Diluent Effects On Drug Release From Sustained Release Compritol® 888 ATO Tablets

G. Treanor, M. Roberts, S. Mostafa[1], C. Miolane[2]

School of Pharmacy & Biomolecular Science, Liverpool John Moores University, Liverpool, UK.

[1] Gattefossé (UK) Ltd, Bracknell, UK

[2] Gattefossé SA, St Priest, France

Introduction

Glyceryl behenate (Compritol® 888 ATO) is commonly used in formulating sustained-release lipid matrices [1]. When compressed, Compritol® 888 ATO forms an insoluble network structure, allowing water to penetrate and subsequent drug release to occur through diffusion. The aim was to assess the effects of various diluents on the release of the soluble drug, theophylline, from Compritol® 888 ATO matrices produced via direct compression under simulated production conditions using a Stylcam® 100R rotary press simulator.

Materials & Methods

Formulations comprised; 16.7 %w/w anhydrous theophylline, 15 %w/w Compritol® 888 ATO, 3 %w/w magnesium alumino silicate (Neusilin® US2), 1 %w/w magnesium stearate and 64.3 %w/w diluent(s) (either; Microcrystalline cellulose (MCC, Avicel® PH101), Lactose (Lactopress® spray dried), dibasic calcium phosphate anhydrous (DCPA, Fujicalin®) 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). Tablets (600 mg, 12 mm) were produced using a Stylcam® 100R rotary press simulator (Medel'Pharm, France) at 12, 20 or 30 kN and 30 rpm (equivalent to rotary press production rate of ~120,000 tablets per hour). 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.

Results & Discussion

Robust tablets were obtained from all formulations at each compaction force (Fig. 1). Tablet strength was significantly higher with MCC in comparison with all other diluents(s) due to the compressibility of MCC. Tablets comprising lactose were weakest, whilst those with DCPA alone and in combination lactose were comparable. Figure 2 shows release profiles from tablets produced at 12 kN. Initial drug release was rapid due to dissolution of drug particles on the surface of the matrix and release was analogous to the Higuchi diffusion model. Drug release was sustained over 12 h from the tablets comprising DCPA: Lactose (2:1) and DCPA alone as the diluents(s). Faster and less consistent release was achieved from the tablets comprising MCC and the structures were observed to swell and split laterally during dissolution testing (Fig. 3), which was ascribed to the nature of MCC promoting disintegration. A three-phase release profile (0-2, 2-6 and 6-12 h) was evident for the tablets comprising lactose, possibly due to the solubility of the diluent increasing solvent penetration into the matrix . Increasing compaction force to 20 kN (Fig. 4) and 30 kN (Fig. 5) decreased release rate from all tablets and resulted in more consistent release profiles for tablets comprising MCC. The three-phase release profile for tablets with lactose was less evident at higher compaction forces.

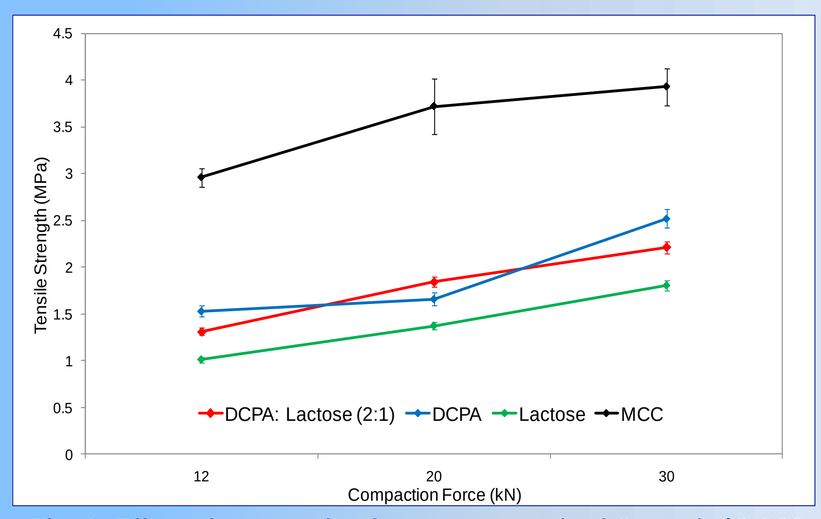

Fig. 1. Effect of compaction force on strength of Compritol® 888 ATO tablets produced with various diluents (mean ± SD, n = 10)

