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Review article

Potential for pharmaceutical excipients to impact absorption: A mechanistic review for BCS Class 1 and 3 drugs

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ABSTRACT

The potential for certain excipients to impact drug absorption is the subject of numerous publications. Reflecting this, current Biopharmaceutics Classification System (BCS) guidelines place restrictions on the level of change in excipients to be eligible for a BCS biowaiver. The degree of change permitted between test and reference formulations varies between BCS Class 1 and 3, and also across different regulatory authorities. This article reviews the literature evidence for excipients to impact drug absorption, with a particular focus on identifying effects which may be important for BCS Class 1 and 3 compounds and formulations. Literature examples were categorised according to the mechanism by which the excipient was believed to impact drug absorption, and the relevance of these mechanisms for compounds within BCS Class 1 and 3 was assessed. The likelihood of using the excipient in solid oral immediate release formulations (i.e. formulation types which would be eligible for BCS biowaivers) was also considered. Using this mechanistic and risk-based approach, potential critical excipients for BCS Class 1 and 3 compounds were identified. Based on the literature data, there are only a limited number of mechanisms by which excipients could affect the absorption of a BCS Class 3 drug. For BCS1, absorption is very unlikely to be affected by excipient changes. For many of these excipients, there is no *in vivo* evidence of such an effect having occurred. The risk can be mitigated to a large extent by applying some compound-specific understanding of the absorption site, rate and mechanism of the particular API under consideration.

1. Introduction

The Biopharmaceutics Classification System (BCS) is applied by several Regulatory Authorities worldwide, including US FDA [1], EMA [2] and Health Canada [3], and is currently the subject of an ICH draft guideline [4]. The BCS classifies drug substances according to solubility across the physiological pH range and permeability, to identify compounds which are low risk from a drug absorption perspective. For BCS Class 1 (high solubility, high permeability) and BCS Class 3 (high solubility, low permeability) compounds, a biowaiver can be granted in lieu of performing a clinical bioequivalence study, provided that additional criteria on formulation dissolution and compositional changes are fulfilled. This includes restrictions on the level of permitted excipient change between the test and reference formulations.

The various global BCS guidelines all have slightly different restrictions regarding permitted excipient changes, these are summarised in Fig. 1. In general, larger excipient changes are permitted for Class 1 drug products, including use of different excipients between the test and reference formulations. For BCS3 drug products, the guidance is more restrictive, reflecting a concern that their low permeability may make them more susceptible to excipient effects [1]. For BCS3 biowaivers, excipients must be qualitatively the same, and quantitatively very similar. For both BCS classes, additional restrictions are placed on excipients which may impact bioavailability (sometimes called 'critical excipients').

There is a large body of published literature regarding excipient effects on bioavailability, including several review articles (e.g. Sjogren et al. [5], Zhang et al. [6]). These span a wide range of API properties, formulation types, and excipient quantities. However, in the framework of the BCS, biowaivers are restricted to APIs with high solubility across the physiological pH range, formulated in standard immediate release dosage forms (i.e. tablets or capsules), which is a relatively low-risk area of the biopharmaceutics space. Some of the excipient effects reported in the literature will therefore not be relevant for BCS-based biowaivers; for example, the mechanism by which absorption is affected may not be applicable to BCS Class 1 or 3 compounds, or the excipient may not be relevant for a standard immediate release formulation.

In this manuscript, the literature evidence for excipients to impact drug absorption is reviewed in the context of the BCS biowaiver

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BCS1

FDA: quantity consistent with intended function, excessive quantities of certain excipients, e.g. surfactants, sweeteners may be problematic.

EMA: excipients that might affect BA qualitatively and quantitatively the same; use of the same excipients in similar amounts is preferred.

Canada: some differences in formulation permitted; critical excipients within 10% of amount in reference product.

BCS3

FDA: excipients qualitatively the same, quantitatively very similar.

EMA: excipients that might affect BA qualitatively and quantitatively the same; other excipients qualitatively the same and quantitatively very similar.

Canada: qualitatively the same and quantitatively very similar; critical excipients within 10% of amount in reference product

Fig. 1. High level snapshot of permitted excipient differences for BCS biowaivers.

