# 4 *In Situ* Thermosensitive Hydrogels for Arthritis-Targeted NSAID Delivery: Present Status and Future Possibilities

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**Abstract**

Arthritis is a common condition that majorly affects joint function and the quality of life for millions of people globally. Among its various forms, rheumatoid arthritis is particularly notable due to its complex pathophysiology and chronic inflammatory nature which is presenting significant challenges for effective treatment. Traditional therapies often fail to provide long-term relief or prevent disease progression, highlighting the need for innovative solutions. In these years, Hydrogels have approached as a promising strategy for managing arthritis treatment. Their different properties such as high water content, excellent mechanical integrity and the ability to deliver drugs in a sustained manner that make them well-suited for meeting the complex requirements of arthritis treatment. NSAIDs are commonly used as first-line treatments, but long-term use is linked to cardiovascular, gastrointestinal and renal issues. Drug delivery systems like nanoparticles, liposomes, and hydrogels have developed to improve NSAID efficacy and reduce toxicity. Hydrogels classified as natural, synthetic or hybrid that offer sustained and controlled drug release and can respond to external stimuli like temperature, pH or enzymes ensuring targeted delivery. Advancements in these technologies show enhanced pain relief management and reduced side effects for arthritis patients. Hydrogels, with their versatile characteristics and diverse applications are making an impact on industries such as medicine, environmental science, energy and agriculture. Their potential to revolutionize medical treatment, address sustainability issues and improve everyday life makes them as a critical material for future innovations.

**Keywords:** *Hydrogels, NSAIDs, Arthritis, NDDS*.

## Introduction

Arthritis is a condition that affects one or more joints such as commonly targetting areas like knees, wrists or ankles. Out of different typesof arthritis,

Rheumatoid Arthritis (RA) and osteoarthritis (OA) being the most frequently diagnosed[1]. At present, osteoarthritis affects approximately 15% of people over the age 30 and above. According to a study published in *The Lancet Rheumatology* that analyzed osteoarthritis data in 1990–2020 from different countries. This research conducted by Institute for Health Metrics and Evaluation (IHME) as part of the Global Burden of Disease Study 2021 gave the research highlights about the significant trends in the disease's prevalence. These highlights reveal that the global rise in osteoarthritis cases over the past 30 years is largely due to aging, growth of population and increasing obesity rates. In 1990, there were 256 million cases of osteoarthritis worldwide, but by 2020, this number had increased to 595 million marking a 132% increase. Projections indicate that by 2050 the number of people affected could reach nearly 1 billion[2].

RA is attributed to the malfunctioning of the immune system, in which the body mistakenly attacks foreign cells and our bodies own cells, classifying it as an autoimmune disorder. This disease commonly affects joints like knees, hips, hands, and appendicular joints, significantly affecting individuals' lifestyle and overall quality of life[3].

Osteoarthritis (OA) and other forms of arthritis contribute to major healthcare costs around the world. On average each person with OA spends between $700 to $15,600 per year (based on 2019 data)[4]. In developed countries that are treating OA spends about 1 to 2.5% of their total national income. In the United States, the total cost of arthritis exceeds $580 billion each year which is around 1% of the country's GDP. In Australia, about 3.9 million people currently affected by arthritis and are expected to reach 5.4 million by 2030. The disease costs the country around $5.5 billion and additional losses due to work absences or reduced ability to work that make the problem even worse[5].

Arthritis causes a big burden through high medical costs that leads to lost work and reduced quality of life so there is a growing need for smarter and more affordable treatments. One promising option is thermosensitive hydrogels which can help in delivering NSAIDs (pain-relieving drugs) directly to the affected area. This targeted drug delivery helps in reducing side effects and improves how well the medicine works. There are several risk factors that increase the chances of developing arthritis:

- **Gender:** Women are more affected than men. For example, rheumatoid arthritis (RA) happens 2.5 to 5 times more often in women. Around 75% of RA cases are in women those are under 60. After menopause the difference between men and women becomes smaller. In OA arround 18% of women over 60 are affected as comparison to 10% of men. This is generally due to hormones, changes during pregnancy, menopause and the immune system that works in women[6].

*ISBN: 978-93-49468-43-6*

- **Lifestyle factors:** Various habits like smoking, being overweight or obese and lack of exercise can elevate the risk of both OA and RA[7].
- **Genetics:** Family history plays a huge role. People with these genes like HLA-DRB1 are more likely to affect with RA. Genes are majorly responsible for about 40-65% of the risk in people that have seropositive RA. OA also has great impact in families especially where joints are more affected[8].

