Mechanistic assessment of excipient changes for BCS Class 1 and 3 drug products

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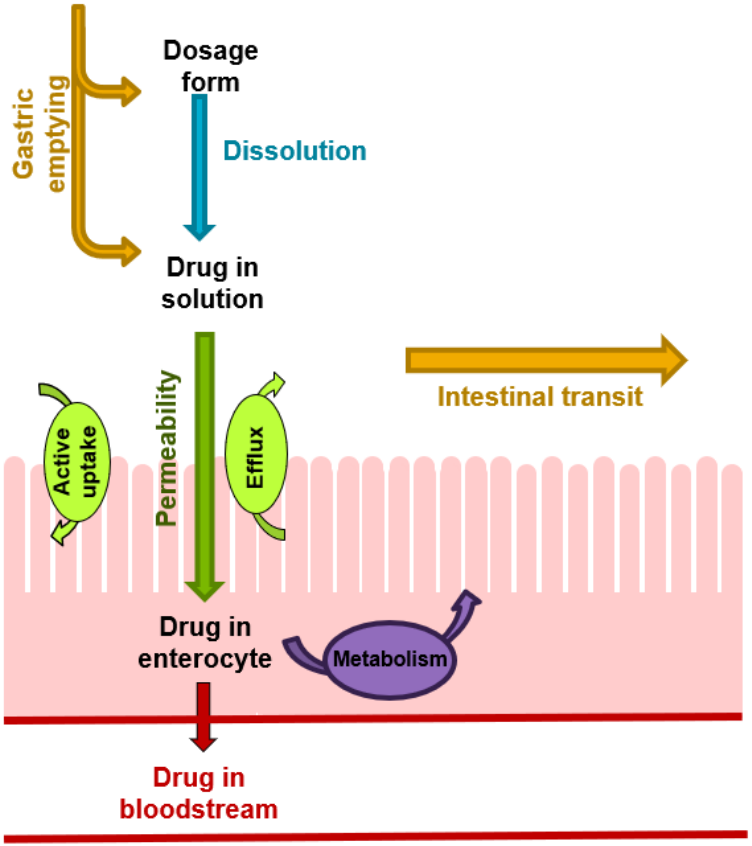
Outline

- Mechanisms by which excipients can affect drug absorption
- Excipient changes and biowaivers: ICH M9
- How can we mechanistically assess the potential impact of excipient changes?
- Conclusions

Mechanisms by which excipients can affect drug absorption

Through what mechanisms can excipients impact drug absorption?



Release rate/amount of drug in solution
- Altered disintegration time
- Altered dissolution rate
- Altered local pH
- Complexation (excipient-drug complexes)

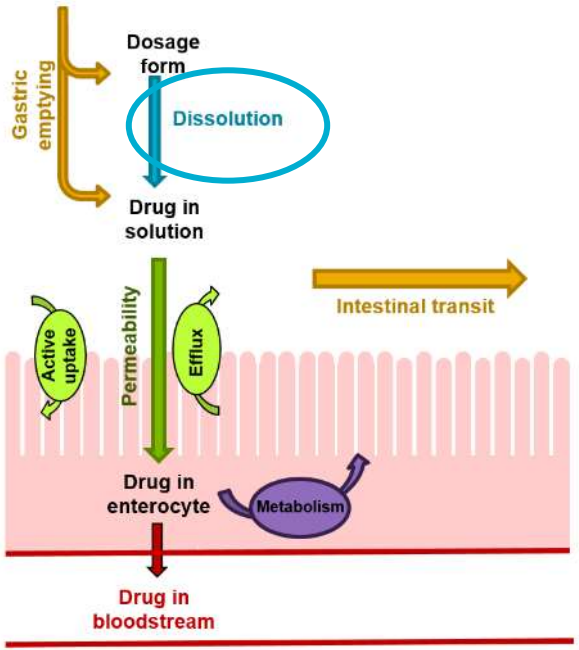
Transit and luminal volumes
- Faster gastric emptying
- Increased luminal volume (osmotic effect)
- Altered small intestinal transit time

