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Effect of excipients on oral absorption process according to the different gastrointestinal segments

Alejandro Ruiz-Picazo, Isabel Lozoya-Agullo, Isabel González-Álvarez*, Marival Bermejo, Marta González-Álvarez

Engineering: Pharmacokinetics and Pharmaceutical Technology Area, Miguel Hernandez University, Spain

***Correspondence**

Isabel González-Álvarez

Edificio Muhammad Al-Shafra, Facultad de Farmacia, UMH, Carretera Alicante Valencia km 87, 03550 San Juan de Alicante, Alicante, Spain

Email: isabel.gonzalez@umh.es

Tel.: +34 965 919217

Abstract

Introduction: Excipients are necessary to develop oral dosage forms of any Active Pharmaceutical Ingredient (API). Traditionally, excipients have been considered inactive and inert substances, but, over the years, numerous studies have contradicted this belief. This review focuses on the effect of excipients on the physiological variables affecting oral absorption along the different segments of the gastrointestinal tract. The effect of excipients on the segmental absorption variables are illustrated with examples to help understand the complexity of predicting their in vivo effects.

Areas covered: The effects of excipients on disintegration, solubility and dissolution, transit time and absorption are analysed in the context of the different gastrointestinal segments and the physiological factors affecting release and membrane permeation. The experimental techniques used to study excipient effects and their human predictive ability are reviewed.

Expert opinion: The observed effects of excipient in oral absorption process have been characterized in the past, mainly *in vitro* (i.e. in dissolution studies, *in vitro* cell culture methods or *in situ* animal studies). Unfortunately, a clear link with their effects *in vivo* i.e. their impact on Cmax or AUC, which need a mechanistic approach is still missing. The information compiled in this review leads to the conclusion that the effect of excipients in API oral absorption and bioavailability is undeniable and shows the need of implementing standardized and reproducible preclinical tools coupled with mechanistic and predictive physiological based models to improve the current empirical retrospective approach.

Keywords: Biopharmaceutical Classification System of Excipients; Excipient; Gastrointestinal segments; Oral Absorption.

Article highlights

- Excipients are no longer considered inert. They can significantly affect the bioavailability in rate and extend of the API, which could be a desired effect, as in controlled release (CR) formulations or in bio-enabling formulations, to improve/modulate absorption or an undesired aspect on the bioequivalence setting.
- The Excipient Biopharmaceutical Classification System (BCSE) is a new practical classification where the excipients are grouped in four classes according to their effect over metabolism and efflux transporters.
- Excipients can affect all the main variables determining drug absorption from the physicochemical characteristics of the API to the physiological environment. Those effects need preclinical and mathematical predictive models to be used in the oral dosage development according to the expected absorption outcome.
- The effect of excipients can be greatly different depending on the gastrointestinal segment considered due to their particular physiological aspects and functions, consequently a basic understanding of the gastrointestinal variables is essential in formulation development.
- Most of the *in vitro, in situ* and *in vivo* used to study drug absorption are of application to characterize excipients effects, but more efforts to scale up the information from those systems to the *in vivo* situation are needed.

1. Introduction

The absorption of an oral drug formulation is a complex process that can be affected by different factors. Usually, a drug formulation is composed by an Active Pharmaceutical Ingredient (API) and several excipients. The main objective after administering an oral drug formulation is that the API reach the target in the organism and provides the desired effect. The role of the excipients is to help the API to achieve its objective.

According to the basis stablished by Amidon *et al*. in 1995 [1], the solubility in the gastrointestinal environment and the permeability through the gastrointestinal membrane are the main factors implicated in the drug oral absorption [2]. Systemic bioavailability (F) is the composite of oral fraction absorbed (fa) times fractions escaping intestinal (fg) and hepatic (fh) first pass losses, F=fa*fg*fh. Fraction absorbed will increase up to its maximum with higher solubility, dissolution rate and permeability values. All those parameters can be affected by excipients. First-pass losses can be also diminished by excipients and in consequence, an increase in oral bioavailability (up to its maximum of 100%) achieved with formulation strategies [3]. On the other hand it has been demonstrated that the interaction among drug parameters (permeability, solubility) and gastrointestinal environment (fluid volumes, pH, transporters and enzyme expression levels, membrane tightness) is complex and change during transit, thus a closer look on segmental differences is useful to understand excipient effects [4,5].

Otherwise, the excipients included in oral dosage forms have traditionally been considered inert substances, unable to disturb the API absorption [6]. Nowadays, it is well-known that some excipients have shown the ability to modify drugs absorption [7–11]. Several recent reviews have addressed this issue in particular focusing on the objective of improving oral absorption. Dahlgren *et al* proposed the key elements of the preclinical models to be predictive *in vivo* [7]. Flanagan *et al*. focused on the risk-based BCS approach for BCS 3 biowaivers and excipient changes [12] also addressed by Dash *et al.* [13]. Al-Ali *et al.* discussed excipients interactions with ABC transporters and SLC carriers [14] while Schittny *et al.* covered the solubility-supersaturation phenomena with amorphous solid dispersion formulations [15]. Formulation approaches to overcome the food effect have been addressed

extensively [16,17], as well as the design of bio-enabling formulations [18]. Most of these compilations address the concept of improving oral absorption while the concept of not changing it, relevant for bioequivalence considerations, has been in general overlooked, but to point out the so called “problematic” or “critical” excipients (mainly sugars and surfactants) [19,20]. Taking into account that in many cases APIs absorption is segmental-dependent, the effects of the excipients can also vary according the physiological changes along the GIT [21]. Therefore, in this review we address some relevant physiological features that changed along the GI tract and in the second part we summarized some examples of excipients that exert their effects on different gastrointestinal segments.

2. Gastrointestinal variables relevant for formulation performance and drug absorption

The gastrointestinal environment changes from stomach to small intestine and colon. These three segments are the main sites where absorption after oral intake could take place or that affect formulation performance [22]. Table 1 shows examples of physiological variables or formulation processes that can be affected by excipients in different gastrointestinal segments.

Recently Flanagan T. [12] performed a mechanistic review of excipients effects on the absorption of Biopharmaceutics classification system (BCS) Class I and III drugs. Flanagan categorized the excipients effects at four levels; Effects on the drug release from the dosage form, which involves dissolution, disintegration, micro-environmental pH changes and complexation. Secondly effects on transit times and fluid luminal volumes; Effects on the membrane which could be at transcellular or paracellular level or by affecting influx or efflux transport mechanisms; and finally effects on the metabolism via direct or indirect mechanisms.

In this review, we are going to summarize examples of all those mechanisms with a particular focus on the mentioned physiological mechanisms and their different impact on stomach, small intestine and colon.

pH of luminal secretions is one of the relevant features that can be modulated by excipients at least in the micro-environment around the dissolving particles. pH at the

solid surface determine drug solubility for weak acid and bases and consequently govern the dissolution rate. Some pH-modifying excipients have been reported as one of the causes for bioequivalence failures of weak acids [23]. This approach has proven to be a successful strategy to modulate ionisable drug dissolution and absorption [24].

Volume of luminal fluids determine the drug bulk concentration and thus the dissolution gradient. Excipients affecting water reabsorption or fluid secretion as those with osmotic effect could eventually affect not only dissolution rate but also permeation process [25,26].