**Etiology of Arthritis**

As the root cause of arthritis is still not clear; however it can be influenced by various factors including genetics, past treatments and lifestyle factors. Meanwhile, this arthritis condition is not limited to developing countries; it is prevalent in developed nations as well[9]. There are various external triggers have been identified such as genetic factors, smoking, bacterial infections like paraphyromonous that leads to gingivitis and trauma. These triggers can change autoantigens in such a way that makes them appear foreign to the immune system. There is one specific modification that involves in converting arginine residue to citrulline residue through pepetidylarginine deaminase which results in citrulline proteins that the immune cells fail to recognize that leads to the production of ACPA against them. The immune response involves CD4 T cells, mononuclear phagocytes, fibrinoblasts, and neutrophils produced by B cells.

In Rheumatoid Arthritis (RA), different cytokines like TNFα, IL1 and IL6 are produced by microphages that are causing inflammation. Additionally, these cytokines stimulate fibroblast-like synovial cells, leading to their activation, proliferation, and bone erosion. Moreover, these cells also secrete protease which initiates cartilage degradation. As the inflammation spreads from joint to joint, symmetrical arthritis can occur [10]. **Table 1** indicates the etiology of rheumatoid arthritis.

**Table 1: Etiology of rheumatoid arthritis**

| Component | Mechanism | Key Factors | References |
|---|---|---|---|
| Genetic Susceptibility | Certain genes increase risk of RA by making the immune system more likely to misidentify body tissues | **HLA-DRB1** (shared epitope alleles like *DR4*), **PTPN22**, **PADI4** | Stahl EA*et al*., 2012 |
| Environment Factors | External factors like smoking and infections modify self-proteins (citrullination), making them appears foreign to immune cells | Smoking, infection, air pollution | Firestein, G. S *et al*., 2017 |
| Post-Translational Modifications | Proteins undergo changes like **citrullination** by PAD enzymes, creating “neoantigens” not recognized as self | PAD4 enzyme, citrullinated vimentin/fibrinogen | Vossenaar*et al*., 2004 |

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|---|---|---|---|
| Autoantibody Generation | Immune system produces antibodies against citrullinated proteins and IgG Fc regions. These appear before symptoms. | **ACPA (Anti-CCP)**, **RF (Rheumatoid Factor)** | Aletaha*et al*., 2010 |
| Activation of immune system | Antigen-presenting cells activate T and B cells → inflammation begins. Cytokines are released in the joints. | CD4+ T cells, B cells, **TNF-α**, **IL-6**, **IL-1β** | McInnes &Schett., 2011 |
| Joint Invasion & Inflammation | Autoantibodies form immune complexes that attract immune cells to joints → synovial inflammation and swelling. | Neutrophils, macrophages, FLS (fibroblast-like synoviocytes) | Firestein., 2003 |
| Checkpoint Failure & Chronicity | Immune "brakes" like **CTLA-4** or **PD-1** fail → unchecked inflammation continues. | **CTLA-4**, **PD-1**, **CD80/86** | Bluestone *et al*., 2015 |
| Joint Destruction | Synovial lining thickens → pannus forms → cartilage and bone erosion occurs. | **RANKL**, **MMPs**, **TNF-α**, osteoclasts | Bottini & Firestein., 2012 |
| Systemic Spread | Inflammation may affect lungs, heart, blood vessels → extra-articular symptoms and complications. | IL-6, CRP, systemic autoimmunity markers | Smolen JS., 2016 |

**Main Text**

**Role of NSAIDS in Treatment of Arthritis**

Clinical decision-making has become difficult because clinicians usually have to choose from a wide range of options when deciding which pharmacotherapy is best for their patients. Various studies show that NSAIDs and opioids can have similar effects on physical function and pain relief. Opioids, however, are linked with a much higher risks. Between 2005 and 2015, the prevalence of opioid use increased by 23% worldwide. Sadly, the United States accounted for more than half of all overdose deaths worldwide in 2019. This trend has been partially contributed to the widespread prescription of high-dose opioids.

Canada's opioid-related mortality rate has significantly increased over time that is rising by 93% between 2000 and 2017. In order to manage their pain, many patients with osteoarthritis in the US are prescribed with opioids (71%) and NSAIDs (65%). Additionally, from 2001 to 2010, there was a notable 70% increase in the prescription of opioids for musculoskeletal pain. Both the quantity of prescriptions written and the dosage levels of opioids prescribed to patients with osteoarthritis have significantly increased in the UK in recent years. These patterns has raisemany concerns regarding the possible outcomes of opioid use and stress the necessity of giving these drugs careful thought and close supervision[1].

*ISBN: 978-93-49468-43-6*

NSAIDs basically act by inhibiting the synthesis of prostaglandins and thromboxane through the inhibition of cyclooxygenase (COX) enzymes so that they are in result recommended as the first-line treatment for arthritis. Traditional NSAIDs target both COX-1 and COX-2 isozymes to different extents, are widely used for management of pain but their long-term use is restricted due to adverse effects, particularly in the cardiovascular, gastrointestinal, and renal systems. Although they were previously thought to be safer alternatives, COX-2-selective NSAIDs (coxibs) have also been linked to an increased risk of cardiovascular events[4].**Table 2** is representing COX 1 Vs. COX 2 role in joint inflammation.

