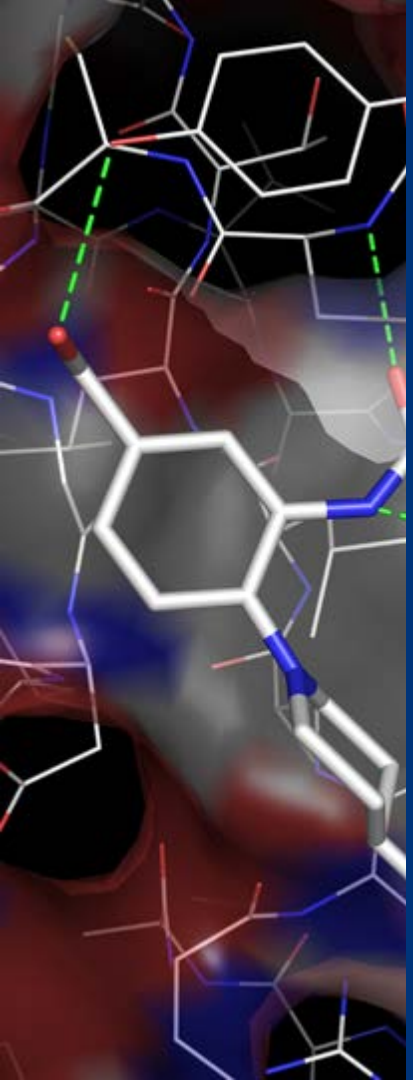

Dissolution test strategies for colon-targeting drug products

QC and concept selection

Dr. Federica Giusti
CPDS – AD – Dissolution Sciences

Janssen Research & Development, LLC

The COLOTAN 1st Symposium: Colon targeting of drugs: current state of the art
June18th, 2021

Art credit: *Close-up of the inhibitor binding site of the colony-stimulating factor-1 receptor kinase domain.*

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Setting the stage

Multiple compounds in Janssen pipeline targeting local GI inflammatory diseases
(ex. IBD, ulcerative colitis)

Compound characteristics acting as drivers for advanced drug delivery strategies

- Often middle- to large-sized molecules, degradation-sensitive (pH, enzymes)
- Need for **adaptive formulation design** facilitating localized drug delivery at site of action

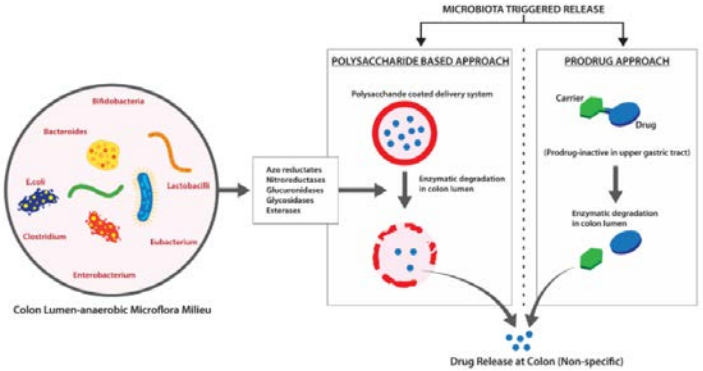
Ex. enzymatic-digestion based release-mechanisms for colonic drug delivery

New landscape / uncharted territory for QC method development and formulation concept screening

Enzymatic-digestion based release in colon Technology

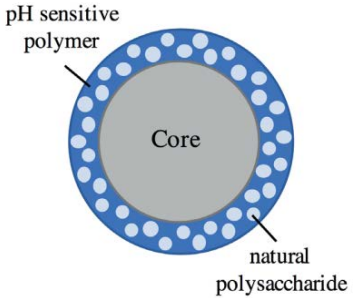
COLAL®(-like)

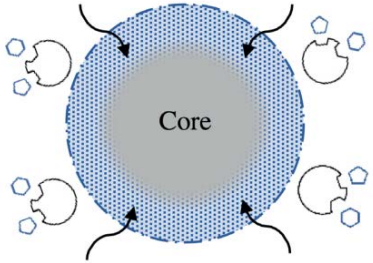
- Alizyme technology - patent expired
- **Coating composition:**
  Ethyl Cellulose + Starch-derivative (e.g., EC: Nutriose)
- **Release mechanism:**
  Enzymatic digestion of starch-derivative by colonic microflora



PHLORAL®(-like)