The third variable with impact on formulation performance is GI motility, starting from gastric emptying to intestinal transit and colon arrival. Gastric motility could affect dose form disintegration as it was shown with paromomycin tablets administered in phase I or II of the MMC (Myoelectric migrating complex). In that study tablet administration in Phase II produced a more homogeneous drug distribution in the stomach [27]. Gastric motility as well determines gastric emptying/residence time. This parameter could be the limiting factor for absorption for high permeability, high solubility drugs in rapidly dissolving formulations. A reduction in gastric emptying time associated with an excipient could be reflected in Cmax as it was shown for sodium bicarbonate [28]. For high solubility but low permeability drugs a decrease in intestinal transit time could lead to a reduction in absorption extent as was shown with sodium acid pyrophosphate [29]. Gastric residence time is also a relevant parameter in enteric-coated formulations. Gastro resistant pellets emptying kinetic will determine their intestinal dissolution profile and consequently the absorption rate [30].

Sugars and polyols (PEGs) have been frequently associated to changes in GI motility and fluid secretion even at the standard amounts used in dosage forms but their cut-off limit for exerting this effect is still not clearly stablished but for a few drugs for which a linear relationship between effect on Cmax and osmotic activity has been characterized [25].

Alterations of intestinal motility can change fraction absorbed of low permeability compounds as the effective time for absorption could be reduced [31]. On the other

hand motility changes are associated with fluid secretion changes a phenomenon known as secretomotor complex [32], thus altering motility can affect eventually dissolution rate.

Excipients effects on those variables will be discussed in the next sections with examples observed in the different intestinal segments

3. Concept and classification of excipients

The excipients objective is to facilitate the use of an API by increasing its stability, patient acceptability or increasing API safety and bioavailability [33]. According to the Food and Drug Administration (FDA), excipients are considered inactive ingredients and they are defined as “any component other than active ingredient” [34], where the “active ingredient” refers to the API. Moreover, the FDA has an inactive ingredient database that provides information of the excipients included in their approved drug products as a tool for new drug product development [35].

Nowadays, multiple reports have shown the effect of excipients over the API rate and extent of absorption [19,36]. Furthermore, excipients are not exempt from patient-specific adverse reactions, as lactose in lactose intolerant subjects [37]. In consequence, quality and safety of the excipients and their interactions with the API must be also assessed during formulation development [33]. Furthermore, currently, regulation and definition of excipients are complex tasks, because the same excipient can be employed in different products, such as cosmetic or food products. Moreover, some excipients can have multiple functions, not have an official name or not enough information can be found in pharmacopoeias [38]. On the other hand, the development of novel forms of delivery implies an increase of the number of excipients and novel excipients mixtures. Indeed, the “Handbook of Pharmaceutical Excipients”, a guide that collects physical properties, uses and safety data of excipients, has increased the number of excipients included in their pages from 145 in its first edition to 300 in the last one [39].

Excipients can be classified in different ways according to several factors [40]:

- Origin: organic chemicals or inorganic chemicals

- Function: fillers, diluents, coatings, extenders, binders, solvents, flavouring agents, wetting agents, colorants, preservatives, suspension and viscosity agents, absorption enhancers, disintegrants, sustained-release matrices, lubricants and glidants, etc.
- Administration route: parenteral excipients, topic excipients, oral excipients, others.

An exhaustive classification of oral excipients can be found in Chaudhari *et al*. [6], where the excipients are grouped according to whether they are employed in liquid, semisolid and solid pharmaceutical forms. Moreover, the study includes the excipient category, function, working mechanism and some examples.

4. Biopharmaceutical classification system of excipients

Vasconcelos *et al*. developed in 2017 the Biopharmaceutical Classification System of Excipients (BCSE) [41]. The objective of the BCSE is to help in the development of new pharmaceutical products. It is a classification similar to the BCS, where the excipients are grouped in four classes according to their effect over metabolism and efflux transporters [41]. The reason of this classification is that the metabolism and efflux pumps are the two main protective mechanisms against foreign molecules present in GIT and some excipients can interact with these mechanisms and modulate the absorption process [42].

Excipients in BCSE Class I have low or negligible impact on metabolism and efflux transport, so API safety and its bioavailability will remain unchanged. This class includes excipients such as phthalates, cellulose microcrystalline or lactose (in normal subjects).

Class II excipients can interact with metabolization processes. Thus, APIs that undergo intestinal metabolism will experiment alterations in oral absorption if they are included in a pharmaceutical dosage form with a class II excipient. Some examples of class II excipients are modified cyclodextrins, hydroxypropylmethylcellulose (HPMC), croscarmellose sodium or acetic acid.

BCSE Class III excipients are able to interact with efflux pumps. Therefore, if the API administered with a class III excipient by oral route is an efflux transporter substrate, it will suffer changes in its oral absorption. Sodium lauryl sulphate, PEG300 and span 20 are examples of class III excipients.

Finally, the excipients of class IV are the most complex to use. They interact with metabolism and efflux transport, so these excipients can modify the oral absorption of APIs subjected to intestinal metabolism, efflux transport or both. Tween 20, tween 80 or brij 35 are excipients included in class IV.

Hence, the chosen excipient could be determinant for the oral absorption of a drug product. For example, a low permeability API substrate of an efflux pump will have a low intestinal permeability if it is administered with a BCSE class I excipient. However, if the same API is administered with a class III or IV excipient the permeability could be enhanced.

Nevertheless, the studies related with the ability of excipients to interact with metabolism and/or efflux transport are insufficient and *in vivo* and human data are scarce [41]. Therefore, more robust methods and studies are needed to complete and stablish a strong BCSE that eventually will be an extremely useful tool to develop safe and effective pharmaceutical products.

Furthermore, the BCSE could have an important role to stablish biowaivers. A biowaiver refers to the replacement of the *in vivo* bioequivalence assay by an *in vitro* dissolution bioequivalence test. A biowaiver can be applied to immediate release oral solid forms of BCS class I and III drug (high solubility), provided some other conditions are fulfilled. However, some human bioequivalence studies have shown that high solubility drugs, such as isoniazid and zolpidem, in oral immediate release dosage forms can have similar *in vitro* dissolution profiles, but presenting differences in absorption rate (Cmax) in *vivo*. These studies demonstrated that the problem lied in the excipients employed in the tablets which affect processes other than dissolution [43,44]. Therefore, excipients could compromise the safety of BCS-based biowaivers, thus, completing the BCSE would be beneficial to avoid biowaivers failures. [42].

The BCSE could be further completed and improved to incorporate the effects over various SLC influx transporters including OATPs, OCTs and OATP, as shown in Table 1 and 2 [45–47].

5. Effects of excipients on oral absorption

This review is focused on the effect of excipients on drug absorption along the different gastrointestinal segments. To understand the mechanisms of their interactions the most important processes in the different gastrointestinal segments

are briefly described and the excipient impact discussed. Table 1 summarizes some examples of excipients effects according to the process and gastrointestinal segment involved. Potential applications of their effects are included in Table 1 as well.

5.1 Stomach

The stomach is the first part of the GIT where the API could be absorbed after dose form disintegration. It is generally recognized that small intestine is the primary absorption site due to the specialized epithelium and increase surface area. Stomach contribution is deemed to be negligible due to its comparatively lower surface, its thick mucus layer which increase diffusional resistance and short residence time in fasted state [48,49]. Moreover, the presence of influx or efflux transport mechanisms is negligible [50]. Nevertheless, absorption from stomach cannot be completely ruled out, even if lower compared to small intestine permeability some authors have demonstrate effective permeation of acidic molecules in preclinical perfusion models [51,52].

