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Biopharmaceutics classification systems for new molecular entities (BCS-NMEs) and marketed drugs (BCS-MD): Theoretical basis and practical examples

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ABSTRACT

The aim of this work is to develop biopharmaceutics classification systems for new molecular entities (BCS-NMEs) and marketed drugs (BCS-MD). The kinetics of gastrointestinal (GI) wall permeation and dissolution were re-considered theoretically. The relationships between the solubility/dose ratio and the fractions of dose dissolved and absorbed, were also examined. Mean time calculations for drug dissolution (MDT) and permeation (MPT) of the GI wall were analyzed in respect to the mean intestinal transit time (MITT) to identify a cutoff point for drug dissolution and GI wall permeation. Dissolution experiments for marketed drugs were carried out. NMEs were classified into four classes of BCS-NMEs, based on solubility/dose ratio and apparent permeability estimates. A physiologically based cutoff time point for dissolution and permeation was used to differentiate rapidly from slowly dissolving-permeating marketed drugs, which were classified into four classes of BCS-MD using their dissolution index (DI = MITT/MDT) and permeation index (PI = MITT/MPT) values as follows: I (DI $\geq$ 3, PI $\geq$ 3), II (DI < 3, PI $\geq$ 3), III (DI $\geq$ 3, PI < 3) and IV (DI < 3, PI < 3). In conclusion, two classification systems were developed, one for NMEs based on solubility/dose ratio and permeability estimates and one for marketed drugs based on MDT and MPT estimates.

1. Introduction

In the biopharmaceutics classification system (BCS) (Amidon et al., 1995) and the relevant FDA guidance on biowaiver of *in vivo* bioavailability and bioequivalence (FDA, 2000), a drug is classified in one of four classes based on its aqueous solubility and intestinal permeability. However, several concerns have been raised for the solubility and the dissolution criteria of the FDA guidance. In this context, Yazdanian et al. (2004) suggested that the high solubility definition of the FDA guidance on BCS is too strict for acidic drugs. Also, the current dissolution specifications (FDA, 2000) are not correlated with the drug's dimensionless solubility/dose ratio, which has been shown to control the extent of drug dissolution and absorption as well as the mean dissolution time (MDT) (Rinaki et al., 2003a,b, 2004). In addition, the dissolution criteria of the FDA guidance have been characterized as conservative (Yu et al., 2002; Kaus et al., 1999; Fagerholm, 2007) and suggestions for broadening them have been pointed out (Fagerholm, 2007; Polli et al., 2004).

The reports (Yazdanian et al., 2004; Yu et al., 2002; Kaus et al., 1999; Fagerholm, 2007; Polli et al., 2004; Rinaki et al., 2003a,b) dealing with solubility, dissolution issues related to BCS, prompted us to re-examine theoretically the role of the dimensionless solubility/dose ratio in the dissolution and GI absorption kinetics of drugs. In parallel, this study pays attention not only to the theoretical basis for the biopharmaceutics classification of new molecular entities (NMEs), but also for marketed drugs. To this end, mean time calculations for drug dissolution (MDT) and GI wall permeation (MPT) were analyzed in respect to the physiological mean intestinal transit time (MITT) to identify a meaningful cutoff point for drug dissolution and permeation. These considerations allowed us to develop two approaches for the biopharmaceutics classification of NMEs and marketed drugs.

2. Materials and methods

2.1. Dissolution tests

Dissolution experiments were performed using various marketed drugs, namely, naproxen (Naprosyn® 250 mg lot # 050 10

Abbreviations: BCS, biopharmaceutics classification system; BCS-MD, biopharmaceutic classification system for marketed drugs; BCS-NMEs, biopharmaceutic classification system for new molecular entities; DI, dissolution index; GI, gastrointestinal; MAD, maximum absorbable dose; MAT, mean absorption time; MDT, mean dissolution time; MITT, mean intestinal transit time; MPT, mean GI wall permeation time; NMEs, new molecular entities; PI, permeation index.

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27 and Naprosyn® 500 mg lot # 050 10 30, Minerva), ibuprofen (Brufen® 200 mg lot # 4C 22 and Brufen® 600 mg lot # 4C 105, Vianex S.A.), nitrofurantoin (Furolin® 100 mg lot # 041 008, Farmanic), allopurinol (Zylapur® 300 mg lot # 040 708, Farmanic), paracetamol (Depon® 500 mg lot # 7G070, Bristol Myers Squibb) and metoprolol (Lopresor® 100 mg lot # 5B054, Novartis). Various drug doses were utilized in order to obtain dissolution data reaching complete or incomplete dissolution, i.e. 250 and 500 mg of naproxen, 200, 600 and 1200 mg (used as two tablets of 600 mg) of ibuprofen, 100 and 200 mg (used as two tablets of 100 mg) of nitrofurantoin, 300 mg of allopurinol, 500 mg of paracetamol and 100 mg of metoprolol.

In all cases dissolution experiments were conducted in triplicate at 37 ± 0.5 °C, using 500 mL of dissolution medium, while the pH was adjusted to either 4.5 or 6.8. All other conditions were in accord with the USP monographs (U.S.P 29-NF 24, 2006), i.e. for Naprosyn®, Brufen®, Depon® and Zylapur® tablets the paddle method was used at 50 rpm, except for Zylapur® tablets, for which the rotation speed was set at 75 rpm, while the basket method at 100 rpm was used for Furolin® and Lopresor® tablets. In all cases drug assay was performed spectrophotometrically, at 332, 221, 375, 250, 244 and 275 nm for naproxen, ibuprofen, nitrofurantoin, allopurinol, paracetamol and metoprolol, respectively.

When complete dissolution was reached, the MDT values for the dissolution profiles, were calculated as the area over the dissolution curve divided by the percentage dissolved (100%). In case of incomplete dissolution, the mean saturation time (MDTs) was calculated as the area over the dissolution curve divided by the percentage of the dose dissolved at steady state. In all cases, the trapezoidal rule was applied for the calculation of the areas.

2.2. Data analysis

The Noyes and Whitney (1897) equation was modified taking into account the dose and the volume of the dissolution medium (Rinaki et al., 2003a; Dokoumetzidis et al., 2006) and was used to express the rate of dissolution in terms of the fraction of dose dissolved, Φ:

$$\frac{d\Phi}{dt} = k\left(\frac{1}{q} - \Phi\right) \quad (1)$$

where k is the dissolution rate constant and q is the dimensionless dose/aqueous solubility (C_s) ratio since the volume of the dissolution medium, V has been taken into account (q = dose/$C_s \cdot V$) (Rinaki et al., 2003a). Eq. (1) reveals that $1/q$ is the primary parameter for the rate of drug dissolution in terms of Φ; this was one of the reasons justifying the recent use of $1/q$ in the quantitative-BCS (Rinaki et al., 2003b). In addition, the value of $1/q$ determines the final fraction of dose dissolved (Rinaki et al., 2003a; Dokoumetzidis et al., 2006).

A new absorption parameter Π, which can predict in a semi-quantitative way whether or not a candidate drug will be well absorbed was recently developed (Yalkowsky et al., 2006; Sanghvi et al., 2003). Yalkowsky et al. (2006) used a relationship relating the aqueous solubility, C_s with the melting point, MP and the 1-octanol–water partition coefficient of the drug, K_{ow} and expressed the absorption parameter Π as follows:

$$\Pi = \frac{K_{ow}}{\max(1, (4M_0/\mathrm{MW} \times 10^{[0.5-0.01(\mathrm{MP}-25)-\log K_{ow}]}))} = \frac{K_{ow}}{\max(1, (4M_0/C_s))} = \frac{K_{ow}}{\max(1, q)} \quad (2)$$

where M_0 is the dose administered and MW is the molecular weight of the compound. According to Yalkowsky et al. (2006) the gastrointestinal absorption of passively absorbed drugs is most efficient when Π is greater than unity and this mostly happens when the denominator in Eq. (2) is equal to unity (rule of unity). Simple visual inspection of Eq. (2) reveals the importance of parameter q for the "rule of unity". The fraction of dose absorbed, F_{abs}, is related to Π according to Eq. (3) derived in the Appendix:

$$F_{abs} = \frac{\lambda\Pi}{\lambda\Pi + \xi(1/\Pi)} = \frac{1}{1 + (\xi/\lambda)(1/\Pi)^2} \quad (3)$$

Johnson and Swindell (1996) introduced the concept of maximum absorbable dose (MAD), which is defined as the amount of drug that could be absorbed in a time equivalent to the mean intestinal transit time (MITT) following first-order kinetics, if the concentration of drug in solution could be hypothetically maintained at its solubility:

$$\mathrm{MAD} = k_a C_s V t \quad (4)$$

where k_a is a first-order absorption rate constant, V is the volume of the fluid in the GI tract and t is equal to MITT.

Gu et al. (2007) found that for drugs with MAD < clinical dose (i.e. poorly absorbed drugs), the key parameter for the observed positive food effect on drug absorption is the value of $1/q$. Indeed, Eq. (5) is derived from Eq. (4) if one divides both sides with the dose administered:

$$F_{abs} = \frac{\mathrm{MAD}}{M_0} = \frac{C_s \cdot V}{M_0} \times \mathrm{MITT} \times k_a = \frac{1}{q} \times \frac{\mathrm{MITT}}{\mathrm{MAT}}, \quad (F_{abs} \le 1) \quad (5)$$

This equation reveals that F_{abs} is proportional to the values of $1/q$ and the absorption rate constant, k_a. The latter parameter has been expressed as the reciprocal of the mean absorption time (MAT) assuming first-order kinetics while time, t, has been set equal to MITT.

3. Results and discussion

Eqs. (1)–(3) and (5) demonstrate that the dimensionless solubility/dose ratio, $1/q$, is a key parameter for the kinetics of drug dissolution and one of the major determinants of the fraction of dose absorbed. We have also shown (Rinaki et al., 2004) that an appropriate modification of the differential equations utilized for the development of BCS (Oh et al., 1993; Amidon et al., 1995) unveils the major role of $1/q$ in drug absorption kinetics. Experimental verification of these theoretical results can be found in literature in studies dealing with the effect of dose on the extent of absorption. In fact, sporadic studies in literature have demonstrated dose-limited absorption on the basis of nonlinear AUC versus dose plots (Faassen and Vromans, 2004; Mueller et al., 1994). However, the significant role of $1/q$ for drug absorption was fully verified in the recent study of Gu et al. (2007). In this study, the maximum absorbable dose (MAD) concept was used to develop a statistical model based on physicochemical properties for the prediction of food effect on the extent of drug absorption. Analysis of all sets of data of this study by plotting the relative bioavailability (fed/fasted) values as a function of dose number expressed in terms of volume of the intestinal contents as defined in (Gu et al., 2007), is presented in Fig. 1. As can been seen the borderline value of the volume for drug classification in Class I (no food effect) lies in the range of 250–500 mL. These values are based on the analysis of 92-marketed compounds and represent a global, reasonable range for the volume of the intestinal contents.

In order to further explore the validity of the estimates for the volume of the intestinal contents we calculated the Π values from Eq. (2) of all drugs reported in (Yalkowsky et al., 2006) for a range of volumes from 10 to 1500 mL. Subsequently, Eq. (3) relating the fraction of dose absorbed, F_{abs}, and Π was fitted to all series of

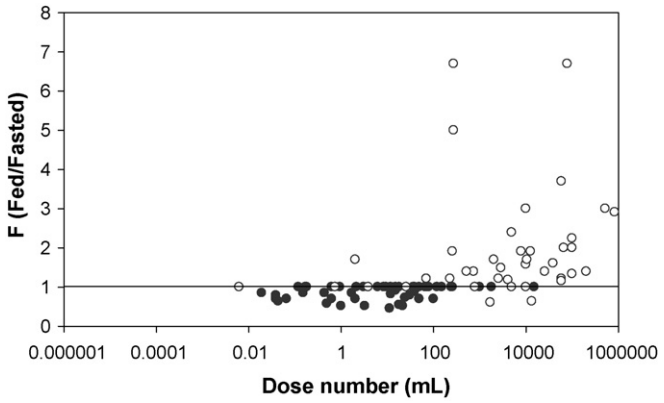

Fig. 1. Plot of F_{ratio} (fed/fasted) vs. the dose number (ratio of dose to solubility at pH 7.0 in unit of mL) for the data of Gu et al. (2007). Note that the reciprocal values for F_{ratio} reported are used due to the wrong definition of F_{ratio} in the footnotes of Tables 2 and 3 of the original article (Gu et al., 2007). Open symbols correspond to compounds with MAD < clinical dose and closed symbols correspond to compounds with MAD > clinical dose.

data (Yalkowsky et al., 2006). The best fit was used to indirectly derive an estimate for the volume of the intestinal fluids. The values of the correlation coefficients derived ranged from 0.795 (10 mL) to 0.856 (500 mL) and equal correlation coefficient values were found for volume values 250 and 500 mL. Fig. 2 shows the best fit ($R^2 = 0.856$), which corresponds to the reported fraction absorbed data (Yalkowsky et al., 2006) against the parameter Π calculated by assigning the intestinal volume equal to 500 mL. The estimate derived for the ratio of proportionality constants ξ/λ was found to be 0.864 (±0.2). This analysis provides an experimentally based estimate for the volume of intestinal contents. In other words, assigning the volume of the GI contents to either 250 or 500 mL, the limiting dimensionless solubility/dose ratio values are equal to 1 and 2, respectively. As a matter of fact the lower volume value of 250 mL has been adopted in all studies dealing with the analysis of the gastrointestinal drug absorption (Amidon et al., 1995; Dressman et al., 1985; Willmann et al., 2004; Rinaki et al., 2003b, 2004; Johnson and Swindell, 1996; Sanghvi et al., 2003) as well as in the BCS guideline (FDA, 2000). However, several concerns have been raised for the suitability of 250 mL in representing the volume of the intestinal fluids (Yu et al., 2002; Kaus et al., 1999).

3.1. Biopharmaceutics classification system for new molecular entities (BCS-NMEs)

The analysis of the previous section allows us to propose scientifically based changes for the current biopharmaceutics classification system (FDA, 2000). These changes have to be used for new molecular entities (NMEs) exclusively. According to our findings, the consideration of the maximum dose of the BCS could be replaced by the specific dose, i.e. use the dimensionless solubility/dose ratio, $1/q$ with a borderline region of 1–2 assuming 250 and 500 mL, respectively as the volume of the intestinal contents. NMEs with $1/q$ values higher than 2 have high solubility/dose ratios while NMEs with $1/q < 1$ have low solubility/dose ratios. Since the clinical dose is unknown at the initial stage of drug discovery, the investigator has to consider a range of doses in order to classify the NMEs in terms of solubility/dose ratio (high, borderline or low). As an example, several drugs used today in clinical practice in different doses are listed in Table 1 and classified using the solubility/dose ratio values as well as the current solubility definition of the BCS guidance (Kasim et al., 2004; Lindenberg et al., 2004). As can be seen, the classification is not always the same for a given drug and can be different and dependent on dose. Since no formulations for NMEs are available at the very early stage of drug development, no dissolution requirements are pointed out. As far as the permeability of NMEs is considered, the criteria for *in vitro* data supporting high permeability required by the FDA (2000) based on direct permeability measurements can be considered sufficient despite the criticism reported (Wu and Benet, 2005; Benet et al., 2008). The apparent permeability range of values suggested in (Rinaki et al., 2003b) can be used as a basis for permeability classification of NMEs. In reality, the biopharmaceutics classification system developed in (Rinaki et al., 2003b) is rediscovered here using theoretical aspects of drug dissolution and absorption phenomena and taking into account relevant experimental observations (Gu et al., 2007; Faassen and Vromans, 2004; Mueller et al., 1994).

3.2. Biopharmaceutics classification system for marketed drugs (BCS-MD)

Both mathematically and intuitively one can easily conclude that the permeation and dissolution rates are the major determinants of oral drug absorption. However, both rates change continuously over time and therefore are impractical to be used for

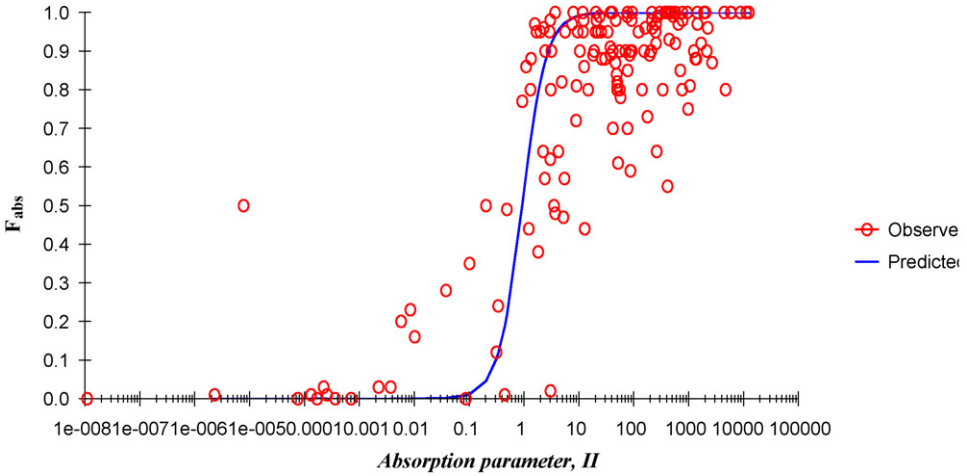

Fig. 2. Plot of the fraction of dose absorbed vs. Π utilizing 500 mL for the volume of the intestinal contents. Key: (○), observed data from (Yalkowsky et al., 2006); continuous line, prediction based on Eq. (3).

Table 1
Solubility classification of marketed drugs based on $1/q$ values in comparison to the current BCS classification used in (Kasim et al., 2004) and (Lindenberg et al., 2004)

Drug[a]	Dose	$1/q$	This work	BCS	
				Data from reference Kasim et al. (2004)	Data from reference Lindenberg et al. (2004)
Dapsone	25	1	Borderline	Low	Low
	50	0.5	Low	Low	Low
	100	0.25	Low	Low	Low
Glibenglamide	2.5	1	Borderline	Low	Low
	5	0.5	Low	Low	Low
Haloperidol	0.5	5	High	Low	Low
	1.5	1.67	Borderline	Low	Low
	2	1.25	Borderline	Low	Low
	5	0.5	Low	Low	Low
Theophylline	100	2.5	High	Low	High
	200	1.25	Borderline	Low	High
	300	0.83	Low	Low	High
Nitrofurantoin	50	0.95	Low	Low	Low
	100	0.475	Low	Low	Low
Trimethoprim	100	1	Borderline	Low	Low
	200	0.5	Low	Low	Low
Valproic acid	200	1.625	Borderline	Low	Low
	500	0.65	Low	Low	Low

[a] These are examples of how to classify NMEs at the initial stage of drug development when dose is unknown.

biopharmaceutical classification purposes. Alternatively, a stochastic consideration of both processes based on the mean dissolution time (MDT) and the mean GI wall permeation time (MPT) can be used to develop a biopharmaceutics classification system for marketed drugs.

The analysis associated with Eq. (1) provides (Rinaki et al., 2003a) explicit relationships between $1/q$, the fraction of dose dissolved at infinite time, Φ_∞ and MDT as shown in Table 2. The data listed in Table 2 reveal a clear cut-off for the various $1/q$ values in terms of the MDT. When $1/q < 1$, a specific MDT exists since the entire dose is dissolved ($\Phi_\infty = 1$). On the contrary, when $1/q < 1$ the MDT is infinite since the entire dose is not dissolved ($\Phi_\infty < 1$).

Assuming the worst scenario for drug dissolution using doses which can be completely dissolved, namely, the dose is equal to the amount needed to saturate the dissolution medium, the MDT is equal to $1/k$ since $1/q = 1$, Table 2. Under these limited conditions, simple mean time calculations can be made using the integrated form of Eq. (1) as reported in (Rinaki et al., 2003a). Thus, at time t = MDT, 63% of the drug is dissolved, at $t = 2 \times$ MDT, 86% and at $t = 3 \times$ MDT, 95%. The mean intestinal transit time (MITT) is a physiologic limit for the dissolution process. Therefore, a dissolution specification limit ensuring complete absorption for highly permeable marketed drugs can be based on physiological grounds. We propose that this physiological limit can be adjusted to MDT_{phys} = MITT/3, since at time $t = 3 \times$ MDT, 95% of the drug is dissolved, under the assumption of a perfect *in vitro–in vivo* correlation. Accordingly, the MDT_{phys} limit for biopharmaceutics classification purposes can be set equal to 66 min using 199 min (Yu et al., 1996) as an estimate for the MITT.

Table 2
Relationships between the dimensionless (solubility/dose) ratio, $1/q$ and the dissolution parameters[a] (Rinaki et al., 2003a)

$1/q$	Φ_∞[b]	Time[c]	MDT
>1	1	$-[\ln(1-q)]/k$	$[q-(q-1)\ln(1-q)]/kq$
1	1	Infinite	$1/k$
<1	<1	Infinite	Infinite[d]

[a] Dissolution is assumed to take place in a closed system of constant volume.
[b] Fraction dissolved at time $t \to \infty$.
[c] Indicates the time for the completion of dissolution.
[d] When $(1/q) < 1$, the mean time for the saturation of the medium, MDTs is equal to $1/k$ (Rinaki et al., 2003a).

The MDT_{phys} limit of 66 min allows relevant simulations to be made on the basis of Eq. (1) for the current FDA dissolution criteria (FDA, 2000). Since all definitions for q (Rinaki et al., 2003b) or dose number (FDA, 2000) refer to 250 mL, all $1/q$ values should be multiplied by 3.6 in calculations related to the official *in vitro* dissolution test of 900 mL. For example, when the amount needed to saturate the volume of 250 mL is equal to the dose ($1/q = 1$), the actual amount, which can be dissolved in the dissolution medium of 900 mL, is 3.6 times higher than the dose. Therefore, the FDA criterion of 85% dissolution in 30 min can be applied to the appropriately modified (using V = 900 mL) integrated form of Eq. (1) (Rinaki et al., 2003a):

$$\Phi = \frac{V}{250q}(1-\exp(-kt)) = \frac{3.6}{q}(1-\exp(-kt)) \quad \text{for} \quad t < -\frac{\ln(1-(q/3.6))}{k}$$
$$\Phi = 1 \quad \text{for} \quad t \geq -\frac{\ln(1-(q/3.6))}{k} \tag{6}$$

to calculate the limiting value of the dissolution rate constant and subsequently the corresponding MDT value for marketed drugs with $1/q \geq 1/3.6$, using Eq. (6) (see Table 2):

$$\text{MDT} = V \cdot \frac{(250q/V) - ((250q/V)-1)\ \ln(1-(250q/V))}{250q \cdot k}$$
$$= 3.6\frac{(q/3.6) - ((q/3.6)-1)\ \ln(1-q/3.6)}{q \cdot k} \tag{7}$$

Fig. 3 shows the dissolution curve generated from Eq. (6) using the current FDA criterion for a borderline-marketed drug (amount needed to saturate the volume of 900 mL is just equal to the dose, $1/q = 1/3.6$) in comparison with the MDT_{phys} limit of 66 min. The dissolution curve based on the FDA criterion in Fig. 3 not only underlines but also, if compared to the MDT_{phys} limit of 66 min, quantifies the conservatism of the dissolution specifications of FDA guideline for the worst dissolution scenario considered for drug doses completely dissolved in the dissolution medium. Roughly, the physiological MDT_{phys} limit of 66 min is fourfold higher than

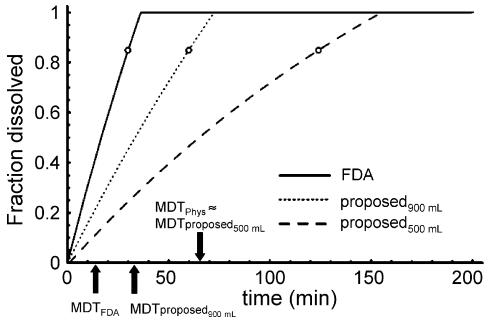

Fig. 3. Time profiles of fraction of dose dissolved (Φ) generated from Eq. (6) using $1/q = 1$. The solid line describes the dissolution of a drug following the FDA criterion, $\Phi = 85\%$ in 30 min, $V = 900$ mL. The dotted line is the dissolution curve of another drug following the proposed$_{900\,mL}$ criterion, $\Phi = 85\%$ in 60 min, $V = 900$ mL while the dashed line indicates the same drug but considered to be dissolved in 500 mL (instead of 900 mL) exhibiting $\Phi = 85\%$ in 123 min. The small circles on the curves, indicate the 85% dissolution time for FDA, the proposed$_{900\,mL}$ and the proposed$_{500\,mL}$ criteria. The arrows correspond to the MDT values of the FDA, proposed$_{900\,mL}$ and proposed$_{500\,mL}$ criteria; MDT$_{phys}$ corresponds to the physiological limit.

the MDT value of the formulation with $1/q = 1/3.6$ based on the FDA criterion, Fig. 3. Relying on these results one can reasonably propose an immediate release product of a marketed drug as a rapid dissolution product when not less than 85% of the labeled amount of the drug substance is dissolved within 60 min. The MDT value derived from the proposed (designated as proposed$_{900\,mL}$) criterion along with the corresponding dissolution curve for this borderline drug ($1/q = 1/3.6$) is also shown in Fig. 3. The plots in Fig. 3 reveal that the proposed$_{900\,mL}$ criterion is much more physiologically sound than the current FDA criterion. Accordingly, the results in Fig. 3 for the proposed$_{900\,mL}$ dissolution criterion provide the scientific basis for the intuitive consensus on the specification "... no less than 85% dissolution in 60 min" of the workshop on BCS (Polli et al., 2004).

The present criteria of FDA guideline (FDA, 2000) for solubility and dissolution refer to media of 250 and 900 mL, respectively. The harmonization of the two volumes into a single volume of 500 mL can be envisaged if one takes into account the general consensus (Yu et al., 2002; Kaus et al., 1999) for the increase of the volume from 250 to 500 mL for the solubility classification as well as the results of the present study presented in Figs. 2 and 3. According to Eq. (6) a formulation with $1/q = 1$ exhibiting 85% dissolution in 60 min for a volume of 900 mL has a dissolution rate constant, k equal to 4.5×10^{-3} min^{-1}. Using this value for k and assigning $1/q = 1$, $V = 500$ mL in Eq. (6), the fraction of dose dissolved versus time curve for this formulation in a medium of 500 mL was generated, Fig. 3. Solving Eq. (6) ($\Phi < 1$) for t, the time needed for Φ dose fraction of the drug to be dissolved in a medium of volume V, is

$$t = -\frac{\ln(1 - (250 \cdot q \cdot \Phi/V))}{k} \tag{8}$$

For, $\Phi = 0.85$, $q = 1$, $k = 4.5 \times 10^{-3}$ min^{-1} and $V = 500$ mL, the time for the 85% dissolution of the drug dose in 500 mL medium, can be calculated to be 123 min and MDTproposed$_{500\,mL}$ = 68.2 min ≈MDT$_{phys}$, Fig. 3. This means that a reasonable equivalent dissolution specification for a volume of 500 mL to the proposed$_{900\,mL}$ criterion would be the so-called proposed$_{500\,mL}$ criterion, i.e. "no less than 85% dissolution in 120 min using a 500 mL volume".

The permeation of GI wall is the second important element of drug absorption. In a similar manner to that used for dissolution, permeability considerations can be based on mean GI wall permeation time (MPT) in relation to the MITT. Again, the physiological limit MPT$_{phys}$ can be adjusted to MPT$_{phys}$ = MITT/3 = 66 min since at time $t = 3 \times$ MPT, 95% of drug is absorbed under the assumption of first-order kinetics. Hence, we propose the following criterion to be used to define high permeability for marketed drugs: following single IV bolus and oral solution doses to humans, a non-compartmental calculation of MPT results in a MPT value ≤66 min, using the trapezoidal rule based on the following equation:

$$\mathrm{MPT} = \mathrm{MRT_{PO}} - \mathrm{MRT_{IV}} \tag{9}$$

where MRT$_{PO}$ and MRT$_{IV}$ is the mean residence time after *per os* and IV administration, respectively, that can be calculated using the following equation:

$$\mathrm{MRT} = \frac{\mathrm{AUMC}}{\mathrm{AUC}} \tag{10}$$

where AUC and AUMC is the area under the concentration versus time and the concentration × time versus time curves, respectively.

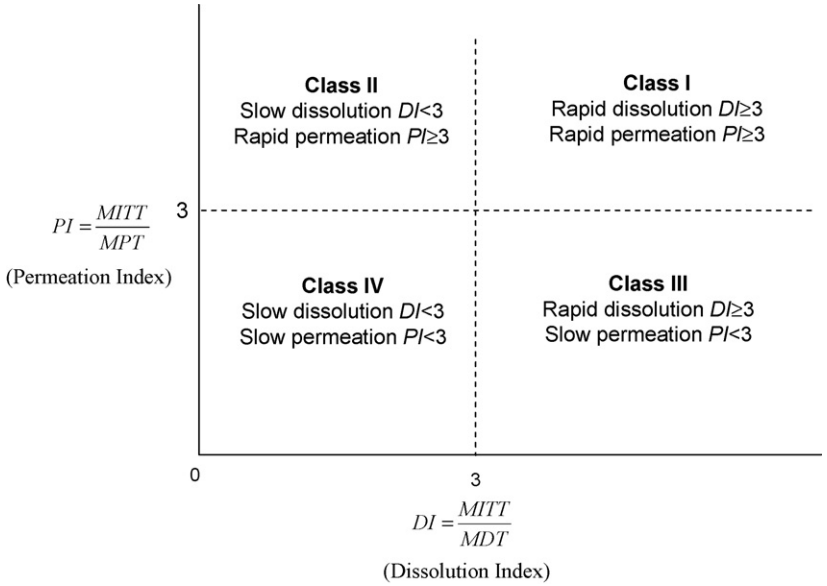

Fig. 4. The biopharmaceutics classification system for marketed-drugs (BCS-MD) with the specific cutoff points utilized for drug classification (dashed lines). The cut-off values for both dissolution and permeation have been expressed in terms of their respective mean times and have been normalized in terms of MITT.

Overall, the biopharmaceutics classification system for marketed drugs (BCS-MD) based on dissolution and permeation criteria normalized in terms of MITT is schematically presented in Fig. 4. For drugs used in different dose strengths, each one of the doses should be examined.

In order to evaluate our permeation classification, the drugs reported in (Benet et al., 2008) were analyzed using Eq. (11) which is based on the compartmental absorption transit model (Linnankoski et al., 2006):

$$F_{abs} = 1 - \frac{1}{(1 + 0.32k_a)^7} \quad (11)$$

F_{abs} values were taken form literature (Rinaki et al., 2003b; Yalkowsky et al., 2006; Winiwarter et al., 1998) while MAT estimates were derived from Eq. (11) as the reciprocal of the respective k_a values. The permeability classification results shown in Table 3 indicate that this approach based on MAT estimates and Benet's et al. (2008) method based on the metabolism criterion are quite similar. The classification of drugs of Table 3 into the BCS-MD is shown in Fig. 5. This plot also contains the six drug-formulations studied at pH 6.8 (data for dissolution studies at pH 4.5 are not shown); the respective MAT values of the six marketed drugs were calculated as described above using literature F_{abs} values (Rinaki et al., 2003b; Yalkowsky et al., 2006; Winiwarter et al., 1998) assuming that F_{abs} values are not dependent on dose.

Although the two biopharmaceutics classification systems developed for NMEs and marketed drugs seem to be different, in essence are interrelated because of the relationships between $1/q$ and MDT as well as between apparent permeability and MPT. Thus, the parameter $1/q$ is linked with the MDT as shown in Table 2; similarly, the apparent permeability is linearly related (Bergstrom et al., 2003; Sun et al., 2002) to the effective permeability, P_{eff} which in turn have been expressed for the homogeneous and heterogeneous tube model of radius R (Amidon, 1997; Kalampokis et al., 1999) as $P_{eff}=k_aR/2 = R/2$ (MPT). Finally, the parameters MITT/MDT, MITT/MPT used in the BCS-MD have been considered as the stochastic–kinetic expressions of the fundamental dissolution and absorption numbers (Amidon, 1997; Yu et al., 1996), respectively. This observation underlines the physical–physiological basis of the BCS-MD.

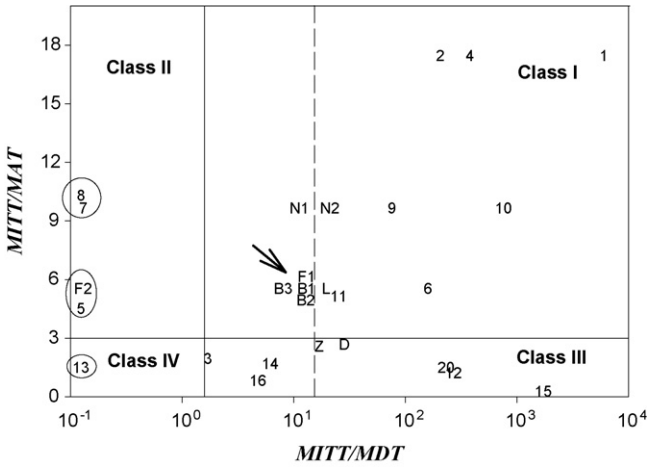

Fig. 5. Biopharmaceutics classification in the MITT/MDT, MITT/MAT plane of (i) the 20 drugs of Table 3 and (ii) the six marketed drugs in various doses, using experimental dissolution data at pH 6.8. For clarity reasons the data of compounds indicated by the arrow are slightly moved. The numbers correspond to the drug numbers quoted in Table 3. The solid lines are drawn on the proposed cut-off points for MITT/MDT and MITT/MPT values. The dashed line indicates the cut-off value for MITT/MDT of the current FDA dissolution criterion for a borderline drug ($1/q = 3.6$). Data in the ellipses correspond to compounds with infinite MDT and zero MITT/MDT value. Key: B1, B2 and B3, ibuprofen 200, 600 and 1200 mg, respectively; N1 and N2, naproxen 250 and 500 mg, respectively; F1 and F2, nitrofurantoin 100 and 200 mg, respectively; L metoprolol 100 mg; D paracetamol 500 mg; Z allopurinol 300 mg.

Table 3
The 20 model drugs suggested by the FDA for use in establishing suitability of a permeability method together with predictability using $c\log P$ (or $\log P$) and extent of metabolism (Benet et al., 2008) vs. MITT/MAT

No.	Drug	Permeability class	Predicted by $c\log P$ or $\log P$	Predicted by extent of metabolism[a]	Predicted by MITT/MAT[b] (estimate)
1	Antipyrine	High (potential IS candidate)	No	Yes	Yes (17.4)
2	Caffeine	High	No	Yes	Yes (17.4)
3	Carbamazepine	High	Yes	Yes	No (1.95)
4	Fluvastatine	High	Yes	Yes	Yes (17.4)
5	Ketoprofen	High	Yes	Yes	Yes (4.5)
6	Metoprolol	High (potential IS candidate)	Yes	Yes	Yes (5.5)
7	Naproxen	High	Yes	Yes	Yes (9.6)
8	Propranolol	High	Yes	Yes	Yes (9.6)
9	Theophylline	High	No	Yes	Yes (9.6)
10	Verapamil	High (potential IS candidate)	Yes	Yes	Yes (9.6)
11	Amoxicillin	Low	Yes	Yes	No (5.1)
12	Atenolol	Low	Yes	Yes	Yes (1.2)
13	Furosemide	Low	No	Yes	Yes (1.5)
14	Hydrochlorothiazide	Low	Yes	Yes	Yes (1.7)
15	Mannitol	Low (potential IS candidate)	Yes	Yes	Yes (0.3)
16	a-Methyldopa	Low	Yes	Yes	Yes (0.8)
17	Polyethylene glycol (400)	Low	Yes	Yes	Yes (≈0)
18	Polyethylene glycol (1000)	Low	Yes	Yes	Yes (≈0)
19	Polyethylene glycol (4000)	Low	Yes	Yes	Yes (≈0)
20	Ranitidine	Low	Yes	Yes	Yes (1.5)

[a] Using 70% as the cutoff limit.
[b] Using MITT/MAT = 3 as the cut-off limit.

4. Conclusions

The theoretical analysis presented and the relevant experimental observations point to the key role of solubility/dose ratio, $1/q$ for the GI absorption processes. In this context, the present study relies on the value of $1/q$ together with a permeability estimate for the biopharmaceutics classification of NMEs. Needless to say that *in vivo* absorption data are not available at the early stages of drug development. Therefore, apparent permeability estimates are proposed for permeability classification (Rinaki et al., 2003b) in view of the criticism raised (Wu and Benet, 2005; Benet et al., 2008) for the use of effective permeability estimates. For marketed drugs, the biopharmaceutic classification system proposed (Fig. 4) utilizes meaningful, physiologically based estimates for MDT and MPT since dissolution, and absorption data are either available and/or can be asked from the applicant for a waiver of *in vivo* studies of bioequivalence.

This work relies on dissolution and permeation, which are the fundamental processes of drug absorption and provides specific dissolution and permeation criteria for the biopharmaceutics classification of marketed drugs. It is hoped that the theoretical basis of this study if coupled with the extensive experience in drug dissolution of researchers in academia, industry and regulatory agencies will contribute towards the refinement of the proposed dissolution criteria. Similarly, the vast amount of archives for oral solution studies in humans in regulatory agencies can be used to test and refine the permeation criteria of the present study.

Appendix A. Derivation of Eq. (3)

Building on the same principles used for the development of the quantitative absorption potential concept (Macheras and Symillides, 1989), one can argue that the drug properties, which lead to poor absorption for passively absorbed drugs, can be expressed in terms of the reciprocal value of the absorption parameter Π:

$$\frac{1}{\Pi} = \frac{\max(1, (4M_0/\mathrm{MW} \times 10^{[0.5-0.01(\mathrm{MP}-25)-\log K_{\mathrm{OW}}]}))}{K_{\mathrm{ow}}} \quad \text{(A.1)}$$

while the fraction of dose absorbed, F_{abs} can be written as

$$F_{\mathrm{abs}} = \frac{k_{\mathrm{a}}}{k_{\mathrm{a}} + k_{\mathrm{n}}} \quad \text{(A.2)}$$

where k_{a} is the first-order absorption rate constant and k_{n} is a composite first-order rate constant for the processes leading to non-absorption in the gastrointestinal lumen. Similarly, the kinetic parameters k_{a} and k_{n} can be considered proportional to Π and $1/\Pi$, respectively (Macheras and Symillides, 1989):

$$k_{\mathrm{a}} = \lambda\Pi \quad \text{(A.3)}$$

$$k_{\mathrm{n}} = \xi\frac{1}{\Pi} \quad \text{(A.4)}$$

where λ and ξ are proportionality constants with $(\mathrm{time})^{-1}$ units. Combining Eqs. (A.2)–(A.4) gives

$$F_{\mathrm{abs}} = \frac{\lambda\Pi}{\lambda\Pi + \xi(1/\Pi)} = \frac{1}{1 + (\xi/\lambda)(1/\Pi)^2} \quad (3)$$

Eq. (3) reveals that F_{abs} is related nonlinearly with Π and asymptotically reaches the limiting value one (complete absorption) as Π increases.

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