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Recent advances in intra-articular drug delivery systems for osteoarthritis therapy

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Highlights:

1. Precision medicine is necessary to treat multiple facets of osteoarthritis
2. Disease-modifying osteoarthritis drugs (DMOADs) and drug delivery systems (DDSs) are discussed
3. DMOADs should be combined with adequate DDSs for long-term intra-articular (IA) therapy
4. Clinical trials of small molecules delivered by IA injections are summarized
5. Hydrogels, liposomes, nanoparticles and microparticles are reviewed

Teaser: Optimized intra-articularly administered drug delivery systems associated with potent disease-modifying osteoarthritis drugs that can stop and/or reverse osteoarthritis evolution represent a promising approach for effective therapy.

Osteoarthritis (OA) is the most common degenerative disease of the joint. Despite many reports and numerous clinical trials, OA is not entirely understood, and there is no effective treatment available for this disease. To satisfy this unmet medical need, drug delivery systems (DDSs) containing disease-modifying OA drugs (DMOADs) for intra-articular (IA) administration are required to improve the health of OA patients. DDSs should provide controlled and/or sustained drug release, enabling long-term treatment with a reduced number of injections. This paper reviews the role and

interaction among different tissues involved in OA and summarizes recent clinical trials and research on DDSs, focusing on small-molecule delivery. To achieve an ideal treatment, various key criteria have been identified to design and develop an IA DDS matching the clinical needs.

Keywords: Osteoarthritis; drug delivery; intra-articular; DMOAD; carriers; polymers.

Introduction

Osteoarthritis (OA) is the most common type of arthritis and degenerative joint disease. OA is a leading cause of chronic disability and progressively affects cartilage, the synovial membrane, bone and periarticular tissues [1–3]. Knees, hips, fingers and the lower spine region are frequently affected by the occurrence of OA inducing chronic pain, inflammation and stiffness. Age, trauma, occupation, exercise, gender, ethnicity, genetics, obesity, diet and bone density are risk factors for the incidence and development of OA. The WHO estimates that 9.6% of men and 18.0% of women aged over 60 years have symptomatic OA [4,5]. Eighty percent of OA patients will have limitations in movement and 25% cannot perform major daily activities. Among people over the age of 70 years, 40% suffer from OA in the knee. The estimated medical care cost in the USA for 27 million diagnosed osteoarthritis patients is US$185.5 billion per year (US$6870 per patient) [6]. The average total annual cost of OA per patient is similar in Europe, ranging from €1330 to €10 452 [7].

The objective of this review is to discuss elements of OA physiopathology and recent advances in long-term treatment options involving intra-articular (IA) drug administration. Because biopharmaceuticals (e.g., peptides and proteins >10 kDa) are rarely stable over long periods of time [8], we have focused this review on small molecules (<10 kDa) that could provide IA treatment over extended periods without requiring frequent re-injections. Additionally, this review identifies potent drug delivery systems (DDSs) for OA treatment in the body's major joints (e.g., knee, hip), based on clinical needs.

OA physiopathology

A clear understanding of joint anatomy and OA physiopathology is necessary to design new treatments for OA patients (Figure 1). Healthy joints are composed of two bones covered by cartilage and, depending on their mechanical role, these joints are stabilized by ligaments, muscles and/or menisci [9]. The IA space is surrounded by a capsule, the synovial membrane, that retains synovial fluid. The cells of these different tissues express various biomarkers [10] maintaining the fragile homeostasis of IA tissues, which ensures the efficient function of the joint. In OA patients, only a few joints are affected and progressively impacted by the disease. Disease evolution is associated with cartilage damage and loss, bone outgrowth (osteophytes) and attrition, subchondral bone (sclerosis and cysts) alterations, synovial tissue inflammation and altered synovial fluid properties [11].

Interdependence can be found among the mechanisms involved in the subtypes of primary OA (idiopathic, intrinsic; i.e., genetic determination, hormone dependence and aging) and secondary OA (extrinsic; i.e., trauma and metabolism, e.g., obesity, crystal-induced). The tissue first involved at the onset of the disease is unknown but several biological mechanisms and biomarker levels enable a partial understanding or appreciation for the interactions occurring among OA joint tissues [3,12,13].

The cartilage matrix chronologically suffers from several injuries. First, small fibrillations, which are vertical clefts extending just below the superficial layer, followed by the partial loss of surface lamina, and, later, vertical clefts and calcified cartilage erosion appear. During these structural changes, essential components of the cartilage [extracellular matrix, e.g., collagen type 2 and aggrecan (proteoglycan)] that offer tensile strength and compressive resistance are affected. These components are cleaved by molecular cues and molecular signals such as matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase with thrombospondin motifs (Adamts), aggrecanases or cathepsins. At the same time, various proinflammatory cytokines, such as interleukins (IL) or tumor necrosis factor (TNF)α, are secreted by chondrocytes, the constitutive cells of cartilage. Cytokines, with the help of chemokines, stress-related factors and extracellular matrix degradation products trigger articular cartilage and synovial tissue degradation, leading to chronic inflammation and systemic joint failure. Additionally, nuclear factor (NF)-κB promotes the expression of catabolic factors by synovial fibroblasts and macrophages and the hypertrophic chondrocyte phenotype, leading to cartilage destruction. Furthermore,

chondrocytes express growth factors, for example the transforming growth factor (TGF)-β superfamily, that induce angiogenesis, leading to osteophyte formation, and control chondrocyte metabolism, such as MMP production. In addition, various angiogenic factors secreted by chondrocytes, such as vascular endothelial growth factor (VEGF), have been shown to play a key part in the penetration of blood vessels into hypertrophic cartilage during endochondral ossification in the processes of angiogenesis.

The subchondral bone and epiphysis are directly impacted by ossification and vascular penetration. Trabecular bone architecture changes and its volume tends to decrease, yielding to cortical bone. In OA, evident imbalanced activity of osteoblasts, which synthesize bone, and osteoclasts, which breakdown bone tissue, leads to bone densification and altered morphology. Bone densification, compression and erosion lead to sclerotic bone, subchondral cyst and osteophyte formation at advanced stages of OA, inducing severe pain for the patient.

The synovial membrane, composed of two or three layers of synoviocytes, plays a key part in homeostasis and in maintaining joint lubrification by secreting biomacromolecules, such as hyaluronic acid (HA) and lubricin (proteoglycan 4), into the synovial fluid for cartilage. The synovial membrane is also the major barrier and interface between the IA space and the rest of the body. Blood vessels irrigate the synovial membrane and participate in delivering nutrients to avascular cartilage. In synovial membranes affected by OA, immune cells, such as T cells, neutrophils and macrophages, surge and induce the expression of cytokines, chemokines (e.g., TNFα, IL-1, IL-6, IL-15) and inflammatory mediators (e.g., nitric oxide, prostaglandin E) that are responsible for cartilage breakdown and inflammation. The inflammation is also caused by poor synovial fluid drainage by the altered lymphatic vessels of OA patients.

The volume of the knee synovial fluid of a healthy human is ~1 ml. This fluid is mainly composed of water, HA, lubricin, dialyzed blood plasma and mucopolysaccharides, mineral salts, small molecules (glucose, uric acid and bilirubin) and proteins. HA and lubricin provide viscoelasticity to the fluid. Synovial fluid delivers oxygen and nutrients (glucose) to avascular cartilage and clears metabolites (lactate, carbon dioxide). In OA patients, synovial fluid composition is altered and indirectly reflects the disease condition [14].

