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In Vivo Evaluation of Capsugel® Enprotect® Capsule

In Vivo Evaluation of a Gastro-Resistant HPMC-Based "Next Generation Enteric" Capsule*
(Rump A, Kromrey M-L, Scheuch E, et al. Pharmaceutics 2022;14:doi.org/10.3390)

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Introduction and purpose of this study

Oral drug formulations are commonly used to dose active pharmaceutical ingredients (API); however, several APIs would not survive the acid milieu of the stomach, requiring a gastro-resistant dosage form to deliver the drug payload to the desired absorption site in the intestine.

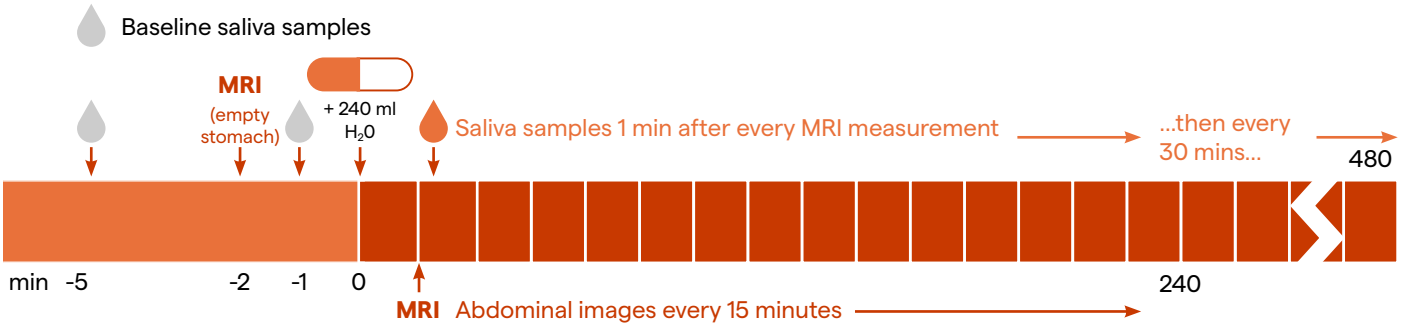
Furthermore, release of the drug in the distal small intestine also protects fragile APIs and nucleic acid therapeutics from the high enzymatic environment of the proximal small intestine.

One common solution is coating of the final dosage form or of the fill formulation with enteric polymers; however, coating in particular can be a complex and time-consuming process. Ready-to-use hard capsules would minimize risk and costs, while providing a solution to assessing enteric formulations for new APIs. In this regard, the development of the Capsugel® Enprotect® capsule, composed of hypromellose (HPMC) and HPMC-acetate succinate (HPMC-AS), is a promising advance. The Capsugel® Enprotect® capsule also provides a shorter manufacturing process, thus reducing time and cost.

This study examined the *in vivo* performance of these HMPC-based Capsugel® Enprotect® capsules to confirm the gastro-resistance of this dosage form, and to determine where in the intestine the capsules start to disintegrate. It is the first time two independent and established, but complimentary, techniques–magnetic resonance imaging (MRI) and caffeine detection in saliva – were used to evaluate gastro-resistant capsules in the fasted state.

Methodology

- Capsugel® Enprotect® size 0 capsules were used, supplied by Lonza Capsules & Health Ingredients, Colmar, France
- Hand-filled capsules, powder ingredients mixed and homogenized, including ^{13}C-labelled caffeine and iron oxide
- Eight healthy volunteers (mean age: 27.1 years; mean body mass index [BMI]: 22.5 kg/m^2)
  - Experimental design: (10-hour overnight fast)



  - Image acquisition terminated upon confirmed disintegration of capsule; if no disintegration occurred after 240 minutes, additional imaging could be performed
  - Stable-isotope ^{13}C-labelled caffeine, so subjects did not need to abstain from caffeine intake
  - 1 mL samples of saliva were taken and freeze-dried at –80 °C for later analysis
  - MRI was performed in the supine position; transversal and coronal image slices obtained
  - Capsule disintegration determined by the shape and size of the artifact in the GI tract
  - Capsule performance criteria:
    - ***Gastric residence time (GRT):*** the mean of the last time the capsule was in the stomach to the first time point it was located in the duodenum
    - ***Site of disintegration:*** the point where the capsule disintegrated in the GIT; additionally determined by the first appearance of caffeine in the saliva
    - ***Disintegration time (DT):*** from the measurement point when disintegration was first observed to the last measurement point immediately before that
    - ***Intestinal transit time until disintegration (ITT_D):*** the difference between GRT, and both DT, measured by MRI, and DT, measured by saliva

Results

The following table shows the transit time and disintegration site and time, as determined by the MRI and caffeine appearance:

	Disintegration site	GRT (min)	DT_{MRI} (min)	DT_{CAF} (min)	ITT_D_{MRI} (min)	ITT_D_{CAF} (min)
Subject 1	Ileum	7.5	52.5	52.5	45	45
Subject 2	Ileum	22.5	82.5	82.5	60	60
Subject 3	Ileum	82.5	127.5	127.5	45	45
Subject 4	Jejunum	82.5	97.5	82.5	15	0
Subject 5	Cecum	22.5	142.5	37.5	120	15
Subject 6	Jejunum	67.5	112.5	112.5	45	45
Subject 7	Jejunum	7.5	52.5	52.5	45	45
Subject 8	Ileum	52.5	112.5	82.5	60	30
Mean		**43**	**98**	**79**	**54**	**36**
SD		**30**	**31**	**29**	**28**	**18**

Discussion

None of the capsules showed any signs of disintegration in the stomach. In Subject 5, the capsule reached the ascending colon, whereupon it disintegrated 142.5 minutes after ingestion. This capsule also had the shortest DT_{CAF}, i.e., 37.5 minutes, indicating that it probably still underwent some disintegration in the colon; nevertheless, after 45 minutes salivary ^{13}C-caffeine was detected, suggesting that the capsule was no longer intact upon arrival at the ileocecal valve.

Apart from Subject 5's capsule with an exceptionally fast oro-caecal transit, the DT_{CAF} of the other seven capsules were either identical or just slightly earlier, compared with the DT_{MRI}.

The ITT_D is a parameter that describes the disintegration properties of capsules, which the authors consider suitable for evaluating overall capsule performance. There was no significant correlation between GRT and ITT_D, indicating that GRT did not influence the disintegration properties of capsules. The high variability seen in GRT is due to the phases of the inter-digestive migrating motor complex (IMMC); the third phase of the IMMC (the so-called 'house-keeping waves') determines the rate of gastric emptying and has a cycle length of 90 to 120 minutes, before starting the next cycle.

Conclusions

The Lonza Capsugel® Enprotect® capsules demonstrated robust gastro-resistant and enteric disintegration properties after ingestion in the fasted state in two independent methods, using MRI and ^{13}C-labelled caffeine. Despite one capsule having a more rapid transit, these results indicate that both detection methods confirmed the Capsugel® Enprotect® capsule as a robust enteric formulation, and are reliable methods for measuring capsule disintegration times.

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Abbreviations:

API: active pharmaceutical ingredient.

BMI: body mass index.

DT_{CAF}: disintegration time measured by caffeine appearance.

DT_{MRI}: disintegration time measured by MRI.

GI: gastro-intestinal.

GIT: gastro-intestinal tract.

GRT: gastric residence time.

IMMC: inter-digestive. migrating motor complex.

ITT_D: intestinal transit time until disintegration.

HPMC: Hypromellose.

HPMC-AS: HPMC-acetate succinate.

MRI: Magnetic resonance imaging.