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The Biopharmaceutics Classification System: Subclasses for in vivo predictive dissolution (IPD) methodology and IVIVC

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Abstract

The Biopharmaceutics Classification System (BCS) has found widespread utility in drug discovery, product development and drug product regulatory sciences. The classification scheme captures the two most significant factors influencing oral drug absorption; solubility and intestinal permeability and it has proven to be a very useful and a widely accepted starting point for drug product development and drug product regulation. The mechanistic base of the BCS approach has, no doubt, contributed to its wide spread acceptance and utility. Nevertheless, underneath the simplicity of BCS are many detailed complexities, both in vitro and in vivo which must be evaluated and investigated for any given drug and drug product. In this manuscript we propose a simple extension of the BCS classes to include subspecification of acid (a), base (b) and neutral (c) for classes II and IV. Sub-classification for Classes I and III (high solubility drugs as currently defined) is generally not needed except perhaps in border line solubility cases. It is well known that the , pKa physical property of a drug (API) has a significant impact on the aqueous solubility dissolution of drug from the drug product both in vitro and in vivo for BCS Class II and IV acids and bases, and is the basis, we propose for a sub-classification extension of the original BCS classification.

This BCS sub-classification is particularly important for in vivo predictive dissolution methodology development due to the complex and variable in vivo environment in the gastrointestinal tract, with its changing pH, buffer capacity, luminal volume, surfactant luminal conditions, permeability profile along the gastrointestinal tract and variable transit and fasted and fed states. We believe this sub-classification is a step toward developing a more science-based mechanistic in vivo predictive dissolution (IPD) methodology. Such a dissolution methodology can be used by development scientists to assess the likelihood of a formulation and dosage form functioning as desired in humans, can be optimized along with parallel human pharmacokinetic studies to set a dissolution methodology for Quality by Design (QbD) and in vitro–in vivo correlations (IVIVC) and ultimately can be used as a basis for a dissolution standard that will ensure continued in vivo product performance.

Keywords

BCS Class II; Sub-classification; In vivo predictive dissolution; Simulation; GastroPlus™

1. Introduction

The Biopharmaceutics Classification System (BCS) and the corresponding guidance issued by the FDA categorize drug substances into 4 groups based on aqueous solubility and intestinal membrane permeability (Amidon et al., 1995).It is very important to study the BCS for new research. The FDA BCS guidance allows biowaivers for BCS Class I drugs based on drug product in vitro dissolution for immediaterelease (IR) solid oral dosage forms (CDER/FDA, 2000). The criterion for high solubility, high permeability and product dissolution is likely conservative relative to the current in vivo bioequivalence (BE) (80–125%) standard for BCS Class I drugs. However, as noted by Butler (Butler and Dress-man, 2010) it does not capture the most significant physicochemical differences that are critical to dosage form design and performance for BCS Class II and IV drugs/drug products. Drugs and drug products within BCS Class II, for example, low solubility and high permeable drugs, would be absorbed completely, if in solution. Thus in vivo dissolution is the critical determinant of in vivo absorption, bioavailability (BA) and the subsequent bio-equivalence (BE) determinations. Clearly the in vitro dissolution methodology needs further development, relative to the in vivo conditions, in order to be predictive of in vivo oral performance.[1]

BCS Class II and IV drug product dissolution in vivo and in vitro is highly dependent on the acidic or basic nature of the drug, the drug solubility and formulation factors, in addition to the in vivo luminal environment. While these factors can be complex, in this manuscript we propose a BCS Class II and IV sub-classification with a, b, and c subclasses dependent on the acidic (a), basic (b), or neutral (c) characteristics of the drug in the physiological pH range (~pH < 7.5). pH is very important factor here . Further, we propose developing a corresponding drug product in vivo predictive dissolution (IPD) methodology, based on these classes and subclasses that will be predictive of in vivo performance.[2]

In the WHO and European Medicines Agency BE standards, as well as recommendations from several scientific workshops, certain BCS Class II drugs (e.g. BCS Class IIa, see below) have even been recommended as, or are candidates for a biowaiver. BCS Class IIa drugs, typically carboxylic acids with a pKa in the range of 4 to 5, are insoluble at typical, fasted, gastric pHs but soluble at intestinal pHs and, hence, are classified as BCS Class II or IV depending on intestinal jejunal permeability at pH = 6.5 or fraction dose absorbed determination in humans. With intestinal pH of ~6.5, the solubility and hence, likely the dissolution rate, of the acidic drugs (pKa ~ 4–5) would increase up to ~100 fold or more on entering the small intestine. Thus dissolution would likely be significantly faster than the average gastric emptying rate (half-time ~15 min) depending on dose and intrinsic solubility. Thus, as with BCS Class I drug products with rapid dissolution, the plasma levels for a BCS Class IIa drug would likely reflect gastric emptying and luminal pH differences, and not product differences. The objectives of this investigation are to use simulation methods to illustrate the oral absorption profiles of BCS Class II drugs.[2]

2. Methods

Drug dissolution and fraction absorbed from the gastrointestinal tract were predicted using physicochemical and pharmacokinetic properties approximating those of the selected drugs and input into GastroPlus™ (version 7.0). Here the method are the important while performing experiments . First-pass metabolism and systemic availability were not considered at this stage. Such considerations are essential for

optimal product development and systemic availability prediction. Our goal in this study is to illustrate the general expected oral absorption curves for BCS II subclasses simulated using approximate 'real' drug properties. Here we know full information. We did not attempt to provide a detailed absorption and systemic availability analysis of the chosen drugs. Virtual trials with a 250-ml dose volume for an immediate release (IR) dosage form were performed to predict the oral absorption (Cmax, AUC0-inf, and Fa %) of 6 BCS Class II drugs, two in each BCS subclass, with the consequently varying dissolution in the GI tract. The predictions of oral absorption for BCS Class II drugs revealed absorption patterns, as expected, that depend on their biopharmaceutical (physicochemical) properties. The results demonstrate that the dissolution profiles of BCS Class II drugs along with pH changes in the GI tract would have intestinal absorption patterns and dissolution rates, which will vary depending on the luminal environment and drug product composition. BCS class II drugs are oral absorbed . This would control the overall rate of oral absorption for BCS Class II drugs, though systemic availability may be further reduced and complicated by intestinal or hepatic first-pass metabolism and excretion (including subsequent reabsorption). These BCS Class II absorption patterns are clearly shown to be dependent on the sub-classification, as expected. We believe the proposed BCS sub-classification can be used to set improved predictive dissolution methodology and standards for BCS Class II drug products and will provide better assurance of in vivo bioperformance.[3]

