Identification of Biowaivers Among Class II Drugs: Theoretical Justification and Practical Examples

Eleni Rinaki,[1] Aristides Dokoumetzidis,[2] Georgia Valsami,[1] and Panos Macheras[1,3]

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Purpose. To set up a theoretical basis for identifying biowaivers among Class II drugs and apply the methodology developed to nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods. The dynamics of the two consecutive drug processes dissolution and wall permeation are considered in the time domain of the physiologic transit time using a tube model of the intestinal lumen. The model considers constant permeability along the intestines, a plug flow fluid with the suspended particles moving with the fluid, and dissolution in the small particle limit. The fundamental differential equation of drug dissolution-uptake in the intestines is expressed in terms of the fraction of dose dissolved.

Results. The fundamental parameters, which define oral drug absorption in humans resulting from this analysis, are i) the formulation-related factors, dose, particle radius size, and ii) the drug-related properties, dimensionless solubility/dose ratio (1/q), and effective permeability. Plots of dose as a function of (1/q) for various particle sizes unveil the specific values of these meaningful parameters, which ensure complete absorption for Class II drugs [(1/q) < 1]. A set of NSAIDs were used to illustrate the application of the approach in identifying biowaivers among the NSAIDs.

Conclusions. The underlying reason for a region of fully absorbed drugs in Class II originates from the dynamic character of the dissolution-uptake processes. The dynamic character of the approach developed allows identification of biowaivers among Class II drugs. Several biowaivers among the NSAIDs were identified using solubility data at pH 5.0 and in fed-state–simulated intestinal fluid at pH 5.0. The relationships of formulation parameters, dose, particle radius, and the drug properties, dimensionless solubility/dose ratio (1/q), and permeability with the fraction of dose absorbed for drugs with low 1/q values [(1/q) < 1] can be used as guidance for the formulation scientist in the development phase.

KEY WORDS: absorption; biopharmaceutic classification; biowaivers; dose; dose/solubility ratio; particle size; permeability.

INTRODUCTION

The experience gained with the development (1) and implementation of the biopharmaceutics classification system (BCS) has shown that drug regulatory aspects (2–4) are benefited if are scientifically based. One of the most important advances in this field of research with a direct impact in pharmaceutical industry is the FDA guidance on biowaiver of *in vivo* bioavailability and bioequivalence studies (4). According to this guidance, petitioners can request biowaivers for highly soluble-highly permeable compounds, formulated as immediate release oral dosage forms. A drug is considered as highly permeable when more than 90% of the orally administered dose is absorbed whereas a drug is defined as highly soluble "when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0–7.5" (4). Drugs with these properties are classified in Class I of the BCS.

However, Blume, and Schug (5) suggested that Class III compounds (high solubility and low permeability) are better candidates for a waiver of bioavailability and bioequivalence studies since bioavailability is not so much dependent on the formulation characteristics but on the permeability of the compound. Besides, concerns have been arisen with respect to the class boundary of solubility and various proposals for further research have been pointed out (6). In a similar vein, Yazdanian *et al.* (7) suggested that the high solubility definition of the FDA guidance on BCS is too strict for acidic drugs. Their recommendation was based on the fact that several nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit extensive absorption and according to the current definition of the FDA guidance are classified in Class II (low soluble-high permeable) of the BCS.

An important concluding remark of the Yazdanian *et al.* (7) study refers to "an inherent limitation in the solubility classification is that it relies on equilibrium solubility determination, which is static and does not take into account the dynamic nature of absorption". Besides, the measurement of intrinsic dissolution rates (8) or the use of dissolution-absorption *in vitro* systems (9) has been suggested as more relevant to the *in vivo* drug dissolution dynamics than solubility for regulatory classification purposes. Also, Rinaki *et al.* (10) developed a quantitative version of BCS, termed QBCS, using the solubility/dose ratio as the key parameter for solubility classification since it is inextricably linked to the dynamic characteristics of the dissolution process (11). The QBCS utilizes a solubility/dose ratio, permeability plane with scientifically-physiologically based cut-off values for compound classification. A large number of drugs were classified into four explicitly defined quartiles of the plane and a borderline region. In general, the classification results were found to be in accord with the experimental observations in regard to the fraction of dose absorbed (10). However, some of the drugs classified in category II of the QBCS (or equivalently Class II of the BCS) exhibit higher extent of absorption than the theoretically anticipated value based on the relevant semi-quantitative analysis of drug absorption (10). This finding coincides with the observations of the Yazdanian *et al.* (7) study for the NSAIDs with respect to their extensive absorption and classification in Class II.

In this study, the dynamics of the two consecutive drug processes dissolution and wall permeation are considered in the time domain of the physiologic transit time. The fundamental differential equation of drug dissolution-uptake in the intestines is expressed in terms of the fraction of dose dissolved. By doing so, the key role of the dose/solubility ratio in controlling the dissolution process and by extension the absorption phenomena is once again (10,11) justified. This analysis enabled us to set up a theoretical basis for identifying biowaivers among Class II drugs. Furthermore, this analysis

[1] Laboratory of Biopharmaceutics and Pharmacokinetics, School of Pharmacy, University of Athens, Athens 15771, Greece.

[2] School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, UK.

[3] To whom correspondence should be addressed. (email: macheras@pharm.uoa.gr)

leads to the suggestion that the discrepancies with respect to the classification of several drugs in Class II and their extensive absorption are due to the static nature of BCS and QBCS.

THEORETICAL

Our analysis relies on the tube model of the intestinal lumen used by Oh *et al.* (12) for the development of BCS (1). We transformed the set of differential equations with independent variable the axial intestinal distance of the tube model (12). The system of the differential equations was expressed in terms of dose, solubility/dose ratio, particle radius size, effective permeability, fraction of dose dissolved and fraction of dose absorbed. By doing so, we are not dealing any more with the normalized parameters e.g., dissolution number and absorption number (12). Instead, we are able to analyze the GI absorption phenomena using the meaningful parameters quoted above.

