Formulation Effects on Drug Release from Sustained-Release Compritol® 888 ATO Tablets & Mini-Tablets

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Introduction

Although most medicinal products are developed as solid oral dosage forms, the significant anatomical differences of the buccal cavity within paediatric and adult patients mean that children, particularly those under 5 years of age, encounter swallowing difficulties[1]. Mini-tablets are a potential dosage form suitable for paediatric drug delivery and can be produced via traditional tableting methods, such as direct compression. Sustained-release mini-tablets may offer distinct advantages over many conventional dosage forms used in paediatric medicine. In addition to their small size, which helps to overcome issues associated with dysphagia, they may be designed to mask unpleasant tastes to improve palatability whilst also modifying the release of the active drug substance from the formulation. Compritol® 888 ATO (glyceryl behenate) is commonly used in formulating sustained-release lipid matrices[2]. When compressed, Compritol® 888 ATO forms an insoluble network structure, allowing water to penetrate and subsequent drug release to occur via diffusion. In a previous study, the effect of various diluents and the compaction force used during manufacture on drug release from Compritol® 888 ATO tablets were reported[3]. The aim of the present study was to assess the effects of various diluents on drug release from Compritol® 888 ATO tablets and mini-tablets of different sizes.

Materials & Methods

Formulations comprised; 16.7 %w/w anhydrous theophylline, 15 or 25 %w/w Compritol® 888 ATO (Gattefossé, France) 3 %w/w, magnesium alumino silicate (Neusilin® US2, Fuji Chemical, Japan), 1 %w/w magnesium stearate (Sigma Aldrich, France) and 64.3 or 54.3 %w/w diluents (either; Microcrystalline cellulose (MCC, Avicel® PH101, FMC Biopolymer, Belgium), Lactose (Lactopress® spray dried, Domo, Netherlands), dibasic calcium phosphate anhydrous (DCPA, Fujicalin®, Fuji Chemical, Japan) or DCPA and lactose (2:1). Materials were blended for 2 min (46 rpm) and subsequently for 1 min (96 rpm) with lubricant (2C turbula mixer, WAB, Switzerland). Compression was performed using a using a Stylcam® 100R rotary press simulator (Medel'Pharm, France) at a production rate of 20 rpm. Tablets (12 mm diameter, 600 mg) were produced at a force of 20 kN, whilst mini-tablets (2mm (7 mg), 3 mm (15 mg) and 4 mm (25 mg)) were produced at forces of 1, 3 and 6 kN respectively. Tablet strength was measured (6D tablet tester, Schleuniger, Germany) and 12 h drug release profiles obtained (USP apparatus 2, phosphate buffer pH 4.5, 37°C) using a Sotax AT7 dissolution bath and an Agilent 8453 DAD Spectrophotometer at 271 nm. Data were analysed for statistical significance ($P < 0.05$) using the Minitab™ software package.

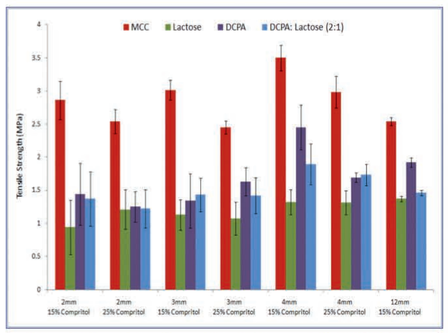

Fig. 1. Tensile strength of Compritol® 888 ATO tablets and mini-tablets produced with various diluents (mean ± SD, n = 10)

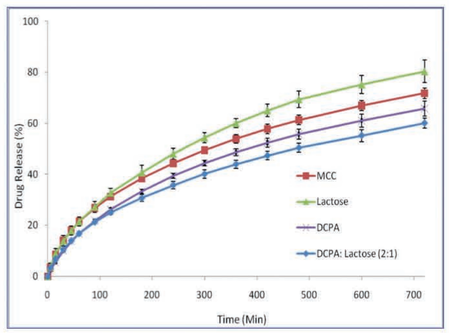

Fig. 2 Theophylline release from 12 mm tablets comprising 15 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

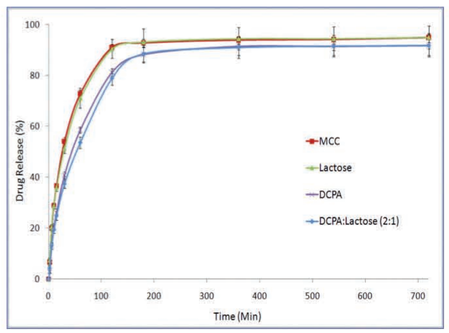

Fig. 3. Theophylline release from 2 mm mini-tablets comprising 15 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

