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Review

The Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS): Beyond guidelines

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ABSTRACT

The recent impact of the Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS) on relevant scientific advancements is discussed. The major advances associated with the BCS concern the extensive work on dissolution of poorly absorbed BCS class II drugs in nutritional liquids (e.g. milk, peanut oil) and biorelevant media for the accurate prediction of the rate and the extent of oral absorption. The use of physiologically based pharmacokinetic (PBPK) modeling as predictive tool for bioavailability is also presented. Since recent dissolution studies demonstrate that the two mechanisms (diffusion- and reaction-limited dissolution) take place simultaneously, the neglected reaction-limited dissolution models are discussed, regarding the biopharmaceutical classification of drugs. Solubility- and dissolution-enhancing formulation strategies based on the supersaturation principle to enhance the extent of drug absorption, along with the applications of the BDDCS to the understanding of disposition phenomena are reviewed. Finally, recent classification systems relevant either to the BCS or the BDDCS are presented. These include: i) a model independent approach based on %metabolism and the fulfilment (or not) of the current regulatory dissolution criteria, ii) the so called ABΓ system, a continuous version of the BCS, and iii) the so-called Extended Clearance Classification System (ECCS). ECCS uses clearance concepts (physicochemical properties and membrane permeability) to classify compounds and differentiates from BDDCS by bypassing the measure of solubility (based on the assumption that since it inter-correlates with lipophilicity, it is not directly relevant to clearance mechanisms or elimination).

"All models are wrong but some are useful"
George Edward Pelham Box (18 October 1919–28 March 2013)

1. Introduction

This review focuses on the advances made in the field of biopharmaceutical classification of drugs and relevant research from 2006

Abbreviations: API, active pharmaceutical ingredient; BCS, biopharmaceutical classification system; BDDCS, Biopharmaceutics Drug Disposition Classification System; BDM, Biorelevant Dissolution Media; BP, British Pharmacopeia; CR, Controlled Release; DCS, Developability Classification system; DDI, Drug – Drug Interactions; DM, Dissolution Media/Medium; EP, European Pharmacopeia; ER, Extended Release; FaSSCoF, Fasted State Simulated Colonial Fluid; FaSSGF, Fasted State Simulated Gastric Fluid; FaSSGF V2, Fasted State Simulated Gastric Fluid Version 2; FeSSGF, Fed State Simulated Gastric Fluid; FaSSIF, Fasted State Simulated Intestinal Fluid; FaSSIF, 1st version of FaSSIF; FASSIF V2, Fasted State Simulated Intestinal Fluid Version 2; FASSIF V3, Fasted State Simulated Intestinal Fluid Version 3; FESSIF, Fed State Simulated Intestinal Fluid; FeSSIF, 1st version of FeSSIF; FeSSIF V2, Fed State Simulated Intestinal Fluid Version 2; FeSSCoF, Fed State Simulated Colonial Fluid; GIT, Gastrointestinal Tract; IP, International Pharmacopeia; IVIVC, In vitro in vivo correlations; IR, Immediate release; PBPK, Physiologically Based Pharmacokinetic; MR, Modified release; SDDS, Supersaturated drug delivery systems; SGF, Simulated Gastric Fluid; SIF, simulated intestinal fluid; USP, United States Pharmacopeia

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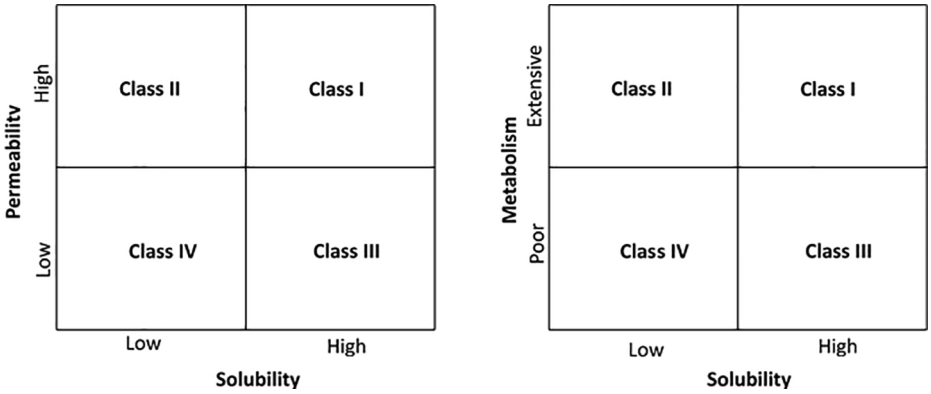

Fig. 1. BCS (left) and BDDCS (right) presented in a Cartesian spatial perspective.

to date. In a previous review (Dokoumetzidis and Macheras, 2006) Dokoumetzidis and Macheras recognized the importance of dissolution to the biopharmaceutical classification of drugs and the first ever dissolution study, published in 1897 (Noyes and Whitney, 1897), was linked to the Biopharmaceutics Classification System (BCS) proposed in 1995 by Amidon et al. (1995). BCS has been endorsed by regulatory organizations and agencies and is incorporated in guidelines for biowaiver granting (European Medicines Agency, 2010; ICH M9 on BCS based biowaivers, 2018; WHO Biowaiver list, 2018; U.S. FDA, 2017; WHO, 2006). Based on aqueous solubility and intestinal permeability (Fig. 1), the four classes of the BCS represent four distinct expectations of *in vitro-in vivo* correlations (IVIVC). These expectations underline the importance of drug dissolution for the biopharmaceutical classification of drugs; in fact, specific dissolution criteria have been incorporated in all regulatory biopharmaceutical guidelines.

According to the guidelines of the FDA (U.S. FDA, 2017), a drug substance is considered to be "highly soluble" if the highest dose strength of the drug can be dissolved in ≤ 250 mL of aqueous media at a pH from 1 to 6.8 (including pH = pKa, pH = pKa + 1 and pH = pKa-1) and a temperature of 37 °C ± 1 °C. For a drug dose larger than the highest drug strength, additional data are required. Chemical stability of the substance must be guaranteed for a period that includes the last dissolution time point plus the time required for the slowest analysis method.

"High permeability" is granted if the fraction absorbed reaches 85% or more, of the dose administered, based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or compared to a referred I.V. dose. When it comes to prodrugs, permeability is influenced by the anatomical site and the mechanism of the prodrug to drug reaction. If the reaction happens after the intestinal permeation, then permeability must be measured for the prodrug. For a prior to intestinal permeation reaction, permeability must be determined for the drug itself.

Finally, the drug product is considered "rapidly dissolving" when ≥ 85% percent, dissolves within 30 minutes (or 15 min for "very rapidly dissolving"). For the dissolution test, USP, BP or IP standard apparatus are being used: Apparatus I (Basket Apparatus) at 100 rpm or Apparatus II (Rotating paddle apparatus) at 50 rpm – or at 75 rpm, if properly justified – in a volume of 500 mL or less in each of the following media:

1) 0.1 N HCl or USP specified simulated gastric fluid (SGF) without enzymes
2) A pH 4.5 buffer
3) A pH 6.8 buffer or USP specified simulated intestinal fluid (SIF) without enzymes

The main purposes of the BCS classification is to improve the efficiency of drug development and meet the challenges of formulation design, allow prediction of *in vivo* pharmacokinetic performance of drug products from measurements of permeability (determined as the extent of oral absorption) and solubility (Wu and Benet, 2005), and for biowaiver status granting of *in vivo* bioequivalence studies (Camenisch, 2016; Bodhe and Kaur, 2018). Biowaiver acceptance is given to Class I immediate release (IR) solid dosage forms if they fulfill the criteria of high solubility and permeability and also rapid dissolution. It also must not contain any excipients that will affect the rate or extent of absorption. In addition, biowaivers may be granted to products of Class III compounds. In that case, Class III IR solid dosage form must meet the solubility and dissolution criteria of the reference product for Biowaiver granting plus a quantitative and qualitative similarity to the Class III accepted compound. Excipients must be the same, as they can drastically affect the characteristics of low permeability drugs (Camenisch, 2016; Levin, 2001).

Wu and Benet introduced in 2005 a derivative classification system, the Biopharmaceutics Drug Disposition Classification System (BDDCS) (Wu and Benet, 2005), after recognizing a strong association between the intestinal permeability and the extent of metabolism. Fig. 1 depicts the BCS and the BDDCS in a Cartesian spatial perspective. Since *in vitro* and *in vivo* permeability estimates not always predict the extent of oral drug absorption, BDDCS has gained wide acceptance (European Medicines Agency, 2010; U.S. FDA, 2017; Verbeeck and Musuamba, 2012); Moreover, BDDCS serves as a complementary tool by predicting the role of transporters in drug disposition and drug-drug interactions (DDIs). According to Chen et al, both BCS-based permeability and BDDCS-based metabolism can be used as a surrogate for the extent of drug absorption and support for a waiver of *in vivo* bioequivalence studies (Chen et al., 2011).

The establishment of the BCS has significantly affected the pharmaceutical industry and hence the scientific development. Particularly, tools to understand *in vivo* performance of BCS class II compounds (low solubility, high permeability) as well as exploration around advanced drug delivery strategies for such compounds took off after the introduction of BCS. A simple search in Pub Med for example, reveals that the number of publications using the keyword "Biorelevant Dissolution Media" gives a sum of 189 publications for the last 13 years, 171 for the last decade and 124 for the last 5 years.

From the industrial perspective, the use of predictive dissolution modeling during pharmaceutical formulation and process development was enhanced remarkably. Extensive dissolution work using Biorelevant Dissolution Media (BDM), coupled or not with *in vivo* studies and physiologically based modeling, were carried out to assess/predict the bioavailability and the time course of Class II compounds in the body. Different solubilizing and supersaturating drug delivery systems such as lipid-based formulations (LBFs) and formulations making use of the amorphous form were more extensively explored. In parallel, the use of BDDCS prompted many studies in the area of drug disposition mechanisms and phenomena (Khandelwal, 2007).

