EUDRACAP™

Functional ready-to-fill capsules for delayed release

Dr. Kamlesh Oza

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Leading Beyond Chemistry

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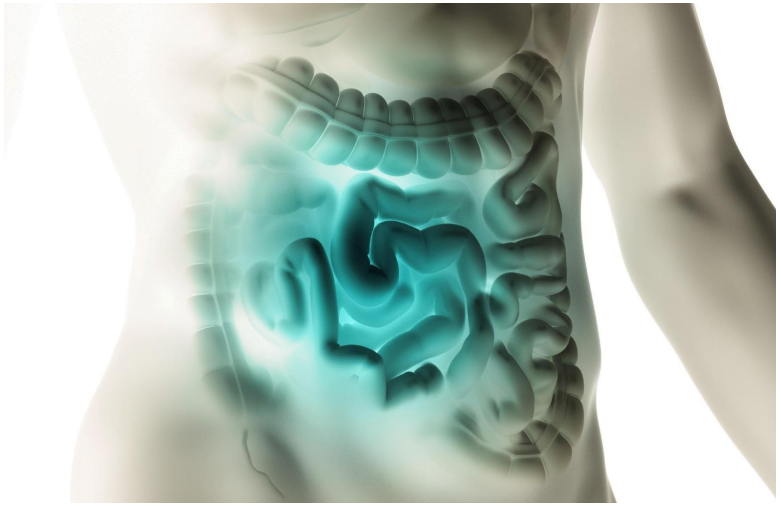
Unmet Market Needs
Introducing the EUDRACAP™ Platform

Key Challenges in Drug Development

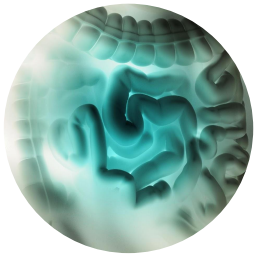
Strong Interest in Targeted Drug Delivery



Increasing Number of Sensitive Actives

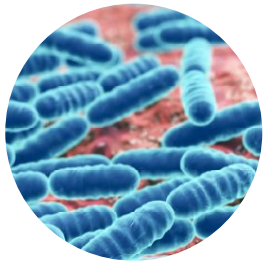
Acceleration of Drug Development Time

Key Challenges in Drug Development



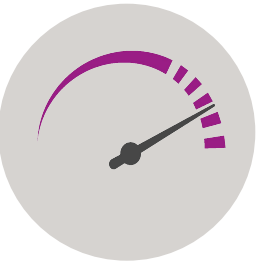
Strong Interest in Targeted Drug Delivery

- Improved *in vivo* drug stability
- Concentrated drug on targeted area
- Reduction of overall dose
- Reduction of adverse effects
- Increase of treatment efficiency
- Improvement of patient compliance
- Precise targeting of drugs with narrow absorption window



Increasing Number of Sensitive Actives

- Increasing number of acid / moisture / temperature sensitive active molecules
- Growing interest in oral delivery
  - Nucleotides
  - Peptides
  - Live Biotherapeutics
- Sensitivity of active molecules to functional coating process conditions



Acceleration of Drug Development Time

- 80% of NCE's tested in hard capsules prior to formulation development
- Use of hard capsules as 'containers' without need for complex formulation development
- Reduction of complexity, time and risk to drug development programs
- Acceleration of clinical trials

Global RNA vaccines and therapeutics market

Increase in chronic disorders due to
- poor lifestyles
- aging populations

Greater adoption rates of **oral biologics** due to high effectiveness

Huge growth potential for mRNA therapies for treatment of chronic disorders. Also for other viral infections like ebola, influenza and HIV

But, nucleic acids e.g. siRNA do not survive harsh environment of gastrointestinal (GI) tract

Need to find delivery vehicle to protect siRNA from GI environment and enable drug entry into cytoplasm of intestinal cells.

