Evaluation of the Enteric Performance of Lansoprazole Mini-Tabs Coated in a Perforated Pan

PURPOSE

There is a growing interest in multi-particulate (MP) modified release (MR) drug delivery systems due to their consistent and reliable in-vivo drug release, with a reduced risk of local irritation along the gastrointestinal tract. [1, 2] Mini-tab technology combines the advantages of MP dosage forms with established manufacturing techniques used in tableting. Additional benefits of mini-tabs include excellent size uniformity, regular shape and a smooth surface, thereby offering an excellent substrate for coating with MR polymeric systems.

The aim of this study was to investigate the potential of successful manufacture and enteric coating of lansoprazole mini-tabs using methacrylic acid co-polymers (Acryl-EZE® aqueous acrylic enteric system, and Eudragit L 30 D-55) in a perforated pan. The produced enteric protection was assessed by both "acid-uptake" test and USP drug release criteria. Lansoprazole is a proton pump inhibitor (PPI), and therefore for the "acid-uptake" test, acid resistance of the enteric coated mini-tabs in 0.1N HCl and at intermediate pH conditions (acetate buffer pH 4.5) was investigated.[3]

METHODS

Formulation and Manufacture of Mini-Tabs

All ingredients (Table 1) except for the magnesium stearate were screened through a 35 mesh (500 µm) sieve and blended in a Turbula mixer for 10 minutes. Magnesium stearate was then added and the complete formulation was blended for an additional minute.

Mini-tabs were produced by direct compression on a 10-station instrumented Piccola press (Riva, Argentina) using 2 mm standard concave tooling (Notter GmbH, Germany) at 35 rpm and 1.2 kN compression force.

Table 1. Lansoprazole Mini-Tab Formulation

Material	*% w/w*	*mg/tablet*
Lansoprazole (Jenson Pharm. Services, UK)	12.0	0.98
Lactose (Fast Flo, Kerry Bio-Science, Ireland)	61.4	5.03
Magnesium carbonate (VWR International Ltd., UK)	13.0	1.07
StarCap 1500® co-processed starch excipient (Colorcon)	13.0	1.07
Magnesium stearate (Peter Greven, Holland)	0.5	0.04
Fumed silica (Aerosil 200, Evonik, Germany)	0.1	0.01
Total	100.0	8.20

Coating of Mini-Tabs

Coating trials were conducted in an Labcoat II-X (O'Hara,Canada) fitted with a custom-made 10" perforated pan with 400 mm mesh insert, a 1 mm nozzle ABC spray gun (Schlick, Germany) and a Perspex shield plate (Colorcon) positioned at the front of the pan to prevent mini-tab loss during coating. The mini-tabs (500 g batch size) were seal-coated with an Opadry® complete film coating system, clear, YS-1-7006 to 5% weight gain (WG) in order to improve mechanical strength of the substrate prior to application of the functional coat. Then the mini-tabs were enteric-coated with either Acryl-EZE, white (93A18597) or L30 D-55 (Evonik, Germany) up to 35% WG.

Testing of Lansoprazole Mini-Tabs

The mechanical strength of ten uncoated and coated mini-tabs was determined using Schleuniger-4M hardness (Schleuniger, Switzerland) and Copley TA friability (Erweka GmbH, Germany) testers.

Enteric protection of the Acryl-EZE coated mini-tabs was evaluated by an "acid uptake" test. Enteric coated mini-tabs (n=6) were weighed individually and placed in a Copley ZT54 (Copley, UK) disintegration tester with a round 500 µm meshfitted to the base of the testing tubes. After 2 hours in either0.1N HCl or pH 4.5 acetate buffer at 37 ± 1ºC, the mini-tabs were removed from the vessel, excess surface moisture was eliminated with a paper towel and the tablets were re-weighed. The difference in the respective weights was reported as percent acid uptake.