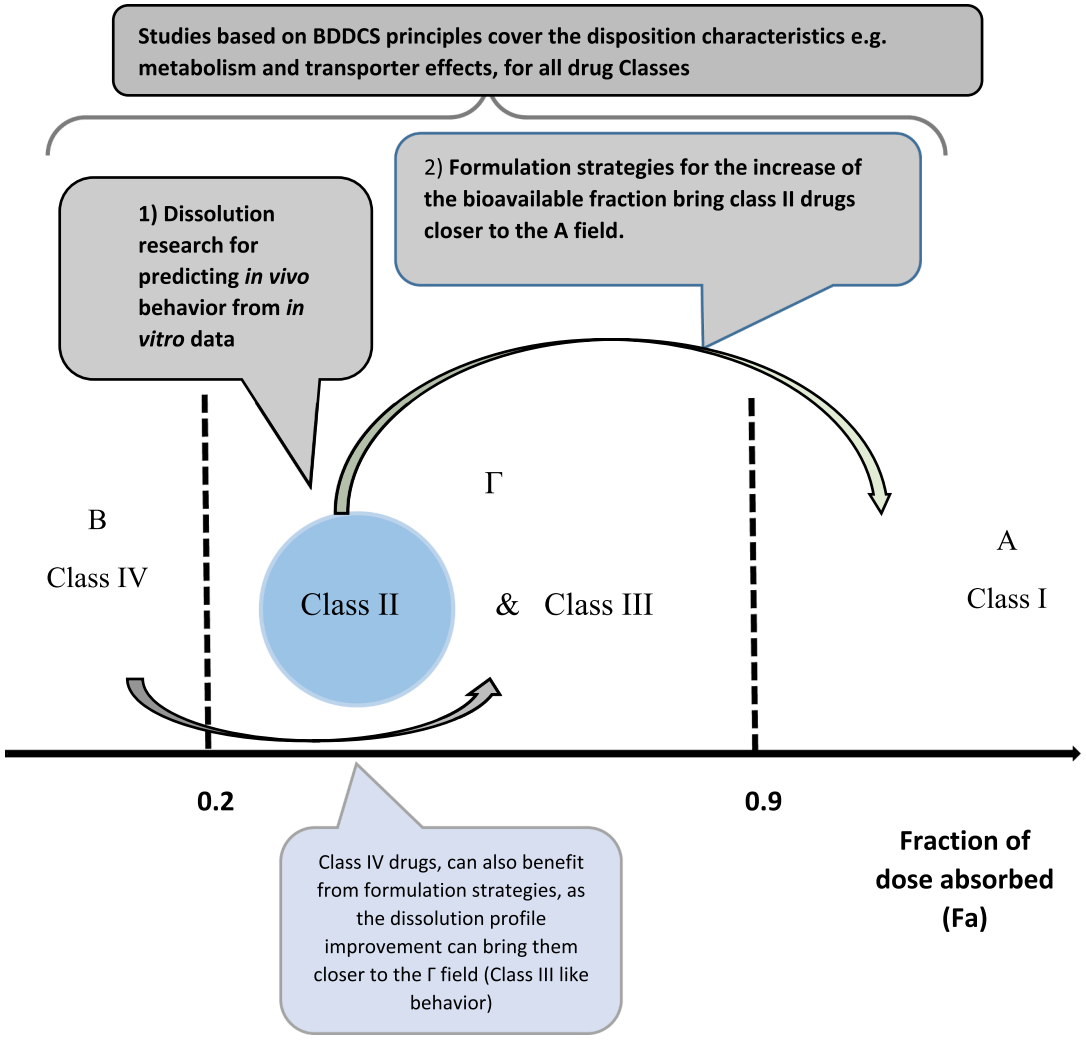

Fig. 2. The four biopharmaceutical drug classes embedded along with the fraction of dose absorbed, F_a axis, following the ABΓ classification system (Macheras and Karalis, 2014). Two main research avenues that change the scenery for class II drugs are indicated: 1) advances in the field of dissolution testing for absorption predictive purposes & 2) formulation strategies that increase the bioavailable fraction, move class II drugs closer to the extent of absorption of class I drugs. Note that class IV drugs also benefit from the novel formulation strategies.

In the sections below, we present aspects of the dissolution work relevant to the biopharmaceutical classification of drugs as well as the formulation strategies focusing on the enhancement of bioavailability of a Class II (or even Class IV) compound to perform as Class I (or III) *in vivo*, which ensures biowaiver status (European Medicines Agency, 2010; U.S. FDA, 2017; Verbeeck and Musuamba, 2012) (Fig. 2). We also present the mechanistic work associated either with *in vitro* dissolution or *in vivo* dissolution/modeling studies relevant to the biopharmaceutical classification of drugs. Finally, we quote some advances associated with the application of BDDCS.

2. Dissolution testing

2.1. Basics

Because of the importance of drug dissolution for intestinal absorption after oral administration of solid formulations (e.g. suspension, capsules, tablets), the medical product agencies have developed dissolution and BCS related guidelines (European Medicines Agency, 2010; U.S. FDA, 2017). These guidelines provide the scientific rational based on dissolution criteria to lower regulatory burden and justify a biowaiver under certain conditions. Importantly, when successful, BCS ensures that clinical studies are focused to necessary studies rather than making use of study participants for repeating studies for which the same clinical outcome is expected. Briefly, a biowaiver is applicable for drug products meeting the Class I criteria (Fig. 1) plus rapid dissolution (≥85% of the drug is released in 30 min or less; – see also above). In addition, a biowaiver can be justified between manufacturers for BCS Class I drugs based on comparisons of the dissolution profiles of the resulting products. This comparison follows a model independent mathematical approach based on the similarity factor (F_2)

$$F_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)\right]^{2-0.5} \times 100\right\} \quad (1)$$

where R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the reference and test product, respectively. According to the regulatory authorities, a public standard of F_2 value between 50 and 100 is used to indicate similarity between two dissolution profiles. Nowadays, official dissolution apparatus are described in Pharmacopeias for drug dissolution testing. The type of dosage form under examination is the primary consideration in apparatus selection.

The European Pharmacopeia (EP) now recognizes eight dissolution apparatus (IP/BP/USP/EP, 2011). These apparatus are classified according to the dosage forms, namely,

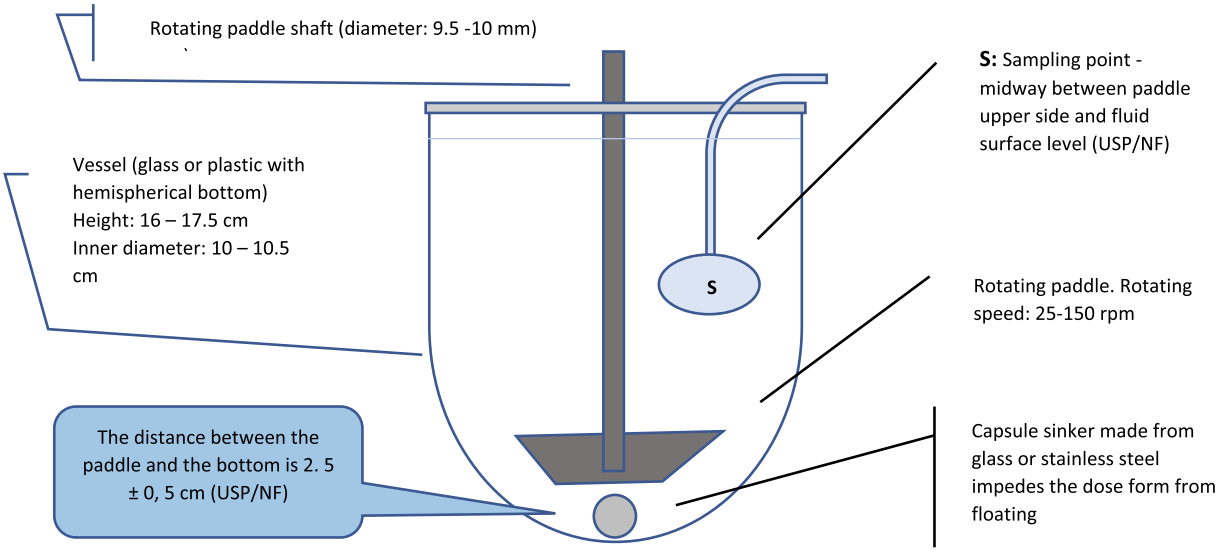

Fig. 3. Basket type (EP) or USP type 2 apparatus – USP/NF, 1976 & USP 23, 1995), (modified from "Google images", USP Type 2 Dissolution Apparatus").

1) Paddle (Fig. 3, USP: Type II), basket (USP: Type I) and flow through apparatus (USP: Type IV) for solid dosage forms
2) Disk assembly (USP: Type V), cell and rotating cylinder method for transdermal patches (USP: Type VI)
3) Chewing and flow through apparatus for special dosage forms

The USP recognizes 7 types (Pharmaceutical guidelines, 2018; Workshop on dissolution, 2019; https://www.slideshare.net/shraddhakumbhar25/validation-of-dissolution-apparatus, 2014):

1) The Basket type or rotating basket or type I: for tablets, suppositories, ER.

It benefits from experience since there are ≈200 monographs for it. Rotating speed is 100 rpm. The pH can be changed during operation which suits ER forms, since those drugs undergo a large pH variability as they release their active ingredient along a large length of the GIT. It can be easily automated which is positive for routine procedures. Disadvantages are the necessity of degassing, the hydrodynamic formation of a "dead zone" under the basket and the fact that due to limited volume (900–1000 mL), sink conditions for poorly soluble drugs are difficult to maintain.

2) The Paddle type (Fig. 3) or type II: Usually the 1st choice, it is identical to the paddle type of EP and also benefits from bibliographic and experimental experience. Useful for IR forms, tablets, capsules, beads, ER forms and enteric coated forms. It can be easily adapted to serve as a type V apparatus and can also be easily automated.

The change of pH during the procedure is not as easy as in type I. Sink conditions are difficult to maintain due to limited volume. Hydrodynamical complexity requires sinkers for the avoidance of sticking and unnecessary floating of drug forms. A typical problem with the apparatus type 2 is the cone formation (Fig. 4) that is attributed to poor mixing on the axis of the apparatus vessel and results in concentration of material in a cone shape below the paddle. An upgraded form of type II with a peak vessel has been developed in order to minimize the coning effect (Fig. 4). (Beckett et al., 1996; Collins and Nair, 1998)

3) The reciprocating cylinder or type III: This apparatus is used for tablets, beads and CR forms. Hydrodynamic profiles are easy to influence by variation of the reciprocation rate. Change of pH is also easy. It is considered useful for beaded pharmaceutical forms as the beads are confined within the cylinder (Shraddha, 2014). Perhaps the main disadvantages of the type are the volume (250 mL) and the lack of experience data.
4) The flow through cell or type IV: It is used for low solubility drugs, implants, suppositories, CR formulations and microparticles. Among its advantages are the easy change of pH, ability to maintain sink conditions and the variability of different modes. Drawbacks with this apparatus are that it needs degassing of solvent, it requires high media volume and is labor intensive.
5) The paddle over disk or type V: useful for transdermal patches. Apparatus type II can be modified to function as type V with the addition of a disk assembly. However, the assembly restricts the size of the transdermal patch tested.
6) The rotating cylinder or type VI
7) The reciprocating disk or type VII

Their proper functioning requires precise calibration following given guidelines (USP 1225). Their calibration and also their suitability is tested according to the USP 711 instructions.

The difference and variability in apparatus types is an effort to simulate the complexity of *in vivo* dissolution phenomena. The pH changes, the rpm variability, the changes in hydrodynamic patterns (reciprocation, rotation etc.), the usage of various DM and the evolution of the BDM, the two compartment and the two phase modifications that simultaneously test absorption and dissolution are all examples of this effort. Fed and fasted intestinal motility patterns have been studied and are included in the design of methods and computational models (Zhang, 2017; FDA workshop, 2016). A step ahead is the crescent shaped spindle that is claimed to be able to replace both the basket of type I and the paddle of type II (Qureshi, 2004) and function at a rotation speed as low as 25 rpm (Qureshi, 2004). More sophisticated systems have been developed (Amidon, 2015) such as the artificial stomach & duodenum (ASD), the gastrointestinal simulator (GIS), a three compartment gastrointestinal simulator that mimics the physiological changes along the GIT (Takeuchi et al., 2014), an *in vivo* prediction methodology by Matsui et al. in 2017 (Matsui et al., 2017) and the TIM gastrointestinal systems (Dickinson, 2012).