Challenges

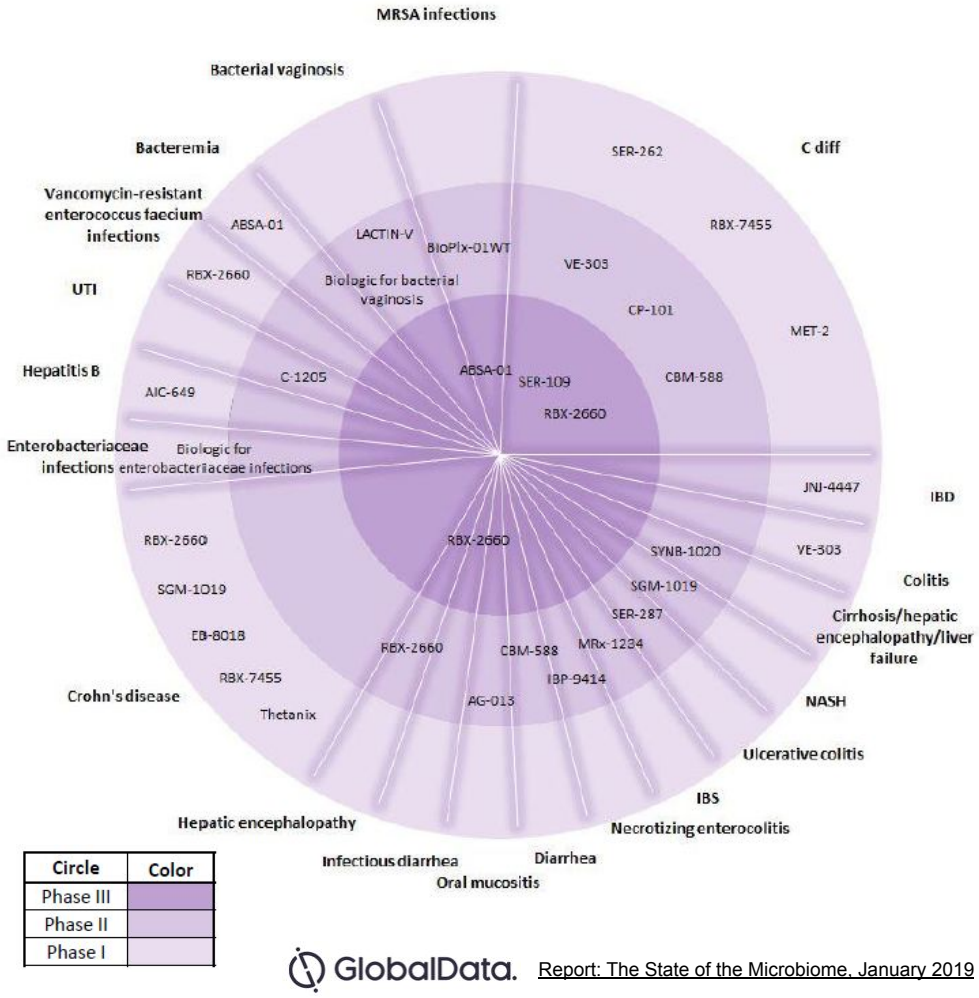
- Drastic pH changes in GI tract
- Digestive enzymes break down proteins, nucleic acids, sugars and other nutrients
  - **Pepsin** in stomach degrades proteins
  - **Pancreatin** – a mixture of enzymes from pancreas (trypsin, amylase, lipase, ribonuclease and proteases) digest macromolecules
  - **Bile salts** emulsify lipids
  - **Mucus** coats intestinal epithelium hinders support of macromolecules

Ball et al. Oral delivery of siRNA lipid nanoparticles: Fate in the GI tract, Scientific Reports (2018) 8:2178
https://www.imarcgroup.com/mrna-vaccines-therapeutics-market

The Gut Microbiome

- Trillions of microorganisms live in the human digestive system and affect our health
  - Bacteria, viruses, fungi and others
  - Hundreds of distinct bacterial species reside in the gut. While most are beneficial, some are pathogenic
- Several diseases are thought to be influenced by processes in the gut microbiome
  - Many types of cancer
  - Autoimmune disorders such as multiple sclerosis
- The gut microbiome can also influence the effects of some drug products such as mental health therapeutics
- Improved microbiome targeting can be the key to enhance patient care for a range of therapeutic areas

Market Development of Global Microbiota Clinical Research



GlobalData. Report: The State of the Microbiome, January 2019

- The number of clinical trials increased to 287 in 2017
- Main therapy areas are Clostridium Difficile Infections, unspecified Gastrointestinal Disorders and Inflammatory Bowl Syndrome
- Interventions investigated comprise
  - probiotics, prebiotics, symbiotics
  - bacterial transplantation
  - antimicrobials
  - microbiome-modulating agents
  - monoclonal antibodies
  - antidiabetic agents
  - vaccines
  - antiretrovirals

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Market and Customer Needs
Evonik's Technical Solution

Strong Interest in Targeted Drug Delivery

Increasing Number of Sensitive Actives

Acceleration of Drug Development Time

EUDRACAP™

A **best-in-class** platform of **functional** ready-to-fill capsules to:

- Optimize the release profile
- Protect your active ingredients
- Help accelerate speed to market

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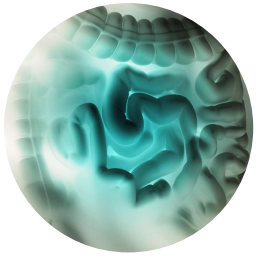
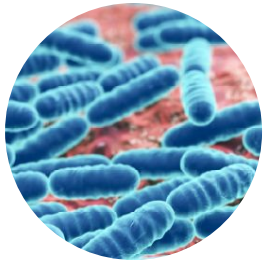
EUDRACAP™
A best-in-class platform of functional ready-to-fill capsules





Targeted Drug Delivery

- EUDRAGIT® functional coatings for a specific release profile of EUDRACAP™ capsules
- Effective pH targeting of sites including the mid-to-upper small intestine and colon

Protection of sensitive actives

- Ideal for use with active ingredients which are:
  - Sensitive to heat, moisture or gastric acids
- Able to optimize absorption and avoid premature dissolution

Reduce clinical risk and accelerate time to market

- Range of catalog and customizable coating options
- Strong regulatory track record
- Extensive formulation development and cGMP services

EUDRACAP™

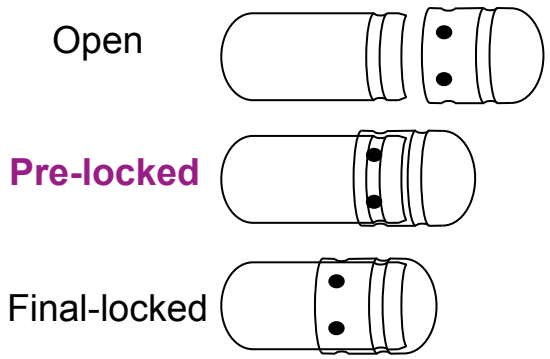
Smooth, evenly coated HPMC capsules that are easy to fill