2.1. Computer hardware and software

GastroPlus™ version 7.0 (SimulationPlus, Inc., Lancaster, CA) was run using an IBM computer with Intel Core™ 2 Duo processors. The computational software allows the input of various dissolution profiles and computes the corresponding pharmacokinetic profiles and parameters. This is very good for testing . [4]

2.2. Simulation design

Oral drug absorption was computed based on (approximating) the physicochemical, pharmacokinetic, and drug dissolution properties of the six selected BCS Class II drugs using the previously reported simulation method (Tsume and Amidon, 2010). The gastric emptying time (15 min) as a mean value was adopted and the mean with coefficients of variation was used for these virtual trials. Since the AUC0-inf of drugs is calculated by extrapolation of the last two data points by GastroPlus™, the virtual trial over 24 h resulted in some variation in AUC0-inf for longer half-life drugs. These virtual trials were performed for 48 h. Simulation design perform very important role .The variations in population physiology were defined as means with coefficients of variation (in log space) and individual trials were randomly selected within those ranges. A virtual trial with n = 500 was used as the IR reference for each drug product (dissolution profile).[5]

2.3. Input parameters for pharmacokinetic simulations

The physicochemical and biopharmaceutical properties of ibuprofen, ketoprofen, carvedilol, ketoconazole, danazol, and fenofibrate used in the GastroPlus™ simulations, as well as the chemical, physiological, and pharmacological parameters for drugs cited in the literature are presented in Table 1 (Abernethy and Greenblatt, 1985; Avdeef et al., 1998; Baxter et al., 1986; Beetge et al., 2000; Cordero et al., 1997; Domanska et al., 2009; Dressman and Lennernäs, 2000; Fei et al., 2013; Geisslinger et al., 1995; GlaxoSmithKline, 2009; Hooper et al., 1991; Huang et al., 1986; Ige et al., 2013; Kasim et al., 2004; Keating and Croom, 2007; Loftsson et al., 2008; Mannisto et al., 1982; Oliary et al., 1992; Peeters et al., 2008; Perez de la Cruz Moreno et al., 2006; Planinsek et al., 2011; Prajapati et al., 2012; Vertzoni et al., 2010; Yun et al., 2006). Since the size of drug particles can significantly affect drug dissolution rate, the relatively larger particle size, a radius of 25 μm, to minimize the particle effects for dissolution was set as the mean particle size with a coefficient of variation (Le et al., 2006; Lin et al., 1982; Mutalik et al., 2008; Sheng et al., 2008; Takano et al., 2008; Tsume and Amidon, 2010). It is hard to predict the mean precipitation time because it depends on the formulation and physicochemical properties of drug compound. The range of precipitation time, 15–75 min, has been calculated from the various experiments (Carlert et al., 2010; Kambayashi and Dressman, 2013; Lindfors et al., 2008). The mean precipitation time of 900 s (15 min) was chosen and was used it with a coefficient of variation for

virtual trials. Virtual trials were performed using the GastroPlus™ standard physiological conditions: Human Physiological-Fasted, which condition simplifies the drug solubility in this set of simulation because of minimal effects of bile components on drug dissolution, and Opt LogD Model SA/V 6.1. In those virtual trials, dose, dose volume, molecular weight, logP, pKa, particle density, and diffusion coefficient of drug compounds were fixed. All other parameters for virtual trials such as effective human permeability, intestinal transit time and pharmacokinetic clearance were defined as variables and there class, which were randomly selected within a 5–20% (coefficient of variation) log–normal distribution based on their mean values. The physiological compartment parameters were adjusted such that the BCS Class II drugs would be absorbed in the entire small and large intestine with no absorption in the stomach.[5,6]

3. Results

The oral absorption of the BCS Class II reference drug product was predicted using GastroPlus™ virtual trials. The mean (reference) Cmax, AUC0-inf and Fa % ± standard deviation (SD), were obtained with an n = 500 virtual trial for an IR dosage.[7,8,9]

3.1. BCS Class IIa drugs; pKa ≤ 5 (weak acid drugs; ibuprofen and ketoprofen)

The predicted oral absorption results, mean Cmax, AUC0-inf and Fa %, for ibuprofen and ketoprofen are shown in Table 1. The percentages of dissolved and absorbed ibuprofen and ketoprofen with an IR dosage were calculated by a GastroPlus™ simulation and plotted as a function of time for the first 10 h (Fig. 1a and b). Ibuprofen and ketoprofen exhibited similar Tmax (ibuprofen 4.6 h and ketoprofen 4.0 h) and Fa % values, and also exhibited nearly complete oral absorption (97.4% and 97.1%), respectively (Table 2). The percentages of dissolved and absorbed ibuprofen and ketoprofen with an IR dosage were also calculated and plotted as a function of time for the first 10 h in Figs. 1 and 2. Fig. 2 illustrates that the nearly complete dissolution of ibuprofen and ketoprofen is predicted to occur by 8 h after oral administration. The percentages of absorbed ibuprofen and ketoprofen were divided by the average transit time of each GI segment and the results were plotted as a function of those segments (Fig. 3). In Fig. 3, ibuprofen and ketoprofen are predicted to be absorbed more in the distal small intestine than in the proximal small intestine due to the environmental pH in the GI tract and their pH-dependent solubility/dissolution. There are many more drug from that ,The absorption pattern of ibuprofen suggests a higher fraction absorbed in the ileum than the jejunum in these simulations.[7]

