ALBUMIN NANOPARTICLES FOR INTRA-ARTICULAR DELIVERY OF CELECOXIB TO TREAT OSTEOARTHRITIS

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Background: Osteoarthritis (OA) is a leading cause of chronic disability and musculoskeletal pain. Oral non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely recommended treatments. Of these, cyclooxygenase type 2 (COX-2) inhibitors have some advantages over other NSAIDs. The only approved COX-2 inhibitor for OA is CELEBREX® (celecoxib) capsules, but it has a black box warning of cardiovascular events and gastrointestinal bleeding. One possible way to avoid these side effects is direct intra-articular (IA) delivery to the OA knee. However, IA-delivered celecoxib is removed from the joints rapidly due to its low molecular weight and high diffusivity. Our hypothesis was to increase IA retention time by loading celecoxib in nanoparticle (NP) delivery system made from human serum albumin (HSA). NPs of size less than 100 nm are known to enter the collagen matrix of cartilage to target chondrocytes.

Methods: We synthesised batches of stable celecoxib-loaded HSA NPs of size less than 100 nm in a novel process without using cross-linking agents, high temperature, oils, or Class I/II solvents. The NPs were characterised using several spectroscopic, microscopic, and scattering techniques. Finally, the cytotoxicity and anti-inflammatory efficacy of the NPs were tested on a lipopolysaccharide (LPS)-stimulated human leukemia monocyte (THP-1) cell line and in primary chondrocytes from OA patients.

Results: The celecoxib-loaded NPs were spherical and had a low polydispersity index of ~0.1. Cell viability assays indicated that the NPs do not have any deleterious effects on cells. *In vitro* anti-inflammatory efficacy studies demonstrated that NPs efficiently reduced inflammatory signals in stimulated THP-1 cells (monocyte chemoattractant protein-1, MCP-1 and prostaglandin E_2, PGE_2) and in primary chondrocytes from OA patients (PGE2).

Conclusions: Having established a reproducible process, the next step is to assess efficacy and joint residence time of the NPs in preclinical animal models of OA following IA administration. These NPs may have the potential to be used for IA delivery of celecoxib to treat OA in humans. The HSA NPs also have the potential to load temperature-sensitive drugs and drugs used to treat other conditions.