Standard HPMC Capsules

- Empty, pre-locked hard capsules
- Easy to open, fill and close
- Fully compatible with conventional manual or high-speed automated capsule filling lines

Complete coating coverage

- EUDRAGIT® functional polymers are homogeneously applied across the entire surface of the pre-locked capsule
- Includes part of the surface area covered by the capsule cap in the final locked stage



Suitable for a range of fillings

- Various dosage forms can be efficiently filled including
  - Powders
  - Pellets
  - Granules

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Key benefits of EUDRACAP™

Effective acid resistance for up to four hours	Superior protection of sensitive actives	Ideal for powders, pellets, granules and other dosage forms	Compatible with high-speed capsule filling systems	Avoids coating, process scale-up & validation by customer
More than 60 years of safety & reliability for EUDRAGIT®	Range of formulation & cGMP scale-up services	A wide selection of customization options	Fully USP and EP compliant to reduce regulatory risk	Reduced complexity and manufacturing process risks

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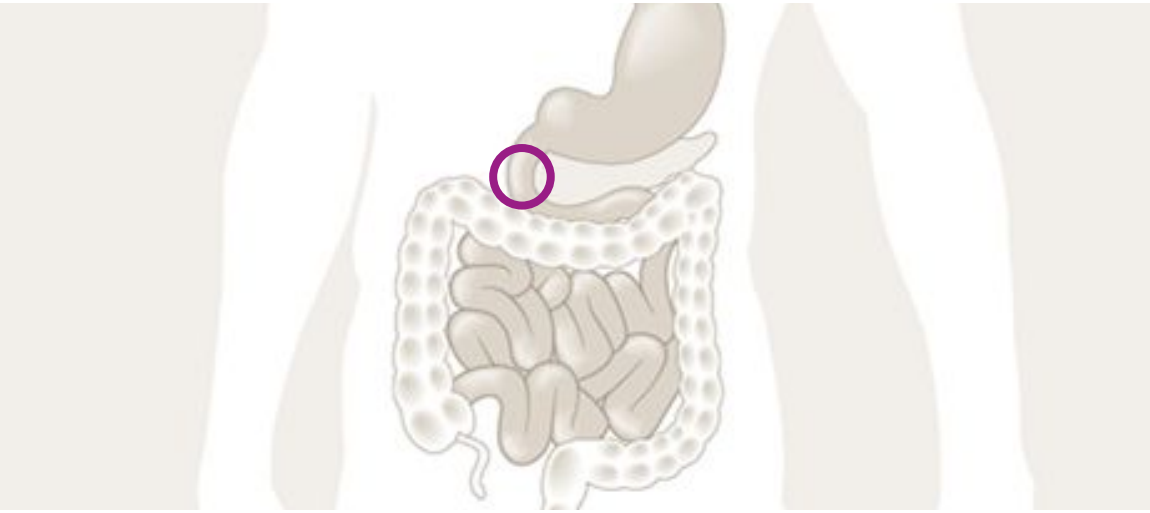
EUDRACAP™ enteric:
Functional ready-to-fill capsules
for release in upper small intestine