3.2. BCS Class IIb drugs; pKa ≥ 6 (weak base drugs; carvedilol and ketoconazole)

The prediction results of mean Cmax, AUC0-inf, and Fa % ± SD for carvedilol and ketoconazole are shown in Table 2. Carvedilol and ketoconazole exhibited predicted oral absorption of 45.9% and 47.0%, respectively (Table 2). The percentages of dissolved and absorbed carvedilol and ketoconazole with an IR dosage were calculated by a GastroPlus™ simulation and plotted as a function of time for the first 10 h (Fig. 1c and d). The percentages of absorbed carvedilol and ketoconazole were divided by the average transit time of each GI segment and plotted as a function of those segments (Fig. 3). Figs. 1 and 2 illustrate the quick dissolution of carvedilol and ketoconazole due to the acidic pH in stomach. The precipitation of carvedilol and ketoconazole was calculated to be 30–60 min after oral administration. Thus, the majority of the absorption for carvedilol and ketoconazole (68.8–77.5%) was predicted at the lower pH environment in the duodenum and proximal jejunum (jejunum 1) due to their higher solubility and their high permeability (Fig. 3) in this region of the intestine. Contrary to weak acids, carvedilol and ketoconazole were absorbed more in the proximal small intestine than in the distal small intestine. Particularly, the absorption pattern of carvedilol clearly revealed more absorption at the duodenum and proximal jejunum than at the ileum. [8]

3.3. BCS Class IIc drugs; No pKa (neutral drugs; fenofibrate and danazol)

The prediction results for the oral absorption of fenofibrate and danazol are shown in Table 2. Fenofibrate and danazol exhibited oral absorption of 47.8% and 36.4%, respectively (Table 2). The percentages of dissolved and absorbed drug with an IR dosage were calculated by GastroPlus™ simulation and are plotted as a function of time for the first 10 h (Fig. 1e and f). The percentages of absorbed fenofibrate and danazol were divided by the average transit time of each GI segment and those results were plotted as a function of those segments (Fig. 3).[9]

4. Discussion

The Biopharmaceutics Classification System (BCS) is a system classifying a drug substance (API) based on its minimum aqueous solubility in the pH range of 1–7.5, dose and human fraction absorbed or intestinal membrane permeability (CDER, 2000). This system categorizes drugs into four classes according to their permeability and solubility (CDER, 2000). It has been suggested that the regulatory criterion for a high soluble drug, whose highest dose (approved) strength is soluble in 250 ml aqueous media over the pH range of 1.0–7.5(6.8), is conservative for BCS Class I drugs and that further biowaivers for acidic drugs, BCS Class IIa, should be considered (Rinaki et al., 2004; Yazdanian et al., 2004). In this report we suggest a further BCS sub-classification based on drug biopharmaceutical properties that can be used as a beginning basis for setting an in vivo predictive dissolution (IPD) methodology.

It has been reported that some BCS Class II compounds, which have particular biopharmaceutical characteristics, such as weak acids, particularly the high permeability, low molecular weight non-steroidal anti-inflammatory drugs (NSAIDs), are rapidly and completely absorbed orally (Davies, 1995; Davies and Anderson, 1997; Faassen and Vromans, 2004). The scientific basis for this is that poorly soluble weak acids with pKa in the physiological range i.e. pKa values ≤5.0, such as ibuprofen and naproxen would have a solubility of ≥1 mg/ml at around pH 6.5, (average pH value of the fasted state in the jejunum), resulting in rapid (less than 0.5 h) and reliable dissolution (Dressman et al., 2001). On the other hand, poorly soluble weak bases with pKa values in the physiological range of 3–6 such as ketoconazole and carvedilol would have high solubility in the stomach, typically at pH 1–3, and subsequently may precipitate in the higher pH of the small intestine (the presence of food, the pH of the gastric contents and intestinal secretions are variable factors). For neutral drugs such as fenofibrate and danazol, the solubility would not be affected by regional pH changes, though luminal composition changes e.g. lipid and bile salt presence, digestion and/or absorption of luminal contents (particularly foods), as well as formulation factors can affect the in vivo dissolution in a complex time dependent manner (Sugano, 2010).[10,11]

From these simulations it was also observed that the colonic absorption of BCS Class II drugs may have a significant impact on their overall oral absorption due to their longer residence times (and high permeability) in the large intestine (Fig. 3). It is generallyassumed for BCS Class II drugs that their incomplete dissolution in the small intestine is due to the limited and variable residence time in the various intestinal segments and the potential small residual intestinal fluid volume (Fadda et al., 2010; Marciani et al., 2010; Schiller et al., 2005). In the fasted state, the small-intestinal transit time, approximately 3–4 h, is significantly longer than the average gastric residence time of approximately 15–60 min (Davis et al., 1986; Kaus and Fell, 1984; Kortejarvi et al., 2007; Oberle et al., 1990; Reddy et al., 1999). Also, it has been reported that the residence times in the caecum and colon are around 3–7 h and 12–24 h, respectively, which are also significantly longer than the average 3 h residence time reported for the small intestine (Ibekwe et al., 2008; Laird et al., 2010; Madsen and Krogsgaard, 1989). In these simulations, the default residence times used for the caecum, and ascending colon were 4.2 h, and 12.6 h, respectively.