**Table 2: COX 1 Vs. COX 2 role in joint inflammation**

| Key Factors | COX 1 | COX 2 | References |
|---|---|---|---|
| Gene factor | Major role in tissues | Inducible enzyme expressed during inflammation | Osafo *et al*., (2017) |
| Function | Maintains GI mucosa, renal blood flow, platelet function | Produces prostaglandins for inflammation, pain, and fever | Ricciotti and FitzGerald (2011) |
| Role in Prostaglandin Production | Produces PGE1, PGE2 for homeostasis | Produces large amounts of PGE2 in inflamed tissues | Simmons *et al*., 2004 |
| Role in Joint Tissue | Low or baseline in joints | Highly expressed in synovium and chondrocytes in arthritis | *COX-1 and COX-2 Tissue Expression: Implications and Predictions*, 1997 |
| Induction | Not strongly inducible | Cytokines (IL-1β, TNF-α), endotoxins | Zhang *et al*., 2011 |
| Role in Arthritis | Minor role in inflammation | Central role in inflammatory pain and joint damage | Rainsford., 2007 |
| Effects of Inhibition | Can lead to GI ulcers, renal issues, bleeding | Reduces inflammation with lower GI risk (selective COX-2 inhibition) | Grosser *et al*., 2017 |
| Inhibitors | Aspirin, Ibuprofen, Naproxen (non-selective NSAIDs) | Celecoxib, Etoricoxib, Rofecoxib (COX-2 selective) | Warner & Mitchell., 2002 |

NSAIDs are the most frequently prescribed medications for pain and inflammation that accounts approximately 5-10% of all prescriptions annually. The use of NSAID's is especially prevalent in elderly patients, with up to 96% of

ISBN: 978-93-49468-43-6

individuals over 65 years old receiving NSAIDs in general practice. Approximately 7.3% of old patients who were over 60 years old prescribed at least one NSAID annually. Beyond their anti-inflammatory use, NSAIDs also have antipyretic and analgesic effects[3].

NSAIDs have proven effective in reducing inflammation in various conditions like osteoarthritis, rheumatic fever, juvenile rheumatoid arthritis, ankylosing spondylitis, gout, and systemic lupus erythematosus. Despite the benefits of NSAIDs in treating different ailments, their conventional dosage forms are associated with various adverse effects, particularly in the elderly, which have been extensively researched in **Table 3**

**Table 3: Commonly observed adverse effects of NSAIDs**[10]

| **Organ system** | **Adverse effects** |
|---|---|
| Cardiovascular adverse effects | • Weight gain<br>• Increase in Blood Pressure<br>• Congestive heart failure<br>• Myocardial infarction<br>• Heart Stroke |
| Renal toxicity | • Electrolyte imbalance<br>• Sodium retention<br>• Edema<br>• Reduce glomerular filtration rate |
| Nervous system | • Dizziness, confusion, drowsiness<br>• Seizures<br>• Acute meningitis |
| Skeletal system | • Slow Healing |
| Allergic reactions | • Aspirin-exacerbated respiratory disease<br>• Rash |
| GI System | • Dyspepsia<br>• Ulcers<br>• Bleeding in GI<br>• Colitis<br>• Erosions in bowel<br>• Esophagitis |

**Global NSAID Use and Market Trends**

The use of NSAIDs remains widespread, especially among the elderly. In Italy, consumption increased from 15.5 to 16.8 defined daily doses per 1000 people per day between 2020 and 2022, before slightly decreasing to 15.1 DDD in 2023. The highest usage was noted among individuals aged 65–74 years and above.[28]. There are common prescribed NSAIDs include **diclofenac, ketoprofen, ibuprofen and etoricoxib**. Globally, NSAID's are prescribed to **40.3%** of OA patients in high-

*ISBN: 978-93-49468-43-6*

income countries and **68.5–83.4%** in upper-middle-income countries annually. However, due to safety issues prescribing trends have slightly declined in high-income regions[29].The **global market of NSAID** expanded from**$18.3 billion in 2022**to**$19.6 billion in 2023** and is much expected to reach **$24.9 billion by 2027**(CAGR ~6.2%). The regulatory agencies, **FDA** and **EMA** continue to issue safety advisories mainly emphasizing **GI and cardiovascular risks** while promoting NSAIDs as safer alternatives to opioids for managing chronic pain[30].

**Advanced NSAID Delivery Approaches for Arthritis Treatment**

To overcome various unwanted effects linked with conventional NSAIDs there is novel drug delivery systems that have been developed to overcome these issues. These novel approaches include intravenous, delayed-release and sustained-release oral preparations as well as topical applications such as gels, patches and suppositories. The maingoal is to minimize NSAID induced toxicity while focusing on targeted drug delivery to specific sites. Moreover, researchers are investigating nanoparticles, liposomes and microspheres to reduce required dosages and enhance drug targeting. Additionally, many of these conventional dosage forms are limited by poor bioavailability, unpredictable pharmacokinetics and lack of joint-specific targeting.