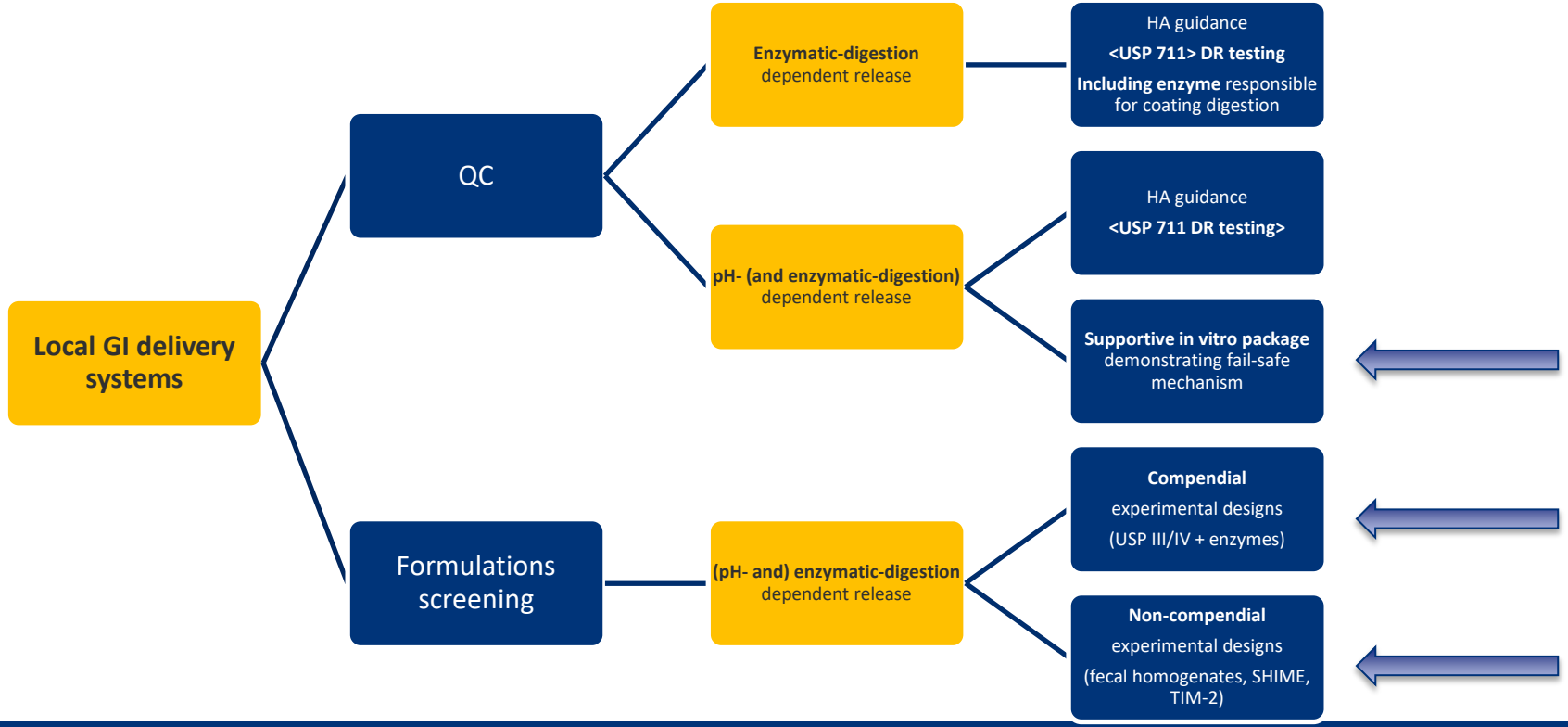
- Proprietary technology Intract Pharma
- **Coating composition:**
  pH-responsive polymer + Starch-derivative
  (e.g., Eudragit S100: Pea starch)
- **Release mechanism:**
  - pH-dependent release
  - Enzymatic digestion of starch-derivative by colonic microflora (fail-safe)





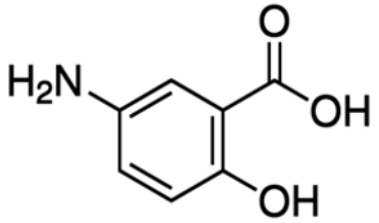
Ph/Enzymatic-digestion dependent release in colon

QC- and formulation concept screening-strategy



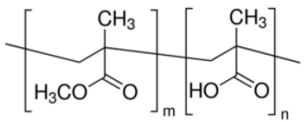
Yaldigo 1600 mg tablets

- OPTICORE™ coating:
  - First commercialized DP with PHLORAL® like technology
  - Combination of Amylo-Maize starch N-400 and Eudragit S 100



Structure mesalamine (2)

Yaldigo/Asacol 1600 mg (1)



Chemical structure Eudragit S (4)

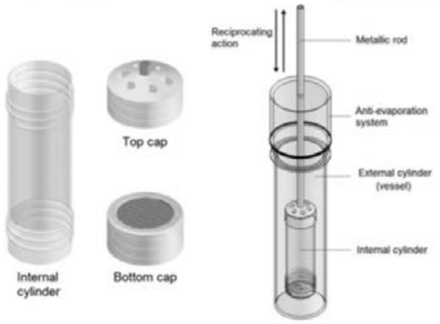
Mesalamine (5-ASA, mesalazine)
- Crohn's disease
- Ulcerative colitis
- BCS class III
- Solubility in water: 0.8-1 mg/mL
- pKa: 2.02, 5.87

(1) https://www.tillotts.com/products/asacol/
(2) https://www.sigmaaldrich.com/catalog/product/sigma/a3537?lang=en&region=CA

Physiological pH range → USP apparatus 3

	In vitro pH (1) (2)	*In vitro* residence time (1)
Stomach	2	45 min
Duodenum	5	30 min
Jejunum	6.5	40 min
	6.8	80 min
Ileum	7.5	60 min
Ascending colon	6	19 h 45 min

USP apparatus 3 (1)