OA is not a single disease but rather the result of a variety of disorders that lead to structural or functional failure of joints. Additionally, multifactorial interactions occur between cartilage and the surrounding tissues. Research on the mechanisms involved is very active and should make it possible to find new therapeutic targets to treat OA [15]. For instance, disease-modifying osteoarthritis drugs (DMOADs), which are drugs that inhibit the structural disease progression of OA and ideally also improve OA symptoms and/or joint function, have been discovered in the past few decades and will be reviewed here.

Diagnosis and current treatment

Currently, after anamnesis and physical examination of patients, an OA diagnosis is conventionally established by X-ray imaging, which is widely considered the gold standard, by MRI or by joint fluid analysis [16,17]. Additionally, optical coherence tomography (OCT) has the potential to be a minimally invasive prognostic biomarker for OA in the future [18]. Treatment options depend strongly on OA severity and the pain felt by the patients. Usually, the first option is treating the symptomatic pain. Analgesics (i.e., paracetamol), nonsteroidal anti-inflammatory drugs (NSAIDs) [19] (i.e., meloxicam, diclofenac, naproxen), specific cyclooxygenase (COX)-2 inhibitors [20] (i.e., celecoxib) and, rarely, opioids are used for systemic drug therapy. NSAIDs, COX-2 inhibitors and opioids present with a significant risk profile and with side-effects on the bowel, heart or brain. With disease progression, the second option is IA injections in addition to oral and topical treatment. Viscosupplementation with HA improves joint function [21]. IA injections of corticosteroids (i.e., dexamethasone, methylprednisolone acetate, triamcinolone acetate) [22] of autologous chondrocytes onto eroded cartilage [23,24], and of platelet-rich plasma [25], are the next and last options before hip or knee arthroplasty. All in all, the treatment options available are only symptomatic, and no disease-modifying therapies are available that stabilize or revert OA progression. Pharmaceutical treatment options are suboptimal, inducing several side-effects and requiring frequent administrations, and invasive surgery offers a solution for only a limited number of years. For these reasons, there is a great need for disease-modifying treatments.

Clinical needs

Key issues for developing successful and effective treatments include the selection, formulation and administration of appropriate DMOADs that are consistent with the primary or secondary OA subtypes. In fact, IA injections are preferred as the last nonoperative modality. IA injections present advantages, such as the delivery of the drug to the active site with limited adverse side effects. Several small molecules have been investigated in clinical trials (Table 1) or are under development (Table 2) and seem to be promising.

IA injections

Because OA affects only a limited number of joints, local treatment administered through the IA route is an appropriate strategy. In 1951, Hollander *et al*. introduced for the first time the IA injection in arthritic joints with hydrocortisone [26]. Compared to oral administration, this technique avoids systemic exposure and potential adverse side effects [27]. Indeed, IA injections enable the delivery of the right dose to the right place (i.e., tissues affected by OA). In addition, the IA route is an attractive alternative modality for delivering drugs with low oral bioavailability. However, injections into joints present some risks and rare complications, such as bacterial infection, bleeding, allergic reaction, nerve damage and synovial membrane inflammation [28]. Various studies have concluded the cost-effectiveness of IA treatments versus conventional therapies [29–31]. For instance, the cost per quality-adjusted life years (QALY) gained with IA HA injections ranges from US$ 5785 to US$9039 compared with US$10 716 for conventional care [30].

CNTX-4975 [32]
SAR113945 [33]
Spiflomin [34]
Corticosterone [35]
Methylprednisolone-acetate [36]
Kondrium [37,38]
Traumeel [39]

Investigated small molecules for OA

As described previously, OA has a complex pathophysiology that is not yet fully understood. Many pathways are involved in disease progression through the various tissues that constitute the joint. For a while, pharmaceutical research has invested in finding solutions for patients, and many active pharmaceutical ingredients (APIs) have been tested in preclinical and clinical trials. Small molecules that have been delivered by IA injection in clinical trials are presented in Table 1. From a pharmacological perspective, APIs can be classified according to tissue-specific

therapeutic targets. Therefore, the APIs mentioned in the following sections relieve pain or are considered disease-modifying treatments for OA (DMOADs), which control local inflammation, targeting cartilage and bone.

Relieving pain

Potential new drugs with a high efficacy for pain relief are being investigated in ongoing clinical trials. CNTX-4975, a derivative of capsaicin that stimulates unmyelinated C-fiber afferents, resulting in the secretion of substance P, has reached clinical Phase IIb. Patients (*n* = 175) affected by chronic moderate-to-severe knee pain receive a single CNTX-4975 dose via IA injection. The results revealed a rapid and efficient reduction in pain occurring over 24 weeks compared with placebo. As many as 67% of patients experienced a reduction in pain of ≥50%, and 22% of patients reached a ≥90% reduction.

MEN16132 is a selective non-peptide bradykinin B2 receptor antagonist that significantly reduces synovial bradykinin and prostaglandin E2 levels [32] and has a long duration of action in OA rat models [33]. A completed clinical trial evaluated the efficacy of MEN16132 following IA knee joint administration in OA patients, but no results have been published yet. GZ389988 is a small molecule targeting the nerve growth factor (NGF) by inhibiting tropomyosin-receptor-kinase A (TrkA). A Phase II trial is recruiting patients after successful pharmacokinetic, safety pharmacology, preclinical toxicology and clinical Phase I studies.

Verapamil is a calcium ion influx inhibitor and suppresses Wnt/β-catenin signaling in human OA chondrocytes. IA administration of verapamil inhibited OA progression in an OA rat model [34]. However, a Phase II study conducted to evaluate IA verapamil for the treatment of knee OA was terminated by the sponsor without justification. Other APIs aim to target specific tissues, such as the synovial membrane (inflammation), cartilage or bone. Some DMOADs are presented in Table 2 and seem to offer great potential for reducing or stopping OA progression.

DMOADs that control local inflammation

Several APIs targeting innovative pathways were unsuccessful in proving their efficacy. SAR113945 inhibits the NF-κB signaling pathway, which might seem to be an attractive way of treating patients with signs and symptoms of OA. The preclinical

study and the results of clinical Phase I appeared promising, but the Phase IIa study failed to show an effect in a larger patient sample size. Additionally, PH-797804, a potent p38 mitogen-activated protein kinase (MAPK) inhibitor, was investigated in a Phase II trial (NCT00620685) via oral administration in patients with rheumatoid arthritis but failed to demonstrate bioactivity after 2 weeks [35]. Another Phase II clinical trial (NCT01102660) is currently ongoing to examine knee-pain relief following the oral administration of PH-797804 versus naproxen in OA patients. In addition to small molecules, biopharmaceutical inhibitors (e.g., infliximab, etanercept [36], anakinra [37]) of proinflammatory cytokines (e.g., TNFα, IL-1) and reactive oxygen species [38] inhibitors are potential DMOADs, targeting the inflammatory pathways of the synovial membrane.

