# Next-Generation Capsule Platforms to Enable Oral Delivery of Peptides

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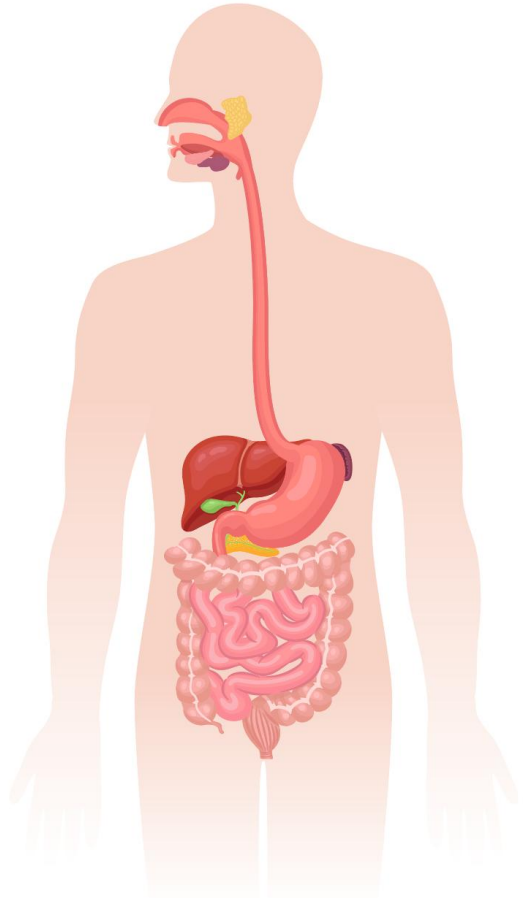
# What limits oral bioavailability of peptides?

**Bioavailability:**
Proportion of an ingested substance reaching the blood circulation

**Main limitations** to oral bioavailability of peptides:

- **Acid** sensitivity
- Sensitivity to digestive **enzymes**
- Poor **permeability** across stomach and intestinal barriers



# Development of a LBF to improve oral bioavailability of Exenatide

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## Context

Exenatide is a GLP-1 receptor analog used in type-2 diabetes mellitus treatment

Current administration via injection:

- Byetta® (AstraZeneca), administration twice daily
- Bydureon® (AstraZeneca), administration once daily

Limited oral bioavailability due to:

- Sensitivity to enzymes (pepsin, α-chymotrypsin)
- Limited permeation due to size (~4.2 kDa)

## Case study

### 1 Develop a lipid-based formulation:

- With Exenatide HIP to maximize payload in LBF
- To protect exenatide from proteolytic degradation
- Including sodium caprate

### 2 Develop a customized capsule:

- Compatible with developed formulation
- Enabling enteric delivery to avoid Exenatide degradation in the upper GI tract

*Dumont, C., et al.* ***2026*** https://doi.org/10.3389/fddev.2026.1770094

# Step 1: Increase peptide lipophilicity by Hydrophobic Ion Pair formation

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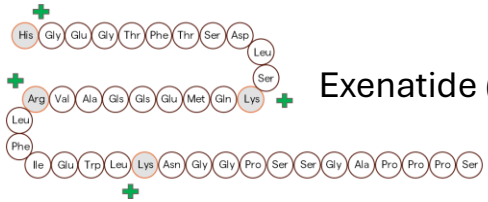
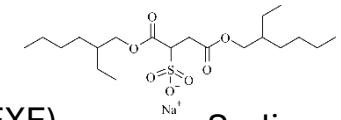
## Method: Hydrophobic Ion Pair

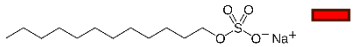
Chemical structures of Exenatide and anionic surfactants in acidic conditions




Exenatide (EXE)




Sodium docusate (DOC)




Sodium laurylsulfate (SLS)

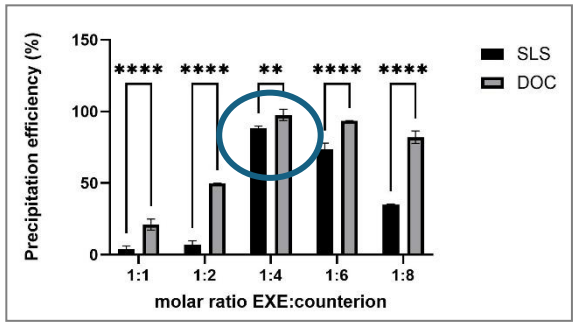
- Exenatide combined with anionic counter-ion at different molar ratios
- Yield determined by quantification of « unpaired » peptide:

$$Precipitation\ efficiency = 100 - \left(100 * \frac{[EXE]_{supernatant}}{[EXE]_{total}}\right)$$

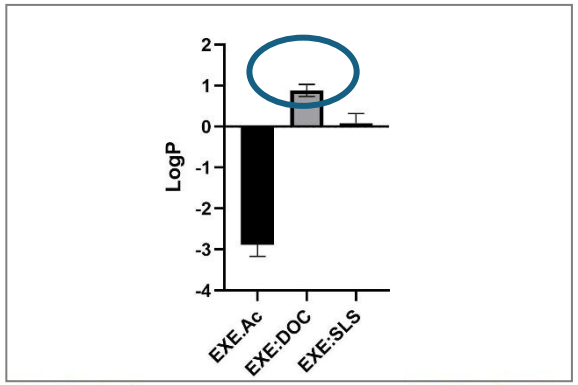
- **Log P** measurements to determine lipophilicity increase.