5.1.1 Modifying gastric pH

The pH modifier excipients are used in the pharmaceutical industry due to their antioxidant properties that help to maintain the stability of pharmaceuticals. Govindarajan *et al*. [53] studied the surface acidity and solid-state compatibility of excipients with atorvastatin calcium (Acid-Sensitive API). The agreement between equilibrium pH and chemical stability of an acid-sensitive compound provided a basis for the classification of the acidic nature of the excipients.
Methods to evaluate the solid surface pH include the slurry method and the dye-sorption method, both with similar results [54].
Micro-environmental pH modulation is used to increase drug supersaturation or to increase dissolution rate and consequently drug permeation gradient and absorption [24,55–59].
Excipient as calcium phosphate with ability to modulate the micro-environmental pH around solid particles in dissolution has been reported as the potential reason for bioequivalence failures of Desketoprofen Trometamol a salt of a weak acid [23].
pH modification has been proposed as part of the mechanism to allow semaglutide absorption which is hypothesized to occur mainly in stomach [60]. The hypothesis is that sodium salcaprozate (SNAC) is able to produce a transient pH increase around

the semaglutide molecules, which protect against pepsin action. Salcaprozate also inhibit oligomer formations so the semaglutide molecules remains as oligomers whose permeation is also promoted by SNAC that incorporates and fluidizes the membrane. The hypothesis of gastric semaglutide absorption was based on radiolabelled drug release monitoring in humans and pyloric ligation studies in dogs [60].

5.1.2 Gastric emptying

The mechanisms governing the rate of gastric emptying – what is the role of osmolality, consistency, differences in the fasted and fed state.

The gastric emptying is a physiological process regulated by myogenic neurogenic and hormonal mechanism [61]. Myogenic mechanism produces antral contractions due to the pacemaker potential which if associated with spike potential produce peristaltic contractions. Neurogenic control refers to the activity of the enteric nervous system (ENS) which can receive extrinsic inputs from vagal and splanchnic nerves. The main ENS influence is mediated by an inhibitory mechanism known as enterogastric reflex which inhibits gastric emptying in response to the presence of fatty acids, digestion products and hypertonic and acidic solutions in duodenum The extrinsic input is attributed to two parallel neural circuits: Gastric inhibitory vagal motor circuit (GIVMC) and Gastric vagal excitatory motor circuit (GEVMC) [62]. Hormonal control includes inhibitory hormones (as gastrin, cholecystokinin, secretin, gastric inhibitory polypeptide and enterogastrones) and stimulatory ones (ghrelin and motilin).

The migrating motor complex (MMC) is a cyclic, repetitive motility scheme prevailing in fasted state and interrupted by food. Phase I is the quiescent period followed by irregular contractions in Phase II and a burst of contractions originating from the antrum or duodenum in Phase III (the “housekeeper wave). The contractions produce movement of luminal content. Vagus nerve, motilin and ghrelin induce Phase III of antral origin [63]. In fasted state emptying of non-caloric liquids is fast and follows an apparent first order kinetic with a half emptying time of 15-20 min [64]. Fluid volume, pH and osmolarity affect gastric emptying, high volumes, alkaline pH and isotonicity produce faster emptying than low volumes [65], acidic pH and hyper or hypo-tonicity. Solid particles need to be reduced to less than 1-2 mm to be emptied if not they wait until the next housekeeper wave. Food interrupt MMC cycle

and delays emptying depending on caloric content (circa 3kcal/min) and composition. Fat and carbohydrates empty slower than proteins. The effect of excipients on the gastric emptying process has been extensively studied [28,66,67]. For example, the gastric emptying is markedly delayed with solutions of 50% saccharose, but it is slightly accelerated with solutions of 1% carboxymethyl cellulose [66]. Furthermore, Pestel *et al*. [67] noted that after administering PEG 400 at 20% concentration a statistically significant reduction of gastric emptying rate in rat was obtained. And it was also reduced with 1% hydroxyethyl cellulose and 20% hydroxypropyl-γ-cyclodextrin. However, 20% hydroxypropyl-β-cyclodextrin and 0.5% polysorbate 80 did not disturb the gastric emptying. Kelly *et al*. [28] demonstrated that acetaminophen administered with sodium bicarbonate shows a gastric emptying faster and consequently faster absorption, than other dosage forms without sodium bicarbonate as excipient on healthy volunteers. On the light of the described mechanisms for gastric emptying control, sugars and fat emulsions effects are related with their caloric nature and osmotic effects. Osmotic mechanisms seem also related with PEG 400 observed effects. Bicarbonate stimulant emptying effect are concentration dependent increasing emptying rate up to 150mM and decreasing with hypertonic solutions [68,69].

5.1.3 Disintegration

As the therapeutic dose of API is generally small excipients are employed to develop the dosage form with the desired size and shape. After oral administration, the disintegration process is the first step to allow the API liberation, because the dose form is broken up in small fragments and particles increasing the surface area and facilitating the dissolution. Indeed, disintegration can condition the API bioavailability and, hence, the therapeutic effect of a solid dosage form. Methods for studying the prevailing disintegration mechanism have been reviewed by Markl and Zeitler [70]. To promote the disintegration process, disintegration agents or disintegrates are required. The most common are a) the starch and its derivatives, such as cross-linked sodium carboxymethylcellulose or croscarmellose sodium, b) cellulose and its derivatives as microcrystalline cellulose, or croscarmellose, c) crospovidone and d) resins as polacrilin [71]. The immediate-release tablets disintegration happens in stomach with the exposure to physiological fluids in a period of time from 2.5 to 10 min [72]. The main factors affecting disintegrates performance are the particle size,

the method of incorporation (i.e. intra or intergranular or both), the compression force and the moisture content. Disintegration mechanism are swelling, wicking (liquid entry by capillarity), strain recovery or reversible deformation and interruption of particle bonds [73].

Modulating disintegration time is a recognized strategy to target the absorption process to a particular GI segment. The two extreme examples would be orodispersible formulations versus some controlled release (CR) formulations targeted to release in small intestine or colon. The orally dispersible tablets are mainly targeted to people with problems in swallowing conventional tablets and capsules. The European Pharmacopeia coined the term orodispersible tablets for them [74]. These tablets experiment a fast disintegration, less than 1 min, when they come into contact with saliva in oral cavity [75]. Orodispersible tablets (ODT) are composed by super disintegrates which ease the fast disintegration and dissolution avoiding problems to swallow the pharmaceutical product [76]. Some examples of super disintegrants employed in orodispersible tablets are croscarmellose sodium, crospovidone, sodium alginate or acrylic acid derivatives [77,78]. On the contrary, some controlled-release formulations are designed to achieve a sustained, delayed or modified release of the API, which means the disintegration will not take place in stomach or upper intestine [70]. For example, the enteric-coated capsules must remain intact in the stomach and disintegrate after a pH threshold is achieved (small intestine conditions). A polymer matrix or coating can modify the disintegration process to achieve the release profile expected [79].

There are not conclusive studies demonstrating disintegration differences among formulations of the same drug are responsible of differences in bioavailability. Mainly because delineating the contribution of disintegration and dissolution is not straightforward and not always the pharmacopoeial disintegration tests is discriminative or in line with *in vitro* dissolution or *in vivo* input.

