Novel orally swallownable IntelliCap™ device guarantee success in MR development by quantitative determination of regional drug absorption in man

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ABSTRACT SUMMARY
Quantitative regional absorption of diltiazem was studied by using the novel IntelliCap™ system. The IntelliCap capsule is an orally swallowable programmable drug delivery capsule capable of real-time monitoring of physiological conditions (pH, temperature), consequently allowing localization of the capsule over time by the typical and consistent physiological pH profiles in dog and man. The plasma concentration–time profile could then be correlated to drug absorption (AUC) in different gut regions.

Diltiazem showed an overall absorption of 84% of the dose in man whereby 55% was absorbed in the colon. This is about 65% of the absorbed drug which is in line with literature ~82% ¹

INTRODUCTION
To develop a modified release formulation, it is critical to know the absorption property of a drug in the entire gastrointestinal (GI) tract. A typical task of modified release systems is to change the dose schedule from multiple daily to once daily. Therefore a drug release of more than 5 hours (human average small intestine transit time) is required and the development is only meaningful if the drug has a sufficient colonic absorption.

According to the FDA² only about 7.3% of the oral drug products are extended release formulations (1,287 out of 17,553) meaning that most drugs (92.7%) do not have colonic absorption.

Conventional approaches to determine regional absorption in vivo have been to use an engineered capsule for targeted delivery in man³ (e.g. InteliSite, Enterion) or by insertion of a catheter⁴. In pre-clinical use intestinal access port animal models may be considered⁵.

The IntelliCap system has successfully demonstrated its utility in a regional drug absorption studies as reported by Zou⁶ and in dozens of unpublished dog studies as well as several human studies performed for customers. The IntelliCap system is available for use in pre-clinical and clinical trials.

EXPERIMENTAL METHODS
The IntelliCap capsule (Medimetrics) is an orally swallowable programmable drug delivery capsule (pump) capable of real-time monitoring of pH and temperature allowing localization of the capsule over time by the typical and consistent physiological pH profiles in dog and man² (Figure 2).

Diltiazem HCl as model drug having significant colonic absorption is used in a human study comparing a commercial modified release formulation (Diltiazem HCl ER 60mg capsules, Mylan; USA as a multi-particulate dosage form) to the IntelliCap system. The IntelliCap reservoir was loaded with an aqueous diltiazem HCl solution 270mg/ml and programmed to mimic the in-vitro dissolution profile (900mL water, paddle, 100 rpm) of the
Mylan ER product. The in-vitro release curves are shown in Figure 1.

Study design: 14 fasted healthy human volunteers, 2-period X-over.

The regional absorption was determined by using GastroPlus (Simulations Plus) version 7 fitting the observed plasma-time curve versus simulated Cp with a goodness of fit R^2 ~ 0.8. The Gastro+ model has been developed using published diltiazem iv data.

RESULTS AND DISCUSSION
The transit times (pylorus, cecum) of the IntelliCap capsule (see Figure 2) were used in the model. Transit for the marketed product could not be measured so average values are assumed.

Table 1 PK parameters of the human study

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Mean IntelliCap</th>
<th>Mean Mylan ER</th>
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<tbody>
<tr>
<td>Dose (mg)</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>6.3</td>
<td>8</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>34.7</td>
<td>39.5</td>
</tr>
<tr>
<td>AUC (ng*h/ml)</td>
<td>494</td>
<td>428</td>
</tr>
<tr>
<td>Cecum arrival time (h:m)</td>
<td>05:34</td>
<td>N/A</td>
</tr>
<tr>
<td>Absorption Small Intestine (%)</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Absorption Colon (%)</td>
<td>55</td>
<td>69</td>
</tr>
<tr>
<td>Total Absorption (%)</td>
<td>84</td>
<td>75</td>
</tr>
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At the cecum passage a decline in both plasma curves is observed with a steeper decline in the IntelliCap profile (Figure 3). This could be explained by the differences in the dosage forms because a multi-particulate form does spread much more during gut transit compared to the mono-lithic IntelliCap capsule.

CONCLUSION
The IntelliCap system allows easy quantification of colonic absorption of diltiazem and many other drugs in dog and man. Results obtained early in development may thereby identify suitable drugs for MR development but also deliver the facts to stop costly MR development early and save money. In addition in-vivo screening for optimal drug release profile can be performed that will result in significantly shortened product development time and improve in-vivo success.

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