## Results

HIP EXE:DOC (molar ratio 1:4) was selected for the following stages of LBF development.




Highest yield with **1:4 molar ratio**




Highest **lipophilicity** increase with sodium docusate.

# Step 2: Formulation design

## Solubility evaluation

| Type | Commercial name | Chemical name (USP NF) | Solubility (mg/g) | |
|---|---|---|---|---|
| | | | EXE | EXE:DOC |
| **Oils** | Maisine® CC | Glyceryl monolinoleate | <LOQ | 0.03 |
| | Soybean oil | Soybean oil | <LOD | <LOD |
| **Surfactants** | Capryol® 90 | Propylene Glycol Monocaprylate | <LOD | 0.02 |
| | Labrafac™ MC60 | Glyceryl Monocaprylocaprate | <LOQ | **9.54** |
| | Lauroglycol™ 90 | Propylene Glycol Monolaurate | <LOD | <LOD |
| | Labrafil® M1944CS | Oleoyl polyoxyl-6 glycerides | 0.7 | <LOD |
| | Labrasol® ALF | Caprylocaproyl Polyoxyl-8 glycerides | <LOD | 5.47 |
| | Kolliphor® ELP | Polyoxyl 35 Castor Oil | <LOD | <LOD |
| | Tween® 20 | Polysorbate 20 | <LOD | 0.06 |
| | Tween® 80 | Polysorbate 80 | <LOD | <LOD |
| **Solvents** | PEG 400 | PEG 400 | <LOD | 2.28 |
| | Propylene glycol | Propylene glycol | **9.9** | **9.04** |
| | Glycerin | Glycerin | 5.2 | 0.89 |

**Labrafac® MC60** identified as best solvent for C10 with solubility of 20 mg/g.

## Miscibility and dispersibility tests

| LBF prototype composition | |
|---|---|
| **Commercial name** | **Amount** |
| Labrafac MC® 60 | 85% |
| Kolliphor® RH40 | 10% |
| Propylene glycol | 5% |
| Exenatide | 6 mg/g |
| C10 | 20 mg/g |
| **Particle size measurements in water, 37°C, 1:1000** | |
| **Z-average (nm)** | **PDI** |
| 104 | 0.1 |
| **Solubility evaluation, 37°C** | |
| EXE | 1.44 ± 0.01 mg/g |
| EXE:DOC HIP | 7.63 ± 0.17 mg/g |

### Corresponding EXE dose:

- 3.0 mg EXE in size #1 capsule
- 4.1 mg EXE in size #0 capsule

# Step 3: In vitro evaluation

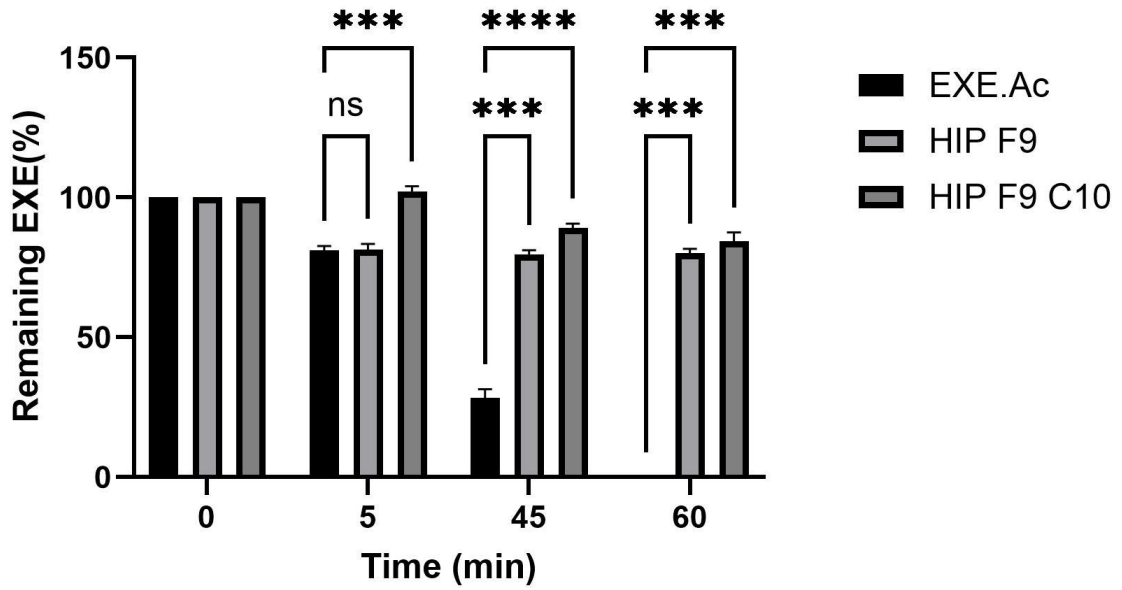
Exenatide is sensitive to:

- Pepsin ➔ need for an enteric dosage form
- α-chymotrypsin

## Method

Formulation was dispersed in buffer and incubated with a solution of α-chymotrypsin for 1 hour. At predetermined timepoints, enzyme activity was stopped and peptide quantified.