2.2. From nutritional liquids to biorelevant dissolution media (BDM)

Historically, Wearly et al. were the first to study the *in vitro*

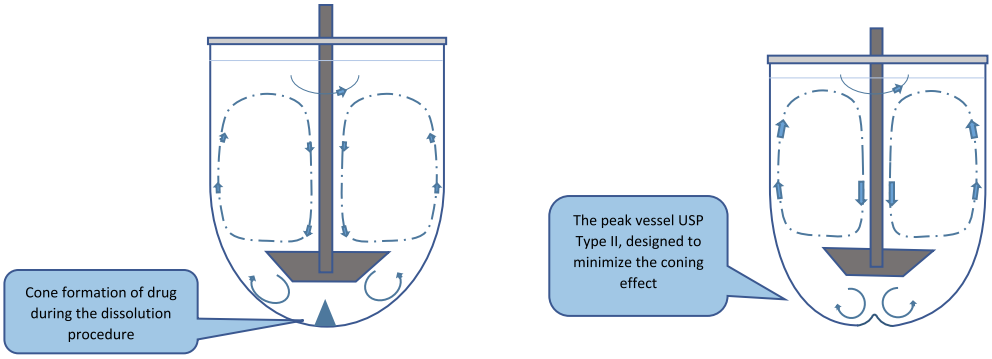

Fig. 4. Coning in Type II apparatus during procedure (left). Peak vessel of upgraded Type II apparatus (right), aims to minimize the coning effect.

absorption using a biorelevant medium (Wearley et al., 1985), In that study, an oral controlled release product of theophylline was studied for absorption using a buffer containing a combination of bile and fatty acids. One year later, Maturu et al. (Maturu et al., 1986) developed an in vitro dissolution test consisting of a pre-treatment of controlled release theophylline products with the first ever used nutritional liquid, peanut oil, followed by a typical dissolution test.

The Macheras research group then introduced the use of milk for dissolution studies in 1987 (Macheras et al., 1989, 1987, 1986). In parallel, milk was used as an inert vehicle for the development of milk based formulations (Macheras and Reppas, 1986; Macheras and Reppas, 1986; Macheras et al., 1991). In this context, large efforts were directed towards understanding drug solubility and drug binding in milk (Macheras et al., 1988, 1990; Dressman, 2017). It is noteworthy that there is a current increased interest in exploring how processing of food components e.g. the digestion of dietary products such as milk, may influence the drug solubilisation in vivo (Bakar et al., 2019; Boyd, 2018; Clulow et al., 2018; Salim, 2018). More than a decade after the introduction of the biorelevant dissolution media, the research groups of Dressman and Reppas developed a series of biorelevant dissolution media to mimic the fed and fasted state in vitro conditions (Dressman, 2014; Dressman et al., 2008; Dressman, 2017; Jantratid et al., 2008). These media gained significant interest from industrial scientists since they may be useful when investigating potential food effects during product development; these media do at least provide information on to what extent food-triggered bile secretion may influence the dissolution rate and solubilization. Of equal importance is the fact that these media can also be used for the prediction of low solubility drugs in fasted state. Most of the dissolution studies in biorelevant media are focusing on class II compounds, which exhibit dissolution-limited absorption. The rate of dissolution depends on, among others, pH, surfactants, buffer capacity, ionic strength and the volume of fluid that is available, motility pattern and the resulting hydrodynamics. Thus, this complexity has to be represented as precisely as possible in the dissolution testing and compendia media in order to provide a sufficiently accurate simulation of the dissolution in vivo. Since the in vivo conditions are complex and heterogeneous (Macheras and Argyrakis, 1997), successful IVIVC studies for IR formulations are not commonly observed in the literature. However, in PUBMED there can be found at least 130 hits for level A IVIVC for modified release formulations.

Instead of reviewing the large number of dissolution/absorption studies associated with BDM, we here present a synopsis of the evolution of them in Tables 1–8. For comparative reasons we also present the official DM according to USP (Shivram, 2014; The United States Pharmacopeia Convention (USP 23), 1996); as well as two DM of International Pharmacopeia (https://www.aatbio.com/resources/buffer-preparations-and-recipes/phosphate-buffer-ph-5-8-to-7-4, 2019; Stippler et al., 2004 in Table 9.

It is apparent that there has been a continuous evolution in the composition of BDM over the last three decades. Overall, there are minor modifications of the original compositions (Table1), as proposed by Dressman et al. (1998), Dressman and Reppas (2000), Dressman (2014), Dressman et al. (2008), Dressman (2017), Jantratid et al. (2008), Jantratid and Dressman (2009), Jantratid et al. (2009), Jantratid et al. (2008), Klein (2010). Galia (1998). Vertzoni et al manufactured in 2005 the fasted state simulated gastric fluid (FaSSGF) (Vertzoni et al., 2005) or Fasted State Simulated Gastric Fluid since the gastric media used up to that date did not contain pepsin or natural surfactants, or contained bile salts and natural surfactants but not in the correct concentrations. This lack of biorelevance affected the dissolution characteristics of the drugs tested. Two years later Jones et al (Jones et al., 2006) proposed the addition of propionic acid to the simulated intestinal fluid. They also used glycocholic acid (Pubchem, 2019) instead of the more common taurocholic acid (Pubchem, 6675) or sodium taurocholate (NaTc) (Pubchem, 2018; ScienceDirect Topics, 2018) for the preparation of FaSSIF and FeSSIF and explained this change by stating that, in human bile salts (Hofmann et al., 2010; Carey and Small, 1972; Russell, 2003; Hofmann and Borgström, 1964), cholic acid is mainly conjugated with glycine instead of taurine. This change did not prevail, perhaps because the biliary taurocholic: glycocholic ratio is, probably, roughly 1:1 according to some studies (Hofmann, 1999).

It is interesting to note that milk is a major component of all fed state simulated gastric fluids, (Tables 4–6) even at the later FeSSGF compositions (Fotaki and Vertzoni, 2010) (Otsuka et al., 2013);table 6). Dressman in fact, mentioned in her work with Reppas “In vitro-in vivo correlations for lipophilic, poorly water-soluble drugs (2000) (Dressman and Reppas, 2000) “ that the 3.5% fat milk & buffer solution is an important compound for the FeSSGF since its fat/carbohydrate/protein analogy seems to be very close to the western diet when simulating the contents of a fed stomach.

Other paths included instant powdered BDM (Boni et al., 2009) (Table 4), attempts to simplify and fasten the composition (Zoeller and Klein, 2007) (Table 3), the usage of more easily available and low cost ingredients (Vertzoni et al., 2004) (Table 2) and occasionally new versions of the old compositions, as can be seen in the work of Fotaki and Vertzoni (2010), Jogia et al. (2009), Jantratid et al. (2008), Jantratid and Dressman (2009), Otsuka et al. (2013), Kaur et al. (2018) (Tables 6 and 7).

Markopoulos et al., in their 2015 study (Markopoulos et al., 2015) stated that luminal contents affect the dosage forms of highly permeable API – which retain a low luminal concentration - much more than luminal hydrodynamics. They estimate the volume of fluid in a close *in vitro* system at 250 mL for fasted and 500 mL for fed state, gastric or upper intestine, and 200 mL for lower intestine. They classify dissolution media, according to their composition to 4 levels (see Table 8 for more details):

a) Level 0: Simple buffer medium that maintain a steady pH throughout the dissolution test. Physiological relevance is not

Table 1
BDM published in the literature between 1998 and 2005. Data taken from references.

Biorelevant Dissolution media, 1998, Galia et al. (1998)	FaSSIF	FeSSIF	Early BDM composition Dressman and Reppas (2000)	FaSSIF	FeSSIF	FaSSGF composition by Vertzoni et al. (2005)	SGF with SLS	SGF with Triton X100	FaSSGF
NaTc[a]	3 mM	15 mM	**NaTc**	3 mM	15 mM	**NaTc (mM)**	–	–	0.08
Lecithin	0.75 mM	3.75 mM	**Lecithin**	0.75 mM	3.75 mM	**Lecithin (mM)**	–	–	0.02
–	–	–	–	–	–	**Pepsin mg/mL**	–	–	0.1
KH_2PO_4	3.9 g (29.4 mM)	–	KH_2PO_4[b]	3.9 g (29.4 mM)	–	–	–	–	–
CH_3COOH	–	8.65 g (144 mM)	CH_3COOH[c]	–	8.65 g (144 mM)	**Sodium Lauryl Sulphate**[d] **(SLS) (% w/v)**	0.25	–	–
KCl	7.7 g (103.3 mM)	15.2 g (204 mM)	**KCl**	7.7 g	15.2 g	**Triton X100**[e] **(% w/v)**	–	0.1	–
–	–	–	–	–	–	**NaCl (mM)**	34.2	34.2	34.2
NaOH	q.s. pH	q.s. pH	**NaOH**	q.s. pH	q.s. pH	–	–	–	–
Deionized H_2O	qs 1L	qs 1L	**Distilled H_2O**	q.s. 1 L	q.s. 1 L	–	–	–	–
Ph	6.5	5.0	**pH**	6.5	5.0	**pH**	1.2	1.2	1.6
Osmolality (mOsm/kg)	270 ± 10 mOsm	635 ± 10 mOsm	**Osmolality(mOsm/kg)**	270 ± 10 mOsm	635 ± 10 mOsm	**Osmolality (mOsm/kg)**	180.5 ± 3.6	157.7 ± 2.9	120.7 ± 2.5
–	–	–	**Buffer capacity**	10 mEq	75 mEq	–	–	–	–
–	–	–	–	–	–	**Surface tension (mN/m)**	33.7	32	42.6

[a] It occurs naturally in the bile of mammals.
[b] The natural buffer bicarbonate is replaced by KH2PO4 in order to achieve greater stability in the given pH.
[c] Acetate is used instead of phosphates so as to keep the pH in the desired value.
[d] surfactant.
[e] Non-ionic surfactant.

considered necessary. Their biorelevance however depends on the GIT place and conditions simulated. For gastric conditions and a gastric emptying rate > dissolution rates, level 0 media may be adequate even for IVIVC, especially with non-ionisable active pharmaceutical ingredient (API) or in cases of ER and modified release (MR) Developability Classification system (DCS) Class I & III forms that are sensitive only to pH changes. Many compendial media fall in this category.

b) Level 1: pH value and buffer choice and capacity are physiologically relevant and distinction between fasted and fed state is made.
c) Level 2: Dietary fat, bile acids and important digestion products are added to reflect the solubilization ability and capacity of gastric and luminal fluids. Fed and fasted state and osmolality are taken into account. Several BDM belong in level 2. Some of them are commercially available in our days.
d) Level 3: They are the most complex compositions, as enzymes and proteins are added to reflect the added effect of viscosity and enzymes' action in the solubilization capacity of gastric and intestinal fluids.

Markopoulos, Dressman and colleagues proposed a decision tree for the choice of biorelevant media to facilitate the desired level of simulation which can be seen in Fig. 5.

