Dissolution and compatibility of hydrocortisone granules following exposure to common paediatric administration fluids and food matrices

Erik Wollmer¹, Lisa Freerks¹, Anna-Elena Hetberg¹, Frank Karkossa¹, Greg Neal², Martin J. Whitaker², Daniel Margetson², Sandra Klein¹

¹ Department of Pharmacy, University of Greifswald, Germany
² Diurnal Limited, Cardiff, United Kingdom

Introduction

Infacort® is an oral multiparticulate (granule) taste-masked immediate release formulation of hydrocortisone which is being specifically developed for use in children from birth as a replacement therapy in adrenal insufficiency. The granules are contained in a hard capsule carrier and the proposed hydrocortisone dose per unit ranges from 0.5 to 5 mg. The capsule is opened and the granules are intended to be administered directly into the child’s mouth and washed down immediately with fluid. However, to increase acceptability of paediatric medicines, co-administration of dosage forms with soft food or drinks is a common real-world practice. Such procedures require sufficient in situ stability of the drug product in these dosing matrices to cover the administration timeframe. Moreover, the type and amount of food/fluid co-administered with the drug product should not affect its clinical performance. The objective of the present work was to study the in situ compatibility of Infacort® in different soft-food and drink matrices commonly used for administration in young children and to study how the pH and physicochemical properties of the different matrices affect biorelevant dissolution properties of the drug product.

Materials and Methods

Dosing conditions were assessed for a representative patient collective, ranging from infants to school children (figure 1). Hydrocortisone doses applied in the in vitro experiments were in the dose range of 2.5 to 5 mg. Test media and volumes were adapted to simulate gastric contents of children of different ages immediately after administering a single dose of hydrocortisone together with an age appropriate volume of the different fluids (40-175 mL, table 1), or after mixing and administering with 1 teaspoon (= 5 mL) a dosing vehicle (figure 2) followed by some water intake (table 1).

Dissolution experiments (n=3) were performed at 37 °C with the Mini-Paddle apparatus (DT 600, Erweka, Germany) using a media volume of 200 mL and an agitation speed of 100 rpm (figure 3). Where necessary both the dose, the amount of administration vehicle and fluid were up-scaled proportionally to allow the use of this setup (table 1). The total duration of the dissolution experiments was 120 min. Samples were removed at predetermined time points and, following appropriate sample preparation, analysed by HPLC.

Results

Figures 4 a-c display the dissolution results obtained when simulating administration of Infacort® 2.5 mg or 5 mg to infants, pre-school children and school children together with fluid and soft food followed by some additional fluid intake.

In all dosing scenarios simulating initial gastric conditions after administering age-related hydrocortisone doses to children of different age groups, in vitro drug release was fast and complete, i.e. > 75 % of the dose was released within 30 min (USP requirements for hydrocortisone tablets: > 70 % within 30 min). This was despite the dosing matrices differing significantly in pH and other physicochemical parameters. Moreover, in all experiments no drug precipitation or degradation could be observed over the entire test duration.

Conclusion

Results from this study confirm the compatibility and chemical stability of hydrocortisone granules with commonly used dosing matrices over a time of 120 min. Results from the biorelevant in vitro dissolution experiments suggest that in vivo dissolution and bioavailability of the granules will not be affected by the composition of the co-administered fluids and soft foods studied.

Acknowledgement

This work was initiated and funded by Diurnal under a collaborative R&D agreement and also by the European Commission under a FP7 Grant (TAIN; No: 281654).

References

Table 1: Estimated typical gastric fluid volumes available after dose administration in children of different age groups and up scaled dose:volume ratios for the in vitro experiments

<table>
<thead>
<tr>
<th>age group</th>
<th>test dose</th>
<th>amount of co-administered food/fluid</th>
<th>resting gastric volume</th>
<th>volume of additional fluid</th>
<th>dose up scaled</th>
<th>total volume up scaled</th>
</tr>
</thead>
<tbody>
<tr>
<td>infants &amp;</td>
<td>2.5 mg</td>
<td>1 teaspoon = 5 mL</td>
<td>10 mL</td>
<td>pH 1.8 - 4.0</td>
<td>35 mL</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>pre-school</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85 mL</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>children</td>
<td>5.0 mg</td>
<td>1 teaspoon = 5 mL</td>
<td>25 mL</td>
<td>pH 1.8</td>
<td>170 mL</td>
<td>5.0 mg</td>
</tr>
</tbody>
</table>

© 2017 Diurnal Limited. All rights reserved.