It has been reported that the measured pH of the human intestine in the fasted state ranged 6.3–7.5 in duodenum, 6.2–6.7 in proximal small intestine, 6.3–7.3 in middle small intestine, 6.7–7.7 in distal small intestine, and 5.5–7.6 in ascending colon (Ibekwe et al., 2008; Perez de la Cruz Moreno et al., 2006). The pH values of the caecum and colon were set to 6.4 and 6.8, respectively, as mean pH values in these simulations. At those pH values, a weakly acidic drug such as ibuprofen (pKa 4.9) would exhibit high solubility in the jejunum, ileum, caecum, and colon and, therefore, have sufficient residence time in the small intestine for 3– 4 h and in the caecum and colon for 15–31 h for complete absorption. As a result, it is highly likely that ibuprofen, for example, would behave similar to a BCS Class I drug in the intestine even though it is classified as a low solubility drug due to its poor solubility at gastric pH. Therefore, weak acids of BCS Class IIa may be completely absorbed due to their high permeability and high solubility and dissolution rate in the small and large intestine and sufficient residence time throughout the whole intestine. In our simulation, ibuprofen and ketoprofen exhibited essentially complete absorption with an IR dose, including a small amount of absorption from the caecum and colon. Indeed, it has been reported that weakly acidic BCS Class IIa drug products have been shown to be completely absorbed orally due to their high solubility at the pH range (pH 6.0–6.4) of the small intestine (Davies, 1998; Dressman et al., 2001). Thus, BCS Class IIa, drugs and drug products with acidic pKa values ≤5.0 in IR oral dosage forms would have sufficient time for complete dissolution and absorption in the small intestine and biowaivers are scientifically sound, if a relevant dissolution test standard is met.

The BCS Class IIc drugs that have biopharmaceutical properties similar to those of fenofibrate will have longer residence times throughout small and large intestines i.e. slower absorption (residence time; 18–35 h) and the absorption of those drugs would be determined by their (in vivo) drug solubility, dissolution rates and permeability along the GI Tract. Neutral drugs would have dissolution rates depending on the in vivo environment, and can exhibit high oral extent of drug absorption from the caecum and colon (5–13% and 13–25%, respectively) due to more drug actually reaching those portions of the intestine.[10,12]

4.1. Absorption profiles

Figs. 1 and 3 summarize the absorption rate profiles and intestinal segmental absorption profiles from the simulation results for the drugs from each BCS Class II sub-class. While the time scales for the oral absorption processes from IR products are often in the early portions of a usual pharmacokinetic profile, we note the expected profiles below. Particularly for BCS Class IIb and IIc, drugs in IR dosage forms, the absorption profile can continue throughout transit through the intestine. From these profiles we can draw some general conclusions regarding absorption from the BCS subclasses.[12]

BCS Class IIa: There will be an initial and variable lag in absorption due to slow gastric disintegration and limited dissolution in the stomach and hence appearance in the systemic circulation. This lag and variability will be dependent on dosing time relative to the gastric motility phase (Oberle and Amidon, 1987; Oberle et al., 1990). The subsequent absorption rate and rate profile will depend mainly on the gastric emptying and dissolution rate.[13]

BCS Class IIb: The absorption rate of drugs in this class will depend initially on the disintegration and dissolution in the gastric environment and gastric emptying, with IR drug products generally showing a relatively rapid initial dissolution and gastric emptying rate limited absorption from the duodenum, relative to motility phase and duodenal environment for Class IIb drug products. Subsequent precipitation, solubilization, dissolution and absorption generally decrease the absorption rate after the initial rapid phase. In these simulations, absorption rate decreases along the gastrointestinal tract due to increasing pH and lower solubility. In general these processes will be complex due to drug, formulation and the in vivo variable intestinal contents. The fraction absorbed may be less than 90% for a BCS Class IIb drug product depending on dose, formulation and in vivo solubility in addition to the variable GI luminal conditions (motility, fluid, and solubilization).[14]

BCS Class IIc: These low solubility drugs in drug products will generally show slow and prolonged absorption depending on the formulation (Williams et al., 2013). The fraction absorbed (Fabs) and systemic availability (Fsys) will be dependent on the in vivo solubilization, dissolution as well as motility (transit). These drugs will likely exhibit the most direct dissolution rate controlled absorption rate correlation with an in vivo predictive dissolution methodology (Williams et al., 2012a). Analogous generalizations can be made for BCS Class IV (not explored in this study), with intestinal permeability and permeability variation along the GI tract playing a larger role. The role of non-sink conditions (confinement effect) in the intestine needs to be further explored.[15]

4.2. In vivo predictive (IPD) dissolution methodology

The proposed BCS sub-classification (Table 3a) distinguishes drug substances based on their relative solubilities in fluids characteristic of the average fasted human stomach and the small intestine. Some generalizations about dissolution and permeation characteristics in vivo can be made based on these relative solubilities, as well as on permeability along the intestine, characteristics of drug substances, which can be used as a starting point for development of an in vivo biopredictive dissolution methodology (IPD) and IVIVC methodology. The in vivo predictive dissolution methodology must be developed and adapted to a particular drug product, and include the most relevant variables while not overly complicating the method. Careful selection of the best methodology can only be made after evaluating (including initial estimates and assumptions) the important drug substance and drug product characteristics, including particle size distribution, dose, and permeation rate across different segments of the GI tract, physical form, disintegration rate, etc. For use in product development and in vivo prediction, a considerable amount of additional research is necessary to define the gastrointestinal variables, in terms of both average values and statistical distributions. Prediction would then entail computational simulation, of Monte Carlo type, over the expected range of these variables. The main focus would be on 'typical' subjects in the fasted and fed states, with fed state requiring further consideration regarding meal type including compositions to represent real meals. Further, consideration would have to be given to disease states that can alter the gastrointestinal physiology e.g. diabetes, achlorhydria and drug–drug interactions that may be mediated by alterations of the gastrointestinal physiology (Budha et al., 2012, 2013).