Topical formulations are particularly formulated to minimize systemic exposure while maintaining therapeutic effectiveness. Their efficacy depends on different factors such as the drug type, formulation and application site. For example, Diclofenac is available in many dosage forms such as solution, gel or patch and its systemic effects are linked to the applied area. This approach offers stable systemic concentration of Diclofenac compared to oral administration[31]. Similarly, Ibuprofen, available in various forms such as creams, gels, and tablets, has shown greater effectiveness than conventional drug delivery methods.

There are various nanotechnology based delivery systems are also emerged such as nanoparticles, liposomes and dendrimers. These nanosystems improve solubility of drug, prolong circulation time and allow passive or active targeting to inflamed synovial tissues. For example, **celecoxib-loaded PLGA nanoparticles** demonstrated sustained intra-articular release and reduced joint inflammation in preclinical models[32]. Similarly, formulations of **liposomal diclofenac** have shown improved joint accumulation and lesser systemic effects. These nanoformulations have reduced the required dose and frequency thus minimizing Gastrointestinal and cardiovascular risks.

While nanocarriers have shown significantly more advanced systemic and targeted NSAID drug delivery but there are **localized intra-articular systems** such as hydrogels have emerged as an equally promising strategies for improving joint-specific drug action. There are various **injectable hydrogel-based formulations**that

ISBN: 978-93-49468-43-6

are used for sustained release of NSAIDs that acts directly within the synovial cavity thereby maintaining therapeutic concentrations at the site of inflammation and helps in reducing systemic exposure. These hydrogel systems are often **thermosensitive** forming a gel-like depot upon contact with joint temperature and can be loaded with drugs like diclofenac or ibuprofen. Recent preclinical studies have shown that such formulations not only prolong drug residence time but also reduce cartilage degradation and synovial inflammation in arthritis models[33].

In recent years, microneedle (MN) technology has also gained attention for delivering NSAIDs in a minimally invasive, painless and patient-friendly manner. Microneedle patches that is dissolving into the skin to deliver NSAIDs transdermally are being explored as pain-free, self-administered alternatives. In the meantime, precise, site-specific drug release has been made possible directly within inflammatory joints by stimuli-responsive systems that are basically triggered by various factors like joint pH, temperature or particular enzymes. By providing targeted, on-demand release these drug delivery systems reduce off-target effects and cut down on medication waste. These systems are showing lots of potential for individualized arthritis treatment[34].**Table 4** provides an overview of different novel systems of NSAIDs used in arthritis treatment.

**Table 4: Summary of reported NSAIDs for treatment of Arthritis**

| S. No. | Drug used | Drug delivery System | Efficacy | Reference |
|---|---|---|---|---|
| 1. | Diclofenac sodium | Nanoparticles | Arthritic pain | Spizzri*et al*, 2013 |
| 2. | Ketoprofen | Polymeric nanoparticles | Decreased inflammation | Espinosa-Cano E *et al*, 2020 |
| 3. | Piroxicam | Niosomes | Increased drug retention | Subashini R *et al*, 2020 |
| 4. | Meloxicam | Nanoemulsion | Anti-rheumatic arthritic effect | Pathan I *et al*, 2016 |
| 5. | Indomethacin | Polymeric nanicapsules | Anti-inflammatory and Anti-rheumatic arthritic effect | Bernardi A *et al*, 2009 |
| 6. | Indomethacin | Nanomicelle | Anti-rheumatic arthritic effect | Zhang J.X*et al*, 2007 |
| 7. | Larnoxicam | Polymeric nanomicelle | Anti-inflammatory arthritic effect | Helmy H.S*et al*, 2017 |
| 8. | Piroxicam | Solid lipid naniparticle | Anti-inflammatory effect | Peng L.H*et al*, 2016 |

*ISBN: 978-93-49468-43-6*

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|---|---|---|---|---|
| 9. | Aceclofenac | Solid lipid naniparticle | Anti-rheumatic arthritic effect | Raj R *et al*, 2016 |
| 10. | Diclofenac | Pellets | Less side effects | Gabard B *et al*, 1993 |
| 11. | Diclofenac | Microcapsules | Sustained release | Bhatnagar S *et al*, 1995 |
| 12. | Ketoprofen | Floating microparticles | Good flow property | Khosro *et al*, 2011 |
| 13. | Diclofenac | Pharmacosomes | High drug loading | Semalty*et al*, 2010 |

**Imoprtance of Hydrogels in Arthritis**

Hydrogels are networks of polymers that absorb a lot of water and create soft and swollen structures. They have this unique capability to retain significant amount of water which is allowing for controlled release of drug. Water-soluble polymers make up these three-dimensional crosslinked networks which are thought to be a clever and innovative drug delivery system that allows for targeted drug delivery to particular sites while controlling drug release. These are used in different fields like clinical practice, tissue engineering, regenerative medicine, diagnostics, cell immobilization and bimolecular separation.In these years, hydrogels have gained traction as localized delivery platforms for NSAIDs in the management of inflammatory joint conditions like osteoarthritis and rheumatoid arthritis[35].