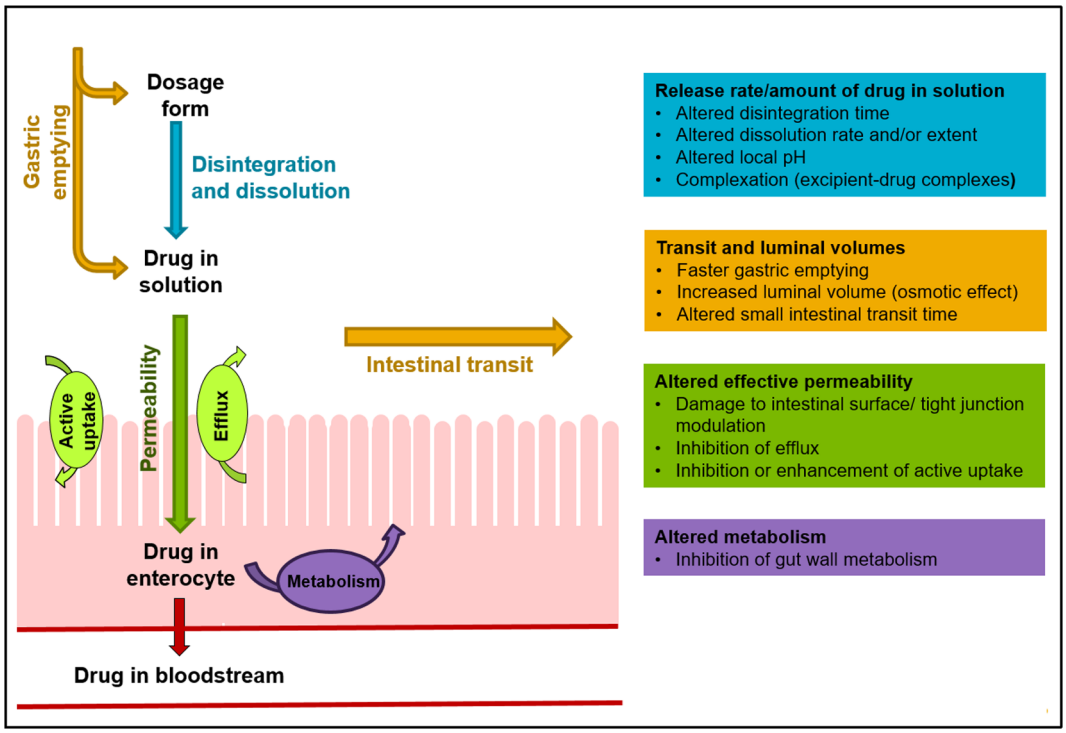

Fig. 2. Simplified schematic showing mechanisms by which excipients may impact drug absorption.

framework, to identify effects which may be important for BCS Class 1 and 3 compounds and formulations. Literature examples were categorised according to the mechanism by which the excipient was believed to impact drug absorption, and the relevance of these mechanisms for compounds within BCS Class 1 and 3 was assessed. The likelihood of using the excipient in solid oral immediate release formulations (i.e. formulation types which would be eligible for BCS biowaivers) was also considered. Using this mechanistic and risk-based approach, excipients which should be considered when making biowaiver decisions for BCS Class 1 and 3 compounds were identified. The mechanisms by which excipients may impact drug absorption are illustrated in Fig. 2, and discussed in detail in subsequent sections of this manuscript. Additionally, several literature reports attributed changes in absorption to a particular excipient, but did not provide a mechanistic hypothesis for how this effect may have been mediated; these reports were captured under a general 'mechanism unclear or unknown' category.

2. Release rate/amount of drug in solution

There are several mechanisms by which an excipient could potentially impact the release rate of drug from a dosage form, or the overall amount of drug which is able to dissolve in the stomach or intestinal lumen. These include: altered disintegration time of the dosage form, altered dissolution rate or extent from the dosage form, altered local pH in the GI tract, and formation of excipient-drug complexes.

Considering these mechanisms in the context of the BCS framework, it becomes apparent that the risk of these having an impact on bioequivalence outcomes for BCS 1 and 3 compounds is very low. BCS Class 1 and 3 compounds are by definition highly soluble across the physiological pH range. Furthermore, for a drug product to be considered BCS Class 1 or 3, it must have rapid (or very rapid) and complete dissolution across the physiological pH range at low agitation [1–3]. The risk of an excipient impacting *in vivo* dissolution for these products is therefore much lower than for BCS Class 2 and 4 products, which contain APIs with low and/or pH-dependant solubility. Additionally, the *in vitro* dissolution tests applied to BCS 1 and 3 products give a high degree of confidence that any relevant impact on product dissolution would be detected. One of the fundamental principles of the BCS is that this suite of *in vitro* tests are able to detect any *in vivo*-relevant change in dissolution (e.g. due to a change in manufacturing process type, API particle size etc.), as they encompass the range of pH conditions that can be found in the human GI tract that the dosage form may need to dissolve in (note however that the potential wetting and solubilising effects of bile salts in the small intestine are not evaluated by the BCS dissolution tests).

Considering the individual mechanisms:

- Altered disintegration time of the dosage form and/or altered dissolution rate of the drug from the dosage form should be detected by the BCS dissolution tests, which encompass the entire physiological pH range and use mild agitation conditions;
- Altered local pH in the GI tract should not impact dissolution of the API, as BCS 1 and 3 APIs are by definition highly soluble across the physiological pH range. Additionally, any significant effect of pH on dissolution of the dosage form is precluded by the BCS dissolution criteria, as described above.
- Formation of drug-excipient complexes which reduce the amount of drug dissolved should be detected as an alteration in the rate or extent of dissolution in at least one of the three dissolution media, depending on which pH the complex forms at.

For this category of excipient effect therefore, none of the mechanisms should be relevant for BCS Class 1 and 3 drug products, provided that the BCS formulation dissolution criteria are met.

Solubilising excipients that are employed to deliberately increase the solubility of a poorly soluble API are not discussed here, as these are not considered to be relevant formulation approach for highly soluble BCS Class 1 and 3 compounds (a summary of such effects can be found in Sjogren et al. [5]).

3. Gastrointestinal transit times and lumenal volumes

Mechanisms by which excipients could affect drug absorption in this category include altered gastric emptying, increased lumenal volume (through exertion of an osmotic effect), and altered small intestinal transit time. None of these mechanisms would be detected in the solubility, permeability or dissolution tests currently outlined in the BCS guidelines. Table 1 summarises reported excipient effects in this category. Studies which have demonstrated that a particular excipient does not impact transit are also included. Reports regarding formulations designed to specifically increase gastric residence time are not considered here, as these would not be eligible for a BCS biowaiver.