However, the predictability of the biorelevant media, in terms of their i*n vivo* performance, has not been clarified as yet; thus, the non-trivial question "which media to use to run which dissolution tests?" posed by Klein et al. is still pending (see Pharmaceutical Dissolution testing – Dressman & Kramer- chapter 7, pg 193 (Dressman and Krämer, 2005). The current opinion is that there is no universal medium available which can be used to predict every drug substance's solubility or a drug product's *in vivo* dissolution behavior (Bou-Chacra, 2017; Nagpal et al., 2010). It seems also likely that important kinetic aspects for the *in vitro* & *in vivo* drug dissolution kinetics remain unexplored. For examble, Niederguell and Kuentz (Niederquell and Kuentz, 2014) have identified fractal like kinetics (Kosmidis and Macheras, 2018) in BDM. Also, reaction limited drug dissolution considerations in BDM have not applied as yet (Macheras et al., 2018), despite of the fact that the complex composition of BDM implies a potential drug – dissolution component(s) interaction.

2.3. Reaction limited Dissolution: Is it an important mechanism for biopharmaceutical drug classification purposes?

The mathematical model of BCS relies on Noyes Whitney relationship published in 1897 (Noyes and Whitney, 1897). The so called "Noyes Whitney equation" is based on the diffusion layer model of dissolution. In fact, dissolution is considered as a first order process and solubility or saturated solution / concentration when saturation is achieved, drives the dissolution rate. Accordingly, solubility became the main parameter of BCS. However, from the early beginning of dissolution research, two dissolution mechanisms were postulated, namely, diffusion-limited and reaction-limited models (Higuchi, 1967). A recent study indicated that drug dissolution follows a combined mechanism with the dissolution-limited and reaction-limited processes taking place simultaneously (Shekunov and Montgomery, 2016). In the following section we briefly present dissolution models which are not based on diffusion principles; instead a reaction between the solid drug particles and the constituents of the buffer or the gastrointestinal fluids is considered as the limiting step for drug dissolution.

The first drug dissolution model, which does not rely on diffusion principles was published in 1997 (Dokoumetzidis and Macheras, 1997). Here, the mass dissolved upon reaction of the solid particles with the dissolution medium constituents is considered to be a function of a discrete time index specifying successive generations (n). A difference equation was developed for the fraction of dose dissolved between generations n and n + 1. The difference equation was nicely fitted to

Table 2
Vertzoni et al., 2004[a]. Data taken from reference.

	NaTc (mM)	Egg Phosphatidyl-choline (mM)	Maleic anhydride (mM)	CH_3COOH (mM)	Citric acid (mM)	NaH_2PO_4 (mM)	NaOH (mM)	NaCl (mM)	pH	Osm/ty (mOsm/kg)	Buffer capacity
FaSSIF	3	0.75	–	–	–	28.66	~13.8	106	6.5	270 ± 10	12
FaSSIFm[b]	3	0.75	25.01	–	–	–	~45	109	6.5	270 ± 10	12
FeSSIF	15	3.75	–	144	–	–	~101	173	5.0	635 ± 10	76
FeSSIFc[c]	15	3.75	–	–	84	–	~200	206	5.0	635 ± 10	76

[a] Vertzoni et al. tried, in 2004, to replace some components of FaSSIF and FeSSIF with more readily available and cost effective ones.
[b] Modified FaSSIF.
[c] Modified FeSSIF.

experimental danazol data. This approach was also used to describe supersaturated dissolution data (Valsami et al., 1999).

Lansky and Weiss modified this discrete time approach and considered the fractional dissolution rate as a decreasing function of the dissolved amount controlled by the dose/solubility ratio (Lánsky and Weiss, 1999). This model was based on the reaction of the undissolved molecules of the solute with the free solvent molecules yielding the dissolved molecules of drug complexed with solvent; the model was also successfully fitted to experimental data.

In 2008, Dokoumetzidis et al. (2008) considered a reaction limited dissolution model using a bidirectional reaction between the solid particles and the components of the dissolution medium. This approach is physically relevant since the backward process corresponds to drug precipitation. It should be noted that mathematical functions based on diffusion layer model failed to reveal the governing role of saturation solubility using experimental naproxen and nitrofurantoin data (Dokoumetzidis et al., 2008). Instead, the model equation developed using the bidirectional reaction was fitted successfully to dissolution data sets of naproxen and nitrofurantoin. A further improvement of the reaction limited models of drug dissolution was accomplished by Charkoftaki et al. (2011); they introduced a time dependent rate coefficient instead of a rate constant to analyze the supersaturated dissolution data of carbamazepine in the presence of d – alpha – tocopherol polyethylene glycol 1000 succinate (TPGS) at various temperatures. The maximum solubility values observed, were found to increase with TPGS in a concentration dependent manner at all temperatures studied. The supersaturated dissolution curves were nicely described by the model developed utilizing a time dependent coefficient for controlling the carbamazepine dissolution process.

2.4. PBPK modeling

Predicting oral bioavailability and time course of drugs in humans by simulating absorption, distribution, metabolism, excretion (ADME) with the use of *in silico* methods, based on *in vitro* and/ or *in vivo* (mainly animal) data, has become an area of great interest, especially the last decade. It goes without saying that dissolution is an important factor to account for and to set in the perspective of transit times through the gut. Physiologically based pharmacokinetic (PBPK) modeling, reduces complex biological systems to detailed mechanistic representations. PBPK models are designed to overcome some of the limitations of conventional compartmental PK models by integrating both drug-dependent parameters (physicochemical properties) and drug-independent (species-specific anatomy, physiology and biochemistry) as well as combined, such as parameters related to biotransformation and excretion. Due to the occasionally empirical nature of these models, the inevitable simplifications and the absolute dependence on literature and experimental data, there is always a possibility of erroneous estimations. Nonetheless, PBPK modeling has been proven a versatile and powerful tool with numerous applications such as *in vitro-in vivo*, intra- and inter-species extrapolations, tissue-, genetics-, age- and disease-specific predictions, DDI assessments and combination with PD models for further response predictions. Software platforms and packages such as GastroPlus™, Simcyp®, and PK-Sim® have been developed to serve these purposes. Physiology based modeling has also been developed to assess the importance of the drug dosage form and its interplay with the physiology (Suarez-Sharp, 2018). Such models go under the abbreviation PBAM (physiology based absorption modeling) or PBBP (physiology based biopharmaceutics modeling). These include mechanistic models that mimic the physiological conditions (typically the physiology of the GIT since oral dosing is the most preferred) and incorporate dissolution information at the same time as they take into consideration relevant physicochemical factors to predict systemic exposure profiles. A thorough review (Jones, 2015) by Jones et al. shows PBPK modeling applications from a pharmaceutical industry perspective. In this section we are going to discuss the use of PBPK modeling as a predictive tool for bioavailability of drugs within the BCS context through some representative examples.

The applicability of PBPK modeling for orally administered drugs is certainly not limited to specific formulations. In a study published in 2012 (Sinha, 2012), Sinha et al. applied PBPK modeling to investigate the absorption and DDI of a lipophilic, Class II Janssen's compound, predominantly metabolized by CYP3A4, when administered as a nanosuspension formulation. The ACAT (Advanced Compartmental Absorption and Transit) model (Agoram et al., 2001) in GastroPlus™ was used for the prediction of the rate and extent of oral absorption, based on rat data. The obtained parameters were used to build a human PBPK model in Simcyp® with the ADAM (Advanced Dissolution Absorption and Metabolism) approach (Darwich et al., 2010), so as to predict the non-linear PK in humans. Interaction with ketoconazole, a strong CYP3A4 inhibitor, was simulated in Simcyp® and the results of the sensitivity analysis showed that the unbound fraction in gut enterocytes could be an important parameter in predicting oral absorption. In 2011 Zhang et al. (2011) used the ACAT model in GastroPlus™ to conduct simulations of four carbamazepine (BCS class II) oral formulations (IR suspension and tablet, ER tablet and capsule), under fasted and fed conditions, in order to identify important factors in formulation design.. The main objective of this study was to assess the utility of physiologically based absorption models in the implementation of "Quality by Design" (QbD) in drug development. A very efficient, physiologically based absorption modeling strategy was presented through the example of carbamazepine.

Food indisputably affects the pharmacokinetics of drugs, especially the absorption stage, in various ways. Several studies present PBPK simulations of food effects on the pharmacokinetics of *per os* administered drugs. A characteristic example of combining BDM testing with PBPK modeling is the work of Wagner (2012) published in 2012. An IR formulation of a weakly basic BCS class IV β_3-adrenergic receptor agonist was tested with BDM and transfer model experiments. The results were used in a modified version of a previously developed STELLA® PBPK model, leading to quantitative predictions of the plasma profiles in fasted and fed state. As PBPK modeling is gaining more and more recognition the onus falls on predictive performance and informativeness. In 2017 Li et al. (2018) described in their review the status of the predictive performance of PBPK models for the food effect on absorption. Among 48 food effect predictions, ~50% were predicted

Table 3
BDM compositions according to Jones et al., 2006[i] and Zoeller and Klein (2007)[j]. Data taken from references.

Substances Jones et al.	FaSSGF (mol/mL)	FeSSGF (mol/mL)	FaSSIF (mol/mL)	FeSSIF (mol/mL)	FeSSIF(HF)[k] (mol/mL)	SIF (mol/mL) I[l]	SIF (mol/mL) II[m]	Substances- Zoeller and Klein (2007)	FaSSIF	FeSSIF
–	–	–	–	–	–	–	–	NaTc	3mM	15 mM
Glycocholic acid[n]	–	–	0.0040	0.015	0.015	–	–	–	–	–
Lecithin	–	–	0.0010	0.0037	0.0037	–	–	Lecithin	0.75 mM	3 mM
Oleic acid	–	–	–	0.0043–0.011	0.043	–	–	–	–	–
KH_2PO_4	–	–	0.050	0.050	0.050	–	–	NaH_2PO_4	3.438 g (28.66 mM)	–
CH_3COOH	–	0.01	–	–	–	0.070	0.025	CH_3COOH	–	8.65 g (144 mM)
CH_3CH_2COOH	–	–	–	–	–	0.030	0.010	NaOH (pellets)	Qs until pH = 6.5	4.04 g
NaCl	0.069	0.069	0.0192	0.0192	0.0192	0.017	0.017	NaCl	6.186 g (105.84 mM)	–
HCl	0.02	–	–	–	–	–	–	–	–	–
pH (adjusted with NaOH)	1.7	5.0						pH	6.5 ± 0.1	5 ± 0.1
–	–	–	–	–	–	–	–	Osmolality (mOsm/kg)	270 ± 15	670 ± 15
–	–	–	–	–	–	–	–	Buffer capacity mM/ (L x ΔpH)	12 ± 2	72 ± 2
–	–	–	–	–	–	–	–	Surface tension (N/m^2)	54 ± 2	48 ± 2

[i] Jones et al. added Propionic acid in the SIF.
[j] Zoeller and Klein, attempted to manufacture a more simplified composition.
[k] FeSSIF (HF) = FeSSIF in High Fat fed State.
[l] SIF I = upper intestine simulated fluid.
[m] SIF II = simulated lower intestine fluid.
[n] Produced by the liver in mammals. Glycocholic and Taurocholic acid account for 90% of human primary bile acids.

within 1.25-fold of observed and 75% within 2-fold. Dissolution rate and precipitation time were recognized as the most commonly optimized parameters. In a recently published, very concise study Tistaert (2018), demonstrated that food effect can be well predicted with established and validated PBPK models by presenting five case studies of BCS class I, II and IV drugs. The simulations were conducted mainly in GastroPlus™ using default and refined models. Along with the case studies, the authors proposed a general, multistep PBPK workflow for food effect predictions for IR formulations of BCS I and II compounds for which clinical data were available in fasted or fed state.