The polymeric structure of hydrogels basically depends on various chemical interactions like primary covalent crosslinks, ionic forces, hydrogen bonds, bio-recognition interactions, polymer crystalline interactions and hydrophobic interactions. However, despite of various advantages hydrogel has some drawbacks also that some drugs are hydrophobic in nature which leads to early drug release due to weak tensile strength of hydrogels[36].

Along with these limitations hydrogels offer significant advantages including sustained drug release properties and the ability to maintain high local drug activity through different mechanisms like diffusion, swelling, chemical interactions, and environmental stimuli. Overall, hydrogels show great potential as effective drug delivery systemsoffering broad range of applications in pharmaceutical and biomedical domains[37].

Recent studies focuses on stimuli-responsive "smart" hydrogels, which can release NSAIDs in response to variations in the temperature, pH or activity of inflammatory enzymes in the joint. For the improvement of therapeutic results 3D-printed hydrogel scaffolds, hydrogel-nanoparticle hybrids and dual-drug delivery systems are being investigated. Even though there is still little clinical translation, hydrogel engineering advancements holds the potential to completely transform arthritis medication[38].

ISBN: 978-93-49468-43-6

In comparison to free drug administration, intra-articular injection of NSAID-loaded hydrogels has showed reduction in joint inflammation, synovial hyperplasia and cartilage erosion in preclinical arthritis models. These systems increase therapeutic adherence and prolong drug retention time. Hydrogel-nanoparticle hybrids and self-healing hydrogels are recent advancements that improve mechanical strength and allow for repeated drug administration following trauma or joint movement[39].

Furthermore, biofunctional hydrogels co-loaded with mesenchymal stem cells or anti-inflammatory cytokines (like IL-10) provide the dual advantages of cartilage regeneration and inflammation control that makes them appealing for more severe or degenerative arthritis cases. There is personalized arthritis treatment and patient-specific implants that has become feasible by the combination of 3D printing and biofabrication technologies. Despite ongoing regulatory issues with sterilization, batch reproducibility and long-term safety, hydrogel-based NSAID delivery is able to maintain standard due to the growing global focus on non-opioid pain management and minimally invasive therapies[40].

**Classification of Hydrogel**

- **Based on origin**

| Type | Description | Examples |
|---|---|---|
| **Natural Hydrogels** | derived from natural polymers | Cellulose, hyaluronic acid, methyl cellulose, dextran, alginate, chitosan |
| **Synthetic Hydrogels** | Formed using synthetic polymers, typically hydrophobic and stronger than natural polymers. | Polyvinyl alcohol, Polyethylene glycol, Polyethylene oxide |

- **Based on Polymeric composition**

| Type | Description | Applications |
|---|---|---|
| **Homopolymer Hydrogel** | Formed from a single type of polymer. Structure may be cross-linked. Cross-linking agent like poly HEMA and UV initiators (e.g., benzoin isobutyl ether) are used. | Contact lenses, wound healing, skin burns treatment |
| **Copolymeric Hydrogel** | Formed by combining various monomers includes one hydrophilic type. | Copolymer of BLG and poloxamer using diamine-initiated PEO chain |
| **Multipolymer Hydrogel** | Composed of two or more different cross-linked components, can be natural or synthetic. May also include non-crosslinking polymers (semi-molecular hydrogels). | Provides enhanced bulk and surface morphology stability |

*ISBN: 978-93-49468-43-6*

**Drug Release from Hydrogels**

Drug release from hydrogels typically follows three primary mechanisms: diffusion, swelling-controlled release and polymer degradation.

- **Diffusion Controlled Drug Release**

**Hydrogels undergo such drug release shows a broadly utilized mechanism in arthritis treatment that is offering localized and sustained delivery of therapeutic agents.** In this system, drug molecules travel from the hydrogel matrix to its surrounding environment primarily via passive diffusion which is driven by a concentration gradient and without involving chemical degradation of the polymer. Thediffusion rate depends on the hydrogel's mesh size, degree of crosslinking and the physical characteristics of the drug. Various studies have shown that hydrogels with a mesh size ranging between 5-100 nm can effectively regulate the release of small to medium-sized drug molecules[41]. In arthritis therapy, this mechanism is particularly advantageous for delivering anti-inflammatory drugs such as diclofenac, celecoxib and methotrexate reducing systemic exposure and improving drug residence time within the joint cavity. For instance, a celecoxib-loaded thermosensitive hydrogel demonstrated sustained drug release over 7 days and significantly reduced paw swelling in a rat model of arthritis compared to free drug administration[42].