In vivo predictive dissolution (IPD) methods will be considerably different from, and more complex than USP quality control (QC) methodologies. A USP type QC methodology, along with additional QC specifications is the standard for keeping a product within the Phase III product specifications, the most essential basis for the safety and efficacy label claims of the drug product (Amidon et al., 2011). The IPD methodology would be most useful for product development and eventually, when fully developed and validated, useful for product changes e.g. SUPAC type changes. The QC methodology would be a subset of the IPD method when the critical performance parameters have been defined. The validated IPD method would have great value in establishing Quality by Design (QbD) product performance specifications.[15,16]

4.2.1. BCS Class I drugs—

The proposed IPD (Table 3b) for BCS I drugs includes pretreatment of the dosage form in 250 ml of Physiological Gastric Buffer (PGB, comprising 0.01 N HCl) for 15 min, after which time the dosage form and PGB should be transferred to 900 ml of Physiological Intestinal Buffer (PIB). To represent fasted state conditions in the upper GI tract, PIB should be a pH 6.5 bicarbonate buffer with a concentration in the range of about 5–15 mM (Mudie et al., 2010), or a buffer with a buffercapacity 'equivalent' to that of a 5–15 mM bicarbonate buffer (Miller et al., 2011; Sheng et al., 2009). Although a BCS I drug with high solubility should dissolve equally well in PGB and PIB, exposure of the dosage form to both buffers is proposed as a conservative method to capture a possible influence of pH and an aqueous environment on potential physical changes of the drug substance or product , e.g. conversion from a salt to a free acid or base, crystal form changes, etc. (Miller et al., 2011). The high solubilities of these compounds should make the dissolution rate

only marginally dependent upon the concentration of drug dissolved in the aqueous buffer. In addition, since the intestinal absorption of the drug is high, with a fast absorption rate across the intestinal membrane, conditions approaching that of a 'sink-conditions' would be maintained in the intestinal lumen. Therefore, dissolution testing may be carried out in a large volume of PIB without the need for adding an "absorption compartment" to the methodology.[16]

4.2.2. BCS Class II—

The sub-classification, a: for acids (pKa < ~5), b: for bases (pKa > ~5, and c: for neutral drugs (pKa < 0 clearly affect drug product dissolution both in vitro and in vivo, the BCS sub-classification is based on fundamental properties determining equilibrium solubility of the drug over the physiological pH range. Non equilibrium solubility and amorphous or 'high energy' forms, while clearlyhaving a potentially significant impact on dissolution and drug oral delivery in vivo, do not change the actual BCS classification (or sub-classification) of a drug and product. The proposed IPD for subclasses IIa, IIb, and IIc are included in Table 3b. For IIa drugs, which would be virtually non-ionized and thus poorly soluble near pH 2, low gastric pH coupled with relatively short gastric residence time would lead to a limited extent of dissolution in the stomach in vivo. However, particularly when the Dose Number is high,1 it may be important to include a separate gastric compartment in the dissolution test and transfer gastric contents (including both dissolved & non-dissolved drug as well as PGB) to the intestinal compartment in a physiologically relevant manner, such as at a first-order rate with a half emptying time of about 15 min (Oberle et al., 1990).or ~ >8) is the clearest starting point for distinguishing and making recommendations for evaluation of low solubility drug substances. While other properties such a particle size, solid state form e.g. crystalline, amorphous etc. [17]

When the Class IIa drug reaches the small intestine, its high extent of ionization and corresponding high solubility should likely lead to relatively fast absorption. The high permeability classification (and likely moderate to high absorption rate of drug across the intestinal membrane) should act to keep the percent drug saturation in the luminal fluid relatively low for cases when Do is low and low to moderate for cases when Do is high. Since dissolution rate should be relatively independent of a low degree of drug saturation when Do is low, simply using 900 ml of PIB in the intestinal compartment should be adequate. However, for cases when Do is high, and the surface area high, it is possible that the intestinal luminal fluid is moderately saturated with drug in vivo, and for some BCS IIa compounds this saturation could cause the dissolution rate to be a function of saturation solubility and also be impacted by a confinement effect (8Wang et al., 2012).[18,17]

For Class IIb drug substances, it is proposed to carry out the IPD using a separate aqueous compartment containing 250 ml of PGB with controlled, first order emptying of contents into 100 ml of PIB with an absorption compartment (especially when Do is high). Use of both PGB and PIB including transfer of drug in a kinetically-appropriate manner is especially important for Class IIb bases due to the high solubility and likely high extent of dissolution in the stomach, followed by low solubility and likely precipitation in the small intestine in vivo. Use of a gastric compartment for BCS IIb drug products has been utilized several numerous times (Carl-ert et al., 2010, 2012; Kostewicz et al., 2002, 2004). Carlert et al. investigated the accuracy of both in vitro and in vitro/in silico methods for prediction of the in vivo intestinal precipitation of basic BCS Class II drugs in humans. One of the conclusions was that "reduction of luminal drug concentration by time due to absorption in vivo must be included in predictive methods," and that without it intestinal precipitation in humans in vivo may be less of a limitation than would be predicted in a simple in vitro method for which an absorption compartment is not included. Similarly, Bhattachar et al. stated that, when used without an absorption compartment, in vitro results in the ASD system over predicted the extent of exposure differences for a BCS II weak base that was dosed using different methods of stomach pretreatment (including low and high pH) in dogs (Bhattachar et al., 2011a,b).[18,19]

