Quantitative Biopharmaceutics Classification System: The Central Role of Dose/Solubility Ratio

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Purpose. To develop a quantitative biopharmaceutics drug classification system (*QBCS*) based on fundamental parameters controlling rate and extent of absorption.

Methods. A simple absorption model that considers transit flow, dissolution, and permeation processes stochastically was used to illustrate the primary importance of dose/solubility ratio and permeability on drug absorption. Simple mean time considerations for dissolution, uptake, and transit were used to identify relationships between the extent of absorption and a drug's dissolution and permeability characteristics.

Results. The *QBCS* developed relies on a (permeability, dose/solubility ratio) plane with cutoff points 2×10^{-6}–10^{-5} cm/s for the permeability and 0.5–1 (unitless) for the dose/solubility ratio axes. Permeability estimates, P_{app} are derived from Caco-2 studies, and a constant intestinal volume content of 250 ml is used to express the dose/solubility ratio as a dimensionless quantity, q. A physiologic range of 250–500 ml was used to account for variability in the intestinal volume. Drugs are classified into the four quadrants of the plane around the cutoff points according to their P_{app}, q values, establishing four drug categories, i.e., I ($P_{app} > 10^{-5}$ cm/s, $q \leq 0.5$), II ($P_{app} > 10^{-5}$ cm/s, $q > 1$), III ($P_{app} < 2 \times 10^{-6}$ cm/s, $q \leq 0.5$), and IV ($P_{app} < 2 \times 10^{-6}$ cm/s, $q > 1$). A region for borderline drugs ($2 \times 10^{-6} < P_{app} < 10^{-5}$ cm/s, $0.5 < q < 1$) was defined too. For category I, complete absorption is anticipated, whereas categories II and III exhibit dose/solubility ratio–limited and permeability-limited absorption, respectively. For category IV, both permeability and dose/solubility ratio are controlling drug absorption. Semiquantitative predictions of the extent of absorption were pointed out on the basis of mean time considerations for dissolution, uptake, and transit in conjunction with drug's dose/solubility ratio and permeability characteristics. A set of 42 drugs were classified into the four categories, and the predictions of intestinal drug absorption were in accord with the experimental observations.

Conclusions. The *QBCS* provides a basis for compound classification into four explicitly defined drug categories using the fundamental biopharmaceutical properties, permeability, and dose/solubility ratio. Semiquantitative predictions for the extent of absorption are essentially based on these drug properties, which either determine or are strongly related to the *in vivo* kinetics of drug dissolution and intestinal wall permeation.

KEY WORDS: solubility; permeability; dissolution; dose/solubility ratio; biopharmaceutics classification system.

INTRODUCTION

The introduction of a biopharmaceutics classification system (BCS) (1) in 1995 was the final result of continuous efforts (2–5) on mathematical analysis for the elucidation of kinetics and dynamics of drug processes in the gastrointestinal (GI) tract. According to BCS a substance is classified on the basis of its aqueous solubility and intestinal permeability. This important achievement affected many industrial, regulatory, and scientific aspects of drug development and research. In the industrial-regulatory setting, the introduction of BCS accompanied in the publication of several guidances from the Food and Drug Administration (FDA) regarding scale up and postapproval changes (6), dissolution (7), and waiver of *in vivo* bioequivalence studies (8). The scientific aspects of BCS have been extensively discussed (9) and have been the subject of numerous studies (10–17).

However, there are inherent drawbacks for the solubility classification of a substance in the BCS. Theoretically, a single solubility value is inadequate for biopharmaceutical classification purposes because drugs are administered at various doses, and therefore, dosage considerations should be taken into account. This is clearly reflected in the FDA guidance for industry: "*In Vivo* Bioavailability Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (BCS Guidance), which refers to the highest dose strength of an immediate-release product for the characterization of highly soluble substances (9). In parallel, solubility is a static equilibrium parameter and cannot describe adequately the dynamic character of the dissolution process for the entire dose administered. This is also reflected in the rapid dissolution criteria imposed by FDA for biowaivers of class I substances in immediate-release solid dosage forms; i.e., no less than 85% of the dose is dissolved within 30 min (9). Moreover, a study dealing with the causes of poor oral drug absorption has shown that absorption, apart for being permeability-limited, can also be either solubility- or dissolution-limited (11). It was found that digoxin exhibits solubility-limited absorption, whereas the absorption of griseofulvin was limited by both dissolution and solubility (11). These findings raise concerns for the proper classification of digoxin and griseofulvin because both are classified in class II for their limited but similar aqueous solubility. This observation indicates the inadequacy of single solubility values for classification purposes because the remarkable difference in the extent of absorption of two drugs is likely associated with the large difference in their dose/solubility ratios (12). The importance of the term "percentage undissolved oral dosed drug in 250 ml of water" for the prediction of intestinal absorption has also been demonstrated recently in quantitative structure–activity relationship studies involving large data banks (14,18).

Recently, theoretical developments for the classic diffusion layer model of dissolution were reported (20). We demonstrated that the mean dissolution time (MDT) of the entire dose is dependent on the dose/solubility ratio when this ratio is low. It was also found that when the dose/solubility ratio is high, the MDT is infinite; besides, when only a fraction of dose is dissolved, the corresponding mean time was termed mean dissolution time for saturation, MDT_s, and it was found to be equal to the reciprocal of the dissolution rate constant. These findings not only unveil the central role of dose/solubility ratio for the dissolution process but also signify their importance in regard to the extent of a drug's absorption

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from the GI tract (20). These observations, coupled with the aforementioned limitations of the BCS, prompted us to reexamine the biopharmaceutical classification of drugs. In this study, we approach the biopharmaceutical classification of drugs in a quantitative manner, relying on the central role of dose/solubility ratio for the absorption phenomena in conjunction with mean time concepts for dissolution, transit, and uptake of drug in the intestines. These considerations lead us to the development of a quantitative version of BCS, termed QBCS.

