AGE RELATED BIORELEVANT DISSOLUTION TESTING FOR PAEDIATRIC FORMULATIONS

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INTRODUCTION

- Dissolution of oral dosage forms depends on the GI tract physiological conditions, and definition of the dissolution profile in conditions that reflect the in vivo GI environment can lead to accurate prediction of the in vivo performance (1).
- Whenever IVIVCs are achieved clinical studies assessing product bioavailability can be reduced in number and size and this aspect is of primary importance for paediatric patients (2). Successful predictions of the in vivo performance of drugs can be achieved based on biorelevant in vitro experiments (2).
- Biorelevant media reflective of age specific paediatric populations (i.e. new born and infant) have been developed (3).

Aim: to develop biorelevant dissolution methods that are representative of the paediatric gastrointestinal tract by applying experimental parameters based on physiological relevant parameters in order to assess the possible effects on dissolution/release proprieties of oral formulations for paediatric patients.

MATERIALS AND METHODS

Tegretol® 200mg tablets (Novartis) traditionally used to treat epilepsy in children and adults have been investigated. Two paediatric age groups were investigated: namely neonates (0-28 days) and infants (1-12 months). Biorelevant media simulating age specific parameters in GI fluids (i.e. pepsin, bile acids, pH, osmolarity) in the fasted state were used (Table 1).

Table 1: In vitro biorelevant dissolution testing parameters based on physiological relevant parameters (i.e. media/hydrodynamics) and used for USP IV apparatus dissolution tests

<table>
<thead>
<tr>
<th>Age group</th>
<th>Gastric conditions (open mode)</th>
<th>Gastric conditions (closed mode)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Media</td>
<td>Time (min)</td>
</tr>
<tr>
<td>Neutonnes</td>
<td>P-FaSSGF</td>
<td>45</td>
</tr>
<tr>
<td>Infants</td>
<td>P-FaSSGF</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Intestinal conditions (open mode)</td>
<td></td>
</tr>
<tr>
<td>Neutonnes</td>
<td>P-FaSSGF 50%</td>
<td>240</td>
</tr>
<tr>
<td>Infants</td>
<td>FaSSGF</td>
<td>240</td>
</tr>
</tbody>
</table>

Carbamazepine (CBZ) was not completely dissolved in all the conditions tested. An age dependent dissolution profile of carbamazepine from Tegretol tablet is observed in the two paediatric groups studied (figures 2 and 3), revealing the impact of the gastrointestinal differences (fluid composition and transition times) between the age groups on dissolution.

RESULTS

- Taking into account age related physiological parameters has an impact on dissolution of oral solid dosage forms.
- Age related biorelevant dissolution testing can be a valuable tool for the evaluation of dissolution-release properties of oral formulations and the assessment of potential implications for paediatric oral drug delivery.

CONCLUSIONS

Acknowledgements: Work completed on behalf of SPaeDD-UK (Smart Paediatric Development), a project co-funded by Innova UK and the contributing companies of AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Juniper Pharmaceuticals and Pfizer

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