The relevance of the different mechanisms in this category for the absorption of BCS Class 1 and 3 drug products is considered below:

- Faster gastric emptying should not be relevant for BCS 1 or 3 drug products, as dissolution is rapid (or very rapid) across the physiological pH range. More rapid transit into the small intestine would therefore not be expected to result in significantly slower or incomplete dissolution. A potential effect on C_{max} and t_{max} cannot be excluded (i.e. due to gastric emptying time being more consistently at the lower end of the normal range between dosing occasions).
- Increased lumenal volume (through exertion of an osmotic effect) should not affect the dissolution of BCS Class 1 or 3 compounds, as the high solubility criterion is designed to ensure that these compounds can dissolve completely in normal GI volumes; a further increase in lumenal volume would not therefore be anticipated to further increase the amount of API in solution.
- Increased luminal volume could also reduce the concentration gradient for absorption. This may be of importance for BCS 3 compounds with concentration-dependant permeability (i.e. BCS3 drugs with significant active uptake or efflux). However, BCS 1 compounds should not be affected, as the *in vitro* permeability assessment outlined in the BCS guidelines ensures that BCS 1 compounds are highly permeable at lumenal concentrations 10-fold and 100-fold below the clinical dose.
- Faster small intestinal transit time could be relevant for:
  - o BCS 3 drug products, if the compound has a defined window of absorption in the upper small intestine.
  - o BCS 3 drug products, if the rate of permeation is so slow that the reduced residence time in the small intestine decreases the overall amount absorbed.
  - o BCS 1 and 3 drug products, which are subject to significant intestinal first pass metabolism by an enzyme with varying expression levels along the GI tract.

However for BCS 3 compounds that are relatively well absorbed and only narrowly miss the high permeability boundary, a reduction in small intestinal transit time may not be significant.

Table 1
Reported effects of excipients on gastrointestinal transit times and lumenal volumes, categorised by mechanism.

Mechanism	Reported effect	Potential relevance for BCS Class 1 and 3 drug products
Faster gastric emptying	Sodium bicarbonate reduced gastric emptying time of ibuprofen in man [5,7]	Should not be relevant for BCS 1 or 3 drug products, as dissolution is rapid across physiological pH range (ie. rapid transit into small intestine should not result in incomplete dissolution). However, a potential effect on C_{max}/t_{max} cannot be excluded
Delayed gastric emptying	Oleic acid (40 g) slowed gastric emptying in human [8]	Amount studied is far in excess of what would be used in a solid oral dosage form
Increased luminal volume (osmotic effect)	Sugar alcohols reduce intestinal transit time through osmotic effects; these are discussed in the 'altered small intestinal transit time' section	Should not be relevant for BCS 1 or 3 compounds from a dissolution perspective, as the high solubility criterion ensures that these compounds can dissolve completely in normal GI volumes, so a further increase in volume should not impact the extent of dissolution. Increased luminal volume could also reduce the concentration gradient for absorption – may be of importance for BCS 3 compounds with concentration dependant permeability, however should not impact BCS 1 as these are highly permeable at lumenal concentrations 10-fold and 100-fold below the clinical dose
Altered small intestinal transit time	Mannitol, sodium acid pyrophosphate, PEG 400, sorbitol, xylitol, lactulose, reduce small intestinal transit time in human (refer to Table 2 for detailed discussion of levels) [5,7–16]	Relevant for BCS3 as could potentially miss absorption window. For BCS1, high permeability should mean absorption is complete wherever in small intestine this takes place – nb. caveat around high permeability due to active transport, or lower regional permeability for 'borderline' BCS1 compounds. For BCS 1/3 compounds undergoing significant intestinal first pass metabolism by an enzyme with varying expression levels along the GI tract, bioavailability could potentially be affected if the main site of absorption in the intestine is altered
	Oleic acid (300–1200 mg) increased small intestinal transit time in human [5,17]	Potentially increased absorption for BCS 3 compounds. Mechanistically expect no impact for BCS1
No effect on transit time	Sucrose (4.08 g) had no effect on intestinal transit in human [10]	

Note: Reports of formulations designed to specifically increase gastric residence time are not considered here, as these would not be eligible for a BCS biowaiver.

For BCS 1 compounds, high permeability should mean that absorption is complete wherever in small intestine this takes place, so this mechanism is unlikely to be relevant. Tannergren et al. [18] demonstrated that for BCS Class 1 compounds, absorption from the colon usually remains high (F_{rel} > 70%) in the absence of bacterial degradation – however for borderline BCS 1 compounds, or for BCS Class 1 compounds with slow but complete absorption, an impact of regional permeability cannot be completely ruled out. A caveat also exists for BCS 1 compounds which have high permeability due to a site-specific active uptake transporter – for these compounds, faster small intestinal transit time could potentially result in reduced absorption. Excipients which can reduce small intestinal transit time would therefore be potentially critical excipients for BCS Class 1 and 3 compounds, depending on the rate and mechanism of permeation of the API across the gut wall.

- Slower small intestinal transit time could lead to increased extent of absorption for some BCS 3 compounds, due to increased residence time at the absorption site. Excipients which can increase small intestinal transit time would therefore be potentially critical excipients for BCS Class 3 compounds. For BCS Class 1 compounds, absorption is by definition complete, so no impact would be expected.

