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Dexalansoprazole Sodium-Loaded Controlled Release Micro particles 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 hydrophilic derivative of cellulose that swells in presence of water. dexalansoprazole sodium sesquihydrate, is a prodrug, protonated in acid medium of stomach parietal cells that binds irreversibly the H+/K+-ATPase. Therefore, it must be formulated in enteric drug delivery systems. The purpose of this study was to stabilize the Dexalansoprazole sodium gastric acid medium by means of preparing controlled release microparticles, using Eudragit S100® and Methocel F4M® blend.DexlansoprazoleSodium is used to heal and maintain healing of erosive esophagatis and to treat heart burn associated with gastroesophageal reflux disease(GERD). It lasts longer than lansoprazole, to which it is chemically related, and needs to be taken less often, making it possible to better control gastric acid

Key words: DEXALANSOPRAZOLE, MICROPARTICLES, SPRAY DRYING, STABILITY, GASTRO- RESISTANCE

Class name:

Polycyclo ring system having the 1,3-diazole ring as one of the cyclos bicyclo ring system which is benzimidazole (including hydrogenated) chalcogen bonded directly to a ring carbon of the 1,3-diazole ring

Adverse effects

The most significant adverse reactions (≥2%) reported in clinical trials were diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting, and flatulence.

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Mechanism of action

Like lansoprazole, dexlansoprazole permanently binds to the proton pump and blocks it, preventing the formation of gastric acid

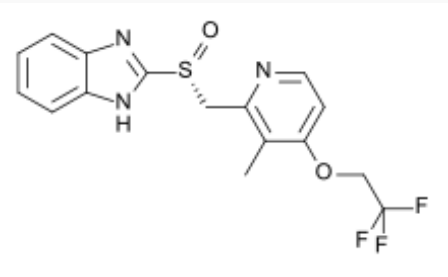
Chemistry

Dexlansoprazole is the R-enantiomer of lansoprazole, which is a racemic mixture of its R- and S-enantiomers.[The Takeda drug has a dual release pharmaceutical formulation, with two types of granules of dexlansoprazole, each with a coating that dissolves at a different pH level.

Pharmacokinetics

Dexlansoprazole has the same binding affinity to the proton pump as the S-enantiomer, but is associated witha three- to five-fold greater area under the plasma drug concentration time curve (AUC) compared with S -lansoprazole. With its dual release pharmaceutical formulation , the first quick release produces a plasma peak concentration about one hour after application, with a second retarded release producing another peak about four hours.

STRUCTURE

Dexlansoprazole

Systematic (IUPAC) name
(*R*)-(+)2-([3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methylsulfinyl)-1*H*-benzo[*d*]imidazole

PREPARATION OF CRYSTALLINE DEXALANSOPRAZOLE

A mixture of acetone (30 mL) and Dexlasoprazole sodium (10 g; sulfone impurity content: 6%) was stirred at 20° C. to 25° C. and filtered through 0.45 filter. De-ionized water (10 mL) was added to the filtered solution at 20° C. to 25° C., followed by addition of aqueous sodium hydrogen sulfate (2.5 g of sodium hydrogen sulfate in 7 mL of water) drop-wise till pH 7.3 was reached. The mixture was stirred for 10 to 15 minutes, followed by the addition of de-ionized water (50 mL) and stirred

for further 1 hour at 20° C. to 25° C. The mixture was filtered under vacuum, washed with de-ionized water (10 mL), followed by addition of acetone (30 mL) and 6% aqueous ammonia solution (0.5 mL; 6%) to attain a pH of 9.5. De-ionized water (60 mL) was added to the mixture, stirred for 1 hour at 20° C. to 25° C., filtered under vacuum and washed with de-ionized water (10 mL), followed by the addition of de-ionized water (30 mL) and dichloromethane (60 mL). The mixture was stirred and then allowed to settle, and the organic layer was separated. Dichloromethane was recovered under vacuum at 35° C. to 40° C. to obtain 10 to 15 mL of reaction mixture. Diisopropyl ether (150 mL) was added drop-wise to the reaction mixture, stirred for 1 hour at 20° C. to 25° C., filtered under vacuum, washed with diisopropyl ether (10 mL) and dried under vacuum at 20°C. to 25°C. for 8 hours to 10 hours to obtain.the.title.compound.

