Polymeric Nanoparticles and Conjugates
For Site-Specific Drug Retention

Novel Platform Releases Medicine over Time, Reducing Required Frequency
Of Intra-Articular Injections for Osteoarthritis

Overview
Drug administration directly to the joint via intra-articular injection is an attractive delivery method for treating osteoarthritis. However, improving drug retention within the joint after injection is an unmet technical challenge.

Bend Research has developed a novel drug-delivery platform that addresses this issue, increasing the retention of medicine at the intended site of action and reducing the frequency of injections patients must receive.

The approach involves the use of positively charged polymeric nanoparticles or positively charged drug/polymer conjugates that form crosslinked hydrogels with hyaluronate, a naturally occurring negatively charged biopolymer, within the synovial cavity. These hydrogels increase the retention time of therapeutic agents in the targeted joint. The architecture of the drug-containing nanoparticles is shown in Figure 1 and described below.

In a recent study, we demonstrated improved retention of a fluorescent model drug using the nanoparticle platform. In this test, 70% of the drug was retained for 1 week after injection into rat knees. In contrast, drug disperses within 1 to 2 days with most current injectable formulations.

The gelling mechanism on which this novel drug-delivery platform is based has been demonstrated in vitro using synovial fluid of osteoarthritis patients and should be applicable to a wide range of small-molecule compounds for other indications. Development of the technology is proceeding and Bend Research is seeking partners to advance new medicines using this new technology.

Background
With the aging of the U.S. population, the prevalence of arthritis is expected to increase in the coming decades. By the year 2030, the number of adults is expected to increase to 67 million (from 42.7 million in 2002). Of this 67 million, 25% is expected to be diagnosed with arthritis.

Management of osteoarthritis currently focuses on controlling the symptoms. The most common treatment—nonsteroidal anti-inflammatory drugs (NSAIDs)—has experienced dramatic growth, with COX-2 inhibitors taking increasing market share from older drugs. However, the greatest unmet need in osteoarthritis treatment is for disease-modifying osteoarthritis drugs (DMOADs).

While promising DMOADs have been identified, these molecules are often not suitable for systemic administration. Intra-articular administration of a DMOAD directly into the affected joint offers several advantages over oral dosing because this delivery approach can be used with medicines that are (1) not absorbed well, (2) cleared too quickly following systemic administration, or (3) systemically toxic.

The biggest challenge to overcome is increasing the retention time of the DMOAD after intra-articular injection. Most agents are rapidly cleared from the joint after intra-articular injection. For example, the residence time for NSAIDs may be as short as 1 to 5 hours after local injection (Owen et al., 1994). The cost of treatment, patient reluctance for repeated injections, and complications (such as infection, post-injection flare, crystal-induced synovitis, cutaneous atrophy,
and steroid atrophy) are frequently reported (Butoescu et al., 2009).

The nanoparticle and drug-conjugate delivery platforms developed by Bend Research address these issues, offering targeted drug delivery to the affected joint and retention of nanoparticles for more than 1 week.

**Approach**

Our approach employs positively charged polymeric nanoparticles or positively charged drug-polymer conjugates to form crosslinked hydrogels with negatively charged hyaluronate, which occurs naturally in the synovial cavity, to improve the retention time of therapeutic agents in joints after intra-articular injection.

The nanoparticle carriers consist of one or more polymers. Figure 1 shows an example architecture, in which the nanoparticles are comprised of two polymers: a neutral (i.e., uncharged) core polymer and a cationic (i.e., positively charged) surface polymer. The drug molecule can be incorporated covalently or noncovalently into the uncharged nanoparticle core. It is the surface polymer that interacts with the hyaluronate in the joint to form an ionically crosslinked gel (Figure 2). The gel acts as a depot that slows drug escape from the knee cavity.

![Optical Micrograph of Gel Formed from Fluorescently Labeled Nanoparticles Mixed with Synovial Fluid of Human Osteoarthritis Patients](image)

To demonstrate proof of feasibility, a cationic poly(methacrylate) and ethyl cellulose were used as models for core polymers with a positively charged surface and uncharged surface, respectively. Derivatized dextrans—either cationically substituted for use as the surface polymer or substituted with neutral hydrophobic fatty-acid ester groups for use as the core polymer—were also tested, since they are expected to be biodegradable, offering an improved safety profile. Uncharged polyethylene glycol (PEG) nanoparticles were used as a control.

In *in vitro* testing, the release of the cationic nanoparticles into the synovial fluid of human osteoarthritis patients was much slower than that of uncharged PEG nanoparticles. The rate of *in vitro* hydrolysis of an ester-conjugated peptide from the dextran polymer was approximately 20% per week, and the crosslinked hydrogels did not appreciably alter the viscosity of the synovial fluid.

In *in vivo* tests, cationic nanoparticles increased the retention time of peptide active in the joint after intra-articular injection into the knees of rats compared to a solution containing the peptide.

Results are shown in Figure 3 for the gelling nanoparticles and an uncharged free peptide active (used as a control). As the figure shows, 70% of the nanoparticles were retained in the joint for 1 week after injection, demonstrating improved retention over free peptide. These results clearly demonstrate the utility of this novel delivery platform in achieving and sustaining targeted delivery of drug-containing nanoparticles.

![Relative Fluorescent Signal of Gelling Nanoparticles and Free Peptide Control](image)

**Status**

Bend Research is seeking partners with promising compounds that could benefit from this novel drug-delivery platform. Development work to demonstrate the utility of this approach is continuing.
**References**


**About Bend Research**

For more than 35 years, Bend Research has worked with clients to create value by advancing new medicines that improve human health and to solve their most difficult scientific and technical problems. This success is based on the company’s ability to develop, advance, and commercialize pharmaceutical technologies, which grow from a solid base of scientific and engineering fundamental understanding. Bend Research is a leader in novel formulations, including spray-dried dispersion (SDD) and hot-melt extrusion (HME) formulations, as well as controlled-release, inhalation, and biotherapeutics technologies.

Bend Research is now part of Capsugel’s Dosage Form Solutions business unit headquartered in Morristown, N.J., providing access to additional technologies, R&D capabilities, and global manufacturing infrastructure for the advancement of client compounds from concept through clinical to commercial manufacture.

Bend Research has more than 250 employees based in six state-of-the-art facilities in Bend, Ore., USA, and is part of the global Capsugel network of 3,100 employees.

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