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Review

Recent advances in intra-articular bioactive delivery for the treatment of osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is among the most prevalent debilitating chronic diseases worldwide, with treatment currently strictly palliative. Intra-articularly administered agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and hyaluronic acid (HA) have an edge over systemic medications as they get localized at the site of inflammation, where they achieve higher concentrations to exert their therapeutic effects. However, the repeated injections of these agents are accompanied by discomfort and pain as well as an increased risk of infections. Furthermore, therapeutic agents are rapidly cleared from the intra-articular (IA) space, compromising their therapeutic efficacy. There is an urgent need for solutions to address these challenges. This review explores and highlights recent advances in IA therapies such as viscosupplementation, targeted corticosteroid formulations, colloidal systems (nano- and microparticles) fabricated from an array of materials, and molecularly imprinted polymer (MIP hydrogels and their potential for OA treatment. Delivery systems showcase their ability to prolong the retention of biologics, improve release profiles, and modulate inflammatory and matrix-degrading mediators in OA models. The review further integrates preclinical and clinical evidence, emphasizing the translational potential of such therapies while assessing the strengths and challenges of various therapeutic approaches. The literature provided can be used to identify future novel approaches to address the gaps in OA treatment with translation to clinical applications.

1. Introduction

OA is the most prevalent form of chronic degenerative joint disease that ultimately leads to an overall decline in the quality of life (He et al., 2020). As of 2019, a staggering 528 million individuals worldwide suffered from OA (World Health Organization, 2023). A demographic lens indicates that women and older adults are disproportionately affected, with 73 % of OA patients aged 55 and older, with 60 % comprising females. Knee OA is the most prevalent type, affecting approximately 365 million people, followed by hip and hand OA (Zhang et al., 2025). Despite this enormous burden, no cure currently exists; available therapies primarily provide symptomatic relief and do not halt disease progression. (Hawker and Lohmander, 2021).

Recent advances have fundamentally shifted our understanding of OA from a disease solely of articular cartilage to one of the entire joint structure (Tong et al., 2022). Rather than cartilage damage alone, OA is now recognized to involve synovial inflammation, subchondral bone remodeling, osteophyte formation, and changes throughout the osteochondral unit (Chen et al., 2020; Coaccioli et al., 2022; Gao et al., 2022).

Articular cartilage is an aneural, avascular connective tissue whose resilience and lubricating function depend on a high-water content (~70 %) and an extracellular matrix rich in collagen and glycosaminoglycans such as aggrecan (ACAN), chondroitin sulfate, and HA (Jin, 2020; Primorac et al., 2020) The chondrocytes embedded within this matrix regulate its homeostasis and are finely modulated by structural, physical, and biochemical stimuli. However, this equilibrium is disrupted in OA: oxidative stress, e.g., excessive reactive oxygen species (ROS), pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), and proteolytic

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enzymes matrix metalloproteinases (MMP) and as disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) (MMP-3, MMP-13, ADAMTS) shift the balance towards matrix degradation (Chow and Chin, 2020; Molnar et al., 2021)

As the degradative processes progress, loss of proteoglycans and collagen weakens cartilage architecture, leading to fissuring, thinning, and chondrocyte apoptosis; concomitantly, synovial fluid inflammation, stiffness, and pain intensify (He et al., 2020a; ur Rehman et al., 2024)(;). Meanwhile, alterations in the subchondral bone, including increased remodeling, trabecular microfractures, and exposure of the bone plate, further amplify joint damage by altering load distribution and promoting cartilage breakdown (Coaccioli et al., 2022; Hu et al., 2021). Understanding OA as a multifaceted disease highlights the need to consider not only cartilage but the entire joint microenvironment when developing therapeutic strategies.

Current treatments include physiotherapy, exercise, systemic analgesics (such as NSAIDs), IA glucocorticoids, and, in severe cases, joint replacement. These therapies are often limited by non-specific drug exposure, poor bioavailability at the joint, and short joint retention times that necessitate frequent dosing. They can also cause dose-related side effects, such as gastrointestinal and cardiovascular issues associated with chronic NSAID use (Hawker and Lohmander, 2021). Given its high prevalence, progressive nature, and significant personal and societal costs, there is an urgent need for more effective, locally acting therapies that not only relieve symptoms but also modify joint pathology.

Direct IA delivery addresses this need by administering therapeutics directly into the joint space, where they can achieve higher local concentrations with minimal systemic exposure, thereby enhancing efficacy and safety. IA delivery allows targeted administration of small molecules, peptides, biologics, and cells, which can reduce systemic toxicity and permit lower overall doses. Furthermore, IA routes are compatible with advanced formulations designed for sustained release, enhanced cartilage penetration, or local immunomodulation. Despite these benefits, IA delivery faces key translational challenges such as rapid clearance of small molecules and proteins from the synovium, which often limits IA retention to just hours. Frequent injections increase risks of infection and iatrogenic injury, which can reduce patient compliance, while maintaining therapeutic concentrations in a chronically inflamed joint requires controlled-release strategies that preserve bioactivity and cartilage health. Therefore, there is a strong clinical and practical rationale for developing IA sustained-release systems that prolong therapeutic exposure within the joint while reducing the need for repeated invasive procedures (Cao et al., 2021).

This review provides comprehensive insights, exploiting various advanced drug delivery systems such as nanoparticles (NPs) and hydrogels suitable for IA delivery of anti-OA drugs and biologics in OA therapy. *In vitro* and *in vivo* experiments were investigated to determine the effects of the delivery systems on OA models. Investigations include their anti-inflammatory effects, chondrogenesis, cartilage, and tissue regeneration. Key challenges were identified while offering valuable suggestions and insights to overcome these obstacles, contributing towards advancing the attenuation of OA development using NPs and hydrogel-based delivery systems.

2. Current pharmacotherapy approaches and key limitations of OA therapies

Given that there is no curative avenue, current available treatment regimens for OA are strictly palliative (Chen et al., 2021). Treatment aims to improve the overall quality of patients' lives by treating symptoms, delaying the progression of the disease, reducing pain, attempting to correct deformities, and improving the functionality of affected joints (Maqbool et al., 2021).

The standard care of treatment for mild OA is acetaminophen because of its efficacy, safety, and cost effectiveness (Salgado et al., 2021). Indeed, acetaminophen is a well-tolerated drug, but where acetaminophen is ineffective, intolerable, or OA symptoms are severe, NSAIDs are recommended. NSAIDs pose a risk of adverse effects, which may include renal dysfunction, elevated blood pressure, and gastrointestinal bleeding (Amoako and Pujalte, 2014).

In cases where both acetaminophen and NSAIDs are ineffective or the adverse reactions are intolerable, opiate drugs can be prescribed with caution (Chen et al., 2021). The lowest possible dosage should be used for the shortest period possible to avoid dependence and abuse (Dydyk et al., 2023). The challenge is that OA is a chronic disease often requiring long-term management (Charlesworth et al., 2019).

The use of IA class of anti-inflammatory agents, corticosteroids, can also provide short-term (4–6 weeks) pain relief. These are often injected in conjunction with local anaesthetics to provide immediate relief (Orchard, 2020). Despite this, the administration of injections is limited to four injections annually (Sinusas, 2012). Repeated injections increase the risk of infection, are not cost-effective, and can potentially lower patient compliance. As a result, it is imperative to develop a modified-release system for IA OA therapies such as corticosteroids, NSAIDs and viscosupplements (Bruno et al., 2022; Huang et al., 2022; Liu et al., 2023). Therapeutic agents that are delivered through the IA route have fewer systemic side effects and an increased drug concentration at the joint space (Rai and Pham, 2018).

Since osteoarthritic joints have a lower concentration of HA compared to healthy joints (Li, et al., 2021), exogenous HA can be administered to restore viscoelasticity and provide cushioning effects in the joints (Bowman et al., 2018). In addition, HA also has the potential to enhance chondrocyte synthesis, provide chondrocyte protection, promote cartilage regeneration, and reduce pro-inflammatory mediator production (Testa et al., 2021). Therefore, HA can relieve pain and improve the function of osteoarthritic joints (Kou et al., 2019). Monovisc™ and Orthovisc® (Table 1), high molecular weight endogenous HA formulations, are some of the Food and Drug Administration (FDA)-approved IA HA formulations for OA treatment.

Apart from the previously discussed treatment options, a more recent tool of OA treatment of OA is platelet-rich plasma (PRP) IA injections (Abbas et al., 2023). Leukocyte-poor PRPs specifically, possess the capacity to promote cartilage regeneration while decreasing concentrations of pro-inflammatory cytokines (Gupta and Aratikatla, 2024; Su et al., 2023). The endogenous nature of PRP makes it desirable as it utilizes patient blood products to stimulate the production of autologous growth factors (Smith, 2016). This is appealing because the risk of rejection is low because the injection is a direct derivative of the patient's own blood (Foster et al., 2009). Nonetheless, several limitations hinder the enthusiasm for its widespread clinical adoption. One key concern is the lack of standardization and product variability, which arises from differences in PRP preparation techniques, including centrifugation protocols, platelet concentration, leukocyte content, and activation methods (Ehrenfest et al., 2014; Lana et al., 2019). This heterogeneity not only affects the biological properties of PRP but also complicates reproducibility and comparison across clinical studies (Mautner et al., 2015; Andia and Maffulli, 2013). As a result, establishing consistent quality attributes and release criteria for PRP presents substantial challenges in chemistry, manufacturing, and control, thus hindering its regulatory approval as a standardized biologic or drug product (Fitzpatrick et al., 2017; Kon et al., 2020). Current regulatory frameworks, such as those from the FDA and European Medicines Agency (EMA), lack tailored guidance specific to autologous biologics like PRP, making clinical validation and market approval difficult (Kon et al., 2020)

While some randomized controlled trials have shown that PRP may provide symptom relief and functional improvement superior to HA or corticosteroids, *meta*-analyses frequently report inconsistent outcomes, and long-term structural benefits remain unproven (Belk et al., 2021; Zhang et al., 2024; Yi et al., 2025). Regulatory challenges are further exacerbated by the absence of a universally accepted definition or classification system for PRP formulations, making quality control and

Table 1
A List of approved IA HA products for OA treatment.

Product name	Agent/Bioactive	Delivery system	Company	Approval region
Synvisc	Hylan G-F 20 (crosslinked hyaluronan)	Viscosupplementation	Sanofi	FDA-approved (USA)
Orthovisc	Sodium hyaluronate (HMW)	Viscosupplementation	Anika Therapeutics	FDA-approved (2004, USA)
Euflexxa	Sodium hyaluronate (bioengineered)	Viscosupplementation	Ferring Pharmaceuticals	FDA-approved (USA)
Supartz	Sodium hyaluronate (avian-derived)	Viscosupplementation	Seikagaku Corporation	FDA-approved (USA)
Joyclu (SI-613)	Diclofenac etalhyaluronate	HA-based hydrogel	Seikagaku Corporation	Approved (Japan)
ArtiAid / ArtiAidPlus	Sodium hyaluronate	Viscosupplementation	MBI (Taiwan)	Approved (Saudi Food & Drug Authority, 2024)

reproducibility difficult (Andia and Maffulli, 2013).

NSAIDs are contraindicated with the use of PRP. This is because NSAIDs impair normal platelet function in patients on PRP injections, leading to a decline in the amount of growth factors released, thus diminishing the therapeutic efficacy of PRP (Schippinger et al., 2015). Moreover because PRP is a biologically active and patient-specific product, the timing of preparation and injection, as well as the patient's baseline platelet count and health status, can significantly influence clinical outcomes.

Although there have not been any DMOADs currently approved by regulatory bodies such as the FDA and EMA for the treatment of OA, these have shown potential for therapeutic efficacy in ongoing research (Li et al., 2023; Rodriguez-Merchan, 2023). These drugs aim to exploit the hallmarks of OA by inhibiting the progression of the disease and providing symptomatic relief by either reducing pain or improving the physical functioning of the joint (Oo et al., 2018). DMOADs target, among others, the matrix-degrading enzymes, inflammatory cytokines, and inducible nitric oxide synthase (iNOS) (Yazici et al., 2017). Given this, DMOADs still face hurdles that impede their translation into clinical application (Gao et al., 2022). Insufficient bioavailability of DMOADs in the joint cavity upon systemic administration has proven to be a prominent challenge, which results in inadequate therapeutic efficacy and unwanted side effects (Gao et al., 2022).

The complex composition of the synovial joint, along with the viscosity of the synovial fluid, presents an unfavourable pharmacokinetic environment for most drugs (Siefen et al., 2022). Often, this results in rapid clearance from the synovial cleft into the systemic circulation through lymphatic and blood vessels (Cao et al., 2021). This mandates repeated dosing of drugs at high dosages, which in turn results in toxicity and reduced compliance. The short residence times of drugs in the OA joint have also been associated with the synovial membrane, where macromolecules larger than 100 kDa are well-retained, but smaller molecules, such as NSAIDs, easily leak through the systemic circulation (Mwangi et al., 2018). The proteoglycan and collagen fibres of cartilage ECM form a dense network with an overall negative charge, which presents a hurdle for absorption of the drugs and supplements that are also negatively charged at physiological pH into the cartilage (Theocharis et al., 2016; Li et al., 2021). These include dexamethasone (DEX), diclofenac (DIC), and HA (Al-Owaidi et al., 2021; Basheeruddin et al., 2022; Hintze et al., 2022). As a result, the therapeutic efficacy of such agents is maintained by repeated injections, which is indeed unfavourable in terms of costs, increased risk of infections and iatrogenic injury (Maudens et al., 2018; Martin et al., 2000). It is evident that drug delivery systems with the potential to overcome such obstacles to optimize IA OA treatment are urgently needed. Since small molecules such as corticosteroids and NSAIDs are not effectively retained for sustained periods to exert required therapeutic effects. Using these drugs in their free form for IA injections faces numerous pharmacokinetic challenges (Mancipe Castro et al., 2020) .

To this extent, particulate-based technologies for OA therapy have been explored. Large-sized particles are not considered optimal as carriers for IA drug delivery. Although these can be potentially retained for a relatively long period, their larger size impedes their penetration into the intricate spaces, such as the ECM, therefore lowering their efficacy (Geiger et al., 2018); Huang et al., 2022). Conversely, NPs carriers have shown better potential for achieving this goal. Due to their smaller size, they are more permeable and, therefore, able to reach their target sites efficiently in OA joints (Wen et al., 2023). Considering the recent advances in the particulate IA OA therapy space, this study examines the potential of IA particulate-based therapies to address the aforementioned issues and achieve more effective therapeutic responses.

3. Nanomedicine for targeted and site-specific OA therapy

NPs are approximately a thousand times smaller than the chondrocytes (Li et al., 2021). These nanoconstructs have the potential to solve issues associated with conventional drug delivery systems, which include low solubility, retention time, and efficacy of drugs, as well as their susceptibility to acidic or enzymatic degradation (Bonifacio et al., 2014). Furthermore, these submicron particles have high stability (long shelf life), and both hydrophobic and hydrophilic drugs can be loaded (Gelperina et al., 2005). NPs not only effectively protect drugs from enzymatic degradation, extending their lifespan, but have also been shown to be biocompatible and biodegradable. They can induce controlled and sustained release of encapsulated cargo, improve site-specificity and, in turn, improve the side effect profiles of the encapsulated therapeutics (, Wilczewska et al., 2012; Gu et al., 2013). NPs are more efficiently taken up by cells such as macrophages, primary inflammatory mediators in OA, than microparticles. This cellular uptake can result in phenotypic macrophage reprogramming from M1 to M2, triggering an anti-inflammatory response in OA (Gambaro et al., 2021).

There are various nanocarriers that are made from different types of biomaterials, which therefore offer a variety of properties, including size, morphology, and functionalities, as presented in Fig. 1 (Wang and Wang, 2014). When describing the hierarchical pore structure within cartilage, DiDomenico et al. (2018) mentioned that it has a gap ranging from 4 to 6 nm between glycosaminoglycan chains and from 50 to 100 nm between collagen fibers. This means that particles with a size equal to or less than 100 nm would be ideal for penetration (Rothenfluh et al., 2008; DiDomenico et al., 2018). In contrast, the entry of macromolecules and larger-sized NPs can be challenging (Sophia Fox et al., 2009) . Despite this, larger molecules (MW up to 500 kDa) have been shown to diffuse through the dense cartilage matrix, although their transport mechanism is still unclear due to the unsolved complex structure of articular cartilage (DiDomenico et al., 2018). Either way, unlike microparticles, NPs can easily penetrate through the dense matrix of the ECM to reach target sites, which can potentially improve their retention time. Apart from size, surface charge is also an important factor to take into consideration. The ECM is negatively charged, cationic NPs have the potential to improve the cellular uptake of negatively charged drugs (Honary and Zahir, 2013a,b). Furthermore, the electrostatic interactions between cationic NPs and ECM increase the retention of the drugs (Zhou et al., 2023).