THEORY

Our analysis is based on the tube model of the intestinal lumen, Fig. 1. An ensemble of drug particles [total mass = dose (M_0)] moves down the tube and dissolves in accord with the diffusion layer model, assuming that the volume (V) of the intestinal fluids, the drug's saturation solubility (C_s), and the flow rate remain constant. We assume that the dissolved drug molecules cross the intestinal wall passively according to their permeation characteristics, and the amount of drug transported is equal to its uptake. The first moments, mean dissolution time, MDT when the entire dose is dissolved (or MDT_s when only a fraction of dose is dissolved), and mean absorption time (MAT) can be used to describe drug dissolution and uptake, respectively, stochastically (Fig. 1).

Overall, Fig 1 places particular emphasis on the mean time for dissolution (either MDT or MDT_s) and uptake (MAT) of drug in relation to the mean intestinal transit time (MITT). The dynamic character of the processes involved in intestinal drug absorption implies that a proper biopharmaceutical classification of drugs can be based on fundamental drug properties that determine or are associated with the global kinetic characteristics of the drug processes, MDT (or MDT_s), and MAT, taking into account the time domain of the physiologic restriction, MITT (Fig. 1).

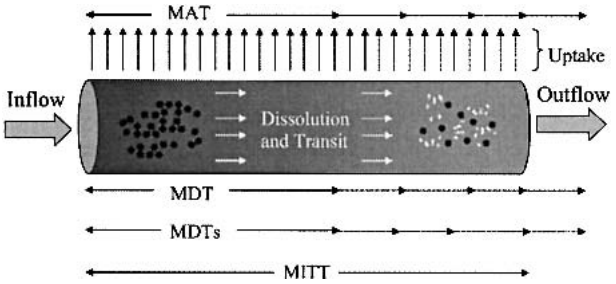

Fig. 1. A schematic of absorption processes in the intestines. The *black dots* represent drug solid particles, and the *white dots* represent dissolved drug species. Drug dissolution in the intestinal fluids and permeation of the intestinal wall are consecutive first-order processes that take place in the time domain of the mean intestinal transit time (MITT) imposed by the physiology. When the entire dose can be dissolved in the intestinal contents, the mean dissolution time (MDT) refers to the dissolution process of the entire dose. When only a fraction of dose can be dissolved in the intestinal contents, the mean dissolution time for saturation (MDT_s) refers to the dissolution process of the fraction of dose dissolved, Φ. If the entire dose is dissolved before its arrival at the end of the tube, then the fraction of dose dissolved, Φ, is equal to 1; otherwise Φ < 1. The mean absorption time (MAT) refers to the permeation process. The positioning of the right end pinpoints of the arrows associated with MDT, MDT_s, and MAT indicate that each of them can be smaller than, greater than, or equal to MITT. When MAT << MDT or MAT << MDT_s, then absorption operates under sink conditions (see text).

Dissolution Classification

We initially define the quantity $q = M_o/(C_sV)$ to denote the dimensionless dose/solubility ratio for the particular drug-formulation considered. It was recently shown (20) that when dissolution takes place in a closed system and follows the diffusion layer model, the entire dose is dissolved, and therefore the fraction of dose dissolved, Φ, is equal to 1 because $q \leq 1$. It was found (20) that when $q \leq 1$, the MDT is dependent on q according to Eq. (1):

$$MDT = \frac{q - (q-1)\ln(1-q)}{kq} \tag{1}$$

where k is the first-order rate constant of the dissolution process.

On the contrary, when the entire dose is not dissolved ($q > 1$), the MDT is infinite. In this case, the time course of the fraction of dose dissolved, Φ follows Eq. (2):

$$\Phi \frac{1}{q}(1 - e^{-kl}) \tag{2}$$

A meaningful stochastic expression for the dissolution kinetics is the mean dissolution time for saturation MDT_s (20):

$$MDT_s = \frac{1}{k} \tag{3}$$

An estimate for k can be obtained (21) from Eq. (4):

$$k = \frac{D\,A}{h\,V} \tag{4}$$

where D is the diffusion coefficient, h is the diffusion layer thickness, A is the surface area of the drug particles, and V the volume of liquids in the intestinal lumen.

In the special case of perfect sink conditions, the fraction of drug dose dissolved, Φ, changes with time according to Eq. (5) (20):

$$\phi = \begin{cases} \dfrac{k_0 \cdot V}{M_0}\,t = \dfrac{kC_sV}{M_0}\,t = \dfrac{k}{q}\,t & \text{for } t < \dfrac{M_0}{k_0 \cdot V} = \dfrac{q}{k}\ (\phi < 1) \\ 1 & \text{for } t \geq \dfrac{M_0}{k_0 \cdot V} = \dfrac{q}{k}\ (\phi = 1) \end{cases} \tag{5}$$

where $k_0 = k\,C_s$. The mean dissolution time under sink conditions, MDT_{sc}, is dependent on the dose (20) according to:

$$MDT_{sc} = \frac{M_0}{2\,k_0\,V} = \frac{q}{2\,k} \tag{6}$$

This analysis reveals the importance of q in dissolution kinetics and allows us to propose the unity as the critical value for the parameter q for dissolution classification. This choice relies on the clear distinction between the two cases of complete dissolution (when $q \leq 1$) and incomplete dissolution (when $q > 1$) as well as the relevant mean time expressions Eqs. (1) and (3), respectively.