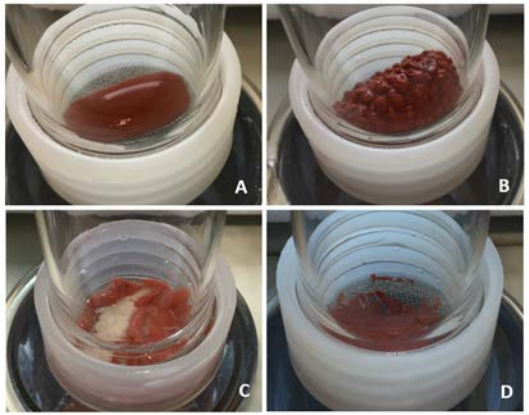
Glass tube USP apparatus 3 (2)

- Reciprocating cylinder
- + pH range → biorelevant
- – Small volume → no sink

(1) Andreas CJ, Chen YC, Markopoulos C, Reppas C, Dressman J. In vitro biorelevant models for evaluating modified release mesalamine products to forecast the effect of formulation and meal intake on drug release. Eur J Pharm Biopharm. 2015;97:39–50
(2) Klein S, Stein J, Dressman J. Site-specific delivery of anti-inflammatory drugs in the gastrointestinal tract: an in-vitro release model. J Pharm Pharmacol. 2005;57(6):709–19
(3) https://badgut.org/information-centre/a-z-digestive-topics/pill-coating/
(4) https://www.ottokemi.com/polymers/e1672.aspx

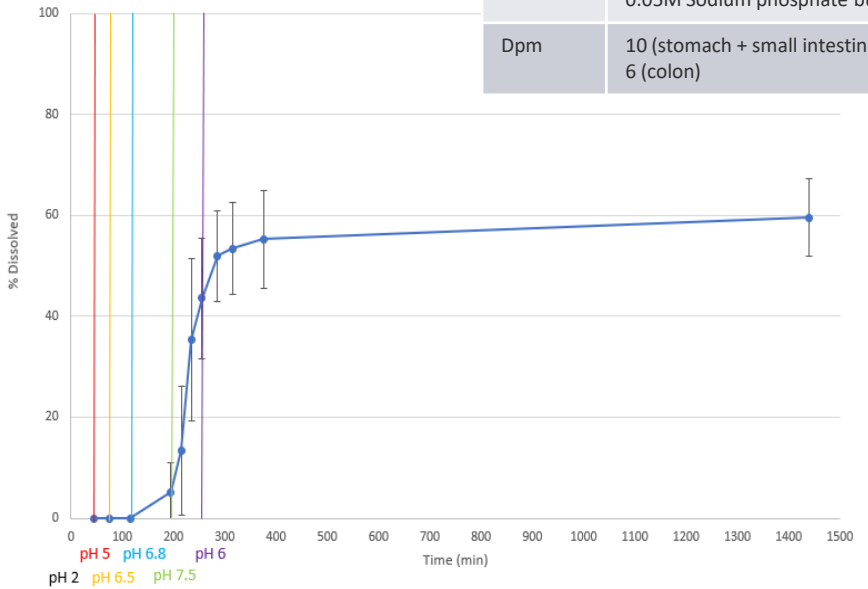
pH-screening: full pH range

	In vitro pH [1] [2]	*In vitro* residence time [1]
Stomach	2	45 min
Duodenum	5	30 min
Jejunum	6.5	40 min
	6.8	80 min
Ileum	7.5	60 min
Ascending colon	6	19 h 45 min



A 115 min; B 195 min; C 255 min; D 24 h

USP3 (n=3)	
pH	2 → 5 → 6.5 → 6.8 → 7.5 → 6
Medium	0.01M HCl 0.05M Sodium phosphate buffer
Dpm	10 (stomach + small intestine) 6 (colon)



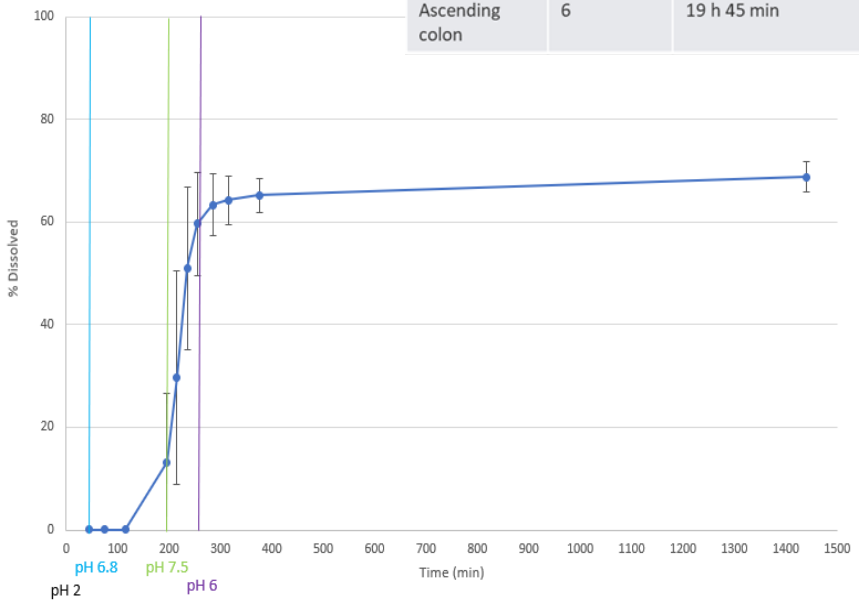
Stomach + duodenum: no release
Jejunum (pH 6.8): start release
Ileum (pH 7.5)+ transcending colon (pH 6): further release