Altered effective permeability
- Damage to intestinal surface/ tight junction modulation
- Inhibition of efflux
- Inhibition or enhancement of active uptake

Altered metabolism
- Inhibition of gut wall metabolism

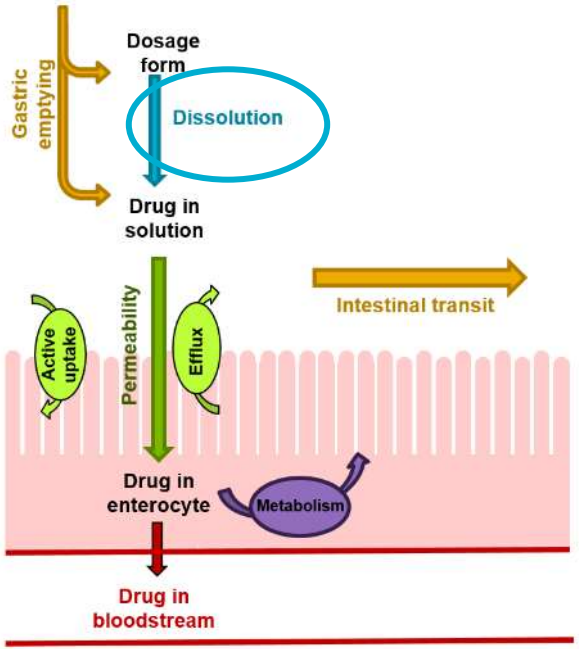
Flanagan, 2019

Release rate/amount of drug in solution



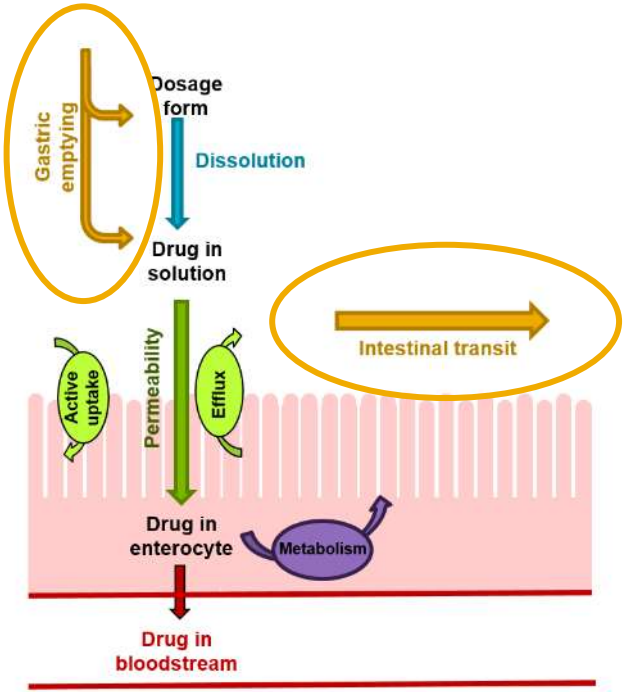
- Excipients can potentially alter drug release rate, or the total amount of drug that can dissolve in the intestine, through:
  - Altered disintegration time
  - Altered dissolution rate
  - Altered local pH for dissolution
  - Complexation (excipient-drug complexes)
- Generally, have a relatively high degree of confidence that these effects are detectable using *in vitro* dissolution testing, provided that the testing conditions have some biorelevance.

