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A non-binary biopharmaceutical classification of drugs: The ABΓ system

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ABSTRACT

The purpose of the present work is to develop a non-binary biopharmaceutical classification system the so called ABΓ system. The original mathematical model used for the development of BCS, appropriately modified, was applied to estimate the limiting values of drug solubility and permeability when the fraction of dose absorbed, *Fa*, was 0.90 or 0.20. The ABΓ system is based on the fraction of dose absorbed and relies on permeability, solubility plane. The first category (A, alpha) includes drugs with $Fa \geq 0.90$, whereas the B (beta) category consists of drugs with $Fa \leq 0.20$. The area lying between the two boundaries of A and B defines the third category (gamma), Γ, ($0.20 < Fa < 0.90$). For comparative purposes, the BCS classes I–IV were co-plotted together with the ABΓ system. Most of the BCS classes II and III are included in category Γ which mainly consists of drugs with properties like moderate or low solubility and permeability. Due to the dynamic character of dissolution and uptake processes, category A is expanded toward BCS Class II. The ABΓ system allows the classification of all compounds into three categories (A, B, Γ) in terms of the fraction of dose absorbed.

1. Introduction

The qualitative and quantitative approaches based on the absorption potential concept for the prediction of the fraction of dose absorbed, *Fa* were the first in late 80s to relate *Fa* with the physicochemical properties of drug (Dressman et al., 1985; Macheras and Symillides, 1989). Few years later, the microscopic tube model of absorption was developed (Oh et al., 1993) and the seminal biopharmaceutical classification system (BCS) article using compound/drug solubility and permeability as the main parameters for biopharmaceutics classification was published (Amidon et al., 1995). This was followed by the relevant Food and Drug Administration (FDA) BCS Guideline (FDA, 2000). Moreover, the concepts of BCS were included in the most recent European Medicines Agency (EMA) guideline on the investigation of bioequivalence (EMA, 2010).

Although the theoretical work (Oh et al., 1993) indicates that *Fa* is a continuous function of drug solubility and permeability (or the corresponding dissolution number and absorption number, respectively), the developed BCS has a simplified, binary structure, namely, Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), Class IV (low solubility, low permeability). The same binary structure has been adopted by the US and European health agencies (FDA, 2000; EMA, 2010) for regulatory purposes as well as in numerous scientific papers dealing with oral drug absorption and in the development of Biopharmaceutics Drug Disposition Classification System (BDDCS) (Wu and Benet, 2005).

A number of articles raised several concerns regarding the BCS and the strict criteria used for the definition of Class I drugs in the FDA BCS Guideline (FDA, 2000). In this vein, it was demonstrated that a large number of Class II drugs like NSAIDs are absorbed extensively while they cannot fulfill the dissolution criteria of the FDA BCS Guideline (Yazdanian et al., 2004). This was proven to be associated with the static nature of the BCS and a dynamic version of BCS which is more physiologically relevant was used to explain the high *Fa* estimates for NSAIDs (Rinaki et al., 2004). Besides, a quantitative version of BCS was developed, which is not binary and introduces two zones between the four BCS classes (Rinaki et al., 2003). Concerns about the predictability of the permeability estimates have been raised (Bergström et al., 2003); two additional classes (V and VI) have been proposed while molecular surface area properties were found to be better predictors of drug absorption. Also, the BDDCS was developed mostly because the permeability estimates of the BCS are rate parameters and do not mirror extent of absorption (Wu and Benet, 2005).

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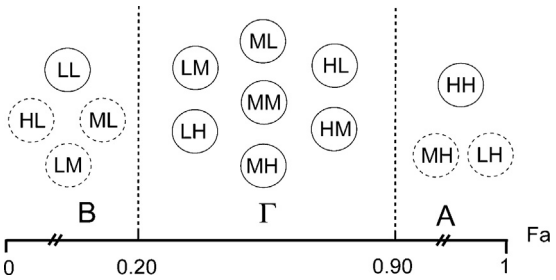

Fig. 1. Biopharmaceutic classification of drugs based on the fraction of dose absorbed, *Fa*. Each pair of letters corresponds to drugs with certain solubility, permeability properties; the first letter refers to solubility and the second to permeability while L, M, and H denote low, moderate, and high values of solubility or permeability, respectively. Drugs which are mostly found in a category are shown with a solid circle, whereas drugs which can occasionally only be found are depicted with a dashed circle.

