DEVELOPMENT OF A NOVEL RATE-MODULATED FIXED DOSE ANALGESIC COMBINATION FOR THE TREATMENT OF MILD TO MODERATE PAIN

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ABSTRACT

Pain is the net effect of multidimensional mechanisms that engage most parts of the central nervous system (CNS) and the treatment of pain is one of the key challenges in clinical medicine (Le Bars et al., 2001; Miranda et al., 2008). Polypharmacy is seen as a barrier to analgesic treatment compliance, signifying the necessity for the development of fixed dose combinations (FDCs), which allow the number of tablets administered to be reduced, with no associated loss in efficacy or increase in the prevalence of side effects (Torres Morera, 2004). FDCs of analgesic drugs with differing mechanisms of nociceptive modulation offer benefits including synergistic analgesic effects, where the individual agents act in a greater than additive manner, and a reduced occurrence of side-effects (Raffa, 2001; Camu, 2002).

This study aimed at producing a novel, rate-modulated, fixed-dose analgesic formulation for the treatment of mild to moderate pain. The fixed-dose combination (FDC) rationale of paracetamol (PC), tramadol hydrochloride (TM) and diclofenac potassium (DC) takes advantage of previously reported analgesic synergy of PC and TM as well as extending the analgesic paradigm with the addition of the anti-inflammatory component, DC.

The study involved the development of a triple-layered tablet delivery system with the desired release characteristics of approximately 60% of the PC and TM being made available within 2 hours to provide an initial pain relief effect and then sustained zero-order release of DC over a period of 24 hours to combat the on-going effects of any underlying inflammatory conditions. The triple-layered tablet delivery system would thus provide both rapid onset of pain relief as well as potentially address an underlying inflammatory cause.

The design of a novel triple-layered tablet allowed for the desired release characteristics to be attained. During initial development work on the polymeric matrix it was discovered that only when combined with the optimized ratio of the release retarding polymer polyethylene oxide

(PEO) in combination with electrolytic-crosslinking activity, provided by the biopolymer sodium alginate and zinc gluconate, could the 24 hour zero-order release of DC be attained. It was also necessary for this polymeric matrix to be bordered on both sides by the cellulosic polymers containing PC and TM. Thus the application of multi-layered tableting technology in the form of a triple-layered tablet were capable of attaining the rate-modulated release objectives set out in the study. The induced barriers provided by the three layers also served to physically separate TM and DC, reducing the likelihood of the bioavailability-diminishing interaction noted in United States Patent 6,558,701 and detected in the DSC analysis performed as part of this study.

The designed system provided significant flexibility in modulation of release kinetics for drugs of varying solubility. The suitability of the designed triple-layered tablet delivery system was confirmed by a Design of Experiments (DoE) statistical evaluation, which revealed that Formulation F4 related closest to the desired more immediate release for PC and TM and the zero-order kinetics for DC. The results were confirmed by comparing Formulation F4 to typical release kinetic mechanisms described by Noyes-Whitney, Higuchi, Power Law, Pappas-Sahlin and Hopfenberg. Using f_1 and f_2 fit factors Formulation F4 compared favourably to each of the criteria defined for these kinetic models.

The Ultra Performance Liquid Chromatographic (UPLC) assay method developed displayed superior resolution of the active pharmaceutical ingredient (API) combinations and the linearity plots produced indicated that the method was sufficiently sensitive to detect the concentrations of each API over the concentration ranges studied. The method was successfully validated and hence appropriate to simultaneously detect the three APIs as well as 4-aminophenol, the degradation product related to PC.

Textural profile analysis in the form of swelling as well as matrix hardness analysis revealed that an increase in the penetration distance was associated with an increase in hydration time of the tablet and also an increase in gel layer thickness. The swelling complexities observed in the

delivery system in terms of both the PEO, crosslinking sodium alginate and both cellulose polymers as well as the actuality of the three layers of the tablet swelling simultaneously suggests further intricacies involved in the release kinetics of the three drugs from this tablet configuration.

Modified release dosage forms, such as the one developed in this study, have gained widespread importance in recent years and offer many advantages including flexible release kinetics and improved therapy and patient compliance.

Key Words: analgesic, pain, paracetamol, tramadol, diclofenac, polymer, PEO, layered tablet, zero-order release, first-order release.