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Review Article

Evaluation and suggested improvements of the Biopharmaceutics Classification System (BCS)

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Abstract

This review has evaluated the Biopharmaceutics Classification System (BCS) and improvements have been proposed. The BCS has a very strict solubility/dissolution limit, a generous P_e-limit (≥ 14-times higher rate constant limit for dissolution than for permeation), and is stricter for drugs with a long half-life (t½). Available human in-vivo, in-vitro, and in-silico P_e-methods cannot classify P_e for moderately to highly permeable substances sufficiently well, and in-vitro data often underpredict the in-vivo dissolution potential and rate. Good in-vivo dissolution and absorption can be expected for most high P_e drug products. It has not been possible to find a highly permeable product with a Dose number (D_o) < 385 (< 2400 in the fed state) that is clearly incompletely absorbed, and near complete uptake has been shown for a drug product with a D_o of 660000. The potential implication of these findings is that many true BCS Class I drug products are incorrectly classified. This could be a reason for the limited use of this system. On this basis, it has been suggested that: the limit for high for solubility/dissolution is decreased (to > 40 and > 95% dissolved within 30 min and 3 h, respectively); the limit for high P_e is increased (to >P_e of metoprolol); accurate P_e-models or in-vivo fraction absorbed data are used; solubility/dissolution tests are performed using real or validated simulated gastrointestinal fluids; in-vitro/in-vivo dissolution relationships are established; the t½ is considered; and the rate-limiting step for in-vivo absorption is determined. A major change could be to reduce the BCS into two classes: permeation-rate (Class I) or dissolution-rate (Class II) limited absorption. It is believed that this could give a better balance and increase the number of biowaivers.

Introduction

Background

The Biopharmaceutics Classification System (BCS) is a regulatory tool developed for enabling replacement of in-vivo bioequivalence studies for immediate-release products by permeability (P_e) and in-vitro dissolution tests (Amidon et al 1995; FDA Guidance for Industry 2000; Lennernäs & Abrahamsson 2005). In the BCS, drug products are classified according to their intestinal P_e, and gastrointestinal (GI) solubility in relation to dose. That is: Class I, high P_e – high solubility; Class II, high P_e – low solubility; Class III, low P_e – high solubility; Class IV, low P_e – low solubility. A drug product is considered highly permeable and soluble when the P_e corresponds to a fraction absorbed (f_a) following oral administration that is not less than 0.9 (or 0.85, depending on regulatory agency), or when the measured f_a is ≥0.9 (or ≥0.85), and the highest clinical dose is dissolved in 250 mL buffer or other aqueous media at pH 1 to 7.5. The BCS requires the test drug product to show in-vitro dissolution profile similarity versus the comparator in three dissolution media. For immediate-release Class I drug products, dissolution in HCl-solution or simulated gastric fluid (SGF), pH 4.5 buffer, and pH 6.8 buffer or simulated intestinal fluid (SIF) must be complete (>85%) within 30 min.

The use of the BCS is very limited and the reasons for this are not clear (Barends 2005). Changes of the system have been proposed. For example, an extension to include Class III drug products in the waiver for in-vivo bioequivalence studies has been proposed (Yu et al 2002).

Requirements of an in-vitro based classification system, such as the BCS, are that: it predicts the in-vivo situation well; it defines the rate-limiting step for in-vivo absorption; the limits for P_e and solubility/dissolution are balanced; the in-vitro methods are sufficiently robust for correct classification; and the systemic half-life (t½) (or the elimination rate constant (k_e)), which is also a determinant of the time (t_{max}) and concentration (C_{max}) of the peak in the circulation, is considered. Changes in dissolution rates have less impact on the exposure profiles

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for compounds with a long t½. The potential implications of poor in-vitro to in-vivo prediction, unbalanced P_e and solubility/dissolution limits and neglect of t½ include incorrect BCS-classification and unnecessary in-vivo bioequivalence studies.

The objective of this study was to evaluate the BCS, and if required and possible, propose improvements. Three questions were asked. Firstly, are the BCS-limits for P_e and solubility/dissolution appropriate? Secondly, are the in-vitro methods sufficiently robust for correct BCS classification, and can the rate-limiting step for in-vivo absorption be well-defined and well-predicted from in-vitro data? Finally, what is the implication of neglecting the t½?

