Biorelevant dissolution and compatibility of hydrocortisone granules following exposure to water, breast-, whole- and artificial (formula) milk

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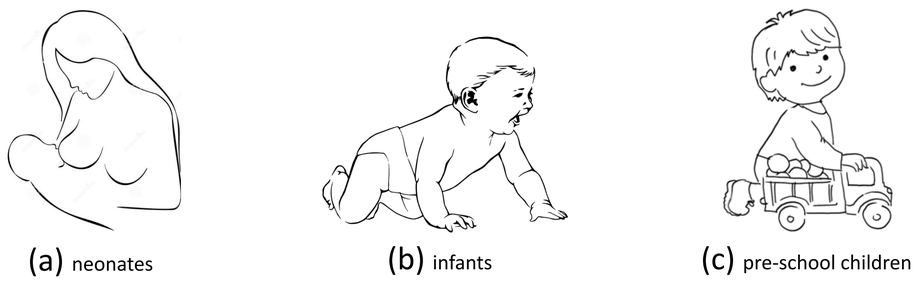
Introduction

Infacort® (Diurnal Ltd, UK) is an oral multi-particulate (granule) taste-masked formulation of hydrocortisone which is being specifically developed in Europe for use in children aged 0-6 years with the rare disease adrenal insufficiency. The proposed hydrocortisone dose per unit is in the range of 0.5 to 5 mg. Infacort® is intended to be dosed to paediatric patients by placing the capsule contents on a dry spoon and then administering directly into the patient's mouth or for the capsule contents to be administered directly onto the child's tongue and washed down immediately with fluid (e.g. water, breast milk, formula milk). The objective of the present work was to study the biorelevant dissolution and compatibility properties of Infacort® granules following exposure to commonly administered fluids in this age groups including breast milk, artificial milk and water.

Materials and Methods

To provide *in vitro* data for a representative patient collective, dosing conditions in newborns (neonates), infants and pre-school children were assessed (figure 1). The dissolution media applied was water for all age groups, breast milk and formula milk (Nestlé Beba PRO) for newborns (#1) and infants (#3) as well as whole milk for the pre-school children (figure 2). The hydrocortisone doses applied were the minimum (0.5 mg) and maximum (5 mg) doses developed. Experiments in breast milk from two different sources (breast milk 1: mother of twins, week 7-8 after birth; breast milk 2: mother of a single child, day 1-8 after birth) were performed to address the variability in composition of breast milk. The test volumes of the fluids were adapted to estimated stomach volumes of the different aged children after administering a single dose with sufficient fluid (50-200 mL).



(a) neonates (b) infants (c) pre-school children

Figure 1: Age groups to be addressed in the study

(a) water, breast milk 1 & 2, formula milk 1 (b) water, breast milk 1 & 2, formula milk 3 (c) water, whole milk

Figure 2: Media used for simulating dosing conditions in the different age groups

Dissolution experiments were performed at 37 °C with the Mini-Paddle apparatus (modified type II apparatus, DT 600, Erweka, Germany) using a media volume of 200 mL and an agitation speed of 100 rpm. All experiments were performed in triplicate. Where necessary both the dose and the respective test volume were up-scaled proportionally to allow the use of this setup (table 1). To prevent the granules from floating on the media surface after adding them to the dissolution media, they were not sprinkled into the vessel, but filled into a straw which prior to this had been sealed with a piece of Parafilm M® laboratory film at its lower end. With the paddle rotating at 100 rpm the filled straw was lowered into the dissolution medium. A small amount of air pressure was used to displace the sample from the straw, resulting in release of the granules followed by immediate dispersion under the paddle (figure 3). The total duration of the dissolution experiments was 240 min to screen both dissolution and compatibility with the different media. Samples were removed at predetermined time points and analysed by HPLC.

