


# Hydrogel-Based Microspheres for Intra-Articular Osteoarthritis Therapy: Multifunctional Carriers for Drug Delivery and Cartilage Repair: A Comprehensive Review

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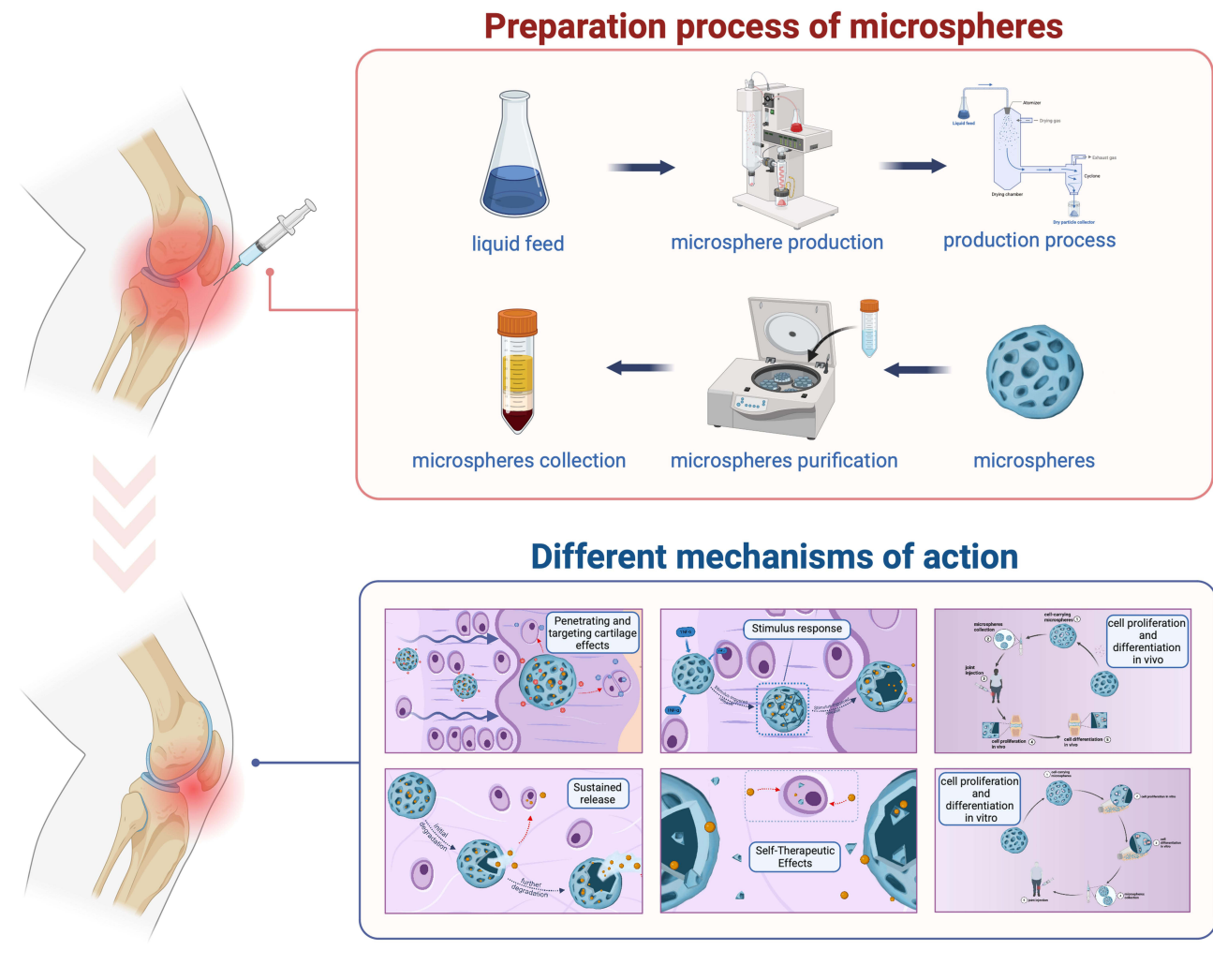
**Abstract:** Intra-articular therapy has long been a key focus in the treatment of osteoarthritis (OA), with both intra-articular drug injection and cell therapy offering significant advantages over systemic administration due to their superior local therapeutic efficacy. However, several challenges remain, including difficulties in maintaining effective drug concentrations within the joint cavity, limited survival and functionality of injected cells, and the inability to accurately target drugs or cells to diseased tissues. To address these issues, hydrogel-based microsphere systems have recently been developed as carriers for drugs, cells, and bioactive factors, enabling more precise and efficient intra-articular therapies. This review summarizes recent advances in hydrogel microspheres for intra-articular injection and classifies them according to their functional properties. From the perspective of drug delivery, we discuss their roles in sustained release, cartilage penetration and targeting, stimulus-responsive release mechanisms, and inherent pharmacological activity. From the perspective of cell therapy, we explore their applications in cell delivery and cartilage tissue engineering, including their ability to enhance cell viability, maintain stemness, and enable the co-delivery of bioactive molecules. In conclusion, hydrogel microspheres represent a promising strategy for improving the efficacy of intra-articular treatments in osteoarthritis.

**Keywords:** osteoarthritis, microspheres, drug delivery, cartilage tissue engineering

## Introduction

Osteoarthritis (OA) is a common joint disease, with risk factors including aging, obesity, and knee joint injuries.<sup>1</sup> The primary pathological changes in OA involve the degradation of articular cartilage, synovial inflammation, osteophyte formation, and subchondral bone sclerosis,<sup>2,3</sup> with cartilage degeneration being the hallmark of the disease. Due to the absence of vasculature, adult cartilage injuries are difficult to repair or regenerate.<sup>4</sup> Factors such as local or systemic inflammation and mechanical loading can disrupt the metabolic balance of chondrocytes in the joint environment, leading to cartilage degradation and promoting the onset and progression of OA.<sup>5</sup> In recent years, an increasing number of studies have highlighted the critical role of microenvironmental dysregulation in the progression of OA. Key factors involved include the release of inflammatory mediators, degradation of the cartilage extracellular matrix, and oxidative stress. Targeted therapies that modulate the joint microenvironment have shown potential in alleviating cartilage damage and

## Graphical Abstract



slowing disease progression. Consequently, preventing cartilage damage and promoting repair after injury have become key areas of focus in OA treatment.

OA treatment encompasses non-pharmacological therapies such as exercise and self-management, as well as surgical interventions for joints with severe functional impairment, while pharmacological therapies are the most commonly used.<sup>6</sup> Intra-articular drug injection is a common approach for the treatment of OA. Compared to systemic administration, it offers lower costs, reduced risk of systemic side effects, and higher local drug concentrations.<sup>7</sup> However, conventional intra-articular drug delivery methods face several limitations, including short retention times in the joint leading to inefficacy, reduced drug permeability due to extracellular matrix (ECM) barriers, and poor drug delivery selectivity, which impedes targeted action.<sup>8,9</sup> To address these issues, recent research has focused on using biomaterials such as hydrogels, nanoparticles, and microspheres as drug delivery systems for intra-articular therapy.<sup>10</sup> These materials, when used as carriers for intra-articular therapeutic agents, can stabilize encapsulated drugs and enhance their efficacy.<sup>11</sup> Microspheres, as a micrometer-sized sphere composed of single or multiple polymers—offer notable advantages in biocompatibility and drug release, depending on the materials used in their synthesis.<sup>12</sup> Compared to hydrogels, which are also commonly employed as delivery vehicles, microspheres exhibit more uniform size and higher porosity. These features help overcome limitations associated with hydrogels, such as irregular shape and insufficient pore space, which can hinder both injection and controlled drug release.<sup>13</sup> Consequently, microspheres demonstrate superior performance in

drug loading capacity, encapsulation efficiency, stability preservation, and targeted delivery. Due to these advantageous properties, microspheres are a central focus of this review.