Permeability Classification

For classification purposes, we initially refer to drugs with very small dose/solubility ratios ($q << 1$). In other words, the drug permeation rate in Fig. 1 is not limited by the dose/solubility ratio. In theory, a simple way to calculate the fraction of dose absorbed, *F,* for a drug with $q << 1$ is to use Eq. (7), which is based on the relative magnitude of MAT and MITT (Fig. 1):

$$F = \frac{\frac{1}{MAT}}{\frac{1}{MAT} + \frac{1}{MITT}} \tag{7}$$

Equation (7) correctly predicts $F = 0.5$ when MAT = MITT, $F = 1$ when MAT << MITT, and $F = 0$ when MAT >> MITT. However, numerous studies have indicated that the vast majority of well-absorbed drugs are predominantly transported passively across the cell membranes. Accordingly, either the rate of drug absorption or the fraction of dose absorbed has been correlated with various measures of lipophilicity or passive membrane transport of the compounds, e.g., the octanol/water partition coefficient, P_{oct} (2,3,22), the distribution coefficient at pH 6.8 (23), the effective wall permeability, P_{eff} (1), and the Caco-2 monolayer permeability P_{app} (19,24). Because both intuitively and mathematically (1) the *MAT* is inversely proportional to an appropriate measure of permeability *P,* Eq. (7) can be written:

$$F = \frac{\frac{P}{d}}{\frac{P}{d} + \frac{1}{MITT}} = \frac{1}{1 + \frac{d}{P\,(MITT)}} = \frac{1}{1 + \frac{\lambda}{P}} \tag{8}$$

where *d* is a characteristic quantity related to the physiologic system, which allows the replacement of MAT with P values. Thus, when *P* is expressed in velocity units, e.g., as P_{eff} or P_{app}, then *d* has distance units. When a dimensionless parameter, e.g., P_{oct} or distribution coefficient is used for *P*, then *d* has time units. The symbol λ in Eq. (8) denotes the quotient *d/MITT*. Equation (8) reveals that a curvilinear relationship exists between the fraction of dose absorbed, *F,* and an appropriate measure of permeability, *P.* In fact, such relationships have been verified in literature when P_{eff} or P_{app} values were correlated with *F* (1,19,24). In addition, correlations between P_{eff} and P_{app} have been developed (15,24).

The experimental results quoted in the review article (19) indicate that drug transport in Caco-2 monolayers can model drug transport *in vivo,* and a cutoff point for highly permeable drugs, $P_{app} = 10^{-5}$ cm/s, ensuring fraction of drug absorbed, $F > 0.95$, has been established. In line with the recent data of Bergstrom *et al.* (15) and Sun *et al.* (24) regarding the cutoff limit of permeability, we use the values for our permeability classification purposes from 2×10^{-6} to 10^{-5} cm/s for P_{app} as a boundary region of highly permeable drugs for complete absorption. These limiting values for P_{app} were used to replace *P* in Eq. (8), *F* was set equal to 0.95, and the corresponding limiting values for λ were found to be 1.05×10^{-7} and 5.26×10^{-6} cm/s. This means that one can get two estimates for the mean absorption time (MAT) of a compound using the P_{app} estimate in the relationship:

$$MAT = \frac{\lambda\,(MITT)}{P_{app}} \tag{9}$$

derived from Eqs. (7) and (8).

RESULTS AND DISCUSSION

The 42 drugs used in our work and related data obtained from various sources are listed in Table I. The use of a larger set of data was not feasible because one or more estimates for the properties—dose, solubility, apparent or effective permeability, fraction of dose absorbed—were missing from the data available in literature. When more than one estimate for these properties was reported in literature for a given compound, we worked separately for each experimental set of data. When more than one oral dose is used in practice according to the *Physician's Desk Reference* (27), the larger one was used for the calculation of *q* unless otherwise specified in the original reference with the experimental data. Because of relatively fewer reports of drugs with low intestinal absorption in the literature, our data set is richer in high-activity values. The latter characteristic is common for all studies dealing with predictions of intestinal absorption (38,39).

The MDT or MDT_s vs. *q* Plot

Because dissolution and permeation are consecutive processes in the GI tract, a preliminary analysis of the data using an MDT (or MDT_s) vs. *q* plot allows one to determine whether or not absorption is dose/solubility ratio limited (Fig. 2).

For the first group of compounds with $q \leq 1$ (62 out of 85 records), absorption is not dose/solubility ratio limited because the entire dose can in principle be dissolved in the intestinal volume of 250 ml. However, a kinetic consideration based on the relative magnitude of MDT and MITT (Fig. 2, dashed line) indicates that digoxin (no. 13), diazepam (no. 12), dexamethasone (no. 11), panadiplon (no. 28), and scopolamine (no. 36) will not be dissolved before their arrival at the end of the tube. Figure 2 also indicates that small *q* values for compounds such as metoprolol (no. 26), chlorpheniramine (no. 5), glycine (no. 18), and clonidine (no. 8) are associated with small MDT values; i.e., the entire dose will be in solution quite rapidly. The group of drugs with $q \leq 1$ can be termed homogeneous because they are mainly in solution in the intestines, and permeation can be the only cause of poor oral drug absorption.

The second group comprises 23 records for compounds with $q > 1$ (Fig. 2). All these compounds exhibit dose/solubility ratio–limited absorption because MDT_s refers only to the fraction of dose dissolved, Φ [Eq. (2)]. Again, one can assess the degree of problematic drug absorption caused by the limited dissolution when $q > 1$ by comparing the MDT_s and MITT values. In this case, the value of *q* should also be taken into account, e.g., for griseofulvin (no. 19, $q = 133.3$), because in a closed system without uptake, the theoretical limit for the fraction of dose dissolved, Φ, is equal to $1/q$ at infinite time [Eq. (2)] (20). This second group of drugs with $q > 1$ can be termed heterogeneous because absorption is at least dissolution-limited.

