Nanocrystals-Polymer Particles: a Novel Drug Delivery System for Knee Osteoarthritis Treatment

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Introduction: The development of new drug delivery systems for intra-articular (IA) injection is essential for an efficient treatment of osteoarthritis (OA), the most common type of arthritis affecting 80 % of the world's population over 75 years [1].
Aims: The aim of this study was to develop Nanocrystals-Polymer Particles (NPPs) as highly loaded particles with extended release properties for a local and potent osteoarthritis treatment and to prove this concept *in vivo*.
Methods: PH-797804 a selective ATP-competitive p38 mitogen-activated protein kinase (MAPK) inhibitor, currently in phase II clinical trial (NCT01102660), was chosen as active pharmaceutical ingredient (API). Subsequently, the steps of the study were, (i) to formulate API nanocrystals and protect them against a crystalline regrowth (wet-milling, followed by SEM, X-ray diffraction, DSC and DLS characterization), (ii) to synthesize a fluorescent polymer allowing intravital tracking of particles, (iii) to encapsulate a high payload of API in 10 to 25 µm-particles (obtained with a Spray dryer 4M8TriX and characterized by laser diffraction, SEM, UHPLC), (iv) to assess *in vitro* the drug release, (v) to evaluate particles cytotoxicity on human synoviocytes (MTT test) and (vi) to investigate *in vivo* the activity of the particles in an antigen-induced arthritis (AIA) mice model.
Results: PH-797804 nanocrystals were produced by a recrystallization/wet-milling process and optimally stabilized at least over 4 weeks by vitamin E TPGS [2]. Nanocrystals had a monomodal size distribution. NPPs obtained by spray-drying had up to 35 % w/w drug loading, with 14.2-µm mean size diameter. They released 20 % of their content over 2 months. NPPs were non-toxic to human synoviocytes at $100\times IC_{50}$. Finally, *in vivo* experiments on AIA murine model showed a good retention of NPPs in the joint during 4 weeks, a significant reduction of the inflammation and inhibition of several cytokines (e.g. IL-1β and IL-6).
Conclusion: New formulations were successfully developed to offer a controlled, sustained release of API from biocompatible polymeric particles containing nanocrystals. They showed an effective anti-inflammatory activity in an arthritis mouse model. NPPs, as a new pharmaceutical technology, could be a safe drug delivery system, providing locally a high drug dose over a long period, towards an effective treatment/cure of the disease.

References

[1] Arden N, Nevitt MC. Best Pract Res Clin Rheumatol 2006; 20: 3-25.
[2] Guo Y et al. Eur J Pharm Sci 2013; 49: 175-186.