As the progression of OA continues, articular cartilage undergoes damage and degeneration, often failing to repair itself, ultimately leading to joint dysfunction. Therefore, for cases of more severe cartilage damage, the effectiveness of pharmacological treatments is limited, and there is often a need to integrate cartilage tissue engineering techniques.<sup>14</sup> These techniques include the use of cartilage repair materials and stem cell therapies to promote cartilage regeneration and improve joint function.<sup>15</sup> In stem cell therapy for OA, the primary goal is to promote the growth and differentiation of stem cells into chondrocytes at the damaged site.<sup>16</sup> Natural material scaffolds and polymer-based hydrogel scaffolds used in cartilage tissue engineering can provide a supportive environment for cell adhesion, growth, and proliferation. However, traditional scaffolds often suffer from poor mechanical strength and uncontrollable degradation, which can compromise their structural support during tissue regeneration. In contrast, microsphere-based scaffolds offer improved mechanical properties and controllable degradation rates, making them more suitable for promoting cartilage regeneration. Furthermore, their ability to achieve controlled release of cells and growth factors during degradation significantly enhances the therapeutic outcomes in osteoarthritis treatment.<sup>17</sup>

This review aims to classify and critically evaluate the diverse roles of hydrogel-based microspheres in OA treatment, with a focus on drug delivery mechanisms and cartilage tissue engineering applications.

## Microspheres as Drug Delivery Systems for Osteoarthritis Treatment

Pharmacological treatment has long been a primary focus in the management of OA. Intra-articular drug delivery, as an alternative to oral administration, offers the advantage of increasing local drug concentrations within the joint while addressing concerns related to systemic side effects and safety.<sup>10,18</sup> However, intra-articular delivery is not without challenges. High concentrations of drugs injected into the joint cavity can lead to adverse reactions, and the initially elevated drug levels often decrease rapidly due to clearance mechanisms, thereby shortening the therapeutic duration.<sup>19</sup> Furthermore, the ECM of cartilage, characterized by its highly dense and negatively charged structure, poses a significant barrier to drug penetration.<sup>20</sup> This coupled with the inability to precisely target damaged areas, often results in suboptimal therapeutic outcomes. In some cases, the injected drugs may inadvertently harm healthy cells, exacerbating the risk of unintended side effects.<sup>9,10</sup>

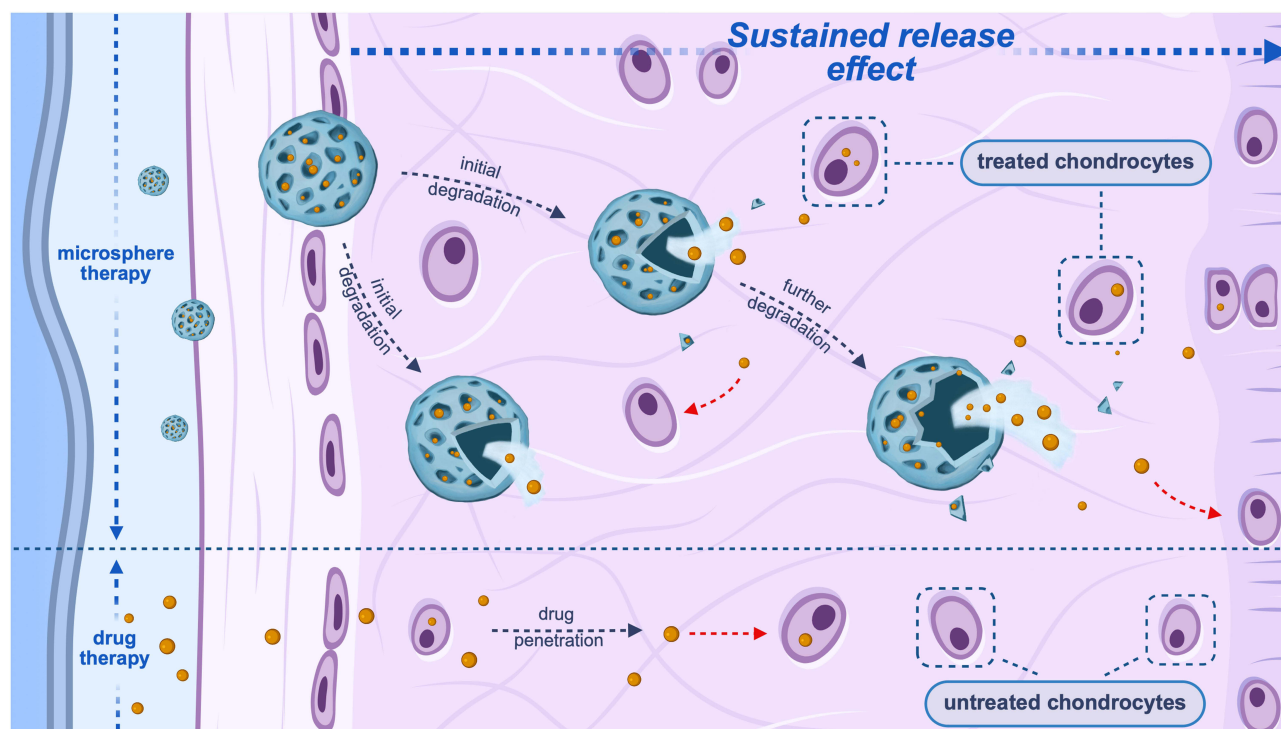
In summary, intra-articular drug delivery for osteoarthritis requires optimization to address the limitations of conventional drug injection. Incorporating drug delivery systems as an adjunct to intra-articular injection offers a promising approach to overcoming these challenges. Microspheres, as a drug delivery vehicle, exhibit unique advantages over other carriers due to their distinctive properties. Previous studies have provided valuable insights into various microsphere-based systems for osteoarthritis treatment. In this section, we classify drug-loaded microspheres according to their specific roles in drug delivery. Furthermore, we discuss their therapeutic effects based on the distinct mechanisms through which they function in these roles.

### Prolonging the Duration of Drug Action

As mentioned above, one of the major challenges in intra-articular drug therapy is the rapid clearance of drugs from the joint. In recent years, considerable research has focused on extending the duration of drug action within the joint. High drug-loaded microspheres that provide sustained release of the drug are a fundamental requirement for the treatment of osteoarthritis. However, the sustained release properties of microspheres vary depending on their composition and structure.<sup>21</sup> Therefore, we classify microspheres based on their material composition and summarize the corresponding characteristics of various microsphere types, along with their drug release profiles (Figure 1).

#### Natural Polymer Microspheres

Natural polymer microspheres are spherical particles composed of biodegradable polymers derived from natural sources. Common examples include gelatin microspheres, chitosan microspheres, dextran microspheres, and hyaluronic acid microspheres.<sup>22</sup> Due to the excellent biocompatibility of natural polymers, microspheres made from these materials generally exhibit minimal side effects and a lower risk of immune rejection during treatment. Additionally, the favorable



**Figure 1** Role of microspheres in prolonging drug efficacy.

**Notes:** This figure illustrates the process by which drug-loaded microspheres achieve the synchronized release of encapsulated drugs through gradual degradation. The sustained release property of microspheres ensures a stable and prolonged therapeutic effect of the drug compared to simple drug injections. This figure was created with BioRender (<https://biorender.com/>).

biodegradability of natural polymer microspheres enhances their drug release capabilities, making them highly effective in therapeutic applications.

Gelatin is a water-soluble protein derivative obtained through the hydrolysis of tissues. As a natural protein, gelatin exhibits excellent biocompatibility.<sup>22</sup> Moreover, it is biodegradable *in vivo*, with the degradation rate influenced by the preparation process and the concentration of degrading enzymes.<sup>7,23</sup> As a result, drug-loaded gelatin microspheres can achieve a sustained-release function by gradually releasing their drug payload through slow degradation within the joint cavity.<sup>7</sup> For example, a gelatin microsphere designed for drug delivery in osteoarthritis treatment can regulate its degradation rate by controlling the crosslinking density and responding to inflammation in chondrocytes, thereby facilitating the controlled release of the loaded drug and improving the therapeutic efficacy for osteoarthritis.<sup>23</sup>

Another natural polymer commonly used for microsphere preparation is dextran. Dextran-based microspheres, such as alkyl-modified dextran hydrogel microspheres loaded with ibuprofen, exhibit excellent biocompatibility and biodegradability. The three-dimensional network structure of dextran microspheres enhances drug retention time while slowing their degradation rate, thus enabling sustained release of the encapsulated drug.<sup>24</sup>

In addition, silk fibroin, known for its favorable physicochemical properties and biocompatibility, can also be used as a material for hydrogel microspheres.<sup>25</sup> Microspheres formed through physical crosslinking tend to have higher rigidity and instability, whereas those obtained via chemical crosslinking overcome these limitations, offering better elasticity and stability. More importantly, chemically crosslinked silk hydrogel microspheres exhibit a more gradual degradation profile and slower degradation rate. Therefore, the development of silk hydrogel microspheres for drug delivery in osteoarthritis holds great potential.<sup>26</sup>

### Synthetic Polymer Microspheres

Synthetic polymers, as another class of biodegradable materials, are also widely used in microsphere preparation. While synthetic polymers may not offer the same level of biocompatibility and biodegradability as natural polymers, their tunable properties can address some of the limitations of natural polymers, such as poor controllability and stability

during fabrication. Additionally, the properties and functionality of synthetic polymer microspheres can be tailored to specific requirements, allowing for more precise and predictable drug release profiles. Common synthetic polymers used in microsphere formulations include polylactic acid (PLA), polyglycolic acid (PGA), and polylactic glycolic acid (PLGA).