4.2.3. BCS Class III—

The proposed IPD for Class III drugs includes pretreatment of the dosage form in 250 ml of PGB for 15 min with subsequent transfer of the dosage form and PGB into 100 ml of PIB. So this BCS class are important . The rationale behind the chosen dissolution medium is similar to that for BCS I compounds due to the similar solubility characteristics. However, for BCS III drugs the low permeability (and expected low permeation rate through the intestinal membrane) in vivo could lead to moderate to high luminal concentrations of drug depending on Do. If the solubility of drug in the intestinal lumen in vivo is high, then the expected higher luminal concentrations of drug due to slow absorption may not affect the dissolution rate. A smaller volume of PIB (100 ml) was chosen for the intestinal compartment (which when combined with the 250 ml of PGB would be equal to a total volume of 350 ml) for Class III drugs to more accurately capture aqueous drug concentration, at least compared to 900 ml. If solubility of the drug in the intestinal lumen is such that the dissolution rate is decreases due to non-sink conditions, then a two-phase dissolution system maybe more appropriate IPD. If a separate absorption compartment is needed, use of a layer of Caco2 cells (Kataoka et al., 2013; Yamashita et al., 1997) or other membrane may be more appropriate than a two-phase system utilizing an organic solvent such as 1-octanol, since some Class III drugs have low logP and logDpH6.5 values. Use of a separate absorption compartment would allow for better evaluation of the confinement effect on dissolution rate. Further, since low permeability drugs must have, based on their incomplete oral absorption, an intestinal position (jejunum, ileum, colon) dependent permeability, an IPD-method needs to carefully consider drug pH dependent properties, and potential carrier mediated, position dependent absorption from the GI tract, in developing an IPD dissolution method. [18,19,20]

4.2.4. BCS Class IV—

As with BCS Class III, the low intestinal permeability may lead to high luminal drug concentrations relative to the drug's solubility and thus non-sink dissolution conditions. Coupled with the low expected solubilities for most BCS IV compounds in the intestinal lumen, these probable non-sink conditions would possibly lead to an impact of saturation solubility and a confinement effect on dissolution rate. Therefore, it is recommended to evaluate all BCS IV drugs (a, b, and c) in 250 ml of PGB contained in a separate compartment, with controlled transfer to 100 ml of PIB (IVa and IVb) or 100 ml of PIB + bile acids and lipids (IVc) with a separate absorption compartment. As with BCS II drugs, possible food effects will depend on the actual solubility and pKa's of the API, leading to variable food effects on absorption.[19,21,22]

5. Summary

In this manuscript we use in silico results to support the proposed BCS Subclassification and present some general recommendations for dissolution methodologies. These subclasses are based on fundamental drug properties and can serve as a basis for developing in vivo predictive dissolution and absorption methodology. An in vivo predictive dissolution methodology when combined with a permeability profile of the gastrointestinal tract would be predictive of drug absorption as a function of time (and position along the GI tract). The drug product quality, i.e. safety and efficacy, would be assured by a dissolution methodology that predicts this in vivo dissolution. The central hypothesis underlying this conclusion is that stated in the original BCS paper (Amidon et al., 1995).

"If two drug products have the same in vivo dissolution profile under all luminal conditions, they will have the same rate and extent of drug absorption".

Since the rate and extent of metabolism depends on the rate of absorption over time, the same can be stated for metabolism. Thus the pivotal dissolution standard is that of the clinically tested Phase III product and matching this in vivo dissolution over the life time of a drug product is the most important and essential pharmaceutical quality standard for oral products (Amidon et al., 2011). The BCS sub-classification and IPD methodology provides a starting point for the development of this pharmaceutical quality standard. We believe the BCS sub-classification approach to setting oral dissolution methodology will be preferable, and occupy a middle ground between the…'one size fits all' approach and an unnecessarily large number of almost independent methods…one or more for each oral 'drug product'…depending on the specific product.

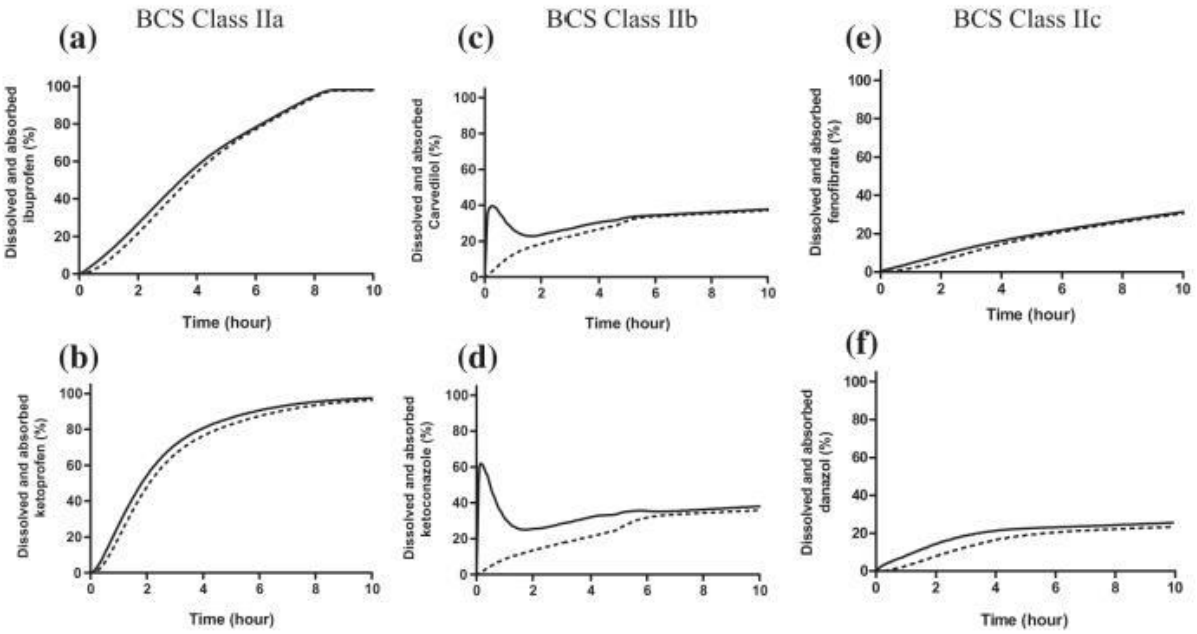

Fig. 1. Amount of BCS Class II drugs dissolved and absorbed calculated in silico: (a) ibuprofen, (b) ketoprofen, (c) carvedilol, (d) ketoconazole, (e) fenofibrate, (f) danazol. Solid lines represent dissolved drugs and dot lines represent absorbed drugs.[23]

