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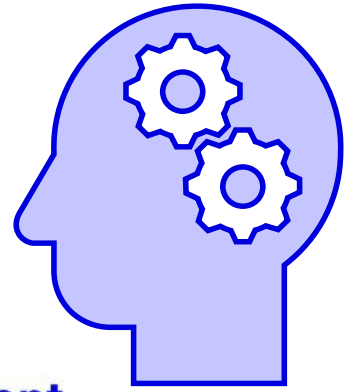
COLONIC DRUG DELIVERY

Associate Prof. Dr. Katerina KUBOVA, Ph.D.

Advanced drug delivery/ Department of pharmaceutical technology

Intellectual property information



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Department of Pharmaceutical Technology

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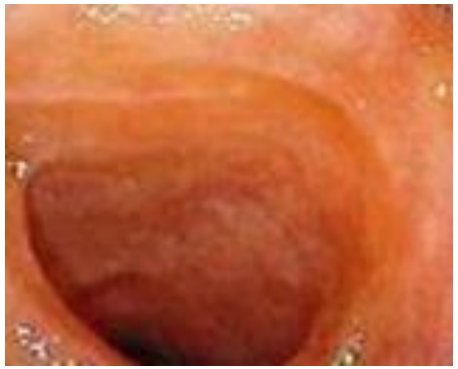
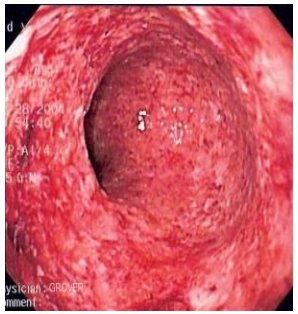
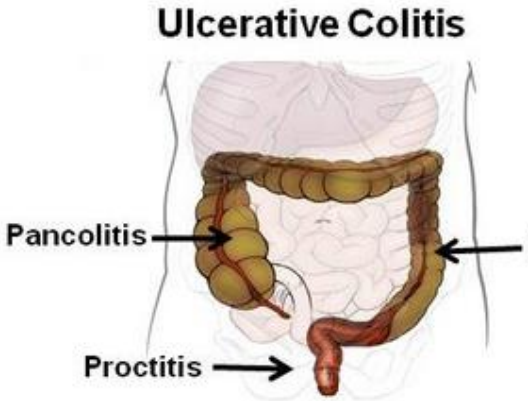
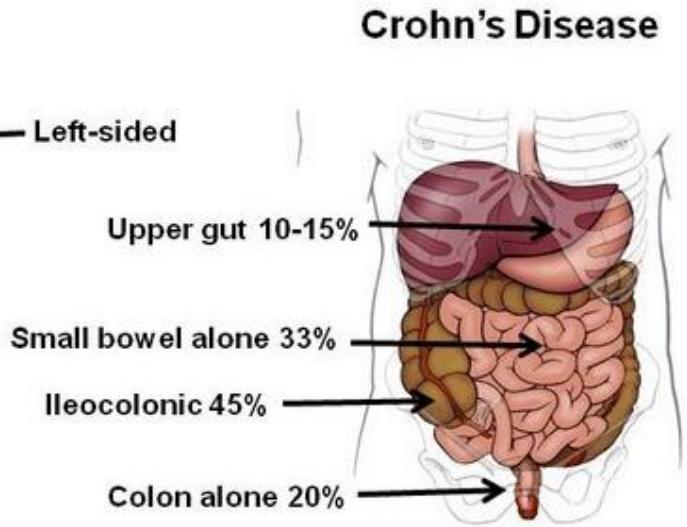
Treatment of local diseases of the colon

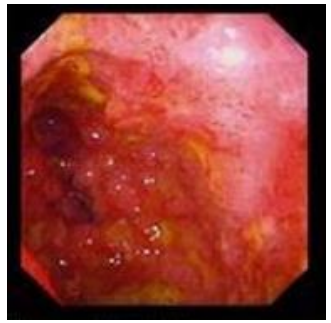
- Inflammatory bowel diseases (IBD) - Crohn's disease, Ulcerative colitis
- Colonic cancer
- Irritable bowel disease
- Polyps











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Systemic drug administration

- Drugs unstable in upper areas of GIT
- Drugs poorly absorbed from the upper GIT
- Especially peptides and proteins (hormones, vaccines)
- Chrono-therapy – anti-asthmatic, anti-arthritic, anti-hypertensive drugs

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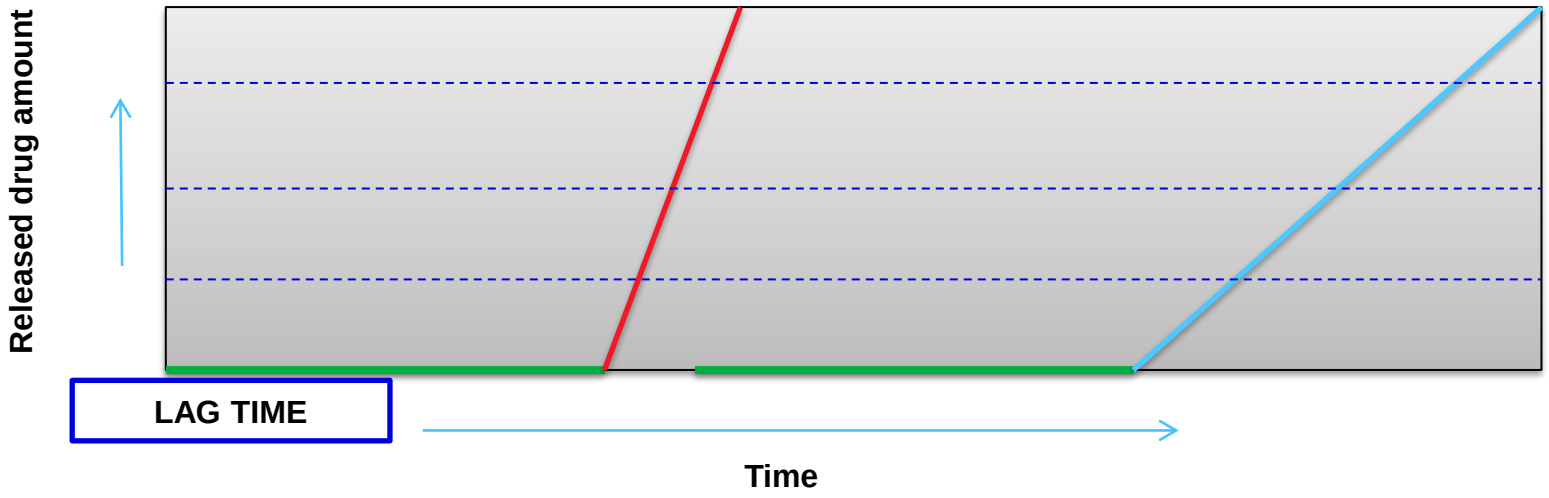
Advantages of colonic drug delivery

- High drug concentration in the affected area
- Possibility of using a smaller dose of a drug - lower side effects, more effective treatment
- No effect on upper GIT - no influence of aggressive gastric conditions, proteolytic enzymes
- Elimination of *first-pass* effect
- Lower proteolytic activity of the colon, long transit time
- Absorption enhancers are effective in this area

Dosage forms for colonic drug delivery

- Different principles of drug release from a dosage form based on GIT physiological conditions
- Aim to prepare universal systems
- Inter- and intra-individual variability of GIT parameters - a major disadvantage



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GIT physiological conditions influencing colon drug delivery

GIT segment		pH	Transit time (hour)	Total amount of microorganism *(CFU/ml)*
Stomach		1.2-5	1-5	10^3
Small intestine	*duodenum*	4.5-6.5	3-4	10^{3-} 10^4
	jejunum	6.6 ± 0.5		10^5
	ileum	7.5 ± 0.5		10^7
Large intestine		5.5 – 8.0 *(4 pro IBD)*	15 – 72	10^{11-} 10^{12}

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Basic strategies for colon drug delivery

SINGLE

MULTIPLE

pH - controlled systems

Time – controlled systems

Microbially triggered systems

ELECTRONIC SYSTEMS

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pH - sensitive polymers

- Applied as a solution or water dispersion of pH-sensitive polymers - polyacrylates, cellulose derivatives on a tablet, pellet, or capsule surface, etc.
- Protection in the stomach and proximal small intestine (stomach 1.2-5, small intestine 6-7.5)
- Poor site specificity – individual pH variability
- Drug release depends on the film thickness, excipients, ionic strength of the medium, drug properties
- A well-known, relatively easy economic method
- Used in pharmacotherapy

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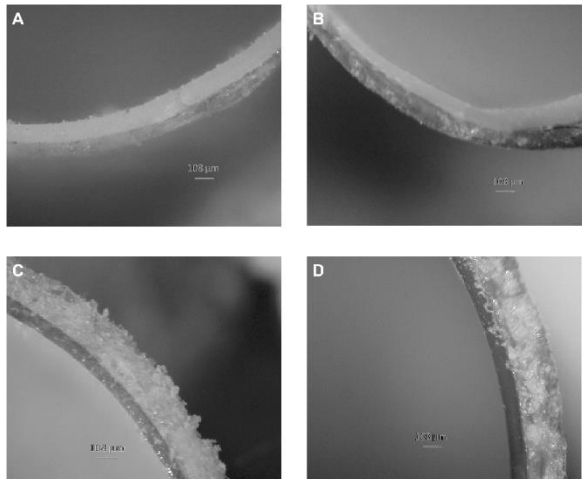
pH - sensitive polymers

Methacrylic polymers of anionic type	Solubility at pH higher than
Eudragit L 100	**6.0**
Eudragit S 100	**7.0**
Eudragit® L-30D	**5.6**
Eudragit® FS 30D	**6.8**
Eudragit® L 100-55	**5.5**

Cellulose derivatives	Solubility at pH higher than
Acetate ftalate cellulose	6.0
Acetate trimelitate cellulose	5.2
Acetate -sukcinate cellulose	4.5
Hypromelose ftalate	5.0 or 5.5 according the type
Polyvinyl acetate	5.0

pH - sensitive polymers

– Capsules -universal system

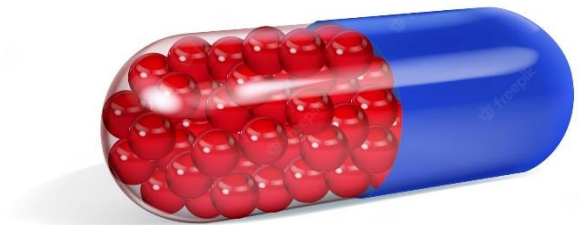


COATED CAPSULES – GELATIN, HPMC

- Drug and filler
- Granules
- Minitablets
- Pellets and microparticles

UNCOATED CAPSULES –GELATIN, HPMC

- Coated granules
- moated Minitablets
- Coated pellets and microparticles



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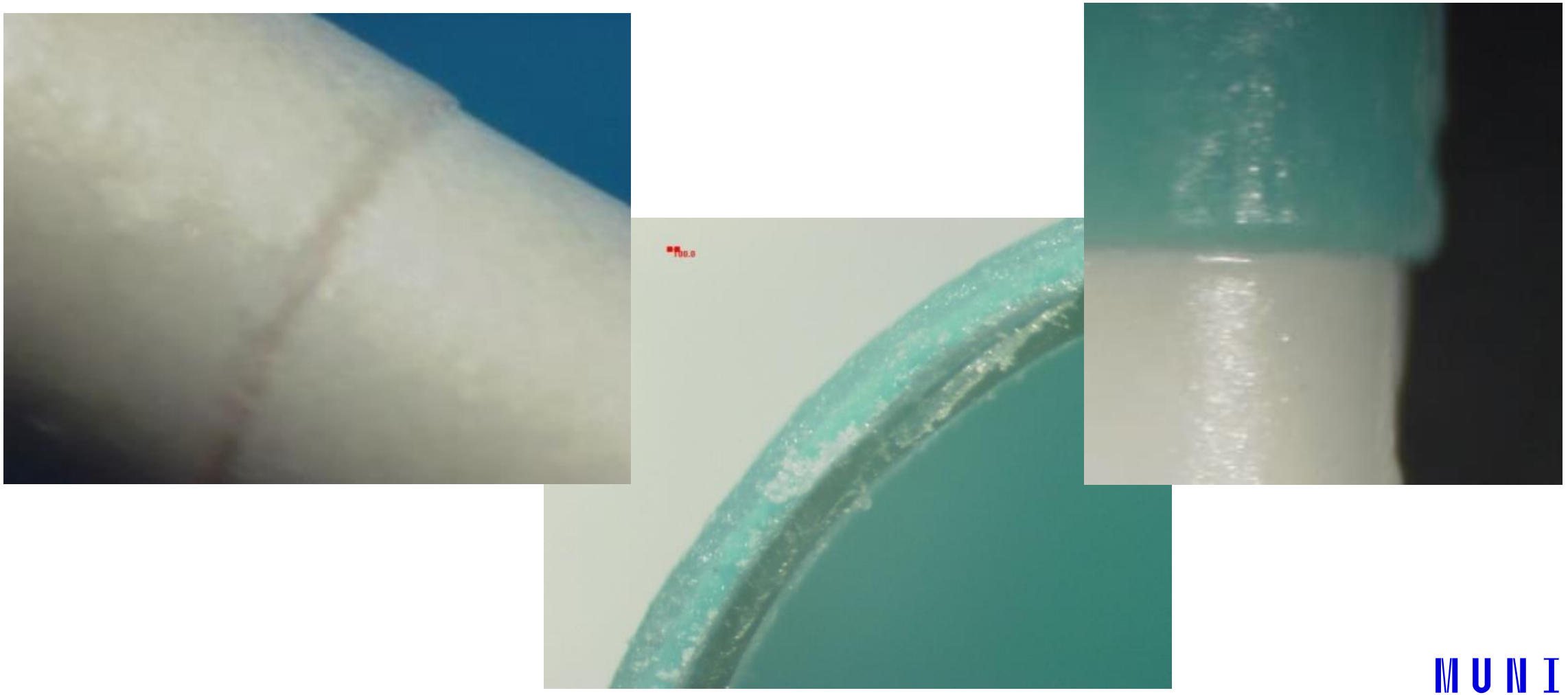
pH - sensitive polymers



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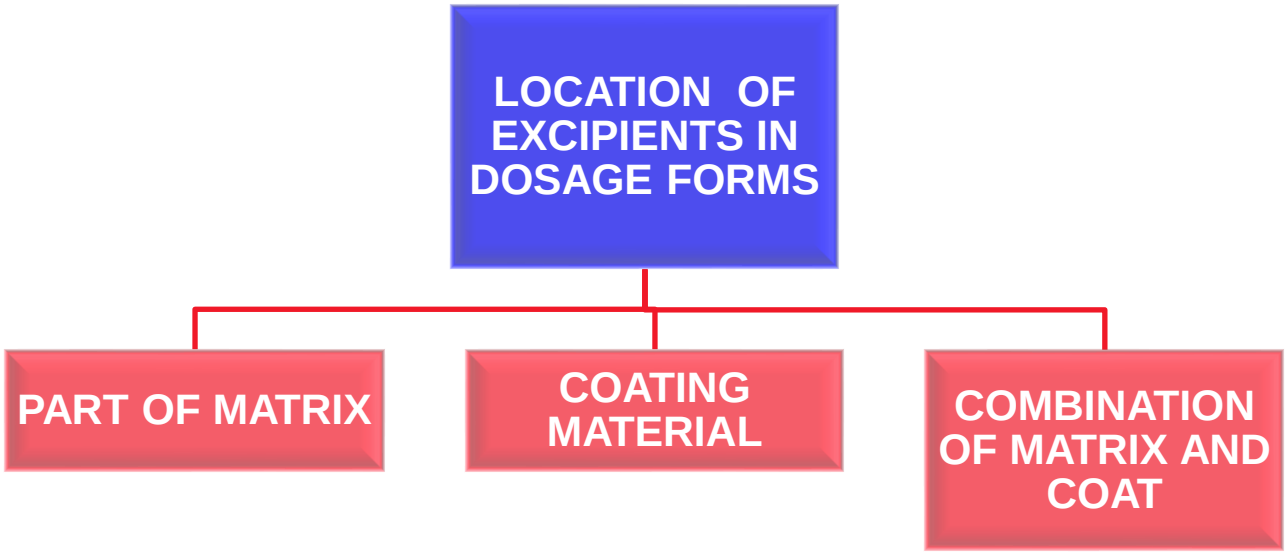
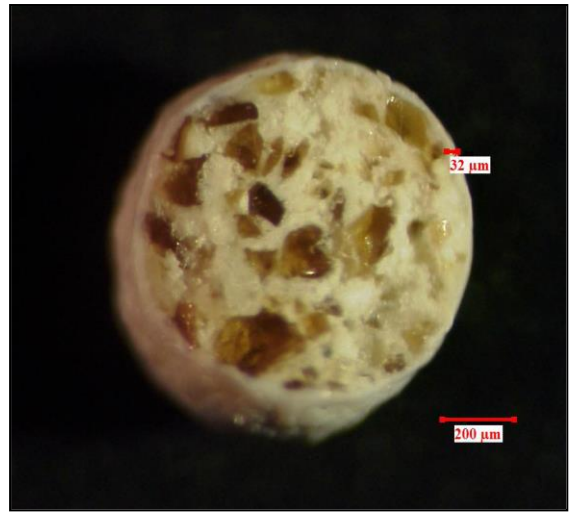
Polymers biodegradable by colon microflora

- Microflora *(enterobecteria)* with specific enzymatic activity
- The sharp increase in number of microorganisms in colon 10^{11}–10^{12} CFU/ml
- Anaerobic - especially species *Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria* etc.
- Enzymes production:
  - β-glucuronidase, β-xylosidase, β-arabinosidase, β-galactosidase, nitroreduktase, azoreductase, deaminase, etc.
- Metabolizing substrates such as carbohydrates and proteins that escape digestion in the upper GIT

Polymers biodegradable by colon microflora



Natural or semi-synthetic polysaccharide-type polymers (advantages vs. disadvantages)



Coated pellets for colon drug delivery :
Chitosan matrix, natrium alginates/chitosan coat

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Polymers biodegradable by colon microflora

Polysacharide	Origin	Application
Chitosan	**animal**	**Capsules, microparticles, pellets, coating materials (in combination with gastro-resistant coat)**
Pectine (Ca^{2+} salt)	plant	Coating prepared by compression
Alginates	**algae**	**Coating pellets (in combination with chitosan)**
Guar gum	plant	Matrix systems
Dextrans	microbial	Hydrogels
Inulin	plant	Hydrogels
Amylose	**plant**	**Coating pellets (in combination with ethyl cellulose)**

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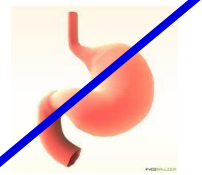
Other excipients for time-controlled systems



GASTRO-RESISTANT COAT

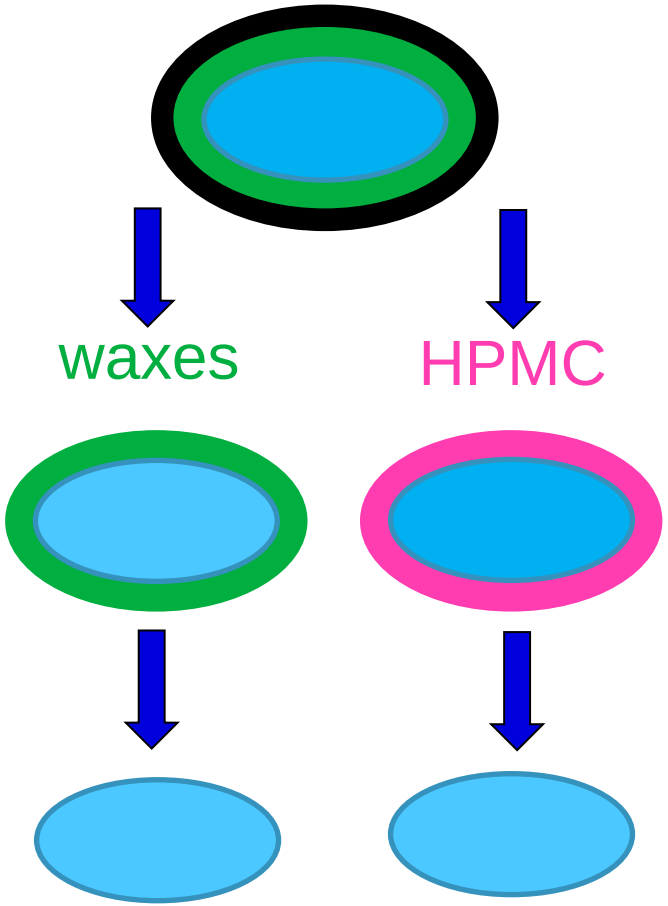
LAG TIME

SWELABLE POLYMERS

OSMOTICALLY ACTIVE SUBSTANCES

LIPOPHILIC EXCIPIENTS

INSOLUBLE POLYMERS



without gastro-resistant coat – *lag time aprox. 5 hours*

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Other excipients

- MMX (Multi-matrix technology) TECHNOLOGY
- Lialda™ – mesalamine - for ulcerative colitis
- Uceris™ / Cortiment™ – budesonide - for ulcerative colitis
- Patent protection till 2020
- Lipophilic and hydrophilic polymers
- pH-dependent coating

ONCE-DAILY
Lialda
(mesalamine) 1.2g
delayed release tablets

Gastro-resistant coating delays release[2]

Delays initial release of mesalamine until the tablet reaches a pH of 7 or greater, normally in the terminal ileum

Hydrophilic component forms a viscous gel[2]

The hydrophilic component is designed to interact with intestinal fluids, causing the tablet to swell and form an outer viscous gel

Lipophilic component slows dissolution[2]

The lipophilic component is designed to slow the penetration of aqueous fluids into the tablet core, prolonging the dissolution of mesalamine throughout the colon

kronportal.ru

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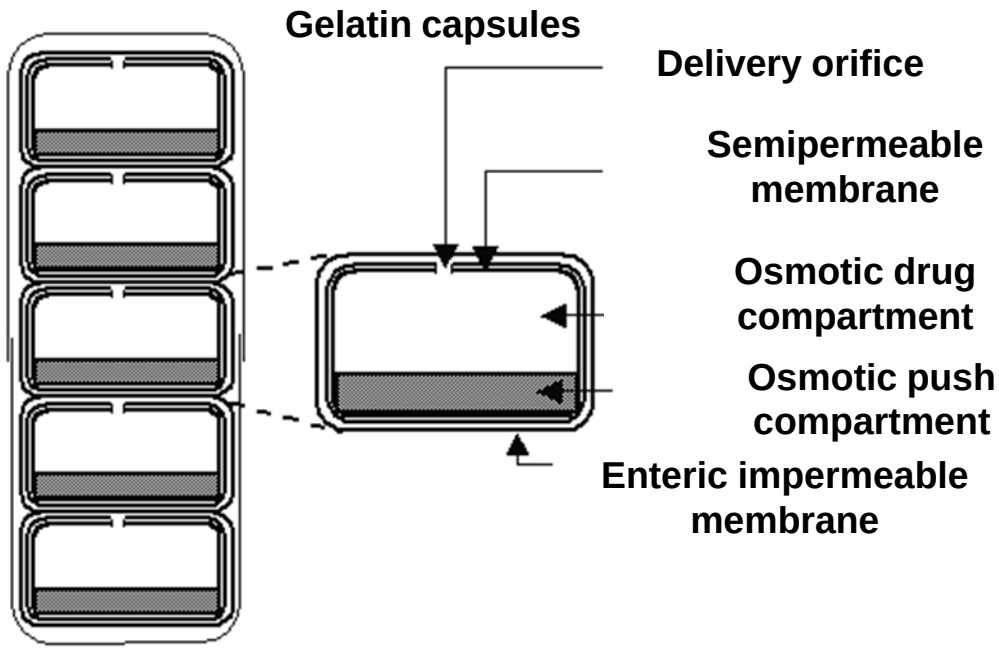
Other excipients



OROS-CT

Osmotic controlled system. After a *lag time*, the drug can be released in two different regimes according to the type of disease.

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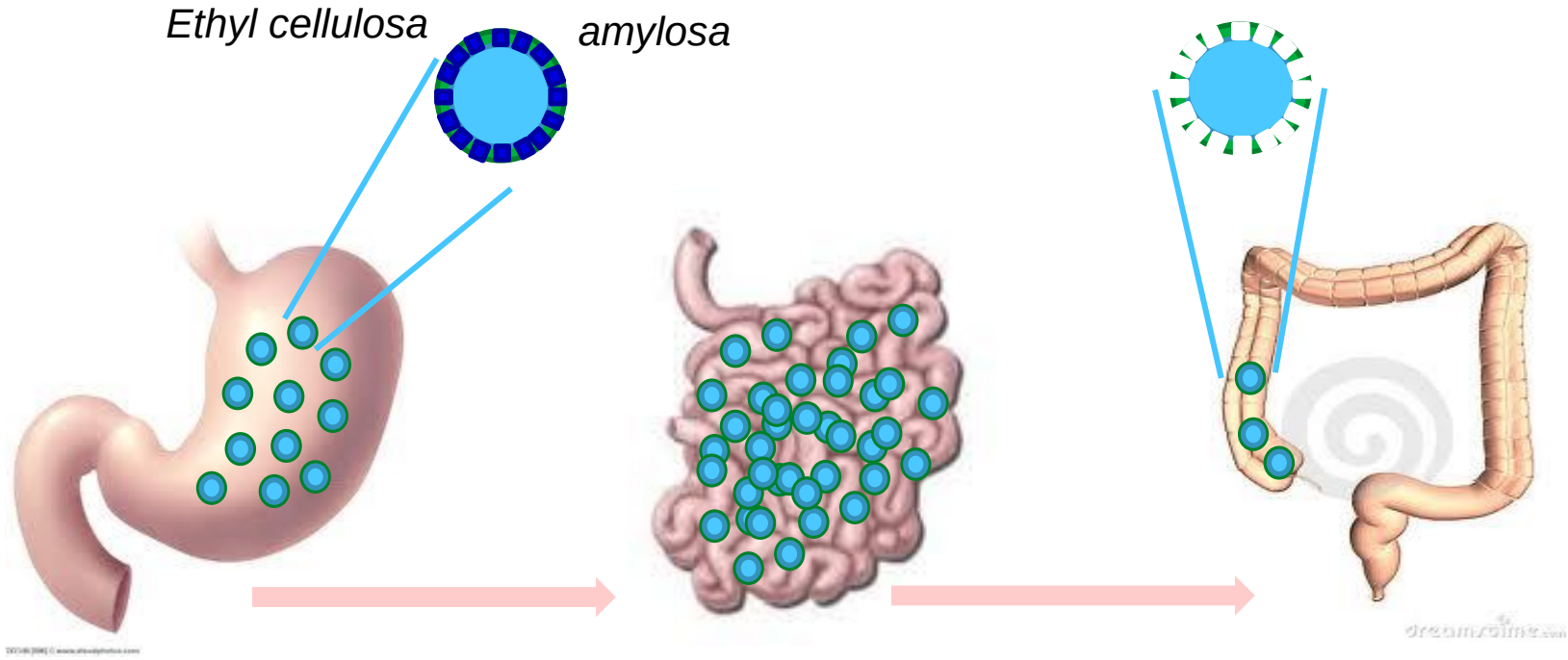
Combination of more approaches

– COLAL-PRED^{TM} TECHNOLOGY

prednisolon-metasulphobenzoate



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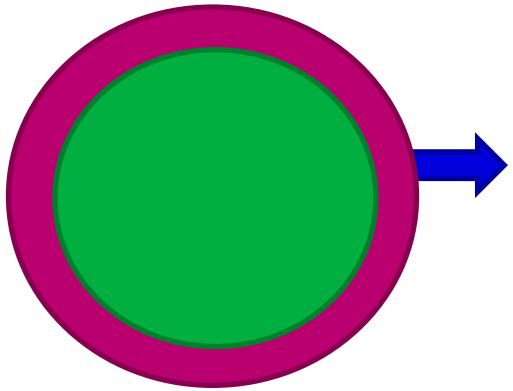
Combination of more approaches

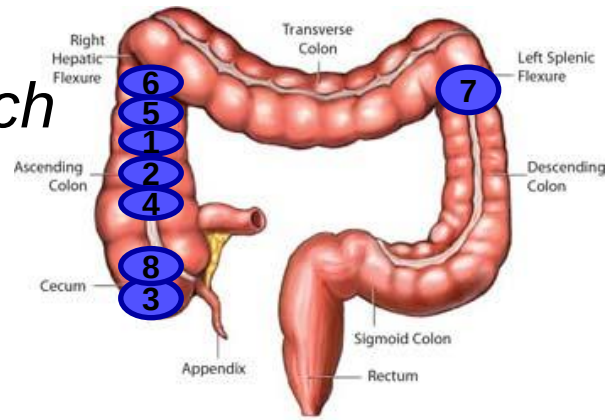
– ENCODE$_{Phloral}^{TM}$



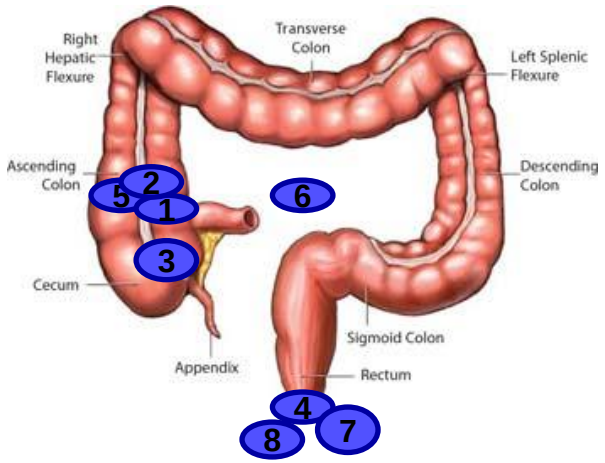
Eudragit^{TM} *S + starch*

Fasted sate

Eudragit^{TM} *S + starch*



Eudragit S



Ibekwe VC, Khela MK, Evans DF, Basit AW. A new concept in colonic targeting: a combined pH-responsive and bacterially-triggered drug delivery technology. Aliment. Pharmacol. Ther. *28*, 911 (2008).

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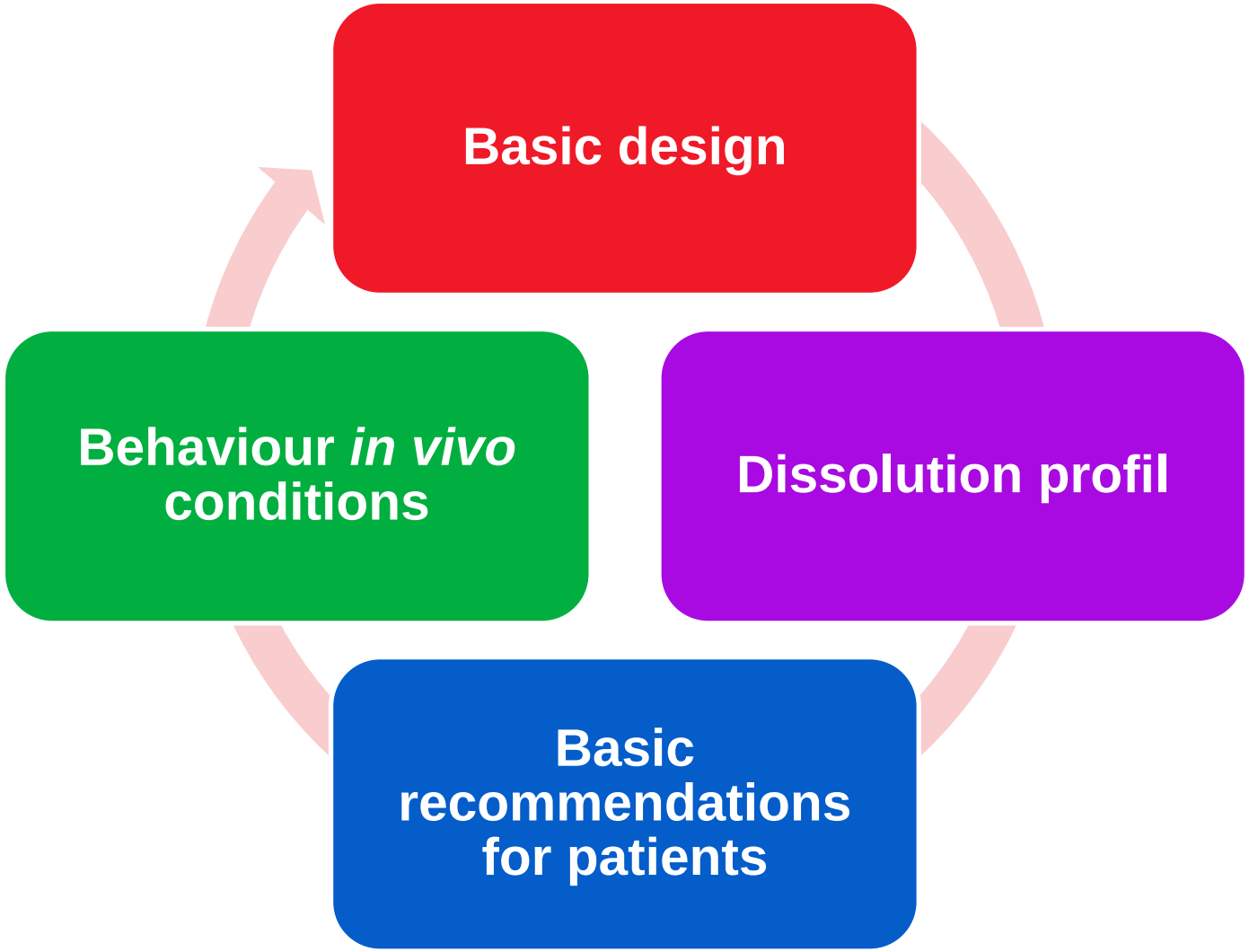
Pharmacutical products for the inflammatory bowel diseases treatment

doc. PharmDr. Kateřina Kubová, Ph.D.

Mainly used drugs

- **5-ASA** (Asacol®, Pentasa®, Salofalk®)
- **budesonid** (Budenofalk®, Cortiment®, Entocort®)
- **Single vs. multiple dosage forms**
- **Matrix vs. reservoir dosage forms**
- **Combination**



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Excipients

Products	Polymer			
	pH-dependent	insoluble	bio-degradable	swelling
Asacol® tablets (400, 800 mg)	Eudragit® S	-	-	-
Asacol® 1600 mg tablets	Eudragit® S*	-	starch	-
Pentasa® tablets	-	ethylcellulose	-	-
Pentasa® sachet microgranules	-	ethylcellulose	-	-
Salofalk® tablets	Eudragit® L	-	-	-
Salofalk® granules	Eudragit® L	Eudragit® NE	-	--
Budenofalk® capsules	Eudragit® L, S	Eudragit® RL, RS	-	-
Budenofalk® UNO granules	Eudragit® L, S	Eudragit® RL, RS	-	
Cortiment® tablets	Eudragit® L, S	-	-	hyprollose + lipophilic component
Entocort® capsules	Eudragit® L	ethylcellulose		-

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Single vs. multiple dosage forms

	Single dosage forms	Multiple dosage forms
Matrix	-	-
Rezervoir	Asacol® tablets Salofalk® tablets	Budenofalk® capsules* Budenofalk® UNO granules Pentasa® tablets* Pentasa® sachet microgranules
Combined	Cortiment® tablets	Entocort® capsules* Salofalk® granules

* Multiple dosage form occurs after capsule dissolving in stomach

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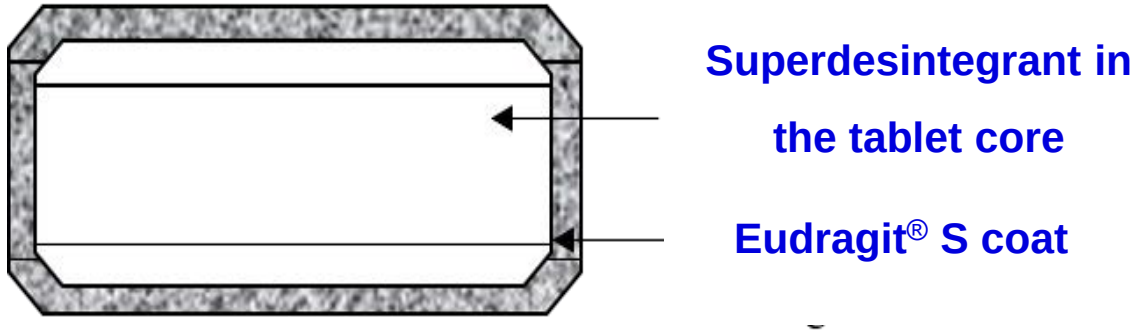
5-ASA pharmaceutical products

Asacol® gastro-resistant tablets (Tillotts Pharma GmbH)

- 400 mg a 800 mg 5-ASA

- pH-dependent polymer >7
- **Super-desintegrant** in the tablet core - sodium carboxymethylstarch
- If IBD patients don´t have pH >7, the drug is not released from the dosage form, and patients **are not treated**



Ulcerative colitis in proximal colonic area

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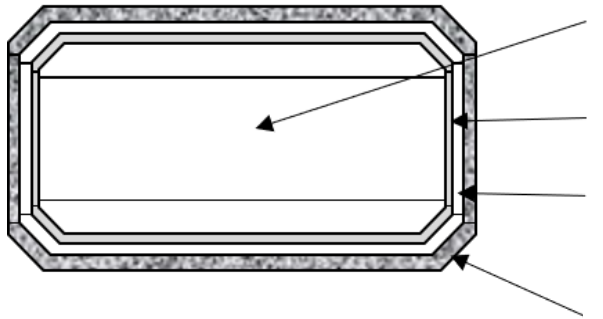
Asacol® 1600 mg, tablets with controlled drug release (Tillotts Pharma GmbH)

- Opticore™= (**OPTI**mized **CO**lonic **RE**lease)
- pH-dependent polymer + polymer biodegradable by microorganisms in the colon
- Drug release also in patients with lower pH value in the small intestine – a failsafe
- Based on the patented technology *Phloral*® (Eudragit® S + starch) with the buffered system for fast drug release



5-ASA tablet core

HPMC coat

buffered layer

External Eudragit® S coat + biodegradable starch

Ulcerative colitis

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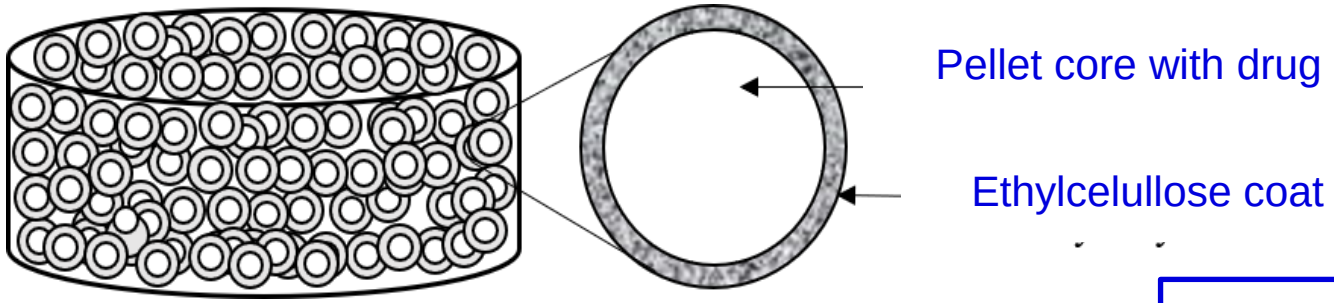
Pentasa® Prolong 500 mg a 1 g, tablets with prolonged release (Ferring GmbH) ®



Crohn's disease

- Prepared by compression of coated pellets
- Disintegration in the stomach followed by continual drug release – the drug release rate increases with rising pH (depending on 5-ASA solubility) - 60 % of 5-ASA in the small intestine area, 40 % of 5-ASA in the colonic area
- Patients take the drug independently of food
- It can be dispersed in 50 ml of cold water to facilitate swallowing

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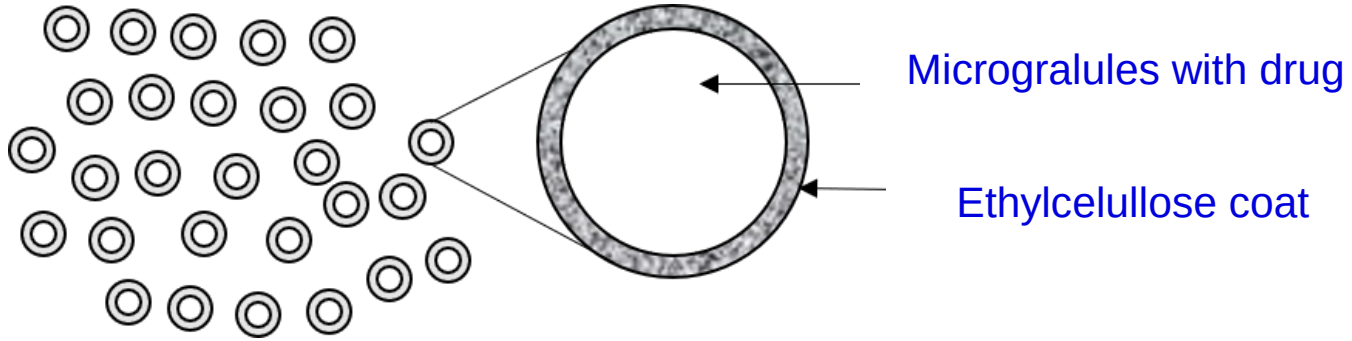
Pentasa® sachet 2 g a 4 g, granules with prolonged release (Ferring GmbH) ®

- The 5-ASA release principle is comparable to Pentasa® Prolong (tablets)
- A short lag time due to tablet disintegration
- An advantage only for patients with swallowing problems, who typically swallow multiple tablets at once to achieve the required dose of the drug



Crohn's disease

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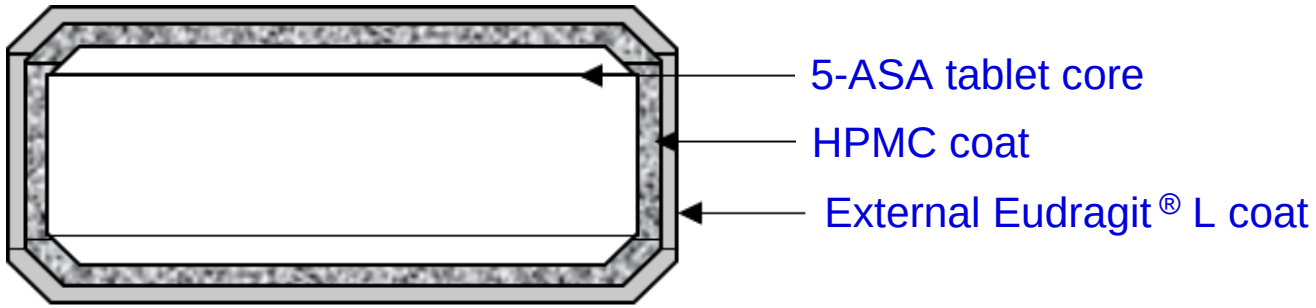
Salofalk® 500 mg, gastro-resistant tablets (Dr. Falk Pharma GmbH) ®



Crohn's disease affecting the larger part of the small intestine and ascending colon

- The dissolution of the polymer coating at pH > 6
- HPMC does not modify the drug release
- 5-ASA starts to be released after approx. 15 min in the small intestine, the complete amount of drug is released in approx. 60 min

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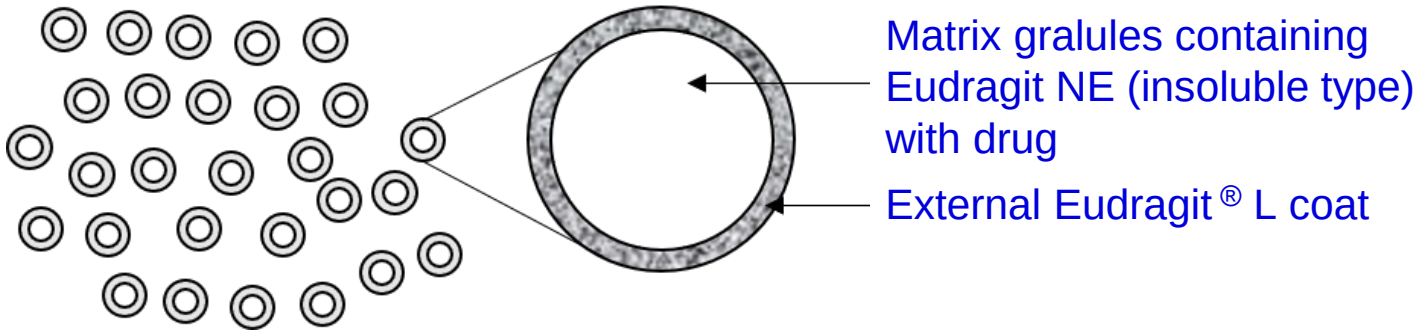
Salofalk® 1500 a 3000 mg, gastro-resistant granules with prolonged drug release (Dr. Falk Pharma GmbH)



Ulcerative colitis, including left-sided forms of inflammation

- Dissolution of the Eudragit® L polymeric coating at pH > 6 followed by the prolonged drug release
  - According to Kruis et al. - 80%/ 3 hours
  - According to Karkossa et al. - 80 %/ 7 hours (*in vitro* predictive dissolution model)
- Compared to Salofalk® tablets, the advantage is the possibility of single-dose administration and a significantly larger surface area – a benefit for patients with swallowing difficulties
- The dose of 5-ASA available in the colon is higher than that of Pentasa®

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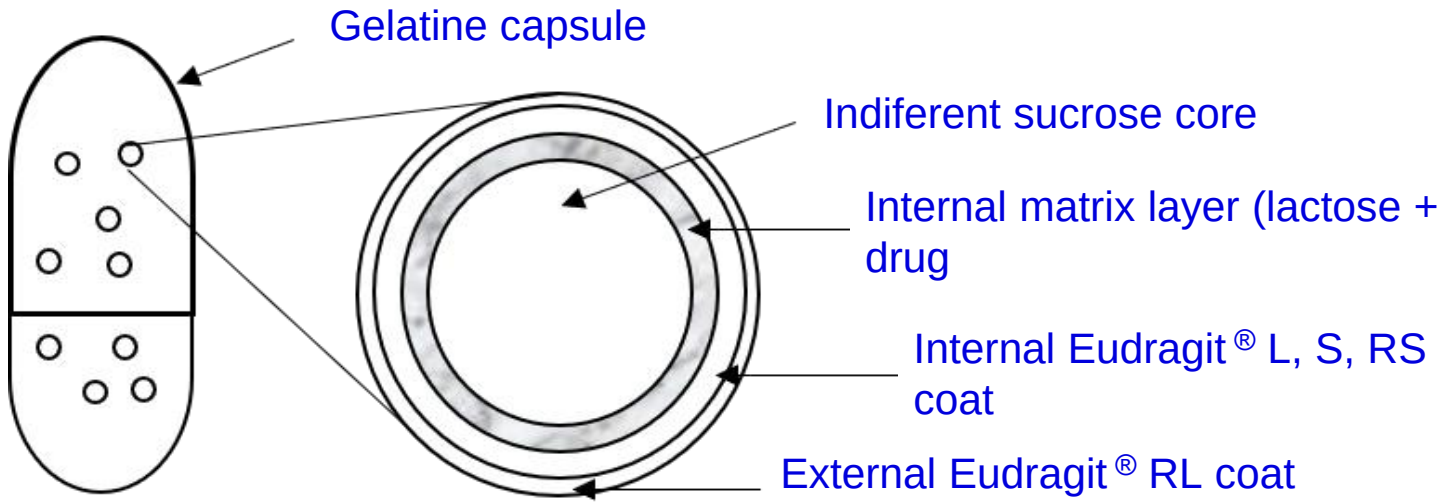
Budnoside pharmaceutical products

Budenofalk® 3 mg, gastro-resistant hard capsules (Dr. Falk Pharma GmbH)®

- Slow dissolution of the polymeric coating at pH > 6.4
  - According to Goyanese et al., in the jejunum - 80% / 120 minutes
- Acting more distally compared to Entocort® - see later
- usually 3 capsules per dose®



Crohn's disease affecting the ileum and/or ascending colon

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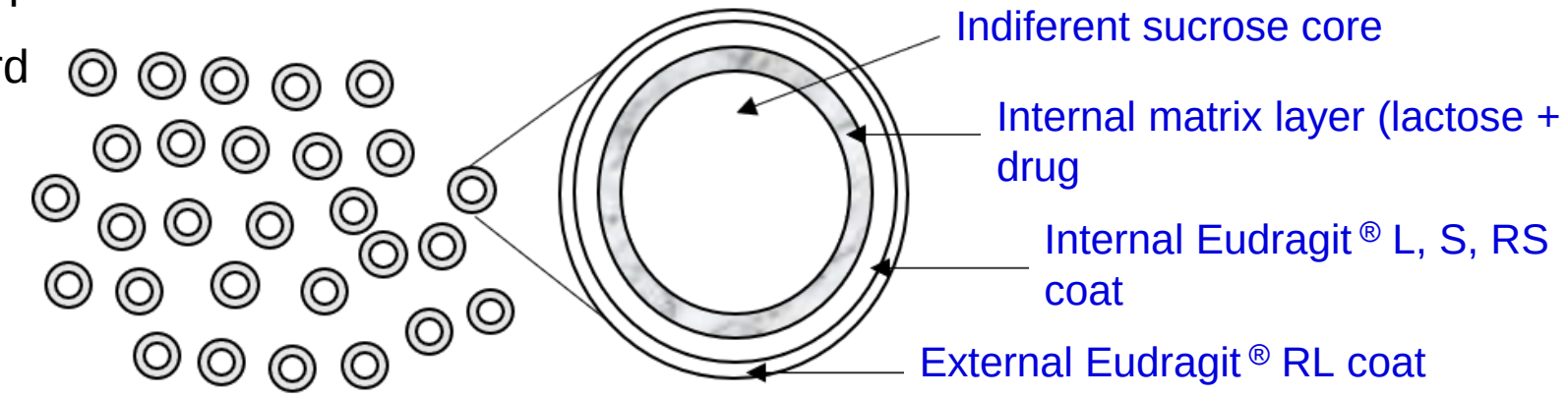
Přípravek Budenofalk® UNO 9 mg, gastro-resistant granule (Dr. Falk Pharma GmbH)

- The 5-ASA release principle is comparable to Budenofalk® gastro-resistant hard capsules
- A short lag time due to the capsule dissolving
- An advantage only for patients with swallowing problems, who typically swallow multiple capsules at once to achieve the required dose of the drug



Crohn's disease affecting the ileum and/or ascending colon

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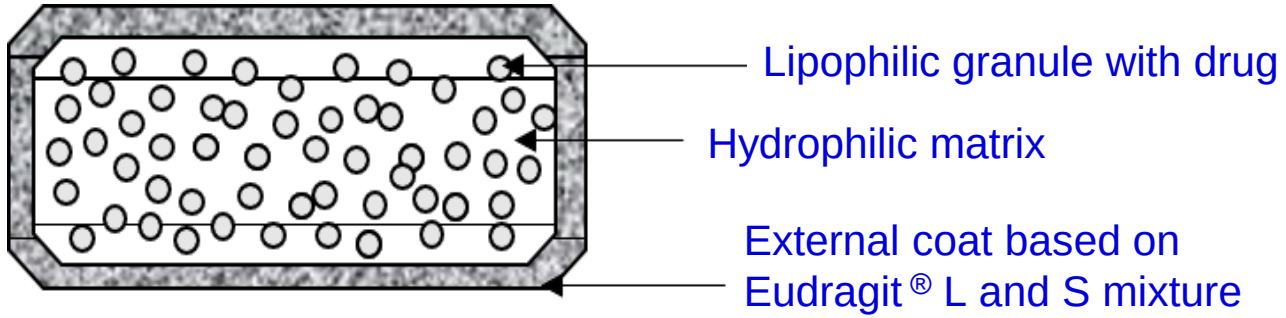
Přípravek Cortiment® 9 mg, tablets with prolonged release (Ferring GmbH)®

- Hydrophilic/lipophilic tablet with gastro-resistant coating = MMX technology
- Lipophilic granules - stearic acid, amphiphilic lecithin containing a drug, evenly dispersed in HPC matrix
- Dissolution of polymeric coating at pH > 7 (according to literature), realistically, this pH value is lower
- Gradual and relatively uniform drug (close to zero order kinetics)



Ulcerative colitis, including left-sided forms of inflammation

- Used in the morning with food or on an empty stomach
- with food - decrease in C_{max} a delay in T_{max}

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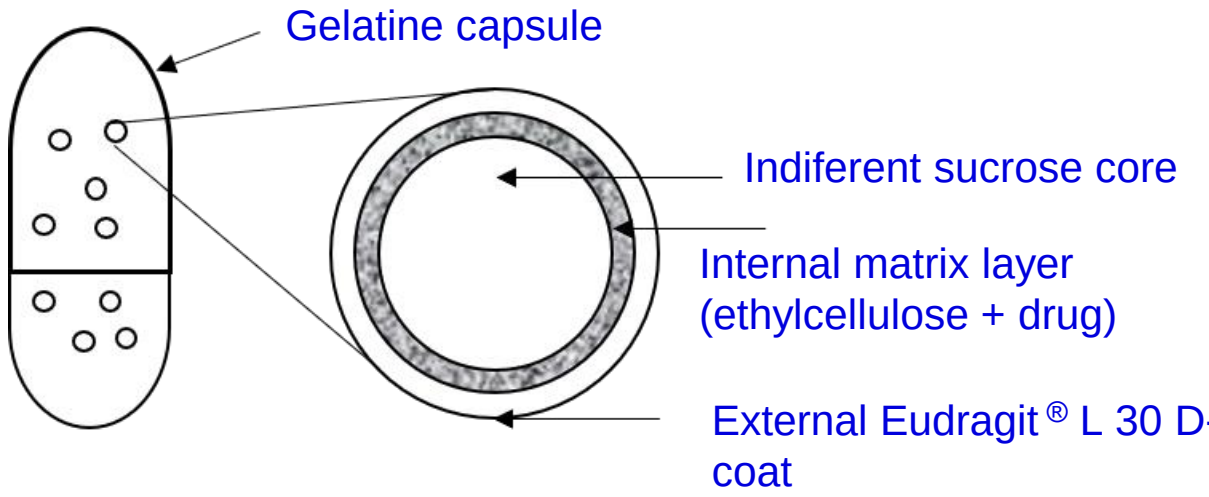
Přípravek Entocort® 3 mg, hard capsules with controlled release (Tillotts Pharma GmbH)

- Coated granules in the hard gelatine capsule
- The capsule does not control drug release
- Dissolution of granule coating at pH > 5.5 followed by the prolonged drug release from the ethyl cellulose layer
- 1st order kinetics (80%/60 min.)



Crohn's disease affecting the ileum and/or ascending colon

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Products in terms of preference from the perspective of pharmaceutical technology - Crohn's disease

1	**Pentasa® sachets Pentasa® tablets**	the 5-ASA release in the stomach (the first among all products), covering the whole small intestine	**Entocort® capsules**	the coating dissolves at pH > 5.5, 80% of budesonide is subsequently released within 60 min.
2	**Salofalk® tablets**	the coating dissolves at pH > 6, the whole amount of 5-ASA is released within 60 min.	**Budenofalk® capsules Budenofalk® granules**	80% of budesonide is subsequently released within 120 min.
3	**Asacol® 400 a 800 mg**	the coating dissolves at pH > 7, immediate drug release; the 5-ASA does not cover the affected areas in the small intestine	**-**	-

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Products in terms of preference from the perspective of pharmaceutical technology – ulcerative colitis

1	**Asacol® 1600 mg**	**accelerated release of 5-ASA even in case of low pH in the distal ileum and colon, high single dose**	**Cortiment® tablets**	**the coating dissolves at pH > 6.4 (ileum), followed by budesonide prolonged released with zero-order kinetics**
2	**Salofalk® granules**	the coating dissolves at pH > 6, prolonged 5-ASA release (up to 7 hours), allowing treatment of more distal forms of UC	-	-
3	**Asacol® 400 a 800 mg**	5-ASA is immediately released at pH > 7, may not be effective enough in patients with low luminal pH	-	-
4	**Salofalk® tablets**	the coating dissolves at pH > 6, 5-ASA is released within 60 min, for the therapy of more distal forms of UC the above preparations are more suitable	-	-
5	**Pentasa® sachets Pentasa® tablets**	the 5-ASA release in the stomach, most of the drug is released in the small intestine, for the therapy of more distal forms of UC the above preparations are more suitable	-	-

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Recommendations

- None of these dosage forms may be crushed or bitten
- Capsule formulations (specifically Entocort®, Budenofalk®) contain a coated multiple dosage forms (coated granules or pellets)
  - The gelatine capsule is only a carrier defining the dose and facilitating the administration
  - Capsules can be opened and swallowed with sufficient liquid (see Budenofalk® UNO).

Recommendations

- Pentasa® Prolong a Pentasa® sachet: these are identical principles; no significant difference exists between them.
- Salofalk ® tablets a Salofalk ® granules show a different drug release profile. Although both products start releasing 5-ASA at pH > 6, Salofalk® (granules) releases the drug significantly slower compared to tablets.

Recommendations

- Asacol® 1600 mg is a combination of a pH-dependent polymer and a biodegradable polymer that ensures the release of 5-ASA even in the case of insufficient GIT pH in IBD patients, where products based on pH-dependent polymers alone may fail. The advantage of the product is the complete 5-ASA dose in the colonic area.
- In some countries, products (Mezavant®, Lialda®) containing 5-ASA at a dose of 1.2 g in the form of MMX are available (for technology, see Cortiment®).

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Thank you for your attention