PLGA is a widely used synthetic polymer material, and its favorable biodegradability and biocompatibility make PLGA microspheres highly effective for drug delivery.<sup>27</sup> The excellent properties of PLGA microspheres arise primarily from the ability to adjust the monomer ratio of polylactic acid (LA) to glycolic acid (GA),<sup>27</sup> as well as the molecular weight and concentration of PLGA, to meet specific requirements.<sup>28</sup> By modifying the molecular weight and composition ratio of PLGA, the encapsulation efficiency, drug loading capacity, and sustained-release properties of PLGA microspheres can be enhanced, thereby improving their application in intra-articular drug delivery for osteoarthritis treatment.<sup>29</sup>

Continuous low-dose intra-articular injections of dexamethasone can alleviate joint inflammation by modulating catabolic and anabolic processes, as well as reduce pain associated with osteoarthritis.<sup>30</sup> PLGA microspheres loaded with dexamethasone, due to their favorable biodegradability, can provide sustained release of dexamethasone *in vitro* to combat inflammation and protect engineered cartilage.<sup>31</sup> Similarly, PLGA microspheres loaded with dexamethasone, prepared using the single emulsion/solvent extraction technique, exhibit prolonged and controllable release profiles, offering a novel approach to drug delivery for intra-articular treatment of osteoarthritis.<sup>32</sup> Additionally, meloxicam-loaded PLGA microspheres, benefiting from good biodegradability, can also provide long-term anti-inflammatory effects.<sup>29</sup>

PLGA lyophilized microspheres loaded with tetramethylpyrazine (TMA) offer an extended drug release duration of up to 32 days and a joint retention time of 30 days. This exceptional sustained release, without a burst release phenomenon, enables TMA-PLGA microspheres to effectively alleviate joint inflammation and improve osteoarthritis-related symptoms.<sup>33</sup>

Triamcinolone acetonide (TAA) is commonly used to relieve knee joint inflammation and pain. However, due to the joint's clearance mechanisms, the drug concentration and anti-inflammatory effects of intra-articular TAA injections rapidly decline within a short period. Therefore, PLGA microspheres loaded with TAA can stabilize its presence in the synovial fluid and extend its therapeutic duration, providing a sustained-release effect.<sup>34</sup> However, some studies suggest that PLGA is not the ideal material for TAA delivery. Although TAA-loaded PLGA microspheres are more effective than free TAA in reducing osteoarthritis pain, the degradation rate and release profile of PLGA microspheres do not meet the clinical requirements for optimal sustained release. Consequently, replacing PLGA with another synthetic polymer, poly (ester amide) (PEA), in TAA-loaded microspheres significantly enhances the sustained-release capacity. PEA, as a carrier material, offers superior biocompatibility and safety, making TAA-PEA microspheres more effective in relieving osteoarthritis pain compared to TAA-PLGA microspheres.<sup>35</sup> Therefore, PEA microspheres, as a carrier for intra-articular TAA injections in osteoarthritis treatment, demonstrate improved therapeutic efficacy over PLGA microspheres.<sup>36</sup>

## Composite Microspheres

With the continued research into microspheres made from single materials, their limitations have gradually become evident. Microspheres prepared from a single material often suffer from certain defects that impair their performance. These issues include poor biocompatibility, inadequate degradation capacity,<sup>22</sup> insufficient mechanical strength, and rapid clearance from the joint cavity,<sup>37</sup> all of which ultimately reduce the sustained-release effectiveness of the drug loaded in the microspheres. To address these challenges, a promising solution is to replace the single material with two or more components, resulting in composite microspheres. Composite microspheres leverage the combination of different materials to compensate for the shortcomings of individual components, thereby enhancing their physicochemical properties and improving their overall performance.<sup>22</sup>

For example, when tripolyphosphate (TPP) is incorporated into the natural polymer chitosan, the interaction between the two can form a tightly structured chitosan/TPP composite microsphere. The porosity of these composite microspheres can be modulated by changes in the pH of the TPP solution. Under acidic conditions (low pH), these microspheres exhibit favorable drug release characteristics, enabling efficient and sustained drug delivery.<sup>38</sup>

Liposomes, as a common nano-carrier, offer excellent biocompatibility and encapsulation efficiency.<sup>39,40</sup> However, their susceptibility to rapid clearance can lead to instability of the encapsulated drugs.<sup>41</sup> To address this, the combination of liposomes with microspheres can enhance the retention time of the drug within the joint, improving the flexibility and stability of the composite microspheres. For example, composite microspheres formed by coupling methacrylate-modified chondroitin sulfate hydrogel with liposomes loaded with glycyrrhizin not only provide high drug loading and good encapsulation efficiency but also protect the liposomes and their encapsulated drugs from clearance,<sup>37</sup> thereby maintaining the drug's retention in the joint. The microspheres' stable degradation rate further contributes to sustained drug release.<sup>10</sup> Similarly, composite microspheres formed by photo-crosslinking liposomes containing arbutin with methacrylated gelatin also exhibit a slower in vitro degradation rate and effective sustained release of arbutin (ARB).<sup>42</sup>

In addition to liposomes, other nano-carriers such as polymeric nanoparticles, nano-micelles, and nanocapsules also offer protective effects for the encapsulated drugs. The unique particle size of nano-carriers enhances their therapeutic potential.<sup>43</sup> For instance, embedding dexamethasone-loaded nanomicelles within GelMA microspheres creates an M1 macrophage-targeted micro/nano drug delivery system (GelMA@FPPD), which protects the drug-loaded nano-carriers from clearance and ensures sustained intra-articular release of dexamethasone, offering promising therapeutic benefits.<sup>44</sup>

In recent years, the incorporation of metal ions into microspheres has emerged as a key area of research. Metal-organic frameworks (MOFs), which possess a large surface area and optimal pore size, are considered promising drug carriers.<sup>45,46</sup> One such MOF, the zinc imidazole framework (ZIF), exhibits high drug loading capacity and good biocompatibility.<sup>47</sup> When ZIF-8 nanoparticles, loaded with esculetin, are incorporated into a hydrogel matrix and crosslinked via photo-activation, they form composite microspheres that not only tightly encapsulate IA-ZIF-8 but also protect it from premature clearance, enabling sustained drug release.<sup>48</sup> Another approach involves the creation of a 3D metal-phenolic network (MPN) by combining metal ions with the chelating sites of tannic acid. This MPN serves as an alternative means of introducing metal ions into microspheres and exhibits both antioxidant and chondroprotective properties.<sup>49,50</sup> When strontium ( $\text{Sr}^{2+}$ ), which has a beneficial effect on the cartilage matrix,<sup>51</sup> is combined with tannic acid, composite microspheres made from gelatin/poly-lactic acid (PLA) incorporating TA/ $\text{Sr}^{2+}$ -MPN not only possess antioxidant activity but also demonstrate more stable degradation rates, enhancing their sustained release properties.<sup>52</sup>

In conclusion, achieving sustained drug release is a fundamental requirement for drug-loaded microspheres used in the treatment of osteoarthritis. However, it is not enough to simply control the release rate; equally important is ensuring that the drug reaches the targeted lesion site accurately and is released in a timely and controlled manner, according to the therapeutic needs<sup>9</sup> (Table 1).