Methods

To evaluate whether the BCS-limits for P_e and solubility/dissolution were appropriate, dissolution rate constant (k_{diss}) and permeation rate constant (k_{pe}) corresponding to the Class I-limits were estimated. The k_{diss} was calculated based on 85% dissolution within 30 min, and the k_{pe} was estimated from $2\times P_e/r$, where P_e is the human in-vivo P_e and r the human small intestinal radius (1.75 cm) (Fagerholm et al 1996). The human in-vivo P_e was calculated using the following equation:

$$P_e = (\ln(1 - f_a)\times r)/(-2\times MTT_{si}\times f) \quad (1)$$

where MTT_{si} and f are the mean small intestinal transit time (3 h) and correction factor (2.8), respectively (Fagerholm et al 1996). The f_a was set to 90% (the limit for high P_e and f_a suggested by the FDA). With this approach the effective time for intestinal absorption was set to 8.4 h ($MTT_{si}\times f$) (Fagerholm et al 1996). This was a strict absorption time approach since the BCS allows 85 or 90% P_e-limited GI uptake during a 40-h average intestinal transit for classification as highly permeable (Davis 1986). To further evaluate the BCS-limits the literature was searched for incorrectly classified drug products, and simulations of plasma exposure profiles for compounds with different levels of k_{diss}, k_{pe} and k_e were performed and evaluated.

The performances of various P_e- and solubility/dissolution-methods were evaluated to answer the question whether in-vitro methods were sufficiently robust for correct BCS classification, and the rate-limiting step for in-vivo absorption could be well-defined and well-predicted from in-vitro data. Dose number (D_o)-values for highly permeable substances with high D_o ($D_o > 10$ in aqueous media or SIF at physiological pH) were collected or calculated, and correlated with available f_a-data. The D_o is a dimensionless parameter used as a measurement of solubility/dissolution potential. D_o is defined as the ratio of dose–concentration to solubility: D_o = (highest dose strength/250 mL fluid)/solubility (Dressmann et al 1985). A D_o-value of 1 implies that the expected highest GI concentration is similar to the solubility, and a high D_o implies a low dissolution potential.

The impact of neglecting the t½ on the systemic exposure profile was evaluated using simulations of four different hypothetical BCS Class I drug products. The drug products (A, B, C and D) had high P_e, were completely absorbed, had similar k_{diss}, but had different t½. The k_{diss} was set to equal that corresponding to 85% dissolution in 30 min. Drugs A and B had a P_e value similar to that of metoprolol (1.5×10^{-4} cm s^{-1}; high P_e according to BCS; $f_a = 0.98$), whereas drugs C and D had a P_e value similar to that of D-glucose ($P_e = 10\times10^{-4}$ cm s^{-1}, the highest measured value in man so far (Fagerholm et al 1996)). Drugs A and C had long t½ (20 h), and drugs B and D had short t½ (2 h). For all drugs Class II formulations (with dissolution 4-times slower than for the reference formulations) were developed. For simplicity, first-order and one-compartment kinetics were assumed. The concentration vs time profiles were simulated using the following equation:

$$\text{concentration} = k_a / (k_a - k_e)\times(e^{-ke\times t} - e^{-ka\times t}) \quad (2)$$

where the absorption rate constant (k_a) is the slowest of k_{diss} and k_{pe} (Rowland & Tozer 1995). In addition, recent similar simulations by Kortejärvi et al (2007) were analysed.

Results and discussion

Are the BCS-limits for P_e and solubility/dissolution appropriate?

The BCS-limit for high k_{diss} is ~14-fold more rapid than for k_{pe} (3.8 h^{-1} vs 0.27 h^{-1}) (Note: Adkin et al (1995) estimated the gastric emptying rate constant for solutions to be 3.8 h^{-1}.) The difference is even greater when assuming 85% absorption (instead of 90%) or a 40-h intestinal transit time (instead of 8.4 h). With such a large difference, the dynamics of sink conditions for dissolution are not fully considered. These data showed that bioequivalence could be expected for two drug products with considerably different in-vitro and in-vivo dissolution rate constants (e.g. 3.5 vs 0.4 h^{-1}), and that there was a high probability for in-vivo Class I drug products to be incorrectly defined as BCS Class II products.