DMOADs that target cartilage

Growth factors {e.g., TGF-β [39], bone morphogenetic protein (BMP)-7 [40], fibroblast growth factor-18 [41], platelet-rich plasma [42]} stimulate cartilage anabolism. Sprifermin, a recombinant human fibroblast growth factor 18 (rhFGF18), was investigated for the treatment of symptomatic knee [43]. The results from clinical Phase I (NCT01033994) showed no statistically significant dose–response in a change in central medial femorotibial compartment cartilage thickness at 12 months. However, a dose-related treatment effect of sprifermin on the cartilage was observed.

In 2012, a screening of 22 000 molecules identified a small molecule called kartogenin that was able to induce chondrogenesis (EC_{50} = 100 nM) [44]. This discovery confirmed in two OA mouse models that kartogenin has great potential for human cartilage repair. Protease inhibitors of MMP (e.g., doxycycline hyclate) and Adamts, inducible nitric oxide synthase (iNOS) inhibitors (e.g., cindunistat) and cell signaling pathway inhibitors (e.g., MAPK, p38 MAPK, c-Jun N-terminal kinase, extracellular signal-regulated kinases) are the major classes of compounds able to inhibit cartilage catabolism.

DMOADs that target bone

Several DMOADs are inhibitors of bone resorption. Calcitonin salmon regulates calcium homeostasis and inhibits MMP activity and cartilage degradation. However, the results from two Phase III trials of oral calcitonin salmon (NCT00704847 and

NCT00486434) failed to demonstrate clinical benefits in patients with symptomatic knee OA [45].

For bisphosphonates, able to retard subchondral bone remodeling, a recent meta-analysis of randomized controlled trials highlighted the limited evidence for their efficacy [46]. For instance, a dose of 2 g per day of strontium ranelate decreased radiographic cartilage volume loss and bone marrow lesions in knee OA. In addition, the occurrence of side effects was evidenced by osteophyte overgrowth [47] in a medial meniscectomized guinea pig model. Additionally, protease inhibitors, such as MMP-13, cathepsin K, osteoprotegerin and receptor activator of NF-κB ligand inhibitors, play a fundamental part in bone resorption. As an example, in December 2016, MIV-711, a cathepsin K inhibitor administered orally once daily, succeeded in a Phase IIa clinical trial study (NCT02705625). Bone formation can also be stimulated by parathyroid hormone, selective estrogen receptor modulators or estrogens [48].

Finally, several clinical trials with small molecules delivered by IA injection were run to fulfill the unmet medical need (Table 1). Interestingly, the drugs that entered clinical trials are mainly glucocorticoids or anti-inflammatory agents. Indeed, pain is the primary target symptom of OA considered by the pharmaceutical companies. Some clinical trials failed to demonstrate the efficacy of APIs (i.e., SAR113945: inhibition of NF-κB signaling, sprifermin: rhFGF18). However, there are some promising DMOADs based on clinical trials and literature for IA therapy of OA, such as kinin B2 receptor antagonists (MEN16132) and transcription factor CBFβ (kartogenin). In the past decade, new and effective DMOADs have been discovered and investigated in clinical trials. However, owing to the long-term disability associated with OA, the major advances in the field need new technologies to treat OA successfully. Therefore, novel and efficient DDSs designed for IA administration must be explored.


IA drug delivery systems

Without a DDS, small molecules injected intra-articularly are cleared rapidly from the IA space. Free drugs are removed from joints within a few hours or less by lymphatic drainage. For instance, the half-lives of methotrexate, ibuprofen and diclofenac are

0.59–2.9, 1.9 and 5.2 h, respectively [49]. Direct drug modification, such as PEGylation, or the synthesis of lipophilic prodrugs are strategies to delay systemic drug elimination and increase drug bioavailability [50], but these methods are not sufficient to provide extended activity over weeks or months. In addition to clearance issues, recent APIs are mostly small lipophilic molecules, classified as class 2 drugs by the biopharmaceutical classification system. This means they are highly insoluble in aqueous media and form a crystal suspension. Long-acting crystal suspension introduces the risk of crystal deposition in the joint and potentially unpleasant crystal synovitis. Therefore lipophilic drugs require an appropriate formulation. Hydrogels, liposomes, nanoparticles and microparticles have been proposed as drug carriers, enabling release over extended periods of time. Furthermore, DDSs composed of biodegradable or bioeliminable materials are required to avoid accumulation of materials that could by themselves induce inflammation or other adverse effects. To this end, 32 studies published between 2007 and 2018 were analyzed (Table 3).

Hydrogels

Hydrogels are preparations containing water-swollen natural or synthetic polymeric materials that can contain APIs and that maintain a distinct 3D structure [34]. HA is a component of the SF and provides protection against cartilage surface wear [51]. Several HA formulations have been commercialized as lubricating and viscosupplementation agents. As a biopolymer, HA appears to be an appropriate compound for developing IA DDSs. Amphotericin B [52] and piroxicam [53] were loaded into HA hydrogels. In both cases, the frequency of injections was reduced compared with that of free drugs. However, HA only slightly improved the retention time of drugs dispersed or dissolved in the biopolymer. Indeed, injected HA by itself has a short half-life in the IA space. For instance, HA with a molecular weight of 3 000 000 Da has a half-life of 13.2 h [54]. One way to improve the retention time at the injection site is to modify HA chemically. For example, Maudens *et al.* developed a thermosensitive HA hydrogel able to form *in situ* nanoparticles. This thermoreversible HA-poly(*N*-isopropylacrylamide) (pNiPAM) improved injectability and IA retention over months and protected cartilage [55].

In addition to thermoresponsive HA, Betre *et al.* designed elastin-like peptides (ELPs), forming *in situ* aggregates that are used to repair cartilage, as a DDS [56,57].

Miao *et al.* synthesized another thermosensitive polymer, a triblock poly(ethylene glycol)-poly(caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG), which improved methotrexate retention in the joint [58]. Alternatively, chitosan, a natural polymer, can form a viscous hydrogel *in situ* in the presence of polyols and could be an ideal thermosensitive DDS candidate for OA [59,60].

Additionally, other viscous hydrogels have been investigated and developed. A triblock copolymer approach was studied by Petit *et al.*, who incorporated celecoxib into a poly(caprolactone-co-lactide)-poly(ethylene glycol)-poly(caprolactone-co-lactide) (PCLA-PEG-PCLA) hydrogel thus providing a biocompatible DDS that remained in healthy horse knees for up to 28 days [61]. If we exclude HA gels for viscosupplementation, no hydrogels are currently commercially available or used as carriers for the IA delivery of drugs.

Liposomes

Liposomes efficiently entrap hydrophobic drugs in their lipophilic outer bilayer (or phase) or hydrophilic molecules in their core. Owing to their structure, liposomes provide slow and controlled drug content release [62]. In addition, compared to crystalline drug suspensions, they reduce the incidence of inflammatory reactions after local injections [63]. Various studies have reported the use of liposome formulations for IA delivery. For example, VX-745, chondroitin sulfate and celecoxib present with an improved drug residence time in liposomes compared with that of the free drug [64–67]. Edwards *et al.* developed a 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)-based liposome to provide a drug delivery system with extended IA retention time. The iodinated CT contrast agent iohexol was used as a model drug. The half-life of liposomal iohexol was 124 h after IA injection into the knees of sheep, whereas iohexol in solution was undetectable at 3 h post injection.

