

Capsugel® Enprotect® Capsule

An innovative capsule for enteric delivery with no post-filling coating required for low pH protection

Introduction

The Capsugel® Enprotect® capsule for enteric delivery features both HPMC and HPMC-AS polymers to create **an oral dosage form with acid resistance up to pH 6.0 with no post-filling coating required.**

Scientific evidence supporting Capsugel® Enprotect® capsules

Scientific evidence that resulted from the testing

- Dissolution performance
- Disintegration
- Mechanical robustness
- In vivo evaluation in fasted and fed states

Dissolution performance

The enteric performance of Capsugel® Enprotect® capsules was assessed using esomeprazole magnesium trihydrate (EMT) as a model acid-sensitive drug. Dissolution test 2 was performed following the USP monograph for esomeprazole magnesium delayed-release capsules (Figure 1). No release and no degradation of the drug were detected in the acid stage (HCl 0.1 N) for up to 2 hours. A complete release of the drug was observed in the buffer stage (30 minutes), confirming the protection of the drug throughout the test.



Average dissolution profiles with SD interval

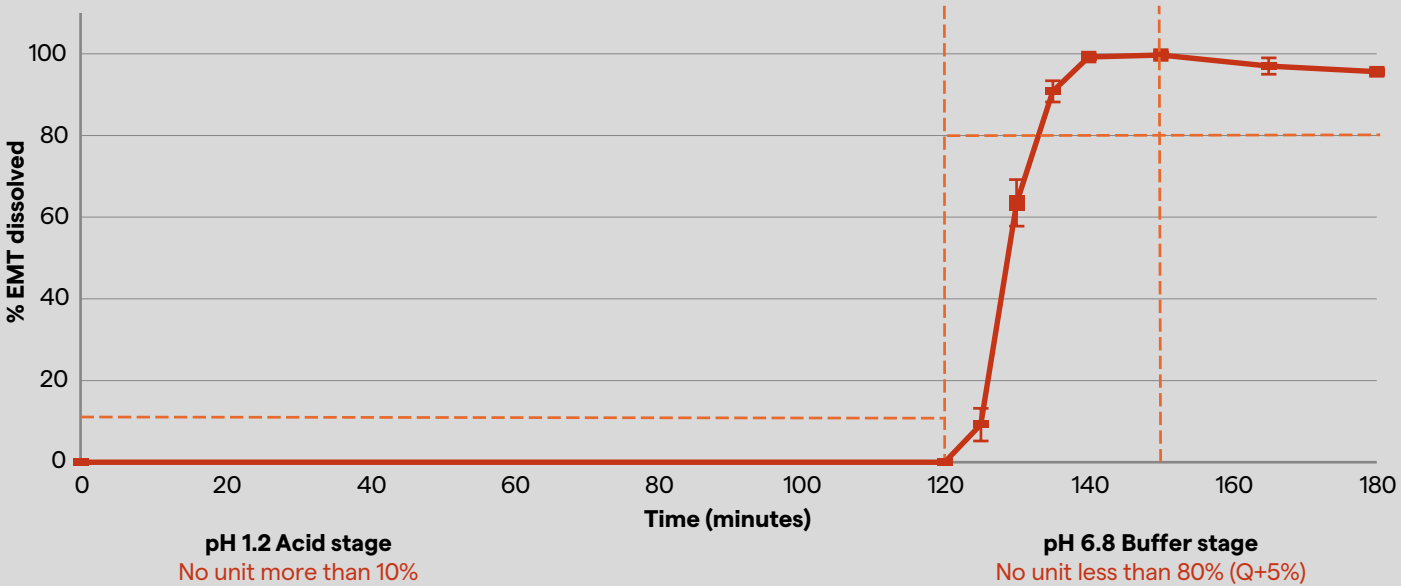


Figure 1: Release of esomeprazole magnesium trihydrate (EMT) uncoated pellets from the capsules conforms to the USP esomeprazole magnesium delayed-release capsules monograph.

Disintegration requirements

Ready-to-use enteric capsule with acid resistance up to pH 6.0.

The Capsugel® Enprotect® capsule meets Ph Eur disintegration requirements for gastro-resistant capsules. Figure 2 highlights a size 0 capsule filled with lactose with 0.1% pure red carrot food coloring. Throughout the 2 hours in HCl 0.1 N, only minor deformations of the capsule were observed. Results were independent of filling levels and required no banding or sealing.