Special populations such as the elderly, children and pregnant women exhibit profoundly different physiology that sometimes leads to big deviations in the pharmacokinetics of drugs when compared to the "typical" subjects that participate in clinical trials. PBPK modeling is being used to simulate these deviations and facilitate decision making concerning these sensitive populations. In 2017 Dallmann (2017) used the PK-Sim® /MoBi® platform to build a 27-compartment pregnancy population PBPK model. The interesting feature of the modeling procedure is the derivation of the pregnancy model from a non-pregnancy one after scaling. The pregnancy model was verified by simulating the pharmacokinetics of three renally cleared cephalosporin antibiotics at different pregnancy stages. In Johnson et al. (2018) developed a PBPK model of paediatric drug absorption, applicable from full term birth onwards, by modifying the adult ADAM model (Jamei, 2009). Both age-specific and adult parameter values were included. The performance of the model was successfully assessed in Simcyp® by simulating the oral absorption of theophylline, paracetamol (BCS class I) and ketoconazole (BCS class II) over a range of paediatric ages, for both fasted and fed states.

3. Novel formulation strategies

3.1. Supersaturation–Supersaturation delivery systems

Almost 90 % of the new chemical (small molecular) entities are poorly soluble compounds, typically found in Class II & Class IV (Kesisoglou and Wu, 2008; Benet and Wu, 2006). For Class II drugs, and partly Class IV, bioavailability correlates with their dissolution rate (Bodhe and Kaur, 2018), and dissolution is affected by solubility (Bodhe and Kaur, 2018; Dressman and Reppas, 2000), so, an increase in solubility should result in *in vivo* bioavailability increase. There are several ways to an increase in the amount of drug that is dissolved. These include micellar solubilisation, micronisation of particles, complexation (e.g. cyclodextrin complexation), adjustment of pH value and supersaturating drug delivery systems (SDDS, such as amorphous drug or lipid based formulations). With the high number of poorly water-soluble compounds in the drug discovery pipelines, SDDS have attracted increased attention as efficient and crucial means to enhance the achieved bioavailability after oral administration. However, a systematic and quantitative synopsis of the knowledge about *in vivo* performance of a wide range of SDDS is currently lacking. Such analysis of the recent achievements is to provide insights for formulation scientists dealing with poorly soluble compounds (Fong et al., 2017).

One of the most attractive means to produce an increased absorption for a poorly soluble drug is to make use of the SDDS, typically by making use of the amorphous and more soluble form. This approach results in an increased free fraction of molecules, which in turn produces a higher flux over the intestinal membrane. By addition of stabilizers such as polymers or low concentration of surfactants a spring and parachute effect may be observed (Brewster et al., 2008; Augustijns and Brewster, 2012). The spring refers to the quick dissolution of the material steaming from the amorphous form whereas the parachute is the delayed nucleation or crystal growth achieved with different excipients. The supersaturated system is directly linked to the increased flux if the additional molecules in solution are truly free molecules dissolved in the aqueous phase. The latter is of importance since there

Table 4
BDM composition, Jantratid et al. (2008), Jantratid and Dressman (2009), Jantratid et al. (2009)[o].

BDM composition, Jantratid et al. (2008)	FaSSGF	FeSSGF	FaSSIF	$FaSSIF_a$	FeSSIF	$FeSSIF_a$	$FeSSIF_b$	$FeSSIF_c$	$FeSSIF_d$
NaTc	0.080 mM	–	3.0	3.0	15.0	7.5	15.0	7.5	15.0
Lecithin	0.020 mM	–	0.75	0.2	3.75	2.0	3.75	2.0	3.75
Pepsin	0.1 mg/mL	–	–	–	–	–	–	–	–
Pancreatin	–	–	–	lipase ca. 100 U/mL	–	lipase ca. 100 U/mL	lipase ca. 100 U/mL	–	–
Na Oleate	–	–	–	–	–	0.8	0.8	0.8	0.8
GMO	–	–	–	–	–	5.0	5.0	5.0	5.0
KH_2PO_4	–	–	3.9 g (29.4 mM)	–	–	–	–	–	–
CH_3COOH (glacial)	–	17.12 mM	–	–	8.65 g (144 mM)	8.65 g (144 mM)	8.65 g (144 mM)	8.65 g (144 mM)	8.65 g (144 mM)
CH_3COONa	–	29.75 mM	–	–	–				
NaCl	34.2 mM	237.02 mM	–	–	–	–	–	–	–
KCl	–	–	7.7 g (103.3 mM)	7.7 g (103.3 mM)	15.2 g (204 mM)	15.2 g (204 mM)	15.2 g (204 mM)	15.2 g (204 mM)	15.2 g (204 mM)
HCl	q.s. until pH	–	–	–	–	–	–	–	–
NaOH	–	–	qs pH	qs pH	qs pH	qs pH	qs pH	qs pH	qs pH
UHT–milk	–	1:1 ratio	–	–	–	–	–	–	–
Deionized H_2O	q.s. until 1L	q.s. until 1L	q.s. until 1L	q.s. until 1L	q.s. until 1L	q.s. until 1L	q.s. until 1L	q.s. until 1L	q.s. until 1L
pH	1.6	5.0	6.5	6.5	5.0	5.8	5.8	5.8	5.8
Osmolality (mOsm/kg)	–	–	270	180	670	390	400	390	400
Buffer capacity mM / (L × ΔpH)	–	–	10	10	76	25	25	25	25

[o] Jantratid and colleagues followed the composition of Galia et al. for FaSSIF & FeSSIF and the composition of Vertzoni et al. for FaSSGF

are several strategies to form supersaturated solutions; some of them are not leaving the molecules without impacting their accessibility for permeation (Dahan et al., 2016).

3.1.1. Making use of the amorphous drug

The most common supersaturated systems are the ones making use of the amorphous form. Common processes producing the amorphous form are spray drying, freeze drying and hot melt extrusion. The interested reader is referred to the recent literature to read more about manufacturing and performance of amorphous drug delivery system (Huang and Williams, 2018; Edueng et al., 2017). Other means to produce the amorphous form is to make use of mesoporous carriers (Qian and Bogner, 2012; Maleki, 2017). The incorporation in and stability of the amorphous form is highly carrier and compound dependent, with loading capacity typically being in the range of 10–40% (Qian and Bogner, 2012). However, significantly higher numbers have been reported for hollow mesoporous silica nanoparticles (Narayan et al., 2018).

From a drug molecules perspective the compounds that would benefit the most by amorphization would be the ones that have a strong crystal lattice and hence, when amorphisized lack the long range order that is the backbone shaping the high lattice energy. A common cut-off value to use for such compounds is a melting point of 200 °C, since it has been shown that at this high melt temperature the crystal lattice starts to play a major role for the solubility (Bergström et al., 2016; Wassvik et al., 2008). Such molecules are colloquially called 'brick dust' molecules. However, also lipophilic compounds may gain from amorphization, in particular if the compounds is defined as being dissolution-rate limited.

The amorphous form was for a relatively long time viewed as a material that was too risky to work with, due to its metastable form. Hence, it was not a first-hand choice of the different enabling formulation techniques explored during product development. However, with the current discovery pipeline, having a majority of the compounds suffering from both solubility and dissolution rate limitations *in vivo* (Benet et al., 2006), all possible enabling formulation tools need to be explored. In a review of the current status of amorphous drug delivery systems it was identified that the literature on such systems was increasing significantly during the time period 2000–2016 (Edueng et al., 2017). It was also noted that, during the last year of the performed analysis (2016) a more holistic approach was used and replaced the 'case studies' previously often published. Indeed, the analysis provided by the authors indicated that the research field moves towards i) laying the foundation to allow more general conclusions to be drawn, and ii) more specific studies that clearly have the depth to mechanistically explore well defined research questions.

It is well-known that the amorphous form is metastable and hence, needs ways to become stable both in the solid (physical stability) and during dissolution when it gets exposed to water. A number of polymers (and drug carriers) have been used for this purpose. However, often the material that may enhance physical stability is not the same as the one that may act as the parachute once the compound comes into solution. Which polymer to choose is compound dependent and also dependent on whether it is the solid or the dissolved material that needs to be stabilized (i.e. amorphous solid form or supersaturated solution). One can argue that if this is known also the manufacturing process can become simplified; if the physical stability is high it would be enough to mix polymer with the already amorphisized material whereas if the physical stability is low an amorphous solid dispersion needs to be produced with the polymer present during e.g. spray drying or hot melt extrusion. Recently, multivariate data analysis was used to predict which polymer is most suitable to stabilize solid dispersion, taking both physical properties of the drug and the production process into account (Fridgeirsdottir et al., 2018). Similarly, such data analysis has been used to predict which type of polymer to select when there is a need to stabilize supersaturated solutions and limit drug precipitation (Warren et al., 2013).

3.1.2. Making use of Lipid-based formulations

Another means to produce supersaturated solutions is through the administration of lipid-based formulations (LBFs). This is a successful formulation strategies for lipophilic, solvation-limited compounds. A partition coefficient between octanol and water (logP) of > 2 has been used as a cut-off for when it is meaningful to choose to target an LBF (Persson et al., 2013). These typically consist of oil, surfactant and/or co-solvent, and the lipid formulation classification system (LFCS) has been developed to sort the compounds dependent on their composition and hence, hydrophobicity, dispersibility and digestibility

Table 5
Powdered BDM Boni et al. (2009), alternative FeSSGF, composition containing a synthetic surfactant.