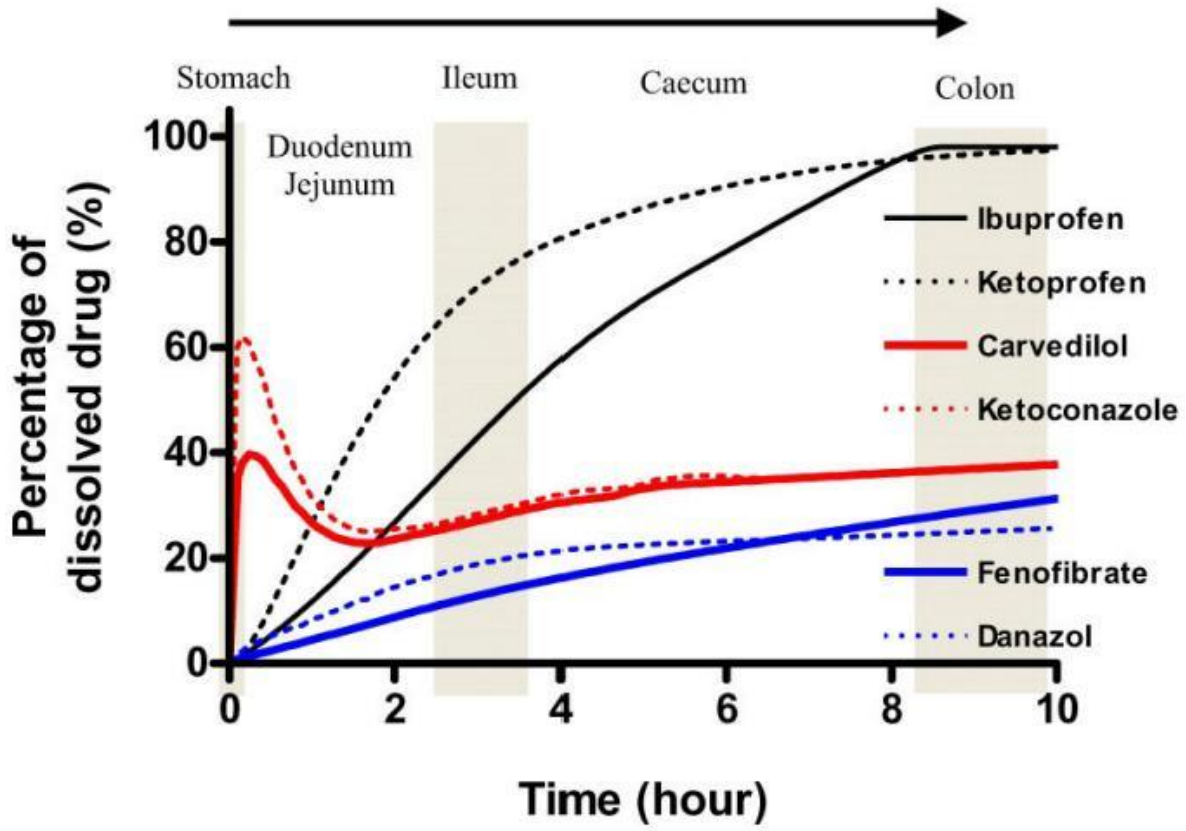

Fig. 2. Percentage of amount dissolved with an IR dosage. Black solid and dot lines represent BCS Class II weak acids, Red solid and dot lines represent BCS class weak bases and blue solid and dot lines represent BCS class neutrals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)[24]