Some authors have proposed a test to measure superdisintegrantes performance for IR tablets demonstrating the relationship with dissolution rate of aspirin tablets, but the potential *in vivo* relevance is not explored [80]. Nickerson *et al*. as well proposed disintegration test as surrogate of dissolution rate [81] for highly soluble drugs while other authors conclude there was not a clear relationship between disintegration time and dissolution rate [82]. For ODT Koner *et al* [83] have proposed a proposed new device with a good relationship between *in vitro* and *in vivo* disintegration times.

The development of biopredictive disintegration tests based on physiological variables as *in vivo* flow and shear rates are currently being attempted and will help to delineate the influence of disintegrants on *in vivo* disintegration [84]. Disintegration process can be different in fasted versus fed state associated with the increased viscosity of the medium, which interfere with the liquid penetration on the tablet. That mechanism could explain the negative food effect observed for some BCS class III compounds [85]. To characterize the effect of food on disintegration and compare three frequently used superdisintegrants croscarmellose sodium (CCS), cross-linked polyvinylpolypyrrolidone (CPD), and sodium starch glicolate (SSG) were assessed for their efficiency. Use of disintegrants that act without gelling or can counteract the effect of gelling is recommended for tablet formulations that have to be administered with food [86,87].

At a different level some authors have explored disintegrants effects not related with their formulation function (i.e. promote disintegration) but with their impact on permeability and drug solubility. Some disintegrants have shown *in vitro* in cell culture inhibition of P-glycoprotein (P-gp) and tight junction opening with rhodamine as model compound. The *in vivo* impact would need further research [11]. Solubility of drugs with different ionization degrees, lipophilicity values and solubility levels were measured in presence of sodium starch glycolate, sodium croscarmellose and crospovidone. Some differences were observed in solubility for drugs with high ionization degree but the authors concluded that the effects were not significant and probably other excipients could be more risky from a biopharmaceutical point of view as binders and lubricants [88].

5.2 Small intestine

Excipients generally included in formulations in standard amounts can affect the transit time, the drug solubility and permeability and consequently the absorption process.

5.2.1 Small intestinal transit time

The small intestine is undeniably the main place of absorption, therefore the time that an API is in the small intestine is crucial for its correct absorption. Consequently, a shorter small intestinal transit time can reduce significantly the absorption [89]. Several factors can modify the small intestinal transit time, among them there are

some excipients. For example, a statistically significant reduction of cimetidine AUC and Cmax values of healthy male volunteers was detected by Adkin *et al*. [90] when it was administered with mannitol. The decrease of these pharmacokinetics parameters was due to a reduction of small intestinal transit time. Moreover, a later study revealed a dose-dependent relationship between mannitol concentration and small intestinal transit time reduction; the higher mannitol concentration, the smaller intestinal transit time was obtained [91]. The effect of mannitol may be due to its osmotic effect, because an increase of the osmotic pressure can induce an increased peristalsis and water retention [36]. Furthermore, Chen *et al*. found out that sorbitol reduced ranitidine bioavailability in healthy volunteers. The authors attributed this finding to the osmotic effect of sorbitol and the increase of intestinal motility that reduce the contact time of ranitidine with the proximal small intestine decreasing its absorption [31]. Polyethylene glycol 400 (PEG 400) also reduces the ranitidine bioavailability as other osmotically active excipients (many sugar alcohols, and sodium acid pyrophosphate) [92], because PEG 400 (at elevated amounts 10 g) increase the intestinal motility and decrease the small intestinal transit time [93]. A subsequent clinical study by Schulze *et al*. [94] (also in male volunteers), with lower PEG 400 doses (1, 2.5 and 5 g) revealed a concentration dependent effects on transit and drug absorption. Surprisingly the presence of 1 g PEG 400 the absorption of ranitidine was increased by 41%. To investigate this unexpected result a further human clinical study by Ashiru *et al*. showed that PEG 400 enhances ranitidine bioavailability in male but not female subjects [95]. The proposed mechanism was P-gp inhibition. The differential effect on men and women could be attributed to differences in the expression of efflux and influx transporters, transit effects of PEG 400 and fluid volumes. Other preclinical studies with excipients (polyethylene glycol 2000, Cremophor RH 40, Poloxamer 188 and Tween 80) have shown differing effects on bioavailability in males and females attributed to the differential expression of P-gp [96].

At the other end on transit effects are the muco-adhesive polymers, which increase the intestinal transit time. Some examples are acrylic acid derivatives and methacrylate derivatives (Carbopol 974P and 971P), microcrystalline cellulose, natural polysaccharides (acacia gum and guar gum) or hydrogels chitosan base [94].

5.2.2 Solubility

According to the Biopharmaceutical Classification System (BCS), the solubility in water is one of the factors employed to classify drugs [1]. The API has to be dissolved to go through the small intestine membrane, therefore, the API solubility in the small intestinal fluids will determinate its absorption [97]. Because the intestinal fluids are aqueous, APIs with low water solubility will have a poor intestinal absorption.

Several excipients and formulation strategies are used to enhance API solubility and all of them represent the most evident demonstration of the excipient impact on absorption. Examples of precipitation inhibitors (for weak acid and bases), lipid-based formulation excipients, surfactants over their critical micelle concentration (CMC), co-solvents, and molecular containers as cyclodextrins are illustrated in this section.

Many APIs are weak acids or weak bases and their solubility is highly influenced by the pH of the medium [98,99]. Therefore, dissolved APIs in gastric fluids can precipitate when the solution goes from stomach to small intestine, which could result in a low oral bioavailability if re-dissolution is slow.

Developing drug formulations that provide an intestinal supersaturation, to obtain API concentrations higher than equilibrium solubility in the small intestinal lumen, is a way to achieve an adequate oral bioavailability with low solubility APIs [100,101]. The supersaturation is a metastable thermodynamic state and it is the driving force of the precipitation process. There are different methods to get the supersaturation of a compound: the solvent change [102], potentiometric methods [103] or pH change. As is well known, the pH change is a physiological process that happens throughout the GIT. Even along the small intestine, there are pH changes associated with the three small intestine segments: duodenum, jejunum and ileum. Therefore, the excipients could be employed to prolong the API supersaturation state to inhibit, as far as possible, the precipitation process in the small intestine and increase its absorption. For example, Yamashita *et al* carried out supersaturation studies according to the United States Pharmacopeia (USP) and revealed that the excipients poloxamer 407 and polyoxyl 40 monostearate can inhibit the precipitation using 96-well plates and bio-relevant media [104]. On the other hand, hydroxypropyl methylcellulose (HPMC) is an excipient widely studied with several drugs.

Bioavailability of tacrolimus, was increased in dogs by HPMC [105]. Paclitaxel shows approximately five-fold higher oral bioavailability with HPMC in the pharmacokinetic study conducted in male Sprague-Dawley rats. [106]. AMG 009 [107] andPNU-91325, showed a five-fold higher bioavailability *in vivo* in dogs, with HPMC [108]. In all those examples the proposed mechanisms were its ability to inhibit the precipitation and consequently, increase the bioavailability.

Li *et al*. used a weakly basic compound as a model compound to which they added; Vitamin E TPGS as a solubilizing agent and Pluronic F127, HPMC or Eudragit L100-55 as precipitation inhibitors.