Additional acid conditions were tested with Capsugel® Enprotect® capsules and the capsule keeps its enteric properties up to pH 6.0 (Table 1). The capsule presents a rapid opening from pH 6.4, which is in line with the dissolution pH of the selected grade of HPMC-AS.

Internal compendial disintegration tests

Test conditions	pH value	1.2	4.5	4.5	4.5	5.0	5.4	6.0	6.4	6.8
	Media	HCl 0.1 N	Phosphate medium	Citrate buffer	Citrate buffer saline	Citrate buffer	Citrate buffer	Citrate buffer	Phosphate buffer	Phosphate buffer
Disintegration results	# capsules open	0/6	0/3	0/3	0/3	0/3	0/3	3/3	3/3	6/6
	Time (min)	NA	NA	NA	NA	NA	NA	>120	<15	<15

Table 1: Enteric capsules withstand disintegration in various acidic media up to pH 6.0

Capsules after 2 hours in HCl 0.1 N

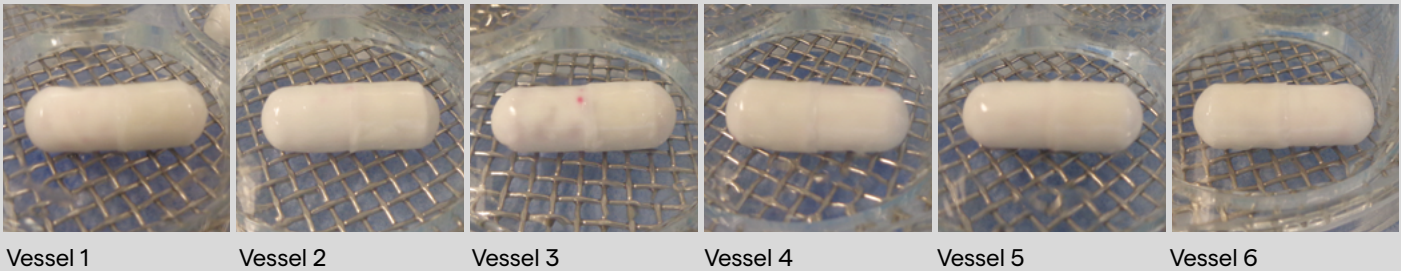


Figure 2: Capsugel® Enprotect® capsules filled with lactose and 0.1% red carrot after 2 hours in HCl 0.1 N.

Capsugel® Enprotect® capsules were developed for solid filled formulations. The capsule is compatible with standard solid excipients and keeps its enteric and acid protecting performance even after 6 months' storage in accelerated conditions.

Excipients	Disintegration (n=6)	Dissolution (min-max, n=6)	
	Max. disintegration time in pH 6.8 (min)	EMT after 2 hours in HCl 0.1 N (%)	EMT released after 30 min in pH 6.8 (%)
Arabic gum	<30	<LOQ-0.9	96-98
Dicalcium phosphate anhydrous	<5	0.2-0.9	100-102
Lactose monohydrate	<10	0.2-0.4	99-101
Maltodextrin	<10	<LOQ-0.8	100-102
Mannitol	<5	0.2-1.0	98-100
Microcrystalline cellulose	<5	0.2-0.7	98-100
Sorbitol	<10	<LOQ-0.7	99-102
Sucrose	<15	<LOQ-0.5	99-102
Starch	<10	<LOQ	98-101
Xylitol	<10	<LOQ	101-103
Reference: empty capsule	<10	<LOQ-0.2	98-100