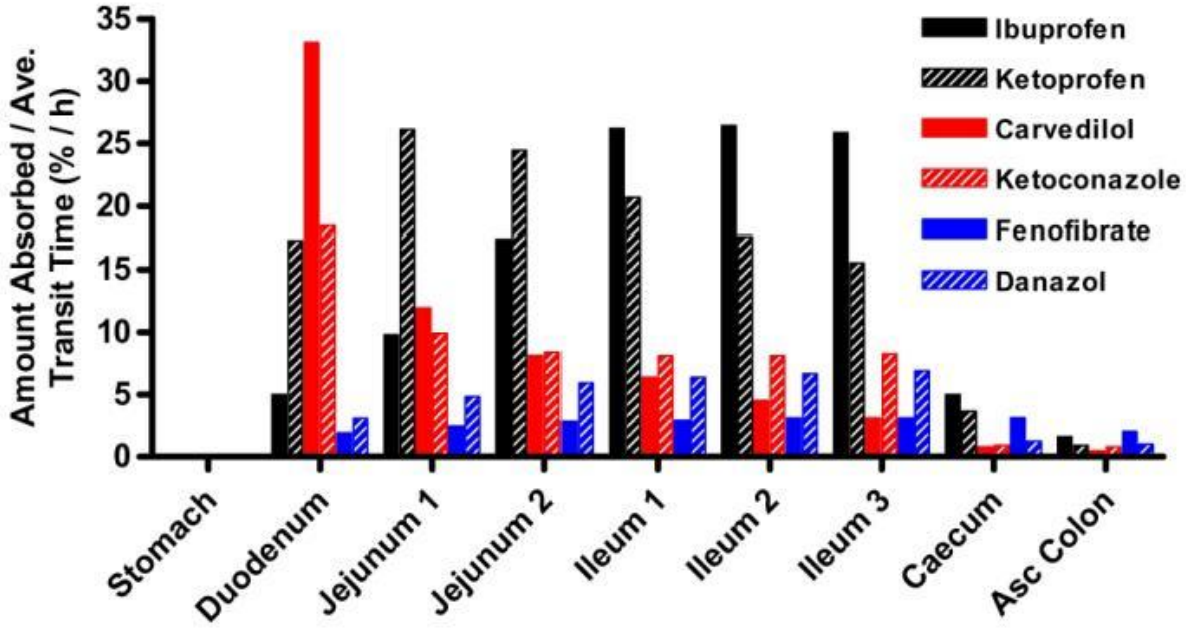

Fig. 3. The absorption rates of BCS Class II drugs in each GI segment. Percentages of amount absorbed after oral administration of an IR dosage are divided by the average transit time and are plotted as a function of each GI segment. Black bars represent BCS Class II weak acids, Red bars represent BCS class weak bases and blue bars represent BCS class neutrals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.[24,8]

Table 1

Chemical/physiological/pharmacological parameters of BCS Class II drugs for GastroPlus™ simulation.

		Ibuprofen Acid	Ketoprofen Acid	Carvedilol Base	Ketoconazole Base	Fenofibrate Neutral	Danazol Neutral
MW		206.3	254.3	406.5	531.4	360.8	337.5
Dose	mg	800[a]	50[f]	25[j]	200[m]	100[r]	100[v]
Dose number		1792[A]	197[A]	835[A]	61[A]	1429[A]	23[A]
Dose volume	ml	250	250	250	250	250	250
Solubility	mg/ml	9.0×10^{-2}[b]	5.1×10^{-2}[g]	5.8×10^{-4}[k]	1.8×10^{-2}[n]	2.8×10^{-4}[s]	1.8×10^{-2}[w]
log*P*		3.6[c]	2.8[g]	3.8[l]	4.3[o]	5.3[t]	4.5[x]
p*Ka*		4.9[d]	4.5[h]	7.8[l]	2.9/6.5[p]	NA	NA
Mean precipitation time	s	900	900	900	900	900	900
Human P_{eff}	$\times 10^{-4}$ cm²/s	4.10[B]	8.70[i]	4.04[B]	1.37[B]	2.83[B]	1.21[B]
Body weight	kg	70	70	70	70	70	70
Vc	l/kg	0.2[e]	0.4[f]	1.6[j]	0.7[q]	0.4[u]	118.8[v]
Total clearance	l/h/kg	0.10[a]	0.06[f]	0.51[j]	0.38[m]	0.02[r]	9.90[v]

Table 2

Simulated C_{max}, AUC, and Fa of selected BCS Class II drugs with an IR dosage.

	C_{max}($\times 10^{-2}$ µg/ml)	AUC($\times 10^{-1}$ ng/ml h)	Predicted Fa (%)
Ibuprofen	1582.0 ± 160.2	1159.3 ± 51.7	97.4 ± 1.2
Ketoprofen	102.7 ± 13.9	111.1 ± 8.3	97.1 ± 2.1
Carvedilol	2.6 ± 0.5	2.3 ± 0.4	45.9 ± 1.0
Ketoconazole	44.6 ± 8.9	63.0 ± 4.0	47.0 ± 6.9
Fenofibrate	93.3 ± 17.4	433.9 ± 80.2	47.8 ± 6.7
Danazol	3.5 ± 0.7	42.0 ± 1.2	36.4 ± 4.3

Table 3a

Solubility and permeability characteristics of drug substances based on BCS sub-classification.

BCS sub-classification	Solubility at pH 2	Solubility at pH 6.5	Permeability
I	High	High	High
IIa[a]	Low	High	High
IIb[b]	High	Low	High
IIc[c]	Low	Low	High
III	High	High	Low
IVa[a]	Low	High	Low
IVb[b]	High	Low	Low
IVc[c]	Low	Low	Low

[a] With a p*Ka* < 5.

[b] With a p*Ka* > 6.

[c] With no p*Ka*(s) or p*Ka*(s) < 0 or >8.

Table 3b

Proposed relevant bioperformance dissolution methodology (apparatus and media).

BCS sub-classification	Gastric medium	Consider gastric compartment?	Intestinal luminal medium	Consider absorption compartment?[a]
I	250 ml PGB[e]	No[b]	900 ml PIB[c]	No
IIa		Yes[d]	100 ml PIB	Yes
IIb		Yes[d]	100 ml PIB	Yes
IIc		Yes[d]	100 ml PIB + bile acids/ lipid	Yes
III		No[b]	100 ml PIB	No
IVa		Yes[d]	100 ml PIB	Yes
IVb		Yes[d]	100 ml PIB	Yes
IVc		Yes[d]	100 ml PIB + bile acids/ lipid	Yes

a An organic medium (such as 1-octanol) can be used for the absorption compartment when logDpH6.5 > than about 0.5–1 (Mudie et al., 2012). Otherwise, an alternative such as an artificial or caco2 membrane (Kataoka et al., 2003, 2006, 2012, 2013) may be used. Surface area of organic medium (or membrane) to volume ratio of luminal medium (A/V) must be chosen properly (Mudie et al., 2012).

b Pretreat dosage form with gastric medium for 15 min and subsequently transfer dosage form + gastric medium to intestinal luminal medium. Determine contribution of gastric emptying rate to delay in onset of appearance in plasma computationally.

c Physiological intestinal buffer (PIB), which should be pH 6.5 bicarbonate buffer with a buffer concentration between about 5–15 mM, or an aqueous buffer with an equivalent buffer capacity.

d Empty gastric contents in a first order manner with a rate coefficient of 2.8 h−1 (half-emptying time of 15 min).

e Physiological gastric buffer (PGB), which is 0.01 N HCl[25]

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