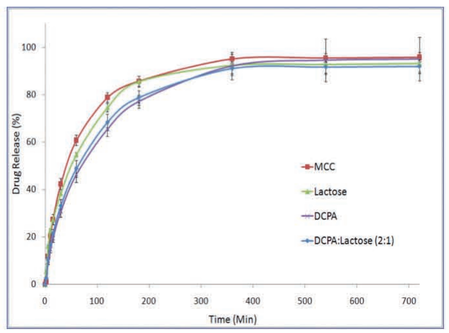

Fig. 4. Theophylline release from 2 mm mini-tablets comprising 25 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

Results & Discussion

Robust tablets and mini-tablets were obtained from all formulations (Fig 1) tablet and mini-tablet strength was significantly higher in tablets containing MCC due to its compressibility properties. Drug release from 12 mm tablets comprising 15 %w/w Compritol® 888 ATO was sustained over 12 h (Fig 2). Significantly faster release was achieved from tablets with lactose, presumably due to the solubility of the diluent increasing solvent penetration of the matrix, and from the tablets with MCC. The latter structures were observed to swell and split laterally during dissolution testing due to MCC promoting disintegration. Drug release from mini-tablets with 15 %w/w Compritol® 888 ATO was more rapid in comparison to the 12 mm tablets (Figs. 3, 5 & 7). The same diluent effect trends were seen with mini-tablets, with significantly faster release occurring from tablets containing lactose or MCC. Release from mini-tablets was retarded further by increasing the Compritol® 888 ATO level to 25 %w/w (Figs 4, 6 & 8), whilst the slowest and most consistent release rates were obtained from the formulations comprising the insoluble DCPA as diluent, alone or in combination with lactose. Release rates decreased as mini-tablet size increased (2 mm > 3 mm > 4mm) due to the shorter diffusion pathways. Results indicate that higher concentrations of Compritol® 888 ATO are required to sustain drug release from mini-tablets and that the solubility of the diluent(s) play a key role in modifying release rates.

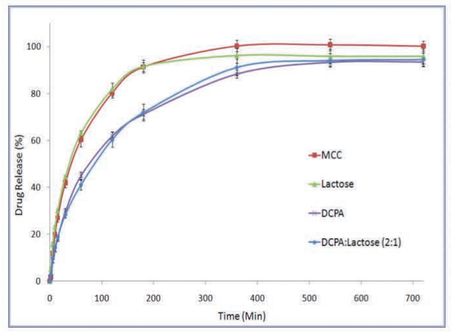

Fig. 5. Theophylline release from 3 mm mini-tablets comprising 15 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

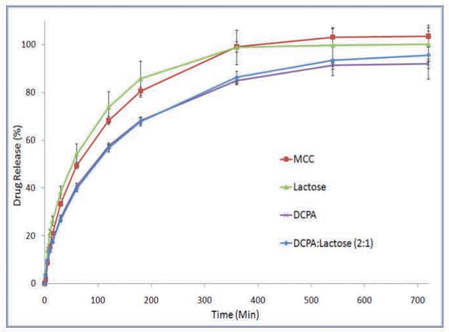

Fig. 6. Theophylline release from 3 mm mini-tablets comprising 25 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

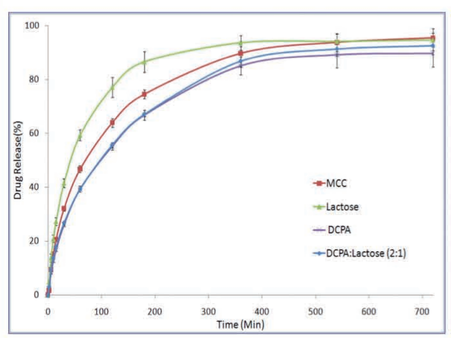

Fig. 7. Theophylline release from 4 mm mini-tablets comprising 15 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

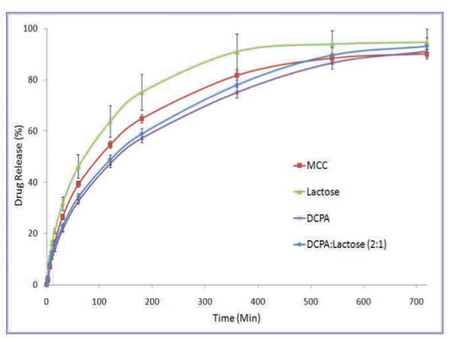

Fig. 8. Theophylline release from 4 mm mini-tablets comprising 25 %w/w Compritol® 888 ATO with various diluents (mean ± SD, n = 6)

Conclusions

Although a relatively low concentration of Compritol® 888 ATO is sufficient to sustain drug release from matrix tablets over a prolonged period, drug release is significantly faster from mini-tablets. The choice of diluents(s) also effects the release profiles obtained, with MCC and lactose likely to increase the rate of solvent penetration. Further studies are warranted to explore the development of sustained-release mini-tablets using lipid matrix formulations.

References

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2. Obaidat, A.A.; Obaidat, R.M. *Eur. J. Pharm. and Biopharm.* 2001 **52** 231-235
3. Treanor, G.; Roberts, M.; Mostafa, S.; Miolane, C. *J. Pharm. Pharmacol.* 2010 **62** 1419-1420