PhD thesis: Chronotherapeutic Drug Delivery in Early Morning Pathologies: Design and Production of new NSAIDs/SAIDs polysaccharide-based systems

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Abstract

The major technological challenge encountered when formulating new dosage forms is to find a way to adapt drug release kinetics to specific clinical requirements, with the aim to enhance the therapeutic action of both new and old drugs. Research in chronopharmacology has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems which are required to enable the drug release timing and control. This approach has a strong impact on the treatment of chronic inflammatory-based diseases which symptoms are circadian-dependent such as the so-called early morning pathologies (EMPs_e.g. arthritis, arthrosis). The conventional treatment of these pathologies consists of daily administrations of anti-inflammatory medicines (NSAIDs or SAIDs), which are often unable to coordinate drug release with clinical symptoms onset resulting in inefficient therapy and poor patient compliance. In the case of individuals who suffer from rheumatoid arthritis and related painful joint disorders, the NSAIDS may be more effective when the drug is administered at least 4 to 6 hours before the pain reaches its peak in the early morning.

In this context, my PhD project focused on the design and development of chronotherapeutic drug delivery systems characterized by time-specific and prolonged release of model anti-inflammatory drugs able to fit with the specific therapeutic needs of EMPs.

In particular the PhD program involved the design and development of: chronotherapeutic systems loaded with short half life (Ketoprofen and Ketoprofen lysine salt) or with long half life NSAIDs (Piroxicam); and chronotherapeutic systems loaded with SAIDs (Prednisolone). These formulations were designed as monolayer, core/shell and floating microparticles tested as self-consistent formulation or into specific capsules as final dosage form.

Formulations were produced by prilling/ionotropic gelation technique using natural (alginate, pectin), semi-synthetic (hydroxypropilmethylcellulose) or synthetic (methacrylic acid - methyl methacrylate copolymer) polymeric carriers as release modifiers. These formulations were characterized in terms of drug content and encapsulation efficiency (UV), morphology (SEM, SEM-EDX), solid state (DSC, FT-IR) swelling behavior and drug release profile (USP *apparati* II and IV). The *in vivo* anti-inflammatory effectiveness of the formulations showing the better *in vitro* technological features was studied using a modified protocol of carrageenan induced edema in rats.

The optimized drug delivery systems showing a delayed and time-specific drug release *in vitro* as well as a delayed and prolonged *in vivo* anti-inflammatory effect compared to pure drugs, could be considered as potential chronotherapeutic agents to be taken at bedtime and able to act in the early morning.