Dpm= dips per minute

pH-screening: intermediate pH range

USP3 (n=3)	
pH	2 → 6.8 → 7.5 → 6
Medium	0.01M HCl 0.05M Sodium phosphate buffer
Dpm	10 (stomach + small intestine) 6 (colon)

	In vitro pH [1] [2]	*In vitro* residence time [1]
Stomach	2	45 min
Duodenum	5	30 min
Jejunum	6.5	40 min
	6.8	80 min
Ileum	7.5	60 min
Ascending colon	6	19 h 45 min



Stomach + duodenum: no release
Jejunum (pH 6.8): start release
Ileum (pH 7.5)+ transcending colon (pH 6): further release

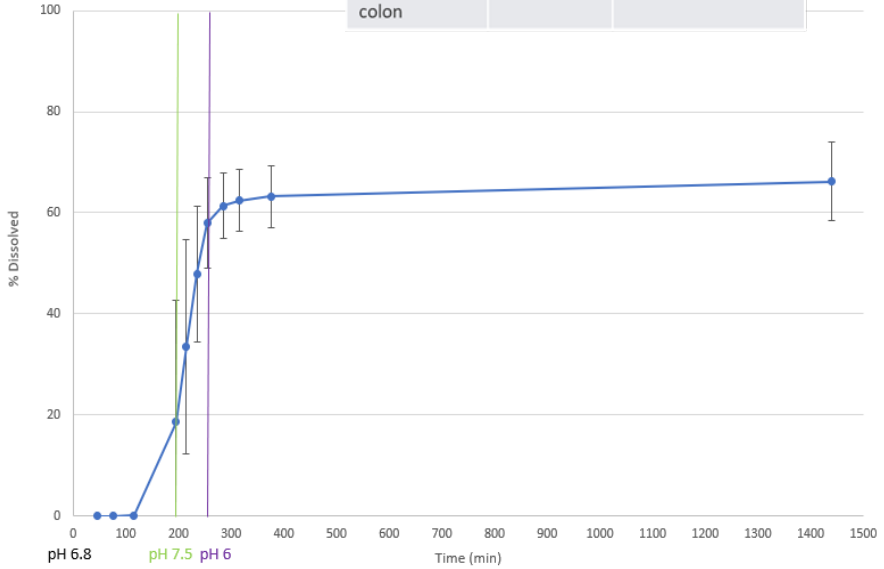
Conclusion
No difference in onset release (195 min)

Dpm= dips per minute

pH-screening: short pH range

USP3 (n=3)	
pH	6.8 → 7.5 → 6
Medium	0.05M Sodium phosphate buffer
Dpm	10 (small intestine) 6 (colon)

	In vitro pH (1) (2)	*In vitro* residence time (1)
~~Stomach~~	~~2~~	~~45 min~~
~~Duodenum~~	~~5~~	~~30 min~~
Jejunum	~~6.5~~	~~40 min~~
	6.8	80 min
Ileum	7.5	60 min
Ascending colon	6	19 h 45 min



Stomach + duodenum: no release
Jejunum (pH 6.8): start release
Ileum (pH 7.5)+ transcending colon (pH 6): further release

Conclusions

No difference in onset release (195 min)
Gastric phase
pH 5 and 6.5
→ No influence

