

Novel, ready-to-fill  
capsules with gastric  
resistant functionality for  
fast, high-performance  
drug development

**EUDRACAP™**

Functional  
ready-to-fill  
capsules





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## ABSTRACT

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Developing a delayed release formulation of acid-sensitive actives that can be used in solid dosage forms such as tablets, pellets and capsules can be costly. Usually several stages are involved starting from R&D development to scale up and validation steps, all of which require significant investment of time and money. Sourcing a ready-to-fill functional capsule is an effective way of saving costs, reducing time to market, and boosting the performance of oral drug delivery products.

EUDRACAP™ is a recently launched non-animal-derived platform of functional, ready-to-fill capsules for fast-track development of sensitive drugs. The HPMC (hydroxypropyl methyl cellulose) capsules are functionalized with a coating based on EUDRAGIT® polymers and can be easily opened and closed on standard manual and automatic capsule filling systems.

EUDRACAP™ capsules allow targeted drug delivery (also of sensitive actives), reduce clinical risk and accelerate time to market. One type of capsule in the EUDRACAP™ portfolio is EUDRACAP™ enteric, which is designed to optimize gastric resistance and improve absorption of drug products targeted for release in the upper small intestine.

In this white paper we outline the challenges in drug delivery of sensitive actives, the unmet market need for enteric-coated capsules and provide data illustrating the acid resistance and release performance of EUDRACAP™ enteric capsules.

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## Introduction

Hard capsules are one of the most common solid dosage forms used for oral administration of active ingredients. Capsules are relatively simple to use compared with tablets which need more formulation development and quality control and, therefore, take longer to produce. Capsules present a more convenient delivery system without the need to develop a complex formulation. Also, for drugs undergoing animal or clinical trials, capsules are often employed for their simplicity and quick turnaround during the early stages of drug development.

Capsules can be manufactured in different sizes and using different materials, depending on their main purpose and content. Most capsules are still produced using gelatin. HPMC-based capsules are the most common non-animal-derived alternative, and although they are a good substitute for gelatin, they have limitations, particularly when intended for enteric formulations because they are not resistant to gastric acid.

Nevertheless, when a gastro-resistant formulation is required, the most conventional and common practice is to coat tablets with gastro-resistant polymers. Coating of filled hard capsules is not a common industrial practice because the usual approach is to fill enteric coated granules or pellets into a conventional hard capsule.

However, this supposedly simple solid dosage form becomes even more complex – as explained in the next section. Instead, preparing a capsule shell with built-in gastro-resistance for production using standard capsule filling machines has distinct advantages.

Such functional ready-to-fill capsules have wide applications in controlling drug release and gastrointestinal targeting as they allow encapsulation of almost any drug for preclinical and clinical evaluation.

# The trend towards targeted drug delivery

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During the last few decades there has been an increased interest in targeted drug delivery for improvement of patient compliance, increase of treatment efficiency and reduction of adverse effects. By using targeted drug delivery concepts, we have seen improved *in vivo* drug stability and precise targeting of drugs with narrow absorption windows. The most proven concept for targeted drug delivery via the oral route is to coat the dosage form using film-forming polymers with different pH solubilities.

For the increasing number of acid, moisture, and temperature-sensitive active molecules like nucleotides, peptides and live biotherapeutics, functional coating process conditions are not suitable because they could cause damage or degradation. For the oral delivery of such sensitive actives a new approach is needed which enables reliable protection and provides an efficient and accelerated drug development timeline. The use of hard capsules is popular because this approach enables accelerated drug development time by reducing complexity and risk.

## Gastro-resistant capsules are an unmet need

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Filling sensitive actives in gastro-resistant capsules is the best approach for developing a formulation that avoids harsh processing conditions and provides protection against gastric pH. Intrinsically enteric capsules with inherent functionality provided by the capsule shell composition are available on the market for delayed release applications.

However, use of these intrinsic enteric capsules is not always recommended for acid sensitive actives due to limited protection against gastric pH caused by the capsule shell composition. In addition, targeted drug delivery is only feasible for lower parts of the intestine. These unmet needs for formulating, protecting, and targeting sensitive actives can be fulfilled with the novel EUDRACAP™ platform.

## Solutions for gastric resistance with the EUDRACAP™ portfolio and services

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To provide gastro-resistant capsules, the EUDRACAP™ portfolio combines functionalized EUDRAGIT® polymer coatings with empty pre-locked HPMC capsules. EUDRACAP™ capsules are suitable for different formulations such as powder, pellets, granules, and other forms, and can be easily opened and closed on standard manual and automatic capsule filling systems. EUDRACAP™ leverages the exceptional functionality from EUDRAGIT® polymers which provide excellent protection to sensitive actives in gastric pH and fully comply to the United States Pharmacopeia (USP) and European Pharmacopoeia (EP) requirements of delayed release or gastro-resistant capsules.

Different regions of the intestine such as the upper intestine, ileum and colon can be targeted using EUDRAGIT® polymers. In addition to this, the EUDRACAP™ Select platform, which is another product in the EUDRACAP® portfolio, provides a flexible range of custom options including a choice of size and color of capsules and customization of a release profile by combining different EUDRAGIT® polymers. A range of challenging drug delivery targets such as acid-sensitive actives, nucleotides, peptides and live biotherapeutics can easily be formulated using different EUDRACAP™ products.

# Using EUDRACAP™ enteric for acid-sensitive actives

Enteric coated formulations are required for pharmaceutical actives which are susceptible to degradation by acidity of gastric fluid, gastric enzymes, as well as for the drugs that can cause irritation to gastric mucosa. EUDRACAP™ enteric is designed to optimize gastric resistance and improve absorption for drug products targeted for release in the upper small intestine. EUDRACAP™ enteric allows the fast track development of sensitive drug products, reduces time to clinical trials and clinical risk, and accelerates time to market. In the following section we explain how we tested the performance of EUDRACAP™ enteric.

