SUSTAINED RELEASE LEVODOPA MINI-TABLETS CONTAINING COMPRITOL® 888: A VIABLE APPROACH FOR SPECIAL PATIENT POPULATIONS

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1 - PURPOSE

Lipid matrix mini-tablets for the sustained-release of levodopa were manufactured using a rotary press simulator. The effects of mini-tablet size (3 & 4 mm), Compritol® 888 concentration (15 – 45 %w/w), levodopa concentration (18.75 & 37.5 %w/w) and compression speed were evaluated. Sustained-release mini-tablets with good weight uniformity, tensile strength and diffusion-controlled release rates were successfully produced over a range of compression speeds. Mini-tablets may provide compliance benefits to elderly patients and the release rate of levodopa may be modified by altering the amount of Compritol® 888 in the formulation and/or mini-tablet size, meaning that the desired release profile can be tailored to suit the clinical need.

2 - INTRODUCTION

Mini-tablets are defined as being no more than 4 mm in diameter[1] and sustained-release mini-tablets may offer clinical and compliance benefits in special patient populations[2]. Compritol® 888 is commonly used in formulating sustained-release lipid matrices and when compressed, forms an insoluble network structure, allowing water to penetrate and subsequent drug release to occur through diffusion. In a previous investigation the potential of Compritol® 888 as a non-swelling matrix-forming agent in the manufacture of theophylline sustained-release mini-tablets was demonstrated[3]. The aim of the present study was to design mini-tablets for the sustained release of levodopa (L-DOPA) for the treatment of Parkinson's disease in elderly patients and to assess the effects of mini-tablet size, Compritol® 888 (C888) concentration, drug dose and compression speed on drug release rate.

3 - EXPERIMENTAL METHODS

Investigated formulations contained: 18.75 or 37.5 %w/w levodopa, 15, 25, 35 or 45 %w/w Compritol® 888 (glyceryl dibehenate), 3 %w/w magnesium alumino silicate, 1 %w/w magnesium stearate and diluents (2:1 DCPA : Lactose). Materials were blended for 2 min and subsequently for 1 min with lubricant (2C turbula mixer). Mini-tablets of 3 and 4 mm diameter (20 and 40 mg target weights respectively) were produced using a Stylcam® 100R rotary-press simulator with flat-faced tooling at compression forces of 2-4 kN and speeds of 10-30 rpm. Mini-tablet strength (kp) was determined using a Pharmatron 6D tester and tensile strength calculated based on tablet thickness (mm) and diameter (mm). Drug release was evaluated using a Varian VK7000 dissolution tester and a Cary 50 UV spectrophotometer at 280 nm. Data were analysed using the equation $Q = K\,t^n$, where Q is the fraction of drug release at time t, K is a kinetic constant and n is the exponent indicative of the release mechanism.

4 - RESULTS AND DISCUSSION

All formulations displayed good flowability, enabling the production of mini-tablets with excellent weight uniformity (CV <2%) under simulated rotary-press production conditions (Table 1). Robust mini-tablets were successfully produced from all formulations. Tensile strength was inversely proportional to the percentage of Compritol® 888 in the formulation but was independent of compression speed (Table 2).

The rate of drug release decreased as the concentration of Compritol® 888 and the mini-tablet diameter increased due to the tortuosity of the matrix and the length of the diffusion pathway respectively. Drug release rate was independent of compression speed. The total amount of drug released from mini-tablets comprising 18.75 %w/w Levodopa varied between 50% from 4 mm mini-tablets with 45 %w/w Compritol® 888 (Figure 1) to 100% from 3 mm mini-tablets with 15%w/w Compritol® 888 (Figure 2). Drug release from mini-tablets comprising a higher dose (37.5%w/w Levodopa) was faster, but sustained-release profiles were achieved even at relatively low levels of Compritol® 888 (Figure 3 & Figure 4). Analysis of data revealed drug release rates were proportional to the square-root of time (n ≈ 0.5), indicating a diffusion-controlled release mechanism.

Table 1: Weight uniformity (mg) of mini-tablets (mean ± SD, n = 10).

Production Speed	3 mm mini-tablets					4 mm mini-tablets				
	18.75% L-DOPA				37.5% L-DOPA	18.75% L-DOPA				37.5% L-DOPA
	15% C888	25% C888	35% C888	45% C888	25% C888	15% C888	25% C888	35% C888	45% C888	25% C888
10 RPM	20.0 ±0.2	20.8 ±0.2	19.8 ±0.2	20.0 ±0.4	20.0 ±0.2	39.7 ±0.4	39.9 ±0.4	40.9 ±0.4	40.5 ±0.5	39.8 ±0.5
20 RPM	20.1 ±0.2	20.2 ±0.2	19.6 ±0.3	20.0 ±0.3	19.9 ±0.2	39.9 ±0.2	39.3 ±0.3	40.2 ±0.6	40.8 ±0.3	39.5 ±0.6
30 RPM	20.1 ±0.1	20.2 ±0.2	19.5 ±0.2	19.8 ±0.2	19.8 ±0.3	40.3 ±0.4	39.1 ±0.1	39.1 ±0.3	41.1 ±0.1	39.3 ±0.2

Table 2: Tensile Strength (MPa) of mini-tablets (mean ± SD, n = 10).