Fagerholm & Björnsson (2005) demonstrated bioequivalence for a BCS Class II product (naproxen) and a BCS Class II or IV product (the naproxen pro-drug AZD3582), and that both products belonged to in-vivo Class I. Naproxen is a highly permeable non-steroidal anti-inflammatory drug (NSAID) ($P_e = 8.5\times10^{-4}$ cm s^{-1} in the human small intestine (Fagerholm et al 1996)) with long t½, whereas AZD3582 is highly lipophilic (log P and log D = 4), neutral and lowly soluble (practically insoluble in water), and has moderate to high P_e (uncertain P_e classification). AZD3582 in a self-emulsifying drug delivery system had slow k_{diss} in human gastric fluid (HGF) in-vitro (1.4 h^{-1}; one-third of the BCS k_{diss}-limit).

Yazdanian et al (2004) demonstrated that the BCS is too strict for acidic drugs. They found that 15 of 18 acidic NSAIDs in BCS Class II (low solubility at pH 1.2 and sometimes also at pH 5; D_o-values at pH 1.2 ranged between 0.6 and 5000) were completely or near completely absorbed in-vivo (in-vivo Class I). One of the explanations to the discrepancy between the BCS and in-vivo outcomes was that orally-dosed drug products reside a comparably short time in the acidic gastric environment and a long time in the main absorptive region (intestines) where the pH is higher. Based on their results, they suggested that a pH > 5 may be more appropriate to use for solubility/dissolution classification. Since sparingly soluble acidic drug products administered as water-soluble salts could precipitate out of solution, clump and be poorly absorbed, it is still important that in-vitro dissolution tests are performed with human gastric fluid.

Simulations shown in Figure 1 clearly demonstrate the potential that Class II drug products are bioequivalent to their