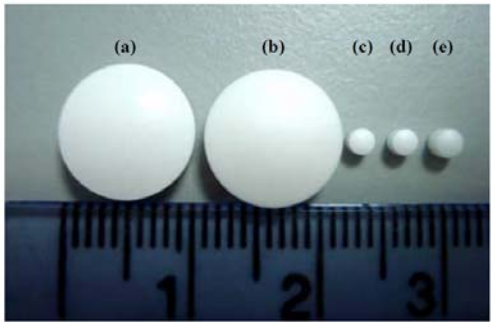
Dissolution testing of the enteric coated mini-tabs in hard gelatin capsules was conducted in a dissolution bath (SOTAX, Switzerland) according to the USP monograph for "Lansoprazole Delayed-Release Capsules" [(4)], using Apparatus II (paddles) at 75 rpm. Drug release was measured for a 15 mg lanzoprazole dose, i.e. 15 mini-tabs were placed into a size 3 hard gelatin capsule. Dissolution protocol was 1 hour in 0.1N HCl (acid stage) followed by pH 6.8 phosphate buffer with sodium lauryl sulphate (buffer stage) at 37 ± 0.5ºC. A dual beam UV/VIS spectrophotometer (Lambda 25, Perkin Elmer Instruments, UK) was used for lansoprazole detection at a wavelength of 306 nm in acid and at 285 nm in buffer.(4) Measurements at each time point were performed in triplicate, and mean and standard deviation (SD) values were calculated.

RESULT S

Coated mini-tabs exhibited good appearance, showing novisual defects in the coating (Figure 1).

Figure 1. Appearance of Mini-Tabs Compared to 10 mmDiameter Round Tablets

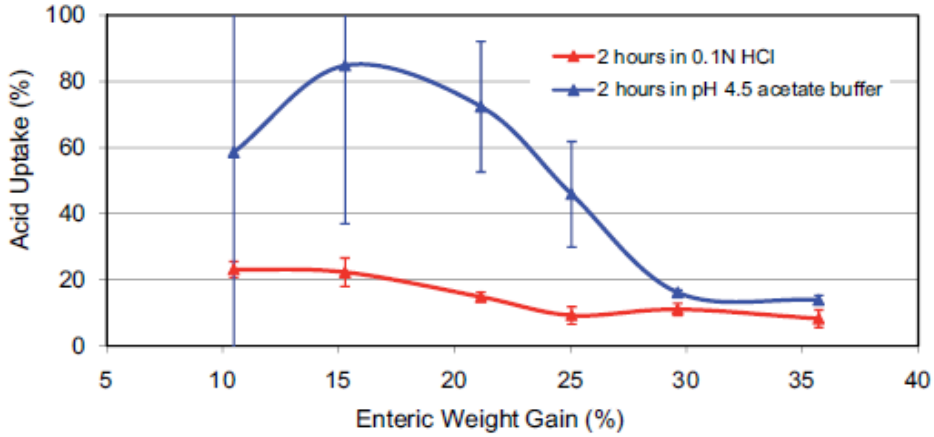
[(a) 10 mm uncoated; (b) 10 mm enteric-coated, 10% WG; (c) 2mm, uncoated; (d) 2 mm seal-coated; (e) 2 mm, seal-coated and 30% WG enteric-coated]



The mechanical strengths of the mini-tabs improved significantly after the application of a seal-coat. Breaking force increased from 1.1 kp (uncoated) to 3.3 kp (seal-coated) and friability was reduced from 0.24% to less than 0.01% respectively.

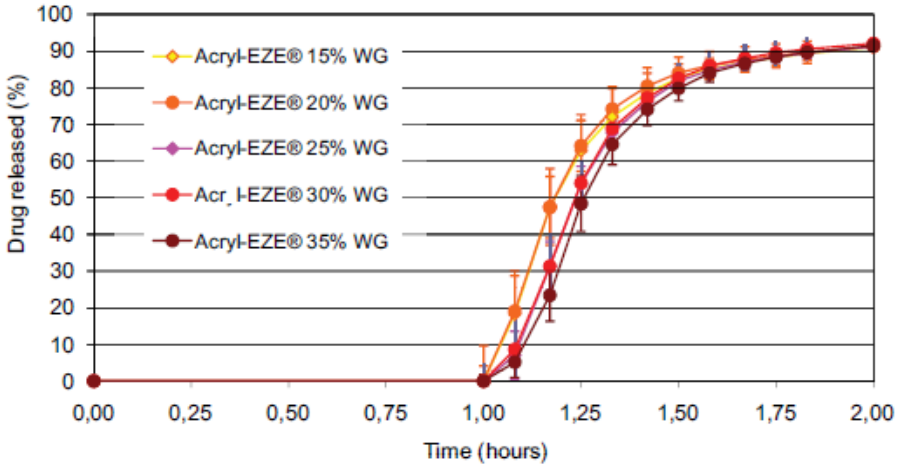
Acid uptake results showed that 30-35% Acryl-EZE enteric coating weight gain was required to obtain sufficient acid resistance, in both 0.1N HCl (pH 1.2) and acetate buffer (pH 4.5) media (Figure 2), and acceptable drug release in USP phosphate buffer (pH 6.8).