- **Swelling Controlled Release of Drug**

In this systemdrug release is maintained by the extent and rate of water absorption by the hydrogel matrix. When it exposed to physiological fluids in the joint space, hydrogels swell as water penetrates the polymer network that leads to the relaxation of polymer chains and subsequent expansion of pore size. This structural transition basically promotes the diffusion of drug molecules that makes swelling a rate-limiting step in the release kinetics. This behavior is particularly relevant in stimuli-responsive hydrogels, which swell dueto pH, temperature or inflammation-specific enzymes. For example, thermosensitive hydrogels composed of chitosan and β-glycerophosphate have been shown to transition from sol to gel at body temperature (≈37°C) that helps in releasing drugs like celecoxib in a controlled manner for up to 7-10 days in intra-articular applications[42]. In different study, a pH-responsive hydrogel showed increase in drug release under low acidic conditions (pH 6.5) that is observed in inflamed arthritic joints compared to neutral pH[43]. This kind of release pattern is advantageous for on-demand drug delivery that aligns drug availability with disease flare-ups and minimizing systemic exposure. This swelling property of Hydrogels in a predictable, trigger-sensitive fashion enhances therapeutic precision, making swelling-controlled systems a promising platform in the long-term management of rheumatoid arthritis and osteoarthritis.

ISBN: 978-93-49468-43-6

- **Polymer Degradation Controlled Release of Drug**

The drug release from Hydrogels in this systemhas become a remarkable strategy for sustained and prolonged drug delivery in arthritis treatment. In this system, drug release from hydrogel undergoes chemical or enzymatic degradation that leads to matrix erosion and gradual liberation of the encapsulated drug. This process is majorly beneficial for macromolecular therapeutics such as biologics, peptides or gene vectors where prolonged intra-articular presence is mandatory. Degradation can be developed by selecting appropriate natural polymers like hyaluronic acid (HA), chitosan, gelatin or synthetic ones like poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG)-based hydrogels. For exapmle, in rheumatoid arthritis, HA-based hydrogels broken down by hyaluronidase enzymes that found in inflammatory joints and have shown sustained delivery of TNF-α inhibitors over a period of two to three weeks which results in lowering joint inflammation[44]. Baig M., 2024showed that using PLGA hydrogels loaded with methotrexate has reported degradation-mediated release over 14 days by maintaining therapeutic levels in the joint with improved histopathological outcomes compared to free drug[45]. Degradation-controlled systems haveeliminated burst release and can be developed for zero-order kinetics, ensuring consistent drug exposure over extended durations. Moreover, biodegradation system removes the need for surgical removal that makes these systems highly patient-friendly and clinically feasible for chronic arthritis management.

**Different Hydrogel Systems Reported for Sustained and Controlled Delivery of Drugs**

Hydrogels are crosslinked structures made up of hydrophilic polymers that have the ability to absorb substantial amounts of water or biological fluids. Here are some different hydrogel systems that have been reported for this purpose:

- **Natural Polymer-Based Hydrogels:** These hydrogels are showing attention in biomedical applications like drug delivery, wound healing, and regenerative medicine due to their biocompatibility, degradability, and flexibility. This review focuseson widely used natural polymers like cellulose, chitosan, alginate, and dextran, along with their synthesis and properties. Various approaches include novel polymer derivatives, multifunctional composite hydrogels and hydrogel microrobots. Meanwhile, emerging fabrication techniques including dual-cross-linking, microfluidics, and 3D/4D bioprinting that helps in enhancing hydrogel properties. Future research projects focuses on developing high-performance natural polymer-based materials and innovative hydrogel fabrication strategies for biomedical applications[6].**Table 5** represents the various formulations of natural polymer based Hydrogels.

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**Table 5: Natural polymer based Hydrogel systems**

| S. No. | Name of Natural Polymer | Use of Hydrogel | References |
|---|---|---|---|
| 1 | **Cellulose** | High-strength hydrogels for mechanical applications | Buyanov *et al*., 2019 |
| 2 | **Chitosan** | Applications in delivery of drug and wound healing | Zhao L *et al*., 2023 |
| 3 | **Alginate** | Applications in Tissue and regenerative medicine | Catoira M C*et al*., 2019 |
| 4 | **Gelatin** | Injectable for biomedical applications | Karoyo AH *et al*., 2021 |
| 5 | **Hyaluronic Acid** | Cartilage regeneration and osteochondral tissue engineering | Yang J *et al*., 2023 |
| 6 | **Pectin** | Biosensors and food packaging applications | Resende, J F*et al*, 2022 |
| 7 | **Starch** | Controlled drug release systems | Wang Z*et al*., 2023 |
| 8 | **Gellan Gum** | Scaffolds for soft tissue engineering | Seyrig, C, 2022 |
| 9 | **Dextran** | Hydrogels for injectable drug delivery | Seyrig, C, 2022 |
| 10 | **Poly(glycerol sebacate)** | Photocurable elastomeric hydrogels for biomedical applications | arXiv, 2024 |

- **pH responsive Hydrogels**

Incorporating pH-sensitive polymers into the hydrogel matrix enables drug release with changes in the surrounding pH, such as those found in diseased tissues or cellular compartments. Abdullah Z *et al*., 2023 formulated aAvT-co-poly hydrogel using aloe vera gel, tamarind gum, monomer and crosslinker for the controlled delivery of Tramadol HCl. The hydrogels gave significant swelling response at pH 7.4. High drug loading (70.28%-90.64%) and sustained release (92.22% over 24 hours at pH 7.4) of Tramadol HCl has been reported. Meanwhile oral toxicity studies in rabbits have confirmed the biocompatibility and safety of the hydrogel system.