EUDRACAP™ enteric
Target application and composition

Drug Delivery Target

Enteric Release

- Gastric resistance
- Release in the upper small intestine

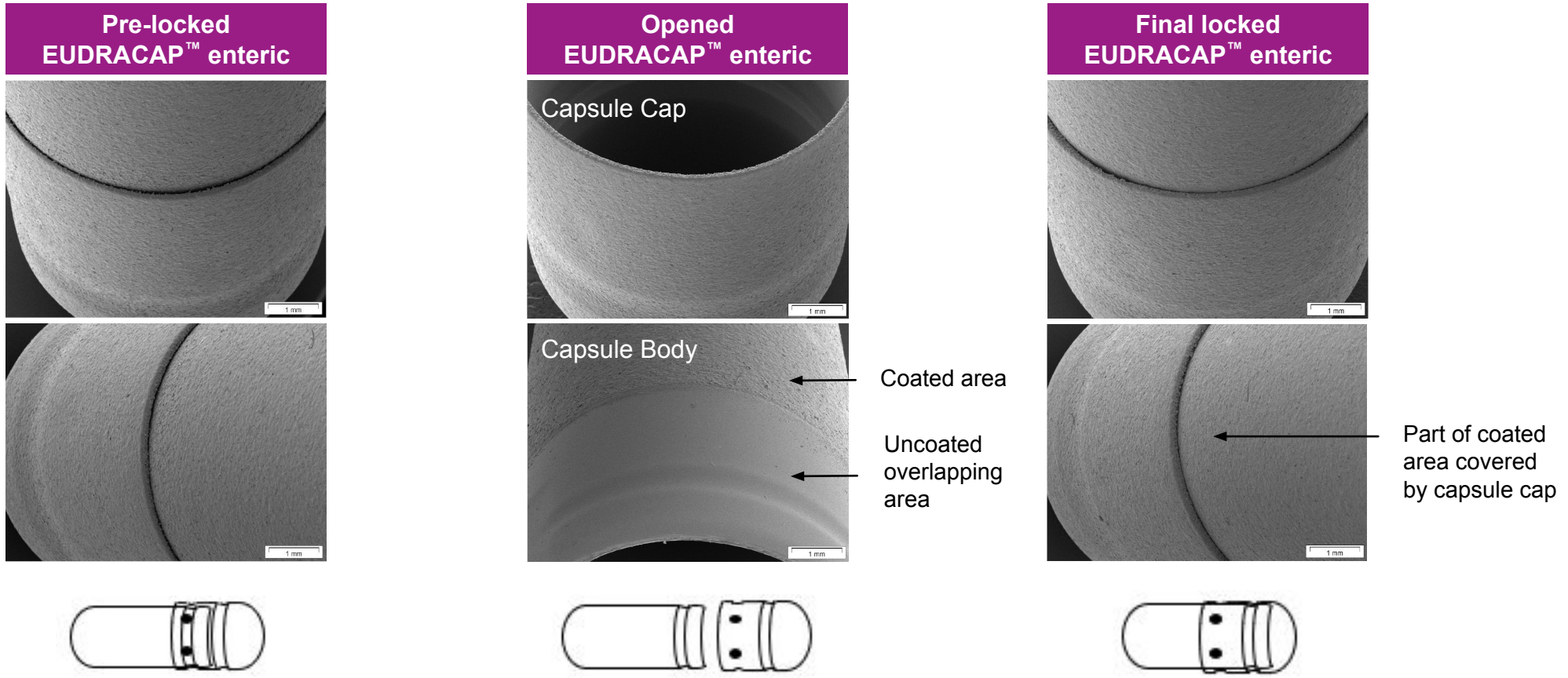


Composition of EUDRACAP™ enteric

HPMC Capsule	▪ Size 0 ▪ White
Functional Coat	▪ Consisting of EUDRAGIT® polymers with long track record

- Manufactured with fully established pharmaceutical excipients (Ph.Eur., USP/NF)
- All excipients quoted with entries in the US FDA's IID database

EUDRACAP™ enteric
SEM Pictures



Microscope: JEOL JSM IT300, Acc: 10 kV, El.Mag: 20 x, Detector: SED

EUDRACAP™ enteric
In vitro dissolution test performance

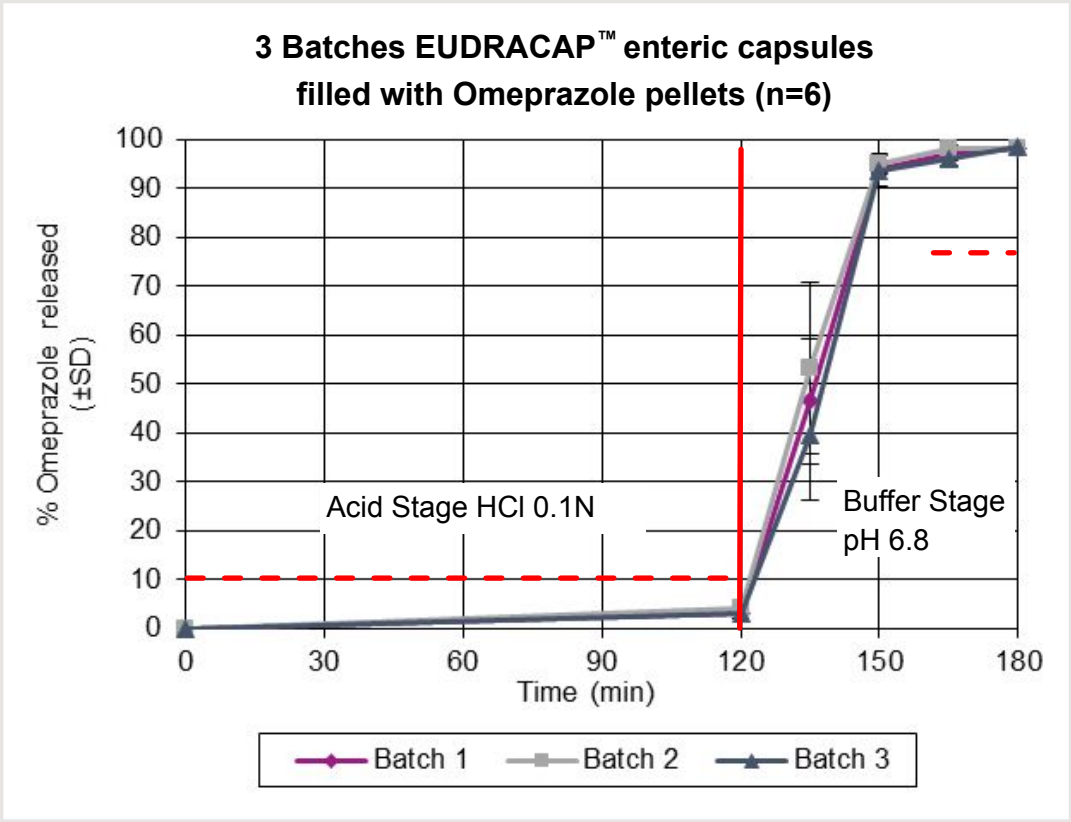
1. Omeprazole

Prototype API:

- Omeprazole selected as an acid labile model compound, proton pump inhibitor

Result:

- All 3 batches showed good acid protection
- Quick release at pH 6.8
- Good reproducibility, good match for all 3 batches
- Fully USP compliant
- Robust enteric release properties



Omeprazole pellets (841-1000 µm): 93.5 w/w% sugar spheres 710-850 µm, 5.3 w/w% omeprazole magnesium and 1.2 w/w% hypromellose 6 mPas

Dissolution method: Paddle apparatus (USP II) with sinkers, detection: HPLC, 37°C, paddle speed: 100 rpm, medium 1: 500 ml 0.1N HCl, 120 min, medium 2: 900 ml phosphate buffer pH 6.8 (KH_2PO_4)

EUDRACAP™ enteric
In vitro dissolution test performance

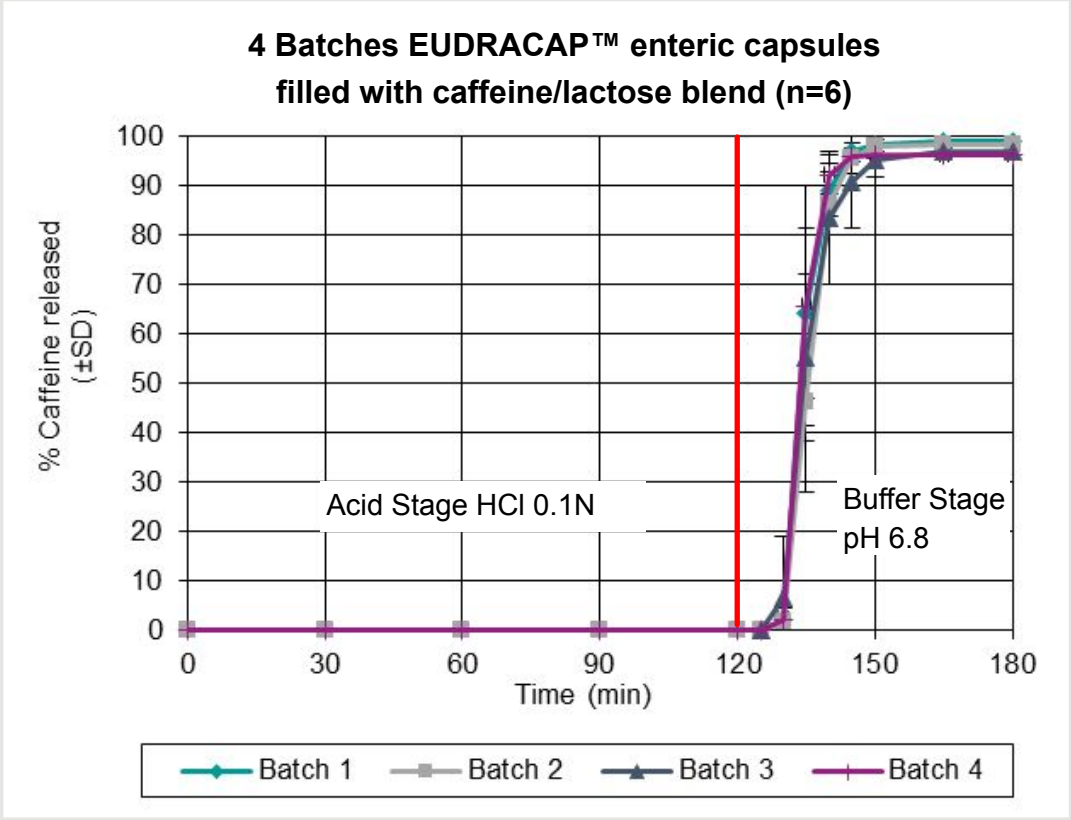
2. Caffeine

Prototype API:

- Caffeine used as model for highly water-soluble APIs

Result:

- No API release in acid stage medium followed by fast release at pH 6.8
- Same performance for all 4 batches
- Good reproducibility



500 mg of caffeine/lactose blend filled in each capsule (containing 200 mg caffeine); Dissolution method: Paddle apparatus (USP II) with sinkers, detection: Online UV, 37°C, paddle speed: 75 rpm, medium 1: 700 ml 0.1N HCl, 120 min, medium 2: 900 ml phosphate buffer pH 6.8 (KH_2PO_4)