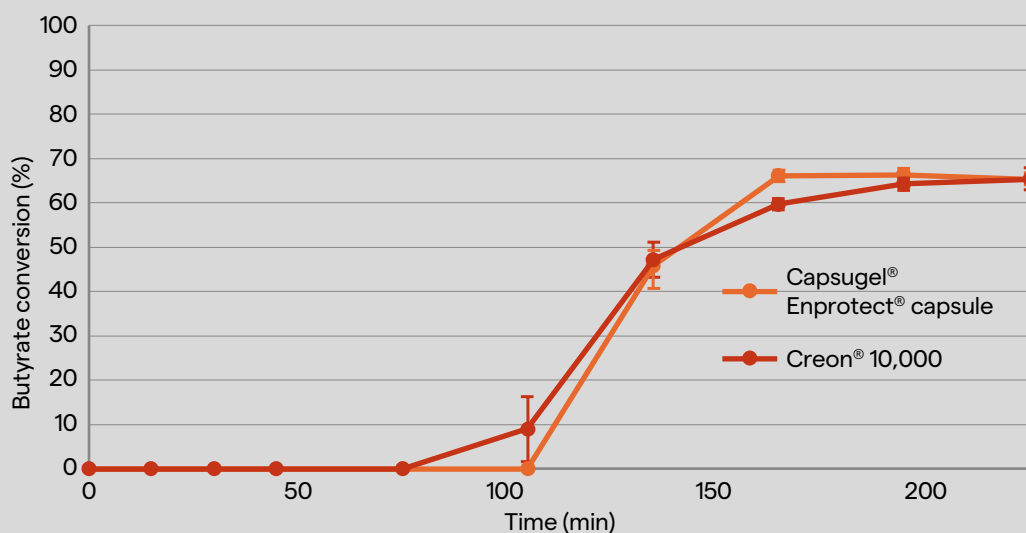
Table 2: Enteric performance confirmed with standard excipients after 6 months in accelerated conditions

Delivering new drug modalities

Gastrointestinal delivery of acid-sensitive pancrelipase* was evaluated with Capsugel® Enprotect® capsule using an exocrine pancreatic insufficiency disease model.^{†1} Proof of enzymatic activity was determined by measuring conversion of tributyrin to butyrate.

*Pancrelipase is a product containing a mixture of digestive enzymes (lipases, proteases and amylases) used to treat patients whose pancreas does not produce sufficient enzymes to properly digest dietary proteins, carbohydrate and fats, a condition called 'exocrine pancreatic insufficiency'

[†]SHIME®, Simulator of the Human Intestinal Microbial Ecosystem



- The pancrelipase activity has been fully protected by the Capsugel® Enprotect® capsule, as the butyrate conversion rate of 66% is the maximum achievable for this enzyme
- Capsugel® Enprotect® capsule had a similar release profile, enzyme protection and efficiency as the Creon® (pancrelipase) 10,000 U capsule

Figure 3: Pancrelipase activity determined by measuring the conversion of tributyrin to butyrate

Mechanical integrity of Capsugel® Enprotect® Capsules

Mechanical robustness test

The capsules demonstrated excellent mechanical properties in all tested conditions. Capsule resistance to breakage was tested using an in-house method whereby empty capsules were subjected to the impact of 100 g weight released from a height of 8 cm. The sample size is 50 capsules per test. Ahead of the test, capsules were equilibrated for 1 week at various relative humidity measures (10%, 16%, 23%, 33%, 45%) at room temperature. Commercially available gelatin and HPMC capsules (Vcaps® Plus) were used as standards for comparison. The brittleness of these new capsules is in line with the mechanical properties of HPMC capsules. They also showed better resistance to impact compared to standard gelatin capsules in conditions with RH below 33%.

