermo-responsive behavior; anti-catabolic effects maintained in inflamed environment.
11	Gelatin–dextran nanogel	Tocilizumab	RA-FLS	Targeted binding to inflamed cells; downregulation of IL-6 pathway.
12	HA–PLGA nanogel	Curcumin	THP-1 macrophages	Enhanced uptake; suppressed oxidative stress and inflammatory cytokine production.

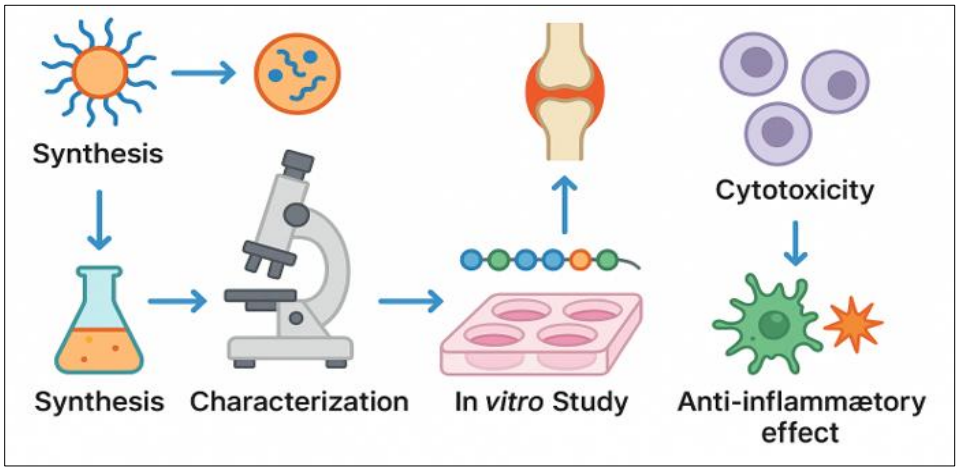

Fig. 2: Workflow for *in vitro* evaluation of nanogels for arthritis therapy [46]

6. *In Vivo* Studies and Preclinical Insights

6.1 Animal Models for Arthritis Evaluation

To get nanogel-based arthritis treatments from the lab to the clinic, *in vivo* investigations are essential. Two of the most popular animal models are the collagen-induced arthritis (CIA) mouse model and the adjuvant-induced arthritis (AIA) rat model. The former simulates the autoimmune process and joint inflammation of rheumatoid arthritis, while the latter assesses chronic inflammation, synovial hyperplasia, and bone erosion. Nanogels' therapeutic potential can be evaluated in a physiologically appropriate and immunologically competent system using these models [48].

6.2 Biodistribution, Joint Targeting, and Retention

Inflamed joints can be effectively treated with drugs delivered using nanogel devices. Fluorescent or radiolabeled nanogels attached to targeted ligands, such as hyaluronic acid (HA) or folate, show a preference for accumulation in arthritic joints in in vivo biodistribution experiments. A mechanism for joint-specific localization, these systems use receptor-mediated endocytosis or the increased permeability and retention (EPR) effect. Evidence suggests that nanogels, when administered intra-articularly, improve local retention even further; research has shown that these gels can remain in the joint cavity for days-if not weeks-after delivery [49].

6.3 Therapeutic Efficacy and Histological Outcomes

Studies in animals treated with nanogel have shown a considerable improvement in joint swelling, paw thickness, and arthritis scores when compared to those given free medication controls. Results from histological examinations of the affected joints show significant improvements, including less synovial inflammation, retained cartilage integrity, and less bone erosion. Reduced systemic adverse effects and more local therapeutic benefits are achieved through the sustained release and focused action of encapsulated medications administered via nanogels, such as methotrexate, dexamethasone, or curcumin. This allows for better efficacy at lower doses [50].

6.4 Safety and Immunogenicity Assessment

Bringing nanogels into clinical application requires utmost care to ensure their safety. Monitoring blood biochemistry, histopathology of main organs (liver, kidney, and spleen), and body weight are all part of in vivo toxicity studies. Low systemic toxicity and good tolerance are characteristics of most nanogel formulations. This is particularly true for formulations made of biocompatible and biodegradable polymers like PLGA, chitosan, or PEG. Future studies should be well-designed and include long-term follow-up because immunogenicity evaluations reveal modest immune activation in most instances, but formulation-specific responses may occur [51].