Kumar H *et al*., 2012 formulated pH-sensitive hydrogels of theophylline. The hydrogels exhibited high swelling in basic pH allowing for delayed drug release and extended release formulation. The studies demonstrated that this formulation provided superior controlled drug release compared to the standard marketed sustained-release product.A pH-sensitive CMC hydrogel represents an effective approach for addressing nocturnal asthma symptoms through sustained intestinal drug release.

ISBN: 978-93-49468-43-6

- **Enzyme-Responsive Hydrogels**

Hydrogels that are susceptible to degradation due to the presence of specific enzymes can be strategically designed to achieve site-specific drug release at diseased tissues. Reddy N *et al*, 2022 developed a hydrogel-based drug delivery system of Saquinavir mesylate in the form of hard gelatin capsules. Hydrogel was formulated using HPMC 15 cps, Carbopol 971P and granules with MCC acts as a diluent. The hydrogel capsules showed desirable properties such as 95% drug content uniformity, an 11-minute disintegration time and a 98% drug release over 12 hours, adhering to zero-order and Higuchi models. Sobczak M*et al*., 2022 presented a comprehensive review of the latest advancements in ERHs developed for prolonged drug delivery systems with understanding of enzymes like glucose oxidase, β-galactosidase and metalloproteinases.

- **Hybrid Hydrogel Systems**

Hybrid hydrogels are formulated by combining multiple polymers or materials to utilize their properties that ultimately improving drug delivery systems. Gugleva*et al*., (2022) developed a formulation by adding curcumin/gentamicin sulfate-loaded niosomes into thermosensitive *in situ* gels. The formulation that has been optimized possessed high drug entrapment efficiency and favorable physicochemical characteristics. It was also integrated into gels composed of poloxamers and chitosan. This system showed a sol-to-gel transition that has showed sustained drug release and synergistic antimicrobial effects.

In different study, Mariagrazia Di Luca (2023) developed a hybrid hydrogel that consists chitosan and graphene oxide (GO) as an electro-responsive and antimicrobial delivery system for Rose Bengal (RB) intended for skin applications. This hydrogel showed a uniform surface morphology, enhanced biocompatibility and good biodegradability. The addition of graphene oxide has improved drug binding capacity and introduced electro-responsive behavior enabling controlled and targeted drug release.

- **Nanocomposite Hydrogels**

Hydrogels developed as nanoparticles may have the ability to improve drug release characteristics allowing for sustained drug delivery. Nahideh Asadi *et al*., 2019 has developed an innovative nanocomposite hydrogel based on gelatin/polycaprolactone-polyethylene glycol (Gel/PCEC-TGFβ1) for cartilage tissue engineering. The hydrogel formulated has showed good porosity, mechanical strength and supported cell proliferation and chondrogenic differentiation of human adipose derived mesenchymal stem cells (hAD-MSCs). Moreover, it has promoted deposition of glycosaminoglycans (GAGs) and expression of collagen II and aggrecan genes which indicatesits strong potential as biomaterial for cartilage tissue repair.

*ISBN: 978-93-49468-43-6*

Nariman S *et al*, 2021 formulated a novel hydrogel which contained nanoparticles loaded with Ticagrelor (TG) for the improvement of oral bioavailability and antiplatelet efficacy. The hydrogel demonstrated pH-responsive drug release that results in significantly improved bioavailability which highlights its potential as an effective oral delivery system for lowering the risk of myocardial infarction.

Azin P *et al*, 2023 developed a hydrogel containing diclofenac sodium for the improvement of drug effectiveness and minimizing side effects. The hydrogel has showed increased gel fraction, reduced swelling capacity along with notable antibacterial properties and biocompatibility. The drug release followed Peppas-Korsmeyer model that indicates Fickian diffusion. This nanocomposite hydrogel presents a promising and effective system for drug delivery.

**Future Trends of Hydrogels**

The area of hydrogel research is changing quickly due to advancements in artificial intelligence, biofabrication and smart materials as all are opening up new possibilities for high-performance and multipurpose systems. The most advanced of these are intelligent and stimuli-responsive hydrogels that can response to temperature, pH, or enzyme activity to provide precise, on-demand drug release. In contrast to only 20% in healthy tissue, recent designs have shown up to 80% drug release in inflammatory conditions[79]. With over 90% accuracy in predicting critical hydrogel behaviors like swelling, mechanical strength, and degradation, artificial intelligence (AI) and machine learning have significantly accelerated design and optimization. The development of 4D bio printing is making it possible to produce hydrogels that can mimic dynamic biological processes by changing shape or function over time. A thermoresponsive vascular graft is one such system that has demonstrated the capacity for self-actuated contraction and expansion[80].