## Results




**LBF provide a protective effect towards α-chymotrypsin induced degradation.**

# Customized capsule for controlled release: Capsugel® Enprotect® capsule

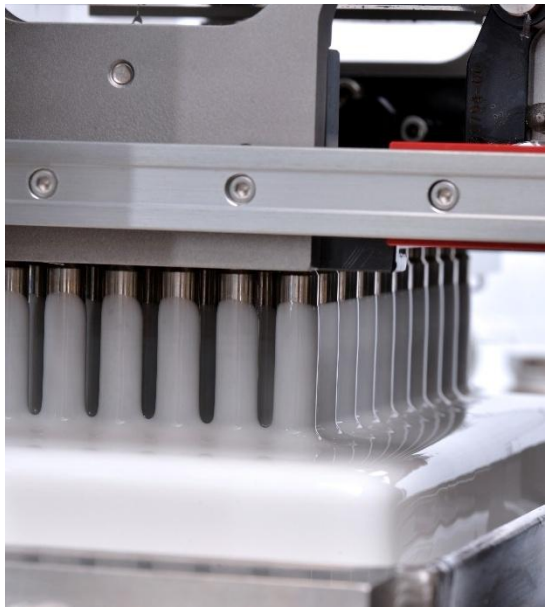
**HPMC and HPMC-AS polymers**

Protect acid-sensitive APIs, prevents gastric irritation and allows for intestinal delivery

**Bi-layer manufacturing technology***

Allows targeted delivery of APIs to the distal intestine **without the need for additional coating excipients**


- **Targeted** enteric drug delivery
- Acid **protection**
- **No additional coating** required
- **Customizable** and scalable



*Pending patent for double-dipping process (patent EP4251126A1)

# Enteric properties confirmed in compendial dissolution test with EMT pellets

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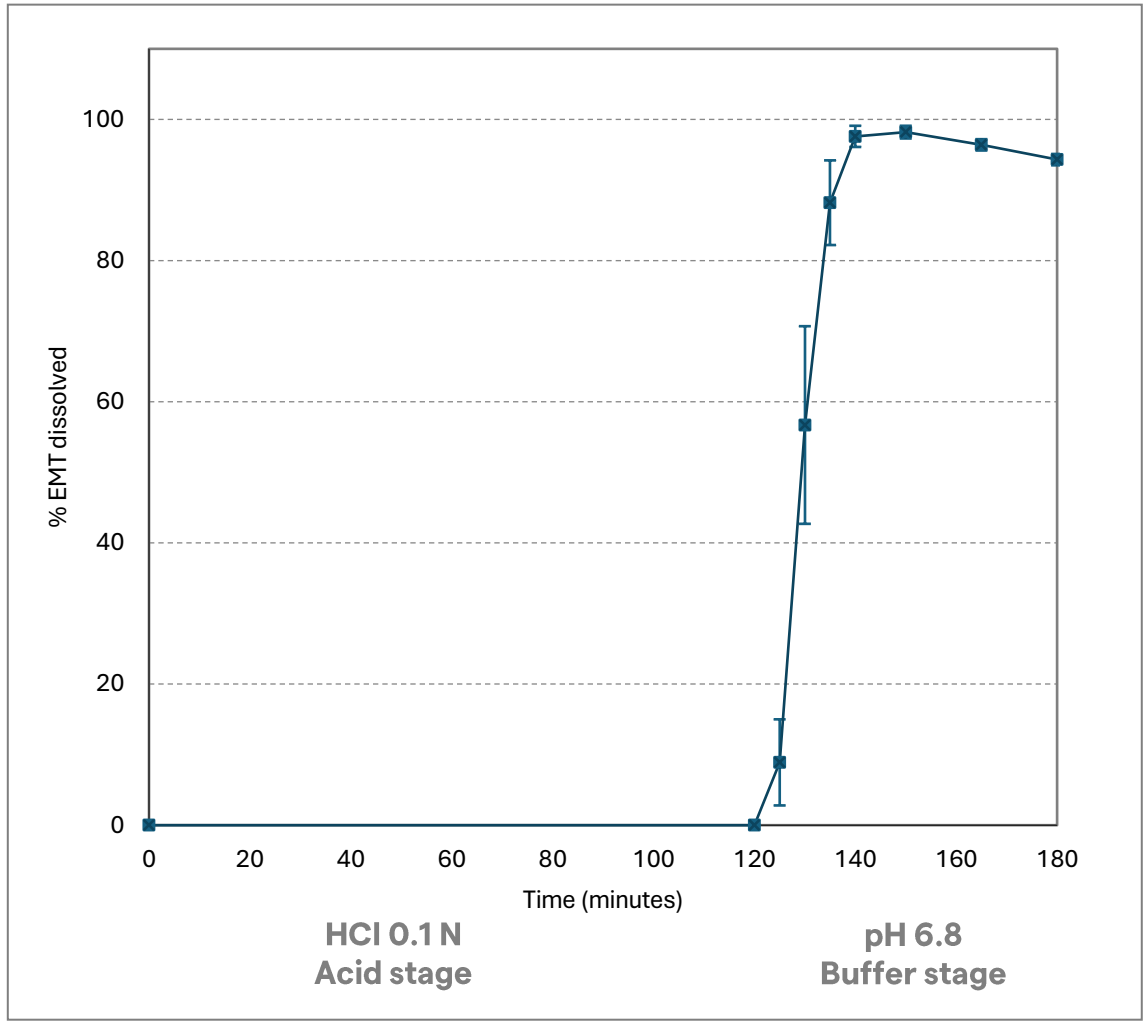
**Enteric performance** according to **USP** monograph for Esomeprazole Magnesium (EMT) delayed-release capsules (very acid sensitive model API)

**Enprotect® capsules are intrinsically enteric**

- Even underfilled
- Without sealing or banding

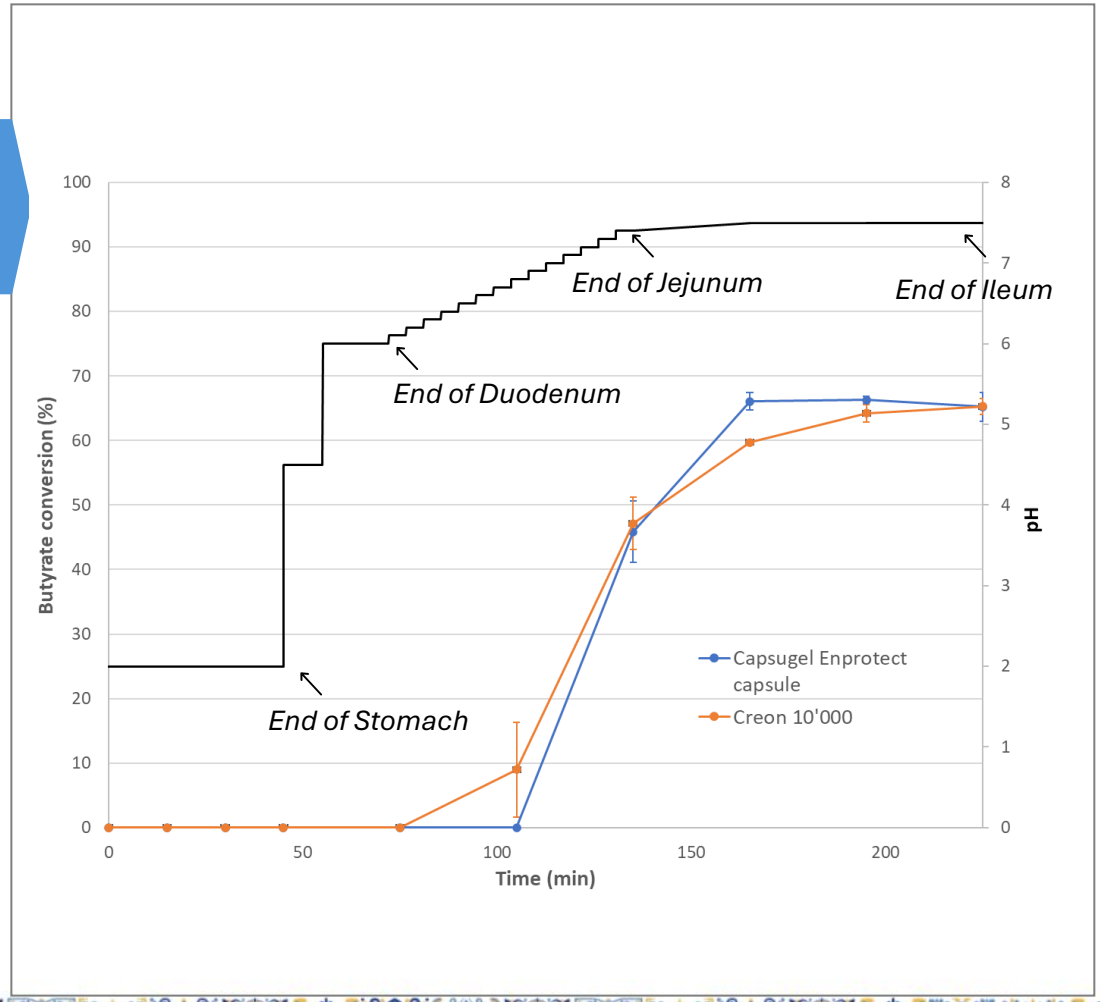
Capsule after 5 min in pH 6.8
**showing start of release**




# Protection of protein from degradation
# Biorelevant in vitro evaluation in disease model

**Capsugel® Enprotect® capsules offer a similar acid/pepsin protection to pancreatin than marketed enteric formulation**

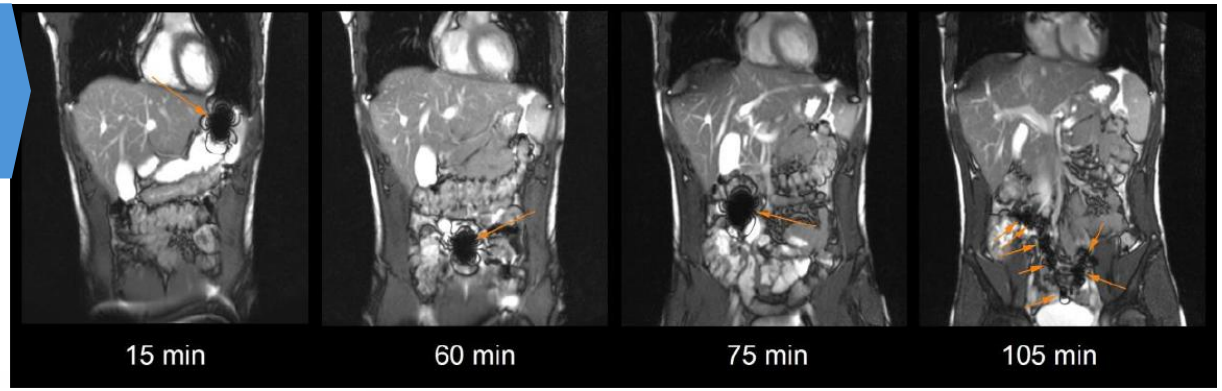
- Capsules filled with pancrelipase for evaluation of lipase activity (conversion of tributyrin in butyrate – GC-FiD)
- The onset of the **release of the pancreatin** corresponds to the **end of jejunum section**
- A commercial product containing the same pancreatin (Creon® 10,000) was used as a benchmark.



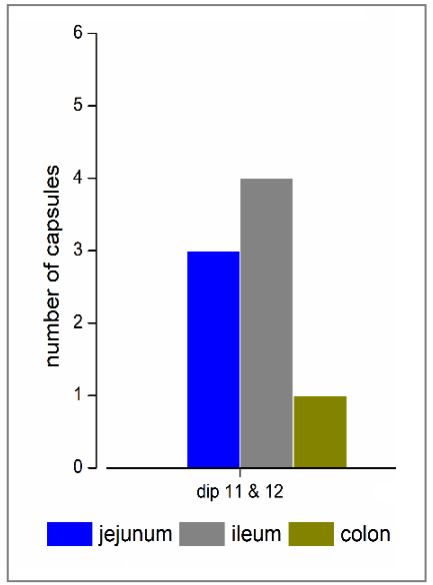

*Jannin, V., et al.* ***2023*** https://doi.org/10.1016/j.ijpharm.2022.122441

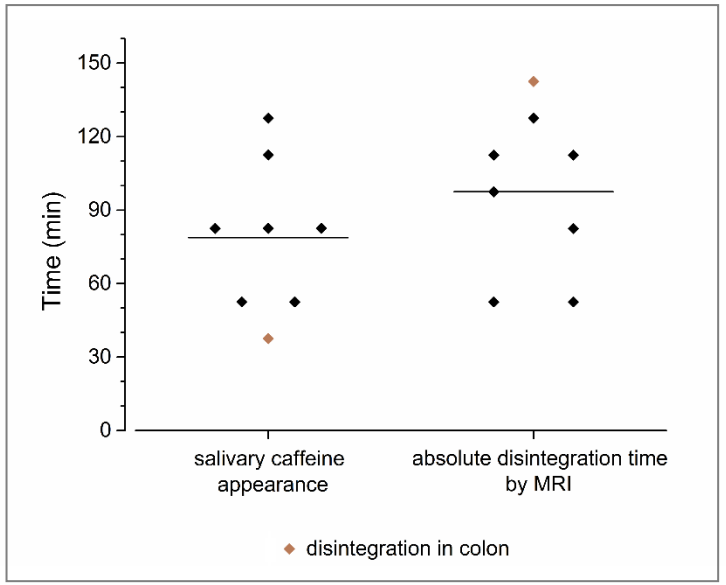
# Capsule performance: enteric properties | in-vivo

## In-vivo evaluation of Capsugel® Enprotect® capsules in fasted conditions, 8 volunteers




- Capsules filled with iron oxide for localization by MRI, and caffeine for detection of caffeine in saliva (LC-MS)
- **Start of release/disintegration in jejunum,** ileum or colon.
  - For one volunteer the gastric and small intestinal transit times were exceptionally fast, the capsule was in the colon after 45 minutes.
- **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.




*Rump, A., et al.* ***2022*** https://doi.org/10.3390/pharmaceutics14101999

* Excluding the capsule that disintegrated in the colon

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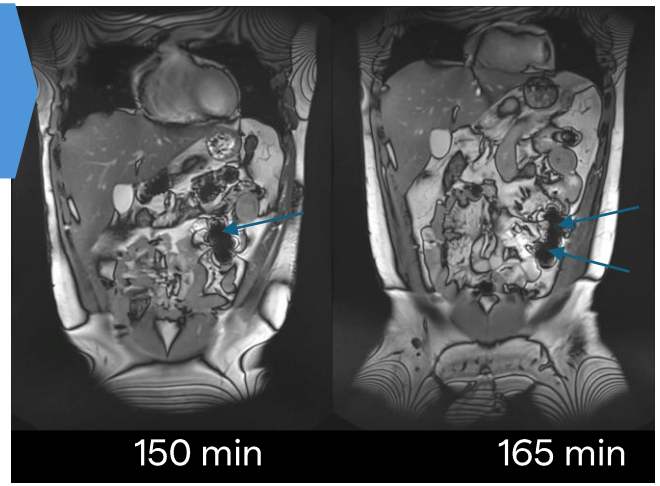
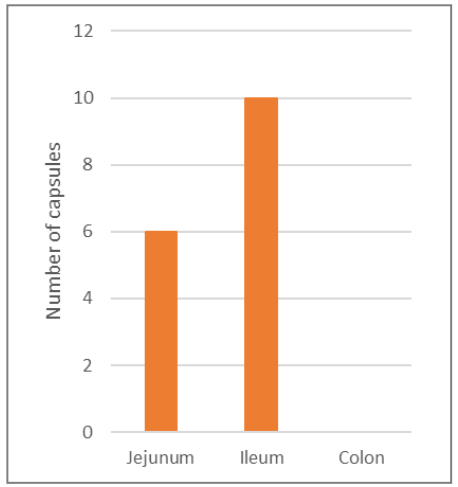
# Capsule performance: enteric properties | in-vivo

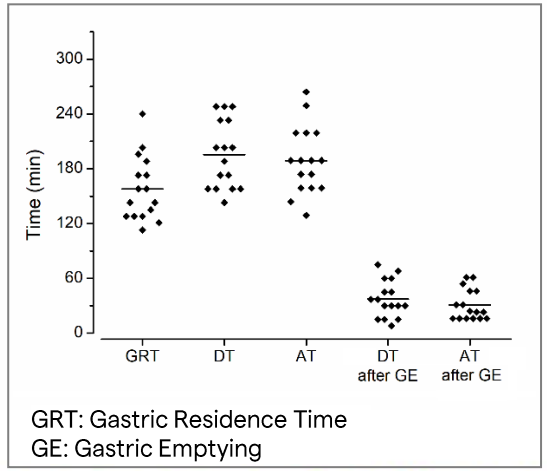
## *In vivo* evaluation of Capsugel® Enprotect® capsules in fed conditions, 16 volunteers:

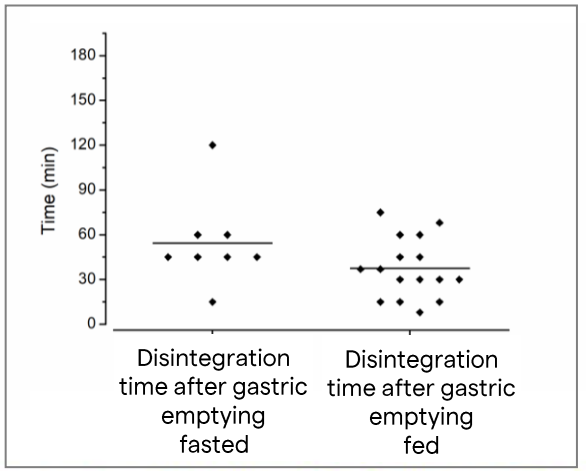
- Dosing 30 minutes after intake of a standard breakfast (500kcal)
- Gastric residence time = 158 ± 35 min (max=248 min)
- **Time to 'start of release/disintegration' after gastric emptying**
  - By MRI = 39 ± 21 min
  - By caffeine appearance = 32 ± 17 min
- No influence of prolonged gastric residence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

*Grimm, M., et al.* ***2023*** https://doi.org/10.3390/pharmaceutics15112576



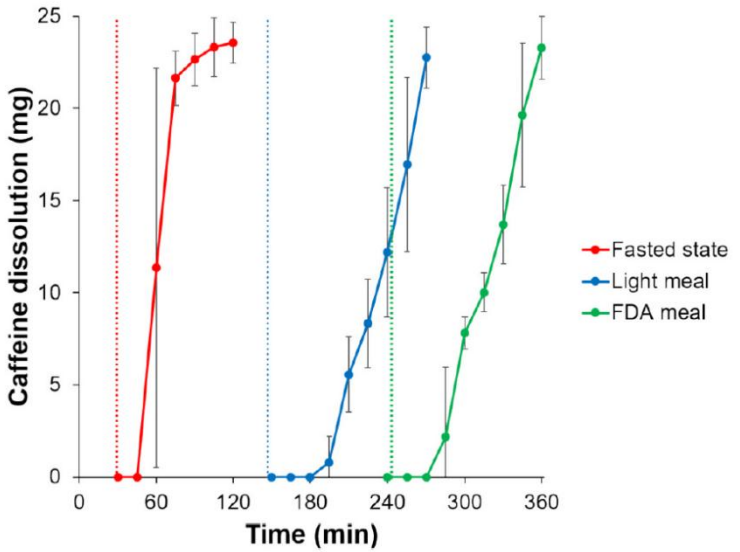



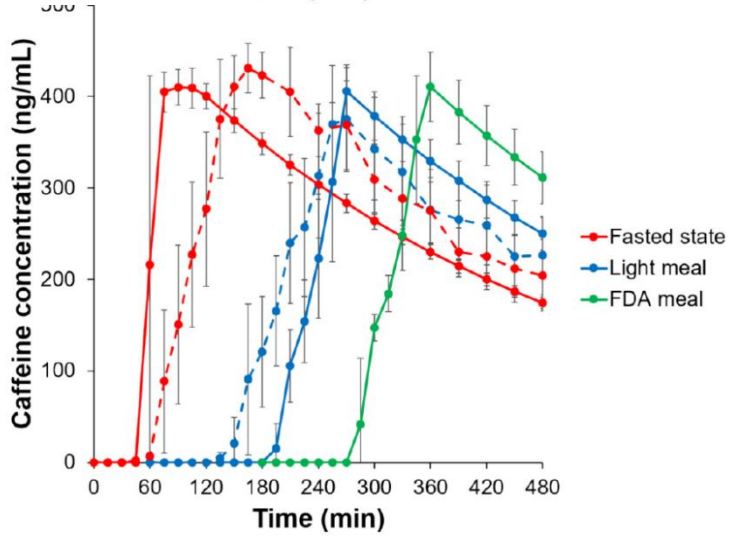




# Robust delivery in the intestine whatever the dosing condition

*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 meal = 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**



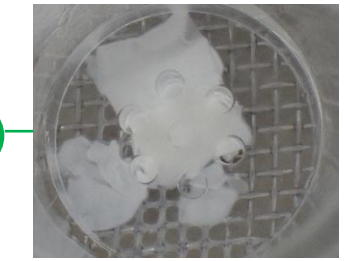

*Knopp, M.M., et al.* ***2026*** https://doi.org/10.1016/j.ejpb.2025.114962

# Incompatibility observed between Labrafac®MC60 and Capsugel® Enprotect® capsules

**Enteric performance** evaluated according to **USP** monograph for enteric dosage forms with 100% Labrafac® MC60 in Capsugel® Enprotect® capsules

**T0** → **T1 month**

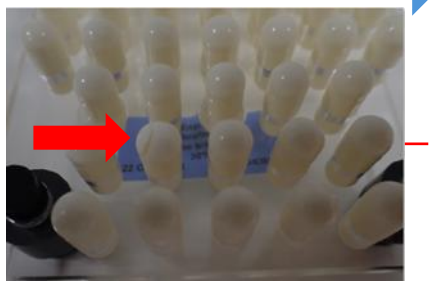
**Storage at 45°C/75%RH**



1 h in HCl 0.1 N

5 min in buffer pH 6.8

Maintenance of capsule enteric properties at T0



Cracks observed on capsules

Incompatibility between capsule shell and fill material

# Capsule customization to facilitate PoC development and optimization

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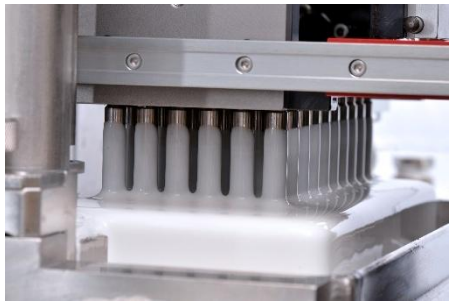
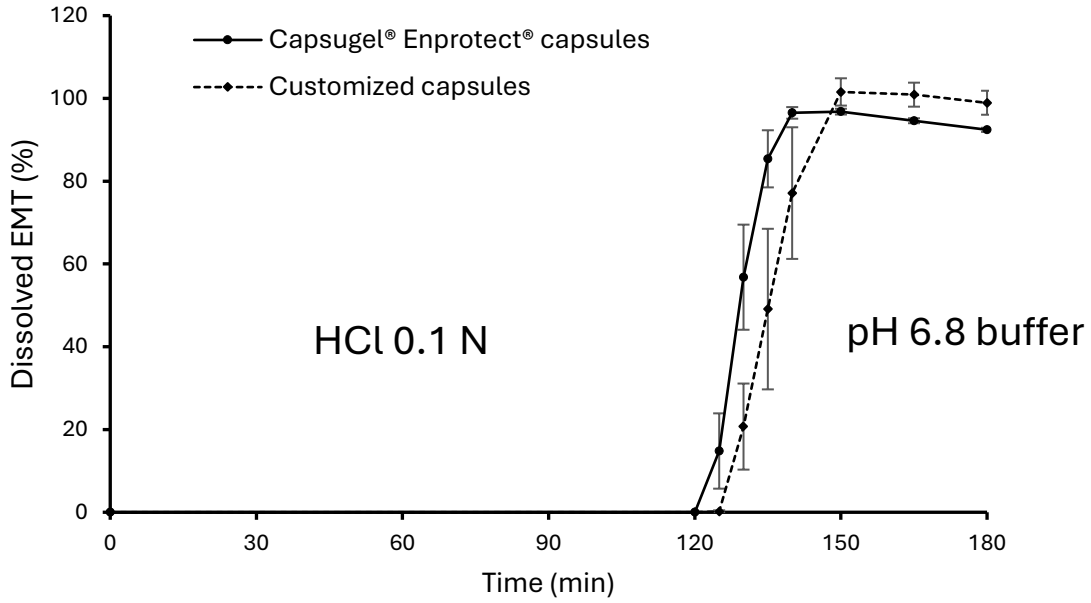
| | |
|---|---|
|  | Size |
| | Design |
| | Polymer |
| | Adjuvants |
| | Single- / bi-layer capsules |
|  | Modify release profile |
| | Optimize content / shell compatibility |
|  | Enables direct evaluation of lab-scale innovative capsule batches |
| | Scale-up possible |