The combination of Pluronic F127 with Vitamin E TPGS resulted in a synergistic effect in prolonging the concentration of the compound after dilution in simulated intestinal fluid. In addition, HPMC E5 and Eudragit L100-55 were found to be effective precipitation inhibitors for compounds tested in simulated gastric fluid. The solid dosage form pre-dissolved in simulated gastric fluid in dogs resulted in 52% oral bioavailability compared to 26% for suspension control, a statistically significant increase ($p = 0.002$). The increased oral bioavailability of the compound tested could be attributed to the generation and prolongation of a concentration of supersaturated drug *in vivo* by solubilizing agents and precipitation inhibitors [109].

Lipid-based formulations (LBF) are well known for their potential to enhance oral bioavailability and are used nowadays in more than 30 commercially approved medications [110]. Pouton proposed a classification system for these formulations [111]:

Type I contains oily components which need digestion for releasing the drug.

Type II are self-emulsifying drug delivery systems SEDDS) with oils and insoluble surfactants that also experience digestion.

Type IIIa or self-micro emulsifying drug delivery systems (SMEDDS) which form micro emulsions, containing oils, soluble and insoluble surfactants and cosolvents that may not need digestion.

Type IIIb which are similar to type IIa but with lower oil content and forming finer micro emulsions and finally

Type IV that does not contains oils but cosolvents and water soluble surfactants forming micellar solutions. In 2008 two groups were added [112] Proliposomes formed by phospholipids, and cholesterol matrix adsorbed on a carrier and liquid

crystalline nanoparticles comprised by polar lipid-based matrix stabilized by surfactants.

Solid lipid formulations have been reviewed elsewhere [113,114].

LBF are mainly used for lipophilic drugs (Log P> 2.5 with some exceptions) in order to enhance its solubilisation on intestinal milieu, in addition as most of them contains surfactants effects on the passive permeability and inhibition of efflux transporters cannot be ruled out [115]. They are mostly used for class II (dose-limited) and IV drugs [110]. Exceptions are ergocalciferol (BCS Class 3), valproic acid (BCS Class 1), ranitidine (BCS Class 3), and topotecan (BCS Class 1). For the Class I compounds the added advantage of LBF could be promoting the lymphatic absorption pathway thus minimizing metabolic first pass effect. For a BCS class III they might experience increased permeability and less food effect. Other reported advantage of LBF is to provide acceptable content uniformity of high potency/low dose drugs, to offer taste-masking and to enable the delivery of drugs with low melting points [116]. The use of colloidal carriers offers protection against enzymatic degradation in the gastrointestinal tract, this aspect in combination with the permeability enhancement makes this strategy good for peptide-type drugs [117]. One of the potential problems of some LBF is the precipitation of the drug upon dilution in the GI lumen thus, PPIs are also included in the formulation to avoid it. Predicting performance of LBF can be modelled *in vitro* by accurately simulating the *in vivo* conditions such as composition, volume, and hydrodynamics of the contents in the gastrointestinal lumen as well as the digestion processes if relevant for the drug release. Several *in vitro* biorelevant dissolution methods and lipolysis/digestion models have been recently reviewed, showing some successful level A *in vitro in vivo* correlations [114,118–120].

The use of soluble cosolvents (glycols, PEG's, methacrylate copolymers etc) and molecular containers as Cyclodextrins are another approaches to increase drug apparent solubility and promote absorption. Nevertheless, based on rat perfusion studies some authors have proposed that a solubility-permeability trade off exists so a careful selection of the cosolvents/container amount and solubility enhancement must be done in order to avoid excessive decrease in the permeability [121–125]. Other effects of Cyclodextrins as permeation enhancers are discussed in the next section.

5.2.3 Permeability

The permeability is the ability of the molecules to go through the intestinal membranes from the lumen to the bloodstream. This parameter is directly related to the bioavailability and oral absorption of drugs [126]. Permeation enhancers can exert this effect through several mechanisms [127]:

- Membrane fluidification
- Payload solubility change
- Tight junctions opening
- Hydrophobization of payload
- Decreasing mucous viscosity
- Inhibition of efflux carriers
- Direct and indirect peptidase inhibition

Only the non-ionized fraction of a molecule can cross the biological membranes. Most of APIs are weak acids or weak basis, so changes in their charge will conditioning their permeability. Therefore, if an excipient alters the environment pH, the permeability of easily ionisable molecules could change, as happens with metformin tested in diabetic rats [128]. Another point to consider is the charge of the excipients. If an ionisable API is included, in a drug formulation with an excipient of opposite charge, both can make an ion-pair and the API could experiment a considerable rise of permeability. The ion-pair formation is a useful strategy employed to increase the permeability of low intestinal permeability drugs. For example, Samiei *et al*. demonstrated how the succinic acid increases the oral absorption of amifostine in Rat *in situ* and *in vivo* experiments because both molecules make an ion-pair improving the intestinal permeability of amifostine [129]. Lozoya-Agulló *et al*. also proved the usefulness of the ion-pair strategy to increase the permeability, in this case the atenolol permeability was enhanced with brilliant blue in Rat *in situ* experiments [130].

Some excipients are able to modify the intestinal membrane structure. They can have an effect on intercellular tight junctions or can interact with membrane lipids, causing chemical and physical changes in the intestinal membrane [131]. The most common and well known example is the group of the surfactants [132–136]. They

decrease the membrane visco-elastic properties and increase its elasticity, which results in an increment of molecules permeability by paracellular and transcellular route [80,81]. The mannitol transport is mainly by paracellular route; therefore, it is employed as paracellular marker to detect changes in tight junctions [131]. The Caco-2 permeability of mannitol was studied in presence of different excipients. The biggest increase in the permeability value was obtained with the anionic surfactant sodium lauryl sulphate in Caco-2 studies [139]. The same study showed that sodium lauryl sulphate also improved the permeability of low permeability drugs such as atenolol, cimetidine, or hydrochlorothiazide. The authors suggest that sodium lauryl sulphate produces a break of tight junctions and, thus, increases the distance between intestinal cells [140]. Takizawa *et al* studied the effect of excipients on paracellular route with other paracellular marker: 5(6)-carboxyfluorescein. They assessed the intestinal permeability of this marker in rat jejunum and rat ileum in presence of the excipients methyl-β-cyclodextrin, sodium carboxymethyl cellulose, hydroxypropyl cellulose and croscarmellose sodium. All of them increased the permeability of 5(6)-carboxyfluorescein in jejunum, but not in ileum. These results suggest that the paracellular route is more sensitive to changes in jejunum than in ileum [141]. Another excipient that can affect the paracellular route is EDTA (ethylenediamine tetraacetic acid). EDTA is used as preservative in several formulations and it can cause the complexation of the calcium present in the extracellular fluid. This calcium is involved in the tight junctions' regulation. Hence, EDTA can increase the permeability of drugs with paracellular transport [131,142]. On the other hand, Larocque *et al* demonstrated the ability of sodium bicarbonate to modify the interaction of fluvastatin with membrane phospholipids of model DMPC/DMPS membranes *in vitro*. Therefore, the passive transport due to transcellular route will be disturbed [143].

Cyclodextrins not only are used to increase solubilisation but some results in preclinical models (rat perfusion and Caco-2 monolayers) indicate that cyclodextrins can enhance intestinal membrane permeability of some lipophilic compounds (curcumin, beta-lapachone) in both transcellular and paracellular route [144,145]. Increased extent of absorption of curcumin in humans has been demonstrated for cyclodextrin formulations [146]. Hydroxypropyl-β-cyclodextrin grafted polyethylenimines (HP-β-CD-PEI) have been also proposed as permeation enhancers in rat perfusion model with tight junctions opening as proposed

mechanism [147]. Sulfobutylether-β-cyclodextrin was able to increase amiodarone absorption in dogs but the proposed mechanism was the improvement in solubility and dissolution [148].

