PANTOPRAZOLE SODIUM-LOADED CONTROLLED RELEASE MICROPARTICLES PREPARED BY SPRAY DRYING

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INTRODUCTION

Multi-particulate drug delivery systems have shown several advantages over single unit ones, such as more uniform transit times through the gastro-intestinal tract, less variability among individuals and a smaller risk of dose dumping and high local concentrations. Polymers blends are widely studied to obtain controlled drug delivery systems, with designed characteristics. Polymer blend formulations can improve mechanical properties, reduce drug toxicity and control drug delivery (1). Widely used to prepare colonic delivery tablets, methacrylates and cellulose derivatives can be blended to obtain microparticles with this exact characteristic, using aqueous solutions. Eudragit S100® (EUD) [methacrylic acid - methyl methacrylate copolymer (1:2)] is an enteric polymer that dissolves in aqueous solution presenting pH higher than 7. Hydroxypropylmethylcellulose (HPMC) is a hydrophilic derivative of cellulose that swells in presence of water. Pantoprazole sodium sesquihydrate (PAN), is a prodrug, protonated in acid medium of stomach parietal cells that binds irreversibly the H⁺/K⁺-ATPase. It is used in the treatment of digestive ulcers, gastro-esophageal reflux disease and Helicobacter pylori infections (2). This drug should only be activated inside gastric parietal cells. Therefore, it must be formulated in enteric drug delivery systems.

The purpose of this study was to stabilize the pantoprazole in gastric acid medium by means of preparing controlled release microparticles, using Eudragit S100® and Methocel F4M® blend.

EXPERIMENTAL METHODS

In order to prepare the microparticles, 1.2 g of EUD was dissolved in 0.05 M NaOH. After its complete dissolution, HPMC (0.6 g) was added and left 24h for hydratation. Immediately after drying, pantoprazole sodium sesquihydrate (0.3 g) was mixed and stirred magnetically during the drying process. The samples were dried in a MSD 1.0 spray drier (Labmaq, Brazil) with 1.2 mm nozzle, 0.44L/h feed rate and inlet temperature of 150 ± 2 °C.

Drug loading was assayed dissolving the equivalent of 10 mg of PAN in 0.05 M NaOH and analyzed by a validated HPLC method (Perkin Elmer serie 200 with acetonitrile:phosphate buffer pH 7.4 (35:65 v/v) as mobile phase and C18 column.

RESULTS AND DISCUSSION

Microparticles were obtained as off-white powders. SEM analysis showed microparticles concave and poor spherical shaped and with a smooth surface (Figure 1).

Figure 1: SEM image of microparticles.
The preparation yield was 39.1 ± 0.8 %, the drug content was 150.8 ± 5.0 mg/g and the encapsulation efficiency was 105.58 %.

DSC analyses (Figure 2) showed an endothermic peak at 130.33°C, followed by degradation for PAN. Melting and dehydration of PAN are parallel processes (4). The neat polymer EUD presented an endothermic peak at 69.01°C and HPMC showed an endothermic peak at 66.84°C, which was correlated to the exit of the adsorbed moisture or solvent from the molecule (5). Regarding the physical mixtures of drug and polymers, the curve showed two endothermic peaks, one correlated to the polymers (64.21°C) and the other one to PAN (108.29°C). No event was observed for PAN in microparticles, only one peak at 82.76°C. As previously reported in microparticle formulations the disappearance of peaks from drugs indicates their encapsulation (6).

The results suggest that pantoprazole-loaded microparticles are composed by a homogeneous phase, in which the polymers present a lower degree of crystallinity than the raw material, and the drug is dissolved in the polymer blend. After the acid stage, unencapsulated PAN showed that only 0.5% of drug remained stable. On the other hand, after 1h in 0.1 M HCl, PAN-loaded microparticles presented 65.71 ± 3.96 % of the drug in the medium. PAN was released in 360 min, showing a sustaining profile (Figure 3).

The gastric ulcer indexes calculated after the administration of ethanol followed the administration of microparticles in rats are showed in the Figure 4. The index values were 0.74 ± 0.34 for the bicarbonate solution, 0.46 ± 0.17 for PAN water solution and 0.06 ± 0.07 for pantoprazole-loaded microparticles.

CONCLUSIONS

Microparticles were successfully prepared and showed sustained release (up to 360 min) and high acid protection. The microparticles are an interesting alternative to achieve multiparticulate dosage delivery forms presenting time/pH controlled release and gastric protection.

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REFERENCES