Forming electrostatic forces with endogenous HA, a negatively charged molecule, Bajpayee et al. (2014) conducted a study whereby NeutrAvidin, the neutral counterpart of Avidin, exhibited a 400-fold lower absorption than Avidin (a highly cationic protein). Furthermore, cartilage explants retained $>$ 90 % of the absorbed Avidin for at least 15 d (Bajpayee et al., 2014). As a result, cationic molecules have shown higher uptake and faster penetration, as well as prolonged release

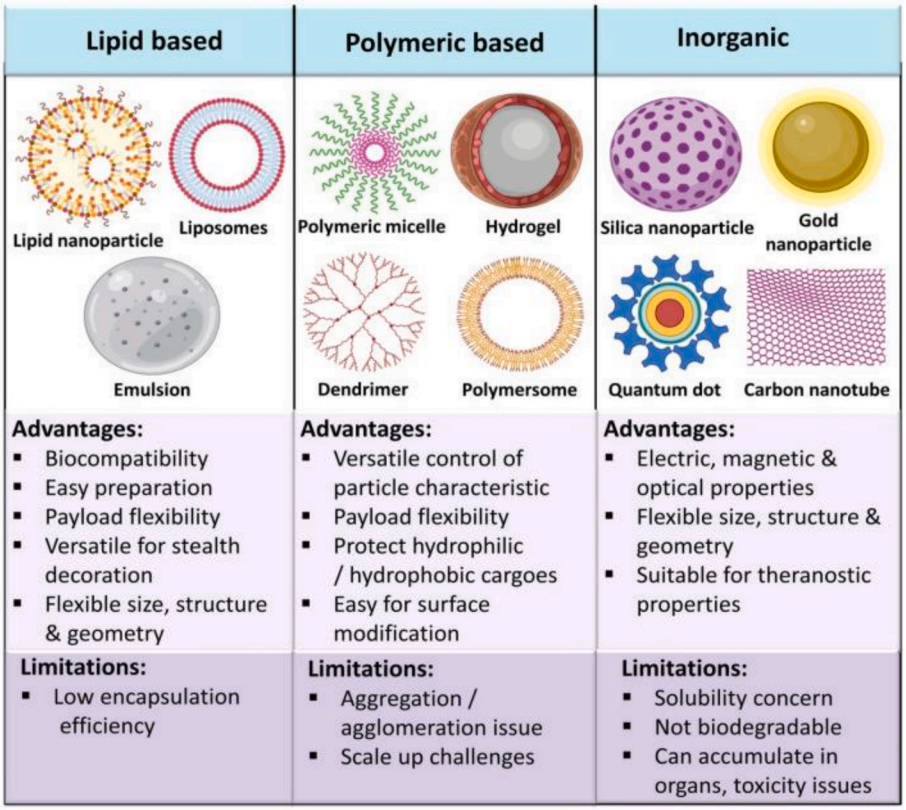

Fig. 1. Categorization and comparison of various types of NPs, including the advantages and limitations of different delivery systems. Adapted from Havelikar et al, 2024, licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (Havelikar et al., 2024).

profiles and retention times compared to their neutral and anionic counterparts (Vedadghavami et al., 2020). However, this can lead to excess accumulation of the cationic NPs can lead to cell membrane disruption and ultimate cellular death (Isibor et al., 2024).

In general, NPs as carriers can be used to improve the pharmacokinetic profiles of drugs for IA administration into the joint space. Their size is well-suited to evade the dense network of the ECM, allowing drugs to reach the site of action at required therapeutic concentrations and possibly extend their retention times. Different types of nanosystems, including micelles, liposomes, polymeric and lipidic NPs, exosomes, inorganic NPs, and microparticles, have been previously studied for application in the treatment of OA and summarized in Table 2.

4. Organic NPs for IA therapy of OA

This subsection reviews micelles, liposomes, PNPs, dendrimers, and lipid NPS, focusing on their ability to encapsulate diverse payloads, tune release kinetics for sustained joint exposure, and attenuation of OA.

4.1. Micelles

Micelles are amphiphilic systems consisting of a hydrophobic core and a hydrophilic shell, generally ranging between 10 and 100 nm in size (Polat et al., 2025). Accordingly, hydrophobic drugs are encapsulated in the lipophilic core, while hydrophilic drugs are bound to the hydrophilic shell (Ghezzi et al., 2021). This means that, unlike most types of NPs, micelles can carry a variety of types of cargo, making them advantageous for OA therapy. Given their low critical micelle concentration, polymeric micelles are more stable and enforce controlled and sustained drug release (Jones and Leroux, 1999). Nevertheless, the application of micelles is limited because of their toxicity, dependence on critical micelle concentration, poor uptake by cells, loading efficiency, and stability (Lu et al., 2018).

Wei et al (2021) exploited some of these properties by employing cationic secretory phospholipase A2 inhibitor (thioetheramide-PC)-loaded micellar NPs (sPLA$_2$i-NPs) for IA injection in OA mouse models. Results showed a significant decrease in overall OA progression, whereby articular cartilage degeneration was attenuated. The free sPLA2i-treated groups showed increased subchondral bone plate sclerosis and osteophyte formation, which were not observed in the sPLA$_2$i-NPs group. This indicates the attenuation of late-stage OA by sPLA$_2$i-NPs compared to free sPLA$_2$i. In comparison to the free secretory phospholipase A2 inhibitor, the phenotype and integrity of articular cartilage improved, whereby the cartilage surface was almost completely intact with no proteoglycan loss for up to 4 months following the NP-based drug injection in surgically induced OA mice (Wei et al., 2021). This was a remarkable outcome since cartilage repair is very challenging to achieve, and full regeneration is currently unachievable (Wei et al., 2021).

Curcumin, the main active component of turmeric, has been reported to have favourable therapeutic properties, such as potent antioxidant and anti-inflammatory activities for the treatment of OA (Tanvir et al., 2017; Peng et al., 2021). Despite its potential, the effectiveness of curcumin is limited due to its low retention, rapid metabolism, poor absorption, and low water solubility (Tabanelli et al., 2021). As a result, the potential of polymeric micelles to overcome these drawbacks was explored by developing an acid-activatable curcumin polymer, an anti-inflammatory polymeric prodrug of curcumin (ACP) (Kang et al., 2020). It is worth noting that polymeric prodrugs have been shown to retain approximately 60 % of the drug as the polymers degrade, which helps with the sustained release of the drug (Luliński, 2017).

In this study, ACP can self-assemble into micelles in water and dissociate under acidic conditions, enabling targeted release triggered by pH changes found in synovial joints of osteoarthritic joints. Previous

Table 2
Summary of recent (2019–2025) advances in OA drug delivery systems with potential IA application.

Type of NPs	Components	Bioactive	Observed biological activities	Reference
Micelles	ACP micelles	Curcumin	• Reduction in the concentrations of ROS in the RAW264.7 cells and in levels of TNF-α and IL-1β in OA mice models. This leads to reduced inflammation both *in vivo* and *in vitro*.	Kang et al.,2020
	sPLA2 inhibitor-loaded micellar NPs	Thioetheramide-PC	• Prolonged retention of thioetheramide-PC in the joint space of OA mice. • Decreased concentration of ECM-degrading MMP-13 and ADAMTS-5 *in vitro* in OA mouse cartilage explants leads to inhibition of cartilage degradation. • Increased expression of COL2A1 and ACAN in OA mouse cartilage explants promoting cartilage regeneration.	Wei et al., 2021
Liposomes	HA-Lipo-DIC/DEX	DEX and DIC	• The *in vitro* cytotoxicity profile of HA-Lipo-DIC/DEX was superior to that of free DIC/DEX in SW 1353 chondrocytes. • HA-Lipo-DIC/DEX showed visibly reduced inflammation on the front paws of mice more effectively than free DIC and DEX	Chang et al., 2021
	DEX-loaded liposomes	DEX	• Improved from 24 to 72 h, showing sustained release. • *In vivo* macrophage repolarization reduced pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 levels in OA mice models. • Enhanced *in vivo* expression of anti-inflammatory cytokine IL-10 in OA mice models.	Teng et al., 2023
	Lipo-RvD1	Resolvin D1	• Improved retention of Resolvin D1 in the joint cavity of mice for 11 d. • M1-to-M2 polarization of macrophages resulting in: – Reduced synovitis as a result of M2 macrophage infiltration in chondrocytes. – Suppression of ADAMTS-5 and MMP-13, suggesting blockage of cartilage degradation in chondrocytes of OA mice models. – Suppression of the formation of the osteophytes, thus slowing OA progression *in vivo*.	Dravid et al., 2023
	Triamcinolone acetonide-liposomes	Triamcinolone acetonide	• Retention for 28 d in the joint cavity • Macrophage polarization from M1 to M2 • Decrease in pro-inflammatory cytokines, chemokines, and matrix-degrading proteins: – TNF-α, IL-1β, and IL-6, – Chemokine (C-X-C motif) ligand 2 and chemokine (C–C motif) ligand 2 – MMP-1, MMP-3, MMP-13, ADAMTS-3, and ADAMTS-14	Deng et al., 2023
Polymeric NPs	Self-assembled polymeric NPs	Triamcinolone acetonide	• *In vivo* inhibition of MMP-3 and MMP-13 expression: – inhibition of pro-inflammatory cytokines IL-6, TNF-α – promotion of anti-inflammatory cytokines IL-4, IL-10, and IL-13	(Seo et al., 2022)
	Berberine Opsonized NPs	Berberinane	• Improved berberine release profile • Effective reduction of the mRNA expression of iNOS, TNF-α, IL-1β, and IL-6 • Effective promotion of anti-inflammatory mediators IL-10 and Arg-1 compared to the untreated control and LPS stimulation group • The M1 to M2 polarization signalled by A significant increase in the Arg-1 of the macrophages occurred	Kou et al., 2022
	PLGA-PEG-PLGA	ETX	• Higher expression of COL2A and ACAN in the ETXNPs group of isolated human OA chondrocytes. • A decline in the expression of MMP-13 and ADAMTS-5 in the ETXNPs group of isolated human OA chondrocytes.	Liu et al.,2019
	Rh-PLGA-NPs@NH_4	Rhein	• Sustained release of Rhein for over 20 d. • Significant reduction of pro-inflammatory markers ROS and IL-1 in human chronic myeloid leukaemia cell lines like THP-1 leading to reduced inflammation in OA. • Slight decrease in levels of pro-inflammatory cytokine TNF-α in the THP-1 cell line.	(Hu et al., 2020b)
	PDA NPs	Polydopamine	• Reduced *in vitro* chondrocyte apoptosis • Reduced levels of ROS, a mediator for cartilage degradation. • Elevation of the levels of proteoglycan, suggesting ECM regeneration. • Inhibition of subchondral bone remodeling in OA rat models.	Wang et al., 2021
	Carboxymethyl chitosan-assisted MnOx	Carboxymethyl	• Increased expression of ACAN and COL2A1 promoting chondrogenesis in chondro-induced BMSCs. • Decreased expression of MMP-13, suggesting decreased cartilage degeneration in OA rats.	Lin et al., 2022
	Rebamipide-loaded NPs	Rebamipide	• *In vitro* and *in vivo* dose-dependent reduction in the mRNA levels of MMP-3 and MMP-13 and pro-inflammatory cytokines IL-1β, IL-6, and TNF-α • Reduction of pro-inflammatory mediator *cyclo*-oxygenase-2. • Attenuated cartilage degeneration better than the pure rebamipide solution	Kim et al., 2022
	HA-NPs	HA	• Resistance to digestion by hyaluronidase • Reduced PGE_2 production • HA-NPs outperformed free high molecular weight HA	Kang et al., 2021
	Superoxide dismutase polymersomes	Superoxide dismutase	• Prolonged retention of superoxide dismutase in the mouse joint – Accumulation occurred in the synovium rather than the articular cartilage	Gui et al., 2022
Lipid NPs	LNP-FGF18 mRNA	FGF18-mRNA	• Efficient cartilage penetration (~50 μm) & retention • Elevated levels of SOX9 and COL2A1 • Reduction of p16INK4a, p21, and p53 • Biocompatibility in ATDC5 and 293 T cells	Kong et al., 2025
		FAP siRNA	• Reduced levels of IL-1β, IL-6 and TNF-α • Reduced levels of MMP-3, MMP-9 and MMP-13 • Increased COL2A1 concentrations	Zhao et al., 2024

(*continued on next page*)

Table 2 (*continued*)

Type of NPs	Components	Bioactive	Observed biological activities	Reference
	LNP-mRNA	mRNA encoding adalimumab	• Penetrating depths exceeding 100 μm • Reduced production of MMP-3, MMP-13, TNF-α • Increased levels of SOX9 and COL2A	(Li et al., 2024b)
	Lipo-AgPEI-miR-200c-3p	miR-200c-3p	• Reduced secretion of TNF-α, IL-6, IL-1β, and MCP-1 • Downregulation of MMP-3, MMP-13, and ADAMTS-4 • Upregulation of COL2	Zheng et al., 2025
Inorganic NPs	Gold NPS	Gold	• Reduced concentrations of pro-inflammatory cytokines • Enhanced levels of: – liver and kidney indices – oxidative stress markers	Abdel-Aziz et al., 2021
	Triamcinolone-gold NPs	Triamcinolone	• Superior expression of anti-inflammatory cytokines IL-10, IL-4, and Arg-1 in fibroblast-like synoviocytes. • Reduced expression of pro-inflammatory cytokines TNF-α, IL-1-β, IL-6, MMP-1, and matrix degrading protein MMP-3 in fibroblast-like synoviocytes.	Park et al. 2020
	PEG-MnO_2 NPs	MnO_2	• Decreased levels of matrix-degrading entities NOS, MMP-1, MMP-13, and ADAMTS-5 in chondrocytes • Retention for 7 d in the joint cavity of OA rat models.	Kumar et al., 2019
	TP-Au@PCN	Tea polyphenol	• Effective repair of cartilage-damaged mitochondria and promoted cartilage regeneration in chondrocytes: – TP-Au@PCN showed a significant reduction in levels of ROS compared to pristine tea polyphenol. – MMP-13 was reduced significantly in chondrocytes treated with TP-Au@PCN compared to other treatment groups. – . TP-Au@PCN significantly increased the expression of COL2 and SOX9 in chondrocytes.	(Xu et al., 2023)
Microspheres	(sPL)-loaded PLGA/chitosan/ gelatin microspheres	Growth factors: IGF, TGF, and VEGF	• Elevation of COL2A1, ACAN, and SOX9 promoting cartilage proliferation. • Reduced number of osteophytes and subsequent reduction of OA progression in rat models. • Cartilage regeneration presented by smoothened cartilage surfaces and increased integrity of cartilage.	Li et al., 2021
	PLGA microparticles	Rapamycin	• Improved joint residence time (35 days) • Decline in levels of MMP-13 and ADAMT-5	(Dhanabalan et al., 2023)
	Microspheres	Parecoxib IL-4	• Improve parecoxib release profile • IL-4 mediated M2 macrophage polarization • Decrease in levels of pro-inflammatory markers PGE_2, IL-1β, and TNF-α • Increase in levels of anti-inflammatory levels COL2, ACAN, and IL-10	(Qiu et al., 2024)
Microplates	DEX-loaded microplates	DEX	• Inhibition of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in ATCD5 chondrocytes. • Inhibition of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in conjunction with matrix degrading protein MMP-13 in over-load induced mice.	Di Francesco et al, 2021

research has indicated that the pH of synovial joints in osteoarthritic conditions can be weakly acidic due to inflammation (Xiong et al., 2020). However, other studies report no pH differences between normal and osteoarthritic joints (Gerwin et al., 2006; Milošev et al., 2017). The ACP micelles increased in size under acidic conditions, further demonstrating their pH dependence due to protonated tertiary amine groups in the ACP backbone. Release profiles at various pH levels showed that in acidic conditions (pH 6.0), the ACP micelles released four times more drug in 7 days than at physiological pH (7.4). Biological tests revealed that ACP micelles had better cell viability against RAW 264.7 cells compared to free curcumin at the same concentrations, indicating improved biocompatibility. Although curcumin alone can suppress ROS production, it was more effective when delivered via ACP micelles. Additionally, ACP micelles significantly reduced the pro-inflammatory markers TNF-α and IL-1β more than free curcumin, suggesting enhanced biological activity. The NPs also showed no toxicity to chondrocytes (Kang et al., 2020). Despite these promising findings, curcumin and curcuminoids have recently been classified as pan-assay interference compounds (PAINS) and identified as candidates for invalid metabolic panaceas (IMPS), likely showing false activity both *in vitro* and *in vivo* (Nelson et al., 2017). Therefore, it is advisable to avoid using these compounds as lead candidates in future research.

4.2. Liposomes

Liposomes, typically formed with phospholipids, are spherical lipid vesicles with at least one lipid bilayer that surrounds an aqueous centre (Pande, 2023). Since they have both hydrophobic and hydrophilic properties, liposomes can encapsulate both hydrophobic and hydrophilic drugs (Sercombe et al., 2015). For example, hydrophilic diclofenac sodium and hydrophobic dexamethasone can be co-encapsulated in the same liposomal system with high entrapment (Chang et al. 2021). Liposomes fuse with the cell membrane at the site of inflammation to release the payload (Liu et al., 2021). This unique ability is useful for targeted drug delivery as it would enhance the efficiency of drug delivery in OA joints (Fig. 2). Although liposomes are good carriers, they have drawbacks, such as leakage of cargo and short shelf life. This means that they cannot be used for chronic diseases as they degrade quickly, and the leakage of drugs would not be sustainable. Liposomes and other lipid-based NPs can also be exploited as potential lubricants as a result of phospholipids present within, thus reducing bone-to-bone friction in OA.