According to the BCS, drugs are divided in two classes for solubility and for permeability. So, those who are not highly soluble (or permeable) are then classified in the other category. Obviously, this binary structure of BCS does not allow a large number of compounds or drugs from the chemical (drug) space to be accurately classified. For example, the classification of compounds with properties like (moderate solubility, moderate permeability), (moderate solubility, high permeability), (low solubility, moderate permeability), etc. into the BCS is questionable.

The aim of the present work is to re-define the biopharmaceutic classification of drugs in terms of "*the fraction of dose absorbed*', *Fa*, which is the fundamental parameter of oral drug absorption. The model used for the development of BCS (Oh et al., 1993; Amidon et al., 1995; Rinaki et al., 2004) is re-considered here and the roles of drug's dissolution and permeation rates are assessed in view to their impact on *Fa*. A new biopharmaceutical classification system is formulated which is not binary and allows the quantitative classification of all compounds in terms of solubility and permeability estimates.

2. Methods

2.1. Background

2.1.1. Absorption continuity

All parameters involved in passive drug absorption e.g. solubility, permeability, absorption number (Oh et al., 1993), dissolution number (Oh et al., 1993; Amidon et al., 1995) are of continuous nature. Plausibly, many articles have shown that the fraction of dose absorbed is a continuous function of one or more of the parameters quoted above or relevant ones (Dressman et al., 1985; Macheras and Symillides, 1989; Oh et al., 1993; Boxenbaum, 1999; Papadopoulou et al., 2008). In a large number of cases, carrier mediated transport is encountered or large drug doses saturating the lumen fluids are used for passively or non-passively absorbed drugs. In these cases, the fraction of dose absorbed is not linearly dependent from the drug dose administered (Yuasa et al., 1986; Charkoftaki et al., 2012). However, these saturable phenomena are continuous and not binary.

2.1.2. Biopharmaceutic classification of drugs based on the fraction of dose absorbed, Fa

Building on the concept of absorption continuity and the extensive experience gained from the application of BCS (Oh et al., 1993; Amidon et al., 1995; Rinaki et al., 2003, 2004; Yazdanian et al., 2004; Papadopoulou et al., 2008; Charkoftaki et al., 2012) one can construct a naïve model of oral drug absorption using *Fa* as the main parameter of classification, Fig. 1. At the right hand-side of the plot, the regulatory defined as Class I compounds (drugs) ($0.90 \leq Fa$) are placed. Although this group is routinely comprised by the highly soluble, highly permeable drugs, one can also include some drugs belonging to the current Class II. This is so since several reports in literature (Yazdanian et al., 2004; Rinaki et al., 2003, 2004) as well as biowaiver articles (Manzo et al., 2006; Shohin et al., 2012) indicate that low dose Class II drugs with not extreme insolubility can exhibit extensive absorption (Charkoftaki et al., 2012). These drugs are depicted in category A (alpha) of Fig. 1 using the symbol LH (low solubility, high permeability), which is enclosed within a dashed circle. Plausibly, if one uses the concept of the absorption continuity, drugs with moderate solubility and high permeability (MH) can also found in the category A of Fig. 1. Accordingly, this non-problematic, in terms of extent of absorption ($0.90 \leq Fa$), group of drugs (HH, MH, and LH) belong to category A, Fig. 1. At the left hand-side of the plot, one can place Class IV drugs (low solubility, low permeability) which exhibit limited absorption ($Fa \leq 0.20$). This level of limited absorption is arbitrarily assigned and other values e.g. $Fa \leq 0.10$ or $Fa \leq 0.30$ equally well serve the purposes of the non binary classification. This group of drugs with problematic and limited absorption ($Fa \leq 0.20$) belongs to the category B (beta). The middle zone ($0.20 < Fa < 0.90$) of Fig. 1 contains a highly heterogeneous group of drugs. Thus, this zone includes (i) the most part of Class II drugs (low solubility, high permeability, LH) (ii) the ensemble of Class III drugs (high solubility, low permeability, HL) and (iii) all drugs exhibiting moderate solubility and/or permeability e.g. (moderate solubility, moderate permeability, MM), (moderate solubility, high permeability, MH), (moderate solubility, low permeability, ML), (low solubility, moderate permeability, LM), (high solubility, moderate permeability, HM). These middle zone drugs ($0.20 < Fa < 0.90$) belong to category Γ (gamma). In some cases, drugs with low or moderate permeability can also exhibit very low extent of absorption ($Fa \leq 0.20$) since permeability is rate limiting regardless the solubility characteristics. For this reason, drugs with the following properties HL, ML, and LM have been also included in category B using the dashed circle symbol.

The naïve biopharmaceutic classification of drugs depicted in Fig. 1 relies on the concept of continuity in absorption and indicates that some drugs can belong to two categories if the extent of absorption is dependent on certain formulation factors e.g. dose (Charkoftaki et al., 2012). Building on the concept of continuity in absorption and utilizing a dynamic model of oral drug absorption we developed a non-binary biopharmaceutics classification system as delineated below.

2.2. The mathematical model

The model used for the development of BCS (Amidon et al., 1995) as modified by Rinaki et al. (2003) was applied to study various aspects of oral drug absorption and biopharmaceutic classification. The system of ordinary differential equations reported for drug dissolution and uptake are as follows:

$$\frac{dr_p}{dt} = \begin{cases} -\dfrac{D \cdot M_0}{\rho \cdot V_0 \cdot r_p}\left(\dfrac{1}{q} - \Phi\right) & \text{if } r_p > 0 \\ 0 & \text{if } r_p = 0 \end{cases} \quad (1)$$

$$\frac{d\Phi}{dt} = \frac{3D \cdot r_p \cdot M_0}{\rho \cdot V_0 \cdot r_0^3} \cdot \left(\frac{1}{q} - \Phi\right) - \frac{2P_{\text{eff}}}{R} \cdot \Phi \quad (2)$$

where r_p is the radius of the spherical drug particles, Φ is the fraction of dose dissolved, D is the diffusion coefficient of the drug, M_0 is the dose of the drug, ρ is the density of the solid drug, V_0 is the luminal volume, q is the dimensionless dose solubility ratio $q = (\text{Dose (mg)}/(250\,\text{(mL)} \cdot \text{solubility (mg/mL)}))$, and P_{eff} is the effective permeability of the drug.

In addition, we can consider a mass balance equation for Fa at the end of the gastrointestinal tube:

$$Fa = \frac{M_0 - M_{solid} - M_{dissolved}}{M_0} \quad (3)$$

where M_{solid} and $M_{dissolved}$ refer to the amount of the undissolved and dissolved drug at the end of the tube, respectively. Eq. (3) can be also re-written in the following form:

$$Fa = 1 - \left(\frac{r_p}{r_0}\right)^3 - \Phi \quad (4)$$

In Eq. (4), the terms r_p and Φ refer to their values at the end of the tube.

The system of ordinary differential equations (1) and (2) was solved numerically in MATLAB® (The Mathworks, Inc.) for several values of the solubility (which in turn corresponds to several q values) and P_{eff}. The solubility values ranged from 10^{-4} to 10^{2} mg/mL, while the P_{eff} values were from 10^{-8} to 10^{-1} cm/min. Two levels of M_0 (10 and 100 mg) and r_0 (10 and 50 μm) were also used in the simulations. Typical values were assigned to the remaining parameters, D (10^{-4} cm^2/min), V_0 (250 mL), R (1 cm), and ρ (1000 mg/mL). The time duration of the analysis was assigned equal to the mean intestinal transit time, i.e. 199 min (Rinaki et al., 2004).

In addition, the limiting solubility and P_{eff} values which lead to $Fa = 0.90$ and $Fa = 0.20$ were found as follows. Initially, the solubility was assumed to be equal either to 1 mg/mL or 0.1 mg/mL. The system of Eqs. (1), (2) and (4) were solved numerically to find the permeability estimate which leads to either $Fa = 0.90$ or $Fa = 0.20$. When $Fa = 0.90$ and solubility is low i.e. 0.1 mg/mL, the P_{eff} estimate found was considered to denote "high" permeability. When $Fa = 0.2$ and solubility is high i.e. 1 mg/mL, the corresponding P_{eff} value corresponds to "low" permeability. The so-derived solubility, permeability pairs were further used to classify drugs in the solubility, permeability plane in terms of the classic BCS. In other words, the high and low solubility and permeability values were used to classify drugs into the four classes of BCS using a Cartesian coordinate system.

Literature solubility (expressed as $1/q$) and permeability data for 40 drugs (Rinaki et al., 2003) were further co-plotted in the solubility, permeability plane. The P_{eff} estimates were derived from apparent permeability values using the relationship found by Sun et al. (2002); the relationship used corresponds to the entire group of data (20 drugs) measured at pH = 6.5. The reported and calculated properties, $1/q$ and P_{eff}, for the utilized drugs are listed in Table 1.

It should be underlined that the mathematical model used in this study leads to the prediction of the *fraction of drug absorbed*, namely, the fraction taken up into the enterocytes. The latter should be discriminated from the net oral bioavailability which further depends on the fractions escaping first-pass gut wall and hepatic metabolism.

3. Results and discussion

Due to the continuous nature of Fig. 1, all compounds can be classified in this naïve biopharmaceutic system. One of the interesting aspects of this simple approach is the middle heterogeneous zone of the classification. This zone (category termed as Γ) contains a large number of compounds since the values of Fa cover 70% of the entire domain of Fa values ($0.20 < Fa < 0.90$). Apart from Class II and Class III drugs, five groups of drugs with combinations of high, low, moderate solubility or permeability belong to category Γ, Fig. 1; these five groups of drugs cannot be classified accurately in the current BCS because of its binary structure. Drugs with limited absorption ($Fa \leq 0.20$, arbitrarily defined) belong to category B and in essence are class IV drugs of the current BCS while category A

Table 1
Reported and calculated properties for 40 drugs (82 cases). The terms $1/q$ and P_{eff} refer to the solubility/dose ratio and the effective permeability, respectively.

No	Name	$1/q$[a]	P_{eff}[b]
1	Acetyl salicylic acid	1.676	0.03361
2	Acetyl salicylic acid	1.676	0.02721
3	Acetyl salicylic acid	1.676	0.01519
4	Acetyl salicylic acid	1.676	0.00636
5	Atenolol	31.750	0.00359
6	Atenolol	63.500	0.00237
7	Atenolol	63.500	0.00139
8	Atenolol	63.500	0.00674
9	Atenolol	63.500	0.00126
10	Caffeine	54.418	0.03370
11	Caffeine	54.418	0.04655
12	Carbamazepine	0.151	0.02665
13	Carbamazepine	0.325	0.02665
14	Chlorpheniramine	7812.5	0.02197
15	Chlorothiazide	0.393	0.00121
16	Cimetidine	1.933	0.00441
17	Cimetidine	7.732	0.00746
18	Corticosterone	2.489	0.02641
19	Corticosterone	1.659	0.04919
20	Corticosterone	1.659	0.04893
21	Desipramine	416.667	0.02895
22	Desipramine	416.667	0.02673
23	Dexamethasone	4.198	0.04017
24	Dexamethasone	4.198	0.01841
25	Dexamethasone	4.198	0.02817
26	Dexamethasone	4.198	0.01879
27	Dexamethasone	4.198	0.01870
28	Diazepam	1.267	0.03554
29	Diazepam	1.267	0.05814
30	Digoxin	12.000	0.04625
31	Diltiazem	1.573	0.04563
32	Diltiazem	1.573	0.04153
33	Disopyramide	14.549	0.00923
34	Furosemide	2.500	0.00314
35	Furosemide	2.500	0.00788
36	Ganciclovir	62.500	0.00191
37	Glycine	104.167	0.06287
38	Grizeofulvin	0.008	0.03786
39	Hydrochlorothiazide	4.667	0.00126
40	Hydrochlorothiazide	2.028	0.00231
41	Hydrocortisone	3.594	0.02014
42	Hydrocortisone	3.594	0.02655
43	Hydrocortisone	3.594	0.02665
44	Ibuprofen	0.098	0.04775
45	Indomethacine	1.000	0.02575
46	Indomethacine	1.000	0.03893
47	Ketoprofen	0.230	0.04127
48	Mannitol	90.909	0.00191
49	Mannitol	90.909	0.00271
50	Mannitol	90.909	0.00676
51	Mannitol	90.909	0.00705
52	Mannitol	90.909	0.00117
53	Metoprolol	2500.0	0.02840
54	Metoprolol	2500.0	0.03086
55	Metoprolol	2500.0	0.03998
56	Metoprolol	2500.0	0.03093
57	Naproxen	0.016	0.04095
58	Panadiplon	1.925	0.01536
59	Phenytoin	0.074	0.03070
60	Piroxicam	0.875	0.03705
61	Propranolol	157.8	0.02689
62	Propranolol	157.8	0.03130
63	Propranolol	157.8	0.04121
64	Propranolol	42.1	0.02060
65	Propranolol	157.8	0.04107
66	Quinidine	0.418	0.02575
67	Ranitidine	4.147	0.00225
68	Salicylic acid	0.725	0.01811
69	Salicylic acid	0.725	0.02705
70	Saquinavir	0.917	0.00243
71	Sulfasalazine	0.050	0.00164
72	Sulfasalazine	0.050	0.00094
73	Sulfasalazine	0.050	0.00095
74	Sulpiride	0.564	0.00282
75	Testosterone	0.306	0.02933

Table 1 (*Continued*)

No	Name	$1/q$[a]	P_{eff}[b]
76	Testosterone	0.306	0.05883
77	Testosterone	0.306	0.05147
78	Testosterone	0.306	0.04733
79	Theophylline	10.284	0.04297
80	Theophylline	10.284	0.05267
81	Verapamil HCl	172.9	0.03040
82	Zidovudine	8.899	0.01272

[a] $1/q$ data were estimated from q values listed in Table I of Rinaki et al. (2003).
[b] P_{eff} data were estimated from the apparent permeability (P_{app}) values, listed in Table I of Rinaki et al. (2003), using one of the transformation formulas found by Sun et al. (2002). The specific relationship between P_{eff} and P_{app} used in our study is $\log(P_{eff}) = 0.6532 \cdot \log(P_{app}) - 0.3036$ which is depicted in Fig. 5 pg. 1405 of the Sun et al. (2002) article.

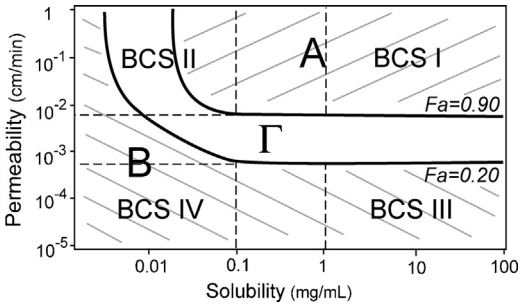

Fig. 3. The ABΓ system is co-plotted with a continuous version of BCS. The latter was constructed using the cutoff values of high, low solubility and permeability estimates reported in Table 2. The dose and particle size values were set equal to 10 mg and 10 μm, respectively.

($0.90 \leq Fa$) does not contain only Class I drugs but also low dose Class II drugs.

A similar 3-zone biopharmaceutic classification of drugs was published 25 years ago when *Fa* was found to be a continuous function of the drug's absorption potential (Macheras and Symillides, 1989). Also, Bergström et al. (2003) introduced Classes V and VI (see Fig. 9 in Bergström et al., 2003) and created a 3-zone biopharmaceutic classification in terms of permeability. Very recently, it was introduced the concept of class migration for low dose Class II drugs and it was proposed a 3-zone classification (Charkoftaki et al., 2012). All above indicate that the one-dimensional classification based on the value of fraction of dose absorbed [low ($Fa \leq 0.20$), intermediate ($0.20 < Fa < 0.90$), high ($0.90 \leq Fa$)] can be also related to the estimates of solubility and permeability, Fig. 1.

Fig. 2A–D presents the non-binary, biopharmaceutics classification system using permeability and solubility as the coordinates of the log–log plot. Here, the three categories A, B and Γ are clearly marked and depicted in a quantitative manner as a function of two levels of dose (10 and 100 mg) and particle size (10 and 50 μm). In all cases considered, category Γ ($0.20 < Fa < 0.90$) lies between category A ($0.90 \leq Fa$) and B ($Fa \leq 0.20$), has a curvilinear shape with two unequal portions at the two ends; the larger portion always corresponds to a larger range of permeability values while the smaller portion to a shorter range of solubility values. This asymmetry arises from the fact that when dissolution is the rate limiting step (low solubility values), a relatively high permeability value leads to a higher extent of absorption. On the contrary, when the permeation rate is low, any increase in solubility does not affect the extent of absorption. This is also reflected on the almost parallel boundary lines of the categories A ($Fa = 0.90$) and B ($Fa = 0.20$) for high solubility values. The exact shape of the category Γ is also dependent on the amount of dose and the drug particle size. Regardless of the shape of category Γ, many drugs of this category could not be accurately classified in the current BCS due to its binary structure. In fact, the category Γ drugs have low, intermediate or high solubility values and intermediate or high permeability values (Fig. 2A–D). As far as the shape of the regions corresponding to categories A and B is concerned, this varies according to the dose and drug particle size examined.

Fig. 3 contrasts the non binary system developed (Fig. 2A) *vis a vis* a continuous version of BCS. The latter was constructed using the estimates of the limiting values for drug solubility and permeability listed in Table 2 when $Fa = 0.20$ and $Fa = 0.90$. Although the use of high–low values for solubility and permeability transforms the binary BCS to a continuous, quantitative system, the cross-shaped region of drugs between the dashed rectangulars of the four BCS classes is clearly shown, Fig. 3. It can be seen that this region of the

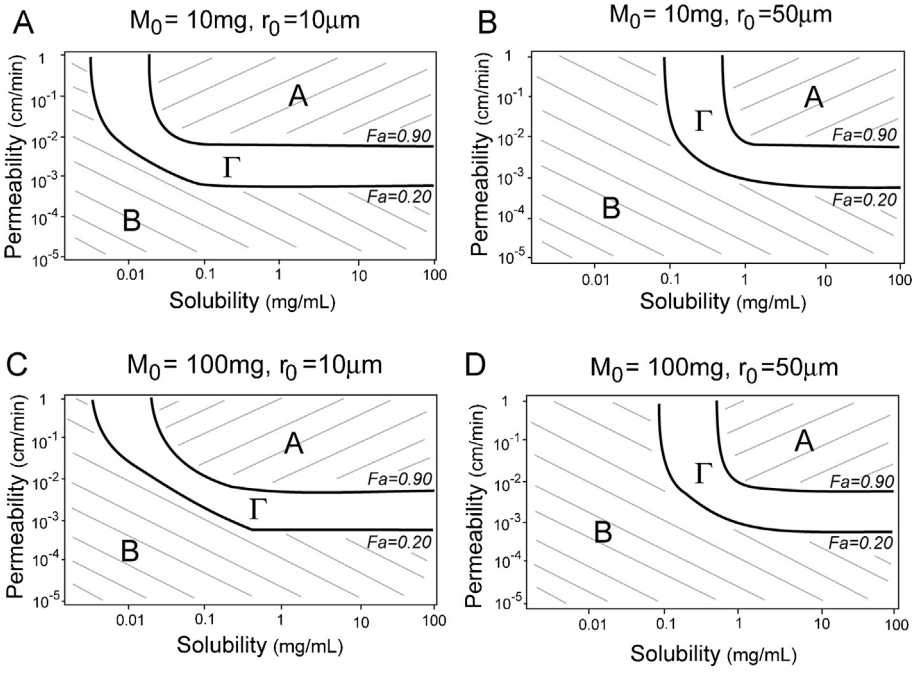

Fig. 2. The ABΓ system. The three drug categories A, B and Γ are shown as a function of two levels of dose (10 and 100 mg) and drug particle size (10 and 50 μm).

Table 2
The limiting (high, low) estimates for solubility and permeability derived from the numerical solution of Eqs. (1), (2), and (4) when *Fa* is assigned equal to either *Fa* = 0.90 or *Fa* = 0.20.

Fa	Dose (mg)	r_0 (cm)	Solubility (mg/mL)	Permeability (cm/min)
0.90	10	0.0010	100	0.0058
			1	0.0058
			0.1	0.0066[a]
			0.01	–[b]
0.20	10	0.0010	100	0.00057
			1	0.00057[c]
			0.1	0.00064
			0.01	0.00490
0.90	10	0.0050	100	0.0058
			1	0.0083
			0.1	–[b]
			0.01	–[b]
0.20	10	0.0050	100	0.00056
			1	0.00076[c]
			0.1	0.0205
			0.01	–[b]
0.90	100	0.0010	100	0.0058
			1	0.0059
			0.1	0.0127[a]
			0.01	–[b]
0.20	100	0.0010	100	0.00057
			1	0.00057[c]
			0.1	0.0021
			0.01	0.0321
0.90	100	0.0050	100	0.0058
			1	0.0088
			0.1	–[b]
			0.01	–[b]
0.20	100	0.0050	100	0.00056
			1	0.00081[c]
			0.1	0.034
			0.01	–[b]

[a] High permeability; the P_{eff} estimate is declared as "high permeability" when solubility is low (=0.1 mg/mL) and *Fa* = 0.90.
[b] The numerical solution of Eqs. (1), (2) and (4) did not converge to a permeability estimate.
[c] Low permeability; the P_{eff} estimate is declared as "low permeability" when solubility is high (=1 mg/mL) and *Fa* = 0.20.

currently unclassified drugs intersects with categories A, B and Γ. Besides, Fig. 3 demonstrates that BCS Class I drugs is a subset of category A which is expanded toward Class II drugs. Also, a large part of Class II drugs belong to category Γ (0.20 < *Fa* < 0.90). Fig. 4 shows an application of ABΓ system for the classification of published data of Rinaki et al. (2003) using a solubility/dose ratio, permeability plane. Fig. 4 reveals that a large number of data points belong either to the heterogeneous group of drugs (category Γ) or to category A which does not include exclusively Class I drugs.

This work has an obvious relation with regulatory issues relevant to biowaiver status. In fact, this study provides a theoretical support of many biowaiver monographs of Class II drugs (Potthast et al., 2005; Shohin et al., 2012). Due to the continuum character of the plots (Fig. 2A–D), the drugs listed in either biowaiver monographs or relevant publications (Kovacević et al., 2009) of the so called "intermediate solubility class" (Potthast et al., 2005), lay close to the boundary of categories A and Γ. Besides, the almost parallel limbs of the boundary curves for drugs of categories (A and Γ), (B and Γ) for high solubility values (Class III), theoretically reconfirm the non dependency of extent of absorption from

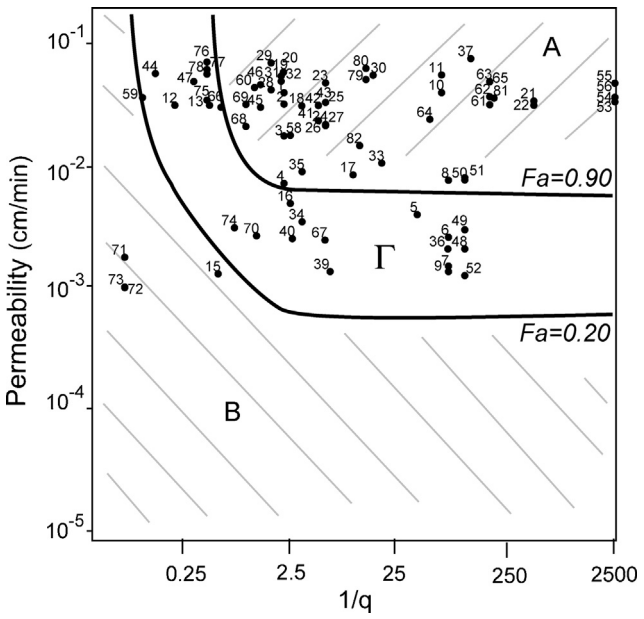

Fig. 4. Classification of the 40 drugs (82 cases), listed in Table 1, in the solubility/dose ($1/q$), permeability plane. The graph was based on the ABΓ system presented in Fig. 2A. The dose and particle size values were set equal to 10 mg and 10 μm, respectively. The plot demonstrates the large number of published data falling into the category Γ. The numbers next to the points indicate the increasing number of each drug/case according to Table 1.

formulation related factors (dose, particle size). In addition, dose consideration seems to be important (Fig. 2 and Table 2) for drug biopharmaceutic classification. The results of the present study and previous studies (Rinaki et al., 2003; Charkoftaki et al., 2012) demonstrate that "the highest dose strength" principle should not be used as a prerequisite for a BCS-based biowaiver, since a smaller dose strength can fulfill the solubility, dissolution criteria (FDA, 2000). However, this principle cannot be applied if a low strength is waived as high soluble and the patients employ it to take the highest dose (several tablets together simultaneously). It should be noted that the World Health Organization (WHO) working document on bioequivalence requirements pays particular attention to the solubility/dose ratio considerations (WHO, 2005).

Some considerations concerning the relationship of the present findings with the BDDCS are due. The development of BDDCS was based on a remarkable observation of Professor Benet and Dr Wu (2005). They found that drugs of Classes I and II have high metabolism and drugs of Classes III and IV exhibit low metabolism. Since the development of BDDCS was based on the pre-existing BCS, the structure of BDDCS has a binary character too. However, the continuous character of the plots in Fig. 2A–D reveals that a number of drugs of Category Γ lay between Classes I and II and many drugs of category Γ have moderate values for at least one of the properties solubility and permeability. Therefore, these drugs have been classified in the four classes of the binary BDDCS since metabolism has replaced permeability of the BCS.

Due to the non binary structure of the present system, the understanding of the molecular basis of drugs classified in BCS and BDDCS will be facilitated and redirected with the use of ABΓ system. This is so since molecular structure features or molecular descriptors used in studies dealing with biopharmaceutic classification of drugs (Khandelwal et al., 2007; Broccatelli et al., 2012) are of continuous nature and can be associated with the ABΓ system. Moreover, approaches applied in binary classifier systems, namely, a given set of objects is classified into two groups on the basis of whether they have some property or not would not be applied if a continuous classification was available (Olivares-Morales et al., 2013).

BCS relies on single estimates of solubility and permeability for biopharmaceutic classification purposes as well as regulatory purposes. However, it has been recognized that this approach is a simplification of the really complex drug processes in the gastrointestinal tract (Macheras and Argyrakis, 1997; Dokoumetzidis and Macheras, 2011). Moreover, a plethora of studies dealing with supersaturated phenomena, drug precipitation in the lumen, micellar formation, pH dependent solubility, solubility in food mimicking media and biorelevant media, attempt in our days to elucidate and quantify oral drug absorption (Macheras et al., 2013). Nevertheless, the BCS has become a favorable tool in biopharmaceutics due to its simplicity and wide applicability for regulatory purposes. In the same vein, the ABΓ system can offer different insights in the classification of compounds. The ABΓ system does not substitute BCS, but it acts complementarily with BCS in order to allow prediction of the fraction of dose absorbed for any combination of solubility, permeability properties of a drug.

Finally, it should be clarified that the ABΓ system relies on the same simple mathematical model as BCS. It is acknowledged that this model is based on some over simplicities e.g. the gut is considered as a simple tube without accounting for factors like segmental pH, fluid volume composition, and intestinal transit times etc. In the same vein, our utilized model assumes spherical drug particles with a single value for the radius and no particle size distribution. Besides, this work focuses on the fraction of dose absorbed in the enterocytes and neglects other phenomena like the first-pass gut wall and hepatic metabolism. However, even though this model is relatively simple and cannot capture all physiological aspects of GI absorption and complexity, it is suitable for the purposes of our work.

4. Conclusions

The ABΓ system developed in this study allows the classification of all compounds in solubility, permeability plane. Even though the present work utilizes the classical model of oral drug absorption of BCS, it offers an alternative approach for biopharmaceutical classification. The ABΓ introduces two different issues: (a) the non-binary character of classification and (b) the organization of drugs in terms of the fraction of dose absorbed which is of crucial importance in biopharmaceutical studies. It is hoped that the use of ABΓ system, in conjunction with the regulatory based BCS, will allow a better understanding of oral drug absorption phenomena.

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