Excipients which can alter small intestinal transit time therefore have the potential to be critical excipients for some BCS3 compounds; theoretically this could also be relevant for a subset of BCS1 compounds as discussed. Several human clinical studies have characterised the effects of these excipients in detail, often including different doses of the excipient; further detail on these studies is provided in Table 2. Note that lactulose has been included in the table only for completeness, as this would not be used in an immediate release solid oral formulation (and so would not be the subject of a BCS biowaiver).

For BCS biowaivers, it therefore seems reasonable to consider alcohol sugars (e.g. mannitol, sorbitol) as potentially critical excipients. The impact of these excipients on small intestinal transit time can potentially reduce the absorption of some BCS3 compounds, due to reduced residence time at the site of absorption; theoretically this could also be relevant for a subset of BCS1 compounds. Furthermore, for compounds which are subject to significant intestinal first pass metabolism by an enzyme with varying expression levels along the GI tract, overall bioavailability could potentially be affected if the main site of absorption in the intestine is altered. Additionally, the increased volume of fluid in the intestinal lumen caused by the osmotic effect of these excipients could be of importance for BCS 3 compounds with concentration-dependant permeability.

4. Effective permeability

Mechanisms by which excipients could alter either the rate or overall extent of drug permeation across the intestinal wall include damage to the intestinal surface/tight junction modulation, inhibition of efflux, and inhibition or enhancement of active uptake. None of these mechanisms would be detected in the permeability assessments currently outlined in the BCS guidelines, as there is no requirement to assess permeability in the presence of formulation components. Table 3 summarises reported excipient effects in this category. Studies which have demonstrated that a particular excipient does not impact permeability are also included.

The relevance of the different mechanisms in this category for the absorption of BCS Class 1 and 3 drug products is considered below:

- Damage to the intestinal surface/tight junction modulation: could potentially increase the bioavailability of BCS3 compounds if these effects manifest *in vivo*. For BCS1 compounds, absorption is by definition complete, so no increase in bioavailability would be anticipated; however the rate of absorption could potentially be increased.
- Inhibition of efflux – For BCS3 compounds, if efflux is limiting effective permeability there could potentially be an increase in bioavailability with an excipient that acts on efflux transporters, however for low passive permeability compounds this should not have an impact. For BCS1 compounds, absorption is complete and therefore not limited by efflux, so no effect would be anticipated *in vivo*.
- Inhibition or enhancement of active uptake – For BCS1 compounds which show high absorption due to an active absorption process, inhibition of this could lead to reduced bioavailability. For BCS3 compounds, either enhancement or inhibition of an active uptake process for which the drug was a substrate could impact bioavailability. However, no reported excipient effects on active uptake transport were found.

According to Table 3, several excipients therefore have the potential to impact on bioavailability for BCS 1 and 3 compounds through altering effective permeability. Four excipients have reported permeability effects in human, due to efflux inhibition (PEG 400, Cremophor EL, Cremophor RH40, TPGS); however, these are unlikely to be used in an immediate release solid oral dosage form for a BCS 1/3 compound at significant levels. Many of the reported studies in this category are *in vitro/ex vivo*, so the relevance of the excipient effects shown to intact human can be difficult to ascertain. Dahlgren et al. highlighted that excipient effects shown in models where normal intestinal transit is not present may overestimate the potential of an excipient to affect permeability, and should be confirmed in intact preclinical models, as several physiological functions (dilution, gastric emptying, degradation, intestinal transit) may reduce the effect of an excipient on the mucosal barrier [24].

The excipients which have shown an effect are mostly in the surfactant and lipid categories, and so their use in an immediate release formulation for a highly soluble drug substance would be unusual. In general, the inclusion of surfactants and/or lipids in the formulation for a highly soluble drug would raise questions (except e.g. very small amounts of polysorbates etc in tablet coatings). The permeation enhancers chitosan and sodium caprate also showed effects on the absorption of some model compounds in preclinical species; however permeation enhancers are not standard pharmaceutical excipients for simple immediate release formulations. Permeability studies using standard excipients (other than SLS) which would be commonly used in immediate release tablets/capsules for highly soluble drug substances (i.e. formulations that would be eligible for BCS biowaivers) showed no impact on permeability [19,20]. For BCS biowaivers, it therefore seems pertinent to consider surfactants (e.g. SLS) as potentially critical excipients on the basis of their potential to impact permeability, especially for compounds where permeability is limited by efflux transporters.

5. Gut wall metabolism

Inhibition of gut wall metabolism could potentially result in increased bioavailability by reducing the extent of first pass metabolism in the gut wall. This could be of potential relevance for BCS Class 3 compounds where bioavailability is low due to gut wall metabolism, and potentially also for some BCS1 compounds having high permeability but lower bioavailability (e.g. where data from an ADME study rather than absolute bioavailability have been used for the permeability classification). Extensive tables summarising the reported effects of excipients on metabolism have been presented by Sjogren et al. [5] and Zhang et al. [6]. 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 [5,6]. Additionally, HPMC, DCP, pregelatinised starch and crosspovidone were reported to reduce CYP3A mRNA expression *in vitro* [6]. All of

Table 2
Excipients which can alter intestinal transit times and lumenal volumes – detailed consideration of excipient levels where effects have been reported.