Freeze–Dried (powdered) Media, Composition/1L Boni et al. (2009)	INSTANT FaSSIF	INSTANT FeSSIF	Alternative FeSSGF (Fotaki and Vertzoni, 2010)	$SSGF_1$ (early)	$FeSSGF_2$	$FeSSGF_3$ (Late)	Composition of experimental BDM with 24–phosphonobile acid[p] Jogia et al. (2009)	PM1[q]	PM2[r]
NaTc (g/1L)	1.65	8.25	–	–	–	–	–	–	–
–	–	–	–	–	–	–	24–phosphonobile acid	3 mM	15 mM
Phosphatidylcholine (g/1L)	0.59	2.954	–	–	–	–	–	–	–
–	–	–	NaH_2PO_4 (mM)	–	–	–	NaH_2PO_4	0.025 M	
–	–	–	CH_3COONa (mM)	–	27.95	32	CH_3COONa	–	0.05 M
–	–	–	CH_3COOH (mM)	–	17.12	–	CH_3COOH	–	Qs. pH
–	–	–	NaCl (mM)	148	237.02	–	NaCl	2 g	5 g
–	–	–	NaOH or HCl	Qs until pH	Qs until pH	122.6	NaOH	Qs. pH	–
–	–		H3PO4 (mM)	–	–	Qs until pH	–	–	–
H_2O mL[s]	10	35	–	–	–	–	Deionized H_2O	Qs. until 1L	Qs. until 1L
–	–	–	Milk: Buffer	1: 0	1: 1	5.5	–	–	–
–	–	–	pH	6.4	5	1: 3	pH	6.5	5
Osmolality (mOsm/kg)	53 ± 0.4	47.4 ± 0.3	Osmolality (mOsm/kg)	559 ± 10	400 ± 10	3	Osmolality (mOsm/kg)	140	272
–	–	–	Buffer capacity mM/ (L × ΔpH)	21.33	25	300 ± 10	Buffer capacity mM/ (L × ΔpH	13	29
Surface Tension (mN/mm)	1.00693 ± 0.004	1.01484 ± 0.015	–	–	–	–	Surface tension (N/m^2)	35	30
Density (mg/cm)	296 ± 3	706 ± 9	–	–	–	–	–	–	–

[p] synthetic surfactant.
[q] It is compared to FaSSIF.
[r] It is compared to FeSSIF.
[s] The water soluble NaTc is dissolved in the water and the phosphatidylcholine is added afterwards to produce a dispersion that is lyophilized at −40 °C. The life span of the powder is expected to be ≈ 3 years at room temperature Dressman and Reppas (2000).

Table 6
BDM further modifications by Otsuka et al. (2013) and Kaur et al. (2018).

Composition(Simulated Gastric fluids)	FaSSGF	FaSSGF V2	FeSSGF	Composition(Simulated Intestinal fluids)	FASSIF	FASSIF V2	FaSSIF V3	FESSIF	FESSIF V2
NaTc (mM)	0.08	0.08	–	**NaTc (mM)**	3	3	1.4	15	10
Lecithin (mM)	0.02	0.02	–	**Lecithin (mM)**	0.75	0.2	0.035	3.75	2
Pepsin (mg/mL)	0.1	0.1	–	**Lysolecithin (mM)**[t]	–	–	0.315	–	–
–	–	–	–	**Glycerol monoacetate** [u,v]	–	–	–	–	5
–	–	–	–	**Oleate Na**	–	–	0.315	–	0.8
–	–	–	–	**Maleic acid**	–	19.1	–	–	55
–	–	–	–	**NaH_2PO_4**	28.7	–		–	–
HCl (mM)	25.1 (or g.s. until pH = 1.6)	q.s. until pH	–	**KH_2PO_4**	–	–	–	–	–
CH_3COO^-(mM)	–	–	17.1	**Glacial CH_3COOH (mM)**	–	–	–	144.2	–
CH_3COONa (mM)	–	–	29.8	**–**	–	–	–	–	–
		–		**NaOH (mM)**	8.7	34.8	–	101.0	81.7
NaCl (mM)	34.2	68	237.0	**NaCl (mM)**	105.9	68.6	–	203.2	125.5
Milk/Buffer	–	–	1/1	**–**	–	–	–	–	–
pH	1.6 ± 0.05	1.6	5 ± 0.05	**pH**	6.5 ± 0.05	6.5 ± 0.05	–	5 ± 0.05	5.8 ± 0.05
Osmolality (mOsm/kg)	120.7 ± 2.5		400 ± 10	**Osmolality (mOsm/kg)**	270	180 ± 10	–	670	390 ± 10
Buffer capacity (mM/ ΔpH)			25 ± 2	**Buffer capacity (mM/ ΔpH)**	10	10 ± 2	–	76	25 ± 2

[t] Used by Otsuka et al. in the composition of FaSSIF V3.
[u] Dressman et al use Glycerol monooleate (Towards Quantitative Prediction of Oral Drug Absorption, *Jennifer B. Dressman*, *Kirstin Thelen* and *Ekarat Jantratid,* 2008).
[v] Otsuka, in collaboration with dr Dressman used Glycerol monooleate as well (Otsuka et al. 2013).

(Pouton, 2006). One of the advantages with LBFs is that they commonly are used to deliver the compound in a dissolved form, although examples of lipid-based suspensions and solidified lipids also exists. Hence, the LBFs are circumventing the dissolution step, and the absorption only becomes dependent on the solubility and permeability. The solvation capacity, which is crucial to maintain the drug in solution, changes over time as the digestible lipids are processed in vivo. Therefore, the formulation scientists need to explore the resulting time dependent solubility during lipid digestion to understand the apparent solubility, potential supersaturation and risk for precipitation. This is done by *in vitro* lipolysis methods in the laboratory (Williams, 2012). While this can inform on the expected trigger for supersaturation it has also been found that the *in vitro* method as such does not properly reflect what occurs *in vivo*. The reason for this may be manifold since the *in vivo* processing is complex, dynamic and facilitated by the absorption to a sink (the system circulation). The latter is missing in the standard lipolysis method although some recent efforts have been made to also combine it with an absorptive membrane (Bibi et al., 2017; Keemink et al., 2019).

LBFs have also been used to target lymphatic absorption and through this route escape first pass metabolism (i.e. changing the clearance pattern) and impact the tissue distribution pattern by influencing the volume of distribution (Caliph, 2013; Trevaskis et al., 2015). This route of absorption is of course of particular interest for diseases sitting in the lymphatic system and holds great potential in the treatment of e.g. autoimmune diseases (Cao, 2019). Lymphatic absorption is powerful but it should be noted that it is limited to compounds with particular properties. It has been proposed that the compound has to be highly lipophilic (logP > 5) and lipid-loving (solubility in long chain triglyceride > 50 mg/g) to be co-transported with the lipids to the lymphatic system (Feeney, 2016). However, when this occurs the absorption can be significantly higher, and medicinal chemistry strategies targeting synthesis of highly lipophilic prodrugs have proven to be a successful strategy to deliver the compound to the lymphatic system (Hu et al., 2016; Han et al., 2016).

4. Recent classification systems

In 2005 Wu and Benet modified BCS and moved its frontiers towards the disposition characteristics of drugs (Fig. 1). The BDDCS was based on studies performed in the laboratory of Benet who found to be useful in predicting overall drug disposition, including routes of drug elimination and the effects of efflux and absorptive transporters on oral drug absorption (Wu and Benet, 2005). A large number of studies based on BDDCS have been published during the last decade. In this context, 927 drugs were classified in the BDDCS while several molecular descriptors were studied in respect to the drugs' classification (Benet et al., 2011). One of the major conclusions drawn, based on the work performed in that study is that, “a combination of high dose and low solubility is likely to cause BDDCS class 4 to be underpopulated in terms of approved drugs (N = 53 compared with over 200 each in classes 1–3)”. Also, BDDCS was used for improving the prediction of the brain disposition for orally administered drugs (Broccatelli et al., 2012). In the same vein, BDDCS was used for the classification of new molecular entities (Broccatelli et al., 2012). It is interesting to note that the intensive work performed in Benet's lab on disposition phenomena associated with BDDCS classification, lead him to re-evaluate the theoretical basis of various models of organ clearance/elimination (Benet et al., 2018). In his most recent work (Benet et al., 2018) the concept of clearance was extended. It can be anticipated that this study will affect not only the biopharmaceutical classification of drugs but also our views concerning biopharmaceutic-pharmacokinetic phenomena. However, it must be noted that counter arguments have been published in literature recently (Rowland and Pang, 2018; Rostami-Hodjegan,

Table 7
Fasted and fed state colonial intestinal fluids by Otsuka et al. (2013) and Kaur et al. (2018).

Composition (Large intestine fluids)	Bile acid extract (mM	Lecithin (mM)	Palmitic acid (mM)	Bovine Serum Albumin (mg/mL)	Maleic acid (mg/mL)	Glucose (mg/mL)	$CNH_2(CH_2OH)_3$ (mg/mL)	NaCl	pH
FaSSCoF	0.15	0.3	0.1	3	8.8	–	5.5	–	7.8
FeSSCoF	0.6	0.5	0.2	3	3.5	14	3.7	34	6

Table 8
Classification of BDM[w] in 4 levels[x] according to (Markopoulos et al., 2015). Data taken from the tables of their 2015 work.

LEVEL 1	FaSSGF	FeSSGF-early[y]	FeSSGF-middle	FeSSGF-late	FaSSIF	FaSSIF-V2	FaSSIF midgut	SIF ileum	FeSSIF	FeSSIF-V2	FeSSIF midgut	FaSSCoF	FeSSCoF
Tris[z] (mM)	–	–	–	–	–	–	–	–	–	–	–	45.4	30.5
Maleic Acid (mM)	–	40.78	–	–	–	19.1	19.3	52.8	–	71.9	46.5	75.8	30.15
NaOH (mM)	–	–	–	–	13.8	34.8	36.5	105	101	102.4	83	120	16.5
KH_2PO_4 (mM)	–	–	–	–	28.7	–	–	–	–	–	–	–	–
NaH_2PO_4 (mM)	–	–	–	32	–	–	–	–	–	–	–	–	–
CH_3COOH (mM)	–	–	18.31	–	–	–	–	–	144	–	–	–	–
CH_3COONa (mM)	–	–	32.98	–	–	–	–	–	–	–	–	–	–
H_3PO_4 (mM)	–	–	–	5.5	–	–	–	–	–	–	–	–	–
HCL or NaOH	q.s. until pH 1.6	q.s. until pH 6.4	q.s. until pH 5	q.s. until pH 3	q.s. until pH 6.5	q.s. until pH 6.5	q.s. until pH 6.8	q.s. until pH 7.5	q.s. until pH 5.0	q.s. until pH 5.8	q.s. until pH 6.5	q.s. until pH 7.8	q.s. until pH 6.0
Buffer capacity (mmol/L)/DpH]	–	21.33	25	25	12	10	10	10	76	25	25	16	15
pH	1.6	6.4	5	3	6.5	6.5	6.8	7.5	5.0	5.8	6.5	7.8	6.0
LEVEL 2	FaSSGF	FeSSGF-early	FeSSGF-middle	FeSSGF-late	FaSSIF	FaSSIF-V2	FaSSIF midgut	SIF ileum	FeSSIF	FeSSIF-V2	FeSSIF midgut	FaSSCoF	FeSSCoF
NaTc (mM)	0.08	–	–	–	3	3	1.5	0.8	15	10	5	–	–
Cholate Na (mM)	–	–	–	–	–	–	–	–	–	–	–	0.15	0.6
Lecithin	0.02	–	–	–	0.75	0.2	0.1	0.2	3.75	2	1	0.3	0.5
Oleate Na	–	–	–	–	–	–	–	–		0.8	0.4	0.1	0.2
Glucose												–	14
Glycerol monooleate (mM)	–	–	–	–	–	–	–	–	–	5	2.5	–	–
Tris (mM)	–	–	–	–	–	–	–	–	–		–	45.4	30.5
Maleic acid (mM)	–	47	–	–	–	19.1	19.3	52.8	–	71.9	46.5	75.8	30.15
KH_2PO_4 (mM)	–	–	–	–	28.7	–	–	–	–	–	–	–	–
CH_3COOH (mM)	–	–	18.31	–	–	–	–	–	144	–	–	–	–
CH_3COONa (mM)	–	–	32.98	–	–	–	–	–	–	–	–	–	–
H_3PO_4 (mM)	–	–	–	5.5	–	–	–	–	–	–	–	–	–
Na_2PO_4 (mM)	–	–	–	32	–	–	–	–	–	–	–	–	–
Lipofundin_/buffer	–	17.5 /82.5	8.75/ 91.25	4.375/ 95.625	–	–	–	–	–	–	–	–	–
NaOH (mM)	–	–	–	–	13.8	34.8	36.5	105	101	102.4	83	120	16.5
NaCl (mM)	34.2	270.1	181.7	127.5	–	68.6	76.1	–	–	125.5	102.6	–	34
KCl (mM)	–	–	–	–	–	–	–	–	204			–	–
HCL or NaOH	q.s. until pH 1.6	q.s. until pH 6.4	q.s. until pH 5	q.s. until pH 3	q.s. until pH 6.5	q.s. until pH 6.5	q.s. until pH 6.8	q.s. until pH	q.s. until pH	q.s. until pH	q.s. until pH	q.s. until pH 7.8	q.s. until pH
Buffer capacity (mmol/L)/DpH]	–	21	25	25	12	10	10	10	76	25	25	16	15
pH	1.6	6.4	5	3	6.5	6.5	6.8	7.5	5.0	5.8	6.5	7.8	6.0
Osmolality (mOsm/ kg)	121	559	400	300	270	180	190	190	635	390	300	196	207