Intestinal permeation enhancers to improve transport of poorly absorbed API across the intestinal epithelium are widely known. In the review by Sam Maher *et al* [149] it is pointed out that some of the experimental method to explore enhancers effects do not consider the dynamic environment in the gastrointestinal tract *in vivo* (for example, intestinal fluid volume and tonicity, and exposure time). The main difficulty to success in permeation enhancement is the simultaneous delivery of the drug and the enhancer in a high concentration for as long as possible.

Some permeation enhancers have reached clinical and commercial formulations with an effective increase in oral bioavailability such as those studied by Twarog *et al* [127]. Salcaprozate sodium (SNAC) and sodium caprate (C10) are two of the most advanced intestinal permeation enhancers that have been tested in clinical trials for oral delivery of macromolecules. Comparing the two surfactants, evidence was found for discrete mechanisms at the level of epithelial interactions in the small intestine, especially at the high doses used *in vivo*. Regarding safety, SNAC has generally regarded as safe (GRAS), whereas C10 has a long history of use in man, and has food additive status. Evidence for co-absorption of microorganisms in the presence of either SNAC or C10 has not emerged from clinical trials to date, and long-term effects from repeat dosing beyond six months have yet to be assessed.

Carrier mediated transport mechanisms are involved in the permeability of many molecules. Some excipients can interact with transporters and modify the API oral absorption. The interaction of excipients with influx transport mechanisms could reduce the permeability of their substrate. On the other side, the interaction with efflux transport mechanism could increase the permeability [131]. Moreover, due to the different distribution of the transporters along the small intestine, an excipient can affect the same API differently depending on the intestinal segment (duodenum, jejunum or ileum). The most studied transport mechanism is P-glycoprotein (P-gp, ABCB1), a secretion transporter expressed on the apical side of enterocytes. There are many documented cases of excipients interactions with P-gp. For example, polysorbate 80 showed a significant increase of digoxin bioavailability in rats, due to its interaction with the apical membrane of intestinal cells which produces the P-gp inhibition [150]. In fact, the surfactants with high HLB (hydrophilic-lipophilic balance)

(between 10 and 17) such as Span 80, Brij 30, polysorbate 80, Myrj 52 or sodium lauryl sulphate, have increased ability to inhibit the P-gp in Caco-2 Cells, resulting in an enhanced drugs bioavailability [151]. Shen *et al* demonstrated how the excipients PEG 400, 2000 and 20000 reduce the secretory activity of P-gp in presence of the P-gp substrate rhodamine 123 in rat intestinal membrane [152]. D-α-Tocopheryl Polyethylene Glycol 1000 Succinate also inhibits the P-gp secretion in Caco-2 [153]. In this case, the inhibition happens by steric hindrance [154], therefore, there is an increase of permeability of P-gp substrates as doxorubicin, vinblastine and paclitaxel in Caco-2. Excipients can affect different transport processes simultaneously, for example, Batrakova *et al* demonstrated how Pluronic block copolymers inhibit the secretion process of P-gp and MRP (Multidrug Resistance Proteins) in different cell lines (COR-L23/R, MDCKII-MRP2, and LLC-MDR1) These compounds not only block the ATPase activity of transporter proteins, but also produce a decrease in available intracellular ATP [155]. Topotecan a substrate of ABCG2/BCRP (Breast Cancer Resistance Protein) showed an increased permeability in presence of Polysorbate 20 and cremophor EL and this effect was also observed with *in situ* perfusion studies in rats [156] and in vivo in mice [157]. Surfactants may inhibit the activity of ATP-binding cassette (ABC) transporters but also solute carriers (SLC). This overlap has been observed at least in cell culture models with cremophor® EL and Solutol® HS 15 [14]. Polysorbate 20 increased absorptive transport of digoxin by P-gp inhibition in Caco-2 cell and *in vivo* in rats in a concentration dependent manner [158]. Different studies and laboratories found different effective concentrations for the enhancing effect of the surfactant and on the other hand, the effective enhancer concentrations *in vitro* are much lower than the needed ones in the *in vivo* setting. As mentioned earlier this can be related with the dilution of the surfactant *in vivo* on the intestinal fluids. Cyclodextrins can also interact with different secretion transporters, specifically P-gp and MRP2, as demonstrated Arima *et al* with Caco-2 model cells [159]. Furthermore, the same authors showed that 2,6-di-O-methyl-β-cyclodextrin increases the oral bioavailability of tacrolimus in rats by inhibition of P-gp and MRP2 [160]. Indirect mechanisms to inhibit transporters have also been observed, for example, surfactants can affect intestinal cells membrane fluidity and modify the cell microenvironment impairing the recognition of the substrates by the transporter protein. [161].

Polyacrylates (acrylic polymers) can act as surfactants or chelators. It has been shown that these compounds can complex bivalent cations such as zinc and calcium and consequently difficult the association of these ions with their transporter proteins and thus prevent their activity in Caco-2 [162].

The modification of permeability by excipients is a big problem for narrow therapeutic index APIs. In this case, if the permeability decrease, the patient will not have the expected response; nevertheless, if the permeability increases, the patient will experiment toxicity. A well-known example is the cardiac glycoside, digoxin. Digoxin is a P-gp substrate, therefore, other drugs, food or excipients can interact with the efflux transporter and modify its permeability [163,164]. Inhibiting the efflux can cause a very high bioavailability rise. For example, Tayrouz *et al* showed how the digoxin bioavailability increases by 20% when it is administered to healthy individuals with Cremophor RH40 as excipient [165].

Permeability enhancers are receiving increased attention arising from their ability to increase trans epithelial permeability and thus, oral bioavailability of but also for their potential cytotoxicity [166]. The question arises as to whether permeability enhancers can cause irreversible epithelial damage and tight junction openings sufficient to permit co-absorption of payloads with bystander pathogens, lipopolysaccharides and exo- and endotoxins that may be associated with sepsis, inflammation and autoimmune conditions [167,168]. For instance, both melittin and Sodium caprate (C10) improved bioavailability of polar sugars across the jejunum and colon of rats *in situ*, which was associated with some degree of mucosal damage. Histology of intestinal sections exposed to either promoter showed mild mucosal damage (truncation of microvilli, and sloughing) at those concentrations effective at promoting absorption [169]. Medium chain fatty acids (sodium caprylate and caprate), cyclodextrins (beta-cyclodextrin, hydroxypropyl beta-cyclodextrin) and bile salts (sodium cholate and deoxycholate) were compared for their enhancing ability with low permeability hydrophilic and lipophilic compounds. These permeability enhancers were found to enhance intestinal permeability of drugs from 2- to 27-fold in rat everted sacs. Rank order of toxicity were cyclodextrins>bile salts ~ medium chain fatty acids [170]. In vitro testing on Caco-2 intestinal cells of lactose-based non-ionic surfactants showed that these excipients present cytotoxic activity over their CMC producing mitochondrial membrane depolarization, increasing nuclear membrane permeability and activation of effector caspases. Nevertheless,

the same substances applied at non-toxic concentrations produced a reversible increase of the transepithelial electrical resistance (TEER), by opening tight junctions, making possible their use as safe permeability enhancers. [171]. An study with *in vitro* Ussing chamber method of permeability enhancers for Insulin showed that sodium glycocholate, sodium caprate and n-lauryl-beta-D-maltopyranoside are useful absorption enhancers due to their high absorption enhancing effects and low intestinal toxicity [172].