EUDRACAP™ enteric
In vitro dissolution test performance

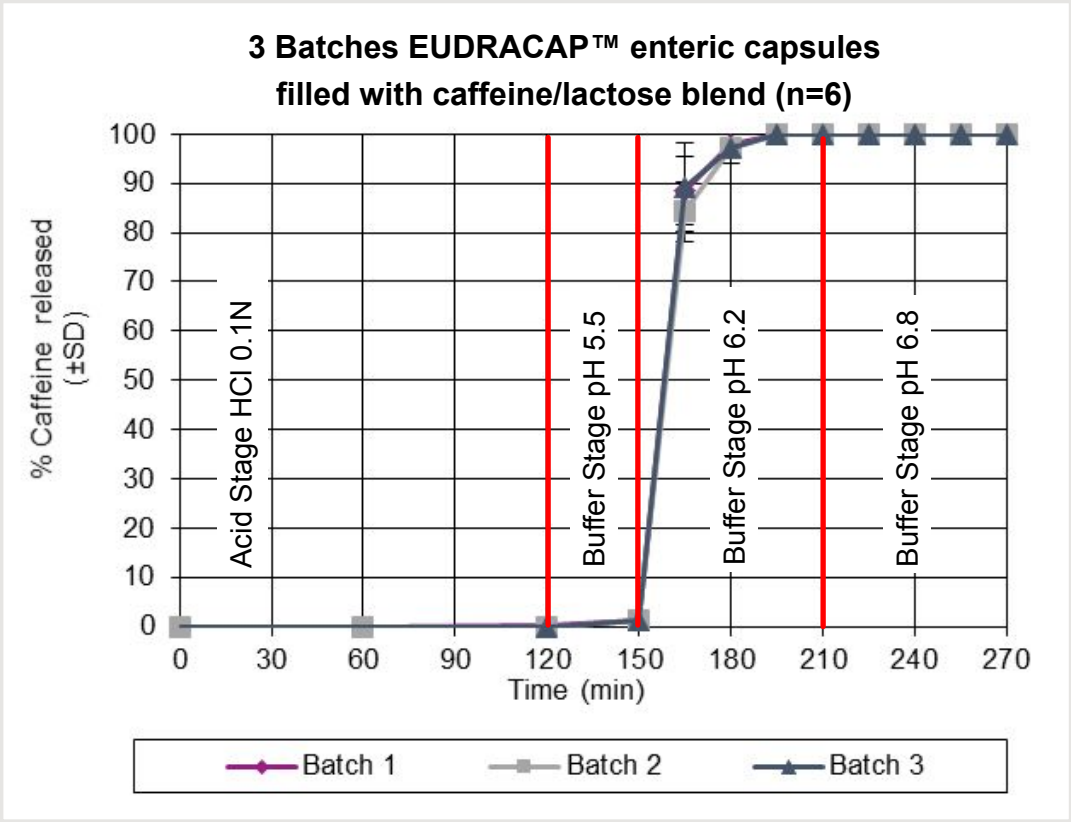
2. Caffeine

Prototype API:

- Caffeine used as model for highly water soluble APIs
- For information purposes additional pH values were tested: 120 min in 0.1N HCl, followed by 30 min at pH 5.5, followed by 60 min at pH 6.2, followed by pH 6.8

Result:

- No API release in acid stage medium (0.1N HCl)
- < 5 % Release after 30 min at pH 5.5 using this specific prototype API
- Fast release at pH 6.2



500 mg of caffeine/lactose blend filled in each capsule (containing 200 mg caffeine); Dissolution method: Paddle apparatus (USP II) with sinkers, detection: Online UV, 37°C, paddle speed: 75 rpm, medium 1: 700 ml 0.1N HCl, medium 2, 3 and 4: Phosphate buffer)

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EUDRACAP™ enteric
In vitro disintegration test performance

Disintegration Test

- Disintegration test was performed according to EP:
  2 hours in simulated gastric fluid (0.1N HCl), then switch to simulated intestinal fluid (pH 6.8)
- Capsules were filled with model filling and then completely closed

Result:

- Integrity of EUDRACAP™ enteric capsules confirmed after 2 hours at pH 1.2 (gastric condition)
- Fully compliant with pharmacopeia requirements
- Robust enteric release properties

Disintegration test of EUDRACAP™ enteric

Start, t=0

Acid Stage HCl 0.1N, t = 60 min

Acid Stage HCl 0.1N, t = 120 min

Buffer Stage pH 6.8, t = 15 min

Model filling: 500 mg lactose/caffeine blend, ratio 3:2.; Disintegration method: Disintegration apparatus according to EP (Test B) with 3 tubes.
Test was performed with sinkers at pH 6.8 acc. to EP. Medium 1: 0.1N HCl (120 min), medium 2: phosphate buffer pH 6.8 (KH_2PO_4), 37°C

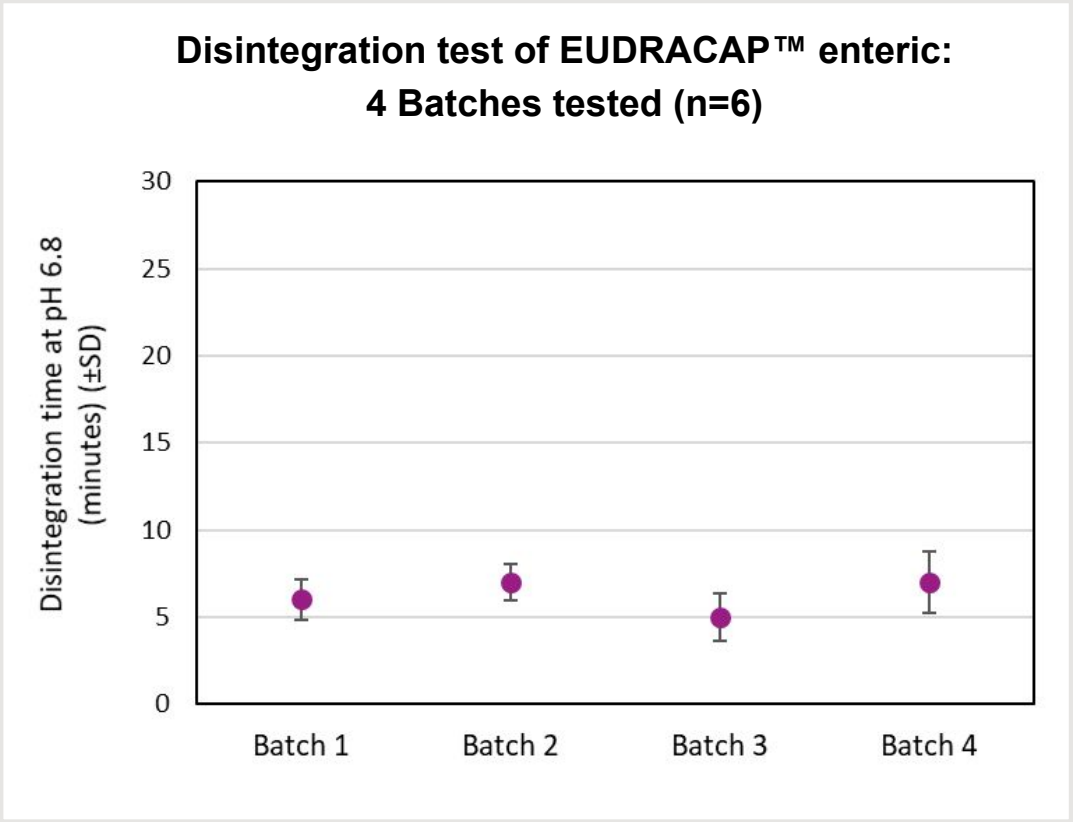
EUDRACAP™ enteric
In vitro disintegration test performance

Disintegration Test

- Disintegration test was performed according to EP:
  2 hours in simulated gastric fluid (0.1N HCl), then switch to simulated intestinal fluid (pH 6.8)
- Capsules were filled with model filling and then completely closed

Result:

- All capsules showed integrity after 2 h at acid stage
- Fast disintegration of all capsules occured after switch to pH 6.8
- Low inter- and intra-batch variability found



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Test was performed with sinkers at pH 6.8 acc. to EP. Medium 1: 0.1N HCl, 120 min, medium 2: phosphate buffer pH 6.8 (KH_2PO_4), 37°C

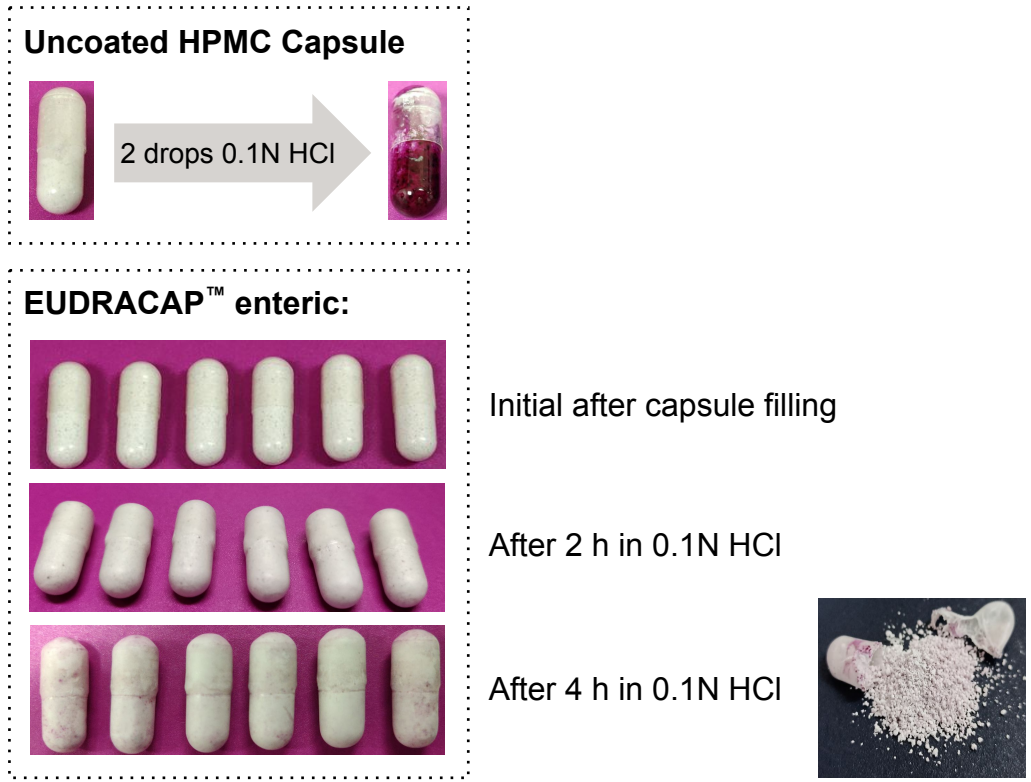
EUDRACAP™ enteric
Acid resistance test with dye filling

Acid resistance test using dye

- Hydroxy naphthol blue as model for acid / moisture sensitives capsule fillings as peptides, live biotherapeutics
- Appearance of red color if the dye gets in contact with small amount of acid
- For better visibility transparent capsules used, filled with dye blend and then completely locked
- No banding or sealing used

Result:

- Good acid protection using EUDRACAP™ enteric over a stomach residence time up to 4 hours



