Unconventional Technologies to Improve Targeted Release of your Oral Formulation

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CRS 2023

EUDRATEC®

EVONIK
Leading Beyond Chemistry

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Leading Beyond Chemistry

A Broad Portfolio of Products, Technologies and Services

Pharmaceutical

Exclusive Synthesis

- Top 3 CMO for API & intermediates
- World's largest HPAPI capacity
- Portfolio of advanced technologies

Oral Drug Delivery

- **EUDRAGIT®** functional polymers
- Formulation and scale-up services
- Oral drug delivery technologies

Generic API & Intermediates

- Keto acids & controlled substances
- Chiral compounds, phosphonium salts
- Benzophenones, boronic acids

Parenteral Drug Delivery

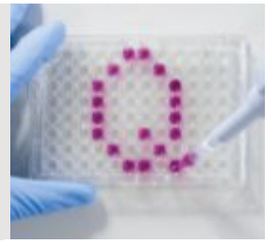
- **RESOMER®** bioresorbable polymers
- CDMO for polymeric microparticles
- CDMO for lipid nanoparticles (LNPs)

Pharmaceutical Amino Acids

- **REXIM®** amino acids, salts, derivatives
- Parenteral and enteric nutrition
- Amino acid API (LOLA)

Cell Culture Applications

- **cQrex™** cell culture ingredients
- Oligopeptides, performance boosters
- Booster screening & development



Nutraceutical

Advanced food ingredients

- **AvailOm®** high-load omega-3 powder
- **Healthberry®** anthocyanin powders

Formulation Enhancement

- **EUDRAGUARD®** functional coatings
- Development & scale-up services

Medical Devices

Biomaterials

- **RESOMER®** bioresorbable polymers
- **Endexo™** for surface modification
- Recombinant collagen

Application Services

- Competence center, analytical labs
- 3D printing materials and services

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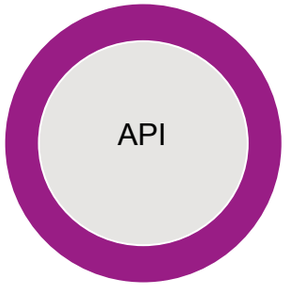
Unrivalled polymer versatility to unlock the potential of your API

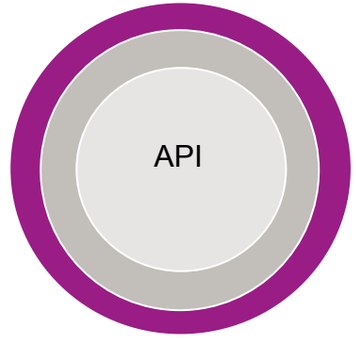
Our platform of polymers can be used individually or in combination to match virtually any target release profile

Single layers

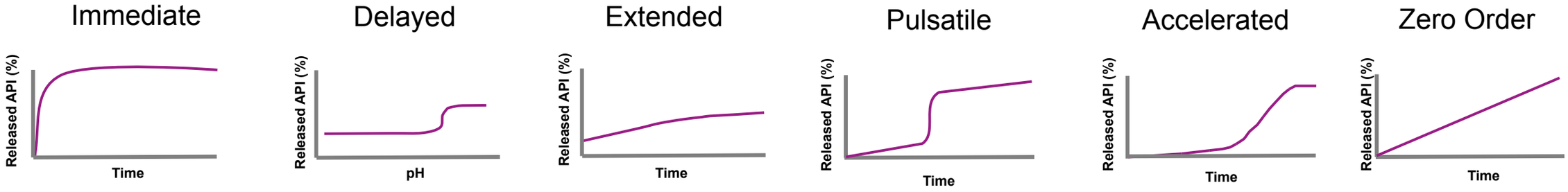


- Single EUDRAGIT® polymer
- Combination of EUDRAGIT® polymers
- Combination of EUDRAGIT® polymers and other excipients or substances

Multiple layers



- Single EUDRAGIT® polymer per layer
- Combination of EUDRAGIT® polymers and other excipients or substances
- Inert core with combination of EUDRAGIT® polymers and API layer



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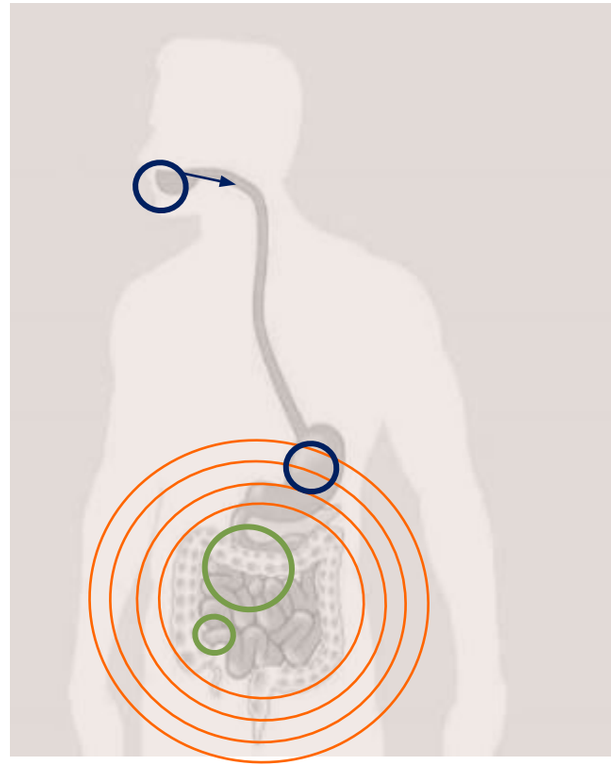
Functional Polymers to address specific API and therapy requirements

Our poly(meth)acrylate copolymers feature physicochemical properties that are determined by functional groups

Functionality		Applications	EUDRAGIT® options
	Immediate Release	▪ Taste and odour masking ▪ Moisture and light protection ▪ Improving swallowability	▪ EUDRAGIT® E ▪ EUDRAGIT® L ▪ EUDRAGIT® RL
	Delayed Release	▪ Protect acid sensitive APIs ▪ Avoid gastric mucosa irritation ▪ pH-triggered GI targeting ▪ Colonic delivery	▪ EUDRAGIT® L ▪ EUDRAGIT® FL ▪ EUDRAGIT® FS ▪ EUDRAGIT® S
	Sustained Release	▪ Sustained, modulated or custom release ▪ Precise control by diffusion barriers ▪ Multiparticulates or matrix formulations	▪ EUDRAGIT® RL ▪ EUDRAGIT® RS ▪ EUDRAGIT® NM
	Solubility Enhancement	▪ Increasing bioavailability ▪ Addressing poor permeability or solubility ▪ Fixing poor API stability in the GIT	▪ EUDRAGIT® L ▪ EUDRAGIT® E ▪ EUDRAGIT® FS



Technology Portfolio

Functional Ready to Use Capsules

EUDRACAP® Enteric /Select

Enteric capsule technology that delivers sensitive drug products and other microbiome therapeutics to targeted GI regions

High-Precision Colon Delivery

PHLORAL®

A single film coating with a dual action mechanism that combines a pH triggered polymer with a polysaccharide

DuoCoat®

A dual-layer coating of enteric polymers with an inner layer customized for rapid dissolution in the ileocolonic region

EUDRATEC® COL

A dual-layer of pH triggered and time-controlled polymers for multiparticulates to boost bioavailability & reduce daily intake

Accelerated Release in the Upper Small Intestine

EUDRATEC® Fasteric ®

A dual-coating of enteric polymer and buffers that provides enteric protection with rapid release at a defined pH from 3.0 to 5.5

Solubility Enhancement Technology

EUDRATEC® SoluFlow

A unique solubility enhancement technology to makes ASD by Emulsion based dispersion method

PHLORAL®

Fail Safe Colonic Delivery

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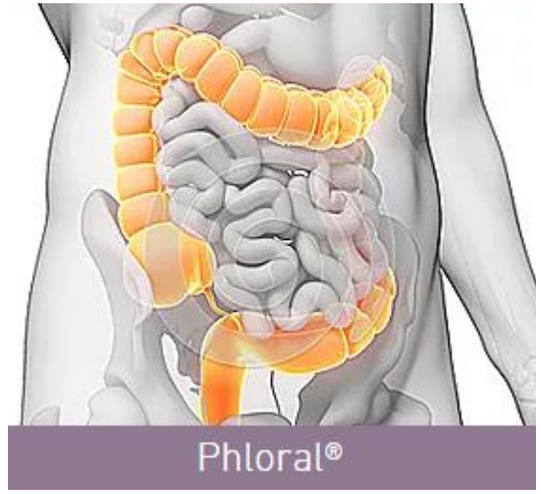
PHLORAL®
Unique Dual-action Coating for Fail-Safe

The world's only dual action coating for fail-safe colonic delivery

- World's only dual-trigger system for **fail-safe** delivery to the colon in both healthy and diseased states
- Unique dual-action coating that provides reliable and precise delivery to the **large intestine**.
- This cutting-edge technology combines a pH-responsive **polymer and natural polysaccharide** as a single film coating.
- **Colonic bacteria and pH changes trigger the site-specific release** mechanism in an independent but complementary manner
- Consistent and **clinically proven** results
- Flexible dosage forms as tablets, capsules and multiparticulates.



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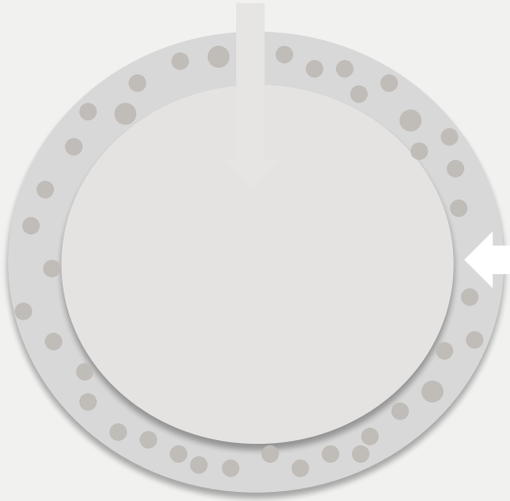
PHLORAL®
A new film coating concept for colonic delivery

Drug in the form of a tablet, capsule or pellet



Coating
Mixture of a polysaccharide and EUDRAGIT® S

Duo release triggering mechanism:

Bacterial
Polysaccharide

pH
Eudragit S

Manufacturing

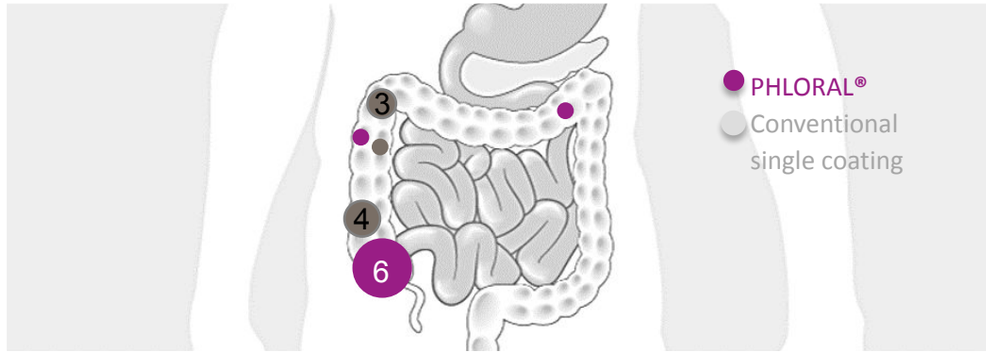
- Applicable to all types of tablets, capsules, and multiparticulates
- Utilizes standard manufacturing equipment
- GRAS materials

PHLORAL®
In vivo proof of concept

In-vivo evaluation of PHLORAL® versus conventional colon targeted formulations

Test conditions:

- Fed, fasted and pre-feed
- 8 healthy male adults,
- cross over study
- radiolabelled tablet
- Tracked by scintigraphy



Fail-safe and Efficient Delivery demonstrated

Results:

- PHLORAL® tablets released in the colon while 3/8 conventionally coated tablets stay intact in ascending colon at imaging end
- Phoral® showed site specificity, as 6/8 released in the ileocaecal junction or caecum
- PHLORAL® showed successful release under all feeding states and less inter- and intra-individual variability

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EUDRATEC® Col

Sustained Delivery in Colon

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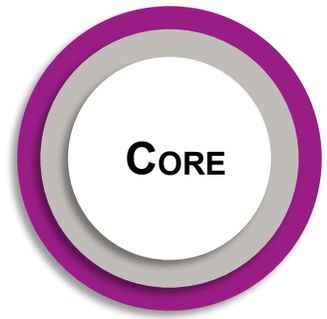
EUDRATEC® COL

Sustained release delivery of drugs to the colon

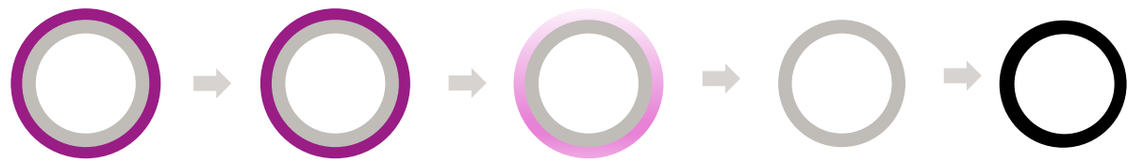
- A multi-layer, pH-triggered coating system for drug protection in the GIT and controlled release in the colon
- Coated pellets can be filled into capsules and compressed into multiparticulate tablets
- Designed to reduce daily intake and improve efficacy for:
  - Local treatment of colonic diseases such as IND or colon cancer
  - Systemic delivery for drugs with absorption in colon



Outer Layer
pH – dependent soluble coating for enteric protection and colon targeting with **immediate release**
e.g. EUDRAGIT® FS 30D

Inner Layer:
Coating with sustained release polymer
e.g. EUDRAGIT® RS/RL to provide **sustained release**

Core:
Drug layered sugar bead or drug pellet



Stomach, pH 1.2

Jejunum, pH 6-7

Ileum, pH 7
EUDRAGIT® FS 30 D
pH controlled release

Colon, pH>7
EUDRAGIT® RL/RS
Time Controlled Release

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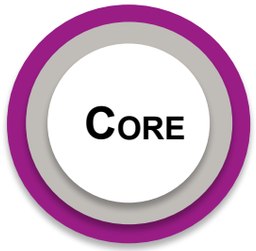
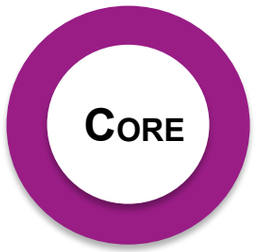
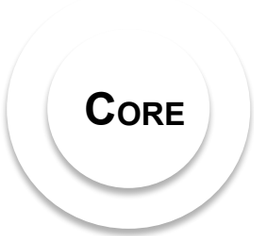
Case Study
Proof of Concept by Human PK Study



- EUDRAGIT® FS 30D
- EUDRAGIT® RS/RL
- Caffeine



- EUDRAGIT® FS 30D
- Caffeine



- IR coating
- Caffeine

Aim of Study: In vivo-in vitro correlation of drug release and absorption.