➔ Short pH range as pH-screening tool

Dpm= dips per minute

Conclusion

- USP 3 Screening tool for pH-sensitive coatings

  Behavior of formulations in pH range

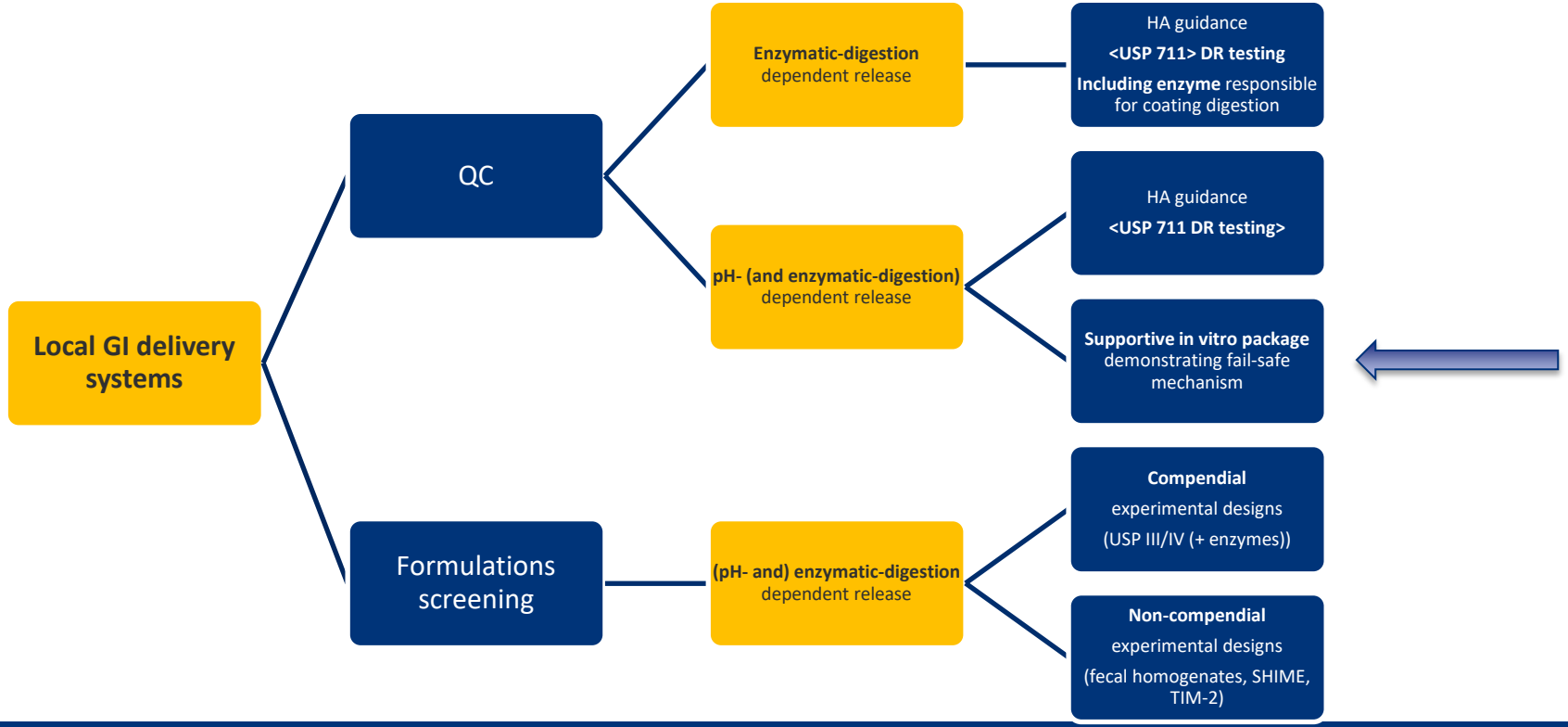
  Onset + further release

  Challenge: variability ↓

- Evaluate the impact of different buffers on specific commonly used polymers
- Use of biorelevant media in order to be more predictive

Ph/Enzymatic-digestion dependent release in colon

QC- and formulation concept screening-strategy



Enzymatic-digestion based release in colon

Developing the dissolution toolbox

Drug product for testing

Yaldigo® 1600 mg (mesalamine, Tillots Pharma)

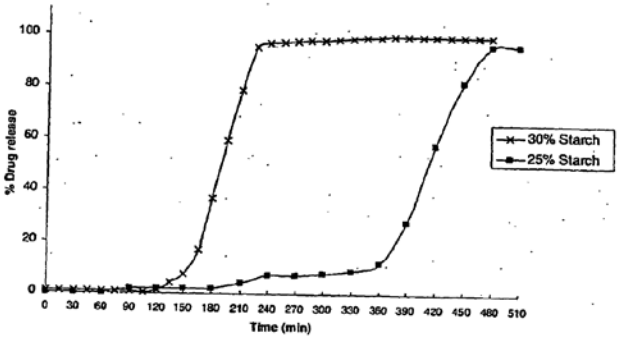
- First commercialized DP with PHLORAL® technology
- Combination of Amylo-Maize starch N-400 and Eudragit S 100
- Solubility: 0.8 – 1 mg/mL (water)

Starting point for development of QC dissolution method

EP 2 018 159 B1 – Colonic drug delivery formulation (Proprietor: UCL, Prof. A. Basit)

[0094] The tablets were dissolution tested in pH 6.8 buffer containing 50 U (units)/ml α-amylase derived from *B. licheniformis* (see Figure 7). A dissolution test was also carried out in pH 6.8 media with pancreatin to test whether the starch is digestible by pancreatic α-amylase (see Figure 6).

[0095] Results of the dissolution tests in the presence of the enzymes show that the starch component of the film is indigestible in the presence of the pancreatin (suggesting resistance in the small intestine), but drug release occurred within three hours in the presence of α-amylase from *B. licheniformis*. These results provide evidence that the mixed film resists drug release in simulated conditions of the upper gastrointestinal tract but is digestible in the presence of bacterial enzymes (even at a pH lower than the threshold pH of the Eudragit® S polymer for dissolution).

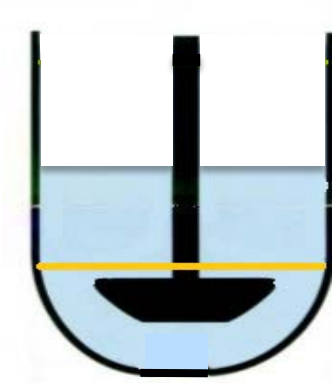


https://pubchem.ncbi.nlm.nih.gov/compound/Mesalamine#section=Solubility

Enzymatic-digestion based release in colon

Developing the dissolution toolbox

USP II apparatus (paddle), mini-vessel scale



100 mL **0.05M NaP buffer pH 6.8**
(with or without enzymes)
24h

Advantages:

+ Availability USP II apparatus across different sites
+ Ease of use
+ Limited complexity experimental setup

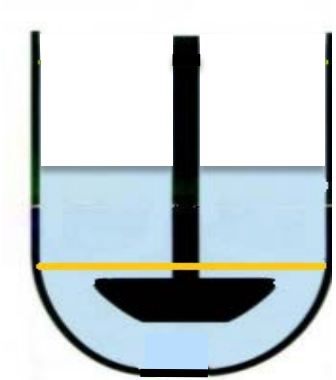
Disadvantages:

– Biorelevant GI factors least captured
  – Formulation concept screening?