Excipient	Details of reported effects and levels	Summary
Mannitol	Reduces small intestinal transit time (t50) in healthy volunteers in gamma scintigraphy studies. 0.755 g reduced transit time by 11%, 1.509 g by 23% and 2.264 g by 23%/34% (different studies) [8,9,10]. Cimetidine Cmax and AUC0-24 significantly lower for tablet and solution formulations containing 2.264 g mannitol than sucrose control; AUC reduced by 31% for tablet and 29% for solution; Cmax reduced by 49% for tablet and 54% for solution [11]	Evidence of effect on SI transit in human at doses of 0.755 g and above. The effect seen at 0.755 g is small ~11%, so this dose is likely near the effect threshold. Evidence of significant effect on drug absorption in human at 2.264 g dose
Sorbitol	Ranitidine Cmax and AUC0-infinity were decreased by approximately 50% and 45%, respectively, by a 5 g dose of sorbitol in human volunteers. Effect shown to be dose dependant; bioequivalence was shown at a 1.25 g dose of sorbitol (although Cmax was reduced by ~7%), and formulations were not bioequivalent at 2.25 g or 5 g sorbitol doses. Sorbitol (5 g) also reduced metoprolol Cmax by 23% but had no significant effect on AUC0-infinity in a human BE study. [17]	Significant effect on AUC and Cmax (as determined by BE pass/fail) shown at doses of 2.25 g and above
	Garcia-Arieta [7] described two unpublished bioequivalence studies where sorbitol (7 mg and 50 mg sorbitol doses) apparently led to bioequivalence failure of risperidone solution formulations, due to the lower bound of the Cmax confidence interval falling outside the acceptable range (90% CIs 77.0–99.2 and 76.20–102.82, respectively). Interestingly, both doses of sorbitol showed a similar effect on the Cmax confidence interval, in contrast to the dose dependency usually reported for alcohol sugars, and reported specifically for sorbitol by Chen et al. [17]. In a separate (published) study, a sorbitol oral solution (60 mg sorbitol) was bioinequivalent to risperidone tablet, with AUC and Cmax confidence intervals falling outside lower the bound (90% CIs 75.0–92.6 for Cmax and 76.2–92.9 for AUC) [20]. Garcia-Arieta reports that the bioequivalence failure in each of these studies was due to a few subjects who appeared to be outliers in terms of the test:reference ratio, and pulled down the lower bound of the mean confidence intervals; if these subjects were excluded, the comparisons passed the bioequivalence criteria. This is attributed to greater sensitivity to the effects of sorbitol on intestinal transit for these subjects	Potentially shows that some subjects have greater sensitivity to effects of sorbitol at lower doses than those studied by Chen et al. Unfortunately, the data for the solution BE studies is unpublished, so it is not possible to assess this in depth and exclude other potential causes (e.g. missed Cmax due to delayed gastric emptying)
Sodium acid pyrophosphate	Doses of ~1.1 g sodium acid pyrophosphate (1.1 g) reduced small intestinal transit time by 39% (1.1 g) [9], and 56% (1.132 g) [15]. Ranitidine AUC significantly reduced (54%, 1.132 g dose) [13]. Both studies used human volunteers	Evidence of significant effect in human at ~1.1 g dose
PEG 400	PEG 400 reduced small intestinal transit time in healthy volunteers in a dose-dependant manner; 9% at a 1 g dose (not statistically significant), 20% at a 2.5 g dose, and 23% at a 5 g dose (gamma scintigraphy). Bioavailability assessed using urine data, also showed dose-dependant effects of PEG 400. Mean cumulative amount of ranitidine excreted was reduced by 38% in the presence of both 2.5 and 5 g PEG (not statistically significant), however significantly increased in the presence of 1 g PEG 400 (from 34 mg to 48 mg). The authors attribute this to altered permeability at the lowest PEG dose [12]. Refer to permeabilty effects summary for details of further studies on lower doses of PEG 400. Small reductions in ranitidine bioavailability in females at lower PEG doses were attributed to possible transit effects by the authors; however the effects observed were not statistically significant, and no measurements of SI transit time were taken in this study [14]	Evidence of significant effect on SI transit time at doses of 2.5 g and above in human
Oleic acid	Dobson et al. [19] examined effect of oleic acid on small intestinal transit time in human volunteers, at doses of 300 mg, 600 mg and 1200 mg. Effects were variable between volunteers but generally observed an increase in transit time with increasing oleic acid dose. The only statistically significant effect was on transit of the 111In- labelled tablet at a 1200 mg dose of oleic acid (> 316 min vs. 217 min for control)	Evidence of increased SI transit times at doses of 300 mg and above, significant effects at 1200 mg. Amount is far in excess of what would be used in a solid oral dosage form
Xylitol	30 g Xylitol decreased the rate of gastric emptying (t1/2 77.5 min vs. 39.8 min) but accelerated intestinal transit in human volunteers (as measured by arrival time of radioactivity in colon; some radioactivity had reached the colon of all 5 subjects after 1 h) [14]	Amount studied is far in excess of what would be used in a solid oral dosage form
Lactulose	Different amounts of lactulose (10 g, 25 g, 40 g) administered to human volunteers as part of a meal showed reduced small intestinal transit time according to a hydrogen breath test; H2 onset time reduced linearly with concentration, with the time for the 40 g dose being approximately half that of the control. 40 g lactulose significantly reduced ileal emptying t1/2 in ileostomy patients [16]	Dose dependant effect on SI transit time at doses of 10 g and above

these effects were identified in *in vitro* or *ex vivo* assays.