The QBCS

The preliminary analysis based on MDT or MDT_s vs. *q* plot (Fig. 2) focuses only on dissolution, which takes place

Table I. Reported and Calculated Properties for the Drugs Classified in the *QBCS*

No.	Name	q	P_{app} (cm/s)	$\%F^a$	Refs.
1	Acetyl salicylic acid	0.597	3.07×10^{-5}	68	25, 26, 27
1	Acetyl salicylic acid	0.597	2.22×10^{-5}	100	26, 27, 28
1	Acetyl salicylic acid	0.597	9.09×10^{-6}	100	26, 27, 28
1	Acetyl salicylic acid	0.597	2.40×10^{-6}	100	26, 27, 30
2	Atenolol	0.031	1.00×10^{-6}[b]	50	27, 31, 32
2	Atenolol	0.016	5.30×10^{-7}	50	27, 28, 32
2	Atenolol	0.016	2.34×10^{-7}	50	27, 32, 33
2	Atenolol	0.016	2.62×10^{-6}	50	27, 28, 32
2	Atenolol	0.016	2.00×10^{-7}	50	27, 30, 32
3	Caffeine	0.018	3.08×10^{-5}	100	26, 27, 29
3	Caffeine	0.018	5.05×10^{-5}	100	25, 26, 27
4	Carbamazepine	6.610	2.15×10^{-5}[c]	70	1, 26, 31
4	Carbamazepine	3.077	2.15×10^{-5}[c]	70	1, 26, 31
5	Chlorpheniramine	1.28×10^{-4}	1.60×10^{-5}	80	27, 28, 34
6	Chlorothiazide	2.544	1.90×10^{-7}	10–40	1, 2, 3, 29
7	Cimetidine	0.517	1.37×10^{-6}	95	26, 27, 29
7	Cimetidine	0.129	3.06×10^{-6}	95	25, 26, 27
8	Clonidine	1.56×10^{-5}	2.18×10^{-5}	100	27, 29, 34
8	Clonidine	5.2×10^{-6}	3.01×10^{-5}	95	25, 27, 34
9	Corticosterone	0.402	2.12×10^{-5}	100	26, 27, 29
9	Corticosterone	0.603	5.50×10^{-5}	100	26, 27, 33
9	Corticosterone	0.603	5.45×10^{-5}	100	26, 27, 30
10	Desipramine	0.0024	2.44×10^{-5}	96	27, 28, 34
10	Desipramine	0.0024	2.16×10^{-5}	100	25, 27, 34
11	Dexamethasone	0.238	4.03×10^{-5}	100	26, 27, 28
11	Dexamethasone	0.238	1.22×10^{-5}	100	26, 27, 29
11	Dexamethasone	0.238	2.34×10^{-5}	92	25, 26, 27
11	Dexamethasone	0.238	1.26×10^{-5}	100	26, 27, 33
11	Dexamethasone	0.238	1.25×10^{-5}	100	26, 27, 30
12	Diazepam	0.789	3.34×10^{-5}	100	26, 27, 29
12	Diazepam	0.789	7.10×10^{-5}	100	25, 26, 27
13	Digoxin	0.083	5.00×10^{-5}[c]	81	1, 11
14	Diltiazem	0.636	4.90×10^{-5}	99	26, 27, 33
14	Diltiazem	0.636	4.24×10^{-5}	99	26, 27, 28
15	Disopyramide	0.069	4.24×10^{-6}	85.3	26, 27, 27
16	Furosemide	0.400	8.13×10^{-7}	70	27, 23, 33
16	Furosemide	0.400	3.33×10^{-6}	61	30, 23, 31
17	Ganciclovir	0.016	3.80×10^{-7}	3	23, 24, 29
18	Glycine	0.0096	8.00×10^{-5}	100	25, 27, 34
19	Grizeofulvin	133.333	3.68×10^{-5}	40	11, 29
20	Hydrochlorothiazide	0.214	2.00×10^{-7}[b]	75	27, 31, 32
20	Hydrochlorothiazide	0.493	5.10×10^{-7}	90	26, 27, 29
21	Hydrocortisone	0.278	1.40×10^{-5}	89	26, 27, 29
21	Hydrocortisone	0.278	2.14×10^{-5}	95	26, 35, 33
21	Hydrocortisone	0.278	2.15×10^{-5}	89	26, 27, 30
22	Ibuprofen	10.214	5.25×10^{-5}	100	25, 26, 27
23	Indomethacine	1	2.04×10^{-5}	100	27, 29, 36
23	Indomethacine	1	3.84×10^{-5}	100	27, 28, 36
24	Ketoprofen	4.348	4.20×10^{-5}[b]	100	26, 27, 31
25	Mannitol	0.011	3.80×10^{-7}	16	18, 29, 34
25	Mannitol	0.011	6.50×10^{-7}	16	18, 25, 34
25	Mannitol	0.011	2.63×10^{-6}	16	18, 33, 34
25	Mannitol	0.011	2.81×10^{-6}	16	18, 26, 34
25	Mannitol	0.011	1.80×10^{-7}	16	18, 30, 34
26	Metoprolol	0.0004	2.37×10^{-5}	95	27, 29, 34
26	Metoprolol	0.0004	2.69×10^{-5}	95	27, 33, 34
26	Metoprolol	0.0004	4.00×10^{-5}	94.5	27, 28, 34
26	Metoprolol	0.0004	2.70×10^{-5}	95	27, 30, 34
27	Naproxen	62.845	4.15×10^{-5}[b]	100	26, 27, 31
28	Panadiplon	0.519	9.25×10^{-6}[c]	79	11
29	Phenytoin	13.478	2.67×10^{-5}	90	26, 27, 29
30	Piroxicam	1.1428	3.56×10^{-5}	100	1, 29, 31
31	Propranolol	0.00634	2.18×10^{-5}	90	26, 27, 29