**Table 1** The Sustained-Release Capabilities of Different Microspheres

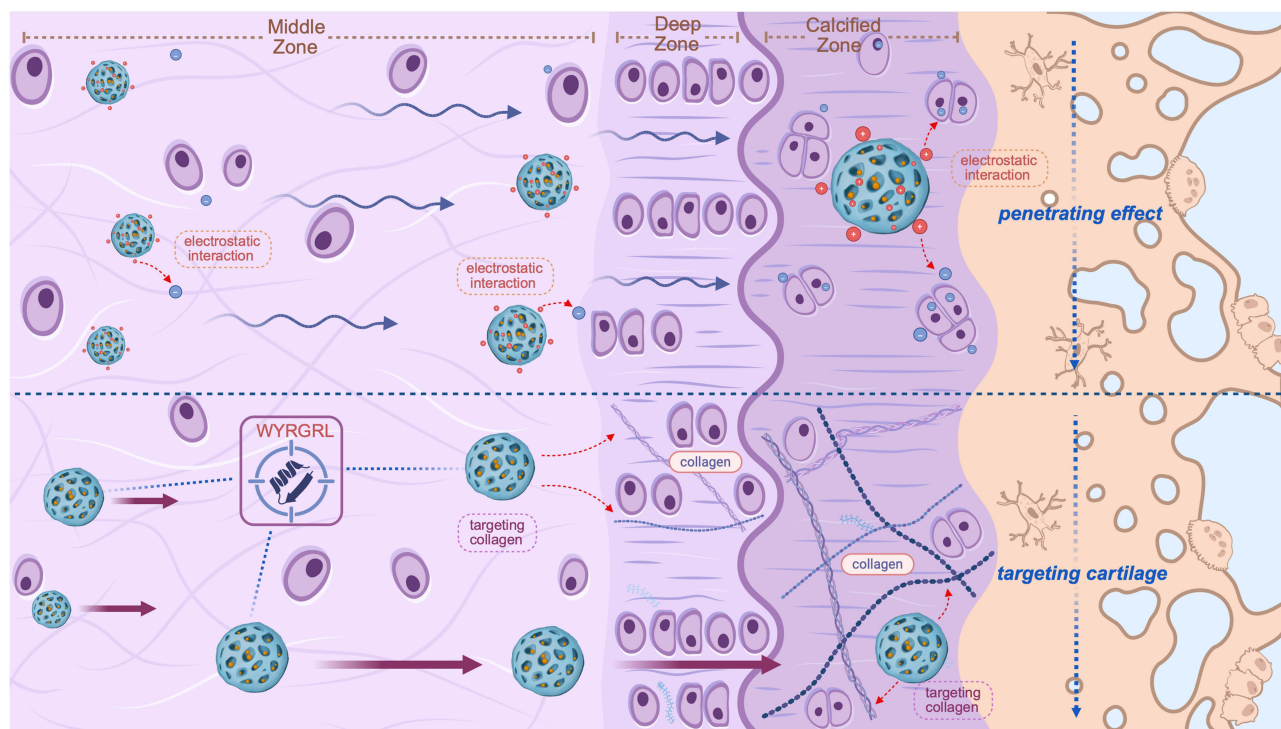
Material	Categories	Drug	Sustained Release Capability	Efficacy	References
Gelatin	Natural polymer microspheres	Anti-inflammatory cytokines (IL-4, IL-13)	Controlled release	Anti-inflammatory	(Park, 2020) <sup>22</sup>
Dextran	Natural polymer microspheres	Ibuprofen (Ibu)	Controlled release	Anti-inflammatory	(Li, 2023) <sup>24</sup>
Silk fibroin	Natural polymer microspheres	Anti-inflammatory cytokines	Controlled release	Anti-inflammatory Reduce pain	(Wang, 2022) <sup>26</sup>
PLGA	Synthetic polymer microspheres	Meloxicam	Controlled release	Anti-inflammatory Reduce pain	(Sun, 2022) <sup>31</sup>
PEA	Synthetic polymer microspheres	Celecoxib	Controlled release	Anti-inflammatory Reduce pain	(Rudnik-Jansen, 2019) <sup>41</sup>
Chitosan/TPP	Composite microspheres	Lornoxicam	Extended release	Anti-inflammatory	(Abd-Allah, 2016) <sup>45</sup>
ChsMA/Liposome	Composite microspheres	Liquiritin (LQ)	Extended release	Antioxidation Anti-inflammatory	(He, 2022) <sup>43</sup>
GelMA/Nanomicelle	Composite microspheres	Dexamethasone (DEX)	Extended release	Anti-inflammatory	(Li, 2023) <sup>53</sup>
GelMA/ZIF-8	Composite microspheres	Itaconate	Extended release	Antioxidation Anti-inflammatory	(Yu, 2023) <sup>57</sup>

## Enhancing Drug Permeation and Targeted Drug Delivery

The penetration capability required by microspheres during drug delivery arises from the complex structure of cartilage tissue. Most chondrocytes are located deep within the tissue.<sup>53</sup> Cartilage is structurally and functionally divided into four distinct layers: superficial, middle, deep, and calcified. The superficial layer is characterized by densely packed collagen fibers and serves as a protective barrier. For microspheres to effectively reach and act within the cartilage, they must first penetrate this surface layer. The middle layer, located just beneath the surface, contains more loosely arranged collagen fibers and is rich in chondrocytes, making it a common target site for therapeutic microspheres. In contrast, the deep and calcified layers lie farther within the cartilage and are more difficult for drug-loaded microspheres to access due to their dense structure and limited permeability<sup>54</sup> (Figure 2).

In addition to the anatomical location of chondrocytes, a major factor limiting the precise delivery of drug-loaded microspheres is the ECM that surrounds them, providing structural support and a conducive environment for cell survival. The ECM is composed of collagen fibers, highly negatively charged proteoglycans, and other macromolecules,<sup>55</sup> forming a dense and complex network. This negatively charged matrix poses a significant barrier to the penetration of large macromolecules and negatively charged substances, thereby hindering the delivery of therapeutic agents to chondrocytes.<sup>56,57</sup> Traditional drug delivery strategies often fail to overcome the ECM barrier, preventing effective targeting of chondrocytes and lesion sites. Moreover, such non-specific approaches may damage healthy tissue and cause undesirable side effects.<sup>58</sup> Therefore, drug-loaded microspheres must be designed to penetrate the dense, negatively charged ECM and achieve targeted delivery to diseased cartilage regions, enabling precise and effective intra-articular therapy<sup>58,59</sup> (Figure 2).

To effectively target chondrocytes, drug-loaded microspheres must first penetrate the various layers of cartilage. Upon intra-articular injection, microspheres encounter the superficial cartilage as the initial physical barrier. While small-sized microspheres can diffuse through the dense fibrous structure of the superficial cartilage due to their size and osmotic properties, their movement within the highly negatively charged extracellular ECM is often restricted.<sup>58</sup> To overcome this



**Figure 2** The barrier-Penetration and cartilage-targeting functions of microspheres.

**Notes:** This figure illustrates the process by which drug-loaded microspheres utilize their intrinsic charge interactions to penetrate the barrier formed by the cartilage extracellular matrix and subsequently target cartilage cells to exert their therapeutic effects, and the process by which microspheres containing type II collagen-targeting peptides can target collagen to achieve cartilage targeting by therapeutic microspheres. This figure was created with BioRender (<https://biorender.com/>).

challenge, surface modification with positively charged materials or loading the microspheres with positively charged drugs can enhance ECM penetration through electrostatic interactions between cations and the negatively charged ECM components.<sup>60</sup>

For instance, cationic liposomes—a class of positively charged nanocarriers—exhibit excellent biocompatibility and drug encapsulation efficiency. Their positive charge facilitates adhesion to the ECM, followed by gradual inward diffusion via electrostatic attraction.<sup>61</sup> One example is GM-Lipo@ARB, a microsphere system composed of arbutin-loaded cationic liposomes encapsulated within methacryloyl gelatin.<sup>62</sup> The cationic liposome coating enables the microspheres to effectively traverse the ECM and target cartilage tissue, while also protecting the liposomes from degradation, thereby allowing arbutin to exert its therapeutic effect in chondrocytes.<sup>42</sup> Another system combines kartogenin (KGN)-loaded poly(amidoamine) (PAMAM) dendrimers with hyaluronic acid methacrylate (HAMA) to form drug delivery microspheres. These microspheres are further surface-modified with polylysine (PLL), creating a dual-positively charged system. The enhanced surface charge promotes targeted interaction with the ECM, facilitating gradual accumulation at the lesion site and contributing to effective osteoarthritis therapy through electrostatic targeting<sup>58</sup> (Figure 2).