Release rate/amount of drug in solution



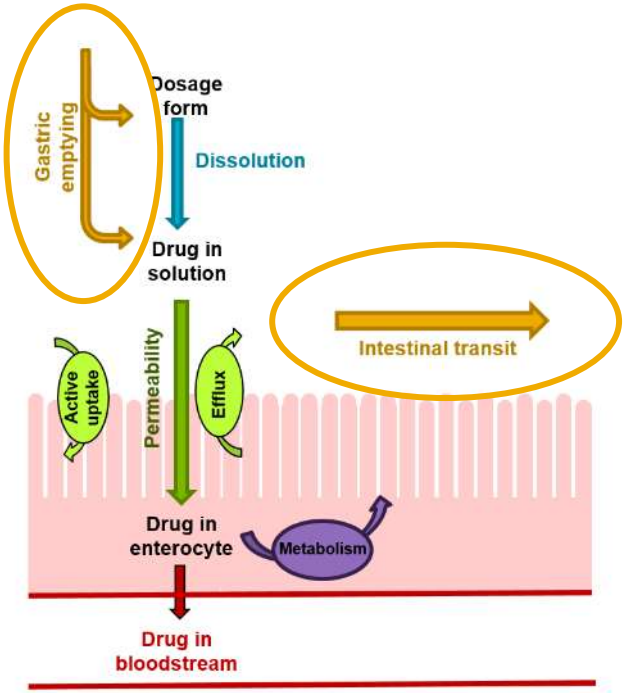
- Examples from the literature include:
  - Formulations containing HPMC (90mg) or magnesium stearate 80mg (with significant mixing) showed somewhat reduced absorption ~10-15% based on point estimates), attributed to slower dissolution (detected in simple aqueous buffers *in vitro*) (Vaithianathan *et al*.) (human)
  - SLS interacted with intestinal micelles reducing solubility of fenofibrate in FaSSIF media; corresponded to reduced C_{max} *in vivo*, but had no impact on AUC (human) (Buch *et al*.)
  - Complex formation, e.g. PEG 4000 formed insoluble complexes with phenobarbital (*ex vivo*), Tween 80 and sodium lauryl sulphate with chlorpromazine salts (*in vitro*) (Sjogren *et al*.), cyclodextrin complexation with itraconazole reduces free fraction available for permeation (Berben *et al.*) (human)
- Should have good detectability with *in vitro* biopharmaceutics tools, provided that these mimic the environment for *in vivo* dissolution (and in particular, the aspects of this which are important for the compound being assessed).

Transit and luminal volumes



- Excipients can potentially alter drug absorption through:
  - Altered gastric emptying
  - Increased luminal volume (osmotic effect)
  - Altered small intestinal transit time
- This would not be detected using standard *in vitro* dissolution testing

Transit and luminal volumes

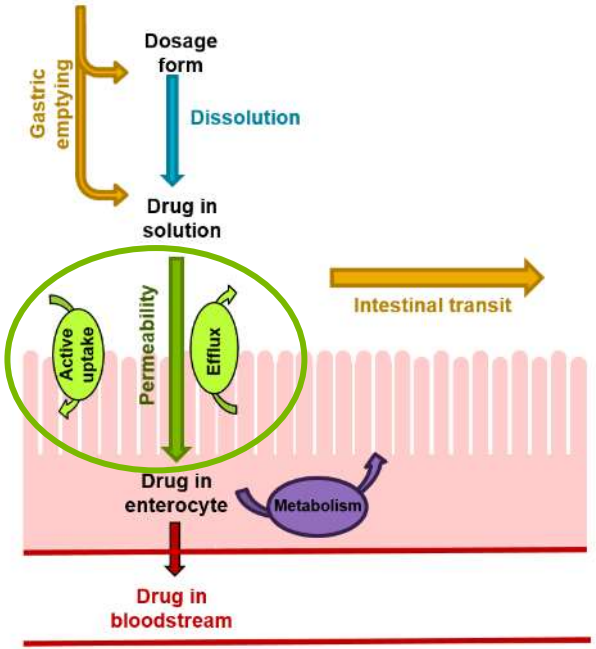


- Numerous literature examples with studies in humans:

Mechanism	Reported effect
Altered gastric emptying	Sodium bicarbonate reduced gastric emptying time of ibuprofen in man (Sjogren *et al*., Garcia-Arieta) Glucose increased gastric emptying time in man (Grimm *et al.*)
Altered small intestinal transit time	Reduced small intestinal transit time in human: • mannitol (0.755g +), • sodium acid pyrophosphate (~1.1g), • PEG 400 (2.5g+), • sorbitol (2.25g+), • xylitol (30g), • lactulose (10g+). (Sjogren *et al*., Adkin *et al*., Schulze *et al*., Koch *et al*., Ashiru *et al*., Salminen *et al*., Read *et al*., Chen *et al.)*
	Oleic acid (300 -1200 mg) increased small intestinal transit time in human (Sjogren *et al*., Dobson *et al*.).
Altered small intestinal fluid volume	Fructose increased small intestinal fluid volume in man (Grimm et al.)
No effect on transit time	Sucrose (4.08g) had no effect on intestinal transit in human (Adkin et al.)

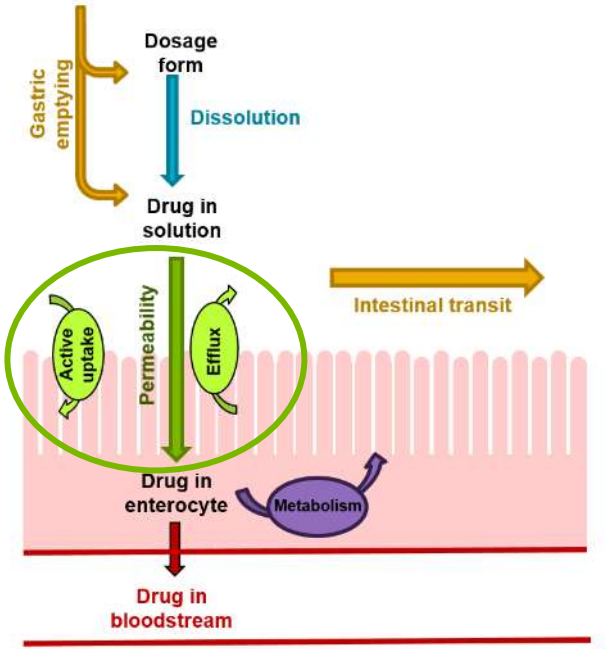
- Mannitol, PEG and sorbitol effects are dose-dependant.

Altered effective permeability



- Excipients have the potential to alter the rate and extent of permeation by:
  - Damage to the intestinal surface/ tight junction modulation
  - Inhibition of efflux transporters
  - Inhibition or enhancement of active uptake transporters
- This would not be detected using standard *in vitro* dissolution testing

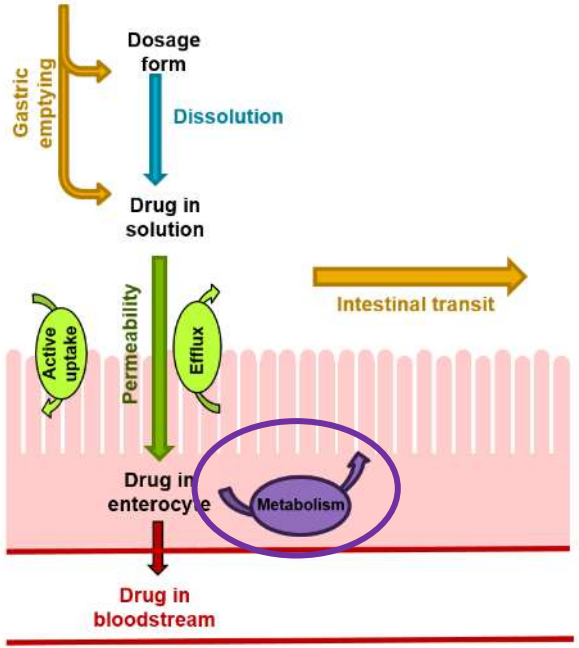
Altered effective permeability



- Selected literature examples:

Mechanism	Reported effect
Damage to intestinal surface/ tight junction modulation	SLS increased permeability of mannitol and other drugs in Caco-2, attributed to opening of tight junctions/loss of membrane integrity (Rege *et al.*, Parr *et al.*).
Enhancement of active absorption process	Eudragit L100-55 (500mg/kg) increased bioavailability of cefixime in rats by ~2x, and increased permeation of cefadroxil and cefixime in an *in situ* ileal closed loop model at concentrations of 10% and above - attributed to enhanced PePT1 activity. (Nozawa *et al.*)
Inhibition of efflux	Numerous reports of increased transport/uptake in *in vitro* systems, attributed to inhibition of active efflux by P-Gp and other transporters (e.g. Tweens, Cremophors, Labrasol, Pluronics, Sodium lauryl sulphate, TPGS, PEG, sodium docusate, etc.) (Sjogren *et al.*, Zhang *et al.*, Rege *et al.*).
	PEG 400 (0.5 – 1.5 g) increased bioavailability of ranitidine in healthy male volunteers in a dose-dependant manner, attributed to increased permeability. This was not observed in female volunteers in the same study. PEG 300/400 significantly reduced ranitidine efflux ratio *in vitro* (Ashiru *et al.*, Ashiru-Oredope *et al.*).
No effect on permeability	HPMC, D-lactose, povidone, PEG 400, propylene glycol, anhydrous cherry flavouring, and EDTA had no effect on permeability across Caco-2 monolayers (Rege *et al.*, Parr *et al.*).

Altered metabolism



- Inhibition of gut wall metabolism by an excipient could potentially lead to increased bioavailability
- This would not be detected using standard *in vitro* dissolution testing.
- Literature reports:
  - Excipients reported to inhibit CYP activity *in vitro/ex vivo* include PEG, Tween, Cremophor, Triton X, Pluronics, sodium lauryl sulphate, Solutol, lecithin, beta cyclodextrin and ascorbic acid (Sjogren *et al*., Zhang *et al.*).
  - Ren *et al.* reported that four non-ionic surfactants inhibited midazolam metabolism by CYP3A *in vitro*, however effects after single or multiple dosing in rats were complex to interpret.

Conclusions from literature review

- Excipients can potentially impact drug absorption through a variety of mechanisms.
- There are numerous reports and review articles in the scientific literature that describe such effects, either *in vitro* or *in vivo.*

- However;
  - These span a **wide range of API properties, formulation types, and excipient quantities**
  - Many of the excipients with reported effects on absorption **would not normally be used in immediate release solid oral dosage forms**
  - The **amounts** of excipients shown to impact absorption in some studies are **much higher than would normally be used** in standard formulations.

Excipient changes and biowaivers: ICH M9

Excipient changes for BCS biowaivers - approach taken by the ICH M9 EWG

- Extensive literature search conducted to support EWG discussions:
  - Identified mechanisms by which excipients could impact drug absorption
  - Divided the literature examples into these mechanistic categories
  - Assessed whether these mechanisms are likely to be relevant for BCS1 or 3 drugs
  - Also considered whether the excipients themselves are relevant to solid oral immediate release formulations

- Data on excipient levels in bioequivalent BCS 3 drug products from Japan (JPMA) and Canada (Health Canada) collated and assessed.

ICH M9 - Assessment of excipient levels in bioequivalent BCS Class 3 products

- **A total of 26 APIs were assessed (9 are common to both Japan and Canada datasets), usually several generic formulations for each**
  - PK and absorption properties of the APIs were also taken into account, to understand the risk from a mechanistic perspective
  - Many examples of changes >SUPAC Level 2
  - Some examples of qualitative changes, including for potential critical excipients (e.g. mannitol);
  - Some examples of dissolution which does not meet the VRD criteria, but the formulations still pass BE.