In a study, Chang et al. (2021) developed hyaluronan-loaded liposomal dexamethasone-diclofenac NPs (HA-Lipo-DIC/DEX) with HA to target OA intra-articularly. DIC is an NSAID that is generally viewed as an alternative to DEX, a glucocorticoid, for the anti-inflammatory effects in OA (Alsaif et al., 2021;). The liposomes of ~103 nm displayed an impressive entrapment efficiency (EE) of 90.5 ± 5.6 % and 94.7 ± 2.4 %, respectively. *In vitro* studies exhibited a sustained release of DIC and DEX over 160 h. Notably, HA-Lipo-DIC/DEX demonstrated superior chondrocyte cell survival rates (93.65 ± 3.77 %) compared to free DIC/DEX-treated groups (65.48 ± 4.01 %) at 24 h with equivalent concentrations. This nanosystem displayed continued cell viability for 72 h, exhibiting improved biocompatibility compared to that of the combination of the free drugs. The *in vivo* studies on mice further validated the HA-Lipo-DIC/DEX nanosystem's anti-inflammatory effects by

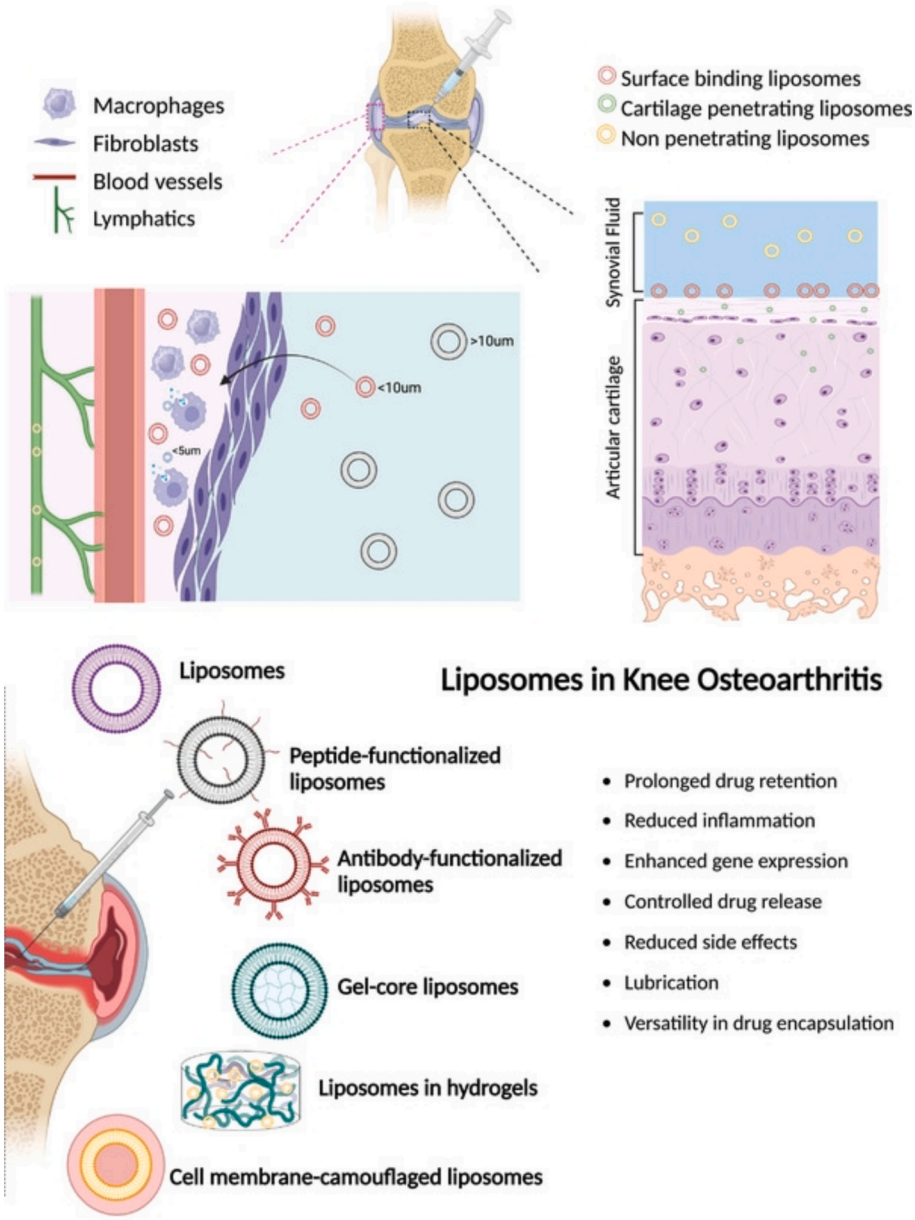

Fig. 2. Liposome-based systems administered through IA delivery in OA therapy. Adapted from Mitsou, E. (2025) *https://BioRender.com/d09w772* under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (Mitsou and Klein, 2025).

significantly reducing OA-induced inflammation better than free DIC and DEX on the paws of mice (Chang et al., 2021).

In another study, Teng et al. (2023) investigated DEX-loaded liposomes on OA. The *in vitro* drug release profile of the DEX-loaded liposomes showed sustained release, whereby 80 % of free DEX was released within 24 h, this improved to 72 h in the DEX-loaded liposomes. Immunofluorescent staining of DEX-loaded liposomes showed a prominent decrease in expression of CD86, an M1 macrophage marker, compared to that of cells treated with free DEX. Notably, there was an increase in the expression of M2 macrophages. This supports a phenotypic change from M1 to M2 macrophages, promoting mice's anti-inflammatory activity. This was corroborated by the quantification of pro- and anti-inflammatory cytokines, where the DEX-loaded liposomes reduced TNF-α and IL-1β levels better than free DEX, while IL-6 levels were similar in both treatment groups. The expression of anti-inflammatory cytokine IL-10 was improved after treatment of the mice with DEX-loaded liposomes compared to free DEX. This indicated that the DEX-liposome could suppress OA inflammation better than free DEX and, therefore, ameliorate OA more efficiently (Teng et al., 2023).

Since small molecules are rapidly cleared by the lymphatic system, this mandates repeated administrations/injections . Dravid et al (2023) encapsulated Resolvin D1 (RvD1) into liposomes, forming a Lipo-RvD1 formulation. This formulation attained prolonged release of RvD1 for ~11 d with close to 10 % of the drug still available at that endpoint. Lipo-RvD1 promoted the M2-type polarization of macrophages in the synovium, which has anti-inflammatory effects. Lipo-RvD1 also reduced the levels of pro-inflammatory M1 cells more effectively as compared to free RvD1 joints. Since M1 macrophages are notorious for being a major source of pro-inflammatory cytokines that contribute to cartilage damage, their reduction suggests that inflammation and cartilage damage were mitigated in the treated mice. Additionally, Lipo-RvD1 reduced synovitis, a hallmark of OA, by preventing the infiltration of leukocytes into the inflammatory milieu in obese mice (Dravid et al., 2023).

Similarly, Deng et al. (2023) targeted synovial macrophages and fibroblasts to attenuate OA (Deng et al. 2023). In this effort, triamcinolone acetonide was encapsulated into apoptotic neutrophil membrane-

camouflaged liposomes, which were administered intra-articularly to rodents. The liposomes were successfully retained in the joint cavity for 28 d while facilitating the effective repolarization of M1-type macrophages to the M2 phenotype. Free triamcinolone acetonide demonstrated moderate downregulation of M1-related pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and iNOS in RAW 264.7 cells. The macrophage repolarization was proven by the upregulation of the genes of M2 macrophage markers, such as CCAAT/enhancer-binding protein beta and suppressor of cytokine signaling 2. Upon induction, pro-inflammatory M1-type macrophages produce pro-inflammatory cytokines IL-12, IL-6, IL-1β, and TNF-α. Conversely, M2-type macrophages produce anti-inflammatory cytokines IL-1β, IL-10, and TGF-β (Mushenkova et al., 2022). There was a subsequent decrease in the concentrations of unfavorable cytokines TNF-α, IL-1β, and IL-6, and chemokines such as CXCL2 and CCL2. At the same time, the genes of ECM-degrading proteins such as MMP-1, MMP-3, MMP-13, ADAMTS-3, and ADAMTS-14 were also significantly reduced in OA joints in comparison to the control group. Dissimilarly, genes associated with M2-type macrophages were upregulated, supporting the presence of decreased inflammation in triamcinolone acetonide liposome-treated rodents compared to the free triamcinolone acetonide. This suggested that the triamcinolone acetonide liposomes had a better inflammation-inhibitory effect compared to free triamcinolone acetonide (Deng et al., 2023).

Lipotalon® (Merckle, Germany), a liposomal formulation, was designed for IA administration in OA treatment. It encapsulates dexamethasone palmitate, a lipophilic corticosteroid prodrug, within liposomes. This formulation aims to enhance drug retention in the joint, reduce systemic exposure, and minimize local side effects. Upon administration, Lipotalon® liposomes are preferentially taken up by synovial macrophages, where the loaded DEX palmitate is hydrolyzed by intracellular esterases to release active dexamethasone. This allows for targeted delivery of the drug, which modulates the inflammatory response within the joint while reducing the risk of systemic corticosteroid-related adverse effects (Bias et al, 2001).

4.3. Polymeric NPs

Polymeric NPs (PNPs) are solid NPs with a size of 10-1000 nm synthesized from biocompatible and biodegradable synthetic and natural polymers (Zielińska et al., 2020). PNPs with smaller sizes can be efficiently delivered through the tightly wound ECM, making them particularly suitable for IA delivery in OA joints. Synthetic polymers include poly (lactide) (PLA), poly (lactide-co-glycolide) copolymers (PLGA), poly (ε-caprolactone) (PCL), and natural polymers such as albumin, chitosan, gelatine, and alginate. As a result of their biocompatibility and biodegradability, PNPs reduce the risk of accumulation in OA joints, mitigating possible adverse reactions. There are two types of PNPs, namely nanospheres and nanocapsules (Gagliardi et al., 2018, Palma et al., 2018). Encapsulated drugs are uniformly dispersed within a polymer matrix of nanospheres, within a reservoir core, or bound to the surface of the nanocapsules (Jin, 2020). This enables the delivery of a variety of therapeutics, including hydrophilic and hydrophobic drugs and compounds of varying molecular weights, such as proteins and small molecules (Wang and Wang, 2014). This versatility allows for the targeted delivery of anti-inflammatory drugs, growth factors, and other therapeutic agents directly to the affected joint, improving efficacy and reducing systemic side effects.

Targeted therapy can be advanced further by functionalizing the surface of PNPs with specific ligands which are compatible with inflamed tissue or cartilage, thus enhancing therapeutic efficacy while minimizing off-target side effects (Wen et al., 2023). An example is how Seo et al (2022) encapsulated triamcinolone acetonide into self-assembled PNPs through the interaction between the hydrophobic core of the polymer- poly(organophosphazene) with hydrophobic parts of the TCA for the long-term anti-inflammatory effect to treat OA (Seo et al., 2022). A one-time injection of the NPs exhibited improved inflammation profiles with *in vivo* inhibition of MMP expressions (MMP-3 and MMP-13) via the inhibition of the expression of pro-inflammatory cytokines (IL-6, TNF-α) and the promotion of the expression of anti-inflammatory cytokines (IL-4, IL-10, and IL-13) (Seo et al., 2022). The repolarization of macrophages from the M1 to the M2 phenotype mediates the inflammatory response in macrophages and synoviocytes by lowering pro-inflammatory responses while enhancing anti-inflammatory responses (Yuan et al., 2024). Kou et al investigated this phenomenon by encapsulating berberine, an anti-inflammatory agent, into opsonized NPs made from an oxidative stress-responsive bilirubin grafted polylysine biomaterial and a layer of immunoglobulin IgG (IgG/Bb@BRPL) (Kou et al., 2022). The system prolonged the release of berberine, whereby free berberine was completely released after approximately 50 h; at the same period, only a maximum of ~ 57 % of berberine was released from the system. Although free berberine and the blank NPs both exerted an anti-inflammatory effect on the macrophages, the nanotherapeutic system loaded with berberine reduced the mRNA expression of iNOS, TNF-α, IL-1β, and IL-6 and promoted anti-inflammatory mediators IL-10 and Arg-1 more effectively compared to the untreated control and LPS stimulation group, but similar to that of free berberine. It is possible that polylysine and berberine exerted a synergistic anti-inflammatory effect. A significant increase in the Arg-1 signals and decreased fluorescence of CD86 staining confirmed that the M1 to M2 polarization of the macrophages had occurred, which signified an anti-inflammatory response, thus attenuating OA.

In a study by Liu et al. (2019), etoricoxib (ETX), a COX-2 selective NSAID, was encapsulated in PLGA and polyethylene glycol (PEG) (PLGA-PEG-PLGA) triblock copolymeric NPs for IA treatment of OA. The *in vitro* drug release study showed a burst ETX release within the first 3 d but showed sustained release over approximately 30 d (Liu et al., 2019). The cell viability study showed that the ETX-loaded NPs had no negative effect on the viability of chondrocytes (Liu et al., 2019). The study revealed a higher expression of COL2 and ACAN in the ETX-loaded NPs group in comparison to the free ETX group. This suggested that the integrity of the cartilage matrix in the chondrocytes improved, and thereby, the ETX-loaded NPs attenuated OA. On the other hand, the expression of MMP-13 and ADAMTS-5 in the ETX-loaded NPs group was more suppressed compared to the free ETX group. This indicated that the ETX-loaded NPs could inhibit the activity of ECM-degrading enzymes, hence maintaining cartilage integrity. The mice treated with ETX-loaded NPs also showed superior osteochondral interface compared to the free ETX-treated subjects, supporting cartilage regeneration as a result of ETX-loaded NPs (Liu et al., 2019).

Hu et al. (2020) used Rhein (Rh), an anti-inflammatory drug, to develop pH-sensitive Rh and ammonium bicarbonate (NH_4HCO_3) laden PLGA NPs (Rh-PLGA-NPs@NH_4). *In vitro* release studies showed an improved Rh release in a synovial fluid environment with lower pHs. Rh-PLGA-NPs@NH_4 showed more sustained release in a simulated synovial fluid environment than in a buffer with pH 7.4 and pH 5. Notably, the Rh-PLGA-NPs@NH_4 improved the release profile of Rh from 1 day to 30 d. There was a significant reduction of OA markers ROS and IL-1, and a slight reduction in the levels of the cytokine TNF-α. The toxicity study revealed an increase in cytotoxicity that was directly proportional to the concentration of Rh. The Rh-PLGA-NPs@NH_4 formulation exhibited higher toxicity than Rh-PLGA-NPs, which means that the addition of NH_4 resulted in increased toxicity compared to Rh-PLGA-NPs (Hu et al., 2020b).

In a different study, Wang and colleagues (2021) introduced a polydopamine NPs (PDA NPs) antioxidative/anti-inflammatory dual task nanoplatform to treat OA. The PDA NPs acted as a dual task platform by serving as reducing agents directly scavenging ROS and by regulating ROS generation in mitochondria, resulting in antioxidant and anti-inflammatory effects. The treatment exhibited excellent biocompatibility of PDA NPs at low doses and lower incubation periods. Reduced chondrocyte apoptosis (53.72 %), and intracellular ROS levels were

observed compared to the lipopolysaccharide group. This suggested that the PDA NPs had a potent *in vitro* chondrocyte protection effect against lipopolysaccharide-induced chondrocyte apoptosis. *In vivo* studies showed increased levels of proteoglycans and effects against subchondral bone remodeling and which are typically decreased during OA and result in matrix degradation, and this supported the alleviation of OA (Wang et al., 2021).

Lin et al. (2022) assessed the role of carboxymethyl chitosan-assisted (CMC) manganese oxide (MnOx) NPs (WY-CMC-MnOx NPs) on early OA. Having shown good viability on the tested MC3T3-E1 and L929 cells, the WY-CMC-MnOx NPs elevated the expression of ACAN relative to the control group. This was because of the presence of SRY-box transcription factor 9 (SOX9), a pivotal transcription factor in the synthesis of the ECM of cartilage (Lefebvre et al., 2019). Therefore, the WY-CMC-MnOx NPs could further promote the *in vitro* synthesis of cartilage ECM. WY-CMC-MnOx NPs also induced a higher mRNA expression of ACAN and COL2 in comparison to the control, which suggested that the NPs had a better impact on attenuation of OA than CMC. (Lin et al., 2022).

PLGA NPs have shown great promise in the targeted delivery of small molecules for treating OA. Kim et al. developed rebamipide-loaded NPs using methoxy poly(ethylene glycol)-b-poly(D,l-lactide) (mPEG-PDLLA) and PLGA polymers to attenuate the Progression and joint cartilage destruction in OA rat models (Kim et al., 2022*)*. Rebamipide is an amino acid analog of 2 (1H)-quinolinone, which possesses antioxidant effects that can help combat oxidative stress and inflammation, which are recognized as key factors in the development and progression of OA (Kudur and Hulmani, 2013). *In vitro* and *in vivo* results showed a dose-dependent reduction in the mRNA levels of MMPs (MMP-3 and MMP-13) and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and pro-inflammatory mediator *cyclo*-oxygenase-2. In addition, macroscopic, radiographic, and histological assessments showed that the IA injection of rebamipide-NPs inhibited cartilage degeneration more than the pure rebamipide solution. This indicates that the rebamipide-NPs improved the inflammatory response while simultaneously decreasing joint degradation and OA progression (Kim et al., 2022*)*. It has been well established that endogenous concentrations and distribution of HA in OA decrease as OA progresses (Altman et al., 2015). In this regard, Kang and colleagues (2021) used self-assembling HA-based NPs (HA-NPs) with HA with MW of 10000 Da to combat cartilage degradation in OA. HA-NPs exhibited resistance to hyaluronidase-mediated digestion and showed elevated retention profiles in the knee joint. The inhibitory effect of HA-NP on IL-1β- and CD44-induced NF-κB activation led to a decline in collagenase activity and prostaglandin E_2 (PGE_2) production. PGE_2 is highly secreted in the subchondral bone of patients with OA and promotes OA progression through osteoclast-induced angiogenesis . Intriguingly, HA-NPs showed better protection against OA than free high MW HA, a current treatment option for OA. Given the data, HA-NPs provided *in vitro* and *in vivo* protection against CD44-mediated cartilage destruction (Kang et al., 2021).

Although not extensively researched in OA therapy, polymeric systems such as polymersomes have shown great promise in OA therapy, showing prolonged retention time compared to phospholipid liposomes. This property is essential because OA treatment is usually not retained in the joint for a sustained period, creating a need for repeated injections, resulting in poor patient compliance. In a study by Gui et al (2022), polymersomes were used to deliver exogenous superoxide dismutase, the major catalytic antioxidant in joint tissues whose delivery is hindered by factors such as low retention and rapid degradation. Superoxide dismutase scavenges ROS by catalyzing the conversion of superoxide radicals to hydrogen peroxide. The Superoxide dismutase-NPs exhibited prolonged retention in mouse joints, with the majority of the system accumulating in the synovium rather than the articular cartilage, thus effectively targeting the disease. The porous nature allowed for improved intrinsic membrane permeability, allowing the superoxide dismutase to penetrate the joint tissues and have full access to ROS once delivered. The study demonstrated that the porous superoxide dismutase polymersomes were more efficient than free superoxide dismutase in the treatment of OA (Gui et al., 2022).

PNPs have emerged as a promising therapeutic strategy for the treatment of OA. Their ability to deliver drugs in a targeted and controlled manner directly to the affected joint enhances therapeutic efficacy while minimizing off-target side effects.