Yield: 71.27%

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, Dexalansoprazole 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 dexalansoprazole Na in 0.05 *M* NaOH and analyzed by a validated HPLC method (Perkin Elmer serie 200 with at 290 nm) using acetonitrile:phosphate buffer pH 7.4 (35:65 v/v) as mobile phase and C18 column. The SEM analyses were carried out using an accelerating voltage of 20 kV after gold sputtering(JeolJSM - 6060®, USA). Differential scanning calorimetry (DSC) was performed in DSC-4 PerkinElmer, USA) after sealing in aluminum pans. DSC tracings were performed from 40 ºC to 180 ºC, at a rate of 10 ºC/min.The gastro-resistance assay was performed in flowthrough cell apparatus, with 37 ºC bath and peristaltic pump (Desaga, Germany). Inside each cell, a pre-filter (Glass Fiber Filters AP25, Millipore®) was placed to avoid escaping of undissolved particles. The samples were placed in the cells and treated with 0.1 *M* HCl (mL/min) at 37 ºC (acid stage). After 1 h, the medium was replaced by PBS (pH 7.4) and samples were collected at predetermined time intervals and analyzed spectrophotometrically at 295 nm. Ulcers were induced by the oral administration of absolute ethanol (5 mL/kg) to 24 h fasted Wistar male rats (n=7), weighing 250 - 300g (3). Control group received 4.2 % sodium bicarbonate aqueous solution. Treated groups receive dexalansoprazole sodium dissolved in water and the microparticles suspended in water (20 mg/kg) of drug orally 1 h before the administration of ethanol. After 2h of ethanol administration, animals were sacrificed (beheaded); the stomachs were removed, opened along the greater curvature and examined for lesion measurements, calculated as follows:
Ulcer Index = 10/x, where *x* is total mucosal area/total ulcerated area

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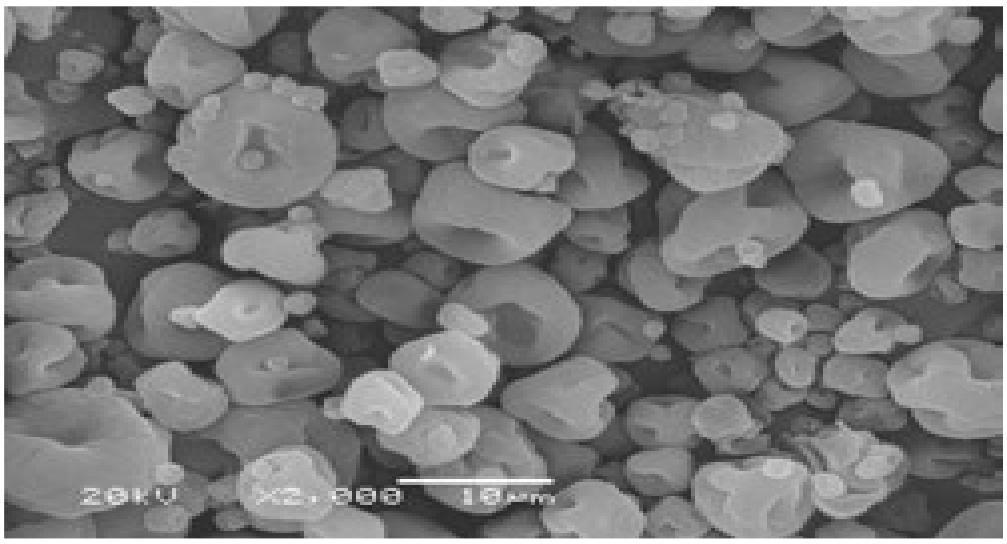
RESULTS AND DISCUSSION

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: image of microparticles Dexalansoprazole sodium



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 dexalansoprazole sodium. Melting and dehydratation of dexalansoprazole sodium 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 ºC) and the other one to dexalansoprazole sodium (108.29 ºC). No event was observed for PAN in microparticles, only one peak at 82.76 ºC. As previously reported in microparticle formulations the disappearance of peaks from drugs indicates their encapsulation.

