The Influence of In Vitro Dissolution Method on Lansoprazole Release from Enteric Coated Mini-Tabs

ABSTRACT SUMMARY

This study investigated the influence of different dissolution methods on lansoprazole *in vitro* release from mini-tabs coated with Acryl-EZE®, aqueous acrylic enteric system. One of the methods utilized novel sinkers specifically designed to prevent mini-tabs from sticking to each other. This method produced the fastest and most reproducible drug release in buffer compared to USP 1 (baskets), USP 2 (paddles) or USP 2 with conventional sinkers.

INTRODUCTION

There is a growing interest in multiparticulate (MP) modified release drug delivery systems. After ingestion, the MP units are released from the capsule shell in the stomach and predictably transit to the small intestine,[1] dispersing along the gastrointestinal tract, leading to consistent drug release with reduced risk of local irritation. MPs generally provide a more reliable in vivo dissolution performance when compared to a single unit dosage form, resulting in a uniform bioavailability and clinical effect.[2]

Mini-tabs combine the advantages of MP dosage forms with the established manufacturing techniques of tableting, and have fewer constraints compared to extrusion-spheronization.[3] Mini-tabs produced via direct compression are an attractive alternative to pellets, since the use of liquids is avoided. Like other MP technologies, mini-tabs can either be filled into hard capsules or compacted into larger tablets which, after disintegration, release the subunits as MPs.[4] Additional benefits of mini-tabs include excellent size uniformity, regular shape and a smooth surface, offering an ideal substrate to coat with polymeric membranes for modified release purposes.

MP systems can also present a number of technological challenges during manufacturing, coating, capsule filling and testing. Deng et al. described sticking of drug-layered and enteric-coated beads to each other during dissolution testing.[5] A similar problem was identified in our previously reported work with mini-tabs coated with enteric acrylic systems, resulting in slower and more variable drug release in buffer.[6]

Therefore, the aims of this study were to investigate the influence of different dissolution methods on lansoprazole release from enteric-coated mini-tabs; and to identify a method that could eliminate the mini-tab agglomeration issue and guarantee the most reproducible results.

EXPERIMENTAL METHODS

Mini-tabs used in this study contained 12% w/w lansoprazole, 61.4% w/w lactose (Fast Flo, Kerry Bio-Science), 13% w/w magnesium carbonate (VWR), 13% w/w starch-based excipient (StarCap 1500®, co-processed starch excipient, Colorcon), 0.1% w/w fumed silica (Aerosil 200, Evonik) and 0.5% w/w magnesium stearate (Peter Greven). They were manufactured by direct compression on a modified instrumented 10-station rotary press (Piccola, Riva) fitted with 2 mm standard concave tooling; at 1.2 kN compression force and 35 rpm. Target weight was 8.2 mg.

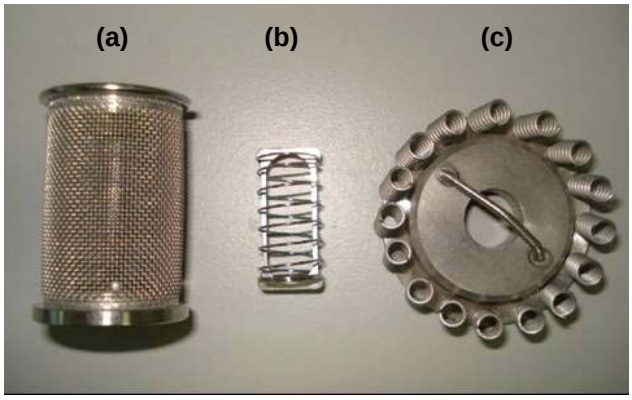
Mini-tabs (0.5 kg batch size) were seal-coated with an 8% w/w aqueous dispersion of Opadry®, complete film coating system, clear YS-1-7006 (Colorcon), to 5% weight gain (WG) and enteric-coated with a 20% w/w aqueous dispersion of a formulated acrylic system (Acryl-EZE white 93A18597, Colorcon) with polyethylene glycol 800 (Whyte Chemicals Ltd) as a plasticizer to 15-35% WG. The trials were conducted in a Labcoat II (O'Hara) coater, fitted with a custom-made 10" pan and 400 μm mesh insert. During trials a 1 mm nozzle Schlick ABC spray gun was used and a Perspex shield plate was positioned at the front of the pan to prevent tablet loss during coating. Process parameters are listed in Table 1.