A single IA injection of dexamethasone-loaded liposomes (TLC599) was developed and tested in humans to treat knee OA. Positive results from Phase I/II trials showed no severe adverse effect regarding the safety profile and significant pain control at week 12 (Table 1). Today, only one liposomal corticosteroid product is commercialized. It is available only in Germany (Lipotalon®, Merckle). Lipotalon® is composed of dexamethasone-21-palmitate dissolved in soya bean oil within a lecithin shell. Liposomes are certainly well tolerated. However, owing to their vesicular

morphology and high water content, which resembles that of cells, they do not generally have sufficient mechanical resistance to cope with the high pressures found in joints. Another disadvantage is that liposomes have a limited ability to load lipophilic APIs and are less physically stable than other DDSs [68]. In addition to liposomes, several polymeric particles have been formulated and tested as potential DDSs for the treatment of OA. Owing to their matrix structure type, they can be better suited than liposomes to provide extended drug delivery.

Nanoparticles

Nanoparticles composed of biodegradable polymers or lipids are solid drug carriers that can encapsulate lipophilic APIs to prevent their fast release. Solid lipid nanoparticles, mainly composed of glycerol or Pluronic® F68, which are unable to form liposomes, were loaded with celecoxib and calcitonin salmon [69,70]. The results revealed that, after IA injection, nanoparticles reduced blood levels compared with the blood levels after free drug administration, thus confirming the extended-release properties of these carriers.

Morgen *et al.* demonstrated the feasibility of using cationic polymeric nanoparticles with a diameter of 100–150 nm and composed of poly(caprolactone) (PCL) and poly(ethylene oxide) (PEO) diblock copolymer crosslinked with anionic HA (dextran) for OA therapy. After IA injections in rat knees, 70% of nanoparticles were retained in the joint for 1 week [71]. Another study reported on the delivery vehicle for cationic peptides. Indeed, Lin *et al.* formulated PEGylated pNIPAM nanoparticles with degradable disulfide crosslinks to deliver anti-inflammatory peptides into chondrocytes. The results of this study revealed a passive targeting of inflamed cartilage *ex vivo* and a suppression of inflammation in various cell types [72].

Nanoparticles can be useful in the short-term to target a specific antigen, and they can also be internalized by phagocytosis into cells [73]. A study investigated the ability of nanoparticles to target cartilage. Indeed, Bajpayee *et al.* demonstrated the efficacy of avidin, a highly positively charged nanocarrier with a half-life of 29 h, to penetrate the full thickness of cartilage, which was achieved via the negative charge of proteoglycans [74].

Overall, nanoparticle-based delivery systems have the potential to increase drug residence times. Pradal *et al.* demonstrated that nanoparticles with 300 nm

diameters were partly eliminated from the joint capsule in 8 days by the microvascular pathway [75]. In another study, Kang *et al.* confirmed that chitosan nanoparticles presented with a shorter retention time in the knee joint than microparticles after IA injection into OA rats [76]. Therefore, besides targeted nanoparticles, larger microparticles could be a potential strategy for delivering drugs over a prolonged period, matching OA needs as this disease progresses.

Microparticles

Numerous publications describe the use of poly(lactic acid) (PLA), poly(lactic-co-glycolic) (PLGA) or poly(caprolactone) (PCL) for the formulation of microparticles (i.e., particles having a mean size above 1 µm). These polymers are already approved by the FDA and EMA (European Medicines Agency) for microparticles used in other therapeutic fields (e.g., Sandostatin LAR®, Ozurdex®, Trelstar®, Decapeptyl®). The degradation of the byproducts of these biodegradable, controlled drug delivery carriers is well-known and safe [77,78]. For example, sulforaphane [79], etoricoxib [80], quercetin [76], anti-TNFα protein [81], rhein [82] and dexamethasone-21-acetate [83] were encapsulated in PCL or PLGA microparticles and were observed in the joints for up to 4–10 weeks after the IA injection. Indeed, Arankumar *et al.* demonstrated the IA retention of PCL microparticles for 6 weeks by using *in vivo* fluorescence imaging [80]. Additionally, Bedouet *et al.* investigated microspheres of a methacrylic derivative of ibuprofen with oligo(ethylene glycol) methacrylate and poly(PLGA-PEG) dimethacrylate and observed slow DDS degradation at 4 weeks after the IA injection in sheep [84]. Janssen *et al.* investigated celecoxib-loaded polyester amide (PEA) microspheres for the treatment of pain associated with knee OA [85]. This study suggested that, in an OA rat model, PEA microspheres are DDSs with autoregulatory behavior that are retained in the joints at least for 3 months after IA injection. Indeed, the presence of alpha-amino acids in PEA makes this DDS vulnerable to degradation by proteolytic enzymes, which degrade proteoglycans in OA [86].

These studies demonstrated that the residence time in the joint space is size-dependent. There is some evidence that microparticles control drug release over a more prolonged period than other DDSs. Nevertheless, the released dose is limited by drug loading, which is often low in these DDSs, thus requiring multiple injections.

Chen *et al.* explored the ability of brucine embedded in chitosan microspheres dispersed in a chitosan hydrogel to reduce the burst effect [87]. Even though the microspheres had a high drug loading of 17% (w/w), 70–80% of the brucine was released *in vitro* over 60 h. To further improve drug loading and sustained release, Maudens *et al.* formulated nanocrystal-polymer particles (NPPs). Up to 31.5% (w/w) of PH-797804 [88] or kartogenin [89] nanocrystals were embedded by spray-drying in a PLA fluorescent matrix. At 3 months, 20–62% of the drug had escaped *in vitro* from the polymeric matrix. This biocompatible DDS enabled drug bioactivity 2 months after IA administration in an OA mechanistic mouse model.

Advances with microparticles for OA have enabled the company Flexion Therapeutics to reach clinical trials with the extended-release formulation of triamcinolone acetonide loaded into poly(lactic-co-glycolic acid) (PLGA) particles that are 45 µm in diameter (FX006) (Table 1). In a Phase IIb clinical trial, two doses of FX006 (20 mg and 40 mg) were compared with a placebo in patients (n = 100 per group) presenting with moderate-to-severe OA knee pain. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) revealed substantial, persistent pain relief until 12 weeks post-treatment. A Phase III clinical trial is recruiting patients to prove the potential benefit compared with a placebo in large patient groups.

In summary, IA injections of drug-loaded DDSs are a highly attractive strategy for OA therapy. Based on the scientific literature, only microparticles provide an adequate, extended retention time for drugs (several months) and controlled and/or sustained release that is long enough to ensure drug bioactivity in the joints over a therapeutically useful period (Figure 2). In this view, hydrogels, liposomes and nanoparticles seem to be promising for targeting tissues (e.g., cartilage, synovial membrane) but are not as efficient as sustained DDSs. Small molecules (<10 kDa) and macromolecules (>10 kDa) escape the joint cavity via blood vessels and lymphatic vessels, respectively. The retention time of free drugs and DDSs in the joints was investigated in several studies. Encapsulated or covalently bound fluorophores were used to analyze retention time and biodistribution by intravital imaging of DDSs [74,75,80,89,90]. In a recent study aiming to select the ideal particle size for IA injections, nanoparticles (300 nm) were eliminated by synovial macrophages and tended to be cleared from the joints too quickly [75]. By contrast, microparticles (~10 µm) are optimal, and larger microparticles (~25 µm) might

promote inflammation. It was also observed that the rate of nano- or micro-particle removal from the joint is increased in the inflamed joint compared with the healthy joint, reflecting enhanced drainage from the joint space as a result of increased synovial lymph flow. In addition, the material used to formulate DDSs and the degradation products could induce adverse effects such as an inflammatory reaction. For example, poly(L-lactic acid) (PLLA) has a slower degradation rate and causes a lower inflammatory response than poly(glycolide) (PGA) [91].

Preclinical considerations in OA

Sterilization is essential for clinical drug use [92]. Only a few studies explored the sterilization of novel DDSs by autoclaving [52,61], γ-irradiation [81] or filtration [56,93], mostly because mice or rats do not formally require sterile formulations because rodents have a more resistant immune system compared with that of larger animals (United States Pharmacopeia 71). A recent article emphasized that radiation sterilization seems to be a promising technique for polymeric DDSs [94].

Once an adequate biocompatible polymer matrix and formulation with specific characteristics for joint persistence have been identified, OA treatments should provide efficient pharmacokinetic profiles over days, weeks or months. To reproduce homeostasis in the human joint, *in vitro* drug release studies are crucial. In the majority of studies, drug-release kinetic studies were carried out in PBS at 37°C with stirring under sink conditions according to European Pharmacopoeia 8.0 (7.17). To accelerate *in vitro* the release of poorly soluble drugs, in the absence of serum proteins, some studies some studies used surfactants such as polysorbate (Table 3) [64,81,83].

Cytotoxicity of experimental DDSs is conventionally evaluated in synoviocytes [76,81], Hl-60 cells [85], RAW 264.7 cells [95], fibroblast-like synoviocytes [64,89] or chondrocytes [74,79,90,96,97] at different concentrations using a viability test related to mitochondrial activity (i.e., WST-1, MTT). Only a few studies presented more-reliable evidence regarding *in vivo* biocompatibility. For instance, subcutaneous injections into the skin of animals, according to international standard ISO 10-993 guidelines [55], or IA injections [58,69,76,84,87] were investigated to evaluate DDS reactivity. Moreover, various *in vivo* models have been used in preclinical studies to reproduce or reflect OA complexity, which changes phenotypes during the disease

evolution. Animal models currently used to study OA can be classified according to the human OA features that they closely reflect [98–100]. Surgical induction models, such as anterior cruciate ligament transection (ACTL) or destabilization of the medial meniscus (DMM), are widely used. Additionally, inflammatory models induced by IA injections, such as collagen-induced arthritis (CIA), antigen-induced arthritis (AIA) or monosodium iodoacetate (MIA) models, focus on OA pain. These surgically and chemically induced OA models mimic the mechanistic and inflammatory facets of the disease.

Concluding remarks

OA therapy via IA-administered DDSs offers many advantages and benefits to stop and/or reverse the evolution of OA, resulting in a promising approach for effective therapy. Indeed, compared with oral administration, reduced side effects and toxicity, limited organ exposure and controlled API release are valuable assets. Various carriers, materials and methods are available to design a specific DDS with extended release over several months. In fact, biodegradable microparticles offer the best characteristic for prolonging sustained API release and retention time in the joint space. Nanoparticles are ideal candidates for tissue-specific targeting. An effective and efficient DDS that is associated with a highly active DMOAD is an essential combination toward precision medicine in OA. Rapid advances in medicine and biotechnology drive the field of drug discovery and lead to the development of highly potent and target-specific drug candidates. Potent DMOADs are able to control local inflammation and target cartilage and bone catabolic processes. Ongoing research on OA biomarkers, new DMOADs, promising DDSs, preclinical models and clinical trials will certainly lead to new treatment schemes that can fulfill this medical need that affects millions of people worldwide.

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Olivier Jordan

Olivier Jordan was trained in physical engineering at the Swiss Federal Institute of Technology Lausanne (EPFL) in Lausanne. During his PhD at Aebischer's lab and later at the University of Geneva, he became an expert in biomaterials for drug delivery. He owns nine patents, two of which are in the field of gel technology and have led to clinical applications. He has authored 55 peer-reviewed publications.

Eric Allémann

Eric Allémann was trained in pharmaceutical sciences. Since 1990, he has been involved in nanomedicine formulation. After his PhD, a postdoc and several years as a research associate, Dr Alléman joined Bracco Research as head of exploratory research. Since 2009 he has been the Chair of Pharmaceutical Technology at the

Geneva–Lausanne School of Pharmacy. He is (co-)inventor of 12 international patents and has 100 publications.

Figure legends

Figure 1. Schematic comparison of a healthy and osteoarthritis (OA) joint. OA involves inflammation, a loss cartilage, bone damage (osteophyte formation) and pain in the joints (the figure was produced using Servier Medical Art).

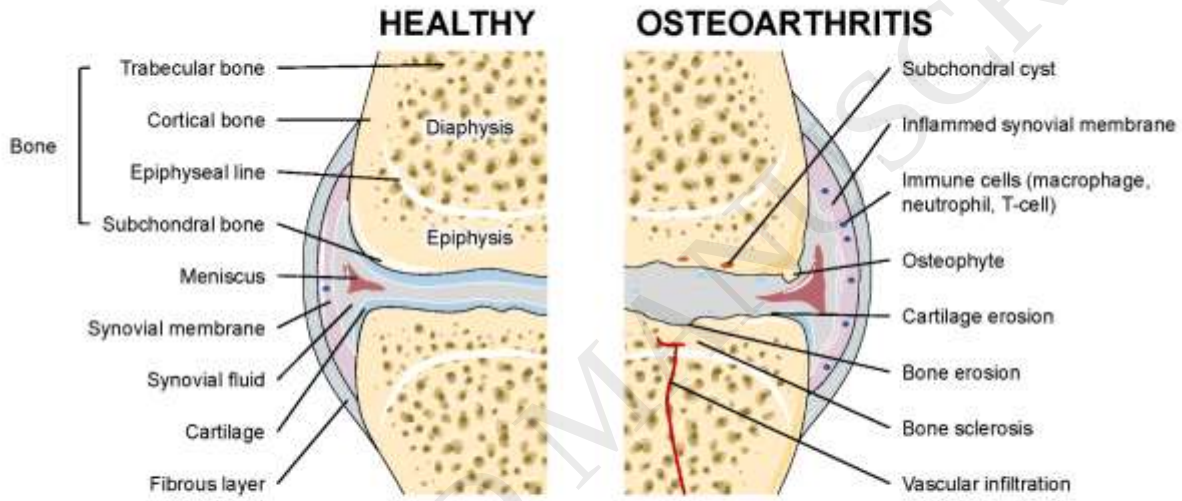

Figure 2. Schematic representation of the retention time and clearance of various biodegradable osteoarthritis (OA) drug delivery systems (DDSs) after intra-articular (IA) administration. Free drugs, hydrogel, nanoparticles and microparticles remain in the joint for hours, days, weeks and months, respectively. Macromolecules (>10 kDa) and small molecules (<10 kDa) are eliminated by two different routes from the joint space (the figure was produced using Servier Medical Art).

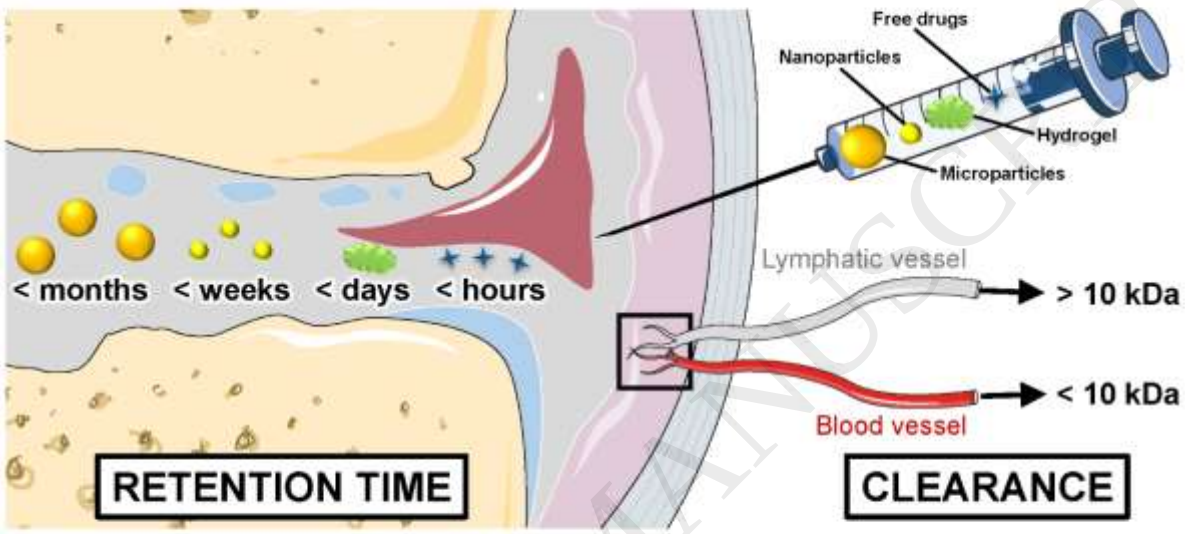

Table 1. Clinical trials of small molecules (alone or in association with a DDS) delivered by IA injection as currently listed on www.clinicaltrials.gov

Drug *vs.* comparator	API class	Study name; ClinicalTrial.gov identifier	Indication	Sponsor / collaborators	Study phase	Study types	Status	Refs[a]
CNTX-4975	DMOAD – relieving pain – targeting the capsaicin receptor (TRPV1)	Safety and tolerability of 4975 in the treatment of moderate to severe knee pain due to OA; NCT00667654	OA of the knee	Centrexion Therapeutics	Phase II	Non-randomized, open label	Completed, Dec 2016	[101]
MEN16132 *vs* placebo	DMOAD – relieving pain – kinin B_2 receptor antagonist	A locally injected bradykinin antagonist for the treatment of OA; NCT01091116	OA of the knee	Menarini Group	Phase II	Randomized, double-blind	Completed, Jan 2013	np
Fasitibant (MEN16132) *vs* placebo	DMOAD – relieving pain – kinin B_2 receptor antagonist	Fasitibant IA injection in patients with symptomatic OA of the knee; NCT02205814	OA of the knee	Menarini Group	Phase II	Randomized, double-blind	Completed, Oct 2015	np
Verapamil *vs* placebo	DMOAD – relieving pain – Wnt/β-catenin inhibitor	Safety, tolerability and efficacy of IA verapamil in the treatment of joint pain in subjects with OA of the knee; NCT01645709	OA of the knee	Calosyn Pharma, Inc.|Health Decisions	Phase I / Phase II	Randomized, double-blind	Terminated, Aug 2014	np
GZ389988 *vs* acetaminophen or paracetamol *vs* combination of paracetamol + codeine *vs* fixed combination of paracetamol + tramadol hydrochloride	DMOAD – relieving pain – tropomyosin-receptor-kinase A (TrkA) receptor antagonist	Proof-of-concept study to assess the efficacy, tolerability and safety of a single IA dose of GZ389988 *vs* placebo in patients with painful OA of the knee; NCT02845271	OA	Genzyme, Sanofi	Phase II	Randomized, double-blind	Completed, Sep 2017	np

SM04690 *vs* placebo	DMOAD – relieving pain – Wnt pathway inhibitor	A study evaluating the safety, tolerability and efficacy of SM04690 injected into the target knee joint of moderately to severely symptomatic OA subjects; NCT02536833	OA	Samumed LLC	Phase II	Randomized, double-blind	Completed, Nov 2017	np
SAR113945 *vs* placebo	DMOAD – inflammation relief – IκB kinase inhibitor (upstream of NF-κB signal transduction cascade)	Safety of single doses of SAR113945 and efficacy and safety of a new formulation given into the knee in OA patients; NCT01598415	OA of the knee	Sanofi	Phase II	Randomized, double-blind	Completed, Oct 2014	[102]
Sprifermin *vs* placebo	DMOAD –stimulating cartilage anabolism - rhFGF18	A multicenter study of rhFGF 18 in patients with knee osteoarthritis not requiring surgery; NCT01033994	OA of the knee	Merck KGaA	Phase I	Randomized, double-blind	Completed, Jun 2014	[43]
FX005 *vs* carrier *vs* placebo	DDS (PLGA microparticles) of p38 MAPK inhibitor	Study of FX005 for the treatment of pain in patients with OA of the knee; NCT01291914	OA of the knee	Flexion Therapeutis, Inc.	Phase I / Phase II	Randomized, double-blind	Completed, Feb 2013	np
FX006	DDS (PLGA microparticles) of triamcinolone acetonide (glucocorticoid)	Study to assess the safety of repeat administration of FX006 administered to patients with OA of the knee; NCT03046446	OA of the knee	Flexion Therapeutics, Inc.	Phase III	Single group, no masking	Active, not recruiting, Oct 2017	np
TLC599 *vs* placebo	DDS (liposomes) of dexamethasone (glucocorticoid)	A Phase IIa, randomized, double-blinded, placebo-controlled, dose-finding study for single dose administration of TLC599 in patients with OA of the knee; NCT03005873	OA of the knee	Taiwan Liposome Company	Phase II	Randomized, double-blind	Active, not recruiting, Jan 2018	np
Corticosterone *vs* HA *vs* bupivacaine	Glucocorticoid	Comparison of HA and corticosteroid IA injections for the treatment of OA of the hip; NCT01079455	OA of the hip	University Hospital Pellenberg	Phase III	Randomized, double-blind	Unknown status, Mar 2010	[103]
IA *vs* IM injection of cortisone	Glucocorticoid	Effectiveness of facet joint infiltration in low back pain; NCT01447160	OA - low back pain	Federal University of São Paulo	Phase III	Randomized, double-blind	Unknown status, Oct 2011	np

