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Estimating in vivo drug release from a new theophylline Compritol® 888 ATO matrix formulation using appropriate biorelevant test methods

N. Fotaki1, C. M. Long1, Y. Cuppok-Rosiaux2, D. Marchaud2, Grzegorz Garbacz3, S. Lange4 and S. Klein4

1University of Bath, Department of Pharmacy and Pharmacology, Bath, BA2 7AY, United Kingdom
2Gattefossé SAS, St. Priest, BP603-F69804, France
3Physiolution GmbH, Greifswald, 17489, Germany
4University of Greifswald, Department of Pharmacy, Institute of Biopharmaceutics and Pharmaceutical Technology, Greifswald, 17489, Germany

Sandra.Klein@uni-greifswald.de

ABSTRACT SUMMARY

The present series of test focused on evaluating the robustness of drug release from lipid based theophylline matrix tablets under a simulated fasted gastrointestinal passage. A robust sustained release was observed in all experiments.

INTRODUCTION

Oral extended-release (ER) dosage forms have represented a broad segment of research and development in the pharmaceutical industry for many years. Housing drugs with a short half-life they can typically enable a reduced dosing frequency which comes along with various potential advantages such as e.g. reduced fluctuations in drug levels, a reduced total amount of drug that has to be used, improved patient compliance, better and more uniform clinical effects, lower incidence of side effects.

Since drug absorption from ER dosage forms is governed by the rate of release from the formulation and since these formulations typically contain much higher drug doses than the respective immediate-release (IR) formulations, it is essential to assure robust and reproducible in vivo drug release to prevent the unwanted toxic peaks and sub-therapeutic troughs in plasma levels caused by “dose dumping” or insufficient/hindered drug release.

Matrix-based formulations, consisting of the active drug embedded in a polymer matrix which controls drug release, have traditionally been the most commonly used ER dosage forms. Traditionally, a whole range of water-soluble or water-swellable polymers with high molecular weight with HPMC being the most representative candidate have been used as matrix formers. However, some of these formulations have shown increased sensitivity to the composition of gastrointestinal fluids and gastrointestinal shear forces [1-2] which could not be predicted by standard dissolution experiments in the paddle or basket apparatus.

To predict whether the ER dosage form meets its in vivo release profile goals, one needs to apply an adequate release test system that reflects conditions relevant to the in vivo conditions of drug release.
Dissolution test setup

Dissolution studies were performed at 37°C with a) the reciprocating cylinder apparatus, (USP III; ERWEKA RRT 10: 200 mL per vessel, 420 µm mesh screens, 10 dpm), b) the flow through apparatus (USP IV; ERWEKA DFZ: 22.6 mm cell filled with 1 mm-size glass beads, Whatman® glass fiber filter (GF/F), tablets on holder, flow rates: stomach: 8 mL/min, small intestine and colon: 4 mL/min), and c) an ERWEKA biorelevant dissolution stress test apparatus intended to reflect phases of pressure waves simulating episodes of high gastrointestinal motility (gastric emptying (GE), ileocecal passage (ICP)) and phases of transport (780 mL, 100 rpm, 3 pressure waves (300 mbar) for gastric emptying and ileocecal passage, 1 min rotation at 100 rpm every 10 min for intestinal transport events). Results in USP III and IV were performed in the buffer media, whereas in the stress test experiments both buffers and the corresponding biorelevant media (with bile compounds) were used. Media and corresponding residence times are given in Table 2.

Table 2: Dissolution media [3] and corresponding residence times

<table>
<thead>
<tr>
<th>GI section</th>
<th>Medium</th>
<th>pH</th>
<th>Residence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>SGF / FaSSGF</td>
<td>1.8</td>
<td>60 min</td>
</tr>
<tr>
<td>Small intestine</td>
<td>(Blank) FaSSIF</td>
<td>6.8</td>
<td>240 min</td>
</tr>
<tr>
<td>Proximal colon</td>
<td>SGOf</td>
<td>5.8</td>
<td>240 min</td>
</tr>
<tr>
<td>Colon</td>
<td>Blank FaSSIF</td>
<td>6.5</td>
<td>180 min</td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSION

Results from the experiments simulating a fasted gastrointestinal passage of monolithic dosage forms show slight differences in the release profile which is most likely due to the nature of the apparatus and the test settings which are likely to result in different hydrodynamic conditions. Overall, both the TheoStat® L.P. 100 mg marketed product and the theophylline Compritol® 888 ATO matrix formulation are neither sensitive towards the changing pH-conditions (Figures 1-3), nor are significantly affected by biorelevant gastrointestinal stress conditions in the fasted GI tract (Figures 3 and 4).

CONCLUSION

Compritol® 888 matrix tablets prepared by direct compression offer a quite robust sustained release in biorelevant fasted conditions even when exposed to simulated mechanical stress in the fasted human GIT. Further studies should be carried out in fed conditions - which exert a significant role in drug dose dumping.

REFERENCES