Design of the study

- Open, controlled, cross-over 12 healthy male volunteers
- 200 mg Caffeine per dose + 500 mg Lactose- [13C] ureide as aqueous solution

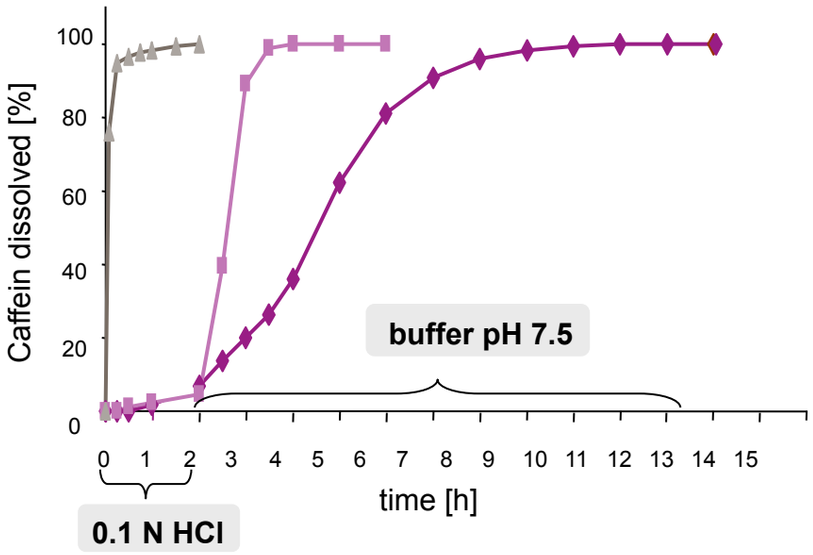
3 Arms:

- Treatment A: EUDRATEC® COL applied on caffeine pellets
- Treatment B: colon targeted caffeine pellets
- Treatment C: IR tablet Coffeinum N 0.2g Merck dura GmbH

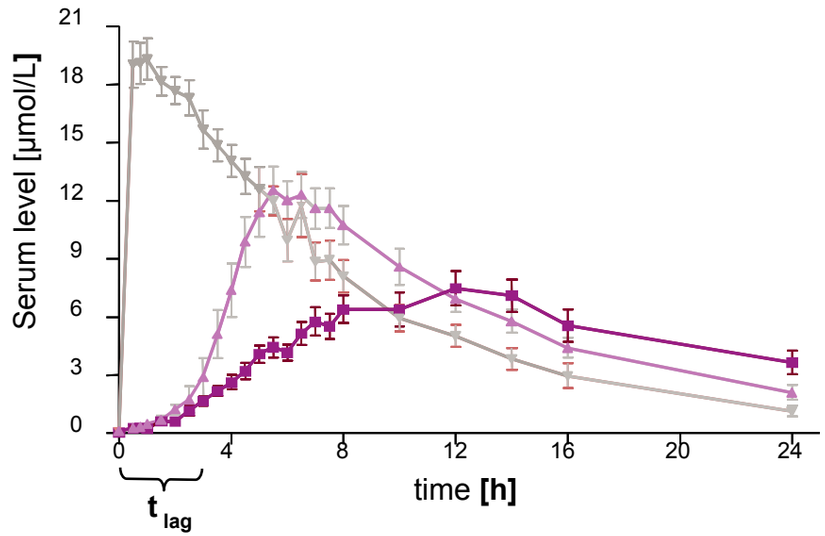
Bioanalytics: Breath test and blood sampling

Case Study -
In vitro – In vivo Comparison

In vitro dissolution profiles



Human plasma profiles



EUDRATEC® COL

delivers drug to the colon and along the colonic transit

FS 30 D Pellets

delivers drug to the colon

IR Reference

releases drug in stomach

- Clear distinction between EUDRATEC® COL and IR colon targeting pellets is observed in *in vitro* and *in vivo* studies.

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DuoCoat®

A Novel Concept in Drug Delivery

Improve efficacy by targeted and accelerated release

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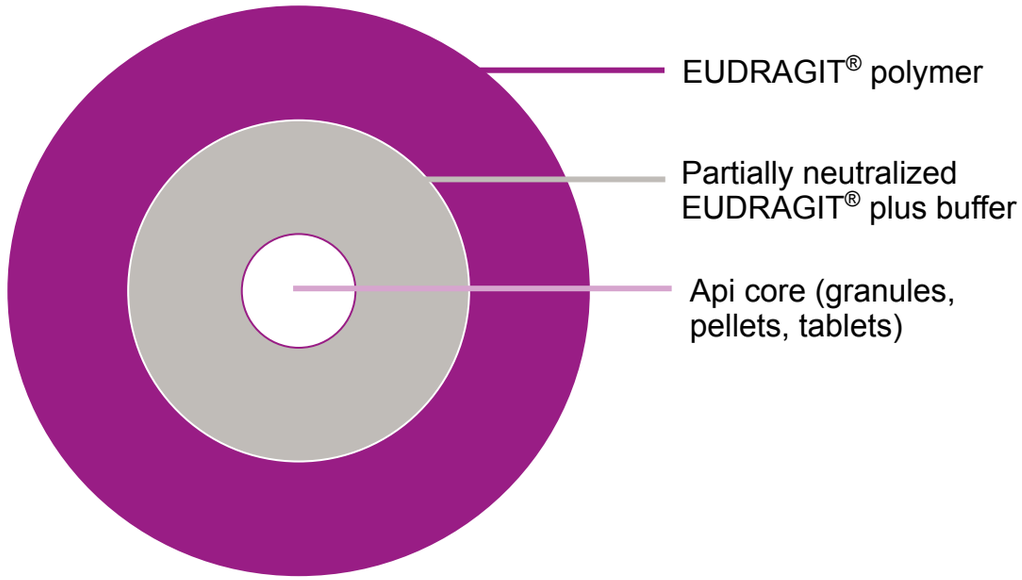
DuoCoat® - The principle

Design



Functionality

- It is a superior gastro-resistant coating for **rapid release** in the upper intestine and up to the colon
- consists of a unique dual-layer system aiming a fast onset of action for **enhanced bioavailability**
- Targets specific absorption window with reduced intra-subject variability and is clinically proven
- offers a unique opportunity for product differentiation, life-cycle management or **patent protection***
- Depending on type of enteric polymer, DuoCoat® promotes rapid release in the upper small intestine or distally in the ileo-colonic region
- The buffer agent in the inner coat facilitates drug release from the double coating system through increased buffer capacity

How does DuoCoat® work?

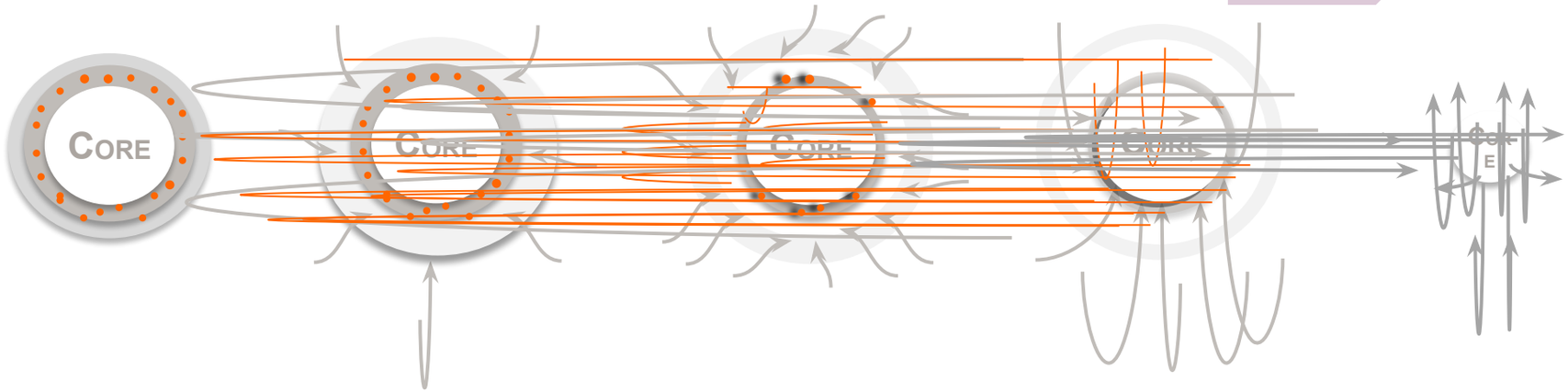
DuoCoat® remains intact in the stomach.

Increased permeability & swelling of enteric outer coating in intestinal conditions. Influx of intestinal fluids into the inner coating.

Dissolution of inner coating and buffer agent. Increase in buffer capacity, pH & ionic strength in inner layer aids dissolution of outer coating.

Rapid dissolution of outer coating from inwards and outwards. Ingress of intestinal fluids into the core promotes drug dissolution and release.

Outer and inner layers dissolve completely. Rate of drug release increases significantly.



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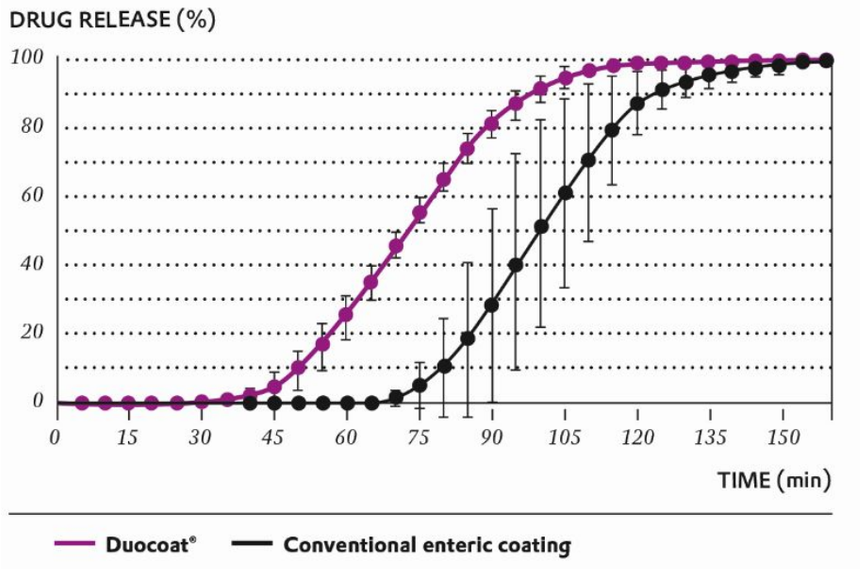
DuoCoat® - Prednisolone Tablets
In vitro conditions for simulated proximal small intestine

Case Study - Duodenum targeting:
Drug release in Hanks Buffer **pH 5.6 with reduced buffer capacity,** simulating **small bowel conditions**



Neutralization of inner coat increase dissolution rate of the final product under upper intestine simulated conditions

Test conditions:

- Pre-incubation 2h at 0.1M HCl
- Phosphate buffer pH 5.6, buffer capacity of 6.5 mmol/L/pH

Results

- No drug released was observed from the single coated tablets
- Duocoat® formulation with a neutralized inner coat shows drug release

Liu et al, J. of controlled release 133, 119-124, 2009

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DuoCoat® - *in vivo* human study

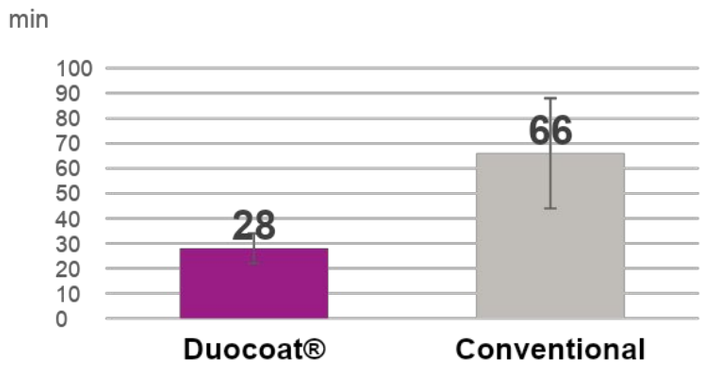
Clinical trial

DuoCoat® vs single coating

Radiolabeled tablet for scintigraphy monitoring

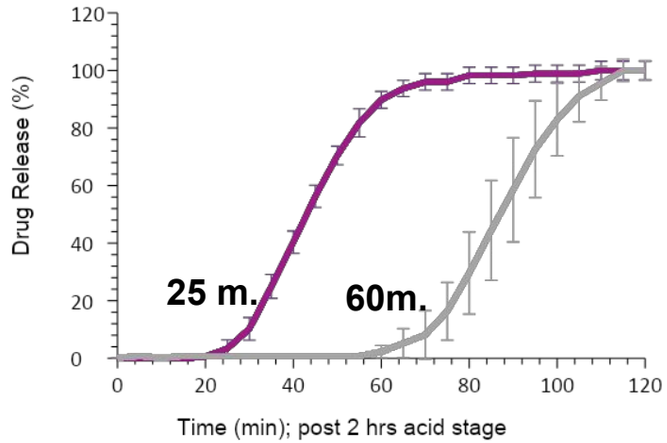
8 healthy adults

Average disintegration time (min)



Dynamic *in vitro* model in bio-relevant media

Dynamic pH changes for simulation of the intestinal transit



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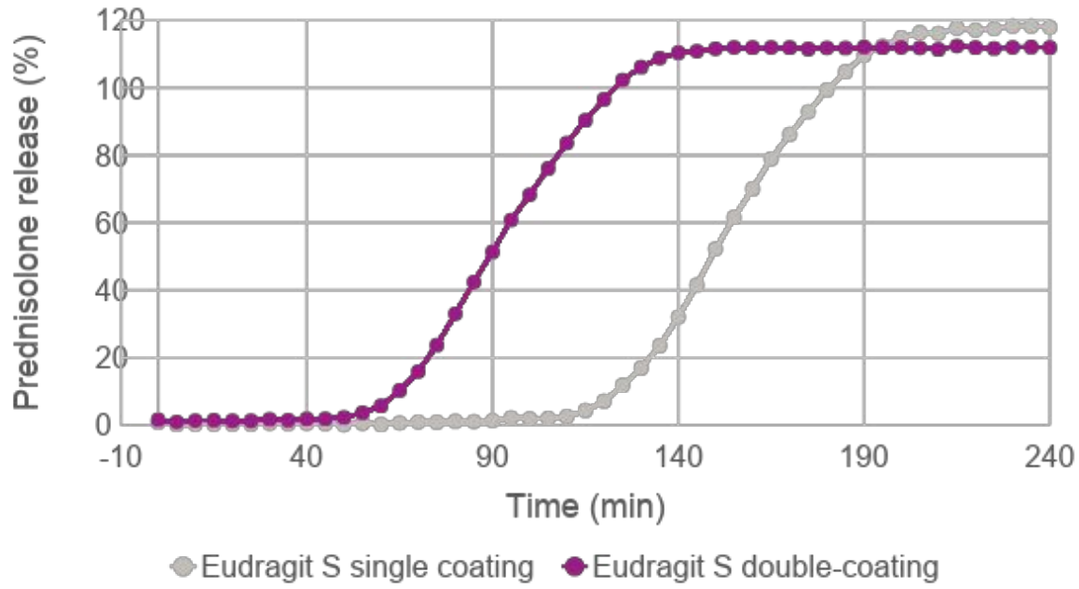
DuoCoat® - Prednisolone Tablets
In vitro dissolution at ileo-colonic simulated conditions

Case Study – Colon targeting:
Drug release in Krebs Buffer **pH 7,4 with reduced buffer capacity,** simulating **human ileal fluid***



Neutralization of inner coat accelerated drug release of the final product under in vitro ileo-colonic simulated conditions

Test conditions:

- Pre-incubation 2h at 0.1M HCl
- Krebs bicarbonate buffer pH 7.4, with a buffer capacity of 5.45 mmol/L/pH

** Buffer capacity of human ileal fluid: 6.4 mmol/L/pH*

Results

- No drug release occurred in acidic medium (data not shown)
- Double coating formulation substantially accelerated drug released compared to the single coating.