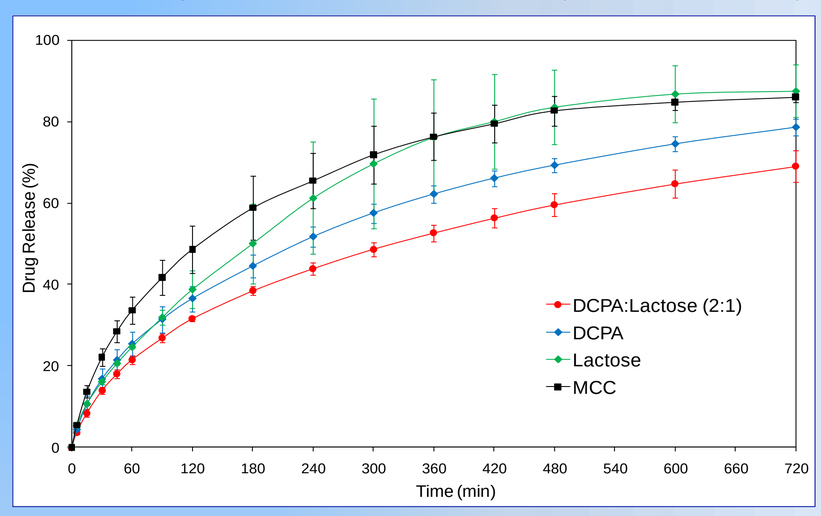

Fig. 2. Theophylline release from Compritol® 888 ATO tablets produced with various diluents at 12 kN (mean ± SD, n = 6)

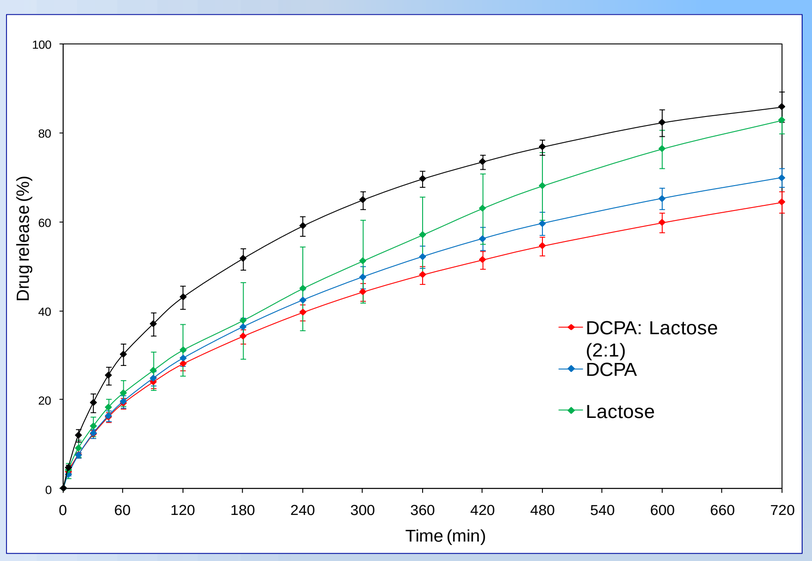

Fig. 4. Theophylline release from Compritol® 888 ATO tablets produced with various diluents at 20 kN (mean ± SD, n = 6)

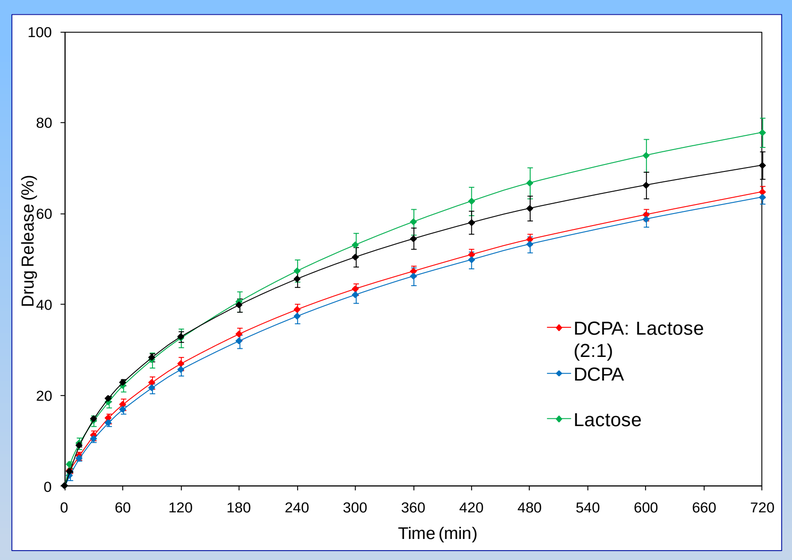

Fig. 5. Theophylline release from Compritol® 888 ATO tablets produced with various diluents at 30 kN (mean ± SD, n = 6)

Fig. 3. Lateral splitting of tablets comprising MCC during dissolution testing.

Conclusions

Robust tablets capable of sustaining drug release over 12 h using Compritol® 888 ATO as the lipid matrix were successfully manufactured at conditions analogous to rotary tablet press production. The type of diluent and compaction force used in producing lipid based matrices via direct compression has a significant impact on the drug release profiles obtained.

Reference

1. A.A. Obaidat and R.M. Obaidat, "Controlled release of tramadol hydrochloride from matrices prepared using glyceryl behenate"
Eur. J. Pharm. and Biopharm. **52** (2001) 231-235