Tube test

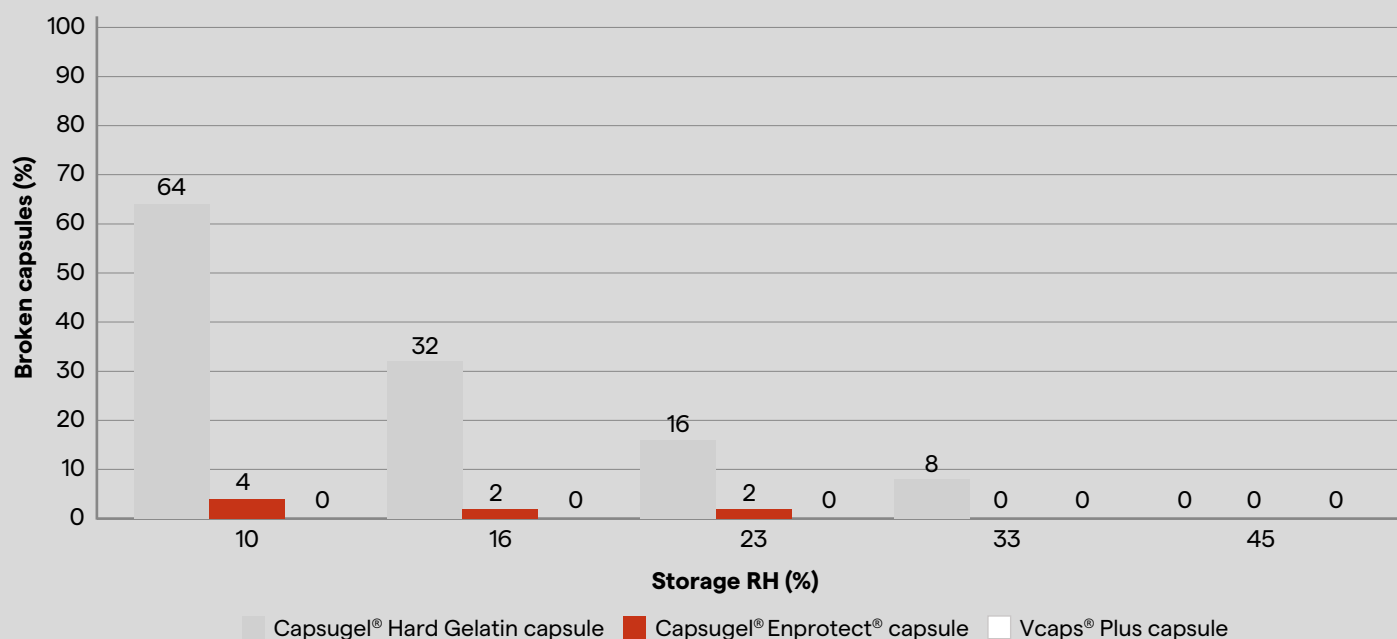
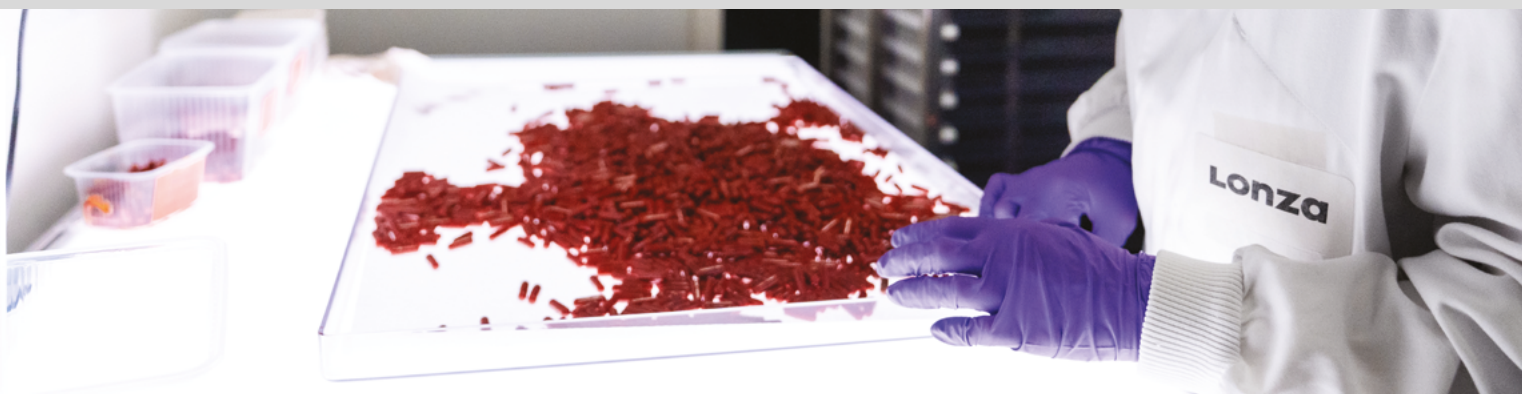


Figure 4: Capsules show very good mechanical properties when compared to pure HPMC capsules (Vcaps® Plus) and gelatin capsules after storage at room temperature and various RH conditions.



In vivo evaluation in healthy volunteers

In vivo performance of Capsugel® Enprotect® capsules was evaluated in healthy volunteers in fasted and postprandial conditions.

In vivo robustness in human **fasted** state

In vivo evaluation of Capsugel® Enprotect® capsules in **fasted** conditions, 8 volunteers:²

- Capsules filled with iron oxide for localization by MRI, and caffeine for detection of caffeine in saliva (LC-MS)
- Gastric residence time = 43 ± 18 min
- Time to 'start of release/disintegration' after gastric emptying
 - By MRI = 45 ± 14 min*
 - By caffeine appearance = 36 ± 18 min
- No influence of gastric residence time on subsequent release/disintegration was observed

*Excluding the capsule that disintegrated in the colon

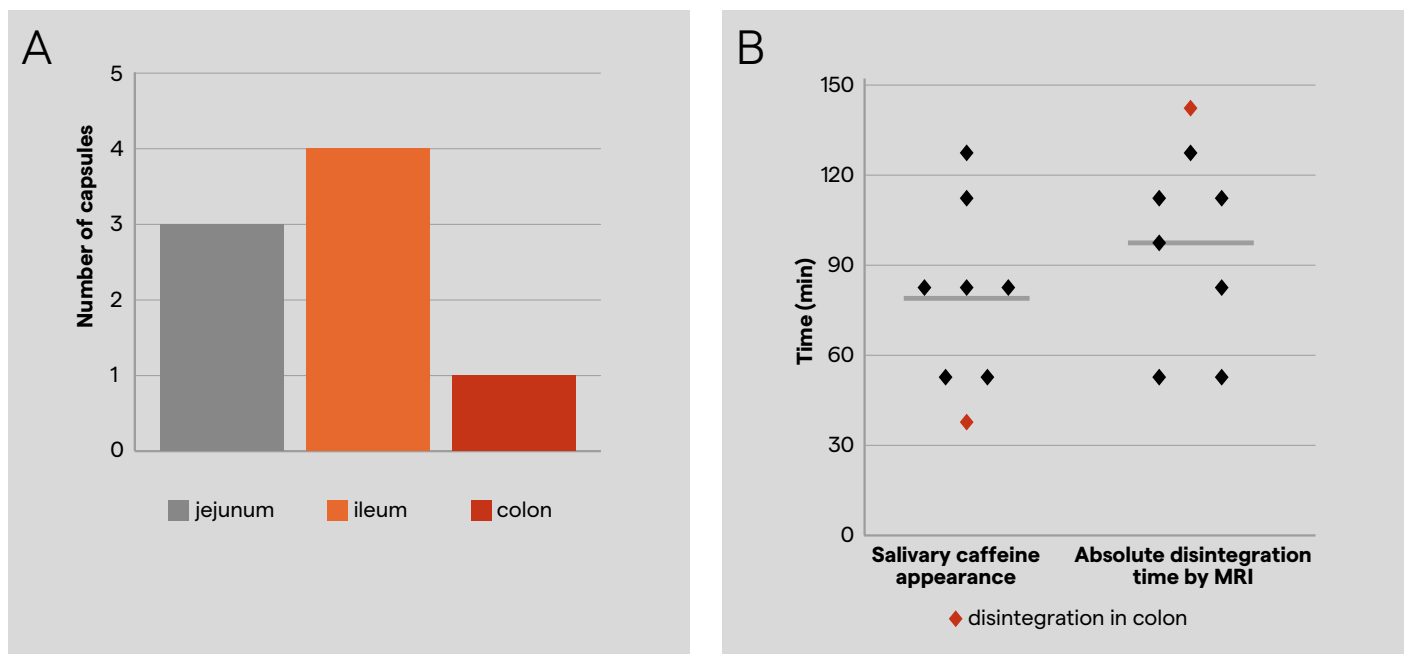
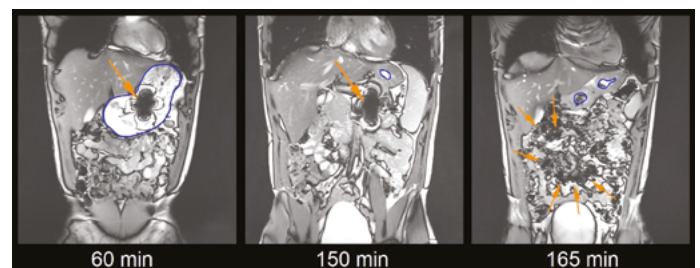


Figure 5: Disintegration of enteric capsules in healthy humans in fasted conditions observed by MRI and caffeine appearance:

A. Localization of the disintegration.

B. Salivary appearance time compared to the absolute disintegration time determined by MRI.



No opening of capsules in the stomach was observed, confirming the enteric properties of the capsule. The capsules opened in the jejunum (3/8), ileum (4/8), or colon (1/8) as seen in Figure 5A. On average the capsules opened in 45 minutes by MRI and 36 minutes by caffeine appearance respectively (excluding the colonic disintegration due to exceptionally fast oro-cecal transit in one subject) after gastric emptying. This time interval from leaving the stomach until the capsules disintegrated also persists after a longer residence time in the stomach, confirming a robust enteric composition of the capsules. An influence of gastric residence time on subsequent disintegration was not observed. No capsule disintegrated nor released caffeine in stomach irrespective of transit times, confirming robust enteric properties by MRI and caffeine release (Figure 5B). Despite minor differences, the same conclusions regarding the capsule's performance could be obtained from both methods, which strengthens the overall results.

In vivo robustness in human **fed** state

In vivo evaluation of Capsugel® Enprotect® capsules in **fed** conditions, 16 volunteers:³

- Dosing 30 minutes after intake of a standard breakfast (500 kcal)
- Gastric residence time = 158 ± 35 min (max = 248 min)
- Time to 'start of release/disintegration' after gastric emptying
 - By MRI = 39 ± 21 min
 - By caffeine appearance = 32 ± 17 min
- No influence of gastric residence time on subsequent release/disintegration was observed (even if increased pH and higher mechanical forces vs fasted conditions).

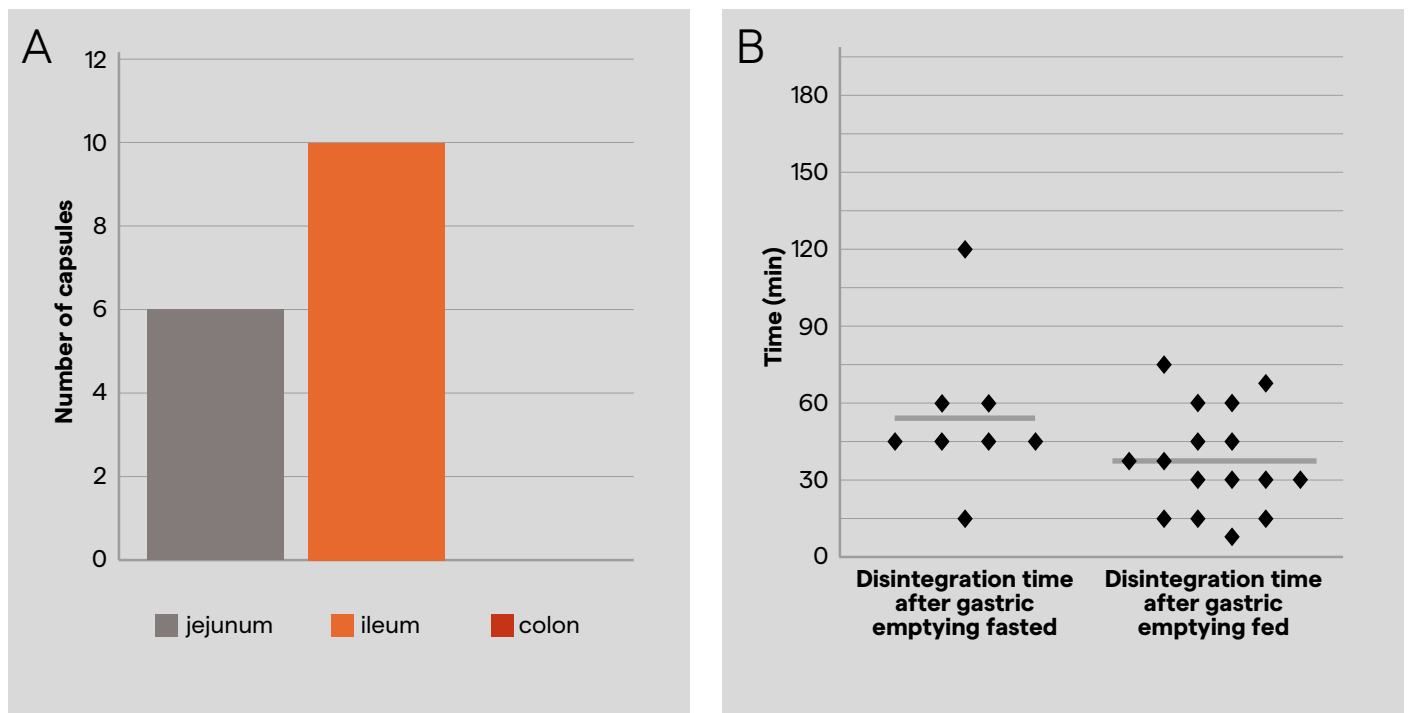
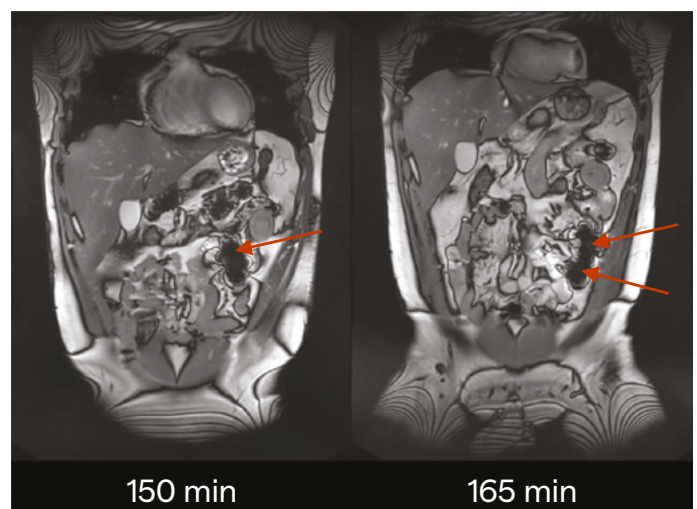


Figure 6: Disintegration of enteric capsules in healthy humans in fed conditions observed by MRI and caffeine appearance:

A. Localization of the disintegration.

B. Same disintegration performance of the capsule after gastric emptying in fasted and fed conditions.



Biorelevant in vitro tests correlate with in vivo performance

Enteric performance of Capsugel® Enprotect® capsules was further evaluated using the Dynamic Gastric Model (DGM). The DGM simulates the hydrodynamics, fluid composition, digestion, emptying, and pH of the human gastrointestinal tract (GIT). This study confirms the robust enteric delivery of the payload to the small intestine in all tested conditions (fasted, light meal, FDA high fat breakfast).

In vitro evaluation of Capsugel® Enprotect® capsules in **fasted** and **fed** conditions:

- Capsules filled with iron oxide and caffeine (same as for in vivo evaluation)
- Test conditions: **Fasted state**, **Yoghurt meal** = 500 kcal, **FDA breakfast** = 900 kcal
- **Robust gastro-resistance and disintegration in intestinal section:**
 - Fasted = 30–45 min after intestinal entry
 - Fed = 45–60 min after intestinal entry
- PK prediction in line with in vivo data

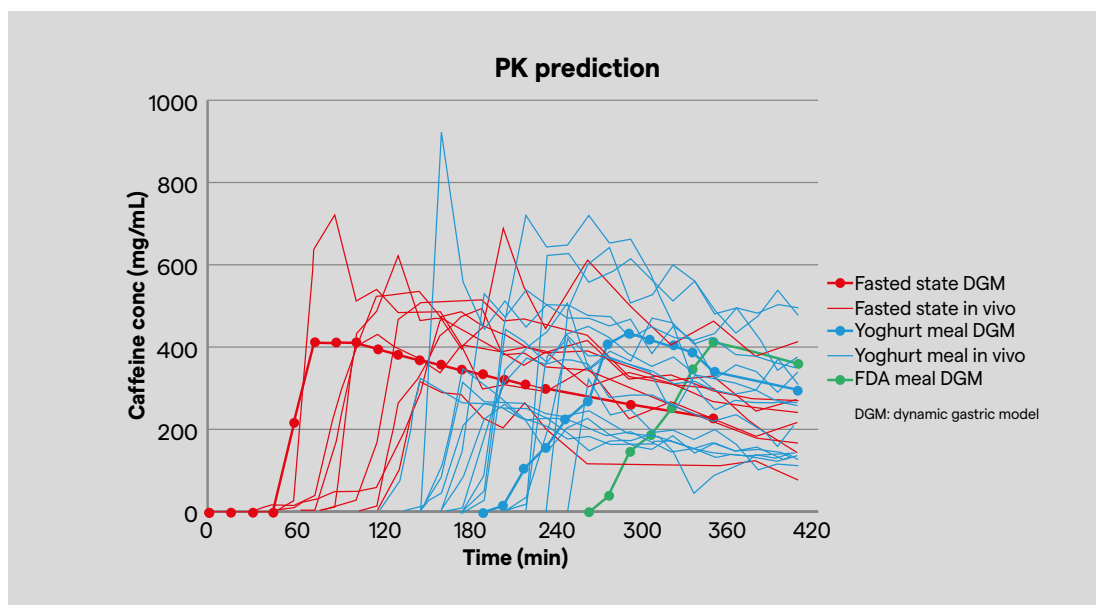
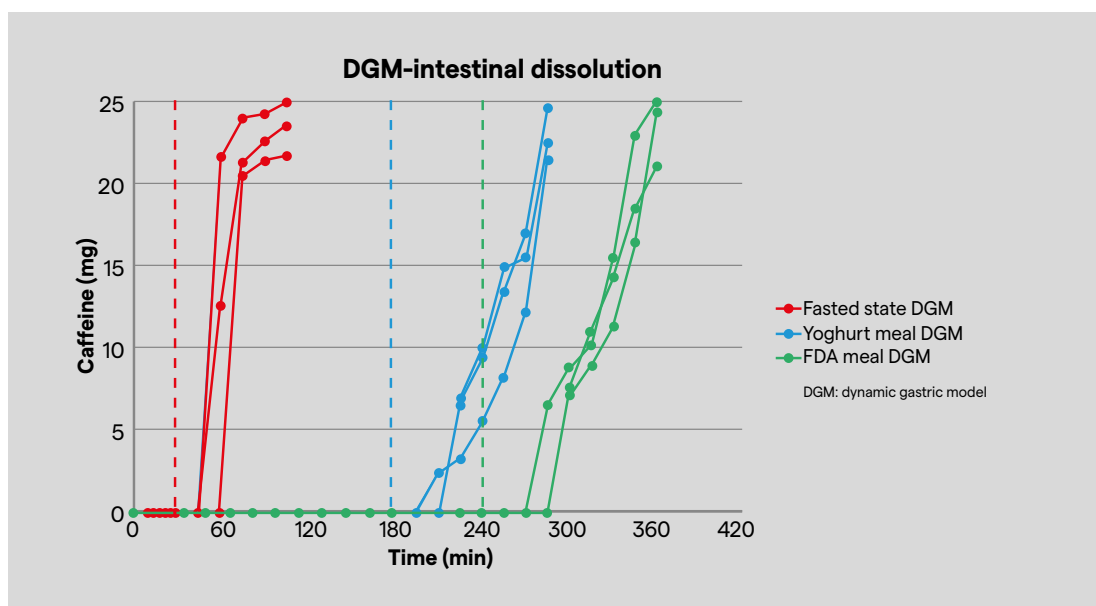


Figure 7: Dissolution and pharmacokinetics of Capsugel® Enprotect® capsules in fasted and fed conditions

Capsugel® Enprotect® Capsule

Oral solid dosage form
with first of its kind enteric
manufacturing technology