Ren et al. [30] investigated the inhibitory effects of four nonionic surfactants on CYP3A *in vitro* and *in vivo*, using midazolam as a probe compound. The surfactants studied were Tween 20, polyoxyl 35 castor oil, polyoxyl 40 stearate and poloxamer 188. In rat liver and intestinal microsomes, all four surfactants showed dose-dependant inhibition of CYP3A-mediated midazolam 1′ hydroxylation. *In vivo* effects were studied in rats after single or multiple oral doses of the excipients (150 mg/kg). Tween 20 inhibited midazolam metabolism after single and multiple dosing, as evidenced by an increase in midazolam AUC and a corresponding reduction in 1′ hydroxy midazolam AUC. The effects of the other surfactants were somewhat complex to interpret. After

Table 3
Reported effects of excipients on permeability categorised by mechanism.

Mechanism	Reported effect	Relevance for BCS Class 1 and 3 drug products
Damage to intestinal surface/ tight junction modulation	SLS increased permeability of mannitol and other drugs in Caco-2, attributed to opening of tight junctions [20]. SLS at concentrations of 0.1 mg/mL and above increased permeability of 4x BCS3 compounds but not the BCS1 compound antipyrine across Caco-2 monolayers, due to loss of membrane integrity [22]. Also attributed to have increased alendronate sodium bioavailability in human (4 mg) in an unpublished study, based on urine data [7] Paracellular transport modulators: EDTA (*in vitro*), Sodium decanoate (*in vitro,* preclinical, *ex vivo* and human), palmitoyl carnitine (preclinical), chitosan and derivatives (*in vitro*/preclinical), sodium lauryl sulphate (*ex vivo*), tetradecylmaltoside (*in vitro*, preclinical), octylglutoside (*in vitro*), chenodeoxycholates (*ex vivo*), sodium taurocholate (*in vitro*), thiolated polymers (*in vitro, ex vivo*), butylated methacrylate copolymer (*in vitro*) [5] Sodium bicarbonate modified interaction of fluvastatin with membrane phospholipids [7] (lipid-to-excipient molar ratio of 15:2, *in vitro*, model lipid membranes) SLS and chitosan increased absorption of low-permeability marker compounds in a rat jejunal perfusion model, correlated to increased transport of the mucosal barrier integrity marker 51Cr-EDTA. Sodium caprate and N-acetylcysteine had no effect on permeability [23]. In a rat intestinal bolus model SDS (5.7 mg) significantly increased C_{max} and AUC of four low permeability compounds (acyclovir, atenolol, enalaprilat, phenol red), accompanied by an increase in P_{eff}; whereas a lower dose of SDS (1.1 mg) had no significant effect. In a dog intestinal bolus model, a dose of 228 mg SDS increased AUC and C_{max} for atenolol only (1.9- and 2.4-fold, respectively), although a trend toward increased P_{eff} ratio was observed for enalaprilat, metoprolol and phenol red [24]. A low dose of chitosan (1.15 mg) significantly increased acyclovir AUC in the rat intestinal bolus model, however a higher dose had no effect [24]. Sodium caprate (228 mg) significantly increased metoprolol exposure (1.3-fold) and reduced phenol red exposure (0.6-fold) in a dog intestinal bolus model [24]	For BCS1 compounds, absorption is complete – unlikely to have any effect on extent *in vivo*, but may affect rate. For BCS3, could increase bioavailability if manifested *in vivo*
Enhancement of active absorption process	Eudragit L100-55 (500 mg/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. This was attributed to enhanced PePT1 activity [25]. Note this is a level far higher than would be encountered in a tablet coating	
Inhibition of active absorption process	No reports found	For a subset of BCS1 compounds, absorption may be high due to an active absorption process (note: PK linearity and *in vitro* permeability data should identify this)
Inhibition of efflux	Tween 80 and docusate sodium increased permeability of various drugs in Caco-2 cells, attributed to efflux transporter effects (*in vitro*) [20] P-Gp inhibition by Cremophor EL (1440 mg human dose) and PEG 400 (0.5–1.5 g human doses) reported *in vitro* and in rat and human; also by Pluronics, Tween and TPGS *in vitro* and in rat/mouse. Other surfactants and cosolvents (β-cyclodextrin, monoolein, monoplalmitin, monostearin) reported to inhibit MRP2/BCRP/OATP *in vitro*. HPMC, pregelatinised starch reduce expression of MDR1 mRNA in cell model [6] Surfactants (Tweens, Cremophors, Labrasol, Pluronics, Sodium lauryl sulphate, TPGS, Softigen, Acconon, n-dodecyl beta maltopyranoside) and PEG, miglyol, Imwitor, increased transport/uptake in *in vitro/ex vivo* systems, attributed to modulation of efflux [5]. Multiple doses of Cremophor RH40 increased bioavailability of digoxin in human (600 mg 3 times daily) [26] *In vitro* inhibition of P-Gp by TPGS and rhamnolipids (*in vitro*). Phospholipids reduce P-Gp expression in Caco-2 cell line. A thiolated polymer (PAA250-Cys conjugate, 20 mg) increased absorption of sulforhodamine 101 in rat by ~270%, and increased permeation across rat intestinal mucosa (0.5% w/v), attributed to MRP2 inhibition. Solutol HS15 increased absorption of colchicine and paclitaxel in rats (400 mg/kg and 273 mg/kg, respectively) [27] PEG 400 (0.5, 0.75, 1, 1.25 and 1.5 g) increased bioavailability of ranitidine in healthy male volunteers by 34%, 63%, 49%, 43% and 6% (note – the only statistically significant effect was at 0.75 g) [14]. Effects attributed to increased permeability. This was not observed in female volunteers in the same study. Similarly Schultze et al. [12] showed a 41% increase in ranitidine bioavailability in male volunteers in the presence of 1 g PEG 400. PEG 300/400 significantly reduced ranitidine efflux ratio ($p < 0.05$) and interacted with P-gp. This showed non-linear concentration dependence for PEG 400 with a maxima at 1% [28] *In vitro* (Caco-2), TPGS (0.005%+) and Poloxamer 188 (0.4% only) increased talinolol permeability, attributed to P-Gp inhibition. In human, TPGS (0.04%) increased talinolol AUC by 39% and Cmax by 100%, while poloxamer 188 did not significantly alter talinolol PK [29] PEG400 (1%, 2%) and PEG 6000 (4%) inhibited P-Gp in Caco 2 cells [28]	For BCS1 compounds, absorption is complete and therefore not limited by efflux – unlikely to have any effect *in vivo* For BCS3, if efflux is limiting effective permeability there could potentially be an increase in bioavailability, however for low passive permeability compounds this should not have an impact
No effect on permeability	HPMC (0.012–2.0 mg/mL), D-lactose (0.024–2.0 mg/mL), povidone (0.0242.0 mg/mL), PEG 400 (0.015–0.3 mg/mL), and SLS (0.01–0.04 mg/mL) did not have any effect on permeability of five BCS1/3 compounds across Caco-2 monolayers [22]. Lactose (2 mg/mL), propylene glycol (1.5% w/v), anhydrous cherry flavouring (0.006% v/v) and EDTA (0.06 mg/mL) did not affect the permeability of 7 low-permeability drugs across Caco-2 monolayers [21]	–