Although several clinical pilot studies have demonstrated that the oral absorption of macromolecules is possible, the bioavailability remains generally low and variable [173]. The most successful approaches for systemic delivery often involve a combination of enteric coating, protease inhibitors and permeation enhancers in relatively high amounts. However, some of these excipients have induced local or systemic adverse reactions in preclinical and clinical studies, and long-term studies are often missing. Therefore, strategies aimed at increasing the oral absorption of macromolecular drugs should carefully take into account the benefit-risk ratio.

Dahlgren *et al* [174] demonstrate in a rat single-pass intestinal perfusion study that a rapid absorption-modifying excipients effect on the mucosa is needed to increase the absorption rate before the yet unabsorbed drug in the lumen has been transported distally in the intestine. Other single-pass intestinal perfusion study [175] investigated the effects on permeability of SLS, caprate and chitosan and how their effects are affected by luminal hypotonicity, nicotinic receptor blockade, and selective COX-2 inhibition. The authors conclude that the *in vivo* relevance of absorption data from perfusion models may be improved by protecting the normal intestinal functions as motility. Evaluation of transport in lumen to blood and blood to lumen directions was also suggested. Dahlgren *et al* also investigated the effect of absorption-modifying critical excipients on the *in vivo* intestinal absorption in rat and dog [176]. SLS and chitosan exerted an absorption-enhancing effect in both *in vivo* bolus models, but the effect was substantially lower than the observed in the rat single-pass intestinal perfusion model. In conclusion, the enhancers effects on the membrane need to be evaluated considering additional gastrointestinal physiological factors. These observations could have profound implications for evaluation of BE and for BCS guidelines, when the types and amounts of excipient are changed.

Osmolarity can also modify the permeability of common drugs and as previously discussed the excipients can also modify osmolarity. It is especially important in

pharmaceutical forms that are saturated like syrups as delMoral-Sanchez *et al* proved with *in situ* experiment in rats [26].

5.3 Colon

5.3.1 Oral controlled release formulations absorption

Oral controlled release (CR) formulations are drug products whereby the API release is modified, either retarded or sustained, and prolonged in time. Therefore, a large part of the absorption process will take place in colon. [79].

The excipients employed in oral CR formulations have a concrete function. For example, pH sensitive polymers as Eudragit or cellulose acetate phthalate are employed to coat the drug and release the API under colonic pH conditions [177,178]. Cyclodextrins are employed as carriers that enable the action of colonic bacteria to release the API in colonic lumen [177,179]. A shell of ethyl cellulose coating a capsule can be employed to take advantages of the effect of pressure in the colonic lumen [180]. Most of CR formulations need a mixture of excipients to reach their aims. A representative example are the osmotic drug delivery systems. They need, among others excipients, swellable polymers (vinyl acetate copolymer or polyethylene oxide), wicking agents (colloidal silicon dioxide or kaolin), resins (poly (4-vinyl pyridine) or citric acid), osmotic agents (magnesium chloride, sodium and potassium acetate, mannose, sucrose, organic polymeric osmo-agents, etc.), semipermeable polymers (cellulose acetate or eudragits), plasticizers (polyethylene glycols, diethyl tartrate) [181–183].

Nowadays, the scientific and technological advances allow developing more complex and sophisticated CR systems. For example, micro and nanotechnology or the employment of functionalized excipients can be used to develop different strategies with the objective of controlling drug delivery [184–188]. However, it should not be forgotten that if new materials are employed as excipients they have to be assessed in terms of safety and potential interactions with the API that can modify its stability or pharmacological effect.

Table 1. Examples of excipients that affect oral absorption process and potential applications of their effects.

Gastrointestinal segment	Process/physiological variable	Excipient	Effect	Potential application	Reference
Stomach	Gastric emptying	Saccharose	Gastric emptying delayed	-	[66]
		Sodium bicarbonate	Fast gastric emptying	Higher acetaminophen absorption	[28]
	Disintegration	Croscarmellose sodium	Fast disintegration	Orodispersible tablets development	[28,77,78]
Small intestine	Metabolism	PEG400	Cytochrome P450 3A4 (CYP3A4)	Inhibit API metabolism to increase bioavailability	[45]
	Small intestinal transit time	Mannitol	Transit time reduction	-	[90]
		Carbopol 974P	Transit time increase	Muco-adhesive products development	[94]
	Solubility	HPMC	Prolong API supersaturation state	Inhibit API precipitation to increase absorption	[105–107]
	Permeability	Succinic acid	Ion-pair formation	Amifostine permeability improvement	[129]
		Sodium lauryl sulfate	Intestinal membrane changes	Permeability improvement of low	[139]

				permeability drugs	
		Polysorbate 80	P-gp inhibition	Digoxin bioavailability increase	[150]
Colon	CR formulations absorption	Eudragit	API release under colonic pH	Delayed API absorption	[177,178]
		Magnesium chloride	Osmotic agent	Osmotic drug delivery systems development	[181–183]

HPMC: hydroxypropyl methylcellulose; API: Active Pharmaceutical Ingredient; P-gp: P-glycoprotein; CR: Controlled Release.

6. Expert opinion

The studies carry out to date evidence that the excipients influence on oral drug absorption cannot be overlooked and must be assessed either to improve absorption or to ensure bioequivalence. The effects of excipients on any process involved in oral absorption (gastric emptying, disintegration, intestinal transit time, permeability) will impact the API bioavailability, increasing or decreasing it which is a serious problem for APIs of narrow therapeutic index. A particular excipient can affect the absorption by several mechanisms depending on the gastrointestinal segment where it is released. To avoid absorption problems related with excipients, standardized and reproducible tests are needed. Nowadays the regulatory approval of any new excipient requires its toxicological evaluation and the ADME characterization of the excipient itself but it is not mandatory but optional the assessment of their effects on GI physiology in the case of excipients intended for the oral route [189]. The validation of *in vitro* and animal test (as cell cultures, artificial membranes, animal intestinal perfusion methods and animal *in vivo* models) with regard to their predictive ability for excipient effects in humans is a necessary step. Identification of mechanism in each model and their scaling up to humans will be essential thus big databases and mechanistic PBPK models as the ones used for drug absorption must

be implemented [190,191]. Not only the new excipients have to be assessed, also the already approved excipients require to be re-visited to characterize their effects on the GI tract. To prevent not desired excipient effects or to profit those effects to improve absorption, the BCSE could be completed and it could be employed as a tool in combination with BCS not only to improve the quality and safety of new oral pharmaceutical forms but also to improve the chances of success in bioequivalence trials of generic drug formulations. API-excipient interaction can be different across BCSE and BCS classes i.e. excipients could be considered “inert” for a particular drug but not for another. Therefore, the correct excipients to develop oral drug formulations would be chosen and biowaivers would be stablished safely. BCSE information should be extended, both for excipients already used and for those that will arise in the future. In the future, this knowledge and tools coupled with PBPK modelling could save time and money in product development by ensuring a predictable effect on human bioavailability in clinical trials [192,193].

Table 2. Examples of excipients that have shown effects on oral absorption through permeability and or dissolution modification and the experimental models used to characterize their effect.