Production Speed	3 mm mini-tablets					4 mm mini-tablets				
	18.75% L-DOPA				37.5% L-DOPA	18.75% L-DOPA				37.5% L-DOPA
	15% C888	25% C888	35% C888	45% C888	25% C888	15% C888	25% C888	35% C888	45% C888	25% C888
10 RPM	1.8 ±0.4	1.4 ±0.3	1.4 ±0.2	1.1 ±0.2	1.4 ±0.3	1.7 ±0.1	1.4 ±0.3	1.5 ±0.2	1.0 ±0.2	1.2 ±0.2
20 RPM	1.6 ±0.2	1.3 ±0.2	1.3 ±0.1	1.2 ±0.3	1.2 ±0.2	1.9 ±0.3	1.4 ±0.2	1.4 ±0.2	1.0 ±0.2	1.2 ±0.3
30 RPM	1.5 ±0.1	1.4 ±0.1	1.4 ±0.3	1.1 ±0.3	1.1 ±0.2	1.8 ±0.2	1.3 ±0.2	1.3 ±0.1	0.9 ±0.1	1.1 ±0.1

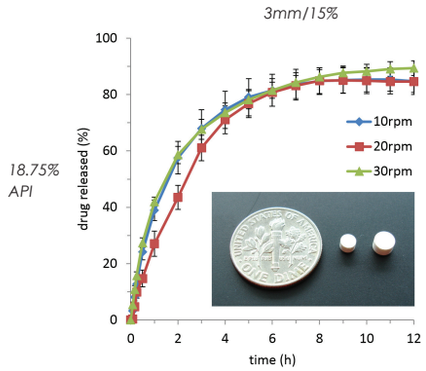

Figure 1: Drug release from 3mm mini-tablets containing 18.75%w/w (3.75mg) L-DOPA & 15%w/w Compritol® 888 produced at different speeds (mean ±SD, n=6).

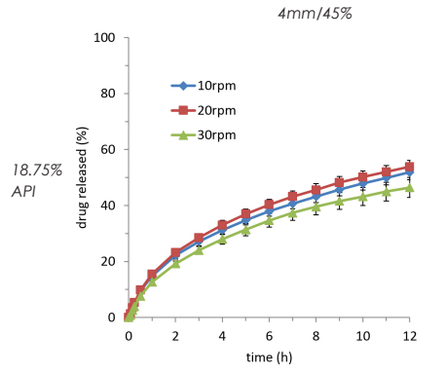

Figure 2: Drug release from 4mm mini-tablets containing 18.75%w/w (7.5mg) L-DOPA & 45%w/w Compritol® 888 produced at different speeds (mean ±SD, n=6).

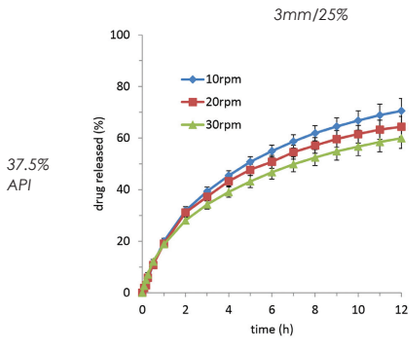

Figure 3: Drug release from 3 mm mini-tablets containing 37.5%w/w (7.5mg) L-DOPA & 25%w/w Compritol® 888 produced at different speeds (mean ±SD, n=6).

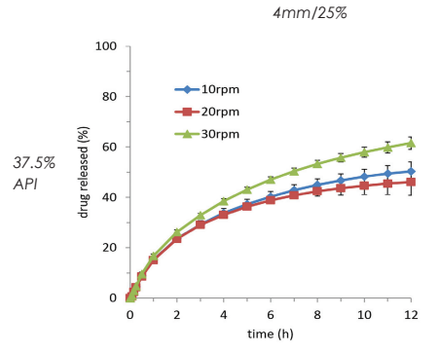

Figure 4: Drug release from 4mm mini-tablets containing 37.5%w/w (15mg) L-DOPA & 25%w/w Compritol® 888 produced at different speeds (mean ±SD, n=6).

5 – CONCLUSION

Sustained-release levodopa mini-tablets (3 & 4mm) were successfully manufactured under simulated rotary press production conditions. The release rate of levodopa from sustained-release mini-tablets may be modified by altering the amount of Compritol® 888 in the formulation and/or mini-tablet size, meaning that the desired release profile can be tailored to suit the clinical need. The small size of mini-tablets may provide compliance benefits in special patient populations.

6 – REFERENCES

[1] World Health Organization (2012) Expert Committee on Specifications for Pharmaceutical Preparations, 46th Report, Annex 5: Development of Paediatric Medicines – Points to Consider in formulation.
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[3] Roberts, M., Vellucci, D., Mostafa, S., Miolane, C., Marchaud, D. (2012) Development and evaluation of sustained release Compritol® 888 ATO matrix mini-tablets. *Drug Dev. Ind. Pharm.* 38 1068 - 1076.