Once drug-loaded microspheres successfully penetrate into the middle or deeper layers of cartilage through particle size advantages and surface charge interactions, targeting chondrocytes to enhance therapeutic efficacy becomes a critical step. To achieve this, hydrogel microspheres can be functionalized with the cartilage-targeting peptide WYRGRL,<sup>55,63</sup> which specifically binds to type II collagen—a major component of the cartilage matrix. These WYRGRL-modified microspheres exhibit selective binding to chondrocytes, enabling site-specific delivery of therapeutic agents such as dexamethasone (Dex) and kartogenin (KGN), thereby enhancing treatment efficacy at diseased cartilage sites.<sup>64</sup> In early-stage osteoarthritis, damaged cartilage expresses type I collagen (Coll) differently from healthy tissue. Based on antigen-antibody interactions, hydrogel microspheres modified with anti-Coll antibodies can more precisely target damaged chondrocytes, offering a promising strategy for localized cartilage repair<sup>65</sup> (Figure 2).

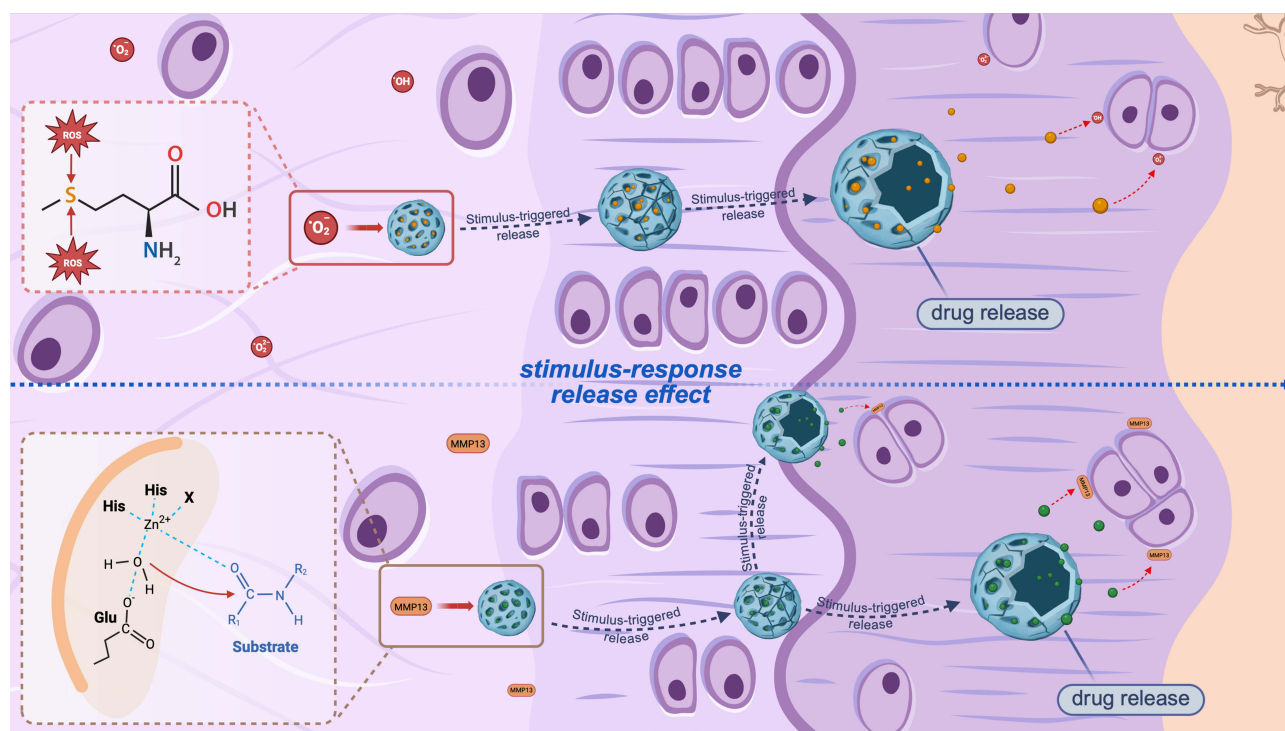
While targeted microspheres in osteoarthritis therapy are commonly designed to deliver anti-inflammatory drugs to chondrocytes, they can also be engineered to target immune cells such as macrophages.<sup>66,67</sup> For example, embedding dexamethasone-loaded folic acid–polyethylene glycol–polypropylene sulfide (FA–PEG–PPS) block copolymers into gelatin methacryloyl (GelMA) microspheres results in a system (GelMA@FPPD) capable of selectively targeting M1 macrophages. This approach enables sustained release of dexamethasone, suppresses local inflammatory responses, and ultimately delays the progression of osteoarthritis by modulating the joint microenvironment.<sup>44</sup>

## Stimuli-Responsive Drug Release

The targeted microspheres discussed above enable site-specific drug delivery; however, optimizing therapeutic efficacy requires not only precise localization but also appropriate timing of drug release. Stimuli-responsive microspheres fulfill both requirements by responding to environmental cues—such as mechanical stress, inflammation, or hypoxia—at disease sites,<sup>68</sup> triggering structural changes that lead to controlled drug release. This mechanism enables both spatially targeted and temporally regulated drug delivery.<sup>69</sup>

Stimuli-responsive hydrogel microspheres have been widely applied in drug delivery across various diseases,<sup>70</sup> with diverse triggering stimuli. In OA, the inflammatory microenvironment plays a key role in disease progression, primarily through the upregulation of matrix-degrading enzymes such as matrix metalloproteinases (MMPs). Microspheres incorporating enzyme-sensitive peptides can respond to this enzymatic activity; the peptide linkers are cleaved in the inflammatory environment, releasing the encapsulated drugs<sup>71,72</sup> (Figure 3).

For example, gelatin microspheres crosslinked with genipin degrade in response to catabolic enzymes present in inflamed joints. Similarly, gelatin microspheres exposed to collagenase *in vitro* mimic this enzymatic degradation.<sup>23</sup> To specifically target MMP13—a key enzyme in OA pathology—bilayer hydrogel microspheres incorporating MMP13-sensitive peptides were developed. These microspheres release celecoxib-loaded liposomes from the outer layer in response to inflammatory degradation, while the inner core gradually releases chondroitin sulfate, thereby providing both anti-inflammatory and cartilage-repair effects in a sequential manner.<sup>73</sup> Oxidative stress is another critical component of the OA inflammatory environment.<sup>74</sup> Reactive oxygen species (ROS)-responsive microspheres have been developed to



**Figure 3** Stimuli-responsive drug release by microspheres.

**Notes:** This figure contains stimuli-responsive microspheres responding to the presence of ROS as well as MMP13 in the OA microenvironment, interacting with the corresponding stimuli through their own specific targets after exposure to these triggers. As the microspheres degrade, they facilitate the sustained release of their encapsulated drug, ensuring localized therapeutic effects and improved treatment outcomes. This figure was created with BioRender (<https://biorender.com/>).

release antioxidant drugs in response to elevated ROS levels.<sup>74</sup> For instance, KGN and dexamethasone were electrostatically loaded into a ROS-responsive copolymer integrated with GelMA hydrogel. The ROS-sensitive bonds within the system are cleaved by excess ROS, triggering the release of the therapeutic agents to reduce oxidative damage and inflammation.<sup>64</sup> Furthermore, dual-responsive microspheres that combine MMP- and ROS-sensitivity have been designed to release dihydromyricetin (DMY) in a stimulus-specific and time-sequenced manner, enhancing therapeutic potential through synergistic response mechanisms<sup>75</sup> (Figure 3).

