ABSTRACT SUMMARY

Capabilities of the IntelliCap drug delivery system have been extended by the development and introduction of the IntelliCap Fast Release (FR) system. The IntelliCap FR system uses a swallowed electronic capsule to monitor pH and temperature while passing the gastro-intestinal tract and to deliver a drug payload with a fast release upon user command. The capsule payload may be of a variety of forms such as powder, solid, or liquid. Operation of the system is validated in-vivo in dog by the delivery of metoprolol to the proximal colon.

INTRODUCTION

Rapid evaluation of absorption within regions of the gastro-intestinal tract has great utility for development of compounds for oral administration. To avoid the time consuming process involved for creating modified release forms in early stages of development, engineered capsules have proved to be valuable development tools.1,2,3 The IntelliCap system is compact and portable providing great flexibility of operation. It makes use of a built in pH sensor for capsule localization and to account for individual variations in transit and pH. Reported here is a new system, IntelliCap FR, to allow increased choice of payload type and increased payload capacity.

The IntelliCap technology uses a swallowed electronic capsule for controlled drug delivery in gastrointestinal (GI) tract.4 The system has been proven effective in evaluating absorption in local areas of the GI tract with both targeted and extended release delivery profiles.5,6 To achieve full flexibility over the delivery profile a liquid payload, solution or suspension, is required. To further address needs, a new variant of the system has been developed. The new system is capable of delivering a variety of payloads, such as powder, solid, or liquid. The payload is delivered with a fast release and is suitable for evaluating delivery to a single targeted region in the GI tract.

Below properties of the new IntelliCap FR system are described. Capabilities of the system were demonstrated with an in-vivo validation test in dog. Metoprolol tartrate, 35 mg in solution, was delivered to the proximal colon and successful results reported below.

EXPERIMENTAL METHODS

The IntelliCap technology is built in a modular fashion. The design of the new fast release system makes use of a majority of hardware and software in the original system. Requirements for the new capsule are to hold and then release a payload in a rapid fashion upon command. Capsule shall use the same electronics and sensors. The actuator is adapted for fast release and a new medication container is created. Two variants of the capsule are designed that vary only in the length of the medication container. The first has an overall length of 26.7 mm, the same as the original IntelliCap. The second is longer at 32 mm and is able to hold and deliver an even larger payload amount.

After design and construction, operation of the capsule was verified with in-vitro bench tests. System operation including programming, capsule activation, wireless communication, and control from a PC were tested. Successful delivery of payload upon command was tested both with fluid (water) and powder (Avicel PH, FMC Biopolymer) payload types. Time from command to release of the payload was recorded.

System operation was validated with an in-vivo test in dog. Aim of the study was to show operation representative of a pharmacokinetic regional absorption study. Single dose pharmacokinetics of metoprolol tartrate was examined when delivered by the IntelliCap FR system to the proximal colon. Metoprolol was chosen as a well characterized, safe and well-tolerated drug with good absorption along the entire GI tract.7,8 Study was performed under contract to WIL Research, ’s-Hertogenbosch, The Netherlands. The study protocol was reviewed and approved by the Animal Welfare Officer and the Ethical Committee (DEC 00-34).

Formulation was prepared on the day before dosing. Water was added to metoprolol tartrate to achieve a concentration of 151.43 mg/mL (35 mg/300μL). IntelliCap FR capsules were filled with 300 μL metoprolol tartrate solution.

Test was conducted with 6 male beagle dogs. Animals were fasted overnight with water available. One half hour before dosing animals were given pentagastrin 6 μg/kg intramuscularly. The IntelliCap FR capsule was administered by deep throat administration followed by an additional rinse of water to assist swallowing.

Measurements of pH and temperature were taken by the capsule every 10 seconds and reported at the control PC. Emptying from the stomach past the pylorus was determined by a rapid rise in pH. The pH then drops quickly by about 1.0 or greater indicating transit past the ileocecal valve into the cecum. The operator then issued a command to initiate release. After elimination capsules were recovered, de-activated, and examined visually.

Approximately 2-mL blood samples were taken from the jugular vein. Blood samples were collected on the following time points:

Before Release; Hourly after dosing until capsule passes ileocecal valve, Release; Immediately preceding, 0.5, 1, 2, 3, 4, 6, 8 and 24 hours post-release.

Within 1 hour after sampling, blood was centrifuged at
5°C. Plasma samples were analyzed according the bioanalytical procedure on record with the vendor.

All pharmacokinetic parameters were calculated from the curves constructed from individual animals, using the Phoenix WinnonLin 6.3 program. Non-compartmental analysis was applied. Parameters were calculated including C_{max}, t_{max}, AUC_{max} and t_{1/2}.

RESULTS

The IntelliCap FR system was designed and constructed according to the system requirements. The electronics portion remained unchanged compared to the previous version of the IntelliCap system. The medication container is designed as an empty cylinder containing a flexible foil membrane. At the end of the cylinder a closure lid is placed. The actuator creates pressure on the bottom side of the foil membrane. The built up pressure acts upon the lid eventually causing it to be removed in a single quick action. Pressure on the foil membrane causes it to push outward thus ensuring full release of the drug payload. A photograph of the IntelliCap FR capsule is shown in Figure 1. There are two versions of the capsule that differ only in the size (length) of the medication container. Main parameters of the two capsules are summarized in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Short</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (mm)</td>
<td>11.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Length (mm)</td>
<td>26.7</td>
<td>32.0</td>
</tr>
<tr>
<td>Payload volume (µL)</td>
<td>450</td>
<td>900</td>
</tr>
<tr>
<td>Release time, mean (min)</td>
<td>3.2</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Table 1: Dimensions and measured release time of the IntelliCap FR capsules.

In the validation study, capsules were administered to and recovered from all subjects without incident. No signs of unusual wear or disintegration were seen. Pylorus passage and cecum arrival was determined in all animals. Release command was given and received successfully for all capsules. Bioanalysis of plasma samples was completed. Sample data for one subject is shown in Figure 2. Data shows successful delivery upon command, good absorption and fast elimination of metoprolol after delivery. Pharmacokinetic parameters are summarized in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (ng/mL)</td>
<td>253</td>
<td>98.9</td>
</tr>
<tr>
<td>t_{max} (hr)</td>
<td>2.4</td>
<td>n/a</td>
</tr>
<tr>
<td>AUC_{max} (hr<em>ng</em>kg/mL/mg)</td>
<td>1890</td>
<td>1150</td>
</tr>
<tr>
<td>t_{1/2} (hour)</td>
<td>2.88</td>
<td>0.890</td>
</tr>
</tbody>
</table>

Table 2: Pharmacokinetic parameters of metoprolol after dosing by IntelliCap FR

CONCLUSION

A new electronic drug delivery system has been created, the IntelliCap FR. This system has the ability to measure real time pH and temperature data and control drug delivery to a targeted area in the GI tract. The new system is able to deliver the entire payload with a fast release. Usable payloads include powder, solid, and liquid. System design was completed and hardware constructed. System was tested successfully both in-vitro and in-vivo. A representative pharmacokinetic study was completed for the delivery of metoprolol to the proximal colon in dog. Results show successful operation of the system and the ability to target and release drug payload upon command. Taken together with the earlier system the new system provides an additional tool for accelerating the development of oral compounds.

REFERENCES