4.4. Lipid NPs

Lipid NPs (LNPs) have recently emerged as a powerful platform for IA delivery of nucleic-acid and protein therapeutics, offering tunable particle size, high encapsulation efficiency, and the potential for targeted, transient local expression or knockdown within joint tissues. Because OA pathogenesis is driven by a balance between catabolic mediators (e.g., MMP-3, MMP-13, IL-1β, IL-6) and anabolic matrix components (e.g., ACAN, COL2A1), LNP strategies that modulate these molecular pathways in situ either by delivering siRNA/mRNA or by enabling local protein expression are especially attractive.

Kong and colleagues (2025) report a preclinical demonstration that IA delivery of FGF18 mRNA, a potential regenerative factor for cartilage repair, in LNPs (LNP-FGF18 mRNA) penetrates deep into cartilage, drives transient local protein expression, and protects against chondrocyte senescence and OA progression. features that plausibly explain efficient cartilage penetration (LNPs reached ~50 μm depth vs surface-restricted recombinant protein). UTR engineering and chemical modification of the mRNA extended local expression: bioluminescence after IA LNP-Fluc injection persisted up to 6 days, with signals declining after 48 h but remaining detectable through day 6. Functionally, LNP-FGF18 restored anabolic and anti-senescence programs in inflamed chondrocytes. Immunofluorescence showed ~30 % increases in SOX9 and COL2A1 intensity, and micromass cultures displayed 20-50 % increases in proteoglycan staining (toluidine/alcian blue) after treatment. At the same time, senescence markers p16INK4a, p21, and p53 were reduced by ~40-60 %, SA-β-gal positive cells fell by ~50 %, and proliferation markers (EdU, Ki67) approximately doubled versus IL-1β-treated controls. In mouse OA models, weekly IA dosing produced superior outcomes to recombinant FGF18 protein, showing a ~60 % reduction in osteophyte number compared to ~30 % with pure FGF18, improved cartilage thickness and area, and better gait parameters (~20 % improvement in contact/print metrics). Cytotoxicity testing in ATDC5 and 293 T cells showed no toxicity at 8 μg/mL. Taken together, this study provides compelling evidence that optimized LNP-mRNA can overcome the short half-life and poor penetration of recombinant proteins, yield biologically meaningful modulation of MMPs, COL2A1 and ACAN, and produce disease-modifying benefits in OA models. This positions LNP-mRNA as a promising platform for IA regenerative and anti-senescence therapies Kong et al., 2025).

Zhao et al. (2024) reported that IA LNP-delivered FAP siRNA markedly suppressed senescence-associated secretory phenotype factors in human OA chondrocytes. Results indicate that IL-6 mRNA was reduced by ~44 % (FAP siRNA-1) and ~66 % (FAP siRNA-2), while MMP-13 fell by ~48 % and ~68 % respectively in relation to siRNA control; other SASP/catabolic mediators (IL-1β, TNF-α, MMP-3, MMP-9) showed consistent reductions in the 20–60 % range. All changes were reported as statistically significant. These molecular changes were accompanied by increased COL2A1 staining and reduced senescent (P21 positive) cell fractions *in vivo*, supporting the conclusion that FAP knockdown by LNP-siRNA mitigates catabolic signalling and cartilage degeneration in OA models (Zhao et al., 2024).

Li and co-workers (2024) reported that IA delivery of an LNP-formulated mRNA encoding a single-chain version of adalimumab produced local antibody expression in the joint, neutralized TNF-α activity, and markedly reduced TNF-driven inflammatory signalling and ECM degradation *in vitro*. In preclinical OA mouse models, LNP-mRNA treatment reached deeper (penetrating depths exceeding 100 μm)

cartilage layers than direct protein administration. Decreased markers of cartilage breakdown (MMP-3, MMP-13, TNF-α) and synovial inflammation and improved structural and pain-related outcomes compared with controls. An increase in anabolic markers was also observed (SOX9, COL2A). These outcome data support the idea that local mRNA-based expression of biologics, here, anti-TNF, can achieve therapeutic concentrations in cartilage and protect joint structure and function in OA models (Li et al., 2024a; Li et al., 2024b).

Zheng et al. (2025) developed LNPs designed to deliver miR-200c-3p. The Lipo-AgPEI-miR-200c-3p formulation produced clear anti-inflammatory and anti-catabolic effects after LPS stimulation. Secreted cytokines TNF-α, IL-6, IL-1β, and chemokine MCP-1 were all substantially reduced versus LPS alone. Cartilage-degrading enzymes MMP-3, MMP-13, and ADAMTS-4 were downregulated while COL2 expression increased. These shifts were larger with the liposome-encapsulated AgPEI-miR construct than with AgPEI or miR-200c-3p alone, indicating a synergistic benefit of the combined carrier-miRNA system for preserving matrix markers and blunting catabolic signalling. Mechanistic work identifies ZEB2 as a direct target of miR-200c-3p. The knockdown of ZEB2 phenocopied miR-200c-3p overexpression, whereby COL2 expression rose while inflammatory cytokines, apoptosis markers, and matrix-degrading proteases fell, supporting a ZEB2-mediated pathway by which miR-200c-3p protects chondrocytes from inflammation-induced degeneration (Zheng et al., 2025).

Together, these studies show that LNP-based IA delivery (siRNA, therapeutic mRNA, or mRNA-encoded antibodies) can (a) reach chondrocytes and deeper cartilage zones that are otherwise poorly accessible, (b) produce biologically meaningful suppression of pro-inflammatory mediators or augmentation of anabolic signals, and (c) improve structural and symptom-related outcomes in preclinical OA models. This supports LNP approaches as a translationally promising platform for disease-modifying IA therapies.

5. Inorganic INPs

Inorganic NPs (INPs) are made from inorganic materials such as metals and carbon-based materials (Fig. 3). INPs can also be biocompatible and have good stability. However, their relative toxicity and low solubility remain a concern (Wen et al., 2023). Common types of INPs include metal NPs, carbon fibers, superparamagnetic iron oxide NPs (SPIONs), and mesoporous silica NPs (Slowing et al., 2007).

Some INPs have shown anti-osteoarthritic activities (Sarkar et al., 2019; Abdel-Aziz et al., 2021), which may make them beneficial in delivering OA therapies where synergistic effects may be attained. For example, gold NPs (GNPs) possess antioxidant activities and have been shown to suppress the activity of IL-1β, PGE_2, and COX-2, which have been proven to play a part in the pathogenesis of OA (Sarkar et al., 2019). Abdel-Aziz et al (2021) showed that the combined treatment of Diacerein® (anthraquinone IL-1 inhibitor-Rhein) and GNPs improved levels of serum cytokines, liver and kidney indices, as well as oxidative stress markers associated with OA better than Diacerein® and GNPs individually. Diacerein® is an OA drug possessing anti-inflammatory, anti-catabolic, and pro-anabolic properties on cartilage and subchondral bone (Pavelka et al., 2016). The untreated OA rats showed a notable rise in renal and hepatic indices (Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase, creatinine, and urea). Nevertheless, the administration of Diacerein® and GNPs individually led to a reduction in all these indices. Notably, the combined treatment of Diacerein® and GNPs (Diacerein®-GNPs) proved more effective than individual treatments, significantly improving hepatic and renal oxidative stress markers (superoxide dismutase, malondialdehyde, and glutathione peroxidase). A significant decrease in inflammatory cytokines (IL-1β, IL-6, and TNF-α) was observed in normal animals that received Diacerein®-GNPs compared with the untreated group. This cytokine decrease was evident in the GNPs-only treated group and further reduced in the group of OA rats that received the combined treatment (Diacerein®-GNPs). This suggested that the developed Diacerein®-GNPs were superior to both Diacerein® and GNPs administered individually, exhibiting synergistic effects and alleviating OA by reducing subchondral bone remodeling and inflammation in rats (Abdel-Aziz et al., 2021).

Taking this further into the OA drug delivery application, Park et al. (2020) synthesized triamcinolone-loaded GNPs for IA delivery of OA. Triamcinolone-loaded GNPs elicited greater expression of anti-inflammatory cytokines (IL-10 and IL-4) and arginase 1 in synoviocytes, accompanied by a low expression of pro-inflammatory cytokines (TNF-α, IL-1-β, and IL-6) and ECM-degrading enzymes (MMP-1 and MMP-3). Furthermore, free triamcinolone could only elicit a pro-inflammatory response in fibroblast-like synoviocytes, nor did it activate macrophage repolarization from M2-type to M1-type, which

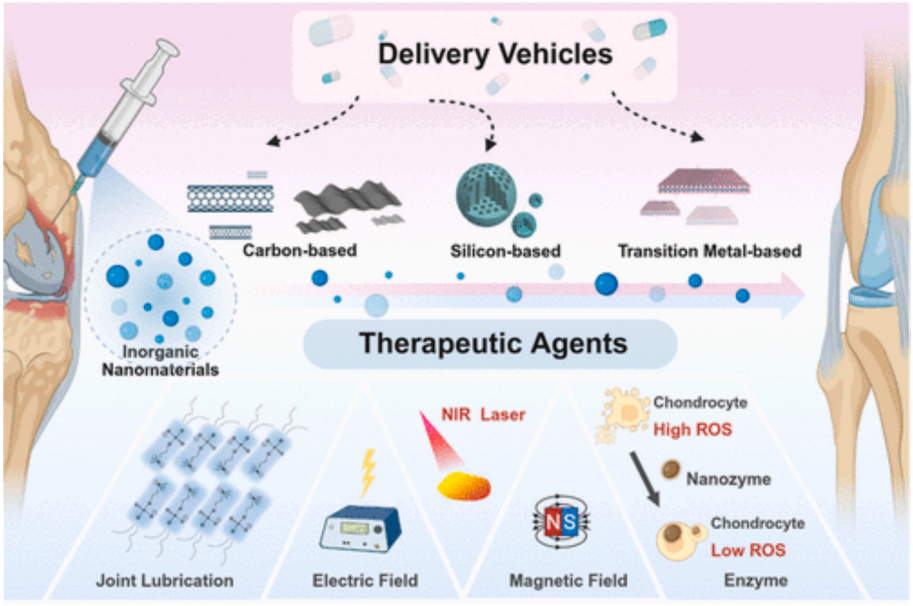

Fig. 3. Schematic of INPs from different types of inorganic nanomaterials and their effect on IA OA therapy, Zhang et al., 2025. Adapted with permission from the American Chemical Society.

favours an anti-inflammatory response that is key for the attenuation of OA (Park et al. 2020). Triamcinolone-loaded GNPs may represent a promising therapeutic option for OA by reducing inflammation and inhibiting the degradation of cartilage.

Lastly, although GNPs are amongst the most commonly used types of metal NPs, they are still potentially dangerous. In a study by Zhang et al. (2014), GNPs were employed in osteoblasts and resulted in elevated levels of Alkaline Phosphatase, which are notably already elevated in OA. Though elevated Alkaline Phosphatase levels are not synonymous with OA, they contribute to bone remodelling, which worsens OA (Zhang et al., 2014).

Following articular damage, the occurrence and accumulation of oxidative stress within the OA joint eventually lead to the progression of OA. Excessive ROS causes mitochondrial damage to chondrocytes, leading to impaired function of chondrocytes, resulting in apoptosis (Hou et al., 2021). Therefore, the effective scavenging of ROS can be instrumental in treating the treatment of OA. Xu et al. used near-infrared light-sensitive tea polyphenol-modified zirconium-based porphyrin metal-organic framework (TP-Au@PCN) to repair impaired chondrocytes in OA (Xu et al., 2023). Tea polyphenol is a free radical scavenger that prevents oxidative damage-mediated inflammation (Musial et al., 2020). Although both pristine tea polyphenol and TP-Au@PCN showed significant reduction in levels of ROS, TP-Au@PCN was more effective in reducing the levels of ROS than pristine tea polyphenol. The chondrocyte-expression level of MMP-13 in chondrocytes treated with TP-Au@PCN was significantly lower than that in pristine tea polyphenol and the untreated groups. There was also a significant increase in the expression of COL2 and SOX9 in chondrocytes. This system showed effective repair of cartilage-damaged mitochondria and promoted cartilage regeneration in chondrocytes, providing a promising platform for OA treatment (Hou et al., 2021).

Some other metals have also been found to possess beneficial properties for the treatment of OA, which can be used in conjunction with OA therapies to combat OA. Kumar and colleagues (2019) utilized manganese dioxide (MnO_2) NPs to assess their cartilage penetration and prolonged retention in the joint. Findings from the study demonstrated no cytotoxicity of murine chondrocytes, synovial cells, mesenchymal stem cells (MSCs), and bone marrow-derived macrophages. The expression of key factors associated with cartilage degradation, such as nitric oxide synthase (NOS), MMP-1, MMP-13, and ADAMTS-5, exhibited a notable decrease after treatment. MnO_2 NPs exert anti-inflammatory effects by catalyzing the breakdown of hydrogen peroxide, thus scavenging ROS produced by chondrocytes (Kumar et al., 2019). The PEG-MnO_2 NPs demonstrated prolonged retention, being retained in the joint cavity for at least 7 d after *in vivo* IA injection (Kumar et al., 2019). The incorporation of an OA drug would help exploit the properties of a nanosystem of this kind and possibly improve the properties of the drug. The inherent toxicity (Table 3) of certain inorganic materials (notably heavy metals) and their tendency to accumulate in tissues have hindered clinical translation of INPs (Li et al., 2025).

This schematic summarizes the main classes of nanocarriers: micelles, dendrimer NPs, PNPs, liposomes, INPs, exosomes, and cell-based carriers and their mechanisms in the osteoarthritic joint microenvironment (Fig. 4). Within the OA joint, pathological features such as cartilage degeneration, synovial inflammation, and osteophyte formation create biological barriers that limit drug penetration and retention. Nanotechnology-based systems overcome these barriers by enabling site-specific accumulation, prolonged drug release, and modulation of inflammatory and degradative pathways. Liposomes and micelles improve solubility and controlled release of small-molecule drugs; PNPs and INPs permit targeted delivery of biomolecules and siRNA; and cell- or exosome-derived nanotherapeutics can deliver bioactive signals that promote cartilage regeneration. Collectively, these strategies represent an integrated nanomedicine approach aimed at restoring joint homeostasis, reducing inflammation, and preventing progressive cartilage loss in OA.

6. Microparticles for IA OA therapy

Microparticles are defined as spherical particles between 1 and 1000 μm in diameter, classified mainly as either microcapsules or microspheres (Cao et al., 2021). The particle size presents an advantage over NPs because of a larger surface-to-volume ratio (Stack et al., 2019). This large size allows them to encapsulate larger molecules, such as proteins and peptides, and larger loads of cargo compared to NPs, which is essential for chronic diseases such as OA. Once administered, microparticles are less likely to be rapidly eliminated via small capillary networks provided that they can penetrate the ECM in the joint, therefore improving retention of biologics delivered, a property necessary for chronic diseases such as OA (Colella et al., 2020).

Li et al. (2021) used super-activated platelet lysate (sPL)-loaded PLGA/chitosan/gelatin microspheres for IA delivery to inhibit and promote cartilage repair in OA rats. Growth factors IGF, TGF, and VEGF were rapidly released from the sPL-loaded microspheres within the first three d followed by stabilization and sustained release of all three growth factors thereafter for the remaining 17 d of the study. Treatment with the sPL-loaded microspheres resulted in increased expression of COL2A, ACAN, and SOX9 in OA chondrocytes, which promotes cartilage synthesis better than the control. The Micro-CT scan results showed new cartilage filling within deeper cartilage layers as well as a smoothened joint surface, with a visible joint space and only a few osteophytes (Li et al., 2021a).

In a preclinical OA model, IA administration of rapamycin formulated as long-acting PLGA microparticles produced robust, disease-modifying outcomes (Dhanabalan et al., 2023). In treated joints, the rapamycin microparticles induced cellular autophagy in the chondrocytes. This was shown by clear reductions in cellular senescence markers (lower SA-β-gal staining and reduced p16/p21 expression), decreased expression of senescence-associated secretory phenotype cytokines, and diminished MMP-13, ADAMT-5 activity compared with controls. These molecular changes were associated with improved cartilage integrity on histology and lower OARSI scores. Functionally, animals receiving the microparticles exhibited preserved cartilage proteoglycan (Safranin-O) staining and reduced cartilage fibrillation versus free drug or untreated groups, and no overt local toxicity was observed. The microparticles were retained in the mouse for up to 35 days. Taken together, the data indicate that sustained rapamycin delivery via microparticles can suppress senescence-linked catabolic signalling in the joint and translate into measurable structural protection against OA progression, while prolonged joint retention significantly reduced the

Table 3
Toxicity profiles of selected INPs used in OA models. Reprinted from Li et al., 2025.

NP	Dosage range	Model system	Route of administration	Toxicological effects
TiO_2	10–100 μg/mL	Chondrocytes (*in vitro*)	Direct culture	ROS generation at > 50 μg/mL
CuO	5–50 mg/kg	Rat (*in vivo*)	IA injection	Dose-dependent inflammation
CeO_2	10–200 μg/mL	RAW264.7 macrophages	*In vitro*	Low ROS and good biocompatibility
$Mg(OH)_2$	1–10 mM	Human OA chondrocytes	*In vitro*	Safe below 5 mM; cytotoxic at higher concentrations

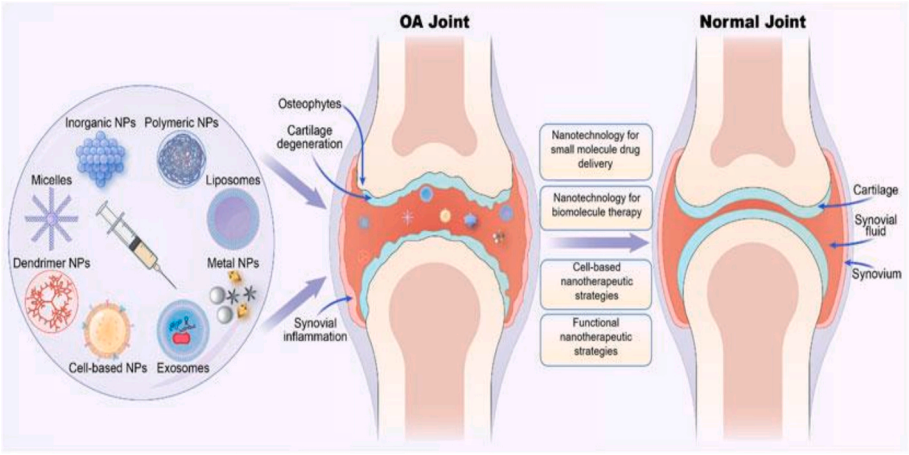

Fig. 4. Structures of NPs used as drug delivery systems in the treatment of OA (image adapted from the open-access article; Guo et al., 2022). Adapted under the terms of the Creative Commons Attribution License (CC BY).

frequency of administration, which is beneficial to improve patient compliance in clinical practice (Dhanabalan et al., 2023).

