Mapping Quantitatively Regional Drug Absorption in Canines with IntelliCap System

Dieter Becker¹, Helmut Schütz¹, Armin Beyerbach¹, Hans Zou², Jeff Shimizu², Ventzeslav Iordanov²
¹Novartis Pharma AG, CH-4056 Basel, Switzerland
²Medimetrics, Philips Research, 345 Scarborough Road, Briarcliff Manor, NY 10510, USA

ABSTRACT SUMMARY
Quantitative regional absorption of a drug under development was studied by using the novel IntelliCap system. IntelliCap is an orally swallowable programmable drug delivery capsule and 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. Such individual correlations of gut location and plasma drug concentration allow more precise PK data interpretation. In addition only a single dose in one pass is necessary to map quantitatively site of absorption compared to other systems (e.g. IntelliSite, Enterion) that need one administration for one location in the gut.

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.

Unfortunately, most of the drugs do not show colonic absorption. According to the database drugs@FDA only about 7.3% of the oral drug products are extended release formulations (1,287 out of 17,553). Despite the fact that drug products cannot directly correlate with drug substance properties and furthermore extended release with colonic absorption, this magnitude is still a meaningful guiding number.

The typical approach determining regional absorption in vivo is an engineered capsule that can be used for targeted delivery in man⁴ (e.g. IntelliSite, Enterion) or an insertion of a catheter⁵. In pre-clinical use intestinal access port animal models could be considered⁴.

Up to now, characterization of regional absorption requires multiple dosing in one study to fully characterize the GI tract. However if the drug under test could be delivered in a reliable fashion at a constant rate, then the entire GI tract could be probed by a single pass dosing study. Using an osmotic pump system to release a drug at zero-order rate for several hours can be a viable strategy. But the concurrent location of the capsule remains unknown. External imaging tools (e.g. gamma scintigraphy, magnetic marker monitoring) may be used to track the location of capsules in real time, introducing another layer of complexity.

It is desirable to have an easy-to-use drug-delivery tool that can release drug in freely programmable profiles and simultaneously monitor release location and physiological conditions of test subjects.

Recently, Medimetrics has developed the IntelliCap system for both programmable drug delivery and real-time monitoring of the GI physiological conditions. The system has successfully demonstrated its utility in a regional drug absorption study⁶. This combination of multiple functions offers several opportunities for exploration in drug development and novel treatment strategies⁷. The IntelliCap system is available for use in pre-clinical trials and soon in clinical trials.

In this paper, we present the results of a regional absorption study in dogs on a drug under development (MW approx. , 500, pKa 3 and 10, poor water solubility, no apparent colonic absorption in vivo) using the IntelliCap system as a tool for both zero-order release and real-time monitoring of physiological conditions. In this manner, the entire GI tract was probed with a single capsule dosing and regional information on capsule transit was determined in all subjects and correlated to the regional drug absorption via the drug’s plasma concentration time profile of each subject.

EXPERIMENTAL METHODS
1. Study Facility
The animal testing was conducted at Novartis preclinical test facility. The IntelliCap system equipment was installed and configured in the animal procedure room on the day of the experiment.

2. Dosage
Drug A was prepared as PEG200 solution (in concentration 17.5% w/w). The target dose was 5.4 mg/kg (or 54 mg/subject) with a target loading dose in the IntelliCap capsule of 60mg drug per subject.

3. Animal Test Protocol
The study was conducted with fasted male beagle dogs (N=4) in two stages 2 days apart from each other. In stage one, each animal was dosed with one IntelliCap capsule without drug and any pre-treatment and was only monitored for the physiological conditions. In stage two, two animals were pretreated with pentagastrin (6 µg/kg, 60 minutes before dosing) to achieve a low gastric pH and two dogs were pretreated with ranitidine (5 mg/kg, 30 minutes before dosing) to achieve a neutral gastric pH. Then each animal was dosed with drug A in one IntelliCap capsule programmed for zero-order drug release up to 6 hours. In both stages, animals were housed individually. Animals were fasted a minimum of twelve hours prior to dosing and until four hours post. On the day of the study, each animal was administered one IntelliCap by placement of the capsule in the esophagus along with
50 ml water. In stage two, blood samples (1ml) were collected from the vena cephalica at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 24 h after dosing to determine drug A concentrations.

4. Delivery Profile

For the stage one study without drug release, an IntelliCap capsule was programmed for monitoring-reporting only. For the stage two study, a 6-hour zero-order release was designed. Based on published data and results of earlier studies with IntelliCap in canines\(^5\), \(^6\), 6 hours should ensure drug exposure to all major GI regions, stomach, small intestine and ascending colon. The programmed 6-hour zero-order release immediately started by a user command after dosing. The whole program sequence of the drug-delivery IntelliCap is shown in Table 1. The actual release profile was verified by an in vitro dissolution test (USP paddle, 900ml phosphate buffer pH 7.4, 50 rpm) before the in vivo study.

Table 1: Program sequence of IntelliCap capsule for zero-order release

<table>
<thead>
<tr>
<th>Segment</th>
<th>Behavior</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Measure and report</td>
<td>Forever</td>
</tr>
<tr>
<td>1</td>
<td>Zero-order release</td>
<td>6 hours</td>
</tr>
<tr>
<td>2</td>
<td>Measure and report</td>
<td>Until end of battery power</td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSION

1. Physiological Data Traces

Obtained pH and temperature traces clearly showed GI landmarks (pylorus, cecum). Figure 1 shows an example data set of a subject pretreated with pentagastrin. Low and high gastric pH values were observed correspondingly as expected. Passage of the pylorus in subjects with high gastric pH was determined by looking at sudden change of pH rise gradient. Table 2 summarizes the regional residence and total transit time of all the test subjects. Except for subject 182, where gastric residence extended beyond the normal fasting time, pretreatment seems to prolong the total transit time. In all subjects, every GI region was exposed to the drug (zero-order release).

2. Pharmacokinetic Data

Variability in gastric residence time leads to variability in Tmax and may impact Cmax and AUC. As shown for drug A in table 2 and 3 a strong shift in Tmax is correlated with the pretreatment of the dogs caused by different gastric residence times. There is also a very good correlation of the Tmax with the total gastric and small intestine transit times measured by the IntelliCap for each individual dog profile.

Table 2: Regional residence and total GI transit time of subjects with and without pretreatment (P=Pentagastrin, R=Ranitidine, time format=hh:mm)

<table>
<thead>
<tr>
<th>Lab ID #</th>
<th>151</th>
<th>182</th>
<th>159</th>
<th>181</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Type</td>
<td>No Pretreatment</td>
<td>Pentagastrin Pretreatment</td>
<td>No Pretreatment</td>
<td>Pentagastrin Pretreatment</td>
</tr>
<tr>
<td>Gastric Residence</td>
<td>0.26</td>
<td>1.38</td>
<td>17.57*</td>
<td>1.27</td>
</tr>
<tr>
<td>Stomach Transit</td>
<td>2.46</td>
<td>2.33</td>
<td>2.54</td>
<td>2.29</td>
</tr>
<tr>
<td>Total Transit</td>
<td>5.25</td>
<td>9.56</td>
<td>28.31</td>
<td>10.43</td>
</tr>
</tbody>
</table>

* Feeding resumed while the capsule was still in the stomach

![Figure 2](image)

Figure 2: pH and temperature profile of test subject 151 with Pentagastrin pretreatment as overlapped with the plasma profile of drug A.

Table 3 Tmax and total transit time of stomach and small intestine

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Pentagastrin</th>
<th>Ranitidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Transit Stomach &amp; SI (h)</td>
<td>4.07</td>
<td>3.56</td>
</tr>
</tbody>
</table>

Table 4 Regional absorption in % AUC of total AUC per subject

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Pentagastrin</th>
<th>Ranitidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Small intestine</td>
<td>100.1</td>
<td>93.6</td>
</tr>
<tr>
<td>Colon</td>
<td>-0.9</td>
<td>4.1</td>
</tr>
</tbody>
</table>

The regional absorption calculated from the residence time in each gut segment and subject receiving drug A showed no colonic absorption as shown in a previous Enterion study. The colonic absorption seen with ranitidine pre-treatment is due to the inaccuracy caused by the plasma sampling time points (hours) compared to the residence time (pH) sampling rate (10 sec).

CONCLUSION

We have successfully and quantitatively mapped the whole GI regional absorption of a drug under development by using the IntelliCap system. Concurrent pH traces allowed us to decouple inter-subject variability and to correlate PK data precisely with regional exposure time window in each subject.

REFERENCES

1. Drugs@FDA status Dec 14, 2010
5. Zou, H.; et. al. *CRS annual meeting* 2010, 5373-1