a single dose, polyoxyl 35 castor oil likewise increased midazolam AUC and reduced 1′ hydroxy midazolam AUC; however after multiple dosing this excipient reduced the AUC of both midazolam and 1′ hydroxy midazolam, which is not consistent with inhibition of CYP3A. Polyoxyl 40 stearate reduced AUC of midazolam and 1′ hydroxy midazolam after a single dose, but after multiple dosing midazolam AUC was increased without a corresponding change in 1′ hydroxy midazolam AUC. Finally, poloxamer 188 reduced midazolam and 1′ hydroxy midazolam AUC after single dosing, and also reduced AUC of the metabolite after multiple dosing. The complexity of these effects suggests that the mechanism cannot fully be explained by simple CYP3A inhibition. However, in the context of assessing risk for BCS 1 and 3 compounds, none of these excipients are likely to be used in a simple immediate-release tablet or capsule. Additionally the doses employed in the study were very high. It is therefore difficult to identify any critical excipients for BCS 1 and 3 compounds on the basis of potential to inhibit gut wall metabolism in man, based on the data currently available.

6. Mechanism unknown or unclear

For some reported instances where excipients appear to have affected *in vivo* performance, a mechanistic hypothesis is not proposed by the authors, or is not apparent from the studies performed.

Vaianathan et al. [31] investigated the impact of high doses of commonly used pharmaceutical excipients on the pharmacokinetics of two BCS 3 drugs, aciclovir and cimetidine. The majority of excipient combinations investigated had no impact (see below), however a tablet formulation containing 40 mg HPMC exceeded the upper bound of the Cmax confidence interval for cimetidine (90% CIs 109.4–136.2); AUC was bioequivalent, although the lower bound of the confidence intervals was greater than 100% (90% CIs 104.4–120.6). The authors note that this is an unlikely outcome for an insoluble excipient; other excipients included in the formulation were MCC and SLS.

Garcia–Arieta [7] discusses the apparent impact of SLS on risperidone bioavailability. Two bioequivalence studies are described; one where a generic product containing 3.64 mg SLS failed to show bioequivalence to the reference formulation (which also contains SLS) (90% CIs 70.01–86.80 for Cmax and 74.74–91.72 for AUC), and another where a generic product containing 1.5 mg SLS failed to show bioequivalence (90% CIs 77.9–95.0 for Cmax and 80.7–98.1 for AUC). The author also states that in other studies, generic products containing no SLS, or very high amounts of SLS (9 g) have demonstrated bioequivalence to the reference product, so this is not a consistent effect. As all of these studies are unpublished, it is not possible to examine the data to assess this from a mechanistic perspective and evaluate other potential causes for the observations.

Further investigation of these examples would be necessary to understand the root cause of these failures to prove bioequivalence, and ascertain whether the excipient changes did have an impact. Application of *in silico* PBPK absorption modelling could be useful to build and test potential mechanistic hypotheses for these observations. However, the fact that the data described by Garcia-Arieta is unpublished means that the specific studies described in the manuscript cannot be assessed. Risperidone is described as a BCS1 compounds by Garcia Arieta, however other authors have assigned a BCS 2 classification [32].