Qui and co-workers (2024) developed multifunctional injectable microspheres for the modulation of macrophage polarization and inflammation by co-administering parecoxib and IL-4. The tunable double-layer microsphere that released parecoxib and Bovine serum albumin more rapidly from an outer shell with decreasing pH. Complete release of Parecoxib was achieved in 9 d, while only approximately 40 % of the drug was released in the same timeframe. Synovial fluid concentrations of PGE_2, IL-1β, and TNF-α were reduced after treatment, and joint swelling (knee circumference) recovered toward the contralateral limb over 12 weeks. Histology at 6–12 weeks showed lower synovial inflammation scores and improved Mankin scores versus free drug or untreated OA controls; microspheres persisted in the joint and provided sequential cargo release with good local tolerability. The decrease in pro-inflammatory markers and increase in anti-inflammatory markers (COL2, ACAN, and IL-10) showed the anti-inflammatory efficacy of Parecoxib and M2 macrophage polarization by IL-4, respectively. The study thus demonstrates that staged release from microparticles can both blunt acute inflammation and support later cartilage repair *in vivo*, a combination desirable for IA OA therapy (Qiu et al., 2024).

Another avenue of microparticles is microplates. Di Francesco and colleagues (2021) deployed DEX-loaded microplates for the IA treatment of OA mice (Di Francesco et al, 2021). Although both free DEX and DEX-loaded microplates downregulated the amount of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α), the DEX-loaded microplates were more effective in inhibiting IL-6 and TNF-α than free DEX in ATCD5 chondrocytes. *In vivo* studies on overload-induced mice also showed that the DEX-loaded microplates had more effective inhibitory properties on pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, as well as key matrix degradation protein MMP-13, than the free DEX. This suggested that DEX-loaded microplates were more effective as anti-inflammatory and anti-matrix degradation agents than free DEX in OA mice (Di Francesco et al, 2021).

In general, the NPs and microparticles bear a promising feature for application in OA intra-articularly delivered therapies.

7. Specialised vesicular carriers in OA therapy

Though much progress has been made, traditional drug delivery systems (e.g., liposomes) still have limitations such as short half-life, low encapsulation efficiency of hydrophobic drugs, membrane instability, making them leaky, and lack of flexibility (Opatha et al., 2020). To overcome these drawbacks, novel vesicular drug carriers such as exosomes, transfersomes, and niosomes have emerged as promising platforms. Their structural adaptability and tunable composition make them especially promising for enhancing localized and sustained drug action in OA therapy.

7.1. Exosomes

Exosomes are extracellular nanovesicles with an average diameter of approximately 100 nm. These vesicles can be secreted by almost all cell types and are found in all body fluids and tissues, including blood, urine, and adipose tissue (Kalluri and LeBleu, 2020). Exosomes have various endogenous effects, which include transporting nucleic acids (DNA, mRNA, siRNA, microRNA, and IncRNA), proteins, metabolites, and bioactive lipids (Tran et al., 2020). Additionally, exosomes have low immunogenicity, good tissue penetration, and low toxicity and are stable under physiological conditions (Chen et al., 2021;(Hu et al., 2020a). Exosomes are usually harvested from chondrocytes and MSCs for OA treatment (Liang et al., 2024). Liang et al. (2022) developed chondrocyte-targeting exosomes to encapsulate and intra-articularly deliver CRISPR/Cas9 plasmid (Cas9 sgMMP-13). Upon delivery to chondrocytes, the plasmid Cas9 sgMMP-13 knocked down MMP-13. The knockdown of MMP-13 resulted in the prevention of COL2 degradation and the decrease of ACAN, preventing cartilage degradation *in vitro* and *in vivo* (rat) OA models (Liang et al., 2022).

Kartogenin (KGN) is a small molecule that has been shown to possess the capacity to induce chondrocyte differentiation of \MSCs, thus stimulating chondrogenesis (Johnson et al.,2012). Despite this, the clinical application of KGN has been limited due to its low solubility, which makes drug administration and dose control very complex. In a study by Xu et al., (2021), KGN was encapsulated into E7 peptide-exosomes and delivered into synovial fluid-MSCs to induce chondrogenesis. The superior expression of COL2A and ACAN in MSCs treated with E7-Exo/KGN, compared to those of free KGN, led to elevated MSC chondrogenic differentiation. This not only suggests that E7-Exo/KGN has higher chondrogenesis capacity but also shows that the use of exosomes as carriers improved the solubility and bioavailability of KGN. *In vitro* studies also showed the superior efficacy of cartilage regeneration in OA rats compared to free KGN. This was evidenced by the presence of clear layers of cartilage tissue and smooth cartilage surfaces from E7-Exo/KGN-treated OA rats compared to coarse, eroded cartilage surfaces in OA rats treated with free KGN (Xu et al., 2021).

Similar to inorganic NPs, non-medicated exosomes have the ability to induce therapeutic effects on OA. For example, He et al. (2020) demonstrated the possibility of using bone marrow MSC-derived exosomes (BMSC-derived exosomes) as a delivery system to target chondrocytes. This is because MSCs have the capacity to enhance and

promote endogenous cell regeneration and cell viability. In OA, MSCs function to maintain chondrocyte homeostasis, promote cartilage regeneration, and expedite tissue repair. (Zhang et al., 2024). The BMSC-derived exosomes led to significant *in vitro* upregulation of COL2A1 and downregulation of MMP13, an enzyme associated with cartilage degradation in chondrocytes. Similarly, the BMSC-derived exosomes treated OA rats showed upregulated COL2A1 and down-regulated MMP-13 compared to untreated rats. In general, BMSC-derived exosomes decreased cartilage destruction both *in vitro* and *in vivo*, followed by inducing cartilage repair *in vivo* (He et al., 2020b).

Zhang et al (2020) assessed the potential to repair damaged cartilage using BMSC-derived exosomes possessing biologically active substances, including proteins, lipids, and nucleic acids. Western blots showed enhanced concentrations of COL2 and SOX9, which promote cartilage synthesis. Further, the results exhibited phenotypic transformation of synovial macrophages from the M1 and M2 subsets, subsequently leading to decreased levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α as well as increased levels of the anti-inflammatory cytokine IL-10, compared to the phosphate-buffered saline (PBS) group. The macrophage phenotypic change from M1 to M2-type favours the production of anti-inflammatory cytokines (Strizova et al., 2023). Therefore, BMSC-derived exosomes showed the potential to combat inflammation and induce cartilage regeneration in OA rats, although the key bioactive substance was yet to be explored (Zhang et al., 2020).

Exosomes contain cell-specific molecular signatures such as proteins, miRNAs, and lncRNAs that mirror disease-related cellular processes. This makes them attractive a next-generation biomarkers (Ghosh et al., 2024). In conjunction, there is an elevated production of exosomes in the synovial fluid of patients with OA compared with that of healthy people. This makes exosomes excellent for OA diagnosis (Fig. 5).

7.2. *Transfersomes*

Transfersomes are a particular type of lipid-based nanovesicular system that consists of at least one inner aqueous compartment, a lipid bilayer (phospholipids), as well as an edge activator (Rai et al., 2017). In a review, (Opatha et al., 2020) discussed that transfersomes are both biodegradable and biocompatible since they are comprised of natural phospholipids and edge activators, therefore making them non-cytotoxic (Opatha et al., 2020). As they are biocompatible, transfersomes are suitable for prolonged retention periods, critical for OA therapy, as they will mitigate the need for multiple injections, making patients liable to possible infections and reducing patient compliance. The presence of the aqueous layer contributes to these vesicles' elasticity. This property is important as it makes it easy for transfersomes to deform and squeeze themselves through constrictions that are smaller than their own diameter to reach the target site intact. This flexibility

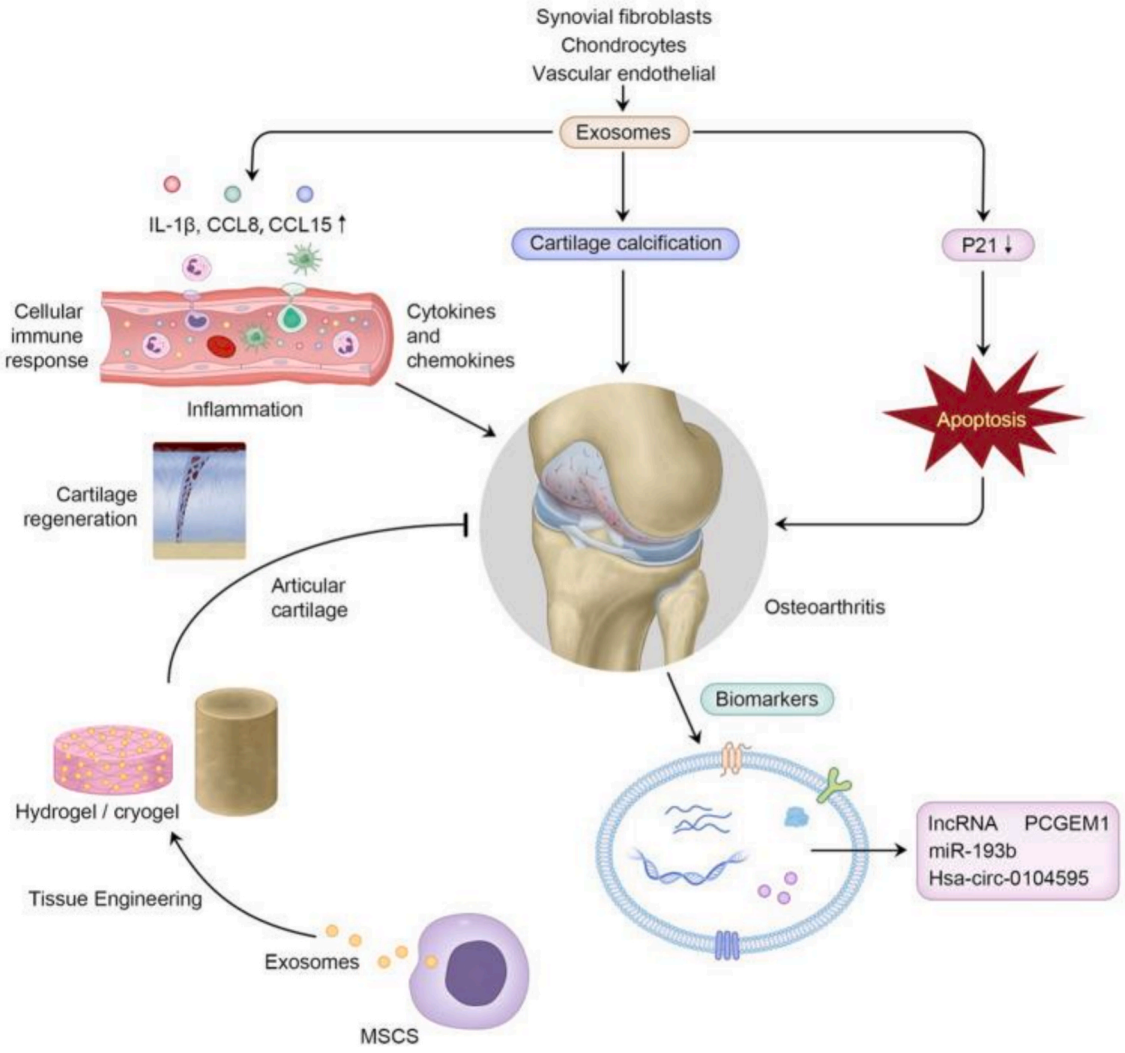

Fig. 5. The clinical potential of exosomes to serve as biomarkers in the diagnosis of OA, and their potential in cartilage tissue regeneration (Fan et al.,2022) under Creative Commons Attribution License (CC BY).

allows these NPs to be able to evade the dense network of the ECM. This results in controlled and sustained drug delivery, thus displaying high penetration resulting in targeted drug delivery in the joints (Rajan et al., 2011). Using transfersomes that have an appropriate size to fit in the ECM, charge for solubility (cationic), and flexibility is critical for the treatment of OA, as they can manoeuvre around the densely packed ECM (Li et al., 2021b). Phospholipids in the transfersomes may also serve as lubricants for the joints to assist in combating joint inflammation by reducing bone-to-bone friction in the OA joint microenvironment (Petelska et al., 2019). The deformability degree depends on the ratio of the edge activator to the lipid mixture. Because edge activators are amphiphilic surfactants with lipophilic and hydrophilic moieties, they help with increasing solubility and entrapping a wide range of drugs. Edge activators bring about membrane ultra-flexibility by acting as membrane destabilizing factors (Opatha et al., 2020).

They also help keep the membranes intact and offer protection against fragmentation of the membrane after penetration into pores smaller (up to a tenth smaller) than their diameter, whilst protecting their cargo from metabolic degradation. Edge activators also affect size and drug entrapment efficiency; the higher the concentration of the edge activator in the formulation, the smaller the vesicles formed. Conversely, the entrapment efficiency decreases with the increased concentration of the surfactant (Akram et al., 2022). As a result, transfersomes can be used to carry a wide variety of molecules almost independent of their size, molecular weight, or structure (Opatha et al., 2020). The hydrophilic compartment of transfersomes stores hydrophilic cargo such as chondroitin sulfate, while the hydrophobic compartment carries hydrophobic cargo such as DIC and curcumin within the lipid bilayers (Çağdaş et al., 2014; Chauhan et al., 2018).

In the treatment of OA, transfersomes have been mainly delivered transdermally (Rother et al., 2009; Rasheed et al., 2022). (Marwah et al., 2022). The edge activator enables transfersomes to create a *trans*-epidermal gradient, facilitating the ultra-deformable nanovesicles to squeeze through the stratum corneum and carry large molecules across the skin. The osmotic gradient is created by the difference in water content between the epidermis and stratum, facilitating the movement of transfersomes from the higher gradient to the lower gradient, thus delivering the cargo to its target across the skin barriers (Walve et al., 2011).

Rasheed et al. delivered glucosamine sulfate transdermally using transfersomes to investigate improved drug delivery for glucosamine for OA treatment in rabbits. Similar to the IA delivery, transdermal delivery has fewer side effects and potentially higher bioavailability compared to the oral route of administration, given that the drugs bypass first-pass metabolism. Glucosamine sulfate, a precursor of glycosaminoglycans, is well-suited as a supplement to cartilage ECM, and a study by Towheed et al. (2005) suggested that glucosamine sulfate was as symptomatically effective as NSAIDs in the short-term management of OA (Towheed et al., 2005). In the study by Rasheed and colleagues (2022), a transfersome-loaded glucosamine sulphate formulation was used to treat OA in papain-induced OA rabbits. A month post-treatment, results showed an improvement in cartilage regeneration in rabbits treated with the transfersomal formulation, while on the other hand, there was no improvement in the rabbits treated with the liposomal formulation. This could be attributed to the lack of permeability across the skin, as liposomes are more rigid than transfersomes (Rasheed et al., 2022). Additionally, since IA delivery is more site-specific, the transfersomal formulations being delivered directly to the joint, along with their high permeability across the ECM, would increase the drug's concentration in the joint.

7.3. Niosomes

Niosomes are non-ionic surfactant vesicles with the ability to improve the pharmacokinetic properties of therapeutic compounds. The lipid bilayer in the structure of niosomes is primarily based on the presence of non-ionic surfactants and lipid compounds (Akbarzadeh et al., 2021). As a result of their special geometry, niosomes can encapsulate both hydrophilic and hydrophobic drugs. Similar to transfersomes, niosomes also possess the potential to safeguard encapsulated cargo from degradation upon administration, provide sustained release of therapeutic agents, are convenient, and achieve targeted drug delivery in OA joints. This, in turn, has the potential to mitigate the toxicity of administered agents, making them ideal for the treatment of chronic diseases such as OA (Masjedi and Montahaei 2021). Niosomes and liposomes are practically the same, with the main difference being that niosomes are made up of uncharged single-chain surfactant and cholesterol, while liposomes are made up of double-chain phospholipids (Gharbavi et al., 2018). Furthermore, niosomes are considered to be good drug delivery systems because of their superior drug entrapment capacity, higher chemical stability, and greater bioavailability (Opatha et al, 2020). Therefore, niosomes can carry higher quantities of therapeutics, which is helpful for sustained release in OA, reducing the need for repeated administration. Although niosomes exhibit great promise as carriers, not enough studies have been conducted on their toxicity, as they have endless permutations of combinations of surfactants and lipids (Gharbavi et al., 2018). Similar to transfersomes, niosomes have been primarily researched for topical delivery in OA, and no research was available during the compilation of this review on their IA delivery in OA, also highlighting an area for future exploration by researchers.

In general, transfersomes and niosomes comprise the surfactants and aqueous compartments that contribute to their flexibility and permeability through the dense ECM, making them suitable for application in IA OA treatment ((Li et al., 2021b); Kazi et al., 2010). The ultra-elasticity of transfersomes allows them to traverse through constricted areas, thus enabling efficient drug delivery (Rai et al., 2017). On the other hand, niosomes are slightly more rigid but are more chemically stable than other vesicles (Mashal et al., 2023). Based on their biocompatibility, biodegradability, and site-specificity, both transfersomes and niosomes hold great potential as drug carriers for OA treatment (Ag Seleci et al., 2016; Akram et al., 2022).

Similar to transfersomes and niosomes, hydrogels are a large class of polymers that have a high aqueous capacity to aid their structural flexibility, hence potential application in OA therapy (Parhi, 2017). For this reason, the loading of vesicular OA formulations into the hydrogel systems bears great promise, given their compatibility in terms of structural deformability.