Enzymatic-digestion based release in colon

Developing the dissolution toolbox

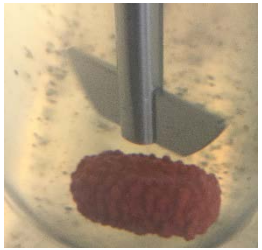
USP II apparatus (paddle), mini-vessel scale*



100 mL **0.05M NaP buffer pH 6.8**
(with or without enzymes)
24h

@ 0.1 mg/mL α-amylase(≈ 80 U/mL)

- 'Bulging' – behavior after 3h in medium
  - Bulges popping open, exposing core tablet
- Core tablet remained intact
- No impact of use of activators (e.g., $MgSO_4$, $CaCl_2$)

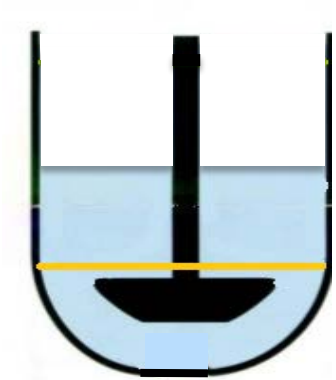


*__Note:__ Setup development currently at mini-vessel scale to limit amount of enzyme needed

Enzymatic-digestion based release in colon

Developing the dissolution toolbox

USP II apparatus (paddle), mini-vessel scale*



100 mL **0.05M NaP buffer pH 6.8**
(with or without enzymes)
24h

@ 1 mg/mL α-amylase(≈ 800 U/mL)

- 'Bulging' – behavior after 2h in medium
  - Bulges popping open, exposing core tablet
- Highly variable behaviour
- No impact of use of activators (e.g., $MgSO_4$, $CaCl_2$)