Excipient	**Drug**	**BCS Provisional class**	**Suggested mechanism**	**Experimental method**	**Effect on absorption**	**Reference**
Acconon E	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat *in vivo*	Increase	[194]
Aluminium Hydroxide	Dicumarol	II	Drug adsorption	Dogs study	Decrease	[195]
Carbopol 934	Amoxicillin	III	MRP (abcb) by reversible ATP depletion	rat jejunum, mounted in side-by-side diffusion cells	No change	[196]
Carboxymethylcellulose calcium	Methylprednisolone	IV	Inhibition P-gp (abcb1)	*in situ* rat intestinal loop	Increase	[197]
Cyclodextrin	Several drugs	Class II-IV	Improved solubility, dissolution	Rat *in vivo* Human	Increase	[198]
Cremophor EL	bromosulfophthalein		OATP1A2, OATP1B3, and	transfected human	decrease	[46]

			OATP2B1	embryonic kidney cells		
	Digoxin	II	abcb1, abcb11, SLC	Everted gut sac and Rat *in vivo*	Increase	[194]
	P-gp substrates		Inhibition P-gp (ABCB1)	Caco-2	Partial Inhibition	[199,200]
	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat in vivo	Increase	[194]
	Amoxicillin	III	MRP not identified (abcb)	Rat jejunum, mounted in side-by-side diffusion cells	=	[196]

	Mitoxantrone	IV	Inhibition of BCRP (abcg2) and P-gp (abcb1)	Transfected MDCK-II cells	Increase	[201]
	Calcein-AM	IV	Inhibition P-Glycoprotein (ABCB1) and MRP2(ABCC2)	Transfected MDCK-II cells	Inhibition	[202]
	Talinolol	II	Inhibition P-Glycoprotein (ABCB1)	Caco-2 cells	Increase	[203]
Cremophor RH40	Digoxin	II	Inhibition P-gp (ABCB1)	*in vivo* Humans	Increase	[165]
Croscarmellose	5(6)-carboxyfluorescein	III	Increase paracellular transport	Rat everted gut sac	Jejunum Increase	[141]
Docusate Sodium	Cimetidine	III	Not explained	Caco-2	Increase	[139]
Ethanol	Talinolol	II	Inhibition P-gp (ABCB1)	Caco-2	Increase	[203]

HPMC	Acyclovir, Antipyrine, Ganciclovir	III	Not explained	Caco-2 , Rat *in situ*	=	[204]
	Atenolol, Nadolol	III	Not explained	Caco-2 , Rat *in situ*	=	[204]
	5(6)-carboxyfluorescein	III	Increase paracellular transport	Rat everted gut sac	=	[141]
Imwitor	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat *in vivo*	Increase	[194]
Labrasol	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat *in vivo*	Increase	[194]
Lactose	Acyclovir, Antipyrine, Ganciclovir	III		Caco-2 , Rat *in situ*	=	[204]
	Atenolol, Nadolol	III		Caco-2 , Rat *in situ*	=	[204]

	5(6)-carboxyfluorescein	III	Increase paracellular transport	Rat everted gut sac	=	[141]
Lecithin	Curcuminoids		Not explained (improved solubility?)	Double-blind, crossover human study	Increase	[205]
SLS	Risperidone	II	unexplained	Human study	Decrease bioavailability (small amount)	[19]
	Alendronate Sodium	III	unexplained	Human study	Increase	[19]
	Amoxicillin	III	SLC	rat jejunum, mounted in side-by-side diffusion cells	Increase	[196]
	Chlorpromazine	III	Micellar solubilization	*in vitro*: dimethyl polysiloxane	Decreased	[206]

				membrane		
Lutrol	Amoxicillin	III	SLC	rat jejunum, mounted in side-by-side diffusion cells	=	[196]
Magnesium Stearate	Cetylpyridinium Chloride			Caco-2	(reduce antimicrobial activity)	[207]
	Acyclovir, Cimetidine		SLC	Caco-2	Decrease	[208]
Microcrystalline cellulose	Methylprednisolone		P-Glycoprotein, abcb1	*in situ* rat intestinal loops	Increase	[197]
	Indomethacin	II	SLC, ABCC family	Caco-2	Increase	[209]
Miglyol	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat	Increase	[194]

				in vivo		
Sucrose monolaurate	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat *in vivo*	Increase	[194]
PEG 400	Ranitidine	III		Human study	Decrease	[95]
	Ranitidine	III		Human study	Increase	[95]
Pluronic L61	Low Solubility drugs			Planar Membranes	Increase	[210]
Pluronic 50	Amoxicillin	III	SLC	Diffusion Camera	=	[196]
Pluronic P85	Topotecan	I	abcg2	Rat *in vivo*	Increase	[157]
PEG 400	Ranitidine	III	ABCB1, SLC	Human study	Increase	[94]
	Rhodamine		P-Glycoprotein: abcb1	side-by-side diffusion cells	Increase	[211]
	Talinolol	II	P-Glycoprotein: abcb1	Caco-2	Increase	[203]

PEG 400	Midazolam	I		Rat *in vivo*	Increase bioavailability	[45]
PEG 4000	Phenobarbital	I	abcb1, abcc3,abcb11, abcc1, abcc2, SLC	Rat intestine: everted intestinal sac	Decrease	[212]
Polysorbate 20	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat *in vivo*	Increase	[158,194]
	Low Solubility drugs			*in vitro* Cells	Increase	[201]
	Topotecan	I	abcg2	Mice *in vivo*	Increase bioavailability	[157]
Polysorbate 80	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat *in vivo*	Increase	[194]
	Talinolol		Inhibition P-gp (abcb1)	Rat in vivo	Increase	[203]
	Talinolol		Inhibition P-gp (abcb1)	Caco-2	Increase	[203]

	P-gp substrates		P-Glycoprotein: ABCB1	Caco-2	Decrease	[199,200]
	Rhodamine		P-Glycoprotein:ABCB1	rat intestine, mounted in side-by-side diffusion cells	Increase (Low dose)	[213]
	Ganciclovir			Caco-2	Increase	[214]
	Digoxin	II	Inhibition P-gp (abcb1)	Rat everted gut sac	Increase	[215]
Colloidal Magnesium Aluminum Silicate		II	Drug adsorption	Dog study	Decrease	[195]
Sodium cholate	Melatonin	II	SLC	side-by-side diffusion cells	Increase	[216]
Sodium Oleate	Melatonin	II	SLC	side-by-side diffusion cells	Decrease	[216]
Solutol HS	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat *in vivo*	Increase	[194]

Sorbitol	Risperidone	II	unexplained	Human study	Decrease bioavailability (small amount)	[13,19]
	Ranitidine	III	ABCB1 SLC	Human study	Decreased small intestinal transit time Decrease bioavailability	[13,89]
Starch	Dicumarol	II	Drug adsorption	Dogs study	Decrease	[195]
Talc	Dicumarol	II	Drug adsorption	Dogs study	Decrease	[195]
	Chlorpromazine	III	Adsorption	*in vitro*: dimethyl polysiloxane membrane	Decrease	[206]
	5(6)-carboxyfluorescein	III	Increase paracellular transport	Rat everted gut sac	=	[141]

TPGS	Cyclosporine	IV	Solubilisation, P-glycoprotein inhibition	Human study	Increase	[217]
Vitamin E TPGS	Digoxin	II	Inhibition P-gp (abcb1)	Everted gut sac and Rat *in vivo*	Increase	[194]

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*** Recommendation for the utility of excipients when precipitation of poorly soluble drugs wants to be avoided.**

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