- **Overall, the EWG were cautious at this time about generalising this across all BCS3 compounds, as we know there are some cases where this will have an impact;**
  - but what we have seen so far suggests that, with the BCS controls at other parts of the 'system', this **may be less of a risk for some BCS3 compounds and excipients**.

ICH M9 – excipient changes

- The guideline states that any excipient changes should be **mechanistically assessed** for their potential to affect drug absorption.
- For **BCS Class 1**, changes in composition are permitted, except for excipients that can impact absorption (qualitatively similar, and within ± 10% of the amount in the reference product).
- For **BCS Class 3**, all excipients should be qualitatively and quantitatively similar between the test and reference products. Additionally, excipients which may affect absorption should be qualitatively similar, and within ± 10% of the amount of excipient in the reference product.
- Tables and flow charts are provided in the guideline which outline the specific requirements.
- The current excipient limits in the ICH M9 guideline are somewhat conservative compared to what some territories are already accepting, and represent a stretch for other territories - however there is a hope that through further analysis and publication of data it **may be possible to widen these further in the future.**
- The current version of the guideline **allows for wider excipient changes to be made, if suitable justification is provided**.

How can we mechanistically assess the potential impact of excipient changes?

Mechanistic assessment of excipient changes

- The criteria for assessing excipient differences in the regulatory guidelines are universally applied to all drug substances, manufacturing processes, formulation types etc.
- These criteria are therefore set on a conservative ‘worst-case’ basis
- This means that **some formulation changes that would be bioequivalent *in vivo,* will be rejected** by these criteria.
- Applying a **mechanistic and risk-based approach** enables the risk associated with a particular excipient change to be assessed on a product-specific basis.

Mechanistic assessment of excipient changes

- The risk of the excipient change affecting absorption can be assessed based on:
  - The **mechanism** by which the excipient is known (or suspected) to impact drug absorption;
  - The **amount and function of the excipient** in the test and reference formulations, vs. the amount at which an effect on absorption has been observed;
  - The **absorption site, absorption rate and absorption mechanism** of the drug substance.

- Data generated during product development can provide evidence to support the assessment of excipient changes.
- Use of modern biopharmaceutics tools such as *in silico* PBBM absorption modelling can facilitate quantitative assessment of the impact, including patient variability.

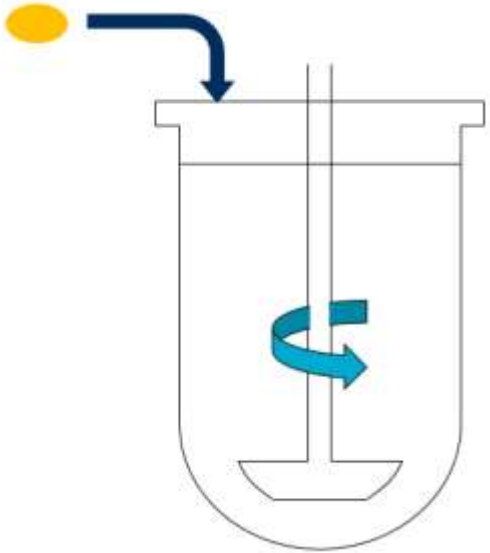
ICH M9 Q&A: role of PBPK modelling in assessing excipient changes

3.1 Excipients

#	Date of Approval	Questions	Answers
3.1.1	Nov. 2019	*In silico* PBPK absorption modelling is widely used in industry to assess the risk of changes in formulation performance. Can a robust risk assessment be used to assess the potential impact (inclusion/ exclusion) of an excipient change beyond the recommended ranges?	Although it is recognized that *in silico* PBPK absorption modelling is used to assess the risk in product performance due to formulation changes, currently such models cannot comprehensively predict all potential differences in absorption due to critical excipients. Validation of *in silico* models for such purposes is further limited by a lack of mechanistic understanding for some observed excipient effects, including a lack of high quality *in vivo* data for some excipient classes. Therefore, a risk assessment based on model predicted effects would not support a change in excipient beyond the recommended range. However, in some circumstances *in silico* PBPK modelling may provide useful supporting evidence as part of a wider excipient risk assessment, for example sensitivity analysis using an appropriately validated PBPK absorption model for excipients where the mechanism of effect is well understood.