Methylprednisolone-acetate (cortisone derivative) *vs* lidocaine *vs* placebo	Glucocorticoid	Preoperative IA injection of methylprednisolone in patients scheduled for total knee-arthroplasty; NCT02253966	OA of the knee	Rigshospitalet, Denmark|Lundbeck Foundation	Phase II	Randomized, double-blind	Completed, Jun 2016	[104]
Kondrium *vs* kondrium-F *vs* methyl prednisolone (corticosteroid)	Relieving pain – sodium bicarbonate and calcium gluconate	Evaluation of a new formulation useful for the OA treatment; NCT00977444	OA	Nucitec|National Council of Science and Technology, Mexico	Phase II / Phase III	Randomized, double-blind	Unknown status, Jan 2010	[105,106]
Traumeel® + Zeel® injectable solution *vs* placebo	Relieving pain – anti-inflammatory, antiedematous, antiexudative combination formulation	Study of IA injections *vs* placebo in patients with pain from OA of the knee; NCT01887678	OA of the knee	Biologische Heilmittel Heel GmbH	Phase III	Randomized, double-blind	Completed, Mar 2018	[107]

[a]Results published as of April 2018. Abbreviations: np: no publication; OA: osteoarthritis; IA: intra-articular; IM: intra-muscular; DDS: drug delivery system; HA: hyaluronic acid; PLGA: poly(lactic-co-glycolic acid); API: active pharmaceutical ingredient; TRPV1: transient receptor potential vanilloid 1; rhFGF18: recombinant human fibroblast growth factor 18; MAPK: mitogen-activated protein kinase

Table 2. Mode of action and physicochemical characteristics of a selection of DMOADs for OA treatment

API	Therapeutic target	Mode of action	Molecular weight (Da)	pKa[a]	Log P[a]	CAS number	Refs
CNTX-4975 (trans-capsaicin)	Relieving pain	Targeting the capsaicin receptor (TRPV1)	305.42	-1.42; 9.93	3.75	404-86-4	[101]
MEN16132	Relieving pain	Kinin B2 receptor antagonist	764.78	8.14; 8.74	-0.5	869939-83-3	[108]

GZ389988	Relieving pain	TrkA receptor antagonist	470.52	4.11	3.54	1788906-96-6	[109]
Verapamil	Relieving pain	Wnt/β-catenin inhibitor	454.61	9.68	5.04	52-53-9	[110]
SM04690	Relieving pain	Wnt/β-catenin inhibitor	505.56	5.18; 8.67	4.66	1467093-03-3	[111]
PH-797804	Inflammation relief	p38 MAPK inhibitor	477.3	-0.72; 14.79	4.24	586379-66-0	[112]
Sprifermin	Cartilage - stimulating Anabolism	rhFGF18	296.41	4.33	3.9	890058-52-3	[113]
Kartogenin	Cartilage-stimulating anabolism	Transcription factor CBFβ	317.34	2.91	4.37	4727-31-5	[44]
Cindunistat (SD-6010)	Cartilage-inhibiting catabolism	iNOS inhibitor	219.3	2.46; 11.68	-2.61	364067-22-1	[114]
Doxycycline hyclate	Cartilage-inhibiting catabolism	MMP inhibitor	512.94	2.13; 6.25	-2.38	24390-14-5	[115]
Calcitonin salmon	Subchondral bone	Bone resorption inhibitor	3431.85	3.86; 11.85	-28.83	47931-85-1	[96]
Strontium ranelate	Subchondral bone	Antiosteoporotic agent	513.49	1.69	0.27	135459-87-9	[116]

[a]Predicted from chemicalize.com. Abbreviations: TrkA, tropomyosin-receptor-kinase A; rhFGF18, recombinant human fibroblast growth factor 18; CBFβ, core binding factor β; MAPK, mitogen-activated protein kinase; iNOS, inducible nitric oxide synthase; API, active pharmaceutical ingredient.

Table 3

Type of DDS	Author/ year	Polymer	Entrapped API	Particle diameter	Drug loading % (w/w)	*In vitro* drug release	Animal	Model or study	Outcome	Refs
Hydrogel	Park 2014	HA	Piroxicam	Ø	20–80[a]	Half-life from plasma = 6–9 h	Rats (n = 8 per group)	MIA model	Therapeutic efficacy of co-treatment (Piroxicam + HA)	[53]
Hydrogel	Guo 2015	HA + glyceryl mono-oleate	Amphotericin B (antifungal agent)	Ø	0.1[a]	~70% at day 40[a] (PBS, pH 7.4, 37°C)	Rabbits (n = 4 per group)	Healthy rabbits, synovial fluid analyzed	*In situ* gel offers sustained release reducing the frequency of injection	[52]
Thermosensitive hydrogel	Miao 2011	PCL-PEG-PCL	Methotrexate	Ø	25–30 % (w/v)	58.9–74.0% in 15 days (PBS, pH 7.4, 37°C)	Rats (n = 6 per group)	Healthy rats	Thermosensitive hydrogel is able to slow down the clearance of the drug	[58]
Thermogelling polymer forming microaggregates	Setton, Betre 2007	ELPs (pentapeptides)	Anti-inflammatory agent/14C (radiolabeled agent)	n/a	n/a	Half-life from joint = 3.37 h (gel) and 87.6 h (aggregates)	Rats (n = 5 per group)	Healthy rats	*In situ* aggregates allow a longer IA half-life	[56,57]
Thermosensitive hydrogel-forming NPs	Maudens 2018	HA-pNiPAM	Dexamethasone	~200 nm	0.06 (solubility limit)	~60% in 28 h (PBS, pH 7.4, sodium dodecyl sulfate, 37°C)	Mice (n = 7 per group)	DMM model	Injectable HA derivative forming *in situ* NPs improves IA retention time	[55]
Hydrogel	Petit 2015	PCLA-PEG-PCLA	Celecoxib	Ø	5–26 % (w/v)	Drug detected in SF at day 28 (*in vivo*)	Horses (n = 5; two different injections per horse)	Healthy horses	*In situ* forming hydrogel well tolerated, injectable	[61]
Hydrogel	Chen 2015	Phytantriol	Sinomenine hydrochloride	Ø	0.6	80%[a] at 24 h (PBS, pH 7.4, 37°C)	Ø	Ø	Injectable and isotonic *in situ* forming a viscous crystalline gel	[93]
Oil vehicle	Thing 2012	Medium-chain triglyceride	Glucosamide esters of naproxen (prodrug) / ropivacaine hydrochloride	Ø	<1 % (w/v)[a]	10–50% at 300 h, tested with 2 different settings (SF or PBS, 37°C)	Ø	Ø	Fast conversion of lipophilic prodrug in SF	[117]