[w] Markopoulos et al. name all DM "BDM", no matter the simplicity or complexity of their composition.
[x] Level 0 are usually simple aqueous media or simple compendial media. Level 3 are not depicted in the article of Markopoulos et al.
[y] These media (early, middle & late) simulate the fed state gastric fluid in various times after the meal consumption.
[z] Tris (hydroxymethyl) aminomethane, or known during medical use as tromethamine or THAM, is an organic compound with the formula $(HOCH_2)_3CNH_2$. It is extensively used in biochemistry and molecular biology as a component of buffer solutions.

2018; Dong and Park, 2018).

Butler and Dressman (Butler and Dressman, 2010) presented in 2010 the Developability Classification System (DCS), a modification of the BCS focusing on drug development. The nature of solubility and the intestinal permeability were of course taken into account in the effort. 8 compounds were tested (Paracetamol 500 mg, Digoxin 500 mg, Griseofulvin 500 mg, Mefenamic acid 250 mg, Ibuprofen 400 mg, Dipyridamole 100 mg, Acyclovir 800 mg, Furosemide 80 mg) and the data were compared to the DCS predictability. For these compounds DCS was found to be of greater value than the widely used BCS in terms of outlining the critical factors that were predictive of the *in vivo* performance.

In 2012 Charkoftaki et al. (Charkoftaki et al., 2012) introduced the concept of dose depended BCS and identified a critical dose (Dose (cr)) after which the amount absorbed is independent from the dose. The corresponding effective solubility, S_{eff} was also defined:

$$S_{eff} = \frac{Dose(cr)}{250mL} \quad (2)$$

where the solubility cut off was making use of the 250 mL water cut-off as proposed by Amidon et al. for the BCS classification. Literature data were analysed and the concept of class migration as a function of dose was introduced. Fig. 6 shows the class migration concept according to the dose strength (Charkoftaki et al., 2012). In fact, the drug dose is a controversial issue since the EMA changed the definition of "dose" in the BCS-based Biowaiver guideline (Daousani and Macheras, 2015). In this context, the newly introduced concept of "highest single oral IR dose" was questioned. Thus, the application of solubility criteria for each specific dose strength was suggested. (Daousani and Macheras, 2015)

In 2014 Macheras, and Karalis developed a non-binary version of the BCS, the so called ABΓ system (Macheras and Karalis, 2014). The original mathematical model used for the development of BCS, appropriately modified, was applied to estimate the limiting values of permeability when the fraction of dose absorbed, Fa, was 0.90 or 0.20 and the solubility was equal to 1 mg/ml (lower limit of highly soluble drugs) or 0.1 mg/ml (upper limit of the poorly soluble drugs). The first category (A, alpha) includes drugs with Fa ≥ 0.90, whereas the B (beta)

Table 9
Standardized Dissolution media (DM) according to USP (Shivram, 2014; The United States Pharmacopeia Convention (USP 23), 1996) and International Pharmacopeia (IP), (https://www.aatbio.com/resources/buffer-preparations-and-recipes/phosphate-buffer-ph-5-8-to-7-4, 2019; Stippler et al., 2004).

USP 26 official DM composition	SGF[aa]	SGF_{sp}[ab]	SIF[ac]	PSB–IP[ad] composition	PSB[ae]	PSB (IP5)
Pepsin	3.2 g	–	–	–	–	–
NaCl	2 g (34.22 mM)	2 g (34.22 mM)	–	–	–	–
HCl	7 mL (≈ 71.5 mM)	7 mL (≈ 71.5 mM)	–	–	–	–
–	–	–	–	**Na2HPO4**	35.3 g	–
–	–	–	–	**Na2HPO4, 7H_2O**	–	20.209 g
–	–	–	–	**NaH2PO4, H_2O**	–	3.394 g
–	–	–	–	**KH2PO4**	34 g	–
KH2PO4	–	–	68.05 g (0.5 mol)	–	–	–
NaOH	–	–	8.96 g (0.225 mol)	**NaOH (or HCl)**	Qs pH	Qs pH
Deionized H2O	1000 mL	1000 mL	1000 mL	**Deionized H2O**	Until 1000 mL	Until 1000 mL
pH	1.2	1.2	6.8	**pH**	6.8	6.8
Osmolality (mOsm/kg)	–	–	113	**Osmolality (mOsm/kg)**	115	–
Buffer capacity (mEq/(LxΔpH)	–	–	18.4 ± 0.2	**Buffer capacity (mEq/(LxΔpH)**	18.6 ± 0.1	–
–	–	–		**Ionic strength**	0.0753	–

[aa] : Simulated Gastric Fluid composed according to USP (usually USP 26 or 23) instructions.
[ab] Simulated Gastric Fluid without enzyme pancreatin), prepared according to USP instructions.
[ac] Simulated intestinal fluid according to USP instructions.
[ad] International Pharmacopeia.
[ae] Phosphate standard Buffer (DM according to IP instructions).

category consists of drugs with Fa ≤ 0.20. The area lying between the two boundaries of A and B defines the third category (gamma), Γ, (0.20 < Fa < 0.90). Fig. 7 shows a co-plot of BCS classes I–IV and the three categories A, B, Γ of the ABΓ system. Visual inspection reveals that most of the BCS classes II and III are included in category Γ which mainly consists of drugs with properties like moderate or low solubility and permeability. Due to the dynamic character of dissolution and uptake processes, category A is expanded towards BCS Class II. The ABΓ system allows the classification of all compounds into three categories (A, B, Γ) in terms of the fraction of dose absorbed. Due to the continuous character of the solubility and permeability, dual classification of drugs in the ABΓ system is avoided while the basic elements of the BCS are maintained e.g. biowaivers should satisfy the inequality Fa > 0.90. In reality, the presence of cut-off limits for low-high solubility and low-high permeability ensures the continuity of the ABΓ system. This approach has similarities with the 6 and 9 level class systems based on *in silico* models proposed by Bergström and coworkers (Bergström, 2003; Bergström et al., 2016). These systems are based on molecular descriptors to predict solubility, cell permeability and/or human permeability values and are applicable in the drug discovery setting already prior to compound synthesis.

Another classification approach, the so called Extended Clearance Classification System (ECCS), relies on clearance concepts. As said in the intro, it differentiates from BDDCS by avoiding the measure of solubility with the assumption that, since it inter-correlates with lipophilicity, is not directly relevant to clearance mechanisms or elimination routes. (Camenisch, 2016) However, explicit inverse relationships between solubility and lipophilicity are under investigation. (Dahan et al., 2016; Hill and Young, 2010).

ECCS predicts the predominant clearance mechanism (rate determining process) based on physicochemical properties (MW, ionization state) and passive membrane permeability (Varma et al., 2015). According to the ECCS the compounds are classified in six classes based on ionization, molecular weight (MW) and cell permeability. The six classes are defined as follows:

-Class 1A: metabolism as primary systemic clearance mechanism (high permeability acids/zwitterions with molecular weight (MW) ≤ 400 Da)
-Class 1B: transporter-mediated hepatic uptake as primary systemic clearance mechanism (high permeability acids/zwitterions with MW > 400 Da)
-Class 2: metabolism as primary clearance mechanism (high permeability bases/neutrals)
-Class 3A: renal clearance (low permeability acids/zwitterions with MW ≤ 400 Da)

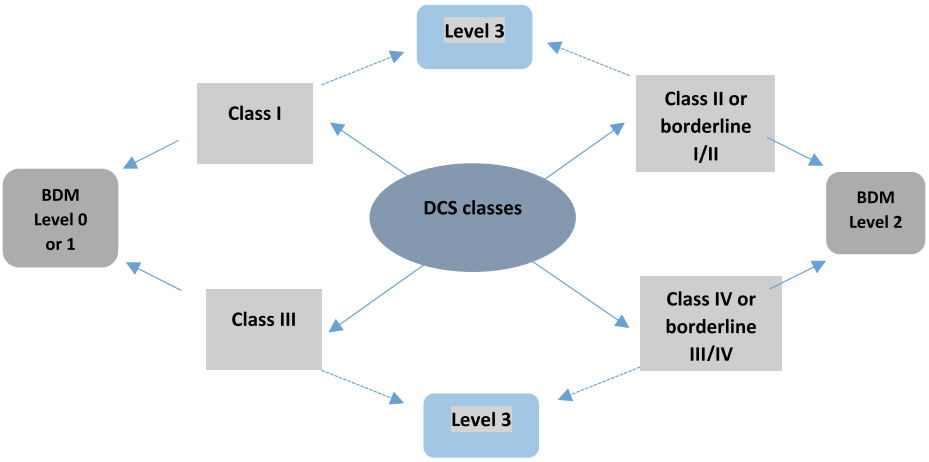

Fig 5. A reproduction of the DM decision tree proposed by Markopoulos et al, aiming to facilitate the level of simulation of intestinal conditions for evaluating the in vivo luminal behavior of drug dosage forms according to the DCS classification of their API. Data taken from Markopoulos et al. (2015).