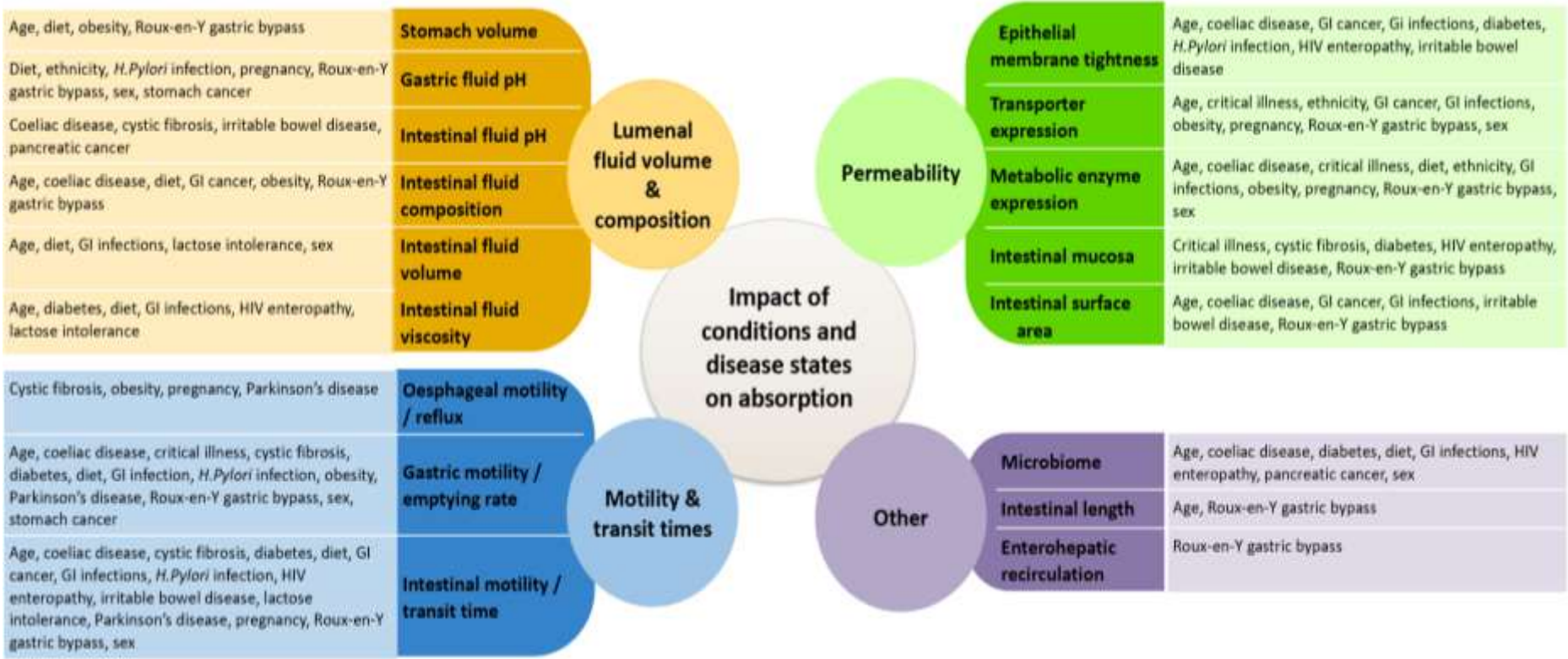
A note on our current model of choice….