2h

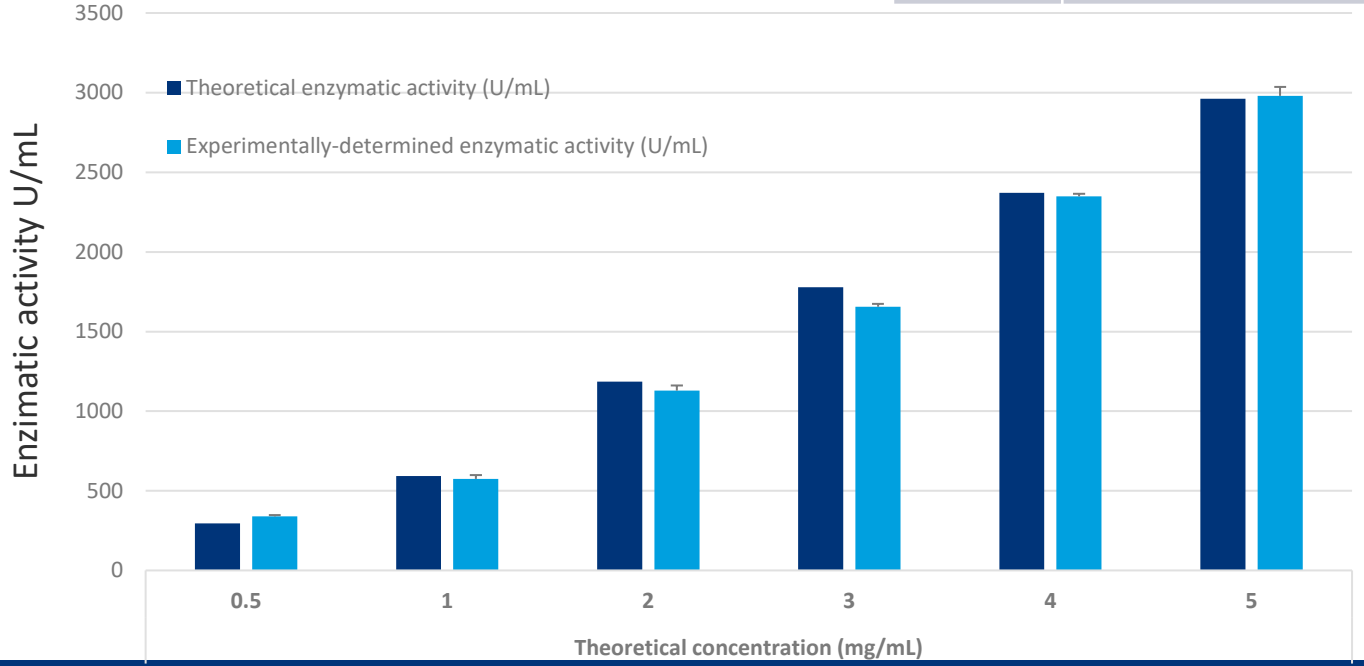
4h

Enzymatic activity ifo concentration

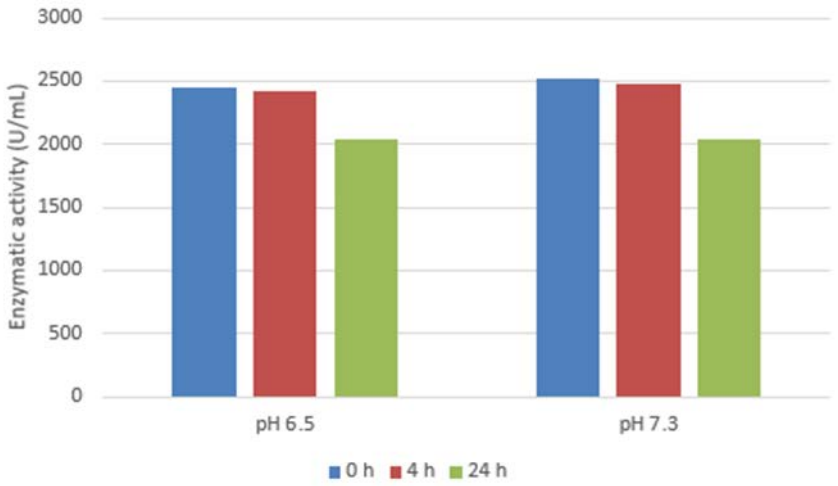
Spectrophotometric analysis	
Medium	0.05M Sodium phosphate buffer pH 6.8
Absorbance	540 nm
Light path	1 cm

α-amylase from *Bacillus licheniformis*

1-3% difference between theoretical enzymatic activity (2500 U/mL) and enzymatic activity at T0



Enzymatic activity ifo time (24h)



Spectrophotometric analysis	
Medium	0.05M Sodium phosphate buffer pH 6.5 0.05M Sodium phosphate buffer pH 7.5
Absorbance	540 nm
Light path	1 cm

- ± 20% drop in enzymatic activity T0-T24h

Enzymatic-digestion based release in colon

Developing the dissolution toolbox

100 mL **0.05M NaP buffer**
pH 6.8
(with or without enzymes)
24h

USP II apparatus (paddle), mini-vessel scale

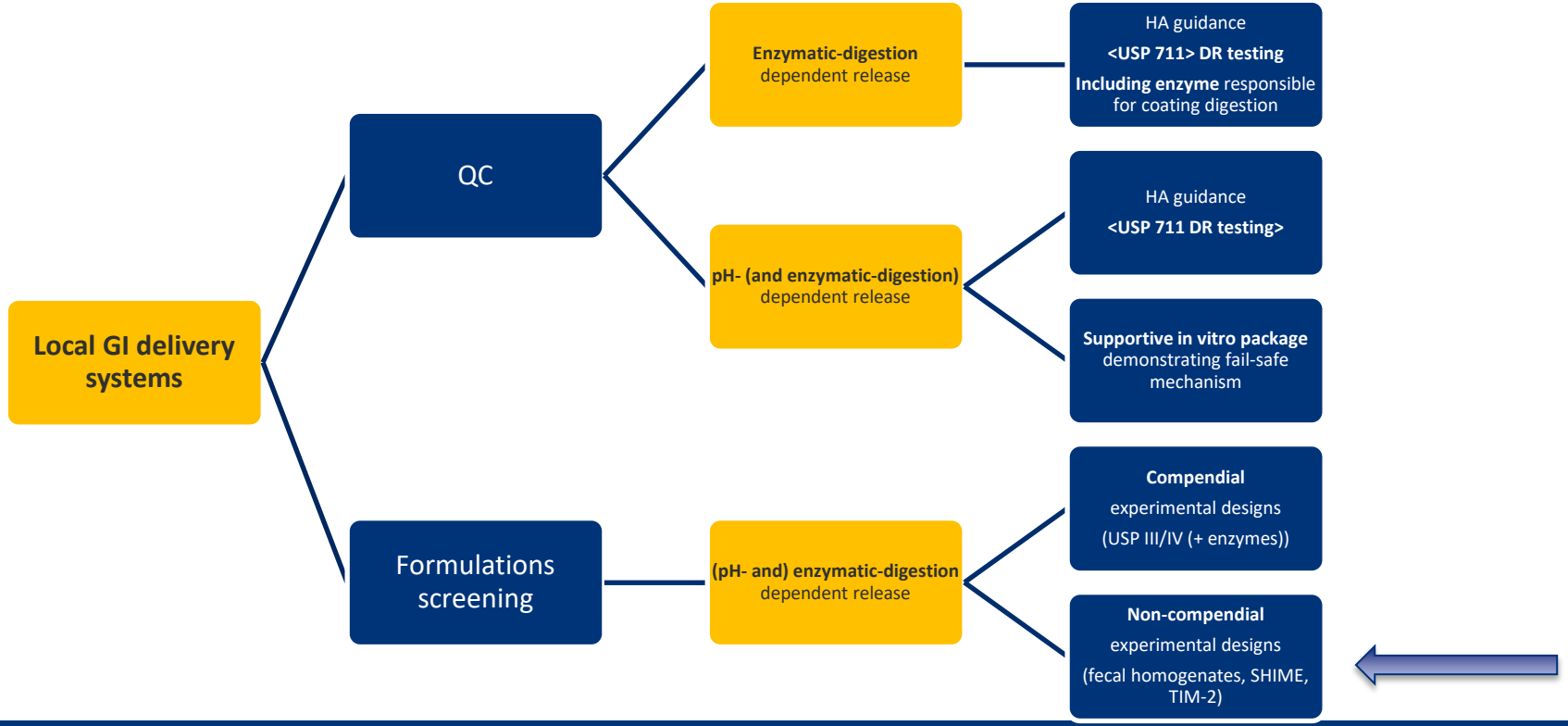
Open questions:

- **Inability of current setups to fully digest coating**
  - Discrepancy enzyme concentration patent vs. in-house experience
  - Impact of (lack of) hydrodynamics
    - USP II mini-vessel vs. standard volumes (i.e., experimental scaling)
    - USP II vs. USP III

- **'Bulging' behavior** → medium ingression through coating?