7. Reports where no impact of excipients was observed

Reports where a particular excipient was concluded not to have an impact on absorption are briefly described in this section. Studies where an excipient was shown to have no impact on a particular aspect of bioavailability, such as permeability or intestinal transit, are discussed in the relevant sections above.

Vaianathan et al. [31] studied the impact of larger than usual amounts of 14 common excipients on absorption of BCS3 drugs in human. Cimetidine and aciclovir were used as model compounds. The authors concluded that sodium lauryl sulfate (25 mg), corn starch (450 mg), SSG (100 mg), coloidal silicon dioxide (20 mg), dibasic calcium phosphate (300 mg) and crosspovidone (50 mg) had no significant impact on bioavailability of either drug. The effects of MCC were indeterminate, as these were confounded with HPMC effects in the study design (refer to 'mechanism unclear' section above).

Kubinga et al. [33] reviewed the potential biopharmaceutic effects of lactose, including an assessment of the amounts used in approved generic products in Europe. The authors concluded that the risk of lactose causing bioinequivalence for BCS 1 products is low, and that any differences are likely to be due to dissolution which is detectable with standard *in vitro* tests. For BCS 3 products, only a relatively narrow range of amounts used in generic products could be evaluated, so the authors conservatively conclude that the probability of bioinequivalence is medium until further data are available for evaluation.

Yu et al. [34] reported that a review of FDA data for more than 10 BCS Class 3 drugs concluded that most of the excipients commonly used in oral solid dosage forms for these compounds do not significantly impact absorption. No specific data from the review is provided in the article.

8. Conclusions

There are numerous reports and review articles in the scientific literature assessing the potential of excipients to affect drug bioavailability. However, these span a wide range of API properties, formulation types, and excipient quantities. To the authors knowledge, this is the first publication which has reviewed the existing literature in the context of the BCS biowaiver framework, which restricts the drug substance properties, formulation type and dissolution performance to an area of low biopharmaceutic risk. Many of the excipients with reported effects on absorption would not normally be used in immediate release solid oral dosage forms for highly soluble drug substances; furthermore, the amounts of excipients shown to impact absorption in some studies are much higher than would normally be used in such formulations.

Most excipients used as components in solid oral IR dosage forms do not appear to influence the *in vivo* absorption of drug substances. Based on the literature data, there are only a limited number of mechanisms by which excipients could affect the absorption of a BCS Class 3 drug. For BCS1, absorption is very unlikely to be affected by excipient changes. Only a limited number of potentially critical excipients have been identified which are relevant to BCS Class 1 and 3 compounds:

- Excipients that can influence intestinal transit (i.e. osmotically active alcohol sugars)
- Surfactants that can alter permeability (through passive mechanisms or effects on transport proteins).

Note that even these excipients will not be critical for all BCS 3 compounds; for example, an excipient which has been shown to inhibit P-Gp would not be of concern for a drug which is not a P-Gp substrate.

The current BCS guidelines contain excipient criteria which are universally applied to all compounds within a particular BCS class. These criteria are therefore set on a conservative basis, and by nature will reject some formulation changes that will be bioequivalent *in vivo*. The criteria for BCS Class 3 compounds could be viewed as particularly conservative, given the limited number of mechanisms by which excipients can affect absorption for BCS3 compounds, and the added reassurance of the very rapidly dissolving criterion for test and reference formulations. The current BCS3 excipient limits effectively restrict excipient changes to SUPAC level 2; this is the same degree of change allowed for BCS Class 2 and 4 compounds without the need for *in vivo* bioequivalence data, and has successfully been applied to these higher biopharmaceutics risk compounds for over 20 years [35].

One potential route forward is to move towards a more risk-based, mechanistic approach. This would enable biowaivers for lower risk excipient changes for BCS3 products to be permitted, without the perceived risk that would accompany a general widening of the excipient criteria. The risk of a particular excipient change leading to bioinequivalence would be assessed by applying compound-specific understanding of the absorption site, rate and mechanism of the particular API under consideration, as well as the amount and function of the excipient in the formulation. Such an assessment would take into account:

- The mechanism by which the excipient is known (or suspected) to impact drug absorption;
- The amount 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.

Tools such as *in silico* PBPK modelling could be applied to support the excipient risk assessment, for example by performing sensitivity analysis for GI transit times and luminal volumes. Such an approach would reduce the likelihood of rejecting biowaivers for formulations that would be equivalent and ensure that changes which would be problematic are identified. However, it may be difficult to implement from a regulatory perspective, as the approach would be somewhat dependant on the judgement of individual reviewers.

One source of data on excipient changes which is currently underutilised, is the assessment of clinical bioequivalence data for drug products where excipient levels have been altered. A thorough mechanistic assessment of both passed and failed studies in comparison with the properties of the API and formulation could yield new insights into the level of risk associated with individual excipients, for BCS compounds with a spectrum of pharmacokinetic and absorption properties. However, these data are difficult to access, especially for failed BE studies. Additionally, study failure for reasons other than the excipient change would need to be excluded. As part of the OrBiTo IMI project, a database was created containing biopharmaceutics data for drug products form across thirteen pharmaceutical companies, including results from human relative bioavailability studies [36]; this database could also be investigated as a potential source of further data on excipient effects. Sjogren et al. [5] propose the creation of a public database on excipient effects; such an approach would enable bioequivalence data to be collated and assessed across companies, and could pave the way for a common understanding of excipient risk between industry and regulators.

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