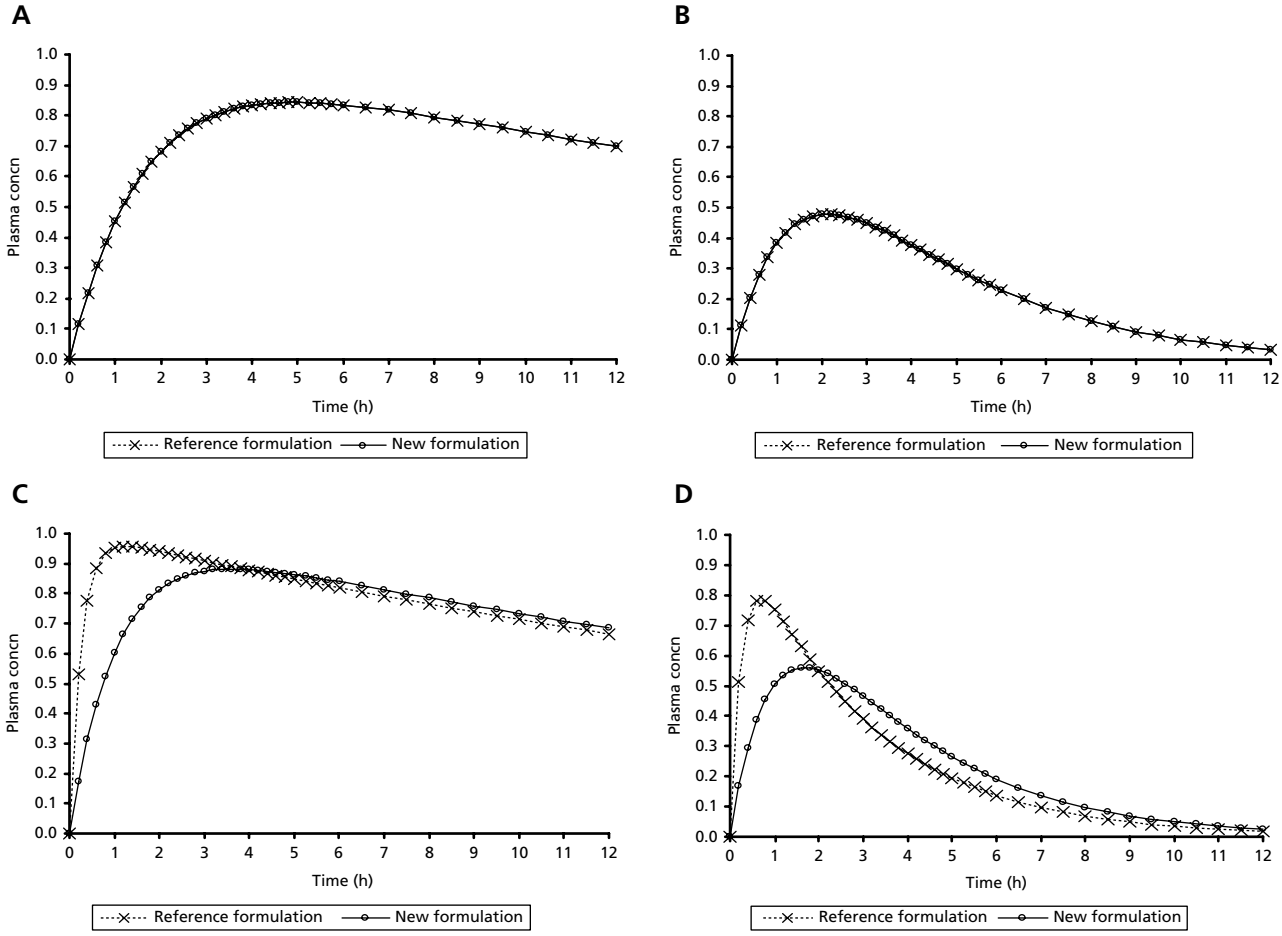

Figure 1 Simulated plasma concentration vs time profiles for two formulations with 4-fold different dissolution rates (one with rapid and one with slow according to the BCS) for four highly permeable compounds with different P_e and t½. The shadowed field denotes the region for complete (predicted) GI absorption. DR, dissolution rate limited uptake. PR, permeation rate limited uptake. A: high P_e, long t½. B: high P_e, short t½. C: very high P_e, long t½. D: very high P_e, short t½.

corresponding Class I formulations. Despite a 4-fold reduced k_{diss} bio-inequivalence was shown only for the drug with very high P_e and very short t½.

Kortejärvi et al (2007) simulated and compared the C_{max} of different formulation products. They demonstrated a greater impact on the C_{max} for drugs with high P_e (in this case k_a) and short t½, and low potential to reach bio-inequivalence for a drug with a $k_{pe} = 0.27\ h^{-1}$ and reference formulation with $k_{diss} = 3.8\ h^{-1}$. They found that all BCS I drugs were not good biowaiver candidates, and that approximately half of BCS Class I drugs had higher risk to fail in bioequivalence studies than BCS Class III drug products.

Are the in-vitro methods sufficiently robust for correct BCS classification, and can the rate-limiting step for in-vivo absorption be well-defined and well-predicted from in-vitro data?

Permeability methods There is a high potential to obtain correct P_e-classification for passively absorbed substances with low and very high P_e. The difficulty is, however, to classify compounds with moderate to high P_e (f_a ~0.7–1.0) and/or significant active transport. Caco-2, artificial membrane and in-silico P_e-methods all failed to categorize such compounds well (Artursson & Karlsson 1991; Lennernäs et al 1996; Yazdanian et al 1998; Clark 1999; Irvine et al 1999; Artursson et al 2001; Salphati et al 2001; Grass & Sinko 2002; Klopman et al 2002; Parrott & Lavé 2002; Clark & Grootenhuis 2003; Tavelin et al 2003a; Sun et al 2004; Willmann et al 2004; Bergström 2005; Matsson et al 2005).

As an example, Parrott & Lavé (2002) used Caco-2 P_e and solubility data, and the IDEA and GastroPlus softwares to predict the human f_a of 28 drugs without solubility limited GI uptake (including compounds with active uptake and efflux). They found that one-third of the compounds with $f_a \geq 0.5$ would have been incorrectly classified according to the BCS.

With the Loc-I-Gut-technique, Lennernäs, Knutson and co-workers generated in-vivo small intestinal P_e-data for at least 30 different drugs and nutrients (Kasim et al 2004). The potential with such an approach is that it generates human

in-vivo data. A drawback is the short residence time during perfusion (~15 min), and consequently, negligible/minor absorption of compounds with low and moderate P_e. The average uptake of enalaprilat ($f_a = 0.10$), atenolol ($f_a = 0.52$) and metoprolol ($f_a = 0.98$) during a perfusion is estimated to ~1, ~6 and ~27%, respectively. The insensitivity is demonstrated in Figure 2, where predicted f_a (from Loc-I-Gut P_e-data; $f_a = 1 - e^{-2 \times Pe \times 3h \times 2.8/1.75\,cm}$ (Fagerholm et al 1996)) and observed f_a for 13 compounds with incomplete f_a are compared. Poor predictions were obtained in groups of compounds with mainly passive and with pronounced active transport. Data for passively absorbed compounds with a value of f_a between ~0.75 and ~0.95 are, however, lacking.