Building on the Capsugel legacy of developing and launching new and innovative oral solid dosage forms, Capsugel has developed a unique manufacturing process to build a **bi-layered capsule to assist in enteric delivery**. Through Innovaform® Accelerator we offer the opportunity to collaborate in order to customize formulation, capsule properties and the encapsulation process—so you can bring a differentiated drug product to market.

Targeted enteric drug delivery

Acid **protection**

No post-filling coating required

Customizable and scalable



With fewer manufacturing steps than alternative technologies on the market today, **Capsugel's enteric manufacturing technology can accelerate time to human and time to market.**

Partner with us to meet compendial enteric delivery requirements and enable accelerated development processes.

Our experts are here to help you at every stage

References:

1. Jannin V, et al. In vitro evaluation of the gastrointestinal delivery of acid-sensitive pancrelipase in a next generation enteric capsule using an exocrine pancreatic insufficiency disease model. *Int J Pharm.* 2023;630:122441.
2. Rump A, et al. In vivo evaluation of a gastro-resistant HPMC-based "next generation enteric" capsule. *Pharmaceutics.* 2022; 14(10):doi.org/10.3390.
3. Grimm M, et al. In vivo evaluation of a gastro-resistant Enprotect® capsule under postprandial conditions. *Pharmaceutics.* 2023;15(11):doi.org/10.3390.

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