Figure 2. Acid Uptake for Acrlyl-EZE® Coated Mini-Tabs in 0.1N HCl and Acetate Buffer (n = 6)



Lansoprazole release profiles from the mini-tabs coated with Acryl-EZE, even at a low weight gain of 15%, was found to comply with the USP specification of <10% drug release after 1 hour in 0.1N HCl and >80% after 1 hour in pH 6.8 phosphate buffer (Figure 3).

Figure 3. Drug Release from Acryl-EZE® Coated Mini-Tabs

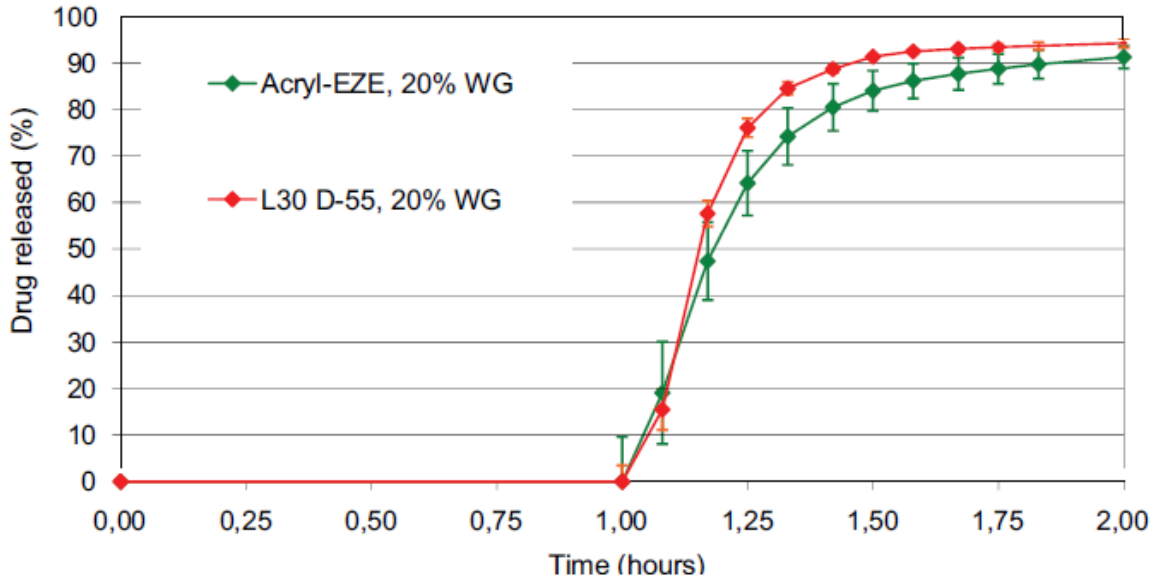


It was also found that after exposure to the acid media, Acryl-EZE coated mini-tabs were sticking to each other (Figure 4) leading to slower and variable drug release profiles when tested in buffer (Figure 3). These results confirm the findings of Deng et al. (5) who reported similar phenomenon with pellets coated with enteric systems based on methacrylic acid copolymer.

To further investigate the mini-tab sticking issue in the dissolution apparatus, the lansoprazole mini-tabs were enteric coated with Acryl-EZE or Eudragit L 30 D-55. Agglomeration of mini-tabs was observed for both systems after 1 hour in 0.1N HCl, affecting their dissolution profiles in buffer phase (Figure 5). Further work is underway to investigate possible methods of preventing mini-tabs agglomeration in acid.

Figure 4. Agglomeration of Enteric-Coated Mini-Tabs During Dissolution Testing

Figure 5. Drug Release from Mini-Tabs Coated with Eudragit L 30 D-55 or Acryl-EZE®



CONCLUSIONS

Lansoprazole mini-tabs (2 mm diameter) were successfully manufactured and enteric coated using a custom-made 10''perforated coating pan, with excellent coating appearance attained. The mechanical strength of the mini-tabs significntly improved upon application of a seal-coat. The enteric coated mini-tabs exhibited low acid uptake in pH 1.2 HCl and pH 4.5 acetate buffer, and consistent drug release
in USP phosphate buffer pH 6.8.

Future studies will investigate the mechanism of agglomeration during dissolution testing and potential resolution of this issue related to mini-tabs coated with enteric acrylic systems.

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