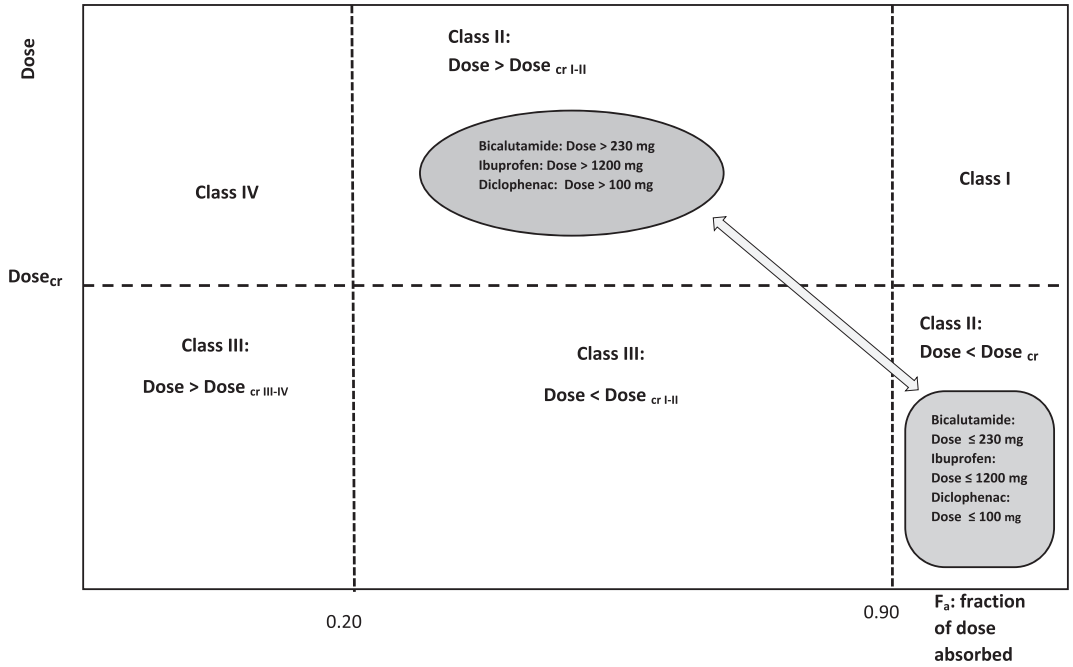

Fig. 6. Dose Dependent Biopharmaceutic Classification System (DDBCS): Three regions are defined by the perpendicular dashed lines corresponding to 0.20 and 0.90 fraction of dose absorbed, F_a. These regions correspond to Class I ($F_a \geq 0.90$), Class II & III ($0.20 < F_a < 0.90$) and Class IV ($F_a \leq 0.20$) of BCS, respectively. See text for the definition of Dose $_{cr,}$ Eq. (2). The concept of class migration is indicated by the arrow. Modified from Charkoftaki et al. (2012).

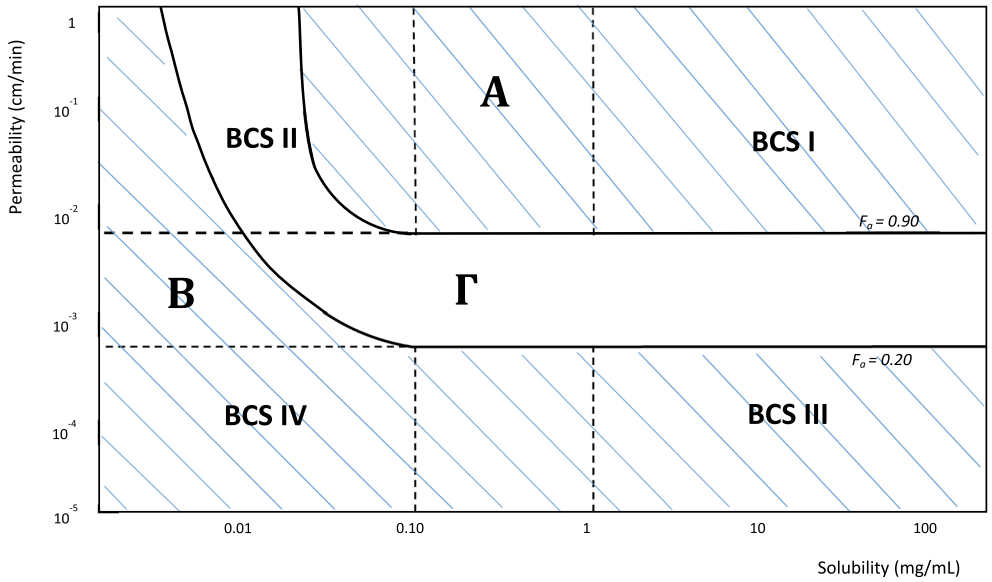

Fig. 7. The ABΓ system co-plotted with a continuous version of BCS. The black lines indicate either $F_a = 0.90$ or $F_a = 0.20$. The solubility and permeability values corresponding to the vertical and horizontal lines indicates high or low cut off limits for the four BCS classes. The shaded areas denote regions with either $F_a > 0.90$ or $F_a < 0.20$ that corresponds to A and B classes, respectively. Modified from Macheras and Karalis (2014).

-Class 3B: transporter mediated hepatic uptake or renal clearance (low permeability acids/zwitterions with MW > 400 Da) and
-Class 4: renal clearance (low permeability bases/neutrals).

The study was based on 307 compounds and revealed that a single clearance mechanism contributed to ≥70% of systemic clearance. The ECCS was recently applied by Varma et al. to evaluate investigational drugs as substrates of drug transporters. Varma (2017). It was found to be a useful tool to support the rational staging of transporter-related DDI.

In 2018 Macheras et al. (2018) published a biopharmaceutic classification scheme using a reaction limited model for the dissolution of drug. In this scheme, solubility is not any longer the main parameter of classification. The dissolution/reaction rate constant, which governs the process of drug dissolution is the principal parameter. The classification relies on the fulfilment or not of the regulatory dissolution criteria. Accordingly, this classification scheme is completely model independent since both parameters, since %dissolved and % metabolized are not associated with any model hypothesis. The pharmaceutical scientist performing the official dissolution tests, relies exclusively on the dissolution results and ignores any dissolution mechanism consideration. Important parameters for the drug dissolution rate are the drug dose and the stoichiometry of the reaction. The modeling work also takes into account supersaturation and precipitation phenomena and in addition some aspects of the classification of drugs were linked with the drug dissolution mechanisms, (Fig. 8). For hydrophilic

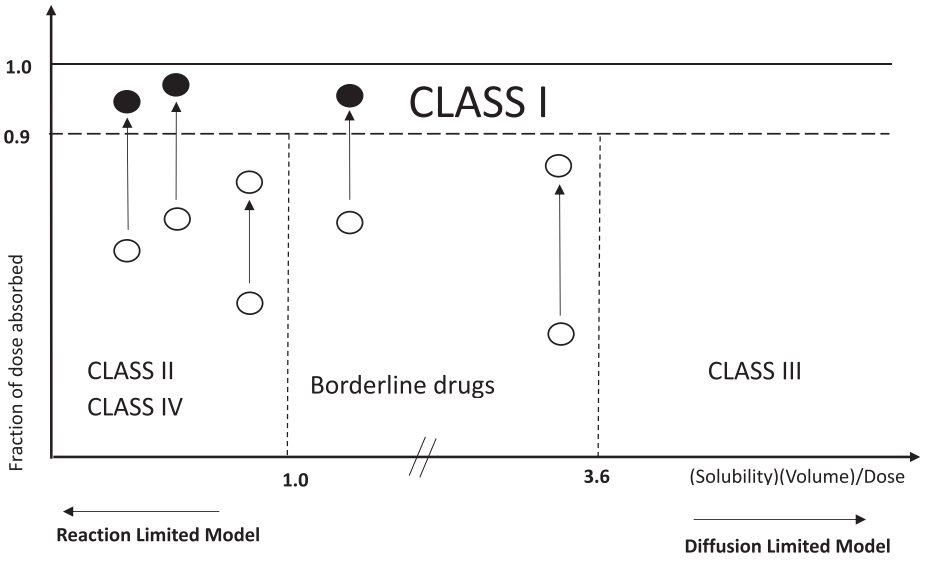

Fig. 8. Fraction of dose absorbed as a function of the dimensionless (Solubility) (Volume)/dose ratio. The arrows indicate the increase in the fraction of dose absorbed because of supersaturation phenomena. The involvement of dissolution mechanisms are indicated at the two ends of the x-axis. See Macheras et al. (2018) for the definition of limiting values 1 and 3.6 for the borderline drugs. (Modified from Kosmidis and Macheras (2018)).

compounds the diffusion -limited mechanism describes the dissolution process while hydrophobic compounds, which frequently exhibit supersaturation phenomena, obey the reaction-limited model of dissolution. The latter observation can justify the extensive absorption of sparingly soluble drugs (Yazdanian et al., 2004; Rinaki et al., 2004).

5. Conclusions

Due to the obvious industrial interest for the BCS guidance, a significant increase in solubility and dissolution-related articles was noted upon its publication in 2000 (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) December, 2017). Usage of the keyword “BCS” in Google Scholar yields 245,000 results, “BCS class” gives 49,400 results, and “BCS Class drugs” gives 17,900 results. The last 10 years result in 7859 findings in PubMed for “BCS”, with 5520 having been published in the last 10 years and 3482 of them the last 5 years (accessed: 2/5/19).

A similar pattern was not observed for the studies related to permeability since the % metabolism property introduced in the BDDCS (2005), and which ‘replaced’ permeability, turned the interest towards the disposition phenomena. However, by using the keyword “BDDCS”, one can find about 1410 citations related to it in Google Scholar from 2005 to 2019. For the same time span, 75 citations can be found in PubMed, of which, 67 regard the last 10 years (– accessed: 2/5/19).

A number of biorelevant media have been developed to mimic drug dissolution under *in vivo* conditions; however, none of these has yet been included as the recommended medium to use in the regulatory guidelines. From the experience gained so far, the quest for the “ideal” medium is utopian. Instead, the range of factors associated with drug dissolution under *in vivo* conditions should be further explored e.g. drug dissolution mechanism(s), the effect of *in vitro* agitation and *in vivo* motility on drug dissolution rate; moreover, the impact of the agitation /motility on the type of dissolution kinetics (classical or fractal) encountered should be clarified . These research results can be further coupled with PBAM modeling, which is a versatile tool encompassing physicochemical, physiological and biochemical processes governing the pharmacokinetic behavior of the formulated drug for an accurate prediction of the oral absorption profile. To better predict drug performance of BCS II and IV compounds, such PBAM is crucial to understand how dissolution (and release) under physiological conditions may be influenced by the enabling formulation as such. There is e.g. a clear difference in complexity between supersaturating systems generated by amorphous dosage forms and lipid-based formulations, where the latter also are physiologically processed via digestion after oral intake.

The evolution of the biopharmaceutical classification systems indicates that we are moving towards model independent approaches. For example, the use of the % dissolved criterion for biopharmaceutical classification purposes is hypothesis free i.e. no assumption is required for the mechanism(s) of dissolution processes operating under in vivo conditions. These models hold as long as the test method as such is biorelevant and produce in vivo predictive dissolution; for this to occur both the medium and the hydrodynamic conditions need to be in vivo like. Finally, the work based on BDDCS and relevant clearance concepts indicates that a better understanding of the disposition phenomena will emerge in the not too distant future. It is likely that consensus models taking all these factors (dissolution, solubility, permeability, metabolism, clearance) into account will allow us to more accurately predict human *in vivo* performance and more broadly predict bioequivalence of orally administered dosage forms.

Declaration of Competing Interest

None.

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