Table 1: Estimated typical gastric fluid volumes available after dose administration in children of different age groups and upscaled dose:volume ratios for dissolution test experiments

age group	test media	lowest dose	highest dose	available volume	lowest dose upscaled	highest dose upscaled	available volume upscaled
neonates	water, breast milk 1, breast milk 2, formula milk 1	0.5 mg	5.0 mg	50 mL	2.0 mg	20.0 mg	200 mL
infants	water, breast milk 1, breast milk 2, formula milk 3	0.5 mg	5.0 mg	100 mL	1.0 mg	10.0 mg	200 mL
pre-school children	water, whole milk 3.5 %	0.5 mg	5.0 mg	200 mL	0.5 mg	5.0 mg	200 mL

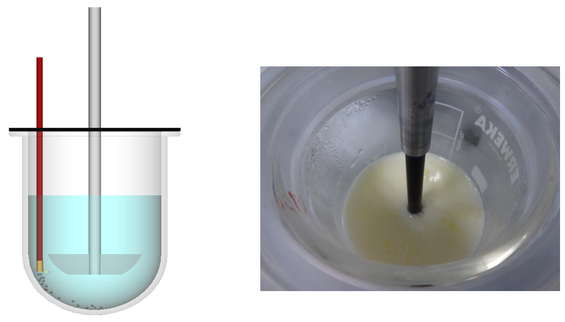


Figure 3: Dose application and setup with breast milk 1

Results

Figure 4 displays the dissolution results obtained when simulating administration of Infacort® 0.5 mg together with water or different age-appropriate milk types to neonates, infants or pre-school children.

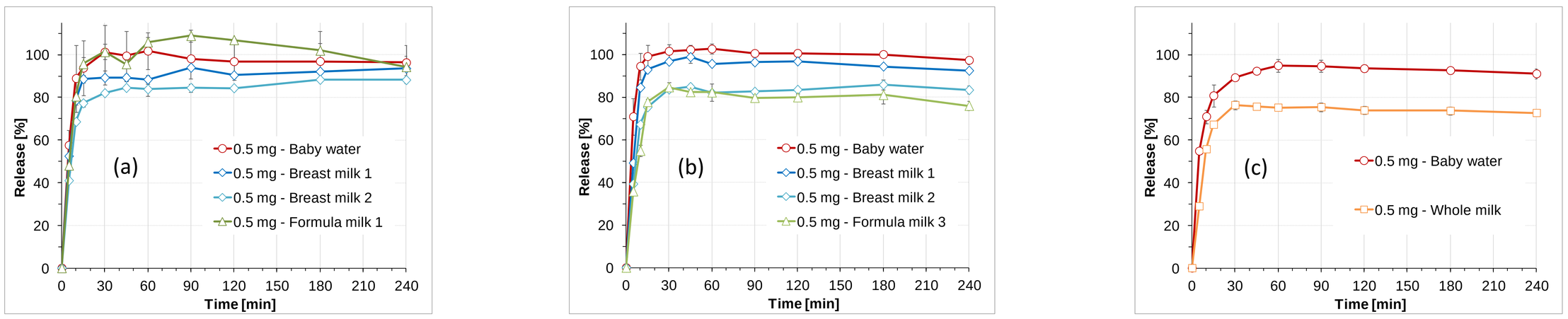


Figure 4: Dissolution of Infacort® 0.5 mg when simulating co-administration with different fluid types to (a) neonates (b) infants and (c) pre-school children (mean of n=3 ± SD).

Dissolution of the 0.5 mg dose in media and volumes intended to simulate initial gastric conditions after dose administration was fast and complete in all scenarios, i.e. ≥ 80 % of the dose was released in the neonate and the infant scenario and ≥ 75 % in the pre-school children setup within 30 min. Results for the 5 mg dose were ~5-10 % lower in all simulated patient scenarios. However, it should be noted that particularly in the case of neonates where stomach capacity significantly increases within the first days/weeks in life [1,2], the estimated typical gastric fluid volume was rather small and that overall, the study focused on gastric conditions only. In all experiments no drug precipitation or degradation could be observed over the entire test duration.

References: [1] Bergmann NJ. Acta Paediatr. 2013 , 102(8):773-7. [2] Zangen S et al. Pediatr Res. 2001, 50(5):629-32.

Conclusion

The results obtained in the present study confirm the compatibility and in-use chemical stability of Infacort® with commonly used dosing matrices like water, breast milk, formula milk and whole milk over a 240 minute period. Results from the biorelevant *in vitro* dissolution experiments suggest that *in vivo* dissolution and bioavailability of Infacort® will not be affected by the composition of the co-administered fluids studied.

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