Development of Hydrocortisone Mini-Tablets for Improved Paediatric Dosing

M. Roberts[1], F. Mohamed[1], R. Saleem[1], U. U. Shah[2], L. Seton[1], J. L. Ford[1]

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

[2] Medicines for Children Local Research Network, Alder Hey Children's NHS Foundation Trust, Liverpool, UK.

Introduction & Objectives

Hydrocortisone, a steroid used as replacement therapy in children with congenital adrenal hyperplasia, is commonly prescribed in 3 - 4 doses of ≤ 2.5 mg to cater for the total daily requirement. Hydrocortsione 10 mg tablets are routinely quartered to obtain the required dose for paediatric patients. Previous work has shown the inaccuracy of dosing via this method and highlighted the need for appropriate paediatric presentations of hydrocortisone[1].

Mini-tablets are compact dosage forms, typically 2 -3 mm in diameter, produced via traditional tableting methods, such as direct compression or wet granulation, and using ordinary tablet machines. Defined sizes and strengths can be easily produced, whilst batch variability is small and the size of mini-tablets helps to overcome dysphagia [2]. A recent study demonstrated that mini-tablets are a suitable dosage form for children aged between 2 - 6 years [3].

Traditionally, compaction simulators have been operated in single-ended rather than double-ended compaction mode and carry the liability of not being a realistic representation of tablet production on a rotary tablet press[4]. The Stylcam® 100R is a high precision, single station, rotary press simulator capable of producing up to 2400 tablets/hour using an automatic feeder and utilising a mechanical cam, which produces a bi-axial compaction profile analogous to that of a rotary tablet press.

The aim of this work was to investigate the feasibility of developing hydrocortisone mini-tablets for improved accuracy of paediatric dosing under simulated rotary press production conditions. The weight uniformity and dissolution behaviour of mini-tablets was compared with quartered tablets.

Methods

Hydrocortisone 10 mg tablets (Auden Mckenzie Ltd, UK) were quartered using a standard tablet cutter. A model formulation for mini-tablet production was developed, comprising; 16.67 %w/w hydrocortisone (Courtin & Warner Ltd, UK), 72.33 %w/w lactose (Tablettose® 80, Meggle, Germany), 10 %w/w Starch 1500® (Colorcon, UK), 0.5 %w/w Aerosil® 200 (Evonik, Germany) and 0.5 %w/w magnesium stearate (BDH, UK). Materials were initially blended for 5 min at 42 rpm using a turbula mixer (Type 2C, WAB, Switzerland) prior to sieving (500μm aperture, Endecotts, UK) and subsequent blending for 2 min with magnesium stearate.

Hydrocortisone mini-tablets, 3 mm in diameter, were manufactured by direct compression using a Stylcam® 100R rotary press simulator (Medel'Pharm, France) at a compression force of 2 – 3 kN and speed of 20 rpm (equivalent to a rotary tablet press production rate of ~ 80,000 tablet per hour).

The weight uniformity of mini-tablets and quartered tablets was calculated and the strength of the mini-tablets determined (6D tablet tester, Schleuniger, Germany). Drug release from quartered tablets and mini-tablets was evaluated under sink conditions (USP apparatus 2, 50 rpm, 900 ml water at 37°C) over a period of 30 min using a Varian VK 7000 dissolution tester and Cary 50 UV spectrophotometer at 248 nm. Data were analysed for statistical significance ($P<0.05$) using the Minitab™ software package.

References

1. K. Heames, P. Riby, U.U. Shah, J. Blair and J.L. Ford. (2009). Accuracy of 2.5 mg hydrocortisone doses from quartered 10 mg tablets. *Endocrine Abstracts.* **23** OC3.1
2. P. Lennartz, and J.B .Mielck. (1998). Minitableting: Improving the compactability of paracetamol powder mixtures. *International Journal of Pharmaceutics.* **173.**75-85
3. S.A. Thomson, C. Tuleu, I.C.K. Wong, S Keady, K. Pitt and A. Sutcliff. (2009). Assessing the acceptability of mini-tablets for use in children aged 2-6 years old. *Pediatrics* **123** 235-238
4. Jain, S. (1999) Mechanical properties of powders for compaction and tableting: an overview. *Pharm. Sci. Tech. Today* **2** 20-31

Results

Robust mini-tablets were successfully manufactured under simulated rotary press production conditions using a model hydrocortisone formulation. Hydrocortisone mini-tablets, displayed improved weight variation when compared to quartered tablets and equivalent or better strength in comparison to whole tablets (Table 1).

Although the time taken to reach maximal dissolution was similar for both quartered tablets and mini-tablets (Fig. 1.), a high variation in the percentage drug dissolved after 30 min was observed with the quartered tablets (83.5 – 115.5%), whilst a significant ($P<0.05$) reduction in variation of percentage drug dissolved after 30 min was attained with mini-tablets (95.1% - 105.7%).

