

Intra-Articular Drug Delivery Systems for Arthritis Treatment

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Background

Arthritis, including osteoarthritis (OA) and rheumatoid arthritis (RA), remains one of the major challenges in medical research and the clinic [1]. For both conditions, damage of cartilage matrix and inflammation are significant symptoms. Although no prevention treatment is known, pharmaceutical approaches are available to reduce or revise joint damage and inflammation. The administration of drugs is achieved through orally, parenterally or intra-articularly. Because of the degradation nature of many drugs (like recombinant proteins) and the limited blood flow in cartilage, oral or parenteral delivery of a drug to an affected joint suffers the difficulty of reaching high bioactive drug concentrations at the site of action with limited systemic side-effects [2-4]. Therefore, intra-articular administration is considered as the most effective way for the treatment of joint diseases or disorders.

Intra-articular drug delivery is a method to apply drug substances or therapeutic composites into the joint cavity. Important to note, drug biodistribution following delivery is quite different from systemic administration or local injection into many other tissues or organs. The diarthrodial joint is surrounded by a highly vascularized synovial membrane that efficiently filters most solutes and drugs in the intrasynovial joint space; with an intra-articular concentration that is generally proportional to plasma concentrations [5]. The synovium also secretes large amounts of hyaluronan and low-molecular-weight solutes and may secrete proinflammatory cytokines and catabolic proteases in the case of arthritis. Additionally, diffusion from intrasynovial spaces into the capillary bed and extrasynovial interstitial spaces is also known to occur, although lymphatic drainage may be the principal route for eliminating many molecules from the joint space. Previous study showed that low-molecular-weight solutes (<500 Da) may persist for less than 1 h after injection in the joint space, whereas those greater than 1 kDa have residence times in the order of hours [6]. The large fat pads in the joint space may retain larger molecules, including a majority of microparticles, leading to sustained presence and delayed (or enhanced) lymphatic clearance. According to these characteristics, several feasible approaches have been developed for intra-articular drug delivery (such as direct injection, polymer encapsulation and nano-device delivery). Each technique has its own advantages and trade-offs.

Intra-Articular Drug Delivery Systems

To apply drugs into joints, the most simple and straight-forward method is direct injection. Such method is attractive since relatively high drug concentrations can be delivered directly at the main desire site and the systemic side effects are minimized compared to oral delivery. Especially, evidences have shown that most small molecular weight and some high molecular treatment substances can diffuse into cartilage matrix via articular injection [7-8]. Therefore, aspirating and injecting the knee or other joints is a common technique for both diagnostic and therapeutic purposes. However, the downside of direct injection of drugs includes: the lack of accessibility of the joint, infection, post-injection flare, crystal-induced synovitis, cutaneous atrophy and steroid arthropathy [9-11]. Moreover, a more important concern is how long the drug can stay at the desired place. Although post-injection rest is required in order to increase the residence time of the administered substance [12], depending on the chemical structures of drugs, some active compounds are rapidly cleared from the joint,

thus requiring numerous injections, which could cause infection or joint disability [13]. Therefore, direct injection is the simplest method to intra-articularly deliver drugs but not the most effective one.

To overcome the shortcomings of the direct injection, researchers and clinicians have developed to use polymers to encapsulate drugs. Such polymers usually present good biocompatibility and adhesion on the articular cartilage. With the degradation of the polymer, encapsulated drugs can release from polymer composites for their designed functions. In this manner, residence time and efficacy of drugs can dramatically increase. Today, many natural or synthetic polymers have been used for this purpose: poly (lactic-co-glycolic acid) (PLGA) [14], albumin [15], chitosan [16], and silk [17]. Beside drug encapsulation, polymeric materials are also widely used for molecular modification to increase the compound's molecular weight, such as PEGylation, as we have seen for the TNF antagonist etanercept [18], or by molecular crosslinking, as we have seen for hyaluronan [19]. More interestingly, some materials have environmentally responsive properties. For example, an elastin-like polypeptide was modified to a thermosensitive gel. After injection to a joint, because of the change of temperature, such materials can intra-articularly form to a "drug depot" to elongate drug release [20].

Beyond the promise and significance of using polymer encapsulation for intra-articular delivery, many have noticed the importance of not only delivering drugs "onto" articular cartilage surface but also "into" its matrix to influence cells in the deeper zone. Therefore, the latest development of intra-articular delivery relies on nano-devices. Nano-delivery vehicles are built on various materials (including polymers). Different from traditional drug encapsulation, they are well-fabricated to have uniformed nano-sizes and structures. Benefit from their large surface area and high reactivity, they can also be tailored to carry a high density of drugs or conjugate functional molecules (like antibody for target delivery or environmentally responsive components). Most importantly, they are small. Since a dense collagen network in cartilage has roughly 60 nm pore size, large therapeutic molecules or polymer composites are difficult to get into cartilage, even for fibrillar molecules, the largest molecule reported before can pass into cartilage is collagen X (~138nm) [21]. Thus, nano-devices with well-controlled sizes are promising for this application. For example, nanoparticles coated with collagen II-binding peptide were shown by fluorescence measurement a 14.9-fold preferential accumulation of 38-nm mean diameter nanoparticles within the cartilage relative to 96-nm diameter ones. Such results demonstrated the importance of limiting particle size to enhance drug permeation into cartilage. Moreover, nano-devices can present multiple functions other than playing as a drug carrier.

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For example, superparamagnetic iron oxide nanoparticles (SPIONs) fabricated with dexamethasone loaded PLGA can be directed by a magnetic field and they achieved a joint residence time of at least 3 months [22-23]. Of course, the complex functions and structures of nano-devices also increase the difficulty and cost to synthesize them. Especially, the toxicity of nano-devices is a new and important issue [24].

Discussion and Conclusion

As discussed in this article, current intra-articular drug delivery techniques are not satisfactory. Direct injection is the most developed method. However, it has significant limitations in drug retention time and efficiency. Polymer encapsulation can slowly release the therapeutic substances, but it does not really assist those bioactive molecules get into cartilage matrix. Nano-devices are the newest approach with a great potential to avoid all shortfalls and accomplish multiple functions at the same time. However, the difficulty in fabrication and the lack of study in toxicity limit the clinical applications of nano-devices. In summary, with the pharmaceutical development to treat rheumatoid arthritis and osteoarthritis, the need for a more effective and safer intra-articular drug delivery system is huge. This is a complicated but very promising area. New breakthroughs in intra-articular drug delivery will bring great value for arthritis treatment.

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