It is important to note that while endogenous stimuli-responsive microspheres can autonomously respond to specific microenvironmental cues in OA cartilage, their drug release kinetics heavily depend on local pathological conditions, which are difficult to control. In contrast, exogenous stimuli such as near-infrared (NIR) light can offer greater control over drug release timing.<sup>76</sup> By incorporating photothermal conversion agents into hydrogel microspheres, NIR irradiation can induce localized heating, modulating microsphere volume and triggering controlled drug release. These photothermally responsive systems allow precise spatial and temporal control over drug delivery, offering advantages over conventional stimuli-responsive strategies.<sup>76,77</sup>

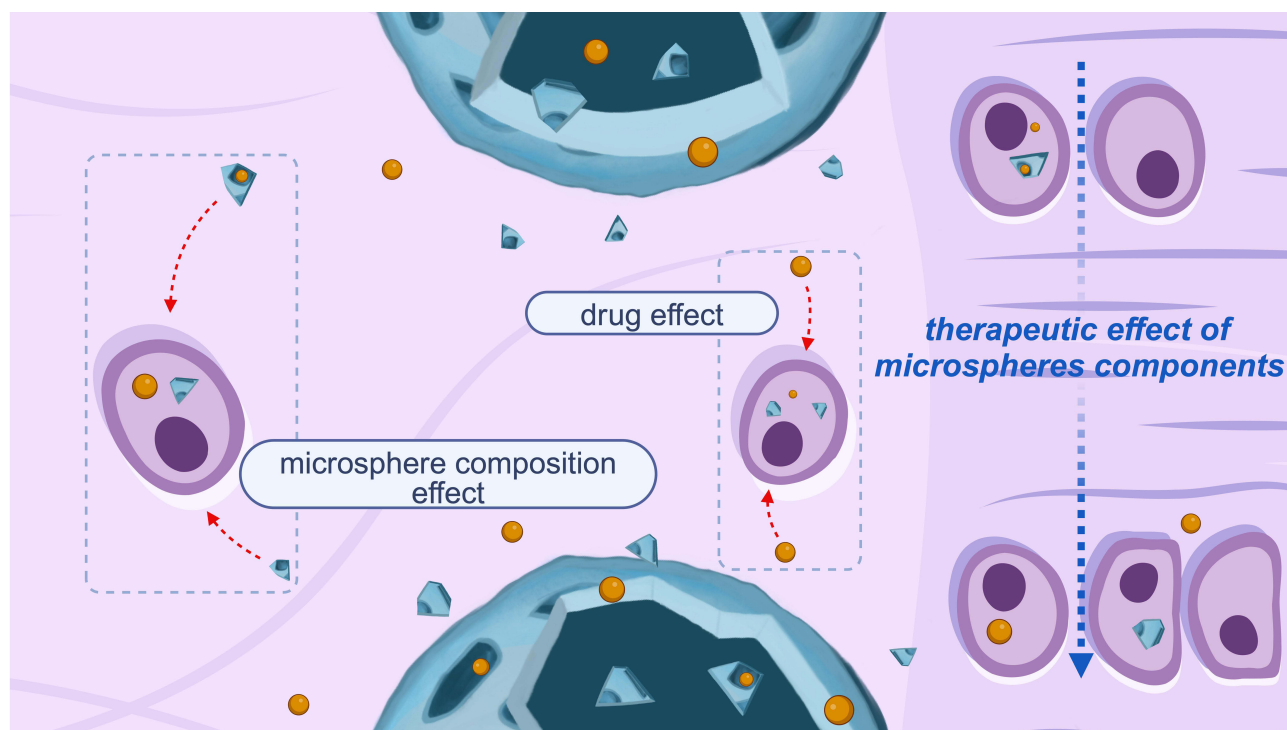
## Self-Therapeutic Effects of Microspheres

In research related to osteoarthritis treatment, microspheres are primarily used as drug delivery carriers, facilitating controlled release, targeting, and other auxiliary functions for the encapsulated drugs.<sup>9</sup> As research progresses, it has become evident that microsphere systems can also exert therapeutic effects beyond their role as carriers for loaded drugs. As microspheres degrade *in vivo*, their constituent materials can exert therapeutic effects alongside the encapsulated drugs. In some cases, microspheres can provide therapeutic benefits even in the absence of loaded drugs.<sup>78</sup> These intrinsic effects may arise not only from the pharmacological properties of the microsphere components but also from their physical characteristics and degradation products. For example, during the drug delivery process, certain microspheres can exert a lubricating effect, contributing to joint protection and symptom relief<sup>79</sup> (Figure 4).

## Therapeutic Effects of Microsphere Components

Excessive ROS produced during OA can induce oxidative stress damage to the cartilage matrix through mechanisms such as the activation of inflammatory signaling pathways, protein modifications, and DNA damage, thus exacerbating OA progression.<sup>80,81</sup> As a result, increasing evidence suggests that ROS can serve as a therapeutic target for osteoarthritis treatment.<sup>82</sup> In microsphere systems designed to alleviate OA-related oxidative stress, antioxidant drugs are typically loaded to counteract ROS, while the ROS-responsive properties of these microspheres can enhance the therapeutic efficacy of the loaded drugs.<sup>82</sup> However, a novel approach proposes that microspheres can exert therapeutic effects independent of any drug loading. Instead, these microspheres utilize their inherent material properties to combat ROS-induced oxidative stress and thereby treat osteoarthritis.

Studies have demonstrated that unloaded polyphenylene sulfide microspheres (PPS-MS), utilizing their intrinsic PPS component, can scavenge ROS and provide antioxidant effects, protecting chondrocytes from toxicity.<sup>78</sup> When applied in an OA model, PPS-MS not only counteract high levels of ROS but also reduce matrix metalloproteinase (MMP) activity, thereby achieving notable anti-inflammatory and antioxidant effects.<sup>83</sup> Similarly, another study developed drug-loaded chondroitin sulfate microspheres, which harness antioxidant and anti-inflammatory effects to treat OA.<sup>84,85</sup> In this research, chondroitin sulfate, a natural compound with both anti-inflammatory and antioxidant properties, was used as the base material for the drug delivery microspheres.<sup>86</sup> Upon degradation in the joint cavity, the released chondroitin sulfate molecules reduce ROS levels and inhibit ROS-related inflammatory pathways, thereby exerting antioxidant effects.<sup>37</sup> Additionally, the microsphere's incorporation of glycyrrhizin enables a dual antioxidant action, ultimately providing a therapeutic effect against OA.<sup>37,87</sup> Thus, microspheres that rely on their own components for therapeutic action not only support intra-articular drug delivery but can also serve as an independent treatment method for alleviating osteoarthritis<sup>83</sup> (Figure 4).



**Figure 4** Therapeutic Effects of Microsphere Components.

**Notes:** This figure illustrates how the intrinsic components of microspheres, upon degradation, can exert therapeutic effects through their inherent drug properties. This figure was created with BioRender (<https://biorender.com/>).

## Treatment of OA Through Self-Lubricating Action

Pain relief remains a central focus in the treatment of OA,<sup>88</sup> with the primary cause of pain being the increased friction resulting from the damage to articular cartilage, which disrupts the joint's water-based lubrication system.<sup>89</sup> Consequently, developing effective lubricants to restore joint lubrication is a key therapeutic approach.<sup>90</sup> Drug delivery microspheres, with their inherent lubricating properties, can help alleviate OA symptoms and offer a promising treatment strategy.<sup>91</sup>

The lipid layer on the cartilage surface can interact synergistically with hyaluronic acid (HA) to form a hydrated lubrication layer.<sup>92</sup> However, as OA progresses, the lipid layer may be damaged, and a lack of lipids in the synovial fluid can impair the formation of this hydrated lubrication layer.<sup>93</sup> To address this, liposomes injected into the joint can serve as supplements to the lipid layer, effectively enhancing lubrication. One study incorporated rapamycin (RAPA)-loaded liposomes into HA microspheres (RAPA@Lipo@HM). These microspheres can continuously release liposomes through a rolling mechanism, forming a self-renewing hydrated lubrication layer on the surface of the HA-based microspheres, providing stable lubrication.<sup>94</sup> Additionally, the cationic liposomes' targeting ability and the chondroprotective effect of rapamycin improve the therapeutic efficacy of RAPA@Lipo@HMs for OA.<sup>95,96</sup> Furthermore, hybrid exosomes, formed through membrane fusion between exosomes and liposomes, can be combined with HA-based hydrogel microspheres. These hybrid exosomes, along with the lubrication properties of HA microspheres, can offer enhanced joint lubrication.<sup>97</sup>