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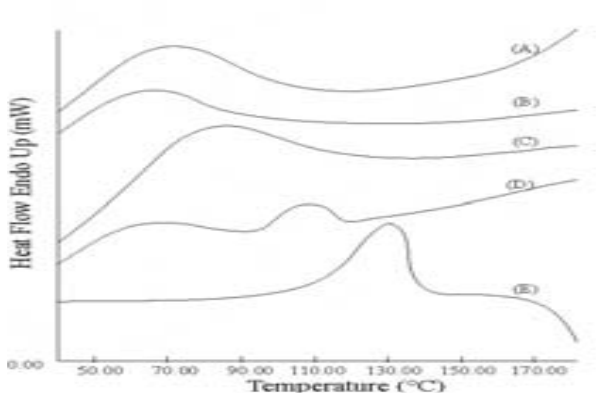

Figure 2: DSC tracing of EUD (a), HPMC (b),
microparticles (c), physical mixture (d) and DLP (e).

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, (Figure 3).

uncapsulated dexalansoprazolesodium showed that only 0.5% of drug remained stable. On the other hand, after 1h in 0.1 *M* HCl, dexalansoprazole sodium -loaded microparticles presented 65.71 ± 3.96 % of the drug in the medium. dexalansoprazole was released in 360 min, showing a sustaining
profile

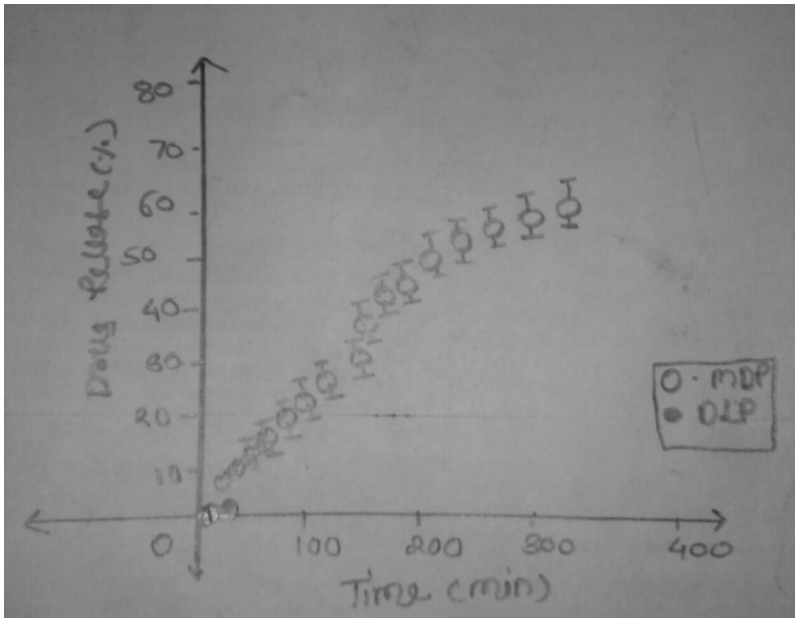

Figure 3: Drug release after 1h in 0.1*M* HCl in phosphate buffer pH 7.4.

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 dexalansoprazole water solution and 0.06 ± 0.07 for dexalansoprazole-loaded microparticles Ulcer indexes of bicarbonate solution, aqueous solution of dexalnsoprazole and microparticles.The Kruskal-Wallis test detected statistically differences ($p = 0.002$) between the ulcer indexes. The multiple analysis (Student-Newman-Keuls) showed that the Dexalansoprazolesodium-loaded microparticles presented a gastric ulcer index statistically lower ($p < 0.05$) than the bicarbonate and dexalansoprazole sodium aqueous solutions groups.These results proved the microparticles were able to protect ulcer formation by ethanol.

CONCLUSIONS

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

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