Table I. Continued

No.	Name	q	P_{app} (cm/s)	$\%F^a$	Refs.
31	Propranolol	0.00634	2.75×10^{-5}	90	25, 26, 27
31	Propranolol	0.00634	4.19×10^{-5}	90	26, 27, 30
31	Propranolol	0.0238	1.45×10^{-5}[b]	95	26, 27, 31
31	Propranolol	0.00634	4.17×10^{-5}	90	26, 27, 33
32	Quinidine	2.391	2.04×10^{-5}	80	25, 26, 27
33	Ranitidine	0.241	4.90×10^{-7}	50	26, 27, 29
34	Salicylic acid	1.38	1.19×10^{-5}	100	27, 30, 34
34	Salicylic acid	1.38	2.20×10^{-5}	100	27, 29, 34
35	Saquinavir	1.091	5.50×10^{-7}	30	27, 33, 37
36	Scopolamine	0.000247	1.18×10^{-5}	100	27, 29, 37
37	Sulfasalazine	20	3.00×10^{-7}	13	27, 29, 34
37	Sulfasalazine	20	1.29×10^{-7}	13	27, 33, 34
37	Sulfasalazine	20	1.30×10^{-7}	13	27, 30, 34
38	Sulpiride	1.774	6.92×10^{-7}	44	26, 27, 33
39	Testosterone	3.264	2.49×10^{-5}	100	26, 27, 29
39	Testosterone	3.264	7.23×10^{-5}	100	25, 26, 27
39	Testosterone	3.264	5.89×10^{-5}	100	26, 27, 33
39	Testosterone	3.264	5.18×10^{-5}	100	26, 27, 30
40	Theophylline	0.0972	4.47×10^{-5}	96	26, 27, 33
40	Theophylline	0.0972	6.10×10^{-5}	96	26, 27, 28
41	Verapamil HCl	0.00578	2.63×10^{-5}	100	27, 33, 37
42	Zidovudine	0.113	6.93×10^{-6}	100	26, 27, 29

[a] Fraction (%) of dose absorbed as reported in literature.
[b] P_{app} values were calculated from P_{eff} estimates (31), using the correlation established between P_{app} and P_{eff}, reported in (24); i.e., for 90% absorption the values for P_{app} and P_{eff} are 10^{-5} cm/s and 2×10^{-4} cm/s, respectively. These drugs belong to the dataset used for the correlation developed in (24).
[c] P_{app} values were calculated from P_{eff} estimates (31), using the correlation established between P_{app} and P_{eff} reported in (24); i.e., for 90% absorption the values for P_{app} and P_{eff} are 10^{-5} cm/s and 2×10^{-4} cm/s, respectively. These drugs do not belong to the dataset used for the correlation developed in (24).

prior or simultaneously with the permeation of drug across the intestinal wall. The next step is to formulate a QBCS based on both biopharmaceutic properties, permeability and dose/solubility ratio, which are directly associated with the fundamental kinetic parameters MAT and MDT (or MDT_s), respectively. This can be accomplished by using a (permeability, dose/solubility ratio) plane with cutoff points for the quantitative classification of drugs in four categories (Fig. 3). For illustrative purposes and in order to keep the same nomenclature of the four drug classes for both classification systems, BCS and QBCS, the quantity $1/q$ is used in the abscissa of Fig. 3.

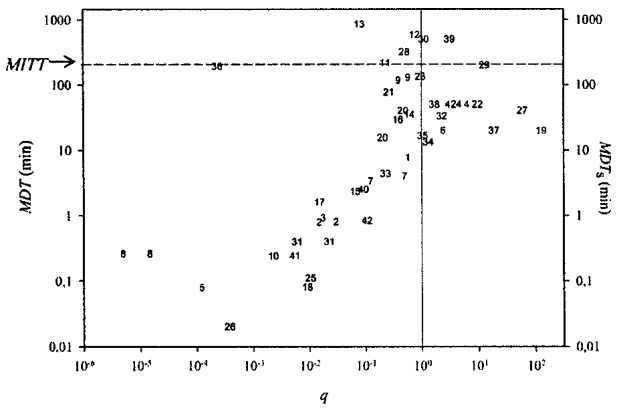

Fig. 2. An MDT or MDT_s vs. q plot for the 85 data listed in Table I. MDT values are correlated with q values ≤ 1. MDT_s values are correlated with q values >1. MDT values were calculated from Eqs. (1) and (4), whereas MDT_s values were calculated from Eqs. (3) and (4). In all cases the following values were used: $D = 5 \times 10^{-6}$ cm^2/s, $h = 3 \times 10^{-3}$ cm, $V = 250$ ml, and spherical particles with radius $r = 25$ μm were assumed for the calculation of A in Eq. (4). The intestinal volume was set equal to 250 ml (1) for the calculation of q. The *dashed line* corresponds to MITT = 199 min (12,41).