Hydrogel and MPs	Son 2015	HA and PLGA	Methotrexate and/or dexamethasone or IR-780 iodide (dye)	52 ± 9 µm	0.0375 – 4.5 % (w/v)[a]	Ø	Rats (number n/a)	CIA model	Simultaneous injection treatments are more efficient for RA repair	[95]
LPs	Edwards 2007	DPPC	Iohexol (contrast agent)	3.88–4.43 µm	n/a	Half-life from joint = 134 h	Sheep (n = 3–5 per group)	Healthy sheep	Pharmacokinetics and biodistribution studies performed in larger animal model	[118]
Solid lipid NPs	Thakkar 2007	Glycerol	Celecoxib	257 nm	<4	95% in 7 days (PBS, Tween 80, pH 7.4, 37°C)	Rats (n = 3 per group)	AIA model	The animal model does not provide long-term evaluation of DDS	[69]
Solid lipid NPs	Jain 2014	Pluronic F68 + SA + citric acid + lecithin	Diacerein (prodrug of rhein) / ChS	396 nm ± 2.7	15.59 % (w/v)	40% at 4 h (PBS, pH 5.8, 37°C)	Rats (n = 8 per group)	Chemically induced model of OA	ChS helped home the agent to articular cartilage for drug targeting	[70]
Nanocarrier (protein)	Bajpayee 2014	Avidin	Ø	7 nm	Ø	Half-life of avidin in cartilage = 24 h	Rats (n = 6) / bovine	Healthy rats / knee explants (*ex vivo*)	Avidin (high positive charge) allows cartilage targeting	[119]
NPs	Ryan 2013	HA + chitosan	Salmon calcitonin	163–193 nm	10 % (w/v)[a]	70–80% in 6 h (PBS)	Mice (n = 5)	CIA model	NPs more efficient than solution or hydrogel, reduced inflammation and preserved bone and cartilage	[96]
NPs	Lin 2016	pNIPAM-PEG	KAFAK (anti-inflammatory peptide)	223 µm ± 9.7	34.6 ± 3.7	7 % at 24 h (PBS, pH 7.4)	Bovine	Knee explants (*ex vivo*)	Cartilage penetration, reducted inflammation in cartilage explants	[72]
NPs	Morgen 2013	PCL-PEO + HA	Dye	100–150 nm	<20–25	Ø	Rats (n = 4)	Healthy rats	Cationic NPs linked to HA increase the IA retention time	[71]
NPs and MPs	Kang 2014	Chitosan	Kartogenin	150 nm ± 39; 1.8 µm ± 0.54	0.05	30–50% in 7 weeks (PBS, pH 7.4, 37°C)	Rats (n = 8 per group)	Surgically induced OA model	DDS induces more efficient chondrogenic differentiation	[90]
NPs and MPs	Pradal 2015	PLGA or PLA	VX-745 (p38 MAPK inhibitor)	0.34–25.39 µm	<2	40–80% at day 84 (NaCl, Tween 80, pH 7, 37°C)	Mice (n = 5 per group)	AIA model	Promising DDS of p38 MAPK inhibitor for IA pain and inflammation	[64]

MPs	Butoescu 2009	PLGA + SPIONs	Dexamethasone-21-acetate	1 µm; 10 µm	<4[a]	50% in 24 h (PBS, Tween 80, sodium azide, pH 7.4, 37°C)	Mice (n = 5)	AIA model	Superparamagnetic microparticles for IA retention of drug	[83,120]
MPs	Natarajan 2011	PCL	Quercetin	61–311 µm	1-89–3.95	50% in 62–355 h (PBS, pH 7.4, 37°C)	Rats (n = 3)	Healthy rats	Promising biocompatible DDS for IA administration	[76]
MPs	Chen 2012	Chitosan	Brucine	2.45 µm	<17[a]	70–80% at 60 h[a] (PBS, pH 7.4, 37°C)	Rats (n = 6) / rabbits (n = 4 per group)	Healthy rats	Biocompatible DDS (synovium) for several treatment days	[87]
MPs	Ko 2013	PLGA	Sulforaphane	14.5 µm ± 0.81	<1[a]	6% at day 30 (PBS, 37°C)	Rats (n = 12 per group)	ACLT model	Injectable DDS delayed the progression of OA	[79]
MPs	Tezcaner 2014	PCL or PEG-PCL-PEG	Anti-TNFα protein	4.9–5.3 µm	3.75[a]	93% of biologically active protein at day 90 (PBS, Tween 20, sodium azide, pH 7.4, 37°C)	Ø	Ø	DDS provides long-term controlled release of proteins	[81]
MPs	Janssen 2016	PEA	Celecoxib (COX-2)	10–100 µm	Ø	50% at day 76 (PBS, pH 7.4, 37°C)	Rats (n = 7 per group)	ACLT + pMMx model	Auto-regulating and safe DDS for the treatment of pain	[121]
MPs	Arunkumar 2016	PCL	Etoricoxib or IR-780 iodide (dye)	16.26 µm ± 10.14	2.67–3.46	91% at day 20 (PBS, pH 7.4, 37°C)	Rats (n = 4)	Synovial drug clearance study	IA retention of microparticles (without drug) >1 month	[80]
MPs	Gomez-Gaete 2017	PLGA	Rhein (anti-inflammatory properties)	4.23 µm ± 0.87	0.81–1.6	45% at 24 h (NaCl, pH 7.4, 37°C)	Ø	Ø	Preliminary study suggests the potential anti-inflammatory benefit *in vivo*	[82]
MPs	Goto Norio 2017	Gelatin + PLGA	Fluvastatin	~25 µm[a]	3.1	27.5% in 7 days (PBS, pH 7.4, 37°C)	Rabbits (n = 5)	ACLT model	Potential DDS of statin for chondroprotection	[97]
MPs	Maudens 2018	PLA or PLGA	PH-797804 / Dexametha-sone-21-acetate (nanocrystals)	10–15 µm	~30	From 20 to 60 in 3 months (PBS, pH 7.4, sodium dodecyl sulfate, 37°C)	Mice (n = 7 per group)	AIA and DMM model	Nanocrystals of drug encapsulated inside MPs allow long-term treatment	[88]

MPs	Maudens 2018	PLA	Kartogenin (nanocrystals)	13.4 µm	31.5	62% in 3 months (PBS, pH 7.4, sodium dodecyl sulfate, 37°C)	Mice (n = 7 per group)	DMM model	Promising DDS of DMOAD for chondroprotection and chondrogenesis	[89]
MPs	Bédouet 2014	Oligo(ethylene-glycol) MA and poly(PLGA-PEG) diMA	S-(+)-ibuprofen	40–100 µm	19 mol%	13% in 3 months (NaCl, Tween 80, pH 7, 37°C)	Sheep (n = 7)	Articular cartilage and joint capsule explants (*ex vivo*)	Promising drugs candidate for the loading	[122]

[a]Estimation suggested from the reading of the publication. Abbreviations: OA, osteoarthritis; IA, intra-articular; MPs, microparticles; NPs, nanoparticles; LPs, liposomes; PBS, phosphate buffered saline; DDS, drug delivery system; SF, synovial fluid; HA, hyaluronic acid; DPPC, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine; PCL, poly(caprolactone); PLGA, poly(lactic-co-glycolic acid); PLA, poly(lactic acid); PCLA, poly(caprolactone-co-lactide); PEG, poly(ethylene glycol); PEA, poly(ethyl acrylate); ELPs, elastin-like peptides; pNiPAM, poly(N-isopropylacrylamide); MIA, monosodium iodoacetate; CIA, collagen-induced arthritis; AIA, antigen-induced arthritis; DMM, destabilization of the medial meniscus; ACTL, anterior cruciate ligament transection; DMOAD, disease-modifying osteoarthritis drug; pMMx, partial medial meniscectomy; ChS, polysaccharide chondoitin sulfate; SA, stearic acid; PEO, poly(ethyleneoxide); API, active pharmaceutical ingredient; MA, methacrylate.