In addition to liposome-containing microspheres, those made from other materials can also exhibit lubrication effects similar to liposomes. For example, silk fibroin (silk) hydrogel microspheres, prepared using diethylene glycol dimethyl ether (BDDE), possess excellent hydrophilicity and a smooth surface.<sup>26</sup> Upon injection into the joint cavity, they can reduce OA-related pain by providing a lubricating effect through ball-bearing and cartilage surface interactions.<sup>98,99</sup> Additionally, PLGA porous microspheres containing nano-fat (NF) have a smooth, uniform surface and form a biological bearing by combining with oil, reducing friction between the joint surfaces and enhancing lubrication.<sup>100</sup>

## Microspheres in Cartilage Tissue Engineering for OA Treatment

Articular cartilage has limited self-repair capacity due to its avascular and aneural nature, as well as the inherently low regenerative ability of chondrocytes.<sup>101</sup> Cartilage damage caused by inflammation or trauma cannot be effectively treated with specific pharmacological interventions.<sup>102</sup> While joint replacement surgery remains a treatment option for end-stage osteoarthritis, it is often unacceptable to patients seeking a higher quality of life.<sup>103</sup> In recent years, tissue engineering has made significant advancements in addressing cartilage repair, a key therapeutic target in osteoarthritis management.<sup>104,105</sup>

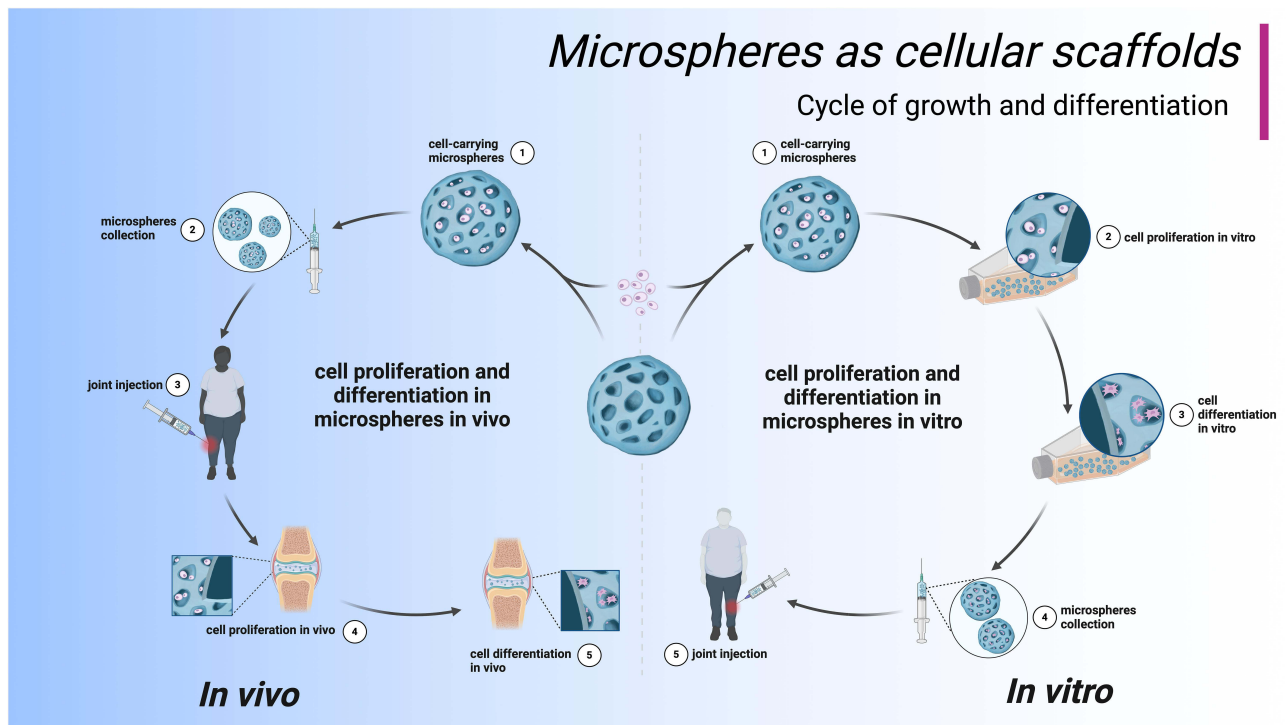
Cartilage tissue engineering typically involves three components: stem cells, scaffolds for cell growth, and growth-stimulating factors.<sup>106</sup> The primary strategy involves combining autologous chondrocytes or mesenchymal stem cells (MSCs) with growth scaffolds to generate cartilage tissue for repairing damaged areas.<sup>107</sup> Microspheres play a versatile role in this process, functioning as scaffolds for cell growth and differentiation, as well as carriers for bioactive materials such as cells and growth factors. As a result, they have become a critical component of cartilage tissue engineering.<sup>102</sup>

## Microspheres as Cell Carriers and Growth Scaffolds

### Microspheres as Cell Carriers

Stem cell therapy has been a major focus in cartilage repair for OA patients,<sup>108</sup> typically involving the intra-articular injection of MSCs to alleviate pain and slow down cartilage degeneration.<sup>109,110</sup> However, the shear forces encountered during the injection process, as well as the complex joint environment, can lead to MSC damage or even cell death, reducing the number of viable cells and ultimately compromising the therapeutic efficacy.<sup>111</sup> Therefore, a carrier is needed that can both protect MSCs and facilitate high cell loading.<sup>112</sup>

Hydrogel microspheres can effectively encapsulate cells, shielding them from shear forces and preventing exposure to unfavorable conditions, thereby protecting the cells.<sup>113</sup> Due to their high porosity and large surface area, microspheres provide abundant space for cell attachment, enabling high cell loading. Porous microspheres made from a combination of chitosan and PLGA, for example, can enhance cell adhesion through their inherent electrostatic properties. These microspheres not only allow for high MSC loading but also offer good mechanical properties to protect the cells from damage<sup>114</sup> (Figure 5).



**Figure 5** The Role of Microspheres as Cell Carriers and Scaffolds for Cell Growth and Differentiation.

**Notes:** This figure illustrates how microspheres function as both cell carriers and scaffolds for cell growth, providing a suitable environment for chondrocyte differentiation both in vitro and in vivo. This figure was created with BioRender.

Moreover, microspheres fabricated with specialized techniques can improve cell proliferation and migration while enhancing cell delivery capacity.<sup>114</sup> Gelatin methacryloyl (GelMA) hydrogel microspheres, for instance, possess a porous structure that provides an optimal environment for cell adhesion and proliferation, thus improving the survival and engraftment rates of loaded cells.<sup>115</sup> Additionally, microspheres made from freeze-gelation techniques, which impart mechanical stability, ensure that the microspheres remain compressible during injection, thus preserving the viability of the cells they carry.<sup>116</sup>

### Microspheres as Cell Growth Scaffolds

After the successful injection of cells into the joint cavity, it is essential to ensure that the cells are safely and accurately delivered to the damaged cartilage area. Janus microspheres, which contain iron oxide magnetic nanoparticles (IONPs) MSCs, not only encapsulate the cells but also utilize the IONPs for targeted cartilage repair through electromagnetic guidance.<sup>117</sup> Achieving optimal therapeutic outcomes requires more than just delivering the cells; it is crucial to provide a suitable environment for cell growth and differentiation once they reach the site of injury.<sup>118</sup> Thus, microspheres used for cell delivery also serve as essential cell growth scaffolds.<sup>119</sup>

In certain cases, cells intended for cartilage tissue engineering need to proliferate in vitro before implantation, but during this culture process, dedifferentiation may occur.<sup>120</sup> To address this issue, injectable cryogel microspheres (ICMs) provide a three-dimensional (3D) environment resembling the extracellular matrix (ECM) and incorporate gelatin RGD sequences for cell adhesion. This structure offers a supportive scaffold that maintains the chondrocyte phenotype, facilitating the growth and differentiation of cartilage cells.<sup>116</sup>

In other instances, the cells need to proliferate after implantation. Once the microspheres carrying the cells reach the damaged area, they act as scaffolds that support the cells, which is equally critical for achieving therapeutic success.<sup>121</sup> Alginate-gelatin microspheres, combining the ECM-like properties of alginate with the cell-adhesive and proliferative qualities of gelatin, provide an enhanced scaffold for adipose-derived stem cells at the injury site. This dual-functional scaffold also addresses the challenges of cell loss due to contact inhibition and dedifferentiation.<sup>122</sup>

As growth scaffolds, microspheres not only simulate the ECM to support cell growth but also promote cartilage repair by recruiting cells and enhancing their adhesion to the microsphere surface.<sup>114</sup> For example, hydrogel microspheres modified with acetaldehyde and carrying platelet-derived growth factor-BB (PDGF-BB) can adhere to the cartilage surface, where they recruit surrounding stem cells and Sn-chondrocytes. These microspheres further mimic the ECM in situ, providing a supportive environment for cell growth and promoting cartilage regeneration<sup>123</sup> (Figure 5).