The Caco-2 monolayer permeability, P_{app}, was chosen as the most appropriate permeability parameter of the y-coordinate of the QBCS (Fig. 3). A number of reasons substantiate

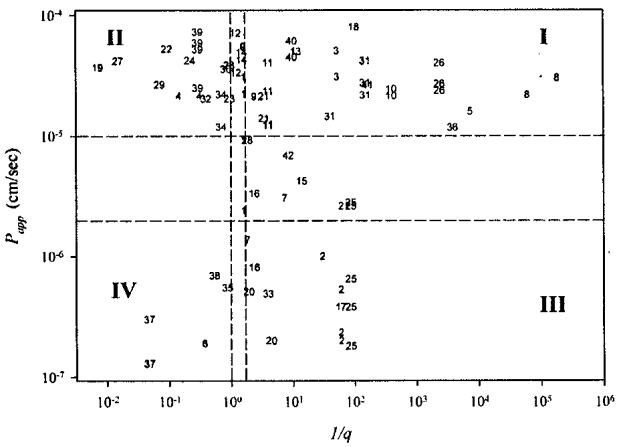

Fig. 3. The classification of drugs listed in Table I in the (solubility/dose ratio, apparent permeability) plane for the QBCS. The intersections of the *dashed lines* drawn at the cutoff points of the two parameters forms the region of borderline drugs.

the choice of P_{app} in the QBCS: (a) it is currently used as the most widespread predictor of drug absorption (15,23); (b) it is relatively easily measured experimentally; and (c) correlations have been developed (15,24) between P_{app} and the wall permeability coefficient P_{eff}, which is directly related to MAT (1). The use of a high-permeability boundary region 2×10^{-6}–10^{-5} cm/s in Fig. 3 is also in agreement with the variability of the experimental findings for P_{app} (19). A similar high-permeability region, $2–4 \times 10^{-4}$ cm/s has also been defined in terms of P_{eff} (1). The concept of a high-permeability boundary region is also in line with recent proposals regarding the uncertainty associated with the definitions of the high permeability requirement (9) and the new intermediate-permeability class boundary (15).

The dimensionless character of the solubility/dose ratio axis of Fig. 3 presupposes the use of a volume value for the intestinal fluids because $q = D/(C_s V)$. It has been suggested that a volume of 250 ml adequately mimics the volume of gastrointestinal contents (1). A volume of 250 ml was also used for the presentation of data in Fig. 2. However, the composition and volume of GI fluids change during the time course of the drug in the GI system, and both vary considerably among individuals (9). Because the physiologic volume of the intestinal fluids varies from 50 to 1100 ml with an average of 500 ml under fasting conditions (9), we adopt in the present classification a volume range of 250 ml as a more realistic approach for classification purposes. The lower boundary of 250 ml refers to the common practice of drug's administration with a glass of water. We arbitrarily set $q = 1$ when $q = D/250C_s = 1$ and create a boundary region $1 < 1/q < 2$ (Fig. 3) to account for variability related to the volume content, using 500 ml as an upper volume boundary.

The homogeneous drugs, $(1/q) \geq 1$, which are in solution for the most part of their transit in the GI tube, lie at the right-hand side of Fig. 3. The heterogeneous drugs, $(1/q) < 1$, which are both in solution and in the solid state as they move down the intestinal lumen, lie at the left-hand side of Fig. 3. The intersections of the dashed lines drawn at the cutoff points for permeability and solubility/dose ratio divide the $1/q$, P_{app} plane of Fig. 3 into four explicitly defined drug categories (I–IV) and a region of borderline drugs. The biopharmaceutical properties of a drug determine the pharmacokinetic characteristics as delineated below.

Category I. $q \leq 0.5$, $P_{app} > 10^{-5}$ cm/s

The drugs of this category are well absorbed. *In vitro–in vivo* correlations are unlikely because gastric emptying controls the rate of absorption. Complete absorption of the dose administered is anticipated. Variability in C_{max} is associated with the physiologic variability of gastric emptying. Variability in AUC will arise only from intra- or intersubject variability of disposition parameters. The definition in the FDA BCS guidance for highly soluble substances (8) is fully compatible with this drug category bcause it refers to a dissolution criterion based on the highest dose strength; i.e., it takes into account the dose/solubility ratio. Examples of the compounds of this category include digoxin (no. 13), caffeine (no. 3), and metoprolol (no. 26).

Category II. $q > 1$, $P_{app} > 10^{-5}$ cm/s

The drugs of this category exhibit dose/solubility-limited absorption. This dependency will be more pronounced for drugs with $q >> 1$. Dosage form factors are crucial for both extent and variability in drug absorption. *In vitro–in vivo* correlations are expected. Examples of compounds of this category include griseofulvin (no. 19), naproxen (no. 27), and phenytoin (no. 29).

Category III. $q \leq 0.5$, $P_{app} < 2 \times 10^{-6}$ cm/s

This drug category can exhibit permeability-limited absorption. This dependency will be more pronounced for those drugs lying well below the borderline region. Variability in AUC and $C_{\max}$ will be higher when variable gastrointestinal transit or pH-dependent permeability is encountered. Examples of compounds of this category include ganciclovir (no. 17) and ranitidine (no. 33).

Category IV. $q > 1$, $P_{app} < 2 \times 10^{-6}$ cm/s

Low extent of absorption is anticipated because both dose/solubility ratio and permeability are rate-limiting absorption for this drug category. Examples of compounds of this category include sulfasalazine (no. 37) and sulpiride (no. 38).

Borderline Drugs. $0.5 < q < 1$, $2 \times 10^{-6} < P_{app} < 10^{-5}$

The exact positioning of a drug in the borderline region of Fig. 3 in relation to drug categories I–IV determines the prediction associated with the pharmacokinetic characteristics. The predictions become more uncertain for drugs lying in or close to the region surrounded by the dashed lines of the four cutoff points. Examples of compounds of this category include disopyramide (no. 15), zidovudine (no. 42), and diazepam (no. 12). Note that atenolol and mannitol can be classified either as borderline compounds or in category III according to their q and P_{app} estimates (Table I).

Semiquantitative Predictions for the Extent of Drug Absorption Using the QBCS

Because dissolution and permeation are first-order consecutive processes, a mean effective time (MET) based on the additivity of mean times (38) expresses globally the kinetics of dissolution-uptake processes:

$$\text{when } q \leq 1 \quad MET = MAT + MDT \tag{10}$$

$$\text{when } q > 1 \quad MET_s = MAT + MDT_s \tag{11}$$

Because the value of MET or MET_s controls drug absorption, their relative magnitudes in relation to MITT provide a clear indication for the extent of drug absorption. This is shown schematically in Figs. 4 and 5 by plotting the MET and MET_s vs. the MAT values of the data listed in Table I incorporating the physiologic restriction of MITT in both axes.

