Development of a Swellable Matrix Tablet for a Novel CNS Drug Candidate

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ABSTRACT SUMMARY
A novel CNS drug candidate demonstrated useful first-in-human safety properties but was challenged by a short half-life and high Cmax-Cmin plasma level variations. A sustained released formulation was assessed. Drug absorption in the distal bowel and ascending colon was found to be equivalent to that in the proximal small intestine. A swellable matrix tablet based on HPMC was generated and optimized such that drug release over a 6 or 12 h time frame could be achieve in vitro. Clinical assessments of these formulation suggested useful biopharmaceutical properties with prolonged absorption.

INTRODUCTION
In cases of drugs with short plasma half-lives or narrow therapeutic windows, the ability to sustain drug release subsequent to oral dosing could not only optimize the therapeutic index of the drug but also improve patient compliance. A number of dosage form concepts have been designed to address these needs including matrix-forming tablets in which drug release is controlled by diffusion and erosion. These systems can often provide for the release characteristic required, are simple to manufacture and scale, are often very cost-effective and make use of well characterized, generally regarded as safe (GRAS) excipients. These systems can retard drug release delaying it to more distal portions of the GI tract meaning that one prerequisite for a useful system is that the drug gives good permeability in the distal small bowel and colon. Compound A is a BCS Class I drug candidate which has been successfully tested in man both as a solution and simple (immediate release) tablet. Biological half-life data suggested that a sustained release formulation might add value. In order to assess the feasibility of a controlled release dosage form, a study was completed wherein drug uptake was assessed when drug was administered in the distal small intestine or ascending colon. HPMC-based matrix tablet were then designed and prototypes generated using in vitro drug release. Selected matrix tablets were then assessed in a clinical trial to evaluate human pharmacokinetics.

EXPERIMENTAL METHODS
Compound A was obtained from Janssen Pharmaceutica, Beerse, Belgium and was characterized with a purity >98%. Matrix formulation were generated using HPMC at two different molecular weights (6500 and 100000), HPC and drug dried waxy maize starch. Tablets were designed to contain 40 mg eq of Compound A with a total tablet weight of approximately 350 mg. Four dissolution paradigms were applied to test the concepts generate all of which involved a USP II apparatus, thermostated to 37 °C and with a paddle speed of 75 rpm and a total media volume of 900 mL. The four media tested included (one phase) 0.01 N HCl, 0.05 M pH 6.8 phosphate buffer, (two phase) (1 h) 0.01 N HCl then (23 h) pH 6.8 phosphate buffer and (1 h) 0.01 N HCl (250 mL) and (23 h) Fessif (1000 mL).

Regional intestinal absorption studies were completed in man using the Enterion® capsule in which the drug was administered as a solution in aqueous 2-hydroxypropyl-β-cyclodextrin to either the distal small intestine or ascending colon and compared to an oral solution delivered po. Subsequently, matrix tablets based on a fast and slow release pattern were also assessed in man compared with a simple immediate release (IR) tablet. The matrix tablets contained 40 mg eq of Compound A and the IR tablets 10 mg eq (two IR tablets were dosed in the clinical evaluation). All studies were GCP-compliant with full informed consent and conducted under relevant national and international law and guidelines. The clinical investigations were completed as open label trials using 12 and 24 healthy subjects (male, Caucasians between age 18 and 55 years and within 20% of their ideal body weight) for the regional absorption and matrix tablet studies, respectively. Each subject received a test formulation as described (either fasted or after a high fat breakfast). Blood was sampled at 0, 1, 2, 3, 4, 5, 6, 8 and 24 h after dosing and analysed using a fully validated HPLC analytical method. Pharmacokinetic parameters including T_max, C_max and AUC_{24h} were determined by standard model-independent methods using actual times of blood sampling.

RESULTS AND DISCUSSION
Drug absorption was assessed using the Enterion® capsule1 which was loaded with a solution of Compound A in a cyclodextrin vehicle with the drug administered either to the distal small intestine (at doses of 2 and 10 mg) or in the ascending colon (at a dose of 10 mg). This was compared to an oral dose of the 10 mg cyclodextrin solution. The AUC of the drug administered to the distal small bowel and ascending colon was similar to that of the orally dosed medication. The Cmax was reduced by approximately 30% when the oral solution was compared to the colon however Cmax were comparable when oral and distal small bowel dosing were assessed. These data suggested that a controlled release dosage form may be feasible. Controlled release tablet was considered with the following properties including a total dose of 40 mg and a drug release window of between 6 and 12 h.
A significant design concern related to the sensitivity of solubility on pH which decreased rapidly with increasing pH. Based on drug release from a swellable matrix, this may negatively impact the release mechanism as the tablet transitions from the stomach to the intestine. To proactively address this, solubility differences as a function of pH were attenuated by adding 2-hydroxypropyl-β-cyclodextrin to the matrix such that diffusion would continue to drive drug release over the life time of the matrix. The excipient space of the tablet therefore included the active API, HPβCD and three polymers including HPMC at various molecular weights/viscosity grades, HPC and drum dried waxy maize starch. Screening experiments found that the optimal amount of the matrix-forming polymers was ~30% with little change in drug release as this percent changes from 20 to 40%. In the case of HPβCD, concentrations between 20 and 50% yielded similar release profiles however excluding the cyclodextrin generated systems that poorly released drug at pH 6.8 and which were also highly dependent on ionic strength of the release media. Two prototype, matrix-based tablets were therefore designed based on high and low viscosity HPMC. A “fast” releasing matrix was prepared based on HPMC 6500 mPa.s and a slow releasing tablet based on 100000 mPa.s material. Four dissolution assessments were completed with the two matrix tablets as is illustrated in Figures 1 and 2.

These tablets were then examined in a clinical assessment under fasted conditions and compared to the simple IR tablets. Two IR tablets (10 mg eq. of Compound A per tablet) versus 40 mg eq in the controlled release tablets were evaluated (Table I).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IR Tablet (20 mg)</th>
<th>Slow Matrix (40 mg)</th>
<th>Fast Matrix (40 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>67.4±21.9</td>
<td>60.2±19.1</td>
<td>70.5±23.5</td>
</tr>
<tr>
<td>AUC_{0-&lt;inf&gt;-&gt;} (ng.h/mL)</td>
<td>715±218</td>
<td>1547±349</td>
<td>1399±361</td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>29.2±7.3</td>
<td>28.7±10.3</td>
<td>26.5±7.4</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1 (0.5-2)</td>
<td>5 (3-14)</td>
<td>5 (3-7)</td>
</tr>
</tbody>
</table>

The peak plasma concentrations obtained for the fast and slow matrix tablet were 53.53%, and 60.44%, respectively, compared to the dose-normalized C_{max} observed with the reference IR formulation indicating slower uptake. The relative bioavailability of the two matrix tablets compared to the IR reference tablet (dose normalized to 40 mg), administered in fasted healthy subjects was 100%. The Tmax was delayed due to slower absorption of the CR formulations with median t_{max} values ranging from 3 to 14 hours for the slow matrix, 3-7 h for the fast matrix versus 0.5 to 2 hours for the immediate release tablets.

CONCLUSION

Drug candidates often do not possess all of the biopharmaceutical elements to translate directly into an optimal drug. Early testing can identify risks some of which may be addressed by formulation intervention. Compound A showed good clinical promise but suffered from a short plasma half-life as well as high Cmin-Cmax variability. Regional absorption testing found good uptake along the GI tract including in the distal small bowel and ascending colon. HPMC-based matrix tablets could be designed which were as bioavailable as the IR tablets and which delayed drug uptake based on Cmax and Tmax data. These improvements may enable the full exploitation of this drug candidate.

REFERENCES