Table 1. Coating Process Parameters

Process parameters	Sub-coat	Enteric coat
Air volume (m^3/h)	200	200
Inlet air temperature (°C)	60 - 63	47 - 50
Exhaust air temperature (°C)	49 - 50	40 - 43
Product temperature (°C)	45 - 46	33 - 37
Atomizing air pressure (bar)	0.8	0.8
Spray rate (g/min)	3 - 6	8 - 12
Process time (min)	66	64

Enteric protection of the Acryl-EZE coated mini-tabs was evaluated by a dissolution test conducted in a Sotax (Switzerland) bath according to the USP monograph for "Lansoprazole Delayed-Release Capsules" at 75 rpm.[7] Dissolution protocol was 1 hour in 0.1N HCl (acid stage) followed by pH 6.8 phosphate buffer with sodium lauryl sulphate, SLS (buffer stage) at 37 ± 0.5 ºC. A dual beam UV/VIS spectrophotometer (Lambda 25, Perkin Elmer Instruments) was used for lansoprazole detection at a wavelength of 306 nm in acid and at 285 nm in buffer. Three tablets were tested; and mean and standard deviation (SD) values were calculated. Drug release was measured for a 15 mg lansoprazole dose, i.e., 15 mini-tabs. The following dissolution methods were used (Figure 1): USP 1 (baskets), USP 2 (paddles), USP 2 with spiral sinkers (11 x 31 mm, Sotax) and USP 2 with novel mini-tab sinker devices. The novel stainless steel mini-tab sinkers were developed and made by Colorcon. Each mini-spiral can accommodate up to three mini-tabs, but, ideally, one mini-tab should be placed in each spiral.

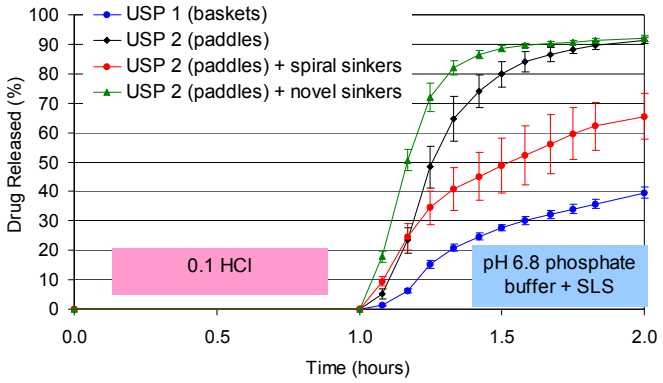
Figure 1. Different Devices Used in the Dissolution Study
(a) USP 1 basket; (b) spiral sinker; (c) novel mini-tab sinker



RESULTS AND DISCUSSION

The amount of required enteric coating is generally dependent upon the substrate size, shape and therefore, surface area. A previous study showed that 30 to 35% enteric coating WG was sufficient to provide acid resistance for lansoprazole mini-tabs.[6] Therefore, mini-tabs with 35% enteric WG were used in this study (Figure 2).

Figure 2. Lansoprazole Release from Acryl-EZE Coated (35% WG) Mini-Tabs



The results obtained indicated that the slowest drug release was observed for the USP baskets, in which the mini-tabs agglomerated the most. In the case of spiral sinkers, hydrodynamic movement of the mini-tabs by the medium was restricted by the device, and hence, slow and variable drug release was obtained in buffer (with SD ≤ 10%). The USP 2 paddle method produced sticking of the mini-tabs during dissolution testing as reported previously.[6] For the newly developed mini-tab sinkers; however, each coated mini-tab was maintained as a discrete unit within the device (Figure 3), eliminating any possibility of agglomeration. As a result, the fastest and the most reproducible drug release in buffer, with standard deviations of less than 4.5%, was achieved.

Figure 3. Use of a Novel Sinker for Dissolution Testing of Enteric-Coated Mini-Tabs

CONCLUSIONS

Lansoprazole release from enteric-coated mini-tabs was significantly affected by the choice of dissolution method used. Sticking of mini-tabs to each other during dissolution testing was most profound in the case of USP 1 baskets. Use of commercially available spiral sinkers resulted in slightly faster, but variable, drug release profiles. The best results were obtained with the newly developed sinker devices that helped to eliminate mini-tab agglomeration after exposure to acid media and produced the fastest and most reproducible drug release in buffer.

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