The low standard deviations in the dissolution profile of mini-tablets demonstrate reproducibility of product performance, whilst the high variation in amount dissolved from quarters at each time point, particularly after maximum dissolution (15 min), is most likely due to poor dose uniformity and supports the findings previously reported[1].

This study has illustrated that quartering of tablets is not an accurate method of drug delivery to paediatric patients as fragmentation and powdering of tablets can lead to variation in mass, which can result in under or over-dosing. These issues can be eliminated with appropriate paediatric formulations such as mini-tablets, which can feasibly be produced on a large scale.

	Mean tablet weight (mg) (±S.D.)	Coefficient of weight variation (%)	Mean tablet strength (MPa) (±S.D.)
Whole tablets (n = 10)	**240.0 (± 1.6)**	**0.7**	**1.07 (±0.1)**
Quartered tablets (n = 40)	**58.9 (±8.0)**	**13.6**	**N/A**
Mini-tablets (n = 10)	**16.1 (±0.7)**	**4.3**	**1.73 (±0.5)**

Table 1. Weight variation and strength of whole tablets, quartered tablets and mini-tablets

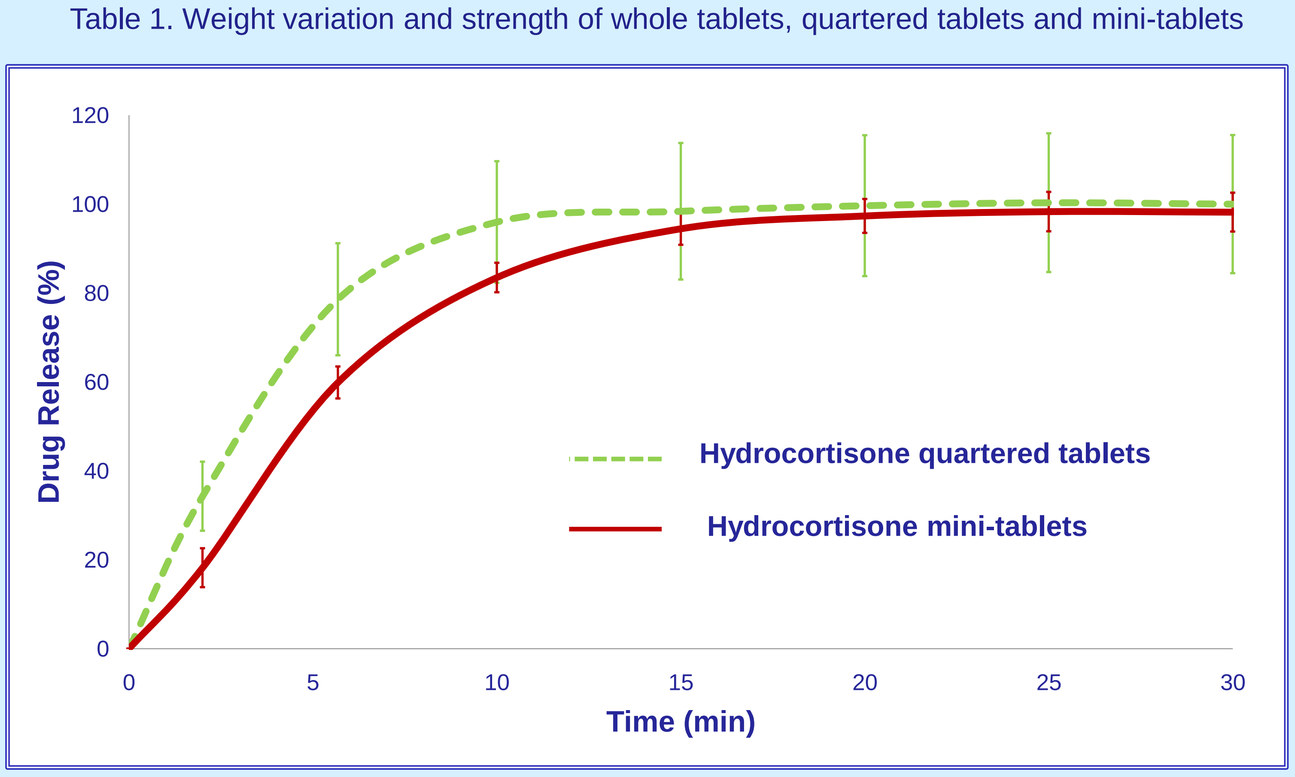

Fig. 1. Hydrocortisone release from mini-tablets and quartered tablets (mean ± SD, n = 6)

Conclusion

An improvement in the accuracy of paediatric dosing of hydrocortisone over the practice of manipulating 'adult' dosage forms by quartering tablets has been highlighted during this study. The feasibility of industrial scale production of hydrocortisone mini-tablets, with good weight uniformity and consistent dissolution performance has been demonstrated