Filling: Dye/microcrystalline blend, ratio 1:99, Test conditions: Disintegration test apparatus (USP), Media: 0.1N HCl, 600 ml, 37°C

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EUDRACAP™ enteric
Capsule filling performance

Capsule Filling Process

- EUDRACAP™ enteric can be filled and closed
  - Manually e.g. using hole plates and
  - Automatically using standard capsule filling machines*
- Fit to standard tooling

Suitable Fillings

- Powders, pellets and granules can be filled
- Semi-solid and liquid fillings: Depending on viscosity of filling banding of capsule is recommended

Cap after capsule opening

Capsule body after powder filling

* EUDRACAP™ enteric successfully tested on BOSCH GKF 400 (20 000 capsules/h) and ACG AFT LAB (5 000 capsules/h)

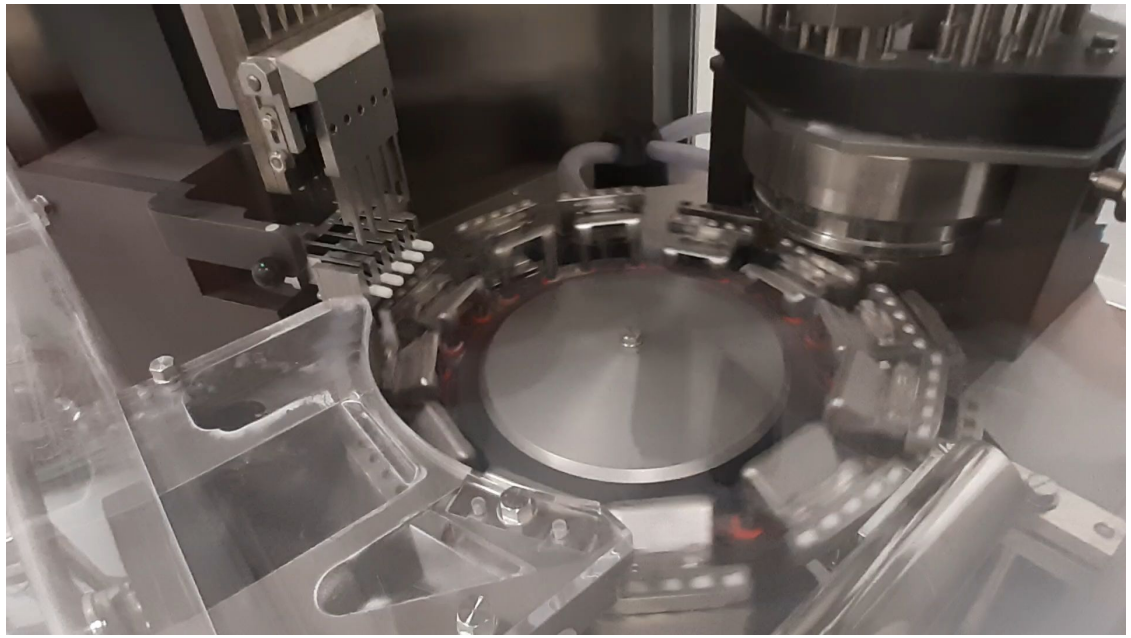
EUDRACAP™ enteric: Capsule filling performance

- EUDRACAP™ enteric can be filled and closed using standard capsule filling machines

- Performance on high speed capsule filling machine **GKF 702** from SYNTEGON (formerly BOSCH) tested:

    - Smooth filling and closing process using standard tooling and standard process parameters
    - Full speed was tested for 2 h
      Output: **700 caps/min = 42 000 caps/h**
    - Very low reject rate (**less than 1 %)** which is very good

Video of capsule filling trial using EUDRACAP™ enteric using GKF 702:



Equipment setting: Capsule separation: -0.29 bar vacuum, capsule segment size 0. Model filling: 300 mg lactose/caffeine powder. During filling process: Temp: 21°C and rel.humidity: 31%.

EUDRACAP™ enteric
HPMC Capsules as starting material

- EUDRACAP™ enteric is based on standard **HPMC capsules (white, size 0)**
- Use of well established **K-Caps®** from CapsCanada®

https://capscanada.com/products/hpmc-capsules/

3

EUDRACAP™ Select:
Ready-to-fill capsules
with custom functionality

Catalog and custom products to match your specific needs

EUDRACAP™ Select

In addition to standard EUDRACAP™ products, EUDRACAP™ Select delivers a flexible range of custom options:

Size

- A range of sizes can be supplied

Color

- Transparent, two-tone, full white or full colored

Release Profile

- Various EUDRAGIT®, drug delivery and process technologies available
- Bioavailability enhancement

EVONIK
Leading Beyond Chemistry

Formulation development and cGMP clinical scale-up services

Working with Evonik

- > 60 years of expertise for complex oral solid dosage forms
- A global leader for formulation development and scale-up
- Integrated portfolio of functional excipients, delivery technologies and CDMO services
- Strong technical expertise in:
  - Colonic delivery
  - Microbiome delivery
  - Bioavailability enhancement
  - Personalized dosage forms

Available services include:

- Fast-track feasibility studies
- Prototype samples for rapid screening and evaluation
- GMP clinical batches for phase I and phase IIa / IIb
- Analytical method development and validation
- Onsite production support and troubleshooting
- Support for technical transfer to manufacturing sites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