The drugs lying close to the origin of the axes (encircled data) at the left-hand side of Fig. 4, are expected to be fully absorbed because MET << MITT. For these drugs the fraction of dose absorbed, F, can be described by Eq. (12):

$$F = \frac{\dfrac{1}{MET}}{\dfrac{1}{MET} + \dfrac{1}{MITT}} \tag{12}$$

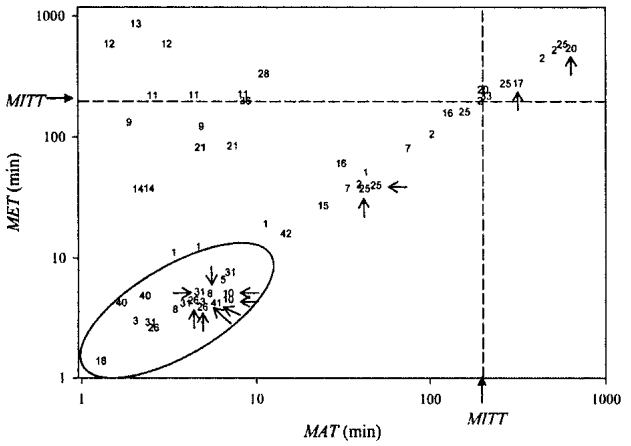

Fig. 4. MET vs. MAT plot for the data listed in Table I. MAT values were calculated from Eq. (9) using MITT = 199 min (12,41) and $\lambda = 5.26 \times 10^{-6}$ cm/s, which corresponds to the upper boundary (10^{-5} cm/s) of P_{app}. The *dashed lines* correspond to the MITT value. For clarity reasons the data on compound nos. 3, 8, 10, 17, 20, 25, 26, 31, and 41, indicated with *arrows,* have been slightly transported to the right.

which yields $F = 1$ for MET << MITT. Indeed, the drugs caffeine (no. 3), clonidine (no. 8), desipramine (no. 10), glycine (no. 18), metoprolol (no. 26), propranolol (no. 31), theophylline (no. 40), and verapamil (no. 41) were found by use of Eq. (12) in conjunction with Eqs. (1), (9), and (10) to be completely or almost completely absorbed in accord with the experimental findings ($F \geq 0.95$, Table I). In parallel, chlorpheniramine (no. 5) was theoretically predicted from Eq. (12) to be fully absorbed while the experimental value for F is 0.80 (Table I). The extensive or complete absorption of all encircled data of Fig. 4 is a plausible finding because all of them have MET values $\leq$ 10 min. As expected, these drugs are all lying in category I of QBCS (Fig. 3). Also, zidovudine (no. 42), disopyramide (no. 15), cimetidine (no. 7), and the four records of acetyl salicylic acid (No. 1) have MET values much smaller than MITT, lie either on or close to the y = x (MET = MAT) line of Fig. 4, and therefore the theoretically

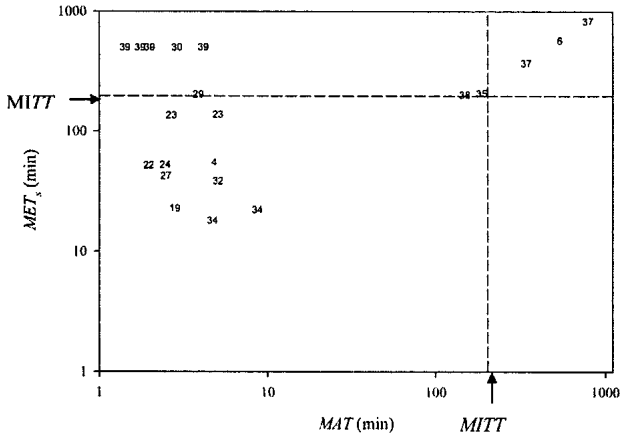

Fig. 5. MET_s vs. MAT plot for the data listed in Table I. MAT values were calculated from Eq. (9) using MITT = 199 min (12,41) and $\lambda = 5.26 \times 10^{-6}$ cm/s, which corresponds to the upper boundary (10^{-5}cm/s) of P_{app}. The *dashed lines* correspond to the MITT value.

anticipated high extent of absorption is in accord with the experimental findings (Table I).

In theory, when MET = MAT = MITT in Fig. 4, one should expect fraction of dose absorbed, $F = 0.5$ and $F < 0.5$ when MET = MAT > MITT. In fact, ranitidine (no. 33, $F = 0.5$) is in full agreement with the theoretical prediction, ganciclovir (no. 17, $F = 0.03$) and furosemide (no. 16, $F = 0.50$ or 0.61) lie, as expected, above and below the MITT bar, respectively, while atenolol's (no. 2, $F = 0.5$) five records are also in agreement with the theoretical expectations because they are scattered around the intersection point of MITT bars. Two of the mannitol (no. 25) records agree with its limited absorption ($F = 0.16$), one of them indicates $F \sim 0.5$, and the other two lead to $F > 0.5$. Lower or close to 0.5 values for F were anticipated for the two records of hydrochlorothiazide (no. 20), which exhibits, however, a higher extent of absorption, $F = 0.99$ or 0.75.