Liu et al, E. J. Pharm. And Biopharm 74, 311-315, 2010

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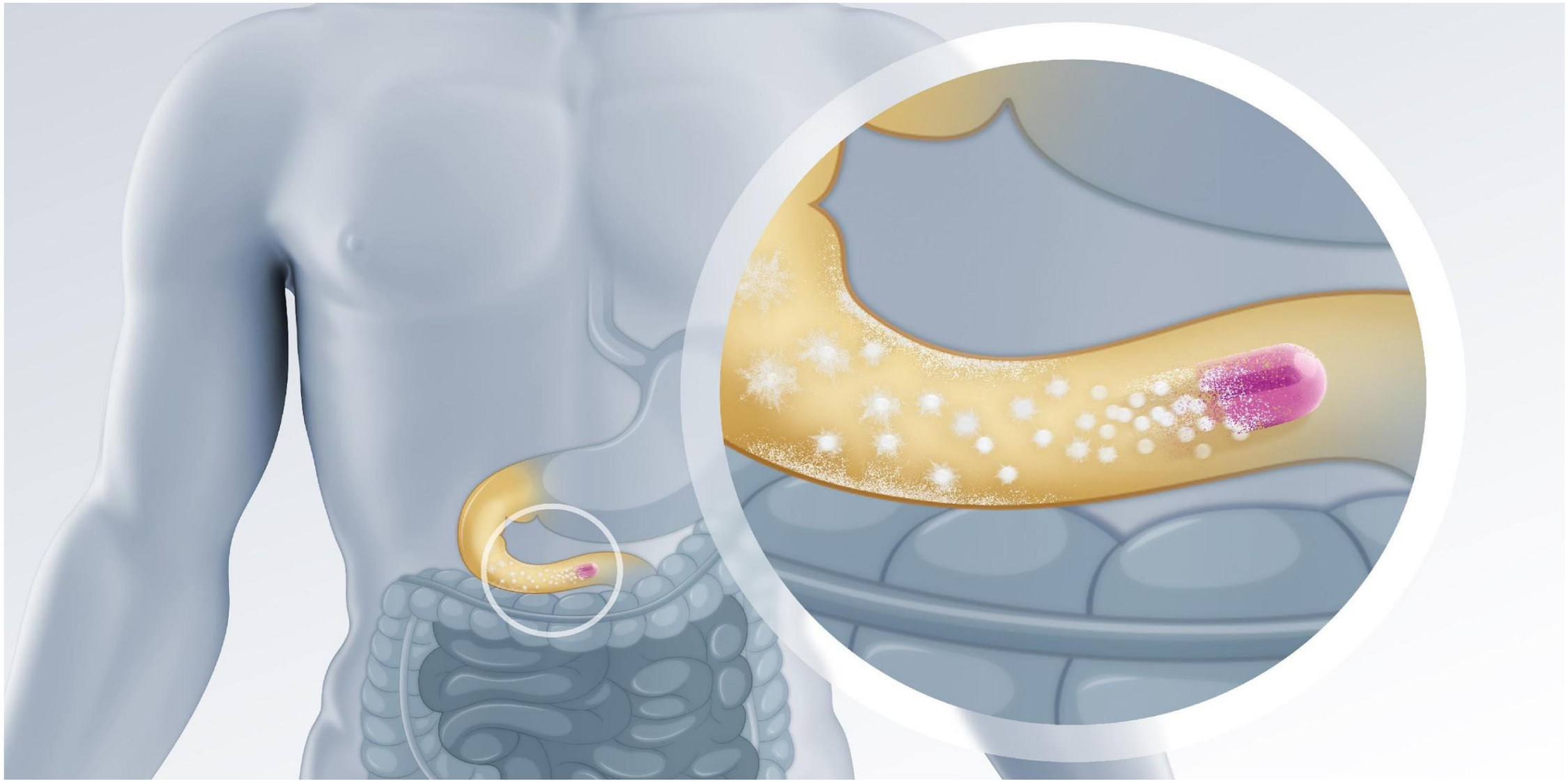
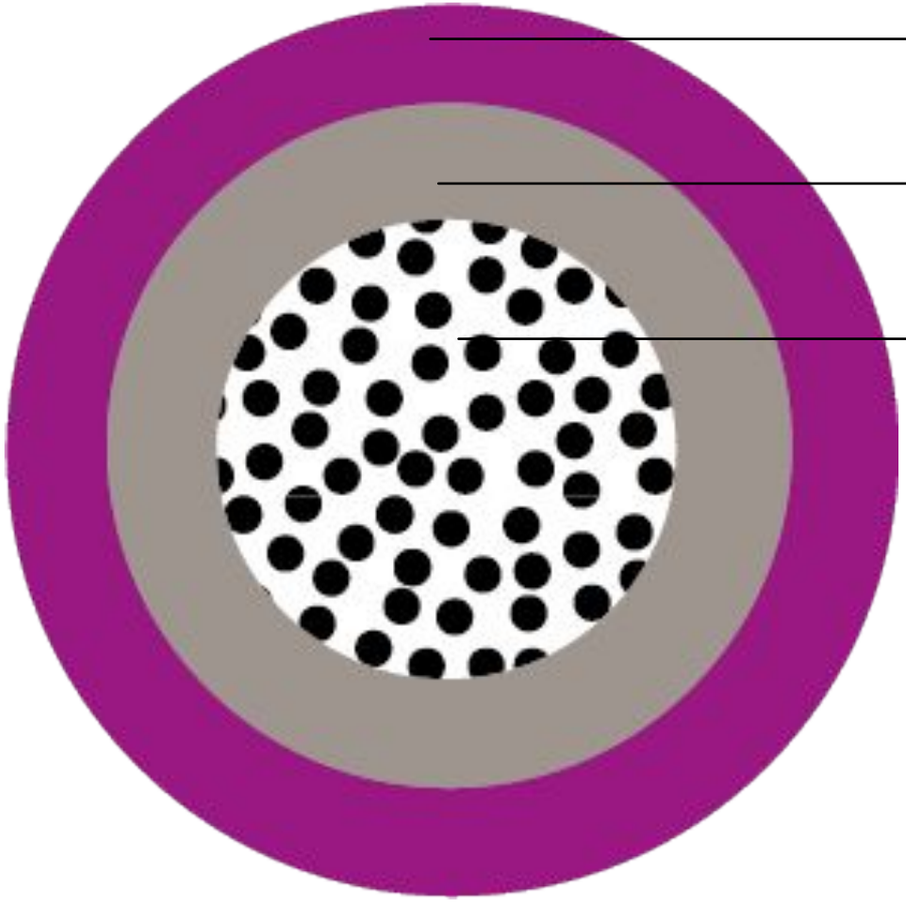
Enteric protection with rapid release at a defined pH from 3.0 to 5.5 for effective small intestine absorption

EUDRATEC® Fasteric



EUDRATEC® Fasteric
An advanced bilayer technology

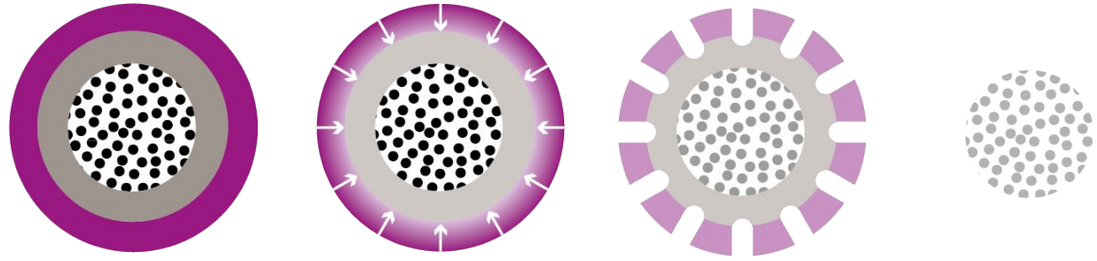


EUDRAGIT® enteric coating

Intermediate coating consisting of a binder, modifying agent

Inner core containing drug (pellet, tablet or capsule)

Rapid duodenal release as a demonstration of functionality



90% of dose released within **30 minutes** at target pH

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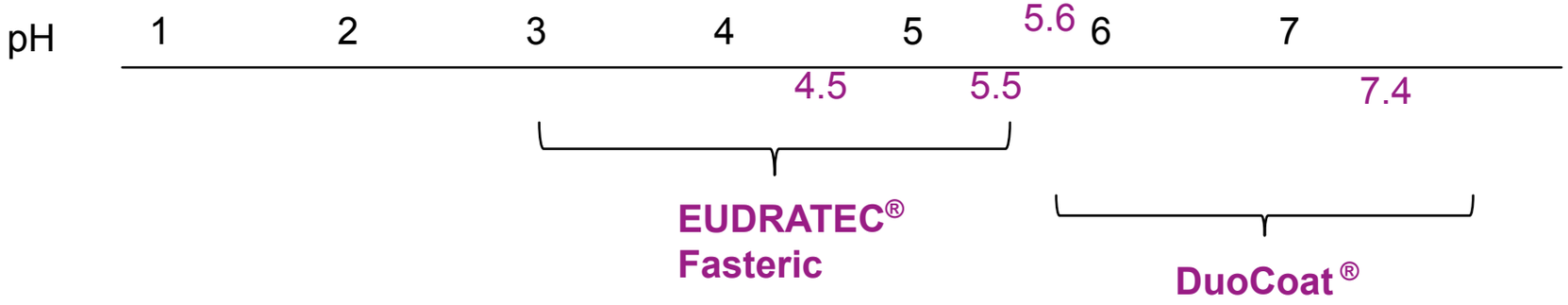
EUDRATEC® Fasteric and DuoCoat®

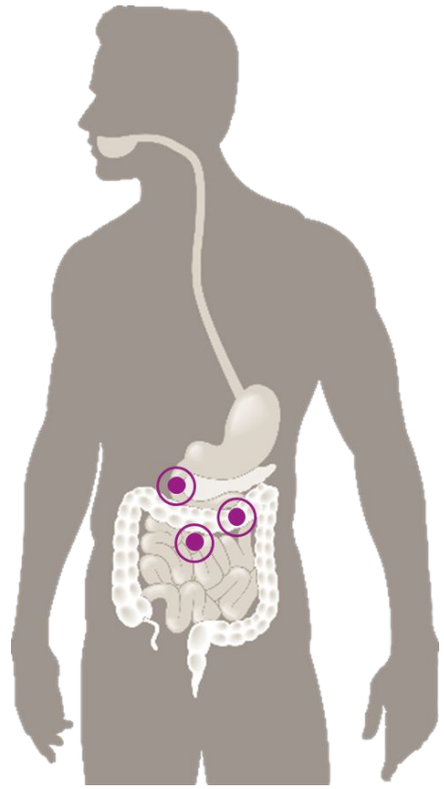
EUDRATEC® Fasteric

- **Rapid release** in the upper small intestine
- pH release 3 - 5.5

DuoCoat®

- **Rapid release** in the upper small intestine and up to the colon
- pH release 5.5 - 7.4





With both oral drug delivery technologies, we can fulfill key pharmacopeia requirements for delayed release formulations

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Case studies for pH and dosage form versatility

Enteric coatings are mainly used in two areas

1.

Drugs requiring protection from gastric acid to avoid degradation

<u>Acid labile drug:</u>

- Pantoprazole Sodium

2.

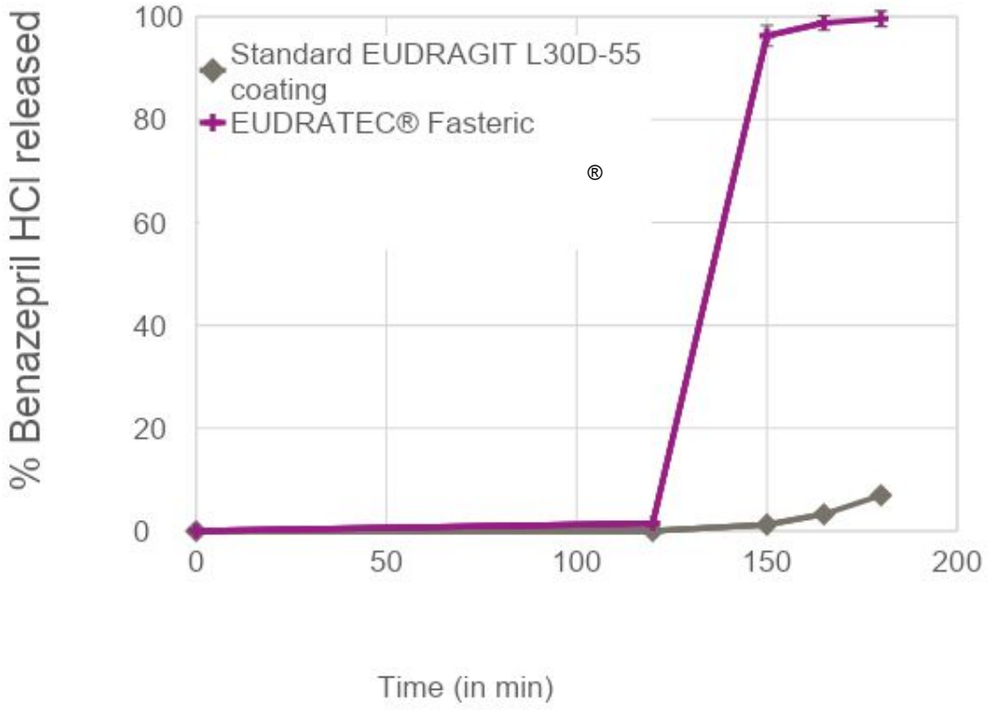
Drugs which require enteric protection followed by early pH release

<u>Acid stable drugs:</u>

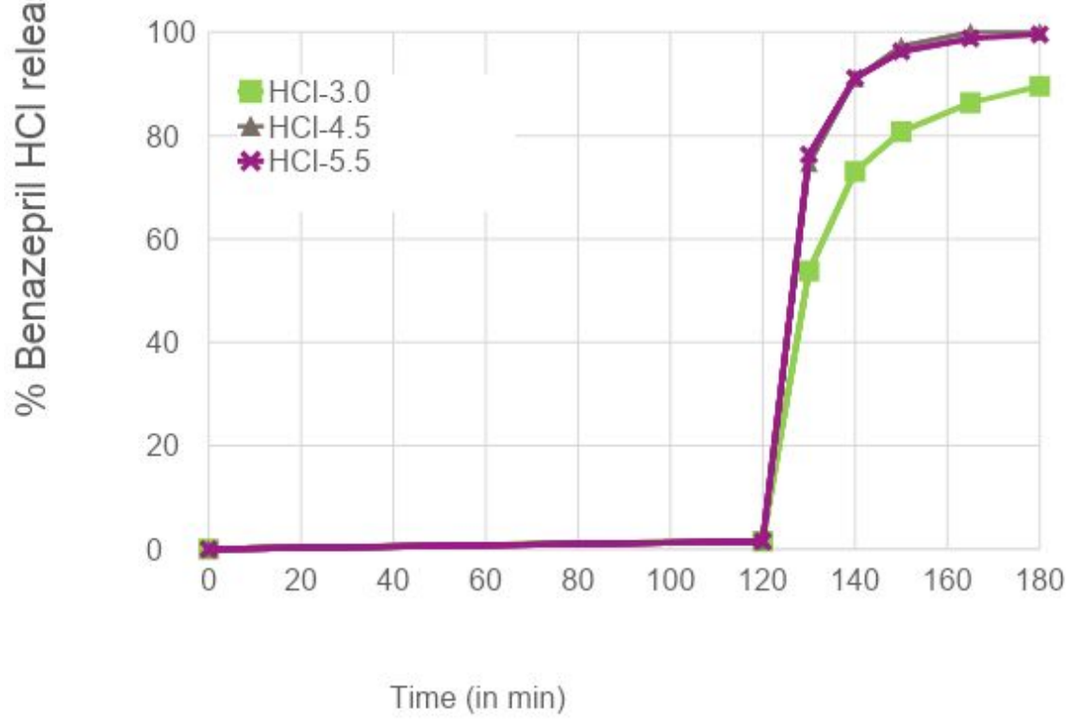
- Benazepril HCl
- Sotalol HCl
- Caffeine

EUDRATEC® Fasteric
Snapshot of the dissolution profile

Comparative dissolution profile of Benazepril HCl pellets with Buffer of pH 5.5 commencing at 120 minutes



Comparative dissolution profile of Benazepril HCl pellets with Buffer of variable pH levels commencing at 120 minutes



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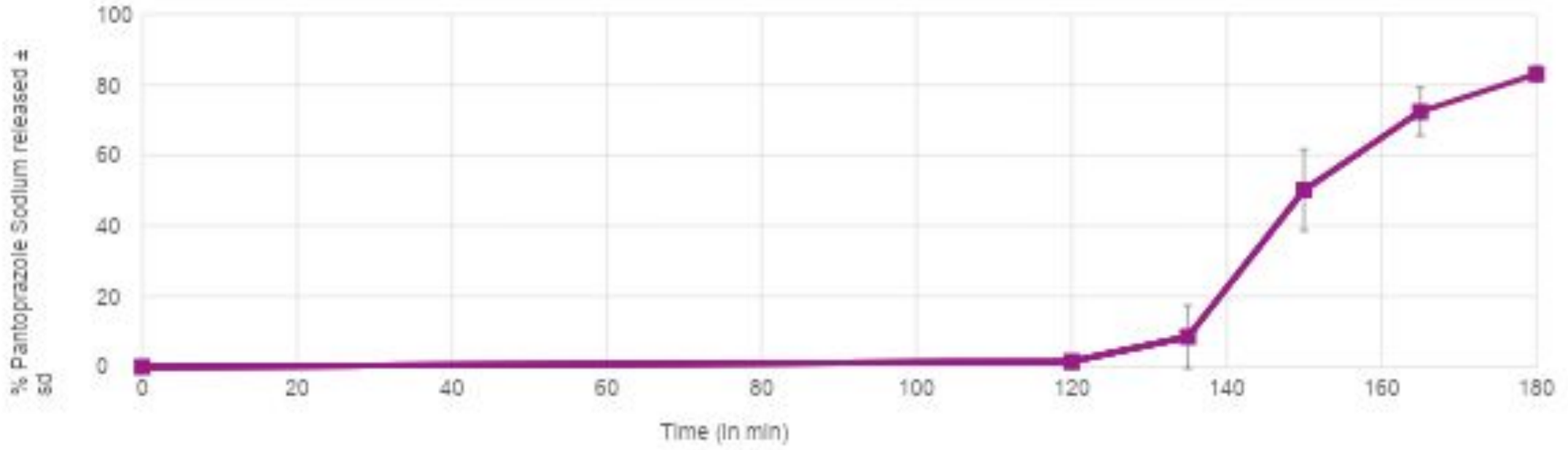
Versatility for use
Pellets as dosage form

Dissolution profile of Pantoprazole Sodium Matrix layered pellets as inner core in 0.1N HCl followed by buffer pH of 5.5



- Enteric protection followed by rapid, complete release in pH 5.5 demonstrated on pellet dosage form using Pantoprazole Sodium as model drug

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EUDRACAP®

Functional Ready to Fill Capsules

For Sensitive Drug Products and Other microbiome Therapeutics

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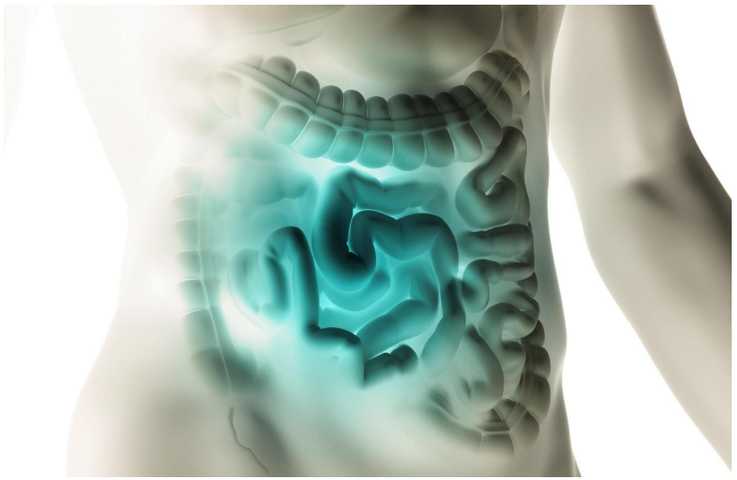
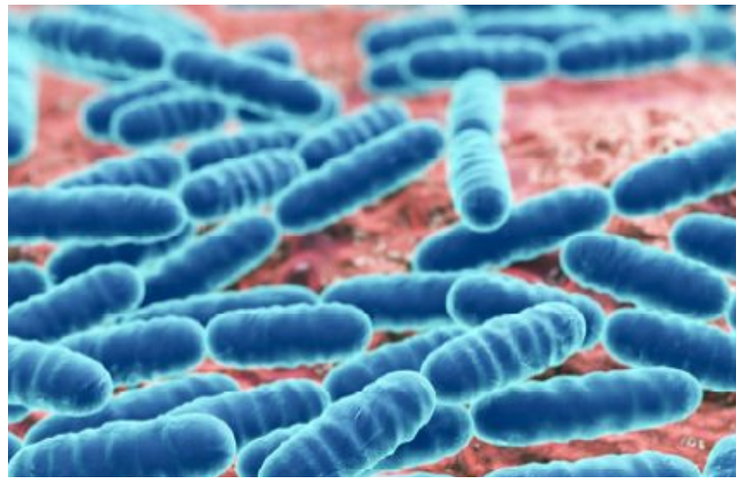
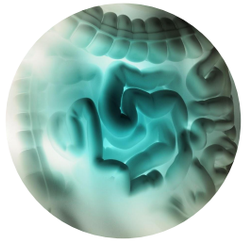
Key Challenges in Drug Development

Strong Interest in Targeted Drug Delivery	Increasing Number of Sensitive Actives	Acceleration of Drug Development Time



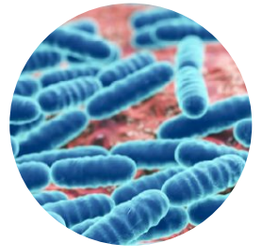


Key Challenges in Drug Development



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



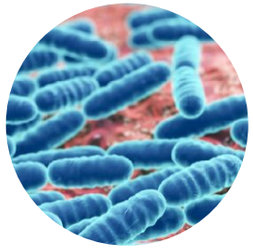
Increasing Number of Sensitive Actives

- 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

Key Challenges in Drug Development



Increasing Number of Sensitive Actives

Live Biotherapeutics

- The intestinal microbiota of an adult individual comprises about 10^{14} bacteria, representing a dominant bacterial metagenome of from 200,000 to 800,000 genes per individual, i.e., 10 to 50 times the number of genes of the human genome.
- The human intestinal microbiota is a very diverse, complex ecosystem that is specific to each individual.
- It is essential for the health of an individual to maintain a stable microbiota that can return to its initial state after a change and is resistant to pathogen invasion.
- Certain pathologies or medical treatments disrupt the microbiota, leading to dysbiosis.

Fecal microbiota transplant is one method that is used today to restore a "healthy" intestinal microbiota.

Importance of microbiome therapy
Preservation of the gut ecosystem can improve clinical outcomes

- Richness and diversity of gut microbiota are increasingly found to be associated with cancer outcomes.
- An adequately responsive immune system seems to rely on the existence of a functioning gut ecosystem that includes the microbiota and its natural environment.
- Cancer and cancer treatments induce gut dysbiosis, impair the constant reparation mechanisms of the gut epithelium, disrupt immune homeostasis, and stunt immune responsiveness.

Microbiome therapy shall be able to:

1	Prevent the decay of the gut ecosystem (dysbiosis) to preserve immune homeostasis
2	Restore and optimize the gut ecosystem to full functionality including its role in repairing the gut epithelium and healthy gut barrier
3	Maintain a restored gut ecosystem and fully functional immune homeostasis

Leading Beyond Chemistry

Importance of microbiome therapy

Reaching the clinical outcome requires both stable microbiota and robust delivery

Effective engraftment demands a targeted, robust formulation to deliver live microorganisms

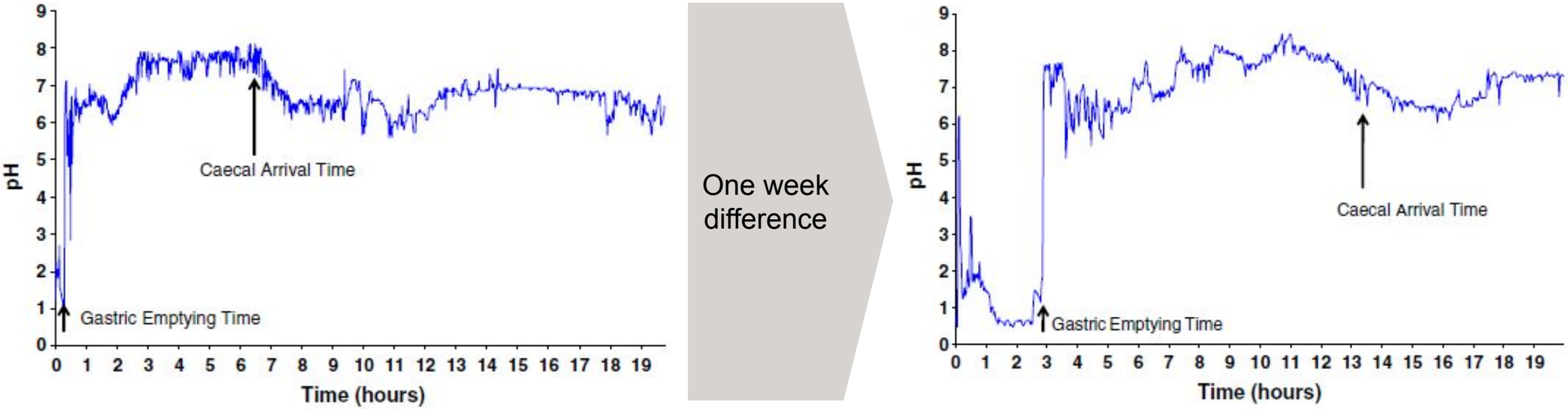
Possible routes of administration includes:

- Naso-duodenal
- Transcolonoscopic
- Enema based
- **Oral formulations**

Lyophilized, stable, pooled, full-ecosystem microbiota

Best-in-class functional ready-to-fill capsules customized for targeted release

Challenges for robust oral delivery of live microorganisms
Intrasubject variability of pH and residence time



- Intrasubject pH and residence time show considerable variation when measured in different time points
- Intersubject variation is also greatly observed both in residence times and pH profile

Fasted subject
Source: Ibekwe et al. Pharmaceutical Research, Vol. 25, No. 8, August 2008

Challenges for robust oral delivery of live microorganisms
Low gastrointestinal fluid volumes and buffer capacity

Gastrointestinal fluid volumes as determined by magnetic resonance imaging (MRI) under fasting conditions and 1 h after a meal (n = 12)

	Stomach [volumes (mL)]*	Small intestine [volumes (mL)]	Large intestine [volumes (mL)]
Fasting			
Minimum	13	45	1
Maximum	72	319	44
Median	47	83	8
Mean (s.d.)	45 (18)	105 (72)	13 (12)
Fed			
Minimum	534	20	2
Maximum	859	156	97
Median	701	39	18
Mean (s.d.)	686 (93)	54 (41)	11 (26)

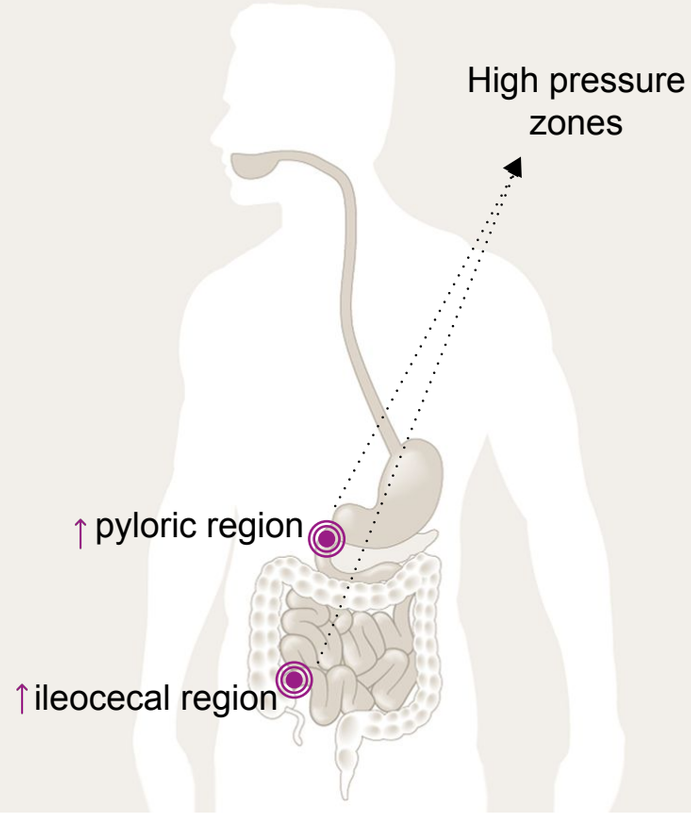
* The volume of the stomach after the meal represents the filling volume (not only fluid).

Composition [mM]	Human Jejunal Fluid	Human Ileal Fluid	Phosphate Buffer (0.05 M)	mHanks Buffer	Krebs Buffer
Bicarbonate	7.1	35		4.17	25
Phosphate			50	0.8	1.1
Potassium	5.1	4.9	50	1.3	5.9
Sodium	142	140	29/39	0.8	143
Chloride	131	125		142	128
Calcium	0.5	4.2		5.8	2.5
Magnesium		2.8		143	1.2
pH	6.8	7.4	6.8/7.4	6.8	7.4
Buffer capacity (mmol/L/pH)	3.2	6.4	23	3.1	5.4

Source: Schiller et al. - Aliment Pharmacol Ther 2005, 22, 971–979
Source: Abdul Basit – Presentation “Gut instincts”, Darmstadt, May 2017

Challenges for robust oral delivery of live microorganisms
High pressure and jet like propulsions

- Numerous adversities are present in the human gastrointestinal tract
- Critical stress zones need to be overcame by the oral formulation
- High motor activity sphincters expose the dosage form to pressures of up to 350 mbar and jet like propulsions with peak velocity of up to 50-70 cm/s.



[1] G. Garbacz, S. Klein, Dissolution testing of oral modified-release dosage forms, J Pharm Pharmacol, 64 (2012) 944-968.

The bacteria needs to be delivered to the ileum and colon
Intrinsic challenges drive the objective of this work

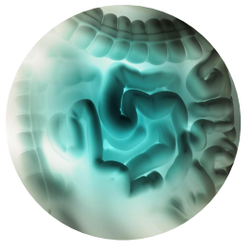
Challenges

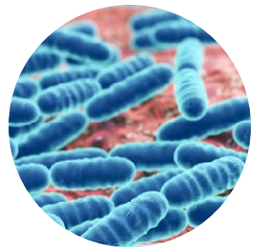
- Sensitive microorganisms to be protected from acid media and released on targeted site
- Variability in time and onset disintegration due to high variable GI transit time
- Low volume and buffer capacity of the gastrointestinal fluidics
- High pressure zones and mechanical stress

Objective

- Development of a suitable oral delivery system for the full-ecosystem microbiota that will be tested for its safety and tolerability in hematological malignant patients, who are exposed to intensive rounds of chemotherapy and antibiotics.

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





Targeted Drug Delivery	Protection of sensitive actives	Reduce clinical risk and accelerate time to market
▪ 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	▪ Ideal for use with active ingredients which are: ▪ Sensitive to heat, moisture or gastric acids ▪ Able to optimize absorption and avoid premature dissolution	▪ Range of catalog and customizable coating options ▪ Strong regulatory track record ▪ Extensive formulation development and cGMP services

Leading Beyond Chemistry

Market and Customer Needs
Evonik's Technical Solution

Strong Interest in Targeted Drug Delivery

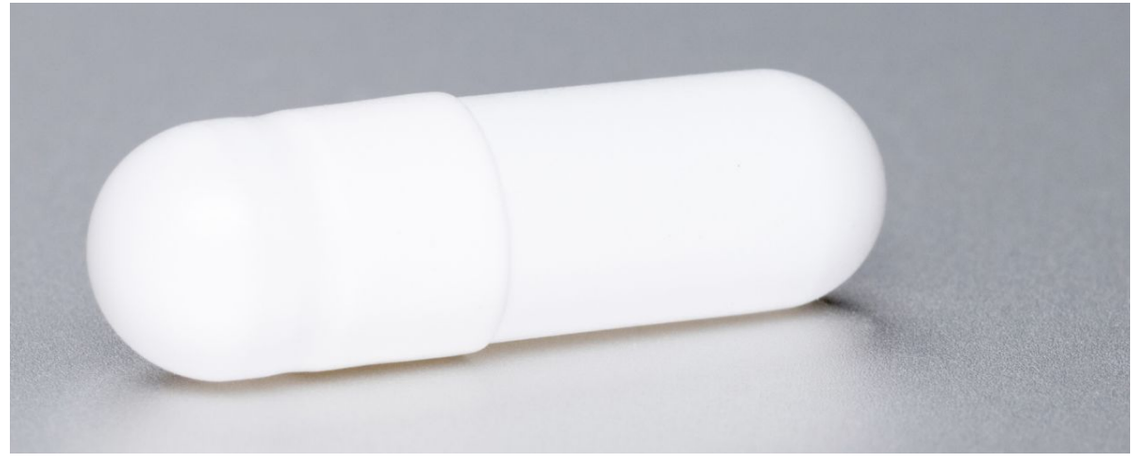
Increasing Number of Sensitive Actives

Acceleration of Drug Development Time

EUDRACAP®

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

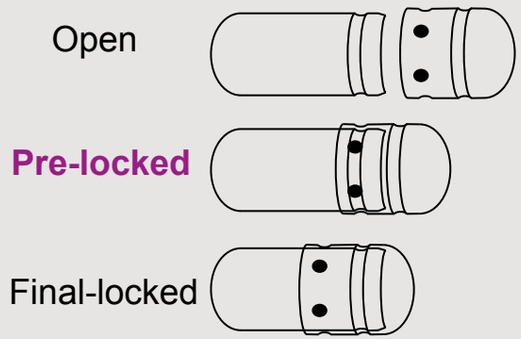
- Optimize the release profile
- Protect your active ingredients
- Help accelerate speed to market



Smooth, evenly coated HPMC capsules that are easy to fill
Method of production

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



1

Coating suspension

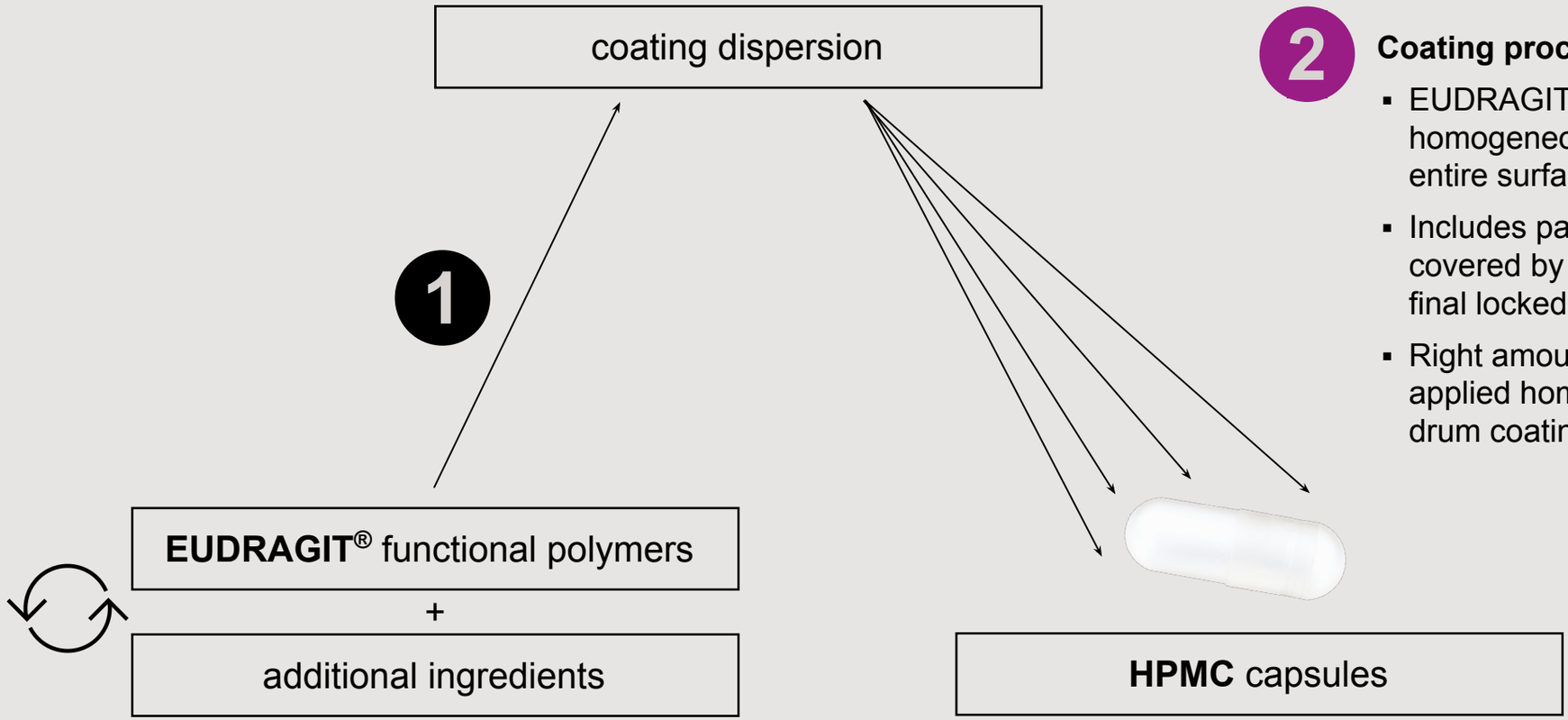
- Combination of **EUDRAGIT®** functional polymers to achieve targeted release profile
- Additional ingredients give the film the right characteristics and processability

EUDRAGIT® functional polymers

+

additional ingredients

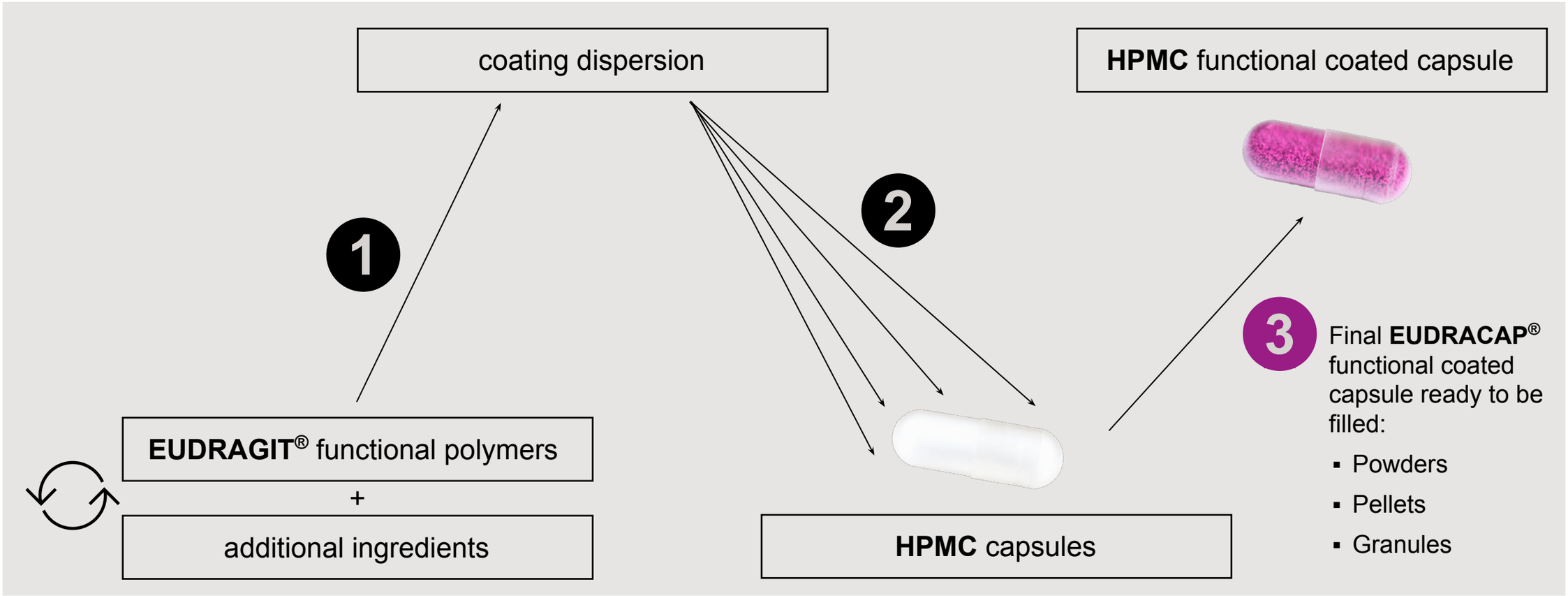
Smooth, evenly coated HPMC capsules that are easy to fill
Method of production



2 Coating process

- 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
- Right amount of polymer (mg/cm^2) is applied homogeneously by regular drum coating

Smooth, evenly coated HPMC capsules that are easy to fill
Method of production

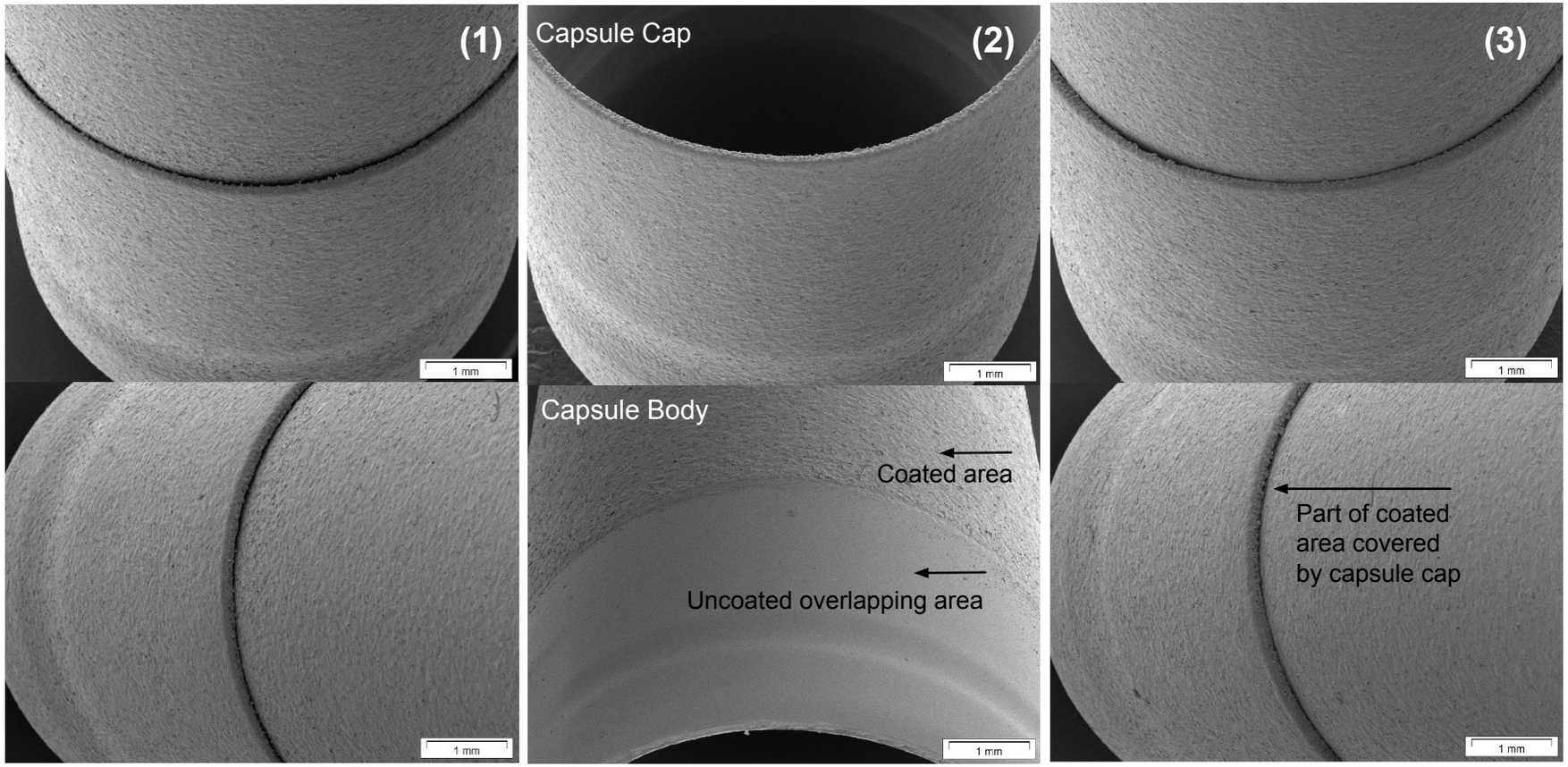


Coated capsules with homogenously functional coating

The overlapping area is later covered at final locked stage

SEM pictures of coated capsules in the pre-locked (1), opened (2) and locked (3) stages.

Pictures are representative and taken from the EUDRACAP® enteric functional coated-capsules.



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

Perfect sealing is needed to ensure content protection
Acid resistance test with dye filling

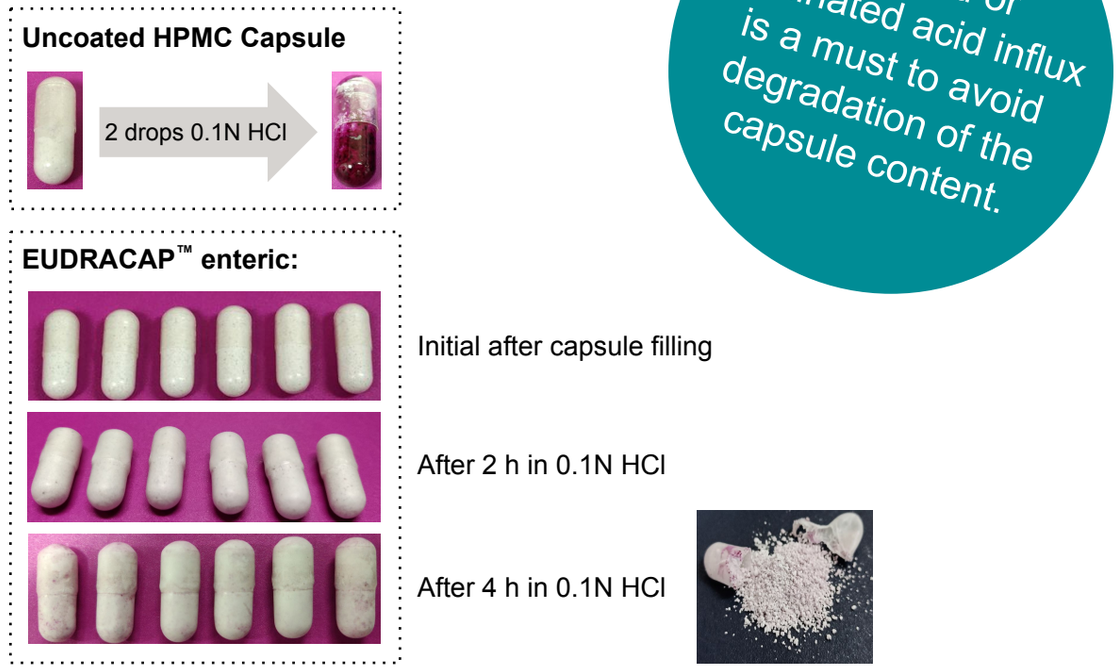
Acid resistance test using dye

This data refers to a commercial EUDRACAP® enteric capsule, data of the customized capsule is not shown

- 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



Reduced or eliminated acid influx is a must to avoid degradation of the capsule content.

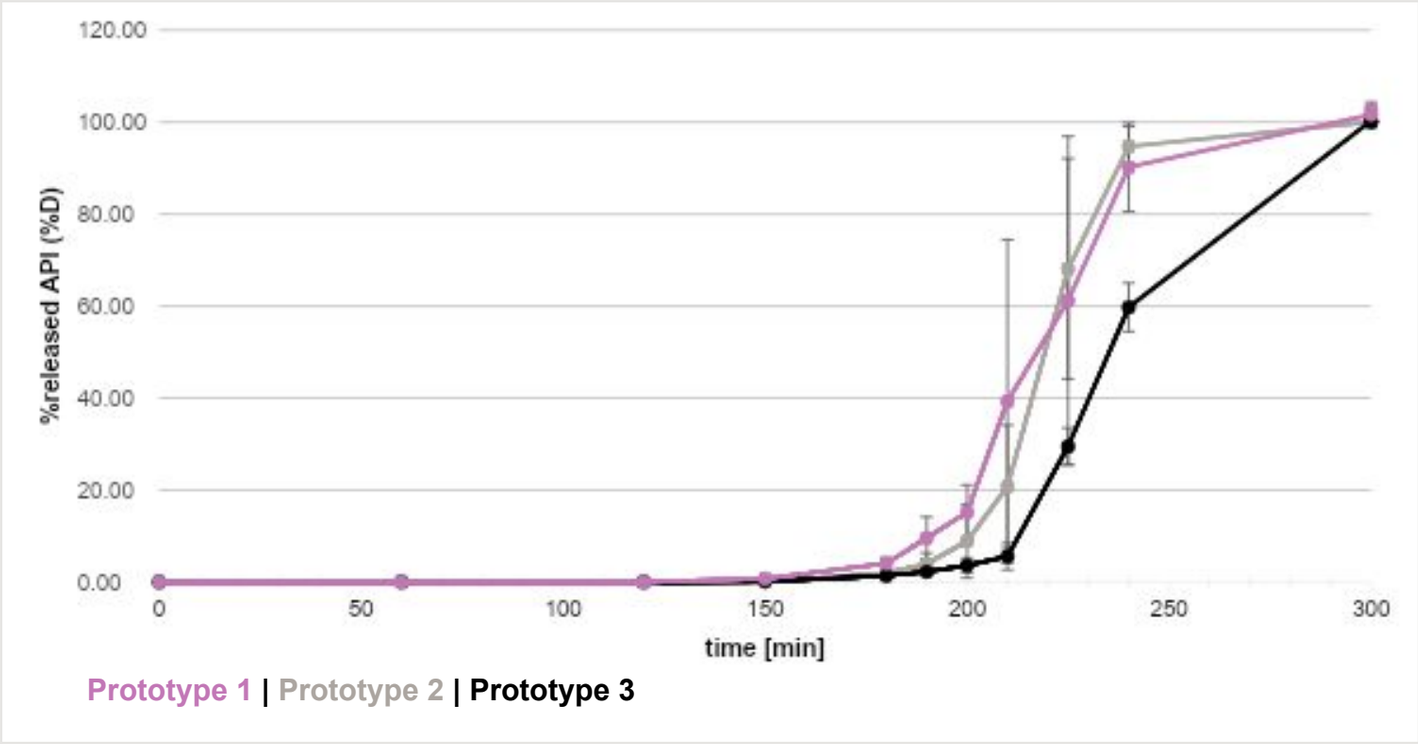
Filling: Dye/microcrystalline blend, ratio 1:99, Test conditions: Disintegration test apparatus (USP), Media: 0.1N HCl, 600 ml, 37°C

EVONIK Leading Beyond Chemistry

Prototypes matching the targeted profile

Different formulations and processes were tested to select the most promising one

Dissolution profile, [%] average of 6



USP type 2, 75 rpm, Dissolution medium: 2h HCl 0.1 M; 1h pH 6.8; 2h pH 7.2

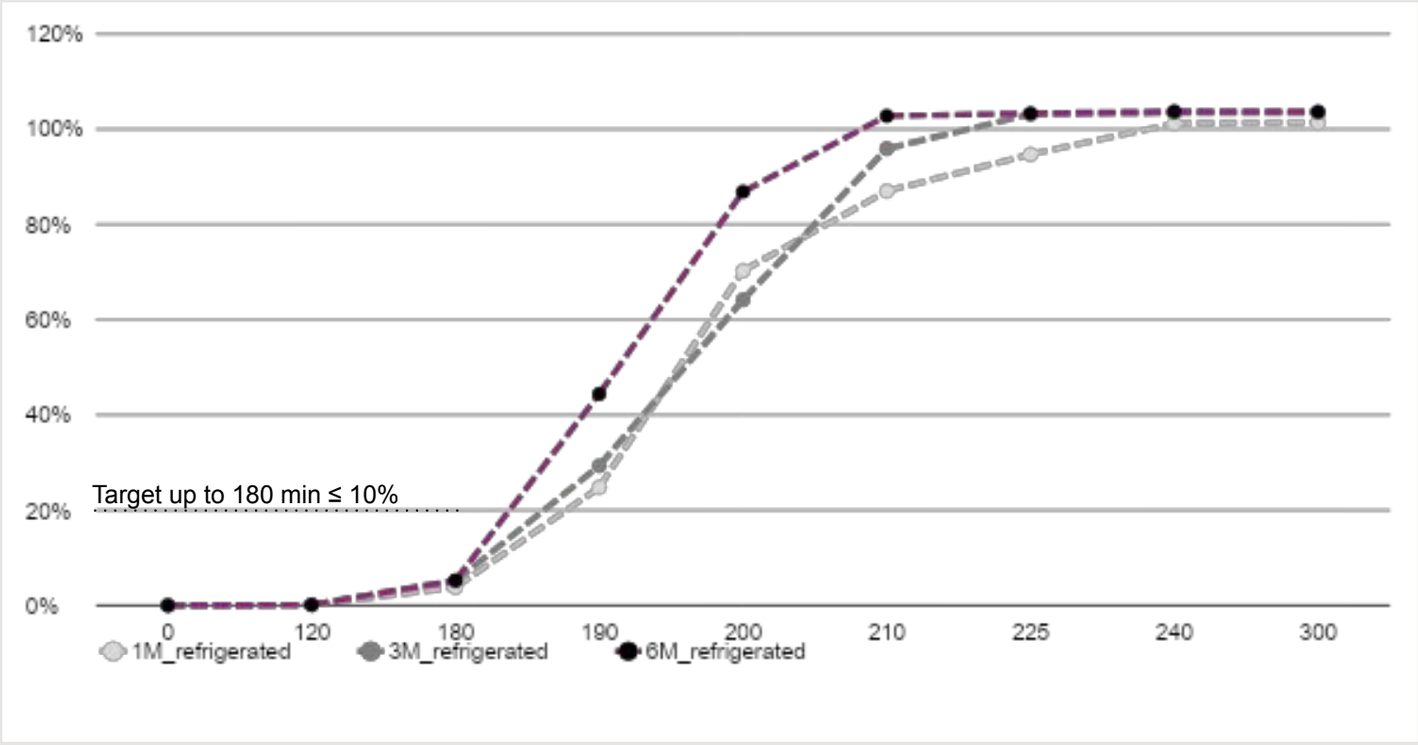
- All 3 prototypes met the targeted requirement (NMT 10% release at pH 1.2 and 6.8
- Prototype 1 shows higher SD
- Prototype 3 delays the release in pH 7.2
- Prototype 2 formulation was selected for the following steps

Most promising formulation was selected among the tested prototypes with different characteristics.

Empty capsules were tested for stability

Formulation maintains comparable behavior after accelerated stability test

Dissolution profile, [%] average of 6



USP type 2, 75 rpm, Dissolution medium: 2h HCl 0.1 M; 1h pH 6.8; 2h pH 7.2
Accelerated: 40°C ± 2°C / 75% RH ± 5% RH | Refrigerated: 5°C ± 3°C

- Stability study refers to the empty capsules of a representative scaled-up technical batch
- Stability of the capsules was given in different test conditions (not all data shown)
- Stability under accelerated condition was achieved
- Refrigerated condition tested due to importance for microbiome formulations

Robustness, functionality and stability are given in *in vitro* trials, but the gastrointestinal tract brings additional challenges…

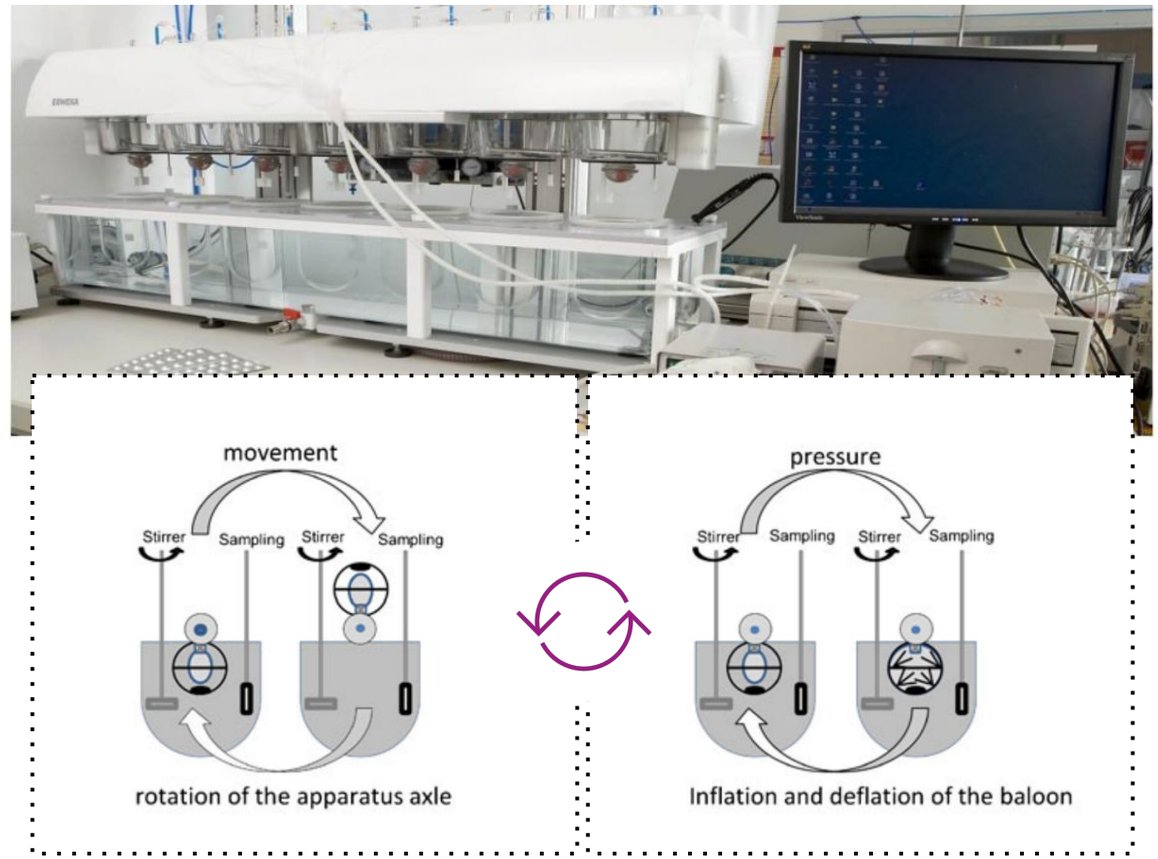
In vitro prediction of the capsule behavior and robustness
Stress test apparatus to simulate high pressures and velocity of the GIT

Testing material

- Prototype 2 was selected for the dissolution stress test
- Capsules were filled with 500 mg of a mixture of caffeine and lactose

Method

- The apparatus aims to simulate the dimensions of physiological mechanical stress that occur during the GI tract passage
- Dosage form is exposed to sequences of movement and pressure fluctuations alternated with static phases and intermittent contact with the dissolution medium as observed in vivo
- Profile of movement and pressure is adjusted according to the method by a controlled by custom-made software
- pH and buffer capacity of fasting condition were simulated

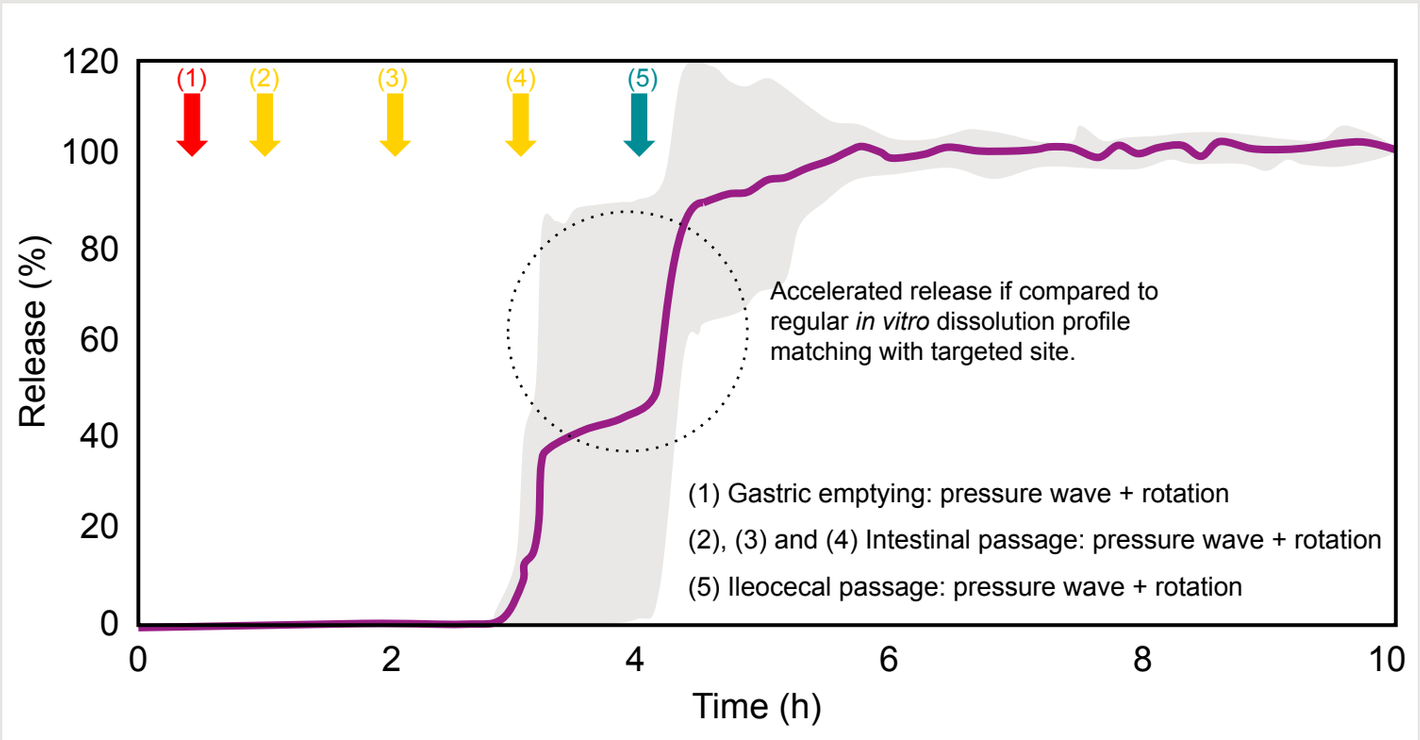


Source: G. Garbacz, et al., Release Characteristics of Quetiapine Fumarate Extended Release Tablets Under Biorelevant Stress Test Conditions, AAPS PharmSciTech, 15 (2014) 230-236.

In vitro prediction of the capsule behavior and robustness

Stress test apparatus to simulate high pressures and velocity of the GIT

Dissolution profile obtained by the stress test, [%] average of 6



- Upon the simulated gastric emptying (2) the capsules yielded no deformation and signs of leakage
- Mechanical stresses of low intensity simulated at 1 h (2) and 2 h (3) have not impacted drug release
- The mechanical agitation simulated at 3 h (4) triggered fast dissolution of part of the tested capsules
- Ileocecal passage at 4 h (5) triggers fast drug release (deformation and perforation)
- Complete dissolution after 0.25 – 1 h of the triggering

The capsules are suitable to deliver the API to distal small intestine and proximal colon, therefore suitable for first-in-human trials.

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Leading Beyond Chemistry

Developed capsules were filled with full-ecosystem microbiota

The final dosage form was tested in phase 1b clinical trial*

Acute myeloid leukemia (AML) treatment combines intensive chemotherapy (IC) with broad-spectrum antibiotics (ATB) that induces a strong gut microbiota dysbiosis, promoting pathological conditions and increasing incidence of complications

Restoration of the full gut microbiota ecosystem is a promising therapeutic tool to improve clinical outcomes in patients with acute myeloid leukemia (AML) receiving IC and ATB.

Sponsor: **MaaT Pharma**

Identifier: **NCT04150393**

Material: delayed-release capsule containing lyophilized pooled full ecosystem fecal microbiota (MaaT033)

Design: phase I, open-label, single-arm, 6 investigational sites in France

Dose: 5 cohorts, dose scalation

Cohort	Week 1	Week 2	Dose	Description
5	*Not performed, sufficient data from cohort 1-4*			
4	———		3	3 caps/day, 2 weeks
3	———		3	3 caps/day, 1 week
2	———		1	1 caps/day, 1 week
1	•	•	1	1 caps/week, 2 weeks

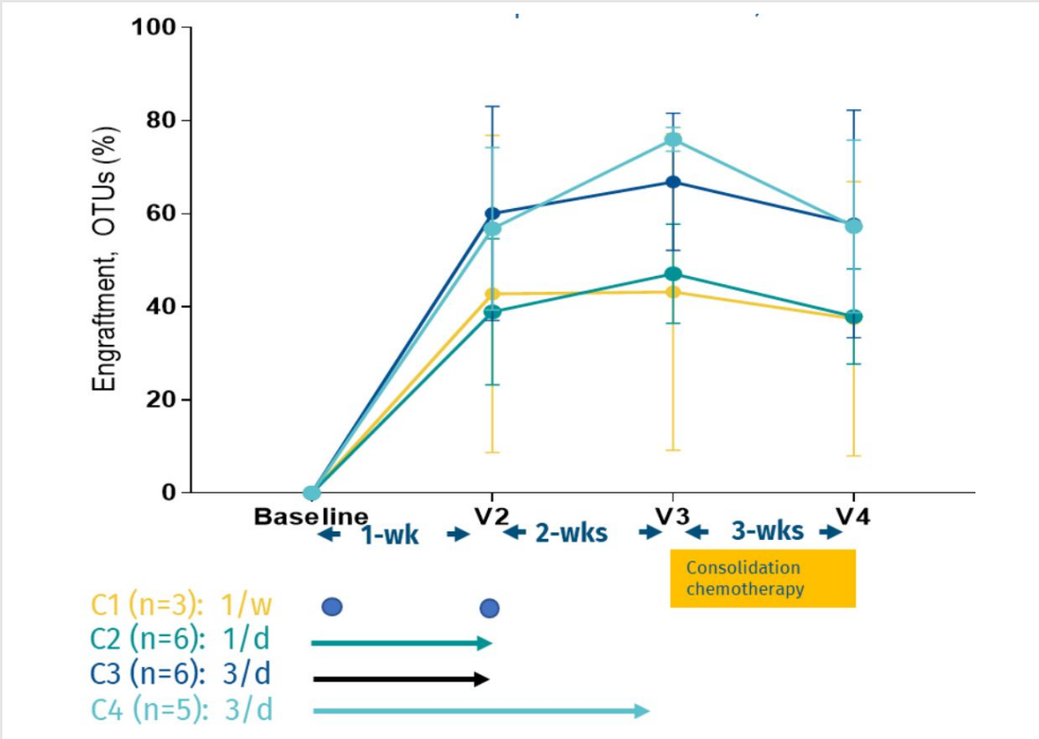
Objectives: tolerability, dose regimen evaluation (safety and activity/engraftment), and patient compliance

Source: https://clinicaltrials.gov/ct2/show/NCT04150393

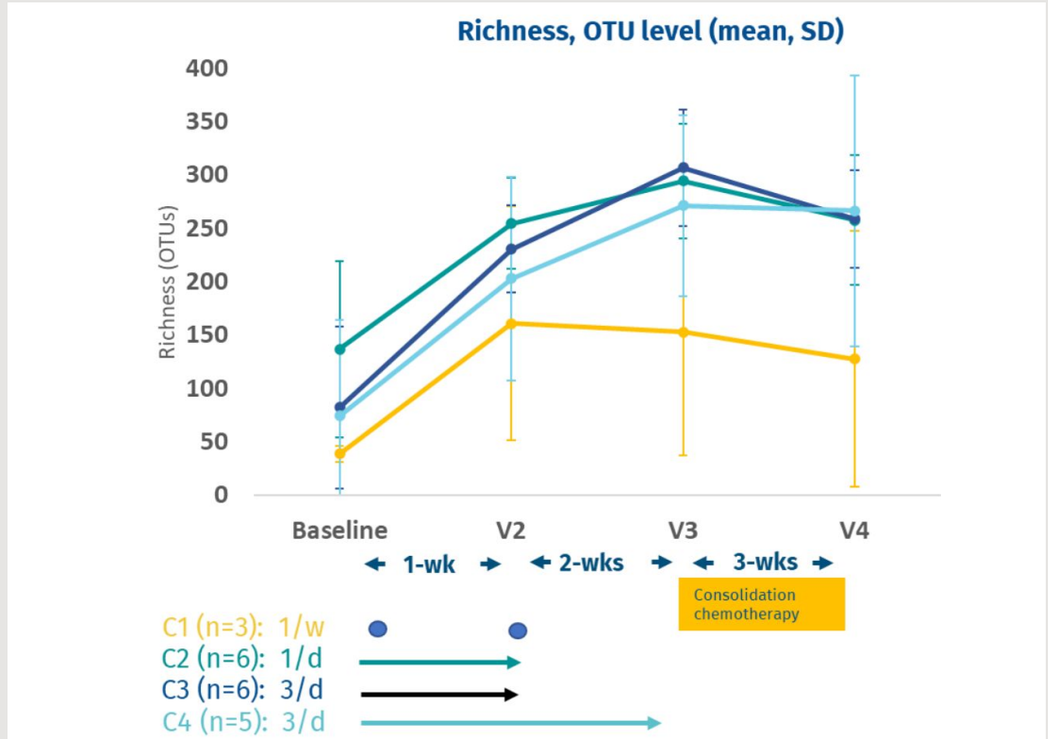
*Provided data was presented at the 2022 Edition of the American Society of Hematology.

String engraftment was observed
Doses regimen influences engraftment and richness level

MaaT033 engraftment (mean, SD)*



Richness, OTU level (mean, SD)*



OTU: operational taxonomic unit
* Result excludes shared OTU's between MaaT033 and patients' at baseline.

MaaT033 with EUDRACAP Select: Safe, effective gut microbiota therapy
Successful results of phase 1b allows starting of phase IIb

Results

- **MaaT033** formulated with **EUDRACAP® Select**:
  - Induces an increased microbiota richness at OTUs level
  - Displays a strong and persistent bacterial engraftment higher when administered 3 times per day (1 or 2 weeks)
  - Bacterial engraftment is inversely correlated with patient's baseline microbiota richness
  - Only one possible related serious adverse event (infectious diarrhea 3 days after treatment initiation

Conclusion

- **MaaT033** formulated with **EUDRACAP® Select** appears to be safe and effective for gut microbiota restoration in AML patients receiving IC and ATB.
- 3 MaaT033 capsules per day for 1 week induce an increase in microbiota richness and an effective and persistent MaaT033 bacterial engraftment in AML patients
- A Phase IIb trial is underway in 2023 to evaluate MaaT033 as an adjunctive and maintenance treatment in patients with hematological malignancies receiving allogeneic hematopoietic stem cell transplantation.

In vitro testing has demonstrated the efficacy of **EUDRACAP® Select** in the development of the **MaaT033** formulation, even under stressed conditions. Promising results were observed during the phase 1b trial with the final formulation with MaaT Pharma's proprietary microbiome technology.

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	Can reduce clinical risk and time to market	Reduced complexity and manufacturing process risks

EVONIK
Leading Beyond Chemistry

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

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EUDRATEC® SoluFlow

Oral Drug Delivery Solutions

EVONIK
Leading Beyond Chemistry

Solubility enhancement still one of the key challenges in oral small molecule drug development

Very high number of new molecular entities are poorly soluble

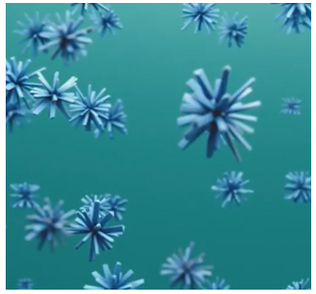
Existing manufacturing technologies cannot overcome all hurdles

Pharmacokinetic performance is highly dependent on formulation and process

New pharmaceutical processing technology
Turning poorly soluble drugs into soluble intermediates

EUDRATEC® SoluFlow

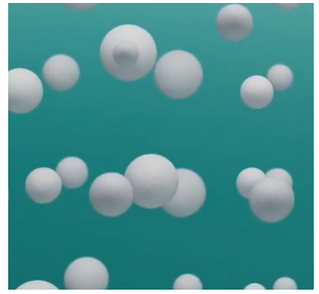
crystalline API



aqueous phase

organic phase with
suitable polymeric carrier

emulsification device

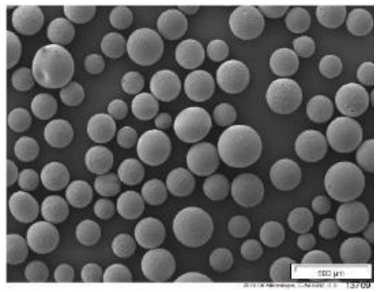


amorphous solid dispersion

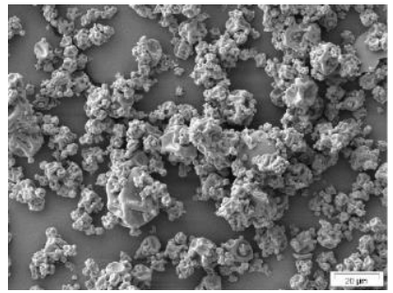
- A crystalline API is dissolved with a suitable polymeric carrier in organic solvent, at the same time an aqueous phase is prepared.
- Both phases are pumped into an emulsification device to produce **amorphous solid dispersions** in the form of round emulsion particles.
- After drying this creates a **free-flowing, ready to fill product**, which can be pressed to tablets or filled into capsules.

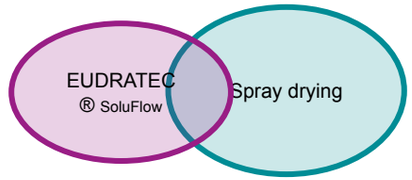
Advantages over established process technologies

EUDRATEC® SoluFlow ⟷ **Spray Drying**



Uniform matrix particles	Fine hollow particles
Particle size 200 – 500 µm	Particle size $\leq 100\ \mu m$
Free-flowing powder	Cohesive powder
High bulk density	Low bulk density
Large choice of solvents	Small choice of solvents
Solid content solution 10-20%	Solid content solution 5-15%
No post-compaction needed	Post-compaction needed





Seamless transition from pre-selection to clinical to commercial is key

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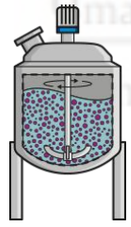
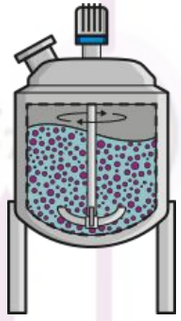
Seamless transition from pre-selection to clinic to commercial using mathematical scaling model and online particle engineering control

©Urs Küster & SOPAT

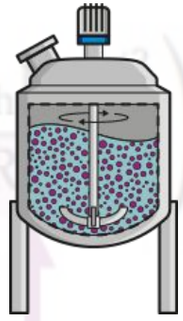
Probe for online particle analysis and control



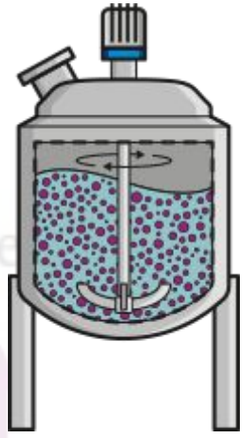
Lab-scale
1 g - 50 g



Technical-scale
100 g - 2.5 kg

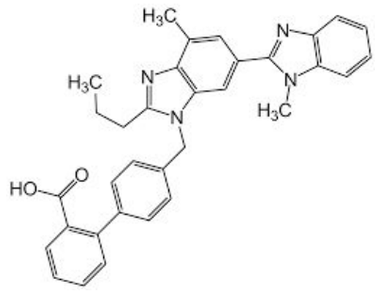


GMP Pilot-scale
2.5 kg / day



GMP Production-scale
50 kg / day

Proof of concept study 1: Telmisartan Emulsion-Based Dispersions (EBD)

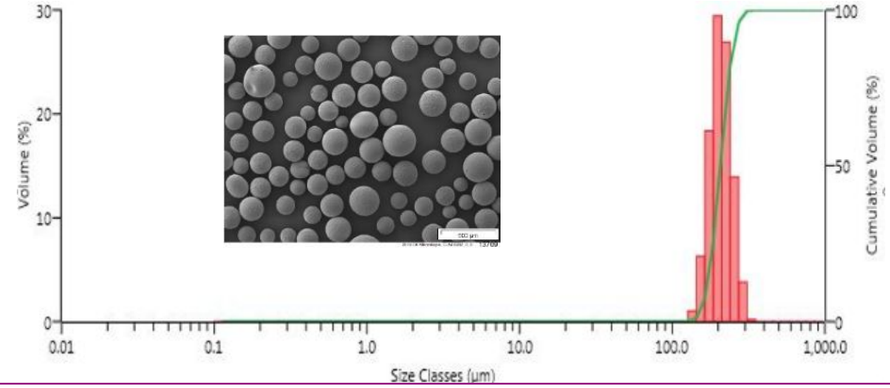


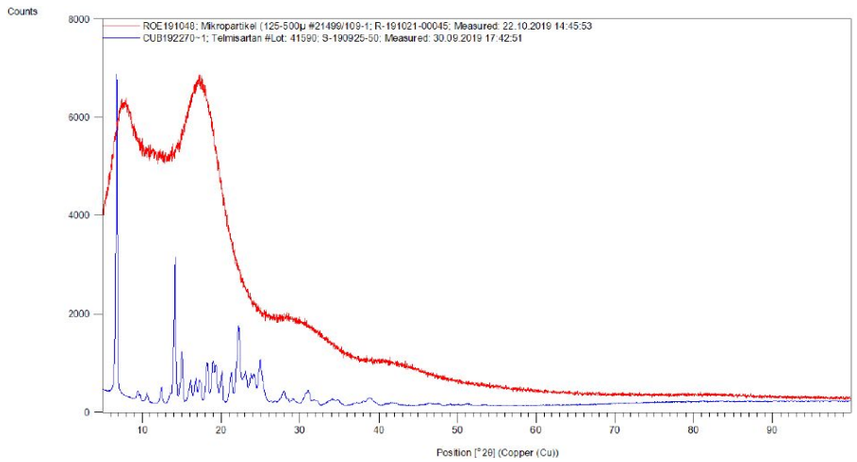
Telmisartan

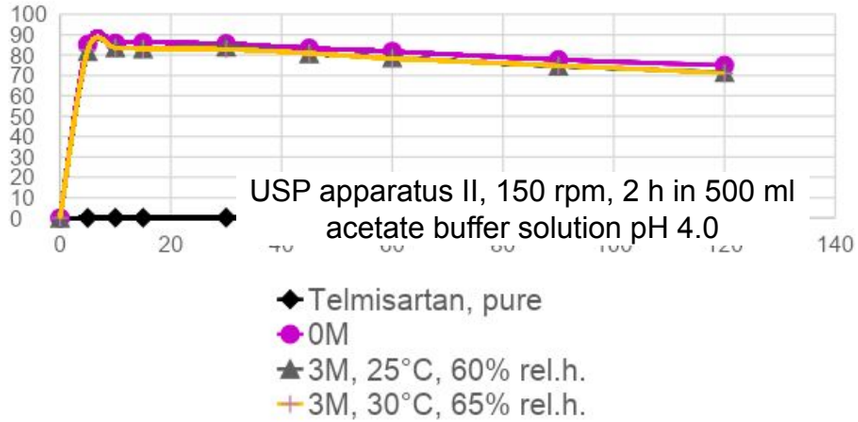
- Cardiovascular
- T_m [°C] = 262
- Practically insoluble
- Daily dose = 20-80 mg

EBD

EUDRAGIT® E







Telmisartan EBD remained amorphous by XRPD and increased the dissolution rate as compared to the crystalline drug (data show powder at initial and 3 month stability timepoint)

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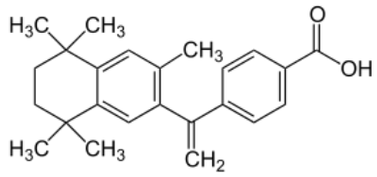
Proof of concept study 2: Bexaroten Emulsion-Based Dispersions (EBD)

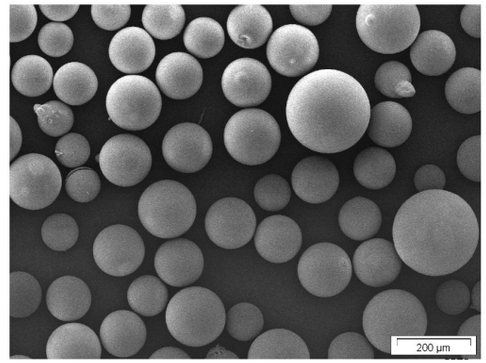


Bexaroten

- Cancer
- T_m [°C] = 230
- Practically insoluble
- Daily dose = 75 mg

EBD

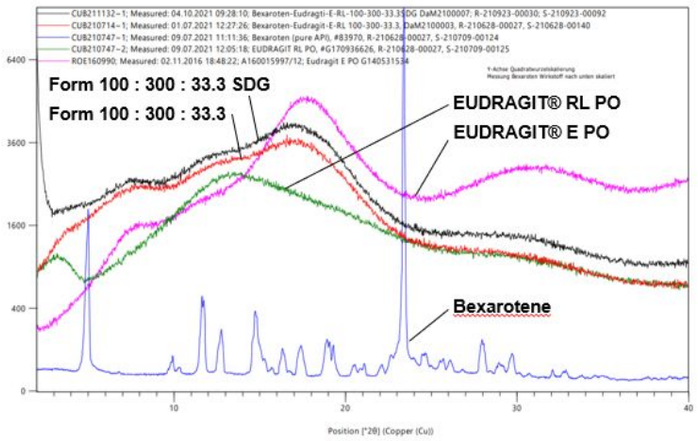
EUDRAGIT® E PO /
EUDRAGIT® RL PO

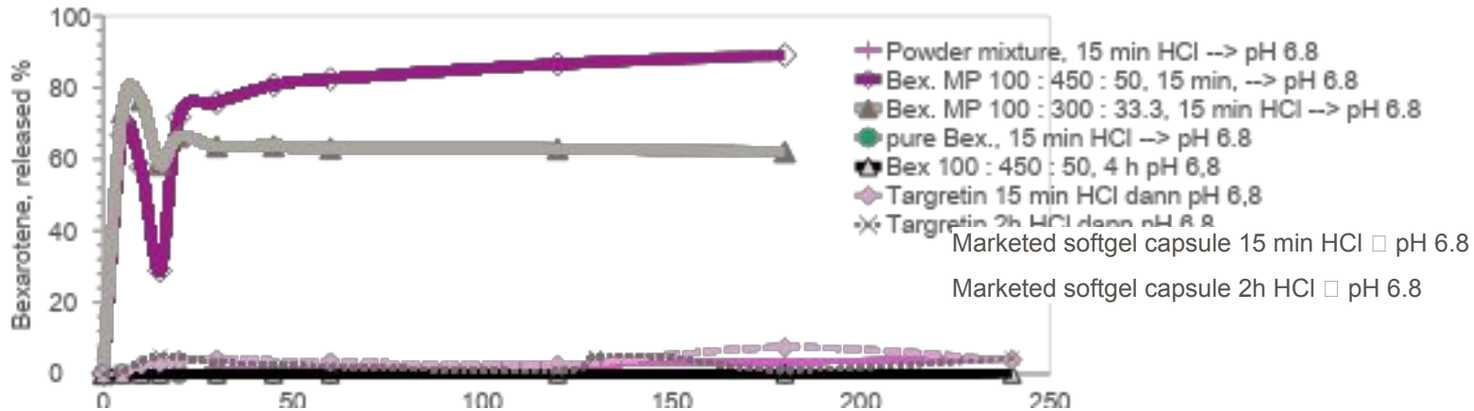


Probenbezeichnung:
Bexaroten-Eudragit-E-RL 100-450-50
DaM2100002

Präparation: Oberfläche

Mikroskop: JEOL JSM IT300
Acc: 10 kV
El.Mag: 100 x
Detektor: SED





Bexoraten EBD remained amorphous by XRPD and increased the dissolution rate as compared to the orginator product.

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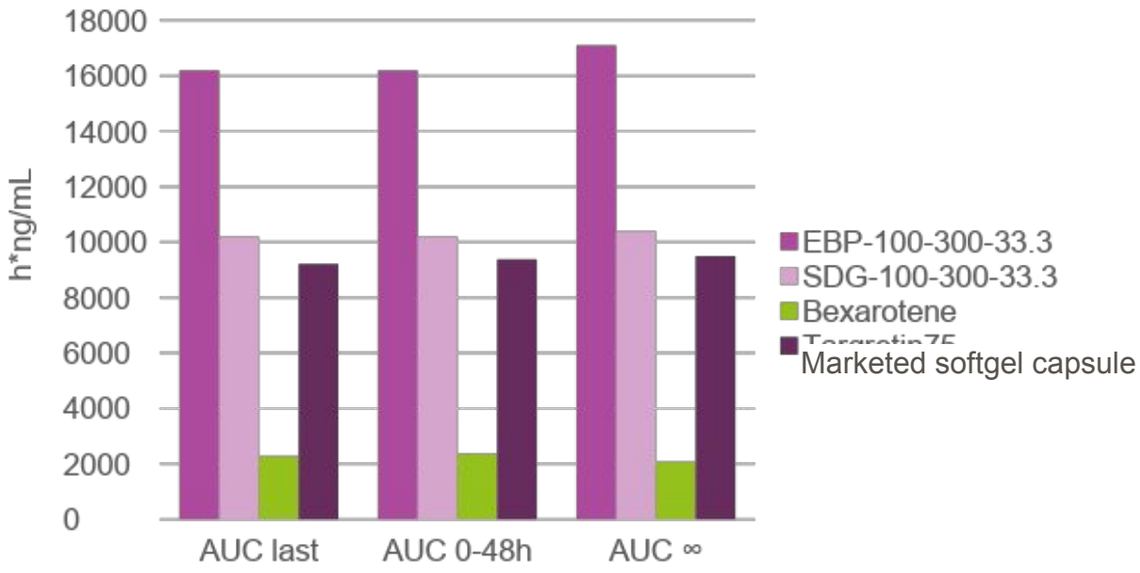
Superior pharmacokinetic parameters in beagle dogs compared to originator and spray dryed amorphous solid dispersion

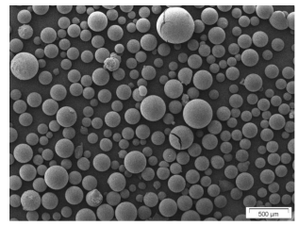


Summary of Bexarotene Pharmacokinetic Parameters in Male Beagle Dog Plasma Following Single Oral Administration

EBP-100-300-33.3

EUDRATEC® SoluFlow

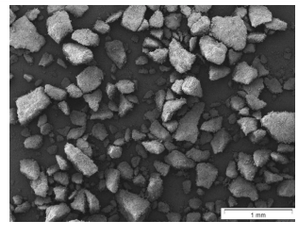
Bexaroten 75 mg
EUDRAGIT® E PO 225 mg
EUDRAGIT® RL PO 22.5 mg



SDG-100-300-33.3

Spray drying + post-compaction

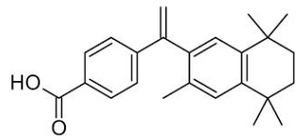
Bexaroten 75 mg
EUDRAGIT® E 225 mg
EUDRAGIT® RL 22.5 mg



Bexaroten

pure crystalline API

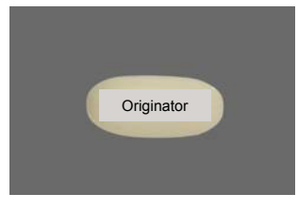
Bexaroten 75 mg



Marketed soft gel capsule

Soft capsule

Bexaroten 75 mg
Macrogol, Polysorbate 20, Povidone, Sorbitol/Glycerol-Mix, Sorbitol, 1,4-Sorbitan, Mannitol, Polyvinylacetate phthalate



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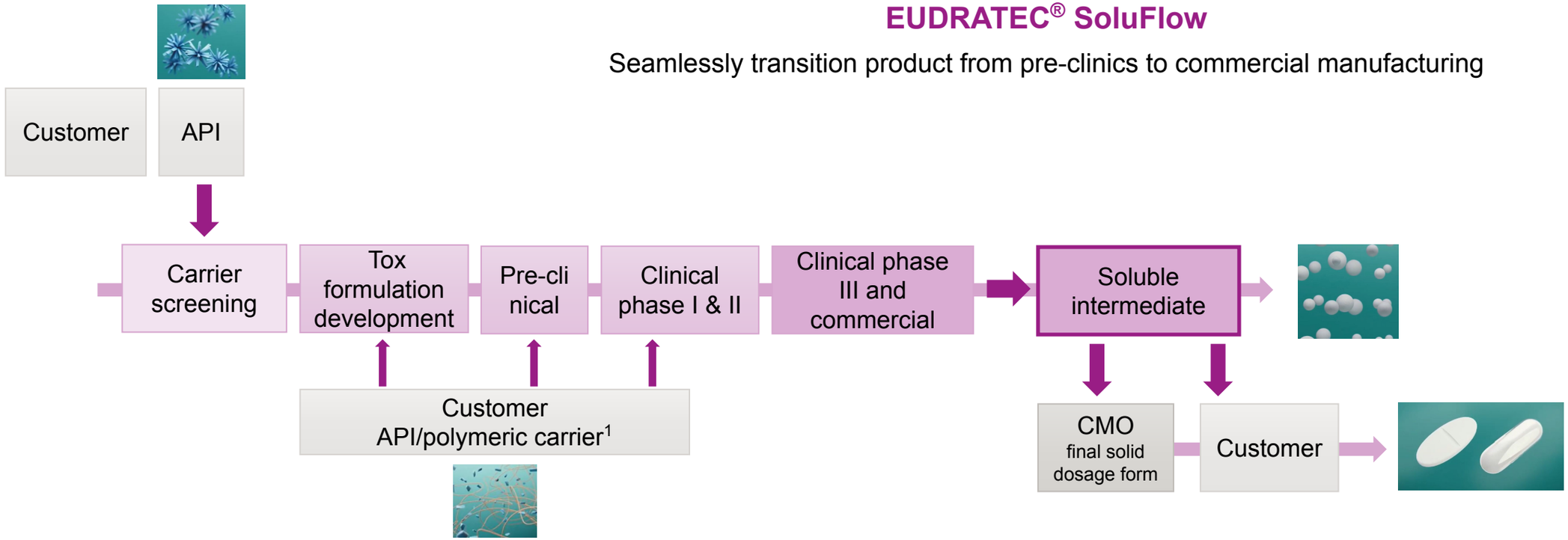
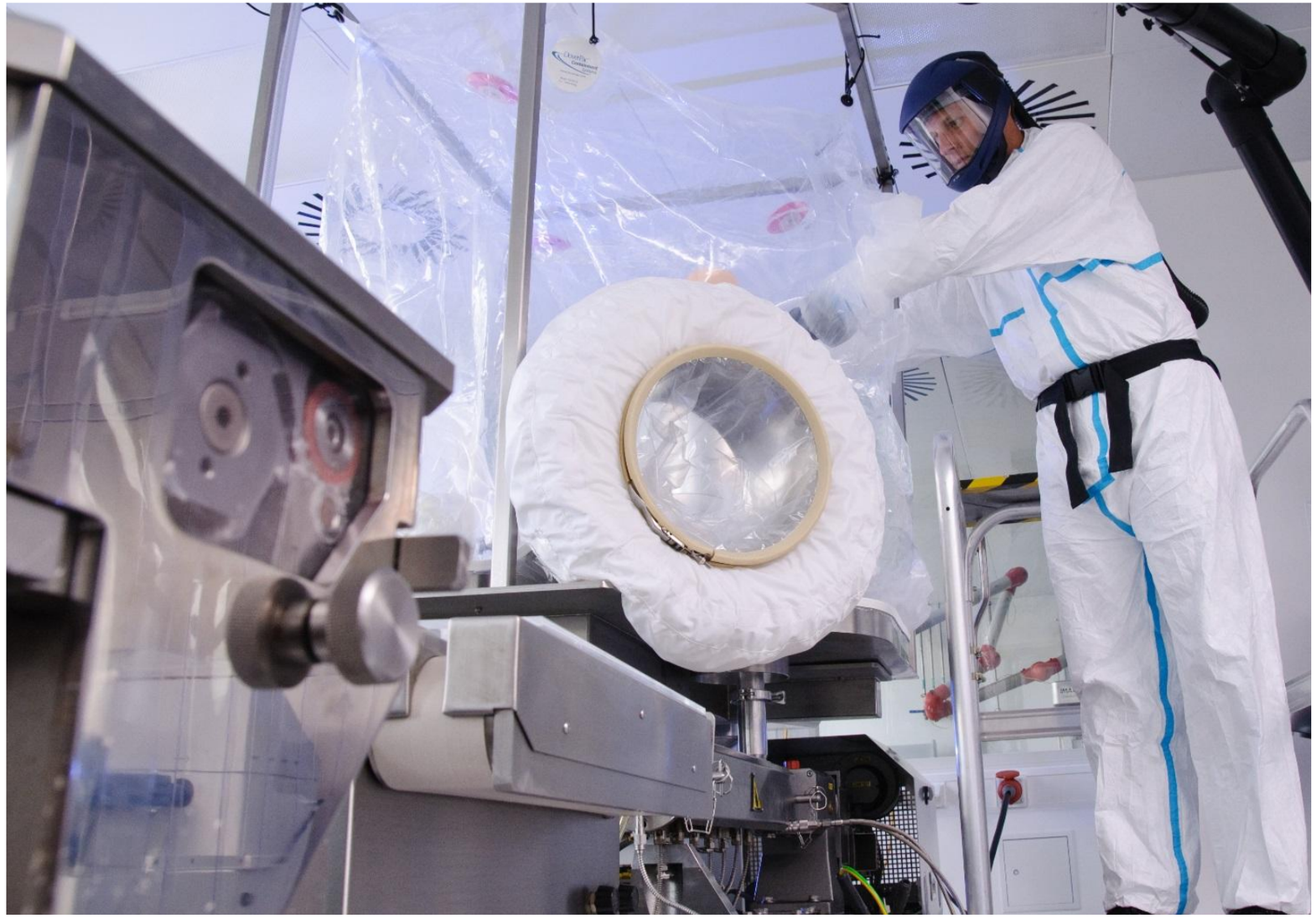
Integrated solution provider from formulation screening to commercial manufacturing of amorphous solid dispersions



[1] Water insoluble polymers such as EUDRAGIT® E, HPMCAS and EUDRAGIT® L 100/L 100-55 can be used as carriers to form amorphous solid dispersions via EUDRATEC® SoluFlow.

Formulation and Application Services



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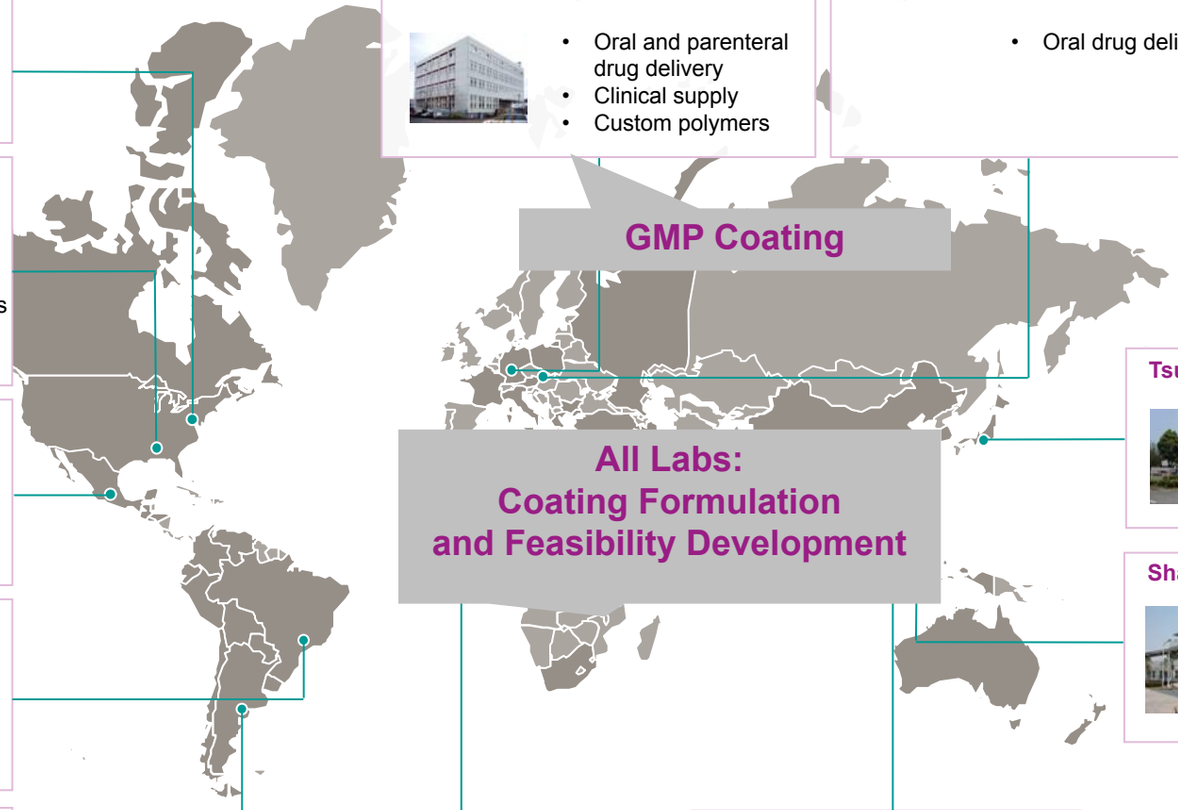
Global Oral Formulation and Application Services (FAS)



Piscataway 2002

- Oral drug delivery
- Solubility enhancement

Darmstadt & Ingelheim 1966/2011

- Oral and parenteral drug delivery
- Clinical supply
- Custom polymers

Szeged 2012

- Oral drug delivery

Birmingham 2011

- Parenteral drug delivery
- Medical devices
- Custom polymers
- Clinical supply

GMP Coating

Tsukuba 2003

- Oral drug delivery

Mexico City 2011

- Oral drug delivery

All Labs:
Coating Formulation and Feasibility Development

Shanghai 2003

- Oral drug delivery

São Paulo (Brazil) 2012

- Oral drug delivery

Buenos Aires 2009

- Oral drug delivery

Mumbai 2003

- Oral drug delivery
- Bio studies
- R&D center

Bangladesh 2012

- Oral drug delivery

PHARMA POLYMERS & SERVICES

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Project Services: Creating value from feasibility to the final dosage form

Pre-Formulation Services

- Fast-track feasibility studies
- Rapid evaluation of excipient options and recommendations
- Evaluation of formulation technologies (small to intermediate scale)

Formulation Development

- Match desired release profile by various technologies
- Quality by Design (QbD)
- Review of formulation and reformulation options
- Analytical method development and validation
- Prototypes for pharmacokinetic and stability studies
- GMP clinical batches for PI-IIA

Analytical Services

- Advanced analytical methods development
- Compendial methods and specifications
- Dissolution testing
- Characterization technologies
- Assay and purity evaluation
- Particle size analysis
- Molecular weight determination

Production, Scale-Up and Transfer Support

- Expertise across all process technologies from initial R&D to commercial scale
- GMP and non-GMP drug manufacturing
- On-site production support and troubleshooting
- CMO review and recommendation for clinical and commercial scale-up
- Transfer to production site

Thank you!

We would like to extend a special thank you to MaaT Pharma for the collaboration.

Additional information on clinical study can be found on:

1. MaaT investors webcast: click here to access.
2. Poster: Restoration of gut microbiota diversity with oral pooled fecal microbiotherapy in acute myeloid leukemia patients after intensive chemotherapy: the phase 1b CIMON trial. click here to access.


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