8. Hydrogels in OA therapy

Hydrogels are cross-linked polymers with hydrophilic groups, allowing them to absorb water up to thousands of times more than their own weight (Parhi, 2017). Water absorption capacity depends on the number of hydrophilic groups present in the polymer. As a result, hydrogels are used as vehicles in smart drug delivery platforms and enhance the sustained drug release profiles (Nunes et al., 2022). The most important characteristics of hydrogels are biodegradability, non-toxicity, biocompatibility, and non-immunogenicity (He et al., 2017). Polymers used in hydrogels can be either natural or synthetic, where synthetic polymers include but are not limited to PEG, poly lactic acid (PLA), PLGA, and polyvinyl alcohol (PVA) (Bashir et al., 2020). Importantly, natural hydrogel polymers are usually derivatives of ECM proteins, e.g., chitosan, HA, collagen, alginic acid, and carrageenan (Bashir et al., 2020), making them highly compatible with the OA joint matrix.

Additionally, with high water content, hydrogels can swell and shrink, exhibiting various behavioural changes upon exposure to different stimuli such as temperature and pH. The temperature responsiveness of hydrogels is brought by the fact that polymers used have a lower critical solution temperature (Zhuo et al., 2022). At temperatures above the lower critical solution temperature, the polymer may lose its hydrophobically bound water, leading to phase separation and a gel

collapse. However, there is increased hydrophobicity with water at temperatures below the lower critical solution temperature, leading to increased swelling (Fig. 6C) (Peppas and Hoffman, 2020). This allows the phase transition from solution to gel and back to solution, depending on the temperature (Abou-Shamat et al., 2020). The pH-responsive polymers are ionic polymers that contain acidic (carboxylic acid) or basic (amine) pendant groups (Tan et al., 2022). In the presence of suitable pH and ionic strength, the various pendant groups of the polymers have the potential to ionize and form permanent charges on the gel, leading to rapid gelation (Fig. 6B) (Bustamante-Torres et al., 2021).

The NP-loaded hydrogel systems have been used to combine and leverage advantages from the NPs as well as advantages from the hydrogels. A brilliant example of hydrogels improving the properties of NPs is a study by Yang et al (2020), whereby KGN-loaded GelMA@Lipo microgels extended the release of KGN for over three weeks compared to the 25 d of the KGN-loaded liposomes. Furthermore, GelMA@Lipo@KGN showed the highest proteoglycan accumulation in BMSCs compared to Lipo@KGN and the Blank, indicating enhanced chondrogenesis, possibly as a result of the sustained release of KGN facilitated by the GELMA. The system also exhibited enhanced levels of COL2A1, ACAN, and SOX9 compared to other treatment groups, suggesting that it could effectively promote chondrogenic differentiation in BMSCs (Yang et al., 2020).

In a study, Han et al (2021) used methacrylate gelatin (GelMA) incorporated within microspheres made of dopamine poly(N, N-dimethyl acrylamide) (DMA) and 2-methacryloyloxyethyl phosphorylcholine (MPC)(GelMA@DMA-MPC), which greatly enhanced lubrication and exhibited sustained drug release of the DIC from the GelMA@DMA-MPC microspheres in OA rats (Han et al., 2021). In addition, the delivery system significantly increased the expression of ACAN and COL2A1 while suppressing the expression of MMP-13 and ADAMTS-5, therefore promoting cartilage regeneration and stopping the degradation of cartilage.

Similarly, Lei et al. (2022) increased the water solubility of rapamycin by encapsulating the drug into cationic liposomes, forming rapamycin-liposome-incorporating HA-based hydrogel microspheres (RAPA@Lipo@HMs). Results revealed that not only were the liposomes able to improve the pharmacokinetic profile of rapamycin, but the RAPA@Lipo@HMs also extended rapamycin's release from the liposomes from 21 d to 28 d. Overall, the RAPA@Lipo@HMs also acted as a biolubricant, alleviating joint wear *in vivo* (Lei et al., 2022).

In another study, Li and colleagues (2021) alleviated articular cartilage degeneration by employing a complex involving G5-AHP (a multifunctional gene vector, arginine, histidine, and phenylalanine-modified generation 5 polyamidoamine) and microRNA-140 (miR-140) to form G5-AHP/miR-140 NPs in hydrogel microspheres. The nano-micron portrayed a high gene transfection efficacy and promoted expression of COL2 by over 3-fold more than the control. Furthermore, ADAMT-5 and MMP-13 expressions were respectively about 0.7 and 0.5-fold less than in the untreated chondrocyte cells. This, accordingly, maintains the metabolic balance of the cartilage matrix in chondrocytes of a mouse model (Li et al., 2022).

In a study by Seo et al. (2022), triamcinolone acetonide was encapsulated into an intra-articularly injectable PNPs hydrogel to treat inflammation in OA mice. Upon treatment, the expression levels of pro-inflammatory cytokines IL-6 and TNF-α significantly decreased with time for four weeks. In contrast, free triamcinolone acetonide-treated mice showed continuous elevation of pro-inflammatory cytokines, suggesting that free triamcinolone acetonide was not as effective as the hydrogel. The system also promoted the activation of anti-inflammatory cytokines IL-4, IL-10, and IL-13 significantly better than the free triamcinolone acetonide. This means that the drug delivery system was more effective in the long-term anti-inflammatory effects compared to free triamcinolone acetonide. The triamcinolone acetonide hydrogel formulation also successfully reduced the expression of matrix-degrading proteins MMP-3 and MMP-13, exhibiting the effective prevention of cartilage degeneration. Similar to its effects on pro-inflammatory cytokines, free triamcinolone acetonide was unsuccessful at reducing MMP-3 and MMP-13 over a span of 4 weeks of treatment (Seo et al., 2022).

In a study conducted by Tsubosaka et al. (2020), eicosapentaenoic acid (EPA) was encapsulated into micelles, which were further incorporated into a gelatin hydrogel for the IA application in OA treatment (Tsubosaka et al., 2020). EPA has anti-inflammatory and immunomodulatory properties, including a reduction in inflammatory cytokine

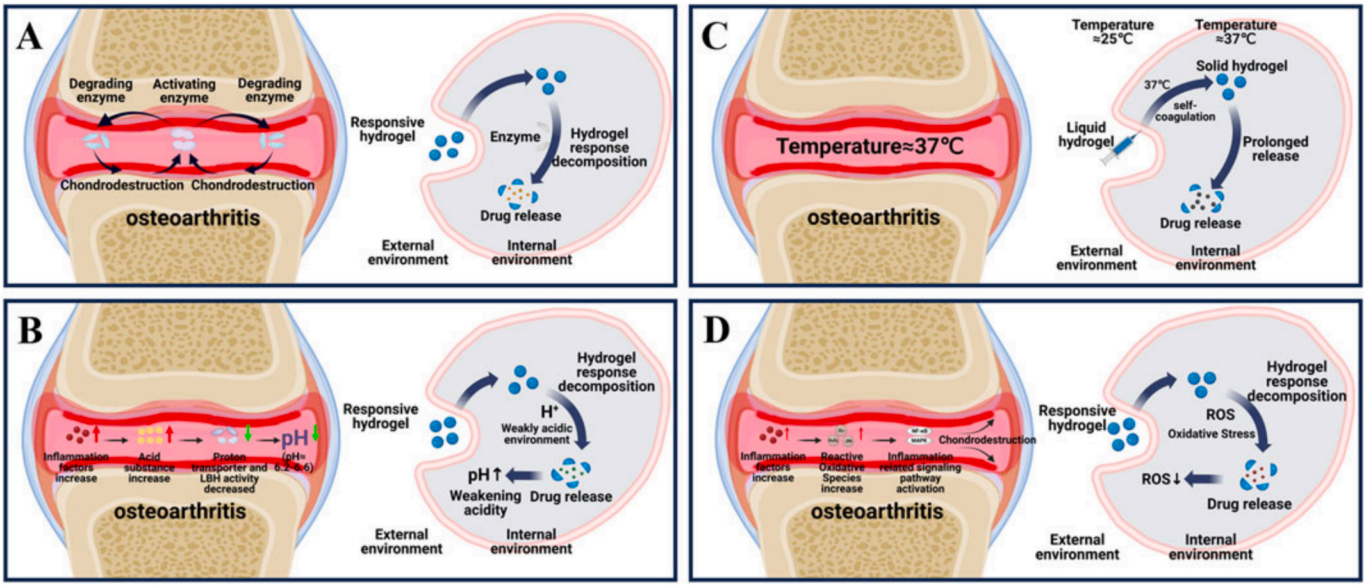

Fig. 6. Principle of endogenous responsive hydrogels. (A) Changes in internal enzymes during OA and the process by which enzyme-responsive hydrogels release drugs in response to internal reactions. (B) Changes in internal PH during OA and the internal response of pH-responsive hydrogels to release drugs. (C) Internal temperature during OA and the process by which temperature-responsive hydrogels respond to self-coagulation and release drugs internally. (D) Changes in internal ROS during OA and the process of drug release in response to ROS-responsive hydrogels. Adapted from Xu et al., 2025 Creative Commons Attribution License (CC BY) (Xu et al., 2025 Feb).

synthesis (Crupi and Cuzzocrea, 2022). Results from the study showed that the EPA-hydrogel formulation slowed the progression of OA by suppressing levels of IL-1β, MMP-3, and MMP-13 better than in free EPA. This suggested that the EPA-hydrogel formulation could decrease inflammation and reduce matrix degradation in OA mice. (Tsubosaka et al., 2020).

Cai et al. (2019) synthesized a vinyl sulfone-modified HA cross-linked by dithiol-terminated poly (ethylene glycol). The modified HA formulation also had superior resistance to enzymatic degradation. While the plain HA solution was completely degraded after 2d, the modified HA formulation took up to 7d before complete degradation. The modified HA hydrogel demonstrated enhanced viscoelastic properties along with elevated resistance to enzymatic degradation, which is pivotal for the treatment of OA (Cai et al. 2019).

To achieve nearly frictionless motion in the joints, some studies have focused on biomimetic viscosupplementation of joints. Amongst these studies, Mou and colleagues (2021) exploited the properties of chitosan by synthesizing an HA-chitosan-based supramolecular hydrogel for OA treatment. The hydrogel relieved pain by significantly inhibiting the inflammatory response by inhibiting TNF-α, IL-1β, IL-6, and IL-17 compared to plain HA. Rat models also showed smooth and intact surfaces with the presence of a thick cartilage layer, indicating cartilage regeneration. The formulated hydrogel was significantly better than the plain HA formulation in attenuating OA in rodents by decreasing inflammation and inducing cartilage regeneration (Mou et al., 2021).

Leone and colleagues cross-linked gellan gum (Leone et al., 2020), a water-soluble anionic polysaccharide, with PVA to formulate a hydrogel with viscosupplementation effects. The resultant hydrogel possessed improved mechanical strength, presented by improved elastic and viscous moduli compared to the bare polysaccharide core. This indicated that the developed formulation had better thixotropic activity and would be able to resist destruction better than the polysaccharide core hydrogel, with approximately 70 % of HA being released, followed by a sustained release in the following 23.5 h (Leone et al., 2020).

Jahanbekam et al. developed an ultrasound-triggered mixed-micelle HA hydrogel of hydrocortisone to treat OA (Jahanbekam et al., 2023). The elevation of temperature levels caused by ultrasound waves triggers drug release in certain temperature-sensitive delivery systems. The sound waves generate shear stress on the micelles, thus inducing the disruption of micelles. Free hydrocortisone was completely released after approximately 2 h. However, the maximum release of hydrocortisone from both the HA hydrogel and the mixed-micelle hydrogel containing Capryol® and Brij® occurred after approximately 8, 4, and 6 h, respectively. Since the quantity of hydrocortisone was not fully released from mixed-micelle hydrogel containing Tween® 60, this suggested that the formulation exhibited a more controlled and sustained release of hydrocortisone as a result of the polymer networks of the hydrogel. This is critical because it shows that the different surfactants had an influence on the drug release and that the formulation containing Tween® 60 will prolong the release of the drug in the joint cavity, thus reducing the need for repeated injection in OA treatment.

Diaz-Rodriguez and colleagues (2021) combined HA with a thermo-responsive polymer to form a hydrogel that would release beta-lapachone (βLap), a natural naphthoquinone that has anti-inflammatory activity. This hydrogel had a phase transition from sol-to-gel at 30 °C. The gel displayed suitable rheological properties suitable for the treatment of OA, as well as a decrease in the secretion of IL-6 in both free βLap and βLap loaded in the HA hydrogel from an ex vivo OA model. This suggested that βLap in both states could decrease pro-inflammatory cytokine IL-6; in parallel, hydrogel-loaded βLap reduced IL-6 secretion better than free βLap. In addition, the secretion of pro-inflammatory chemokine CXCL8 was more effectively reduced by the hydrogel-loaded βLap compared to better than by free βLap. Conversely, free βLap reduced the secretion of matrix-degrading protein MMP-13 better than βLap embedded in the hydrogel formulation. Therefore, the hydrogel formulation had superior anti-inflammatory effects and inferior cartilage regeneration effects compared to free βLap (Diaz-Rodriguez et al., 2021).

Metal NPs have also been used in conjunction with hydrogels; Li and colleagues combined the antioxidant properties of cerium oxide-NPs with cartilage-repairing properties of platelet lysate with an HA hydrogel for IA delivery in OA (Li et al., 2024a). The HA hydrogel loaded with PL and cerium oxide-NPs confirmed the antioxidant properties of the NPs by exhibiting increased expression of COL2 and ACAN while suppressing the expression of COL10, MMP-13, ADAMTS-5, and ADAMTS-9 in the treated group compared to the control. The results suggest that the synthesized injectable HA hydrogel loaded with platelet lysate and cerium oxide-NPs has the potential to be an effective treatment of OA by inhibiting matrix-degrading enzymes and promoting cartilage growth (Li et al., 2024a).

9. Molecularly imprinted materials with potential to treat OA

MIP biosensors and MIP-based materials are gaining attention as versatile platforms for both sensing and controlled delivery in biomedical applications. Their chemical and thermal stability, low cost, and potential for highly selective recognition make them attractive alternatives to biological receptors in diagnostics and promising candidates for smart, target-responsive drug delivery systems (Bahrani et al., 2024; Saylan et al., 2024; Abdulsada et al., 2025). In OA, where inflammation and matrix degradation are central pathological features and IA delivery is an attractive route, MIP-based approaches offer routes to selective cytokine recognition, affinity-controlled release, and composite materials that combine sensing with therapy. Amongst many approaches investigated to address drawbacks connected to conventional delivery systems in OA, molecularly imprinted materials provide a promising platform for potentially target-specific smart drug delivery systems.

Molecular imprinting technology provides a versatile tool for the fabrication of highly selective polymeric materials, viz., MIPs (BelBruno, 2018). The high selectivity of MIPs towards target compounds is derived from the chemically modified surfaces of the resulting material. The surface modification is a result of the synthetic process that is executed in the presence of a template molecule (Janczura et al., 2021). MIPs are obtained in three key steps: the synthetic formation of a prepolymerization adduct, polymerization, and template removal, resulting in modified polymer surface regions that are complementary to the distribution of electrostatic potentials to the template. A prepolymerization adduct can be created via two distinct approaches: (i) a covalent strategy (Fig. 7), where stable chemical bonds are formed between the template and the functional monomers providing a functionalized molecule, most commonly, possessing vinyl groups capable of polymerization or a (ii) non-covalent strategy where different non-covalent interactions, such as van der Waals forces hydrogen bonds or electrostatic forces stabilize the prepolymerization complex between the template and the monomers.

The covalent strategy offers high durability of the functionalized compound, making it advantageous under harsh polymerization conditions, but requires confirmation of the compound's structural integrity and purity prior to the polymerization process. The template also needs to possess functional groups that are able to react with functional monomers, forming ester or imine bonds. Unfortunately, this method necessitates hydrolysis of the template at the removal step, which can potentially alter the polymer's structure. Conversely, the non-covalent strategy simplifies the synthesis process and reduces synthesis time, but its lower stability often results in greater heterogeneity in the binding sites of the final polymer. The selection of a pertinent strategy is largely contingent on the template structural properties, availability, and the intended application of MIPs (Liu et al., 2024).

In most cases, the template molecule and the target compound used in the synthesis of MIPs are the same chemical entities. Therefore, limited availability or high costs of certain templates might be a limiting factor in the synthesis of MIPs. In such a case, MIPs can be obtained using structural analogues of target compounds as alternative templates

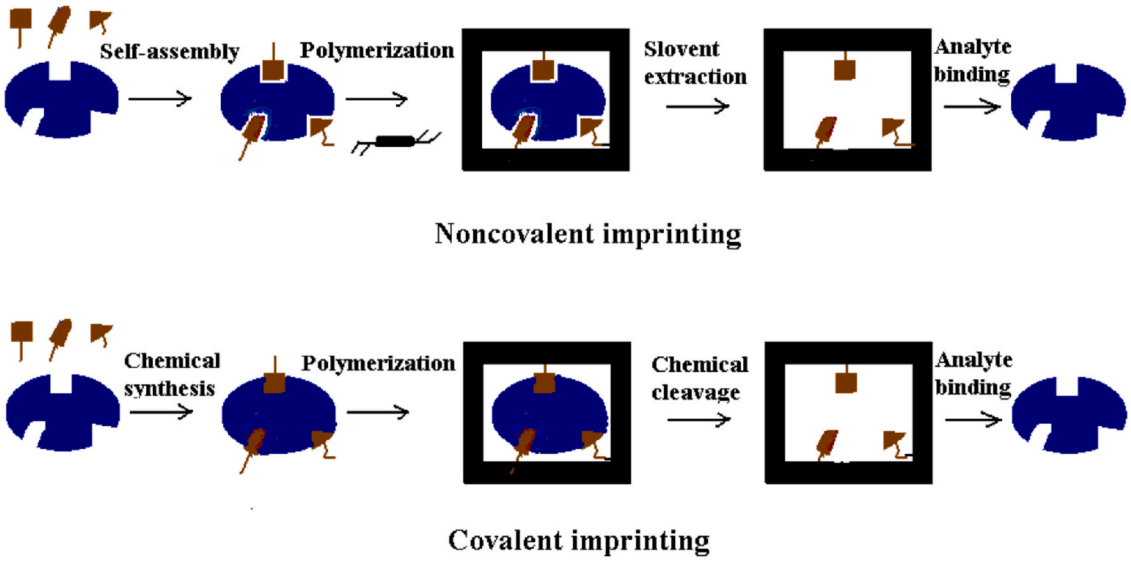

Fig. 7. Schematic representation of covalent and non-covalent molecular imprinting strategies adapted from Yan and Row, 2006, under Creative Commons CC BY license.