The rat small intestinal cell line 2/4/A1 was shown to predict the human f_a of passively transported compounds slightly better than the Caco-2 model (Tavelin et al 2003a; Matsson et al 2005). Data indicated that that method could be the most suitable for P_e-classification of moderately to highly permeable drugs with mainly passive intestinal transport. Five substances with f_a values ranging from 0.96 to 1.00 were correctly classified to have high P_e, whereas one compound with $f_a = 0.92$ was predicted to have f_a~0.85 (incorrect BCS classification). The drawbacks with the 2/4/A1-model, other than the lack of important transporter proteins, were that small temperature changes could introduce variability, and cells grown at 37°C were more poorly differentiated than the fraction that survived at 39°C (Tavelin et al 2003b).

Solubility/dissolution methods Good predictability of the in-vivo dissolution is required to make correct BCS classification and to determine the rate-limiting step for in-vivo absorption. Apparently, there are a limited number of studies with low solubility drug products where the rate-limiting step has been defined.

Data obtained with HCl solution and SGF are commonly used to predict the in-vivo solubility and dissolution rate in the stomach of man (Dressmann et al 1998; Galia et al 1998). A limitation with data obtained in these media and real human gastric fluid (HGF) is the short gastric residence time compared with the intestinal transit time, hence a potential to incorrectly classify acid drug products (as demonstrated by Yazdanian et al (2004)).

Aqueous solubility is also commonly used as a surrogate measurement of in-vivo solubility, and solubility and dissolution data obtained with buffers of different pH and SIF are often used to estimate the in-vivo dissolution behaviour in the small intestine (Dressmann et al 1998). For poorly soluble drug products, the extent and rate of in-vitro dissolution in water has been demonstrated to be considerably lower and slower than in SIFs, respectively (Galia et al 1998; Yazdanian et al 2004). D_o vs f_a-data for 73 high P_e compounds (see Figure 3) clearly demonstrated the poor relationship between in-vitro solubility and in-vivo dissolution (Irvine et al 1999; Kataoka et al 2003; Zhao et al 2003; Kasim et al 2004; Peréz et al 2004; Willmann et al 2004; Yazdanian et al 2004; Yalkowsky et al 2006). In this extensive data set, drug products with very high aqueous D_o were completely or near completely absorbed (telmisartan $D_o = 660000$; toremifene $D_o = 8700$; oxatomide $D_o = 1500$). Only one drug product had a human in-vivo $f_a < 0.8$, danazol ($D_o = 2400$; $f_a = 0.30$), and nine products had a $f_a < 0.9$. This result was inconsistent with the number and