- To be able to interpret what a particular experiment is telling you about formulation performance, you need to understand the conditions of the test…



RPM: ?
Temperature: ?
Volume: ?
Media: ?
pH: ?

Altered GI Tract physiology in disease states and special populations



Based on Stillhart et al. 2020.

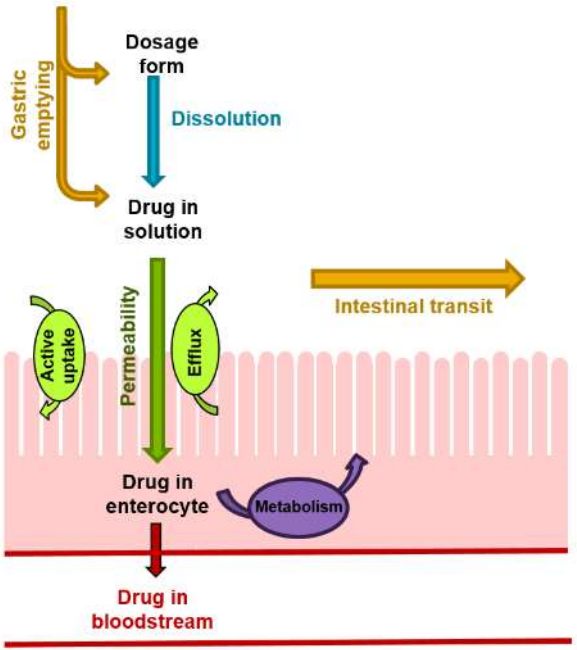
What models can we use to mechanistically understand excipient effects?

	In vitro / preclinical*	*In silico* PBBM
Release rate/amount of drug in solution • Altered disintegration time • Altered dissolution rate • Altered local pH • Complexation (excipient-drug complexes)	Biorelevant *in vitro* dissolution (consider media, volumes, agitation etc.). Combined dissolution/ permeation studies (living or synthetic membranes).	Sensitivity analysis for different dissolution input rates.
Transit and luminal volumes • Faster gastric emptying • Increased luminal volume (osmotic effect) • Altered small intestinal transit time	Difficult to simulate *in vitro* but lots of *in vivo* (human!) data available.	Sensitivity analysis for different intestinal transit times and regions of absorption.
Altered effective permeability • Damage to intestinal surface/ tight junction modulation • Inhibition of efflux • Inhibition or enhancement of active uptake	*In vitro* permeation studies in cell lines or tissues. *In situ* gut loop in preclinical species etc.	Mechanistic simulation of the impact of transporter inhibition on absorption. Sensitivity analysis for increased passive permeability.
Altered metabolism • Inhibition of gut wall metabolism	*In vitro* metabolism studies in cell lines or tissues. *In situ* gut loop in preclinical species etc.	Mechanistic simulation of the impact of enzyme inhibition on absorption.
		Holistic assessment of the potential impact of different mechanisms, including risk assessment for altered GI physiology in patients.

**Some of these data already exist in the literature for common excipients*

Conclusions

Conclusions



- Excipients can potentially impact drug absorption through a variety of mechanisms
- The scientific literature contains many examples of this, however these span a wide range of API properties, formulation types and excipient amounts.
- Applying a mechanistic approach enables the risk of a given excipient change affecting absorption to be assessed based on the properties of the compound and formulation.
- Use of modern biopharmaceutics tools such as *in silico* PBPK absorption modelling can facilitate quantitative assessment of the impact, including patient variability.

Understanding excipient effects in the context of biowaivers – how could we move forward?

- Moving forward in this area requires collaboration between regulators, industry (innovator and generic) and academia, to:
  - Holistically interrogate existing clinical RelBA/BE data comparing drug products with excipient changes – including failed BE studies
  - Assess whether the existing *in vitro* and *in silico* tools would have enabled the risk to be correctly assessed, and whether the same decision would have been made

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Questions?

Thanks!

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