Ph/Enzymatic-digestion dependent release in colon

QC- and formulation concept screening-strategy



Enzymatic-digestion based release in colon

Developing the dissolution toolbox

Non-compendial experimental designs – **fecal homogenates setup**

Sequential simulation of DP passage through upper and lower small intestine

- Gastric stage
- Small Intestinal stage
- Colonic stage (8.3% [w/v] fecal homogenate in buffer)

DP held in a sinker, manually transferred to next stage at predefined times

Nitrogen-sparging to ensure anaerobic conditions

Enzymatic-digestion based release in colon

Developing the dissolution toolbox

Non-compendial experimental designs **– Incubation systems (e.g., SHIME®)**

During colonic stage, DP comes into contact with gut microbiota

Testing in specific target populations possible

Setup customization possible based on DP properties, specific research question

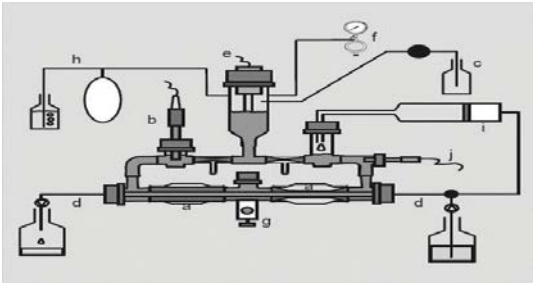
Enzymatic-digestion based release in colon

Developing the dissolution toolbox

Non-compendial experimental designs

Fecal homogenates

SHIME® (Prodigest)



TIM-2® (Triskelion)

Advantages:

+ Close(r) approximations of in vivo GI conditions
+ Possibility to test conditions for a specific population

Disadvantages:

– ‘QC-ability’
– ‘Transferability’ (e.g., need for specialized lab environment)

Key messages

Colon-targeting formulation platforms require specific dissolution strategies for both QC method development and formulation concept screening

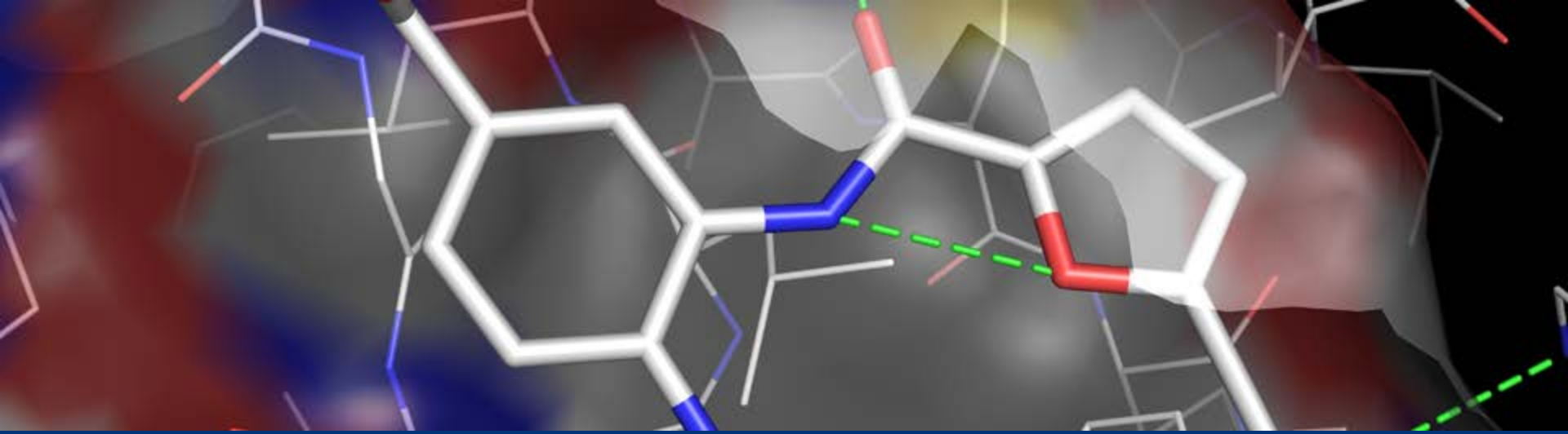
- Uncharted territory → trial-and-error
- Regulatory acceptance regarding QC dissolution strategy currently unclear

Knowledge gap regarding added value of more complex, non-compendial systems

- Trade-off biorelevance vs. ease-of-use
- Need for ‘real-life’ examples / case studies

Aknowledgement

- Dissolution Science Team:
  - Fien Janssen
- AD department:
  - Koen Schrijnemakers
- KULEUVEN



Thank you

Art credit: *Close-up of the inhibitor binding site of the colony-stimulating factor-1 receptor kinase domain.*

The COLOTAN 1st Symposium: Colon targeting of drugs: current state of the art
June18th, 2021

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson