Preliminary In Vivo Evaluation of a Gastroresistant Capsular Device Prepared by Injection Molding

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ABSTRACT SUMMARY
The in vivo release performance of a gastroresistant capsular device based on HPMCAS and prepared by injection molding (IM) was preliminarily evaluated in volunteers with respect to conventional enteric coated dosage forms. IM capsule prototypes demonstrated promising results in terms of opening time after entering the small intestine.

INTRODUCTION
A gastroresistant capsular device prepared by injection molding (IM) was recently proposed [1]. The feasibility of the manufacturing process with hydroxypropyl methyl cellulose acetate succinate (HPMCAS) as the thermoplastic polymeric component was assessed. By improving the basic formulation with a plasticizer and channeling agents (soluble polymers and/or disintegrants), promising results were obtained with respect to in vitro performance and fine tuning of the thickness as well as mechanical characteristics of the capsule shell.

In the present work, a preliminary in vivo evaluation of 600 µm thick HPMCAS capsules containing 30% (w/w on the plasticized polymer) of Exploflat® CLV was carried out. For this purpose an assembled gastroresistant system was devised, consisting of an enteric-coated HPMC capsule filled with both fenazon powder and an acetaminophen-containing HPMCAS molded unit (Fig. 1). The external capsule would dissolve after gastric emptying thus releasing its contents: the appearance of fenazon and acetaminophen in biological fluids would indicate the opening of the assembled system and of the HPMCAS unit, respectively.

![Image of assembled gastroresistant system and HPMCAS molded capsule](image)

Figure 1: assembled gastroresistant system and HPMCAS molded capsule

EXPERIMENTAL METHODS

Materials – HPMCAS (AQUOT-LG®; Shin-Etsu, J), polyethylene glycol (PEG 1500; Clariant Masterbatches, I), sodium starch glycolate (Exploflat® CLV; JRS, D), metacrylic acid copolymer (Eudragit® L 30 D-55, Evonik, D), acetaminophen (Atabay, TR), fenazon (ACEF, I), HPMC capsules sizes 000 and 2 (V-Caps®, Capsugel, B).

Methods – System preparation. IM gastroresistant (IMGR) capsules: co-milled blends of HPMCAS and PEG 1500 were mixed with Exploflat® CLV (55:22:23 ratio) in turbula (Type T2C, WAB, CH), dried in a ventilated oven (40°C, 24 h) and transferred into the IM press (BabyPlast 6/10P, Chronoplast, Rambaldi, I). Previously-set process conditions were adapted to the use of a different mold [1,2]. Each capsule was manually filled with 150 mg of acetaminophen and sealed with a HPMCAS alcoholic solution. Coated gastroresistant (CGR) capsules: size 2 HPMC capsules, filled with 100 mg of fenazon and sealed with HPMC aqueous solution, were coated up to a 10 mg/cm² coating level with Eudragit® L 30 D-55 (LDCS Hi-coater equipped with a 1.3 L capacity perforated pan, Freund-Vector corporation, US; inlet temperature: 30 °C, air pressure: 12 psi; pan speed:18 rpm; rate of spraying 2 g/min). Assembled gastroresistant (AGR) systems: size 000 HPMC capsules were filled with one IMGR capsule, together with 100 mg of fenazon powder, and dip-coated with an alcoholic solution of HPMCAS.

In vitro evaluation. Systems were tested in apparatus 2 USP35 (Dissolution System 2100B, Distek, US) according to the Dissolution test for delayed-release dosage forms (Method B, 100 rpm). Fluid samples were withdrawn and assayed spectrophotometrically. Time to 10% release in pH 6.8 (t10%) was calculated from the release curves.

In vivo evaluation. Two different studies were carried out involving 9 healthy volunteers (age 26-61 years, weight 53-87 kg). In the 1st study the AGR system was administered to 6 subjects; in the 2nd one an IMGR and a CGR capsule were co-administered to 3 subjects. Systems were ingested with 250 mL of water. Saliva samples were collected at predetermined time points and immediately frozen; acetaminophen and fenazon were selected because they can be assayed in saliva. After defrosting, each sample was centrifuged at 4000 rpm for 15 min. 1 mL of supernatant was transferred into 10 mL plastic tubes along with 1 mL of Ba(OH)2 0.3 M and 1 mL of ZnSO4 0.3 M. 100 µL of theophylline monohydrate 0.2 mg/mL were added as the internal standard. After mixing by vortex for 30 s, samples were centrifuged at 4000 rpm for 15 min. Acetaminophen and fenazon were simultaneously assayed by gradient RP HPLC (Waters Co., US) using a MuBondapack™ Phenyl, 150 x 3.9 mm 125 Å column (Waters Co., US) heated at 30 °C. Acetate buffer (pH 5±0.1) and CH3CN were employed as the mobile phase at a flow rate of 1 mL/min (t0-7min = 95.5, t7-10min = 70.30, t10-15min = 95.5 v:v). Detection: spectrophotometer λ 245
The concentration of acetaminophen and fenazon was determined from the tracer to internal standard peak area ratio. Data were processed by means of Breeze™ software (Waters Co., US).

**RESULTS AND DISCUSSION**

All systems showed the expected *in vitro* performance (Fig. 2): fenazon release from CGR capsules and AGR systems occurred few minutes after pH change, whereas a 40-50 min longer latency was observed for IMGR capsules that could be attributed to the shell characteristics, mainly their thickness [1].

![Graphs showing release profiles](image)

**Figure 2: in vitro release profiles of AGR, CGR and IMGR systems (top to bottom)**

As far as the *in vivo* studies are concerned, the time of first detection in saliva of acetaminophen or fenazon, contained in each administered dosage form, was used to define the relevant opening time (see examples in Fig. 3 and Fig. 4). Based on data obtained following administration of the AGR system, a mean opening time of 117 min (CV 43.9) after fenazon appearance was calculated for the IMGR capsule, which was assumed as the time to disintegration/dissolution of the latter. In the subsequent *in vivo* study, the performance of molded HPMCAS (IMGR) capsules was compared with that of conventional enteric-coated ones (CGR). On co-administration of the two systems, acetaminophen release from IMGR capsules on average occurred only 35 min after fenazon release from CGR ones (Tab. 1).

The overall results obtained seem to be in agreement with data reported in the literature relevant to gastroresistant dosage forms, generally indicating up to 2 h for their complete disintegration/dissolution in the human small intestine [4].

![Graphs showing saliva concentration profiles](image)

**Figure 3: saliva concentration profiles following administration of the AGR system (subject #2)**

![Graphs showing saliva concentration profiles](image)

**Figure 4: saliva concentration profiles following co-administration of CGR and IMGR capsules (subject #9)**

**Table 1: *in vivo* data of CGR and IMGR capsules**

<table>
<thead>
<tr>
<th></th>
<th>CGR capsules</th>
<th>IMGR capsules</th>
<th>△ min</th>
</tr>
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<tbody>
<tr>
<td>opening time, min (CV)</td>
<td>160 (42.3)</td>
<td>195 (35.3)</td>
<td>35</td>
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</table>

**CONCLUSION**

An IM gastroresistant capsular device, suitable for conveying different types of drug formulations, was evaluated *in vivo,* demonstrating the ability to release its contents in the intestine. Promising results were obtained in terms of opening time (*i.e.* an only 35 min longer latency as compared with conventional enteric-coated capsules), especially in view of the thickness of the prototypes employed.

**REFERENCES**

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4. Liu F and Basit AW, J Control Rel 147, 242 (2010)