(Chen et al., 2021a) Careful selection of the template also mitigates the risk of template leaching, an undesirable phenomenon where residual template molecules affect the performance of the synthesized MIP. Literature has shown the effectiveness of providing selective MIPs. The efficiency of molecular imprinting is typically assessed using the imprinting factor, which is calculated as the ratio of the template's adsorption capacity on the MIP to that on a non-imprinted reference polymer. To ensure accuracy, the non-imprinted polymer must be synthesized under identical conditions, omitting the template molecule (Lamaoui et al., 2023).

It has to be mentioned that both highly cross-linked rigid polymers and low cross-linked hydrogels can be effectively obtained through molecular imprinting. In highly cross-linked hydrogels, the rigidity of the polymers maintains the geometry of their modified surface regions, preserving electrostatic potential distributions even after template removal, thus ensuring selective adsorption of the target molecule. Conversely, low cross-linked hydrogels exhibit flexible polymer chains, allowing imprinting to function as a macromolecular memory process. Multiple interactions between the template and functional monomers during synthesis drive the hydrogel's polymer chains into an energetically favorable conformation (Lusina and Cegłowski, 2022). Upon template removal, complementary binding interactions between the target molecule and the hydrogel network facilitate adsorption through conformational adjustments, ensuring high-affinity binding (Kakkar and Narula, 2022).

The desorption of target molecules from MIPs or hydrogels is governed by the diffusion and the relaxation of the material network. For highly cross-linked polymers, the degree of cross-linking affects diffusion, making the desorption process less diffusion-dependent. In contrast, in low cross-linked hydrogels, the macromolecular relaxation upon medium absorption induces swelling of the material. Despite this swelling, numerous spatially oriented functional groups within the hydrogel network interact with the target molecule (e.g., a drug), thereby modulating its release. The modified kinetics of the drug release process depend on the strength of those interactions. The migration of the drug through the polymer matrix, from one macromolecular memory region to another with various binding interactions, creates a"tumbling effect", creating efficient complexes by minimizing entropically unfavourable translational and rotational free energies (Venkatesh et al.,2008).

Among the various forms of MIPs, surface imprinting has emerged as a notable advanced molecular imprinting strategy. This technique allows us to provide a thin molecularly imprinted layer on the surface of core-forming composite materials (Kumar et al., 2024). Moreover, surface-imprinted MIPs offer a versatile platform for epitope imprinting, a protocol very effective for the synthesis of protein-targeted MIPs. Epitope imprinting involves using peptide fragments specific to a target protein, thus enhancing the selectivity of the resulting material (Dietl et al., 2021). Facile functionalization of MIP layers with different cores is an important advantage, as this enables further modifications, allowing additional properties to the material, such as integrating magnetic susceptibility properties. Additionally, surface imprinting improves the diffusion kinetics, expediting the effectiveness of the adsorption process. This technique is commonly applied in cancer diagnostics and therapy, where MIPs are employed for targeted drug delivery through the recognition of specific cell surface domains (Balcer et al., 2023).

MIPs exhibit selectivity comparable to that of antibodies while offering greater chemical and thermal stability. Unlike biologics, MIPs do not require specialized storage conditions, making them a more practical alternative to antibodies and biological receptors. Their robust nature compensates for the challenges associated with antibody manufacturing, particularly stability and shelf-life limitations (Liu et al., 2024). MIPs have been extensively utilized in analytical chemistry, primarily as selective sorbents in the solid-phase extraction, selectors in chromatography, and recognition elements of sensors (Sobiech and Luliński, 2024; Su et al.,2024). Despite numerous commercial applications, their potential in drug delivery remains an active area of research (Luliński, 2017; Haupt et al., 2020). Recent studies have validated multiple MIPs as effective operative diagnostic tools or drug delivery devices. Notably, MIPs have not yet been utilized for IA delivery of therapeutics for OA therapy. In OA, MIPs may be designed to trigger the degradation of hydrogel matrices to release drugs/drug-loaded NPs into target areas upon the recognition of hallmarks of OA, such as pro-inflammatory cytokines and matrix-degrading proteins (Gagliardi, 2023). This would potentially allow specific and targeted release and enhance retention times of therapeutics by providing a specific binding site to trigger their release. Thus, in our opinion, a few approaches discussed below could be beneficial to progress IA bioactive delivery for the treatment of OA.

As mentioned, MIPs reveal potential for facile integration with other materials, resulting in composites that increase their value by presenting additional advantages. The resulting hybrid materials could serve dual functions, such as serving as carriers for the delivery of anti-inflammatory agents and simultaneously as selective adsorbents of the

inflammatory cytokines (Mota et al., 2019). To the best of our knowledge, literature surveys show no reports of MIP-based systems that combine these functions for IA treatment of OA, thus providing an opportunity for further investigations. However, it has to be underlined that the investigations of specific MIP systems for anti-inflammatory drug deliveries and towards inflammatory cytokines have been carried out. Most recent and pronounced achievements are briefly discussed below.

In a very interesting paper, Parisi and co-workers (2018) developed a 'smart bandage' incorporating MIPs for DIC, an anti-inflammatory drug, for topical administration, to combat localized pain and inflammation. The 'smart bandage' prepared using MIP loaded with DIC exhibited drug release of 24 % within 6 h and 92 % of DIC released after 72 h. In contrast, the non-imprinted smart bandage' loaded with DIC released 51 % of the drug within the first 6 h and was completely released (100 %) after 72 h. The MIP-integrated version of the smart bandage demonstrated prolonged drug release and improved diffusion kinetics compared to the non-imprinted version, ensuring sustained therapeutic effects. (Parisi et al., 2018).

As an example, for the delivery of an anti-inflammatory drug, Wei et al. (2019) reported a pH-responsive molecularly imprinted hydrogel for DEX delivery. Dopamine, acrylamide, and acrylic acid were utilized as functional monomers to synthesize the hydrogel and DEX as the template molecule. After immersion in DEX solutions, the molecularly imprinted hydrogel had a significantly higher drug loading rate compared to that of the non-imprinted hydrogel. While the release rate of non-molecularly imprinted exhibited an excess of 80 % DEX release after 24 h, approximately 60 % of DEX was released from the molecularly imprinted hydrogel in the same period. The molecularly imprinted hydrogel sustained DEX release for up to 7 days. (Wei et al., 2019). In another study, Zahedi and co-workers integrated MIP NPs within electrospun poly(ε-caprolactone) nanofibers for the release of DEX. The MIP NPs were made using methacrylic acid and ethylene glycol dimethacrylate as functional monomers, and DEX served as the template molecule. Biodegradability could be considered an advantageous property of MIPs for drug delivery. Here, poly(ε-caprolactone) combined with MIP prolonged DEX release following the Fickian diffusion mechanism, confirming their potential for sustained drug release. (Zahedi et al., 2017).

Building on these principles, two practical MIP strategies dominate recent cytokine sensing and potential OA applications. The first is electropolymerized surface MIPs, in which a thin conducting polymer film is polymerized directly on an electrode in the presence of the protein template to create surface-exposed recognition cavities. Electropolymerized films form without added immobilization steps (Dykstra et al., 2025), and they are typically fabricated in aqueous buffers to preserve protein conformation. Template removal is commonly performed using ionic or alkaline washes or by electrochemical regeneration. Representative electropolymerized devices include the IL-1β sensor by Park et al. (2023), which used a fabricated via sequential electropolymerization on custom flexible screen-printed carbon electrodes modified with poly(3,4-ethylenedioxythiophene) (PEDOT) and a 4-aminothiophenol (4-ATP) self-assembled monolayer. The functional monomer, Eriochrome Black T (EBT), was electropolymerized in the presence of the IL-1β template, forming a thin poly(EBT) MIP film. IL-1β removal was achieved by alkaline extraction, revealing IL-1β selective recognition cavities. Park and colleagues reported an LOD of ~252 pg/mL, and a LOQ of ~765 pg/mL with a working range of ~100–1000 pg/mL (Park et al., 2023).

Ting et al. (2024) developed an electro-imprinted IL-6 MIP based on poly(*o*-phenylenediamine) (P(o-PD)) deposited onto a functionalized screen-printed carbon electrode. AuNPs, 3-aminopropyltriethoxysilane, and glutaraldehyde improved template immobilization and film conductivity as a result of the presence of amine and aldehyde groups. After template extraction by NaCl washing, the synthesized IL-6 biosensor showed a linear response from 2 to 400 pg/mL with an LOD of 1.74 pg/mL in serum. Although nonspecific adsorption of serum proteins to P(o-PD) films was observed, this platform demonstrated excellent reproducibility (RSD < 4 %) and robustness for low-volume biological fluids (Ting et al., 2024).

Yang et al. (2023) developed an electropolymerized thiophene-based MIP on gold dendrite electrodes integrated with an extended-gate field-effect transistor (EG-FET) transducer. The monomer thiophene-3-amidoxime (T3A) was electropolymerized in PBS in the presence of TNF-α, forming a conductive MIP film. The MIP-EG-FET demonstrated high sensitivity when in the presence of IL-1β and IL-6, with a selectivity (coefficient (α) > 3) as well as an LOD of ~0.55 pg/mL and LOQ of ~1.82 pg/mL in serum. To complement the sensitivity, the chemosensor was also reproducible, robust, reusable, and stable, making it suitable for a POC device for OA (Yang et al., 2023).

Choi and co-workers (2022) developed an impedimetric screen-printed carbon electrode sensor in which a double-layer electropolymerized molecularly imprinted film was grown to detect IL-1β. The imprinting was performed by electropolymerization directly at the screen-printed carbon electrode surface to form a binary conducting-polymer layer; the whole IL-1β protein served as the template, the electropolymerized monomers were poly(1,2-phenylenediamine) and poly(2-(phenylazo)chromotropic acid), and the initiation was electrochemical oxidation. The electrode fabrication and imprinting were carried out in aqueous buffer (PBS), and template removal was accomplished by an optimized alkaline/ionic wash that generated the recognition cavities. The MIP layer showed high IL-1β adsorption compared to IL-1α, IL-6, and TNF-α, with an LOD of 0.23 pg/mL and an LOQ of 0.78 pg/mL, showing potential practical detection of macromolecular proteins (Choi et al., 2022).

In another paper, Chen et al. report a defect-engineered graphene-nanoribbon (DGNR)-supported voltammetric MIP sensor for IL-6 in which a MIP recognition layer is combined with the high surface area and edge-defect electroactivity of DGNRs. Graphene nanoribbons (EGr) were used as the substrate material of the sensor, IL-6 as the template, and 1,2-diaminobenzene as the functional monomer during electropolymerization. The biosensor demonstrated a wide linearity (0.1–1000 pg/mL), an LOD of 0.025 pg/mL, reproducibility, and selectivity (Chen et al., 2024).

Finally, Siciliano et al. (2023) reported the first electrochemical MIP sensor for TGF-β1, a cytokine with complex roles in cartilage homeostasis and fibrosis. The electropolymerized P(o-PD) film on platinum microelectrodes used TGF-β1 as the template, with template removal achieved using NaOH in ethanol–water solution. The biosensor exhibited a linear range of 0.5–20 ng/mL and an LOD of 0.09 ng/mL when it was tested in both buffer solution and saliva samples with TGF-β1, enabling direct detection in saliva, an easily accessible biofluid relevant for noninvasive screening. These electropolymerized MIPs are well-suited for compact electrochemical POC devices and multiplexed electrode arrays that could be adapted to measure cytokines in synovial fluid or serum for OA phenotyping and IA therapy monitoring (Siciliano et al., 2023).

The second dominant approach is epitope imprinting MIPs, where a short peptide epitope from the target protein is used as the template, and a polymer shell is formed on an NP support. These MMIP strategies mitigate challenges associated with whole-protein imprinting, such as heterogeneous conformations and trapped templates, and enable surface-accessible, uniform binding sites with rapid kinetics. They typically use radical polymerization from acrylamide/methacrylate monomers, methacrylate cross-linkers, and thermal initiators in organic/aqueous porogens. A key example is Radfar et al. (2024), who applied an epitope-mediated magnetic MIP (MMIP) approach to develop fluorescent core–shell magnetic MMIPs for IL-6 detection. Using a surface-exposed peptide fragment of IL-6 as the template, a fluorescent poly(acrylamide) shell containing *N*-(3-aminopropyl)methacrylamide (APMA) was polymerized around magnetic Fe_3O_4 cores via radical initiation. Template removal by magnetic separation produced

core–shell MMIPs with accessible recognition sites. The resulting fluorescent MMIP achieved a practical serum LOD of 0.38 pM (linear dectection range 0.38–380 pM) in 50 % diluted human serum, demonstrating the potential for sub-pM detection in complex matrices. Epitope/MMIP NPs are therefore promising when synovial fluid sample volumes are limited and when the highest sensitivity and matrix robustness are required (Radfar et al., 2024).

Simultaneously, Yellin et al. (2023) further validated the effectiveness of protein-imprinted polymer particles in selectively adsorbing TNF-α. Polymerization was carried out by conventional radical polymerization using acrylamide as the major backbone monomer, custom tyrosine-derived functional monomers, and methylene-bisacrylamide as the cross-linker; initiators were the standard ammonium persulfate (APS)/TEMED redox pair that produces radical polymerization at room temperature. The porogenic/extraction medium was template removal/extraction was done either by SDS-PAGE extraction procedures or by multiple washes with 250 mM NaOH. *In vitro* studies demonstrated biocompatibility and reduced TNF-α-induced cell death in L929 or Caco-2 cells at 5.16–165 μg/mL (Yellin et al., 2023).

Other studies have extended MIP applications to MMP detection, as seen in work by Lee et al. (2023) and Zito et al. (2024), who developed MIP-based photonic nanostructures for MMP-1 and TGF-β, respectively. Zito et al. present an innovative photonic MIP sensor empowered by bound-states-in-the-continuum (BIC) resonances for selective, ultra-sensitive detection of TGF-β. Their approach is a photonic nanostructure functionalized with a thin MIP recognition layer (the template TGF-β protein was used during MIP formation) and read out optically by monitoring resonance peak shifts in the BIC-enhanced photonic crystal spectra. The polymer recognition layer is produced by standard MIP chemistry tailored for thin films (full formulation and curing details are in the methods section of the paper); sensing and template removal are compatible with aqueous buffer regimes and gentle solvent washes. Importantly, the device was validated in spiked saliva and reported an LOD of 10 fM and a resolution of 0.5 pM in physiological concentrations. It is important to note that the lowest LOD of 20 fM in saliva has been reported by (Sanchez et al. (2017)). An ultralow detection limit that demonstrates the potential of combining photonic BIC transduction with MIP selectivity for ultra-sensitive cytokine sensing (Zito et al., 2024).

Lee et al. report a peptide-imprinted conductive polymer deposited onto a continuous monolayer (cML) molybdenum disulfide (MoS_2) electrode to sense MMP-1. Epitope imprinting was employed with a peptide template, and electropolymerized conductive co-polymers (triphenylamine- and EDOT-type monomers co-polymerized on the MoS_2 cML). The authors report responses visible at 1.0 pg/mL and an extended usable range up to 10 pg/mL for their device. The study validated MMP-1 measurements in A549 culture medium with accuracy versus ELISA. Although originally intended for cancer, this peptide-imprint-on-2D-material architecture has the potential to be applied directly in OA because MMPs are key degradative enzymes, and this device promises ultra-low detection of this enzyme. (Lee et al., 2023).

Taken together, the electropolymerized and epitope synthesis approaches can achieve analytical sensitivities from pg/mL to sub-pM that overlap cytokine concentrations reported in human synovial fluid and serum. However, it is important to note that while several cytokine-targeting MIP studies have validated devices in buffer, serum, saliva, or spiked matrices, there are, as yet, no peer-reviewed reports applying MIP biosensors directly to synovial fluid from OA patients or to OA patient cohorts for clinical cytokine profiling. This represents an important translational gap. Systematic validation of MIP platforms in real OA synovial fluid and head-to-head comparison with immunoassays (ELISA, multiplex platforms) will be essential to demonstrate clinical utility for OA diagnosis, inflammatory phenotyping, and therapy monitoring.

For OA translational work, pick the imprinting strategy that matches the clinical need. Electropolymer films integrate easily with screen-printed electrodes, portable potentiostats, and FET architectures for rapid, POC screening and multiplexed readouts suited to clinic use or short-term therapy monitoring. Epitope, by contrast, typically provides superior matrix tolerance and extremely low LODs, which is important when sample volumes are small or when early-stage detection is required. Practical lessons across studies are consistent: electropolymerization is normally performed in aqueous buffers with ionic or alkaline template extraction (e.g., Park's alkaline wash for IL-1β; Ting's 120-min NaCl wash for IL-6), whereas radical polymerization MMIPs use defined porogens (acetonitrile/methanol blends), methacrylate cross-linkers, and thermal initiators with solvent-assisted template extraction and magnetic separation.

Looking forward, MIPs offer a unique opportunity to design multi-functional IA therapeutics for OA. Hybrid MIP composites could combine sustained release of anti-inflammatory payloads with selective sequestration or sensing of pathological cytokines and proteases, enabling closed-loop or responsive IA therapies. To realize this potential, researchers should prioritize (i) validating MIP performance in synovial fluid from OA patients, (ii) developing robust anti-fouling and extraction protocols that preserve cavity fidelity, (iii) demonstrating head-to-head parity with immunoassays in clinical samples, and (iv) evaluating biocompatibility, degradation, and clearance for particulate MIP systems in relevant OA animal models. If these steps are followed, MIP-based composites could provide both diagnostic and therapeutic advantages for targeted OA management.