The model (12) considers constant permeability along the intestines, a plug flow fluid with the suspended particles moving with the fluid, and dissolution in the small particle limit. The radius of the spherical drug particles, r_p, and the concentration of dissolved drug in the intestinal tract, C_L, is modeled (12) by a system of differential equations, with independent variable the axial intestinal distance, z, which is considered to be proportional to time as the fluid flow rate is constant:

$$\frac{dr_p}{dz} = -\frac{D \cdot \pi R^2}{Q \cdot \rho} \cdot \frac{C_s - C_L}{r_p} \tag{1}$$

$$\frac{dC_L}{dz} = \frac{D \cdot (N_0 / V_0) \cdot 4\pi^2 R^2}{Q} \cdot r_p (C_s - C_L) - \frac{P_{eff} \cdot 2\pi R}{Q} \cdot C_L \tag{2}$$

where D is the diffusion coefficient of the drug, ρ is the density of the solid drug, R is the radius of the intestinal lumen, C_S is the solubility of the drug, Q is the volumetric flow rate, N_0 is the number of drug particles in the dose, V_0 is the luminal volume, and P_{eff} is the effective permeability of the drug.

By multiplying Eqs. 1 and 2 with $L/MITT$, where L is the length of the tube and $MITT$ is the mean intestinal transit time, and simplifying, we rewrite them in respect to time:

$$\frac{dr_p}{dt} = -\frac{D}{\rho} \cdot \frac{C_S - C_L}{r_p} \tag{3}$$

$$\frac{dC_L}{dt} = \frac{3D \cdot M_0}{r_0^3 \cdot \rho \cdot V_0} \cdot r_p (C_s - C_L) - \frac{2P_{eff}}{R} \cdot C_L \tag{4}$$

where M_0 is the dose and r_0 is the initial radius of the drug particles.

Dividing both sides of Eqs. 3 and 4 by M_0/V_0, we eliminate C_L and C_s, replacing them with the fraction of dose dissolved, Φ, and the dimensionless dose-solubility ratio, q $(q = M_0/C_sV_0)$, respectively.

$$\frac{dr_p}{dt} = \begin{cases} -\dfrac{D\, M_0}{\rho\, V_0 r_p}\left(\dfrac{1}{q} - \Phi\right) & \text{if } r_p > 0 \\ 0 & \text{if } r_p = 0 \end{cases} \tag{5}$$

$$\frac{d\Phi}{dt} = \frac{3D}{\rho V_0} \frac{r_p M_0}{r_0^3} \left(\frac{1}{q} - \Phi\right) - \frac{2P_{eff}}{R} \Phi \tag{6}$$

We also consider a mass balance equation for the fraction of dose absorbed, F at the end of the tube, similar to that used in Ref. 12:

$$F = \frac{M_0 - M_{solid} - M_{dissolved}}{M_0} \tag{7}$$

where M_{solid} and $M_{dissolved}$ denote the mass of the undissolved and dissolved drug, respectively at the end of the intestine. Eq. 7 simplifies to Eq. 8:

$$F = 1 - \left(\frac{r_p}{r_0}\right)^3 - \Phi \tag{8}$$

where r_p, and Φ in Eq. 8 refer to their values at $t = MITT$.

The system of differential equations 5 and 6 was solved numerically in Mathematica for various values of the parameters r_0, P_{eff}, M_0, and $1/q$ to get estimates for r_p and Φ at time $t = MITT = 199$ min (13). These values were further used to estimate F from Eq. 8. Typical values were used for the constants D (1×10^{-4} cm^2/min), ρ (1000 mg/ml), V_0 (250 ml), and R (1 cm) (12).

RESULTS AND DISCUSSION

The system of Eqs 5, 6, and 8 describes the intestinal drug absorption as a function of four fundamental drug/formulation properties, dose M_0, solubility/dose ratio (1/q), initial radius of the particles r_0 and effective permeability, P_{eff}. However, one can assess, using Eqs 5, 6, and 8, if practically complete absorption ($F = 0.90$) of category II drugs of the QBCS is feasible by setting the permeability in Eq. 6 equal to $P_{eff} = 1.2 \times 10^{-2}$ cm/min, which is equivalent (14) to the upper boundary limit, $P_{app} = 1 \times 10^{-5}$ cm/s of the apparent permeability borderline region of QBCS (10). The correlations developed (14) between effective permeability, P_{eff}, values determined in humans and the Caco-2 system, allowed the conversion of the Caco-2 to P_{eff} estimates. Figure 1 shows the simulation results in a graph of M_0 versus $1/q$ for three-particle sizes r_0: 10, 25, and 50 μm. The shaded areas above the lines for each one of the particle sizes considered correspond to drug/formulation properties M_0, $(1/q)$ which ensure complete absorption, that is, $F > 0.90$ for drugs classified in category II of the QBCS (10). Plausibly, this area becomes larger as the initial radius r_0 of the spherical particles becomes smaller. Also, the correlation of M_0 with $(1/q)$ weakens upon reduction of r_0. It is worth noting that for a given value of $1/q$, a higher fraction of dose is absorbed from a larger than a smaller dose. This finding is reasonable since the common $1/q$ value ensures higher solubility for the drug administered in a larger dose. For example, visual inspection of Fig. 1 reveals that when $(1/q) = 0.4$ and $r_0 = 25$ μm, doses higher than ~200 mg can be fully absorbed.

The M_0 versus $(1/q)$ plot can be also used to assess whether or not a Class II drug can be fully absorbed over the therapeutic dose range used. Figure 2 shows two such drug