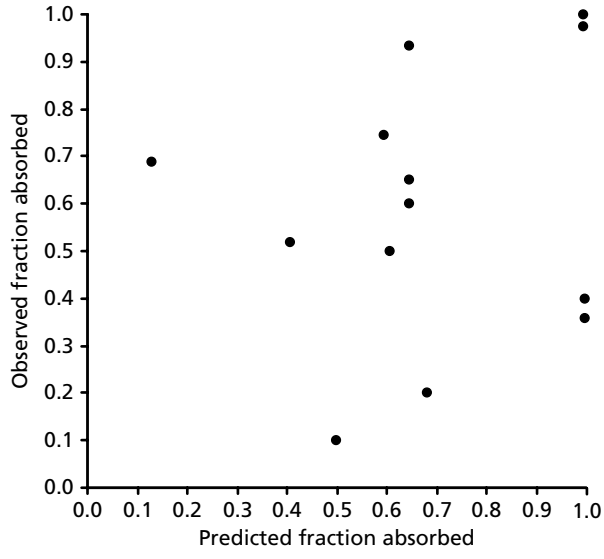

Figure 2 Predicted (from human small intestinal P_e obtained with Loc-I-Gut) vs observed fraction absorbed in man for 13 compounds with $P_e < 2 \times 10^{-4}\,cm\,s^{-1}$. P_e-data were obtained using the Loc-I-Gut-technique (Kasim et al 2004), and the f_a was calculated as $f_a = 1 - e^{-2 \bullet Pe \bullet 3h \bullet 2.8/1.75\,cm}$ (Fagerholm et al 1996). The compounds are amoxicillin (observed $f_a = 0.94$*), atenolol ($f_a = 0.52$), cephalexin ($f_a = 1.00$*), cimetidine ($f_a = 0.75$), enalapril ($f_a = 0.40$*), enalaprilat ($f_a = 0.10$), furosemide ($f_a = 0.65$), hydrochlortiazide ($f_a = 0.62$), lisinopril ($f_a = 0.20$*), metoprolol ($f_a = 0.98$), ranitidine ($f_a = 0.50$), terbutaline ($f_a = 0.60$) and valaciclovir ($f_a = 0.36$*). *Denotes drugs with significant active transport.

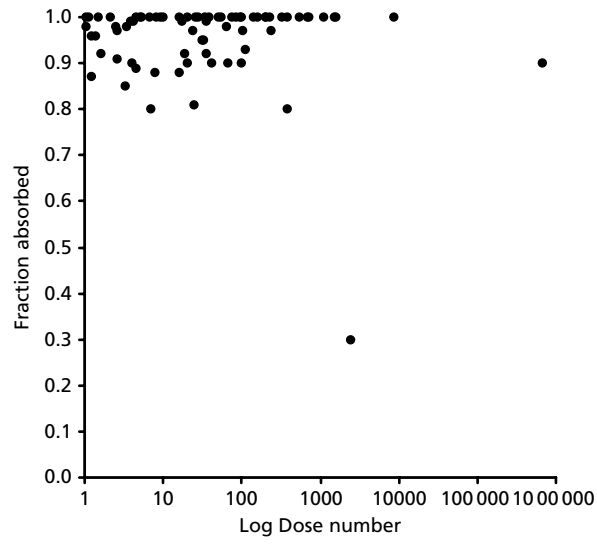

Figure 3 Log Dose number (D_o) vs fraction absorbed (f_a) for high P_e-drug products with low solubility ($D_o > 10$) (n = 73). D_o-data were taken from Kasim et al (2004), Yazdanian et al (2004) and Yalkowsky et al (2006), or calculated from dose and solubility data presented by Willmann et al (2004). F_a-data (and P_e-data for verifying high P_e) were taken from Irvine et al (1999), Kataoka et al (2003), Zhao et al (2003), Peréz et al (2004), Willmann et al (2004) and Yalkowsky et al (2006). The compound with low f_a is danazol ($D_o = 2400$; $f_a = 0.30$).

fraction of drug products in BCS Class II. Wu & Benet (2005) showed that 41 to 44 (31–34%) of 131 substances belonged to BCS Class II. Based upon this finding it appeared that highly permeable drug products would be sufficiently well absorbed regardless of the in-vitro solubility (at least up to a D_o of 660000). It further demonstrates the strictness of solubility/dissolution limits.

The oral bioavailability of some poorly soluble products, such as danazol ($f_a = 0.30$; $D_o = 2400$), griseofulvin ($f_a = 0.80$; $D_o = 385$) and atovaquone, were dramatically increased when they were administered together with a meal (US Pharmacist website). This indicated that those drug products were incompletely dissolved in the fasted state. The f_a-values used in Figure 3 may include data obtained in the fed-state (such as for griseofulvin), and therefore, there is a potential that there are more highly permeable drug products with dissolution-limited in-vivo uptake than this figure shows.

For obvious reasons, an evaluation of Class IV products was not possible (or at least not easy to make). Recently, there were only five to ten drug products in this class (Wu & Benet 2005). An example of a drug product with low P_e (high passive P_e; efficient efflux), high D_o (385) and low f_a (0.13) is sulfasalazine (Liang et al 2000; Willmann et al 2004).

Kortejärvi et al (2002) showed that the systemic exposure profile of levosimendan, a highly permeable compound with a t½ of 1 h, was sensitive to changes in dissolution-rate. In-vitro dissolution data obtained with phosphate buffer and at a rotation speed of 100 rev min^{-1} and a pH of 5.8 appeared to best predict the in-vivo profile. Results obtained at a rotation speed of 100 rev min^{-1} and a pH of 7.4 (≥85% dissolution within 30 min for all formulations) did, however, incorrectly predict in-vivo bioequivalence. This further demonstrates the limitation with data obtained with buffers.