The drugs lying at the upper left-hand side of Fig. 4 exhibit dissolution-limited absorption exclusively because MAT < 10 min and MET >> MAT; therefore, MDT >> MAT in accord with Eq. (10). The positioning of diltiazem (no. 14) and hydrocortisone (no. 21) well below the MITT bar explains their high extent of absorption ($F \geq 0.89$, Table I). However, the rest of the compounds [corticosterone (no. 9), dexamethasone (no. 11), diazepam (no. 12), digoxin (no. 13), panadiplon (no. 28), and scopolamine (no. 36)] lying either close to or well above the MITT line exhibit extensive absorption ranging from 79% to 100% (Table I). This unexpected finding is most likely caused by the sink conditions, i.e., MDT >> MAT, prevailing during the intestinal absorption as justified by our calculations for all aforementioned drugs (see Fig. 4). Although experiments are quite frequently carried out under sink conditions to mimic normal absorption, a limited number of studies (39) provide such experimental evidence. Our results provide an indirect piece of evidence for this commonly accepted concept. It should be mentioned that our preliminary analysis data using differential equations to describe both dissolution (under sink and nonsink conditions) and uptake processes along the lines delineated in the Theory section agree with the postulate of sink conditions. This also applies for some heterogeneous ($q > 1$) drugs as discussed below (Fig. 5). Work is now in progress focusing on the prediction of the fraction of dose absorbed using the theoretical framework developed in this study.

The heterogeneous drugs ($q > 1$) plotted in Fig. 5 can also be considered in the light of the mean time concepts and the experimental findings for the fraction of dose absorbed (Table I). Sulfasalazine (no. 37), which exhibits both dose/solubility ratio– and permeability-limited absorption, is a category IV drug (Fig. 3), and the very limited absorption predicted on the basis of Fig. 5 (MET_s>MITT and MAT>MITT) is in accord with the experimental observation ($F = 0.13$, Table I). This also applies to chlorothiazide (no. 6), which exhibits low and variable absorption (Table I). For saquinavir (no. 35) and sulpiride (no. 38), less than 50% absorption is anticipated from Fig. 5; this also agrees with the results quoted in Table I ($F = 0.30$, $F = 0.40$ for no. 35 and no. 38, respectively).

The compounds at the left-hand side of Fig. 5 exhibit dose/solubility ratio–limited absorption exclusively because they are heterogeneous ($q > 1$) and MAT < 10 min. It should be recalled here that MDT_s refers to the fraction of dose

dissolved, Φ which is equal to $1/q$ at infinite time for a closed system (no uptake) [Eq. (2)]. Thus, the complete absorption ($F = 1$) for the drugs lying above or close to the horizontal MITT line—testosterone (no. 39), piroxicam (no. 30), indomethacin (no. 23)—is the result of the low q values (range 1–3.2) in combination with the patent sink conditions [MDT_s >> 10 MAT; Fig. 5, Eq. (11)] prevailing in the intestinal lumen. Similarly, the complete absorption of ibuprofen (no. 22) and ketoprofen (no. 24) and the almost complete absorption of phenytoin (no. 29) can be explained with the same reasoning. Although the same interpretation can be pointed out for the complete absorption of naproxen (no. 27), one should note the high q value (62.8) for this drug. An alternative explanation might be associated with an overestimation of q because the more soluble sodium salt of naproxen is used in actual practice. The limited absorption ($F = 0.40$) of griseofulvin (no. 19) is in line with its extremely high q value (133.3). The adequate but not complete absorption ($F = 0.70$ and $F = 0.80$) for carbamazepine (no. 4) and quinidine (no. 32), respectively, agree with their relatively small q values (6.61–3.08, 2.39) in conjunction with the sink conditions prevailing during the absorption process. Finally, salicylic acid (no. 34) is completely absorbed, $F = 1$ because it has a small q value (1.38), lies well below the MITT horizontal line, and is classified as a category II drug very close to the borderline with category I drugs.

Overall, the approach described for predicting extent of oral drug absorption semiquantitatively gave very good results with two notable exceptions, i.e., hydrochlorothiazide and naproxen. The validity of predictions becomes more important if one takes into account that sophisticated programs (40) or quantitative structure pharmacokinetic relationship approaches (14,18,41), focusing specifically on the prediction of fraction of dose absorbed, do not exhibit ideal predictability.

For the sake of completion, one should add some remarks regarding the approaches developed in the present work in relation to the variability of the *in vivo* processes. It is well known that pH varies down the intestine, and therefore, the dissolution rate and possibly the permeability for drugs with pH-dependent solubility will be affected. For example, weak acids exhibit lower solubility at low pH, whereas at pHs above their pK_as they are much more soluble. Therefore, the classification of weak acids or bases in the QBCS will be dependent on the pH considered. It is also very well known that there is enormous complexity in the GI tract (42) both in terms of structure and function, e.g., villi, microvilli, motility, as well as the variety of dosing conditions, e.g., fed or fasted state, fluid volume administered, etc. In this context, we used a physiologically based range for the intestinal volume, a boundary region for highly permeable drugs, while the transit flow was fixed at 199 min (12,41). Plausibly, the parameter values used should not be interpreted as the only and exact solution for the model of Fig. 1 and relevant calculations. For example, the MITT varies considerably among individuals (43,44); therefore, the MAT estimates derived from Eq. (9) are dependent on MITT value used. However, the values assigned to physiologic parameters, V, λ, MITT, used for the calculation of drug's characteristics (q, MDT, MDT_s, MAT) lead to semiquantitative predictions for F that are in agreement with the current experimental evidence available. This finding validates the scientific basis of QBCS.

CONCLUSIONS

In this study, a QBCS was developed based on the two principal biopharmaceutical properties, i.e., dose/solubility ratio and apparent permeability of the compound. This classification enabled us to point out specific characteristics for the intestinal absorption for each one of the four explicitly defined drug categories using appropriate cutoff points for both properties. The semiquantitative predictions for the extent of drug absorption based on the principles of QBCS were found to be in agreement with the experimental observations. This successful application underlines the scientific basis of QBCS and opens the way for further improvements.

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