# Enteric properties evaluation of customized capsules

## Dissolution test with acid sensitive small molecule




No release of EMT during the 2 h acid phase (<10%)

Fast release of 100% of the encapsulated EMT (>80% in 30 min)

➔ **Enteric properties as defined by USP**

## Disintegration test with LBF

Exemplar image of filled capsules after 1 hr in HCl 0.1N:

Filled w/ T1 + EXE:DOC HIP

No opening after 1 h in HCl 0.1N

Rapid opening (< 5 min) was observed for all capsules upon switching buffer to pH 6.8

➔ **Enteric properties confirmed**

# Capsule customization to support filling with large amounts of Permeation Enhancer

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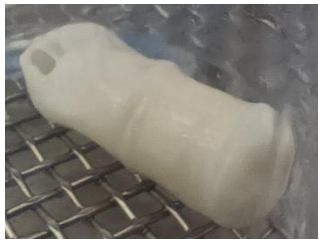
## Need for customization

**Problem statement:** sodium-based permeation enhancers (sodium caprate, C10 or sodium caprylate, C8) can induce early disintegration of the Enprotect® capsules upon shell hydration.



Exemplar image of Capsugel® Enprotect® capsule filled with C8 after 1h30 in HCl 0.1N
(no sinker, no disk)

**Customization:** Higher enteric polymer content and inclusion of hydrophobic agent in internal HPMC layer.

## Performance evaluation

Exemplar image of custom enteric capsule filled with C8 after 2h in HCl 0.1N
(no sinker, no disk)

**Performance**: new capsule shell resist to acid exposition for at least 2 h. On-going stability study

➔ Enteric properties confirmed

# Capsule customization for proximal intestinal delivery

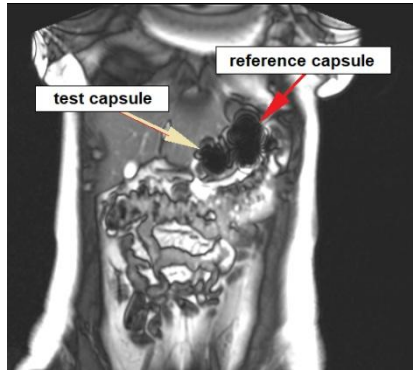
## Need for customization

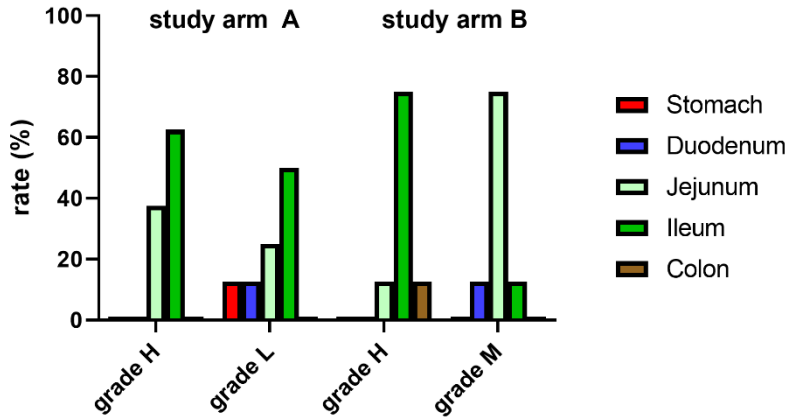
**Problem statement:** Bioavailability of encapsulated API could be improved by targeting jejunum

| Capsule | HPMC-AS | Dissolution pH |
|---|---|---|
| Capsugel® Enprotect® capsule | H grade | 6.5 |
| Customized (pilot scale) | M grade | 6.0 |
| Customized (pilot scale) | L grade | 5.5 |

*Grimm, M., et al. **2026** Submitted*

## HPMC-AS grade influences localization of capsule opening in the GI tract




Gastrointestinal localization of capsule disintegration (observed by MRI).

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# Key learnings

**LBF** can address peptide oral bioavailability issues

**LBF development** facilitated by following well-defined step-by-step process

**Lipid-based systems** in capsules can optimize dosing accuracy

**Licaps® design and CFS technology:** simple and efficient technology to manufacture PoC and final dosage forms

**Drug release profile and compatibility** can be optimized by fine-tuning capsule features

# Thank you

Contact: vincent.jannin@lonza.com