Formulation of Multi-Unit Tablets Combining Pulsatile and Sustained Effects of a Model Drug

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A Thesis Presented by

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Abstract

Oral drug delivery is the most convenient route of drug administration. More efforts were performed to optimize this route for therapeutic maximization and side effects minimization. Controlled drug delivery was developed to enhance drug performance and increase patient compliance. There are several factors affecting the anticipation of developing oral modified release systems. Such factors are either drug or polymer related.

The aim of the present work is to formulate and evaluate controlled release oral dosage forms of etodolac through the manipulation of different formulation parameters to achieve the optimized formulation owning pulsatile and sustained drug delivery. Etodolac was formulated with different polymers (Eudragit® and HPMC) at different ratios.

The work in this thesis was divided into three chapters:

Chapter one: Formulation and Evaluation of Etodolac Hydrophilic Matrix Controlled Release Dosage Forms; Fast and Sustained Release Formulations

Different etodolac formulations were prepared and the resultant dosage forms were evaluated for their physical properties and drug release profiles. Superdisintegrants as sodium starch glycolate and croscarmellose sodium were added in varying ratios for discovering their effect on fast release tablets. Starch was also added as a disintegrant to quicken the tablet disintegration and hence the drug release. Eudragit®

RSPO and Eudragit® RLPO were incorporated, whether separately or in combination, to test the impact of methacrylic acid derivatives polymers on sustaining etodolac release from the matrix tablet. HPMC was added to certain formulations to yield more sustained etodolac release effect. The optimized fast and sustained release formulations were selected for further studies. All formulations were subjected to pre- and post-formulation tests. DSC and FT-IR tests were performed to study whether there were any interactions between the etodolac and the added excipients.

Results of this chapter showed that:

- All formulations, either fast or sustained release, possessed good flowability parameters represented in small angle of repose, optimized values for Carr's index and Hausner's ratio. Also, these formulations passed post-compression tests represented in weight uniformity, thickness uniformity, diameter uniformity, hardness and friability.
- PEG 6000 was added to etodolac (1:1), and mixing was performed by solid dispersion technique using the solvent evaporation method to increase the wettability of the etodolac particles which resulted in enhanced drug solubility.
- Increasing the starch amount in the tablet accelerated the tablet disintegration.
- The same concept was detected in superdisintegrants where increasing the percentage of sodium starch glycolate in the formulations speeded the tablet disintegration and subsequently the drug release.

- *In-vitro* release studies of fast release formulations showed that starch caused lower acceleration in drug release than sodium starch glycolate and croscarmellose sodium.
- Inclusion of croscarmellose sodium in the tablets quickened the drug release but to a limited extent i.e. tablet disintegration was faster until reaching certain concentration of croscarmellose sodium above which the disintegration was not quickened.
- The incorporation of Eudragit® RSPO and Eudragit® RLPO resulted in extending the etodolac release time due to their ability to swell and release the drug slowly by diffusion. Eudragit® RSPO showed better ability in sustaining the drug release than Eudragit® RLPO.
- The addition of Eudragit® RLPO to Eudragit® RSPO resulted in decreasing the sustained effect. This was a result of increasing the hydrophilic groups (from Eudragit® RLPO) in the tablet matrix.
- The addition of 10% HPMC prolonged the etodolac release period. In contact with water, HPMC swelled forming a viscous gel layer around the tablet, which decreased its hydration and hence the pores formation inside the gel layer. Erosion of the tablet occurred after complete hydration of HPMC and Eudragit® polymers. Tablets containing HPMC and Eudragit® showed better sustained release of etodolac than those containing Eudragit® only.
- The *in-vitro* release profile of formulations containing 10% HPMC with Eudragit® were found to be highly retarded, so all these formulations were escalated for further studies.

- DSC study showed the disappearance of the endothermic peak of etodolac in solid dispersion due to its solubility in PEG 6000 at its melting point.
- FT-IR tests were performed on the drug and excipients, and the results suggested that no significant interaction took place between etodolac and any of the excipients.

Chapter two: Formulation and Evaluation of Etodolac Coated Bilayer Tablet Matrix System Combining Pulsatile and Sustained Release Effects

The fast and sustained release formulations chosen from the previous chapter were compressed together forming bilayer tablets. The sustained release formulation was first compressed into the first layer, then the fast release formulation was placed above the first layer and compressed again forming the double-sided bilayer tablets. *In-vitro* drug release study was performed on the bilayer tablets. Evaluation of post-compression tests were performed on the tablets. The optimized bilayer formulation passed through three successive coating processes, starting with 10% Opadry® II forming an isolation layer, then 8% HPMC to form swellable layer, and finally Surelease® (10% ethyl cellulose) to form the outer rupturable layer. The coated tablets were also subjected to *in-vitro* release study and post-compression tests. Surface topography was studied using a scanning electron microscope.

Results of this chapter showed that:

- The fast release layer of the bilayer tablet was completely disintegrated within 15 minutes. This was visually detected through the individual layer coloration.
- The *in-vitro* release profile of the uncoated bilayer tablets showed rapid drug release of the fast release layer containing either 15 mg of croscarmellose sodium or 40 mg of sodium starch glycolate. The optimum fast release layer containing 40 mg of sodium starch glycolate was chosen. The sustained release layers were tested and the optimum formulation was found to contain 400 mg of Eudragit® RSPO and 160 mg of HPMC.
- Successive coating processes resulted in the creation of two hours of lag time prior to the beginning of the drug release. The Surelease® (ethyl cellulose) was furtherly ruptured, also HPMC undergo swelling. The swelling and erosion of the coating layers, permeation of dissolution medium to the matrix core, and outward diffusion of drug solution consumed at least two hours represented as lag time.
- Regarding swellable layer, the addition of small portions of higher grade (HPMC K_4M) was found to prolong the lag time to reach four hours. This was due to the increase in the viscosity of the formed gel layer resulting from the added HPMC.

Chapter three: *In-vivo* Comparative Study of optimized Etodolac Formulation and Conventional Tablet

Optimized tablets were tested in rats. Special 6 mm tablets were manufactured in order to be safely administered by the rats. The rats were divided into three sets; the first set received no treatment, the second set received conventional ETD tablets, and the third set received optimized tablets. Induction of inflammation was performed by injecting the rats' right hind paws with formaldehyde. Assessment of the anti-inflammatory activity of the tablets was performed through the determination of the percentage maximum possible effect and monitoring the swelling degrees.

Results of this chapter showed that:

- *In-vivo* testing of the optimized coated bilayer tablet showed no activity in decreasing the inflammation in rats' hind paws in the first hour, this could be due to the coating of the tablets. At the second hour there is a marked decrease in the edema of the paw indicating the disintegration and release of the fast release layer. Gradual inflammation diminish was detected represented in decreased oedema with time till the end of the six hours.