7. Challenges in Clinical Translation

7.1 Manufacturing Scalability and Reproducibility

It is crucial to provide scalable and reproducible manufacturing when bringing nanogel-based drug delivery devices from the lab to the clinic. Good Manufacturing Practice (GMP) requirements demand precision and consistency, which is sometimes lacking in laboratory-scale processes like emulsion polymerization or ionic gelation. Sterility, irregular particle size, drug loading efficiency, batch-to-batch variability, and clinical results are all factors that can have a significant impact on regulatory approval. There is still a significant challenge in adapting advanced techniques, such as microfluidics and automated nanoprecipitation systems, to commercial scale in order to increase scalability and homogeneity [52].

7.2 Regulatory Classification and Approval Hurdles

The composition and mode of action of nanogels place them in a regulatory gray zone, as they are often vaguely classed as medicines, biologics, or medical devices. Since nanogel performance may not be effectively predicted by conventional toxicological, pharmacokinetics, and bioequivalence data, this creates difficulties in the approval routes. Although regulatory agencies like the FDA and EMA demand a mountain of data on pharmacodynamics, immunogenicity, and safety in

preclinical studies, no one paradigm has been developed with nanogel systems in mind. Particularly for multifunctional or gene-delivering nanogels, the lack of a precise categorization can impede or halt advancement towards clinical trials [53].

7.3 Stability and Storage Issues

Unfortunately, nanogels, especially those made of sensitive materials or natural polymers, do not always hold up well under physiological and storage circumstances. Conditions such as acidity, heat, light, and enzymatic activity might cause aggregation or degradation to occur too soon, which in turn impacts the efficacy of the treatment. Important challenges include keeping physicochemical qualities constant and sterility intact throughout time. Though currently under investigation, potential strategies like lyophilization, cryopreservation, or polymer modification could increase formulation complexity and associated costs [54].

7.4 Interpatient Variability and Immune Response

Nanogel pharmacokinetics and therapeutic results are highly patient-specific and depend on variables like age, immunological status, co-morbidities, and genetic progeny. A number of formulations, particularly those containing cationic polymers or non-endogenous ligands, have the potential to trigger immunological responses. Hyposensitivity, complement activation, or quick clearance could occur as a result of this. An emerging method to limit variability is the development of individualized nanogels or modular platforms suited to specific patient profiles. However, this approach introduces additional logistical and regulatory challenges [55].

7.5 Case Examples of Clinical Translation

A small number of platforms based on nanogels have made it to the early stages of clinical trials, despite the obstacles. Pilot trials for rheumatoid arthritis have demonstrated that HA-modified nanogels delivering methotrexate increase joint retention and lower systemic toxicity, for instance. There is encouraging safety data for the intra-articular use of dexamethasone-loaded nanogels in the treatment of osteoarthritis. There has to be better translational pipelines, multicenter collaborations, and long-term safety data because most are still in the preclinical or investigational stages [56].

8. Future Directions and Emerging Trends

8.1 Smart Nanogels: Toward Multi-Stimuli Responsive and Self-Healing Systems

An enormous leap in the intelligence and adaptability of nanogels is possible in the next generation. Engineers are hard at work creating smart nanogels that can react to a wide range of physiological signals, including changes in temperature, redox state, enzyme activity, and pH. Nanogels that respond to several stimuli improve therapeutic accuracy and reduce systemic exposure by releasing drugs on demand into the microenvironment of arthritic joints. In addition, new self-healing nanogels that mimic the robustness of living tissues show potential for prolonged retention and repeated activation, especially in highly dynamic settings such as the synovial cavity [57].

8.2 Combination Therapy: Drug and Gene Co-Delivery

Emerging as potent tools to modify both symptoms and underlying disease mechanisms in arthritis, combination nanogel systems that carry conventional medicines and genetic material (e.g., siRNA, mRNA, CRISPR-Cas constructs) simultaneously are creating a stir. The use of these platforms allows for therapies that have two functions, such as reducing inflammation with NSAIDs or corticosteroids while simultaneously silencing genes for cytokines like TNF-α or IL-6. Not only can the co-delivery method improve therapeutic efficacy, but it may also help modify the disease and induce remission, which is especially important in cases with treatment-resistant RA [58].

8.3 Personalized Nanomedicine and AI-Driven Design

A rising trend toward individualized nanomedicine is being driven by the high degree of interpatient variability in the presentation of arthritis. Optimized polymer composition, surface changes, and release kinetics are being predicted using patient-specific biomarkers through the application of machine learning and AI-driven algorithms in the construction of nanogels that are tailored to individual patient profiles. By optimizing formulations, speeding up preclinical screening, and improving clinical trial design, these technologies have the potential to close the gap in translation by making predictions more accurately and efficiently [59].

8.4 Integration with Biosensors for Theranostics

"Theranostic systems" are emerging as a result of nanogels' merging with biosensor technologies. These systems integrate therapeutic delivery with real-time illness monitoring. Integrating biosensors into smart nanogels allows them to detect inflammatory markers (such as CRP and cytokines) and adapt the delivery of drugs on the fly. The ability to monitor the progression or recurrence of disease without intrusive procedures is made possible by this real-time feedback loop, which also guarantees precise treatment. Changes from reactive to proactive and adaptive therapy are brought about by these systems, which constitute a paradigm change in the management of chronic diseases [60].

CONCLUSION

Nanogels represent a transformative approach in the treatment of arthritis, offering a versatile, targeted, and biocompatible drug delivery platform capable of addressing the major limitations of conventional therapies. Their unique properties—including high water content, tunable size, responsiveness to biological stimuli, and ability to encapsulate a wide range of therapeutic agents—make them especially well-suited for localized and sustained drug delivery to inflamed joints.

Both *in vitro* and *in vivo* studies have demonstrated significant promise of nanogels in enhancing drug efficacy, reducing systemic toxicity, and improving patient outcomes in various forms of arthritis such as rheumatoid arthritis, osteoarthritis, and gout. Formulations loaded with DMARDs, corticosteroids, NSAIDs, and even biologics have shown potent anti-inflammatory effects, improved joint targeting, and better tissue regeneration in preclinical models. Despite these advancements, the path to clinical translation remains complex. Key barriers include manufacturing reproducibility, regulatory ambiguity, long-term stability, and immune response variability. Only a few nanogel-based formulations have reached early clinical investigation stages, underscoring the need for more robust standardization, interdisciplinary collaboration, and regulatory reform.

Looking forward, the future of nanogel technology in arthritis therapy lies in intelligent, multi-functional systems-those capable of personalized drug delivery, combination therapy, and real-time disease monitoring. Integrating AI-based design, biosensors, and theranostic capabilities may pave the way for truly next-generation treatments that are not only therapeutic but also predictive and adaptive. With continued research and innovation, nanogels have the potential to redefine the clinical landscape of arthritis management.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Hsieh LF, Mao HF, Lu CC, Hsu WL. Rheumatologic rehabilitation. InBraddom's Physical Medicine and Rehabilitation 2021 Jan 1 (pp. 606-626).
2. Brandt KD, Dieppe P, Radin EL. Etiopathogenesis of osteoarthritis. Rheumatic Disease Clinics of North America. 2008 Aug 1;34(3):531-59.
3. Gadzhanova S, Roughead E. Use of analgesic and anti-inflammatory medicines before and after initiation of biological disease-modifying antirheumatic drugs for rheumatoid arthritis. Journal of Clinical Pharmacy and Therapeutics. 2024;2024(1):8040681.
4. Vega-Vásquez P, Mosier NS, Irudayaraj J. Nanoscale drug delivery systems: from medicine to agriculture. Frontiers in Bioengineering and Biotechnology. 2020 Feb 18;8:79.
5. Tahara Y, Akiyoshi K. Current advances in self-assembled nanogel delivery systems for immunotherapy. Advanced drug delivery reviews. 2015 Dec 1;95:65-76.
6. Delgado-Pujol EJ, Martínez G, Casado-Jurado D, Vázquez J, León-Barberena J, Rodríguez-Lucena D, Torres Y, Alcudia A, Begines B. Hydrogels and Nanogels: Pioneering the Future of Advanced Drug Delivery Systems. Pharmaceutics. 2025 Feb;17(2):215.
7. Wang B, He X, Zhang Z, Zhao Y, Feng W. Metabolism of nanomaterials *in vivo*: blood circulation and organ clearance. Accounts of chemical research. 2013 Mar 19;46(3):761-9.
8. Motornov M, Roiter Y, Tokarev I, Minko S. Stimuli-responsive nanoparticles, nanogels and capsules for integrated multifunctional intelligent systems. Progress in polymer science. 2010 Jan 1;35(1-2):174-211.
9. Zhang H, Zhai Y, Wang J, Zhai G. New progress and prospects: The application of nanogel in drug delivery. Materials Science and Engineering: C. 2016;60:560-8.
10. Neamtu I, Rusu AG, Diaconu A, Nita LE, Chiriac AP. Basic concepts and recent advances in nanogels as carriers for medical applications. Drug delivery. 2017;24(1):539-57.
11. Patil SV, Nanduri LS. Interaction of chitin/chitosan with salivary and other epithelial cells-An overview. International Journal of Biological Macromolecules. 2017 Nov 1;104:1398-406.
12. Vincent HK, Percival SS, Conrad BP, Seay AN, Montero C, Vincent KR. Hyaluronic acid (HA) viscosupplementation on synovial fluid inflammation in knee osteoarthritis: a pilot study. The open orthopaedics journal. 2013;7:378.
13. Sobczak M. Enzyme-responsive hydrogels as potential drug delivery systems-state of knowledge and future prospects. International journal of molecular sciences. 2022 Apr 16;23(8):4421.
14. Ibrahim M, Ramadan E, Elsadek NE, Emam SE, Shimizu T, Ando H, Ishima Y, Elgarhy OH, Sarhan HA, Hussein AK, Ishida T. Polyethylene glycol (PEG): The nature, immunogenicity, and role in the hypersensitivity of PEGylated products. Journal of Controlled Release. 2022 Nov 1;351:215-30.
15. Papadakis CM, Niebuur BJ, Schulte A. Thermoresponsive Polymers under Pressure with a Focus on Poly (N-isopropylacrylamide)(PNIPAM). Langmuir. 2023 Dec 27;40(1):1-20.
16. Makadia HK, Siegel SJ. Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers. 2011 Aug 26;3(3):1377-97.
17. Kawee-ai A. Advancing Gel Systems with Natural Extracts: Antioxidant, Antimicrobial Applications, and Sustainable Innovations. Gels. 2025 Feb 8;11(2):125.
18. Li Y, Maciel D, Rodrigues J, Shi X, Tomás H. Biodegradable polymer nanogels for drug/nucleic acid delivery. Chemical reviews. 2015 Aug 26;115(16):8564-608.
19. Huang D, Qian H, Qiao H, Chen W, Feijen J, Zhong Z. Bioresponsive functional nanogels as an emerging platform for cancer therapy. Expert opinion on drug delivery. 2018 Jul 3;15(7):703-16.
20. Sivaram AJ, Rajitha P, Maya S, Jayakumar R, Sabitha M. Nanogels for delivery, imaging and therapy. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2015 Jul;7(4):509-33.
21. Altuntaş E, Özkan B, Güngör S, Özsoy Y. Biopolymer-based nanogel approach in drug delivery: basic concept and current developments. Pharmaceutics. 2023 Jun 2;15(6):1644.
22. Ma X, Li SJ, Liu Y, Zhang T, Xue P, Kang Y, Sun ZJ, Xu Z. Bioengineered nanogels for cancer immunotherapy. Chemical Society Reviews. 2022;51(12):5136-74.
23. Xie Z, Wang L, Chen J, Zheng Z, Srinual S, Guo A, Sun R, Hu M. Reduction of systemic exposure and side effects by intra-articular injection of anti-inflammatory agents for osteoarthritis: what is the safer strategy?. Journal of Drug Targeting. 2023 Jul 3;31(6):596-611.
24. Suhail M, Rosenholm JM, Minhas MU, Badshah SF, Naeem A, Khan KU, Fahad M. Nanogels as drug-delivery systems: A comprehensive overview. Therapeutic delivery. 2019 Nov 1;10(11):697-717.
25. Chacko RT, Ventura J, Zhuang J, Thayumanavan S. Polymer nanogels: a versatile nanoscopic drug delivery

platform. Advanced drug delivery reviews. 2012 Jun 15;64(9):836-51.
26. Grimaudo MA, Concheiro A, Alvarez-Lorenzo C. Nanogels for regenerative medicine. Journal of controlled release. 2019 Nov 10;313:148-60.
27. Mollazadeh S, Mackiewicz M, Yazdimamaghani M. Recent advances in the redox-responsive drug delivery nanoplatforms: A chemical structure and physical property perspective. Materials Science and Engineering: C. 2021 Jan 1;118:111536.
28. Zhang M, Hu W, Cai C, Wu Y, Li J, Dong S. Advanced application of stimuli-responsive drug delivery system for inflammatory arthritis treatment. Materials Today Bio. 2022 Mar 1;14:100223.
29. Abedi F, Ghandforoushan P, Adeli F, Yousefnezhad M, Mohammadi A, Moghaddam SV, Davaran S. Development of stimuli-responsive nanogels as drug carriers and their biomedical application in 3D printing. Materials Today Chemistry. 2023 Apr 1;29:101372.
30. Narayanan KB, Bhaskar R, Han SS. Recent advances in the biomedical applications of functionalized nanogels. Pharmaceutics. 2022 Dec 16;14(12):2832.
31. Attama AA, Nnamani PO, Onokala OB, Ugwu AA, Onugwu AL. Nanogels as target drug delivery systems in cancer therapy: A review of the last decade. Frontiers in Pharmacology. 2022 Sep 8;13:874510.
32. Wen J, Li H, Dai H, Hua S, Long X, Li H, Ivanovski S, Xu C. Intra-articular nanoparticles-based therapies for osteoarthritis and rheumatoid arthritis management. Materials Today Bio. 2023 Apr 1;19:100597.
33. Li M, Tian F, Guo J, Li X, Ma L, Jiang M, Zhao J. Therapeutic potential of Coptis chinensis for arthritis with underlying mechanisms. Frontiers in Pharmacology. 2023 Aug 11;14:1243820.
34. Chen L, Wang Y, Sun L, Yan J, Mao HQ. Nanomedicine strategies for anti-inflammatory treatment of noninfectious Arthritis. Advanced Healthcare Materials. 2021 Jun;10(11):2001732.
35. Di Francesco M, Fragassi A, Pannuzzo M, Ferreira M, Brahmachari S, Decuzzi P. Management of osteoarthritis: From drug molecules to nano/micromedicines. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2022 May;14(3):e1780.
36. Jana K, Ghosh S, Debnath B, Kumar Rout S, Kumar Sarangi M, Halder J, Kanti Rajwar T, Pradhan D, Kumar Rai V, Dash P, Das C. Recent Advancements of Hyaluronic Acid Nanoscaffolds in Arthritis Management. ChemistrySelect. 2024 Aug 27;9(32):e202402035.
37. Cao Y, Ma Y, Tao Y, Lin W, Wang P. Intra-articular drug delivery for osteoarthritis treatment. Pharmaceutics. 2021 Dec;13(12):2166.
38. Kesharwani D, Paul SD, Paliwal R, Satapathy T. Exploring potential of diacerin nanogel for topical application in arthritis: Formulation development, QbD based optimization and pre-clinical evaluation. Colloids and Surfaces B: Biointerfaces. 2023 Mar 1;223:113160.
39. Pinelli F, Ortolà ÓF, Makvandi P, Perale G, Rossi F. In vivo drug delivery applications of nanogels: a review. Nanomedicine. 2020 Nov 1;15(27):2707-27.
40. Wu Z, Ma D, Yang H, Gao J, Zhang G, Xu K, Zhang L. Fibroblast-like synoviocytes in rheumatoid arthritis: surface markers and phenotypes. International immunopharmacology. 2021 Apr 1;93:107392.
41. Cardoso M, Gaspar VM, Ferreira C, Silvestre R, Duarte IF, Mano JF. Macrophage-targeted shikonin-loaded nanogels for modulation of inflammasome activation. Nanomedicine: Nanotechnology, Biology and Medicine. 2022 Jun 1;42:102548.
42. Gu J, Clegg JR, Heersema LA, Peppas NA, Smyth HD. Optimization of cationic nanogel PEGylation to achieve mammalian cytocompatibility with limited loss of gram-negative bactericidal activity. Biomacromolecules. 2020 Mar 24;21(4):1528-38.
43. Kardos D, Marschall B, Simon M, Hornyák I, Hinsenkamp A, Kuten O, Gyevnár Z, Erdélyi G, Bárdos T, Paukovits TM, Magos K. Investigation of cytokine changes in osteoarthritic knee joint tissues in response to hyperacute serum treatment. Cells. 2019 Aug 3;8(8):824.
44. Reeves A, Vinogradov SV, Morrissey P, Chernin M, Ahmed MM. Curcumin-encapsulating nanogels as an effective anticancer formulation for intracellular uptake. Molecular and cellular pharmacology. 2015;7(3):25.
45. Hausig-Punke F, Richter F, Hoernke M, Brendel JC, Traeger A. Tracking the endosomal escape: A closer look at calcein and related reporters. Macromolecular bioscience. 2022 Oct;22(10):2200167.
46. Kesharwani D, Paliwal R, Satapathy T, Paul SD. Rheumatiod arthritis: an updated overview of latest therapy and drug delivery. Journal of pharmacopuncture. 2019 Dec 31;22(4):210.
47. Gharat S, Basudkar V, Momin M. In-Vitro and in-Vivo Evaluation of the Developed Curcumin-Cyclosporine-Loaded Nanoemulgel for the Management of Rheumatoid Arthritis. Immunological Investigations. 2024 Apr 2;53(3):490-522.
48. Choudhary N, Bhatt LK, Prabhavalkar KS. Experimental animal models for rheumatoid arthritis. Immunopharmacology and immunotoxicology. 2018;40(3):193-200.
49. Senobari F, Abolmaali SS, Farahavr G, Tamaddon AM. Targeting inflammation with hyaluronic acid-based micro- and nanotechnology: A disease-oriented review. International Journal of Biological Macromolecules. 2024 Sep 23:135923.
50. Natarajan JV, Nugraha C, Ng XW, Venkatraman S. Sustained-release from nanocarriers: a review. Journal of Controlled Release. 2014 Nov 10;193:122-38.
51. Sarma A, Bania R, Devi JR, Deka S. Therapeutic nanostructures and nanotoxicity. Journal of Applied Toxicology. 2021 Oct;41(10):1494-517.
52. Yang C, Lin ZI, Zhang X, Xu Z, Xu G, Wang YM, Tsai TH, Cheng PW, Law WC, Yong KT, Chen CK. Recent Advances in Engineering Carriers for siRNA Delivery. Macromolecular Bioscience. 2024 Apr;24(4):2300362.
53. Domingues C, Santos A, Alvarez-Lorenzo C, Concheiro A, Jarak I, Veiga F, Barbosa I, Dourado M, Figueiras A. Where is nano today and where is it headed? A review of nanomedicine and the dilemma of nanotoxicology. ACS nano. 2022 Jun 22;16(7):9994-10041.
54. Enaru B, Drețcanu G, Pop TD, Stănilă A, Diaconeasa Z. Anthocyanins: Factors affecting their stability and degradation. Antioxidants. 2021 Dec 9;10(12):1967.
55. Kharga K, Jha S, Vishwakarma T, Kumar L. Current developments and prospects of the antibiotic delivery systems. Critical Reviews in Microbiology. 2025 Jan 2;51(1):44-83.
56. Walvekar P, Lulinski P, Kumar P, Aminabhavi TM, Choonara YE. A review of hyaluronic acid-based therapeutics for the treatment and management of arthritis. International Journal of Biological Macromolecules. 2024 Mar 7:130645.

57. Anwar A, Imran M, Iqbal HM. Smart chemistry and applied perceptions of enzyme-coupled nano-engineered assemblies to meet future biocatalytic challenges. Coordination Chemistry Reviews. 2023 Oct 15;493:215329.
58. Bian X, Zhou L, Luo Z, Liu G, Hang Z, Li H, Li F, Wen Y. Emerging Delivery Systems for Enabling Precision Nucleic Acid Therapeutics. ACS nano. 2025 Jan 21.
59. Radu AF, Bungau SG. Nanomedical approaches in the realm of rheumatoid arthritis. Ageing research reviews. 2023 Jun 1;87:101927.
60. Benjamin SR, Sales AJ, Panicker PS, Bampoky NA, Nunes PI. Nanogels in diagnostics: Sensing and imaging applications. InNanogels 2025 Jan 1 (pp. 191-221). Woodhead Publishing.

How to Cite this article:
Rukhsar S, Sharma RB, Tomar S. Innovative nanogel drug delivery systems for arthritis therapy *in vitro* evaluation and clinical translation challenges. International Journal of Pharmaceutical Science and Medicine 2025; 3(2): 59-69.