## DISSOLUTION TEST PERFORMANCE OF EUDRACAP™ ENTERIC

### Method

EUDRACAP™ enteric empty capsules (white color, size 0) were filled with different types of substrates such as omeprazole pellets, as a model for acid labile actives, and a caffeine blend, as a prototype for highly water-soluble actives. The capsules were filled using an automatic capsule filling machine. An *in vitro* dissolution study was performed on the filled capsules using a paddle apparatus in accordance with USP apparatus 2 with sinkers. The test setup comprises a dissolution investigation in 0.1 N HCl for 2 hours, followed by phosphate buffer pH 6.8 for up to 1 hour.

The omeprazole samples were analyzed via a suitable method using high-pressure liquid chromatography (HPLC), and the caffeine samples were analyzed via a UV visible spectrophotometer. Six capsules were tested for each batch and each model filling.

### Results

Results of the two prototypes drugs omeprazole and caffeine are shown in figure 1 and figure 2. It is evident that EUDRACAP™ enteric capsules showed excellent batch-to-batch reproducibility and acid resistance performance (< 10% drug release) followed by fast release in pH 6.8 buffer. The results of the dissolution study also demonstrate that acid resistance and release performance of EUDRACAP™ enteric capsules are not affected while using different types of drug molecules. We can conclude that EUDRACAP™ enteric could be used for a wide range of drug molecules for gastric protection and enhancing intestinal absorption and bioavailability.

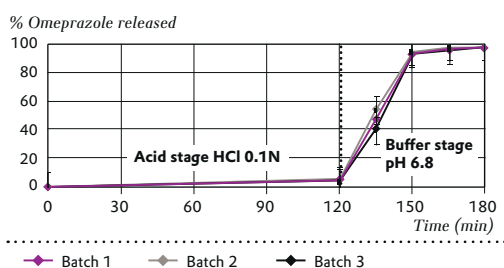


Figure 1: Dissolution profile of omeprazole as an acid labile active filled in EUDRACAP™ enteric

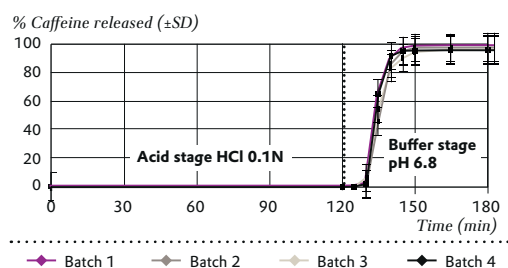


Figure 2: Dissolution profile of caffeine as a prototype drug filled in EUDRACAP™ enteric

# Disintegration test performance of EUDRACAP™ enteric

The disintegration test for EUDRACAP™ enteric capsules was carried out using lactose as an inert filling. The test exposed filled capsules to acid media for up to 2 hours using disintegration test apparatus as defined in USP and EP. After the acid exposure, the disintegration time of the filled capsules was determined in pH 6.8 buffer media. Six capsules were tested for each batch.

All filled capsules remained intact in acid media for up to 2 hours with no sign of disintegration or swelling. Disintegration time in pH 6.8 buffer was less than 10 minutes. And this disintegration test was reproducible for 3 different batches tested. We can conclude that EUDRACAP™ enteric capsules are fully compliant with the disintegration test requirements as per USP and EP.

## ACID RESISTANCE PERFORMANCE USING A DYE TEST

### Method

An acid resistance test of EUDRACAP™ enteric capsules filled with a dye blend was carried out using USP disintegration test apparatus. Hydroxy naphthol blue was used as a dye which shows red color if the dye comes in contact with small amount of acid. No capsule banding or sealing was used.

The exposure of filled capsules in 0.1N HCl was tested for 4 hours in disintegration test apparatus and after completion of the test, the contents of the capsules were analyzed visually for any change in color. Any change in the color of capsule's contents after exposure to acid media would indicate that acid media had permeated the inside of the capsules.

### Results

All capsules were found to be intact after exposure in 0.1N HCl media for up to 4 hours and there was no change in the color of the content of EUDRACAP™ enteric capsules, as shown in figure 3.

This study further confirms the superior acid resistance performance of EUDRACAP™ enteric capsules and its application for protecting the highly sensitive drugs formulations where even a small amount of acid permeation is unacceptable.



Figure 3: Appearance of EUDRACAP™ enteric capsules and filled dye content after 4 hours of exposure to 0.1N HCl in disintegration test apparatus

# Conclusion

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This white paper has presented the challenges of oral drug development for sensitive actives and targeted drug delivery, and outlined how ready-to-fill, enteric coated capsules provide solutions while saving time and costs in the drug development process. The above tests show strong evidence that EUDRACAP™ enteric capsules provide excellent acid resistance performance followed by fast release in buffer media at pH 6.8.

These properties can be used to optimize gastric resistance, improve intestinal absorption, and enhance the bioavailability of sensitive actives targeted for release in the upper part of the small intestine. Using EUDRACAP™ enteric ready-to-fill capsules can accelerate the product development process, reduce complexity and risks during formulation development, and support scale up and validation by replacing several development stages with just a single capsule-filling.

In addition to EUDRACAP™ enteric capsules, the EUDRACAP™ portfolio also includes a customizable product, EUDRACAP™ Select, which allows a capsule to be tailored to the specific needs of the pharmaceutical product.

For questions about EUDRACAP™ or to request a sample please email to [eudracap@evonik.com](mailto:eudracap@evonik.com) or visit [oncare.evonik.com](http://oncare.evonik.com) for customer support, the latest product documentation and information about upcoming webinars.

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