## Microspheres Providing Active Factors to Promote Chondrocyte Differentiation

Recent studies have increasingly focused on the combination of stem cells, growth factors, and scaffolds in cartilage tissue engineering.<sup>124</sup> Microspheres, serving as both cell carriers and scaffolds, play a critical role in this field. In some cases, the mere addition of stem cells is insufficient for cartilage regeneration; it is essential to induce the differentiation of stem cells into chondrocytes for effective cartilage repair.<sup>125</sup> Therefore, incorporating bioactive factors that promote cell differentiation into the microsphere-based delivery systems becomes crucial.

Transforming growth factor-beta (TGF- $\beta$ ) has long been recognized as a key cytokine involved in cartilage differentiation.<sup>126</sup> By developing microspheres that continuously release TGF- $\beta$ , an optimal environment for MSC differentiation into chondrocytes can be provided, thereby enhancing tissue repair.<sup>127</sup> Additionally, PLGA-P188-PLGA-based microspheres not only provide a sustained release of TGF- $\beta$  but also leverage their inherent properties to optimize TGF- $\beta$  release, thereby stimulating cartilage regeneration more effectively.<sup>127</sup> KGN as a small-molecule compound, can promote cartilage formation by activating the SOX9 transcription factor, mimicking the effects of TGF- $\beta$ .<sup>127</sup> Microspheres loaded with KGN and MSCs release the cells in response to the OA environment. As the microspheres degrade, KGN is concurrently released, inducing MSCs to differentiate into chondrocytes and promoting tissue regeneration.<sup>114</sup>

In cartilage tissue engineering, directly adding growth factors is the primary method for inducing chondrocyte differentiation. However, another approach involves indirectly regulating the expression of active factors by altering the environmental conditions.<sup>128</sup> Hypoxic conditions, through hypoxia-inducible factors (HIFs), can influence stem cell differentiation and chondrocyte maturation.<sup>129</sup> For example, pre-treating gelatin methacrylate microspheres loaded with chondroprogenitor cells under hypoxic conditions results in superior cartilage formation compared to those cultured under normoxic conditions.<sup>130</sup> Moreover, dimethylxalylglycine (DMOG), which inhibits HIF-1 $\alpha$  degradation, can be used to simulate a hypoxic environment.<sup>131</sup> By combining DMOG with parathyroid hormone-related protein (PTHrP), which regulates chondrocyte differentiation, and loading them into PLGA microspheres, a promising three-dimensional culture system is created. This system not only enhances chondrocyte differentiation but also stabilizes their phenotype, offering a viable strategy for cartilage regeneration.<sup>132</sup>

## Conclusion and Perspectives

In conclusion, this review systematically summarizes the multifunctional applications of hydrogel-based microspheres in OA therapy, highlighting their capacity for sustained drug release, targeted delivery, and regenerative cartilage repair. In the treatment of OA, pharmacological therapy remains the primary approach, with intra-articular drug delivery gaining attention due to its superior safety profile and therapeutic efficacy.<sup>7</sup> However, to optimize intra-articular drug delivery, it is essential to ensure that the drug reaches the damaged site accurately and has an extended retention time within the joint. Hydrogel microspheres stand out among the various intra-articular drug delivery systems due to their excellent performance. These microspheres not only offer the advantages of hydrogels, such as good drug protection and biocompatibility, but also feature higher porosity and greater structural stability.<sup>64</sup>

This review highlights the synthesis of multifunctional microspheres as drug carriers for osteoarthritis treatment, with a focus on their roles in controlled drug release, targeted delivery to cartilage, and intrinsic therapeutic effects. Due to their structural characteristics, microspheres have a higher drug-loading capacity and can maintain a high drug concentration. More importantly, microspheres can control drug release by altering their structure, thus addressing the issue of rapid drug release and ensuring prolonged drug concentrations. This sustained-release capability is a fundamental requirement for drug delivery systems. In this paper, microspheres for drug delivery are categorized based on their materials, and their effectiveness in drug release is analyzed. By comparison, composite microspheres—due to their complex composition—demonstrate superior sustained-release effects over single-material microspheres. In addition to the basic function of sustained release,

microspheres can enhance drug penetration during delivery by leveraging electrostatic interactions, overcoming the dense structure and charge barriers around cartilage. Moreover, microspheres functionalized with specific peptides, such as those targeting type II collagen, can enable cartilage-targeted delivery. Furthermore, responsive microspheres can undergo structural changes in response to inflammatory or hypoxic conditions, thereby achieving controlled drug release based on environmental stimuli. Beyond drug delivery, microspheres can also contribute to therapeutic effects through their material composition. Some microspheres, composed of special materials, can create lubricating layers or act as biological bearings within the joint, providing joint lubrication and alleviating OA-related pain.

In addition to their applications in drug delivery, this review also summarizes the use of microspheres as carriers and scaffolds in cartilage tissue engineering. While drug delivery has been the primary application of microspheres in OA therapy, the irreversible destruction of articular cartilage in advanced OA cannot be reversed by drugs alone. Thus, microspheres designed for cartilage repair have emerged as promising alternatives. Stem cell therapy, a core component of cartilage tissue engineering, relies on microspheres to protect and deliver cells to the damaged areas, where they provide an optimal environment for cell growth. Moreover, when stem cells need to proliferate before implantation, microspheres can offer support during *in vitro* culture. However, in some cases, transplanted stem cells may fail to differentiate into chondrocytes and complete the repair. To address this, microspheres can carry bioactive factors that promote stem cell differentiation into chondrocytes, enhancing the regenerative process.

Current research indicates that microspheres are highly promising materials for OA treatment. Building on hydrogel technology, microspheres have been further optimized to improve their drug delivery and release capabilities. However, several challenges remain. Despite the advantages of sustained release, some microsphere materials still exhibit poor stability, leading to insufficient control over drug release rates. Both rapid and slow-release rates can negatively impact the therapeutic effect. Additionally, biocompatibility remains a concern, as certain microsphere materials may trigger foreign body reactions, affecting patient outcomes. Although an increasing number of stimuli-responsive and targeted microspheres for osteoarthritis treatment have been developed, there remains substantial room for improvement in their functionality. Future research should prioritize integrating environment-responsive delivery with cartilage-targeting mechanisms to improve therapeutic precision and durability *in vivo*.

Research on microspheres for OA treatment is ongoing, and their applications extend beyond drug delivery and cartilage tissue engineering. Recent studies have demonstrated that stress-electrically coupled hydrogel microspheres can alleviate cartilage damage and promote regeneration by reducing stress-electrical conversion losses under mechanical stimulation.<sup>133,134</sup> Additionally, fluorescently labeled microspheres have been developed to integrate imaging and therapy, enabling real-time monitoring of cartilage repair through fluorescence signals. However, large-scale production of microspheres remains a significant challenge, leading to high manufacturing costs and limiting their clinical application. Moreover, few clinical trials or translational studies have been conducted to date.<sup>135</sup> Therefore, further research is needed to improve the functionality, scalability, and clinical relevance of microsphere systems, ultimately enhancing their therapeutic potential and translational value in osteoarthritis treatment.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that there are no potential conflicts of interest in this study.

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