In-vitro measurements of the extent and rate of dissolution in real GI fluids are recommended. Fresh and frozen human gastric and upper small intestinal fluids (HGF and HIF) are available (collected during Loc-I-Gut experiments (Lindahl et al 1997)) for such studies. In-vitro dissolution studies with the naproxen pro-drug AZD3582 were carried out using HGF (Fagerholm & Björnsson 2005). The in-vitro k_{diss} of AZD3582 ($1.4\,h^{-1}$) was not within the BCS Class I time limit, but predicted complete in-vivo dissolution. Bønløkke et al (2001) estimated the dissolution and absorption of two formulations of spironolactone ($D_o = 14$) in the human jejunum in-vivo during a Loc-I-Gut experiment, and found that the formulations were dissolved differently, but more rapidly than the compound was absorbed. Thus, it appeared that the GI absorption of this BCS Class II drug product was P_e-limited. An alternative could be to use fresh dog GI fluids. Persson et al (2005) compared the solubility and dissolution of four poorly soluble drugs in HIF and dog intestinal fluid collected during the fed state. They found that the dog appeared to be a good model for man with respect to dissolution in the small intestine after food intake.

Drug products with very low solubility and slow dissolution rate must rely on dissolution and absorption from the colon, and these processes are difficult to predict in the colon.

What is the implication of neglecting the half-life?

The impact of changed dissolution rate (from rapid to slow) for four BCS Class I drugs with high, but different, P_e and different t½ are demonstrated in Figure 1. A significantly reduced C_{max} for the new formulation with slow dissolution occurs only for the drug with very high P_e and very short t½ (compound D). Thus, if the P_e is high, but not extremely high, and the t½ is long, bioequivalence can be reached despite a large difference in dissolution rates between formulations. A neglect of the t½ could therefore potentially lead to unnecessary in-vivo bioequivalence studies for many drug products with long t½. These simulations clearly demonstrate the importance of incorporating t½ (or k_e) in a biopharmaceutical classification system, and the BCS strictness on solubility/dissolution. Simulations by Kortejärvi et al (2007) support this.

Suggested improvements of the BCS

Based upon the data and simulations it is proposed that the limit for high solubility/dissolution is decreased (to > 40 and >95% dissolved within 30 min and 3 h, respectively) and that the limit for high P_e is increased (to > P_e of metoprolol and/or ~complete GI uptake; the k_{pe} and f_a of metoprolol are $0.47\,h^{-1}$ and 0.98, respectively). With this, an adjustment of the k_{diss}/k_{pe}-ratio from 14 to 2 is reached. A further decrease of the ratio is not proposed. This is because of the limited knowledge of colonic dissolution potential and the requirement to include some uncertainty margins in the model. An alternative could be to set the dissolution limit to > 40 and > 95% dissolved within 15 min and 1.5 h, respectively. It is further suggested that accurate P_e-models or in-vivo fraction absorbed data are used, solubility/dissolution tests are performed using real or validated simulated gastrointestinal fluids, in-vitro vs in-vivo dissolution relationships are established, the t½ is considered, and the rate-limiting step for in-vivo absorption is determined.

The BCS could be reduced into two classes: permeation-rate (Class I) or dissolution-rate (Class II) limited absorption. With this approach drug products with a predicted in-vivo k_{diss} > predicted in-vivo k_{pe} belong to Class I regardless of the magnitudes of these constants and f_a, and in-vivo bioequivalence studies are potentially required when predicted in-vivo k_{diss} < predicted in-vivo k_{pe} (Class II) and when two formulations of a drug belong to different classes. By definition this opens up for biowaivers of drug products belonging to BCS Classes II and IV. It is still recommended that the t½ is considered, and that in-vivo exposure profiles are simulated before decision-making.

Conclusion

This paper has demonstrated some limitations with the BCS (such as strictness on dissolution, neglect of t½, poor in-vivo prediction and limited use), and proposes how this system could be adjusted to reach a better balance and increase its use. It is suggested that in-vitro/in-vivo relationships are defined, and validated P_e and dissolution-methods are used. Major changes include a reduction from four to two classes (Class I: permeation-rate absorption; Class II dissolution-rate limited absorption) and consideration of t½. With the suggested adjustments it is believed that the BCS will become more balanced and that the number of biowaivers will increase.

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