The potential of MIPs in OA treatment remains largely unexplored. However, emerging studies underscore their utility in drug delivery applications with prolonged release profiles. The adaptability of MIPs for integration with various biomaterials highlights opportunities for designing innovative therapeutic strategies, particularly for inflammatory disease management. Future advancements in MIP technology could facilitate the development of multi-functional MIP composites tailored for OA treatment, combining targeted drug delivery with cytokine modulation for enhanced therapeutic efficacy.

10. Current clinical trials on IA OA therapy

Overall, clinical trials on intra-articularly administered drug delivery systems for OA are inadequate (Li et al., 2021). Clinical trials focused on OA play a pivotal role in advancing researchers' progress in understanding the effect of medical interventions on this debilitating joint disorder in humans. These trials are critical for developing and evaluating novel OA therapies, assisting researchers in gaining insights into essential parameters such as their safety, efficacy, and tolerability (Holford et al., 2000). Though a plethora of research has been conducted on IA drug delivery in OA treatment, its translation into clinical applicability is underwhelming. This failure might be because of the use of small animals for testing and the absence of best-practice standards for animal testing (Mak et al., 2014). Small animals like mice and rabbits are commonly used in *in vivo* studies and can be useful for preliminary studies; howbeit, large animals can be used for validity before conducting clinical trials in humans. Another possible reason can be the failure to simulate the environment of the joint when conducting *in vitro* tests, such as *in vitro* drug release. The wide translational gap remains an enormous hurdle, with concerns such as safety and efficacy at the forefront. As a result, the development of strategies that aim to eradicate this gap is of paramount importance. Table 4 summarizes clinical trials focused on IA drug delivery in OA (ClinicalTrials.gov).

TLC599, a liposome formulation of dexamethasone sodium phosphate (DSP), showed a significant Western Ontario and McMaster Universities Osteoarthritis Index-pain (WOMAC) reduction and improved function for up to 24 weeks in a phase 3 clinical study of knee OA (NCT02803307) (Table 4). Similarly, Cingal® is a hydrogel that was formulated as a crosslinked HA viscosupplement loaded with a corticosteroid triamcinolone hexacetonide, for IA injection (Hangody et al., 2018). Cingal® is Anika Therapeutics' next-generation formulation constructed from the base of Monovisc™, their FDA-approved non-

Table 4
List of clinical trials for IA drug delivery in OA from clinicaltrials.gov.

Product	Aim	Drug(s)	Delivery system	Type of study	Phase	OA type	Identifier
TLC 599	Evaluate the efficacy and safety	Dexamethasone sodium phosphate (DSP)	Liposomes	Randomised, double-blinded, placebo- and active-controlled	lll	Knee OA	NCT02803307
CiNGAL	Relieve symptoms and treatment	Triamcinolone Hexacetonide (TH)	Hydrogel	Randomized, double-blind, placebo-controlled	lll	Knee OA	NCT04231318
CNTX-Capsaincin 4975	Relieve OA knee pain	Capsaincin	Not applicable	Randomized, double-blind, placebo-controlled	lll	Knee OA	NCT03429049
FX006 (Zilretta®)	Efficacy and safety assessment	TCA IR 40	PNPs	Double-blind, randomized	l	Knee OA	NCT02357459
FX-201	Safety and tolerability assessment	Recombinant human interleukin-1 receptor antagonist protein	HDAd vector	Non-randomized	l	Knee OA	NCT04119687

drug-loaded HA viscosupplementation product. Clinical trial studies showed that Cingal® possessed superior WOMAC pain scores than the saline group and exhibited better pain relief for the first 3 weeks, followed by similar pain relief through the remaining 23 weeks (ClinicalTrials.gov).

Another study evaluated the safety and efficacy of high-purity synthetic trans-capsaicin (CNTX-4975) in moderate to severe knee OA (Ghouri and Conaghan, 2019). CNTX-4975 exhibited dose-dependent improvement in knee OA-associated pain through 24 weeks. FX006, a triamcinolone acetonide (TCA) formulation, encapsulated PLGA microspheres (DeJulius et al., 2021). Efficacy studies revealed that FX006 provided sustained clinical improvement in knee OA compared to saline placebo, regardless of the baseline inflammation. Studies on FX006 also showed that treatment-emergent adverse events were similar to saline, elucidating the tolerability of the drug delivery system. Generally, the results from most of the aforementioned studies showed longer duration than that reported for existing IA treatments in OA (Hangody et al., 2018; Gao et al., 2022). Table 4 summarises clinical trials focused on IA drug delivery in OA. Zilretta, the only approved drug delivery system for OA treatment, utilizes PLGA microspheres for the extended IA release of triamcinolone acetonide. In a pivotal Phase 3 randomized, double-blind trial involving 484 patients, a single 32 mg injection of Zilretta demonstrated significant pain reduction compared to placebo, with effects persisting through Week 16. Yet, limitations exist regarding repeat dosing, with regulatory labelling currently discouraging multiple administrations due to unresolved safety concerns.

11. Reducing NP toxicity by material design

While NP-mediated delivery has shown great promise for enhancing IA therapy, long-term safety remains a critical consideration that directly depends on material design. Toxicity in nanocarriers arises from multiple mechanisms, including membrane disruption, oxidative stress, complement activation, and pro-inflammatory phagocyte responses (Egbuna et al., 2021; Isibor et al., 2024).

Because the mechanisms are diverse, safer IA designs use multiple, complementary strategies to avoid those triggers and to promote predictable clearance after payload delivery. A good design workflow begins with choosing a biodegradable backbone that breaks down to non-toxic metabolites. FDA-approved polyesters such as PLGA and related copolymers such as PCL, chitosan, and gelatin are widely used for this reason. When properly formulated, they give controlled release in joints without leaving a persistent particulate burden that can lead to toxicity (Eker et al., 2024; Makadia and Siegel, 2011). Within hydrogels, incorporating labile ester or disulfide linkages introduces controlled biodegradability and prevents accumulation in the joint cavity. These features are particularly valuable in chronic diseases like OA, where repeated IA administration may otherwise lead to long-term particle retention (Dodda et al., 2023).

Surface chemistry is a dominant factor shaping cellular uptake and toxicity. Neutral or slightly negative surfaces generally show lower membrane disruption and reduced phagocytic uptake than highly cationic particles, which tend to be more cytotoxic (Sukhanova et al., 2018). Hydrophilic surface coatings reduce protein adsorption and opsonization and thus blunt early immune clearance. Coating NPs with hydrophilic or zwitterionic polymers such as PEG, HA, or poly(2-methacryloyloxyethyl phosphorylcholine) can suppress protein adsorption, extend joint residence, and improve biocompatibility (Sanità et al., 2020). Biomimetic coatings further improve local biocompatibility and can add targeting. HA coatings enhance cartilage affinity through CD44 interactions and frequently reduce synovial inflammatory responses in joint models. Cell-membrane cloaks (e.g., erythrocyte or platelet membranes) provide another biomimetic route to reduce complement activation and macrophage clearance while preserving targeting motifs (Matalqah et al., 2024).

Physical design parameters remain important levers. Particle size and shape influence joint penetration, retention, and phagocytic clearance: very small particles can diffuse away or penetrate off-target tissues, while large particles are more readily phagocytosed and may provoke local inflammation (Awashra and Młynarz, 2023). Surface roughness and ligand density also modulate cell interactions, so optimizing size, shape and surface presentation is essential for balancing retention with safety (Yang et al., 2021).

Elemental composition and redox activity also influence toxicity. Metallic or metal oxide NPs, such as silver or iron oxides, can induce ROS generation and should be either coated with inert polymers or replaced by polymeric or lipid-based carriers to minimise oxidative stress (Havelikar et al., 2024). Hybrid nanocomposites that combine inorganic cores with organic shells, such as PDA-coated silica or calcium phosphate NPs, exhibit improved stability and lower cytotoxicity compared with uncoated inorganic systems (Shakeel et al., 2022; Yanar et al., 2023).

Finally, robust, mechanism-focused preclinical testing is essential before translation. Evaluate cytotoxicity in primary human chondrocytes and synoviocytes, measure complement activation and cytokine release in human blood or synovial fluid, perform local histopathology after single and repeated IA dosing in relevant animal models, and quantify biodistribution and particulate clearance. These data guide iterative optimisation and de-risk clinical translation.

12. Manufacturing and regulatory challenges for IA delivery systems

Despite encouraging preclinical outcomes, the translation of IA delivery technologies from bench to bedside use remains hindered by intertwined manufacturing, quality, and regulatory challenges. Among these, achieving reproducibility at a GMP-compliant scale-up is often the principal technical bottleneck. The physicochemical properties of nanosystems, including particle size, polydispersity, shell thickness, drug loading, and imprint fidelity, are highly sensitive to subtle variations in critical process parameters (CPPs) such as solvent ratios, pH, mixing intensity, and oxidation conditions (ICH Q6; Lin et al., 2023).

Even slight deviations can alter critical quality attributes (CQAs), leading to inconsistent pharmacological behaviour and safety profiles (ICH Q8 R2; (Paliwal et al., 2014) Recent advances in continuous manufacturing, such as microfluidic synthesis, flash nanoprecipitation, and controlled precipitation, have demonstrated superior reproducibility compared to batch techniques and support the integration of process-analytical technology (PAT) tools for real-time monitoring and feedback control (Niculescu et al., 2022, Costa and Padrela, 2025).

Maintaining sterility and stability poses additional obstacles for IA formulations that must meet stringent parenteral product standards (Vetten et al., 2014). Many nanocarriers and hydrogel systems cannot tolerate conventional terminal sterilization by autoclaving, gamma irradiation, or ethylene oxide without compromising polymer integrity, drug release kinetics, or biological activity (Bernal-Chávez et al., 2021). These effects are particularly pronounced in polydopamine-based systems, where oxidation and cross-linking reactions are temperature- and pH-sensitive. Consequently, aseptic processing is often required, demanding specialized cleanroom environments, validated sterilizing filtration (where feasible), and rigorous environmental monitoring (Voice, 2004). Endotoxin control must comply with the limits outlined in USP < 85 > and EMA guidance, using validated limulus amoebocyte lysate or recombinant factor C assays (United States Pharmacopeia and National Formulary, 2012). Incorporating endotoxin-free reagents, depyrogenated glassware, and controlled water-for-injection systems from early development reduces downstream risk of contamination (Williams, 2019); Hannon and Prina-Mello, 2021).

Regulatory classification further complicates the translation pathway. IA nanocarriers that combine a polymer matrix, bioactive drug, and targeting or imprinting components may be regulated as drugs, devices, or combination products, and each pathway carries distinct chemistry, manufacturing, and control (CMC) requirements (Halwani, 2022). Early engagement with regulatory agencies through scientific advice meetings or pre-submission consultations helps clarify classification and streamline data expectations. Current regulatory guidance emphasizes a Quality-by-Design (QbD) framework and thorough characterization of nanomaterial attributes, including morphology, surface chemistry, stability, and biodistribution (ICH Q9, Q10) (Metselaar and Lammers, 2020). The use of orthogonal analytical techniques such as dynamic light scattering (DLS), electron microscopy, FTIR/Raman spectroscopy, and chromatographic assays remains essential for verifying consistency and demonstrating structure–function relationships across batches (Altammar, 2023).

A cohesive QbD-based development strategy links all these elements, including process design, analytical validation, and regulatory planning, into a single control framework. Early identification of CQAs (size, PDI, drug loading, imprinting factor, sterility, endotoxin), together with mapping of CPPs (mixing energy, solvent ratios, pH, temperature, residence time), allows the establishment of robust design spaces supported by statistical design-of-experiments and process control (ICH Q8; ICH Q9). Demonstrating CQA equivalence between lab and scaled batches using orthogonal analytics and stability data significantly de-risks translation. Such proactive alignment of manufacturing and regulatory strategies is increasingly expected by agencies evaluating advanced nanomedicines and IA combination products.

13. Summary

In OA, nano- and micro-formulations as well as hydrogel-based delivery systems have emerged as promising alternatives to conventional treatments. These systems offer the potential for more localized and sustained release of bioactives, which may allow for reduced dosing frequency compared to current therapies such as HA and corticosteroids (Huang et al., 2022). By encapsulating therapeutic agents, these platforms may enhance local drug concentration within the joint, potentially improving therapeutic outcomes and reducing systemic exposure. Still, these advantages remain largely demonstrated in preclinical settings, and conclusive evidence in human clinical trials is still limited.

In vitro and *in vivo* studies have shown that various nano- and hydrogel-based formulations can reduce the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and iNOS. Such anti-inflammatory effects have been associated with a delay in OA progression. Moreover, certain hydrogel systems have been observed to facilitate macrophage repolarization from the M1 to the M2 phenotype, suggesting an immunomodulatory role (Pérez and Rius-Pérez, 2022; Strizova et al., 2023).

Additionally, these delivery systems have been associated with the inhibition of matrix-degrading enzymes like ADAMTS-5, MMP-1, MMP-3, and MMP-13 in preclinical studies (Kumar et al., 2019; Liu et al., 2019; Park et al., 2020; Wei et al., 2021). This inhibition has corresponded with signs of cartilage preservation and even regeneration in some animal models (Li et al., 2021a; Mou et al., 2021; Xu et al., 2021).

Importantly, one potential clinical advantage of these platforms is the possibility of prolonged IA retention and sustained drug release, which may reduce the frequency of IA injections. While some formulations have demonstrated extended release in synthetic synovial fluid and animal models (Hu et al., 2020b; Teng et al., 2023; Dravid et al., 2023), long-term retention and release profiles in human joints remain to be fully validated.

Hydrogels also offer mechanical benefits in OA therapy by acting as joint lubricants and shock absorbers, which may help reduce pain and inflammation (Gan et al., 2024). Their ability to be engineered with stimuli-responsive properties such as pH or temperature-triggered sol--gel transitions enhances their potential for site-specific drug delivery and safety by minimizing the risk of off-target effects (Kung et al., 2023; El-Husseiny et al., 2023; Neumann et al., 2023). Incorporating nano- or microparticles into hydrogels can confer both structural and therapeutic benefits, enabling dual functionality in controlled drug release and joint cushioning.

While these delivery strategies present exciting opportunities, further studies, particularly clinical trials in humans, are required to confirm their translational potential and therapeutic superiority over existing IA treatments.

14. Future research perspectives

This review explored a selection of developments and advancements in IA therapies for the treatment of OA. The investigation also sheds light on the innovative strategies and therapeutic modalities developed to overcome the complexities of this prevalent and incapacitating joint disorder. It is evident that studies mostly focus on articular cartilage, but there are other hallmarks that not only affect the primary progression of the disease but also secondary developments, such as subchondral bone remodeling. A comprehensive understanding of the disease would benefit the advancement of therapies.

There have been remarkable developments in IA therapies, including viscosupplementation and sustained-release injections, which involve modern methods of nanomedicine. While NPs and microparticles provide a promising platform for IA drug delivery in the treatment of OA, it is, however, noted that incorporating the drug-loaded particles into a hydrogel achieves superior biological results. These IA strategies remain central because they concentrate therapeutics at the disease site, reduce systemic exposure, and can be engineered to release cargo in response to local biochemical cues; nonetheless, taking a broader view of targeting reveals complementary systemic approaches that deserve brief mention.

Systemic targeting strategies now reported in the literature include antigen-specific immunomodulation, biomimetic NPs that home to injured cartilage after intravenous dosing, molecular targeting of degenerated matrix, macrophage-directed antioxidant liposomes, and systemically administered cell-based therapies with protective “backpacks.” For example, tolerogenic NPs that present COL2 epitopes can induce collagen-specific regulatory T cells and ameliorate OA in preclinical models, demonstrating that systemic immune reprogramming is

a feasible, disease-modifying strategy (Sohn et al., 2022). Similarly, biomimetic NPs have been engineered to reach cartilage lesions after systemic administration and to concentrate at sites of cartilage trauma, offering a route to treat diffuse or multifocal disease without repeated IA injections (Mancino et al., 2023). Targeting the degenerating matrix itself is another emerging tactic: collagen-hybridizing peptides and related ligands selectively bind denatured cartilage collagen and thereby improve local delivery and efficacy of therapeutics administered systemically (Fei et al., 2024). In parallel, macrophage-targeted liposomal antioxidants have been used to reduce synovial oxidative stress and inflammation after systemic dosing, pointing to approaches that modulate the joint microenvironment indirectly via immune cells (Zhao et al., 2024). Finally, systemically administered cell therapies are being optimized by "backpacking" MSCs with protective nano-payloads that preserve cell function in the oxidative, inflammatory joint milieu, an approach that enhances engraftment and reparative activity (Xu et al., 2025).

Together, these systemic strategies complement IA platforms in two useful ways. First, systemic targeting can reach multiple affected joints or subclinical lesions that are impractical to treat with repeated IA injection. Second, systemic immunomodulation or macrophage-directed therapy can reprogram the inflammatory milieu and thereby improve the performance of subsequently delivered IA depots or regenerative implants. However, systemic approaches introduce distinct translational challenges: ensuring sufficient joint selectivity to avoid off-target immunosuppression, controlling biodistribution and clearance, and demonstrating long-term safety (for example, risks of immune tolerance induction or persistent modulation of systemic immunity).

15. Conclusions

The body of evidence reviewed here demonstrates that advanced IA delivery systems from NPS, hydrogels, and MIPs can effectively modulate inflammation, protect cartilage matrix, and promote repair in preclinical OA models. Translating these promising platforms into clinical practice will require coordinated efforts on safety-by-design, standardized validation tests, and pragmatic manufacturing strategies. Head-to-head comparisons and well-designed early-phase clinical trials are needed to confirm efficacy, optimize dosing, and assess long-term safety in patients. With these steps, multifunctional delivery systems have realistic potential to move beyond symptomatic relief toward genuinely disease-modifying OA therapies.

CRediT authorship contribution statement

Atang Motaung: Writing – original draft, Methodology, Investigation, Data curation. **Thankhoe A. Rants'o:** Writing – review & editing, Supervision, Formal analysis. **Pavan Walvekar:** Writing – review & editing. **Piotr Lulinski:** Writing – review & editing, Validation, Supervision, Conceptualization. **Yahya E. Choonara:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yahya Choonara reports financial support was provided by National Research Foundation. Yahya Choonara reports a relationship with National Research Foundation that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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