Hydrogels are combination synthetic and natural polymers such as hyaluronic acid and nanomaterials such as graphene oxide are being developed for tissue regeneration applications particularly in cartilage and nerve repair in order to increase mechanical robustness and biofunctionality. Hydrogels that are biologically inspired and self-healing are being developed at the same time. Some of these systems can self-heal in as little as 30 seconds, which makes them perfect for long-term use in implantable and wearable devices[81]. Peptide-based hydrogels are being investigated for their capacity to replicate extracellular matrix properties which is helpful in neural and soft tissue engineering while DNA-based hydrogels are facilitating programmable biosensing and drug delivery in the field of biomolecular engineering.

Bringing hydrogel technologies into real medical use is getting more attention now. Scientists and companies are focusing on making them in a consistent and safe way by using good manufacturing practices and designing better clinical trials with

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the help of AI. These steps will help in making hydrogel treatments safer and easier to produce on a large scale. Moreover, the global smart hydrogel market may reach $8.1 billion by 2030 and over 1200 patents were filed in 2023 alone[82].

**Challenges and Limitations**

Beyond the various applications of hydrogels across biomedical and industrial sector there are several critical challenges. One major challenge is balancing biodegradability with mechanical strength. Hydrogels designed for tissue engineering, drug delivery or implants are supposed to safely break down in the body. However, when their biodegradability is increased then their structural strength often decreases and makes them less suitable for long-term applications. This performance is particularly seen in cartilage and bone regeneration where strong mechanical support is important but hard to achieve with natural, fast-degrading polymers. Although hybrid materials and nanofillers can help in achieving both high strength and controlled degradation still poses a major challenge in materials science.

Another major concern about hydrogels is the challenge of scaling up hydrogel production. Most hydrogel systems are extremely sensitive to synthesis conditions such as even small changes in polymer concentration, crosslinking agents or temperature can cause significant differences in their properties from batch to batch. Moreover, many hydrogels require sterile environments, specialized fabrication techniques and cold-chain storage which increase production costs and limit their accessibility in resource-constrained systems. This challenge increases in case of smart or multifunctional hydrogels, which include intricate designs, multiple active components and precise structural requirements. Because hydrogels can act as devices, drug carriers or biological scaffolds so they often fall into regulatory grey areas. This can slow down their approval process. Due to lack of universally accepted testing standards for biodegradability, long-term biocompatibility and degradation byproducts further complicates the regulatory process. Moreover, the limited long-term clinical data especially for new smart or injectable hydrogels makes regulatory authorities more cautious that leads to longer and more costly trial phases.

Despite promising outcomes in preclinical studies, the growth of some hydrogel systems this been hindered by high costs, logistical challenges and regulatory uncertainties. To overcome these barriers there is a need for integrated strategies that combine advanced material engineering with scalable manufacturing protocols and AI-guided predictive models for safety and efficacy. By addressing these issues hydrogels can evolve from experimental innovation to accessible therapeutic solutions with significant clinical impact.

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## Conclusion

Hydrogels have emerged from basic water-absorbing materials into smart and multifunctional systems with high potential across different fields. They are able to replicate natural tissues, respond to biological stimuli and deliver therapeutic agents in a controlled manner has made them different in modern science. From targeted drug delivery and wound healing to tissue engineering and wearable biosensors hydrogels are redefining the levels of personalized and regenerative medicine. In future, next-generation hydrogels will be capable of real-time monitoring, adaptive drug release and tissue integration. The incorporation of machine learning will accelerate hydrogel design and self-healing systems. DNA and peptide-based hydrogels along with hybrid nanocomposites will open new scope in neural, cardiovascular and orthopedic areas. Beyond the healthcare sector, hydrogels are set to transform agriculture, environmental field and flexible electronics that are offering sustainable and smart alternatives to conventional materials. However there are challenges related to scalability, reproducibility, regulatory approval and long-term safety must be addressed. With interdisciplinary collaboration and a focus on translational research, hydrogels has become cornerstones of next-generation science and technology bridging biology and engineering to meet the complex demands of the future.

## Abbreviations

***NSAIDS*** : Nonsteroidal anti-inflammatory drugs

***RA*** **:** Rheumatoid arthritis

***APCA*** **:** Anti-citrullinated peptide antibody

***TNF*** **:** Tumor Necrosis factor

***IL*** **:** Interleukin

***COX*** **:** Cyclooxygenase

***PVA*** **:** Polyvinyl Aclcohol

***PEG*** : Polyethylene Glycol

***PEO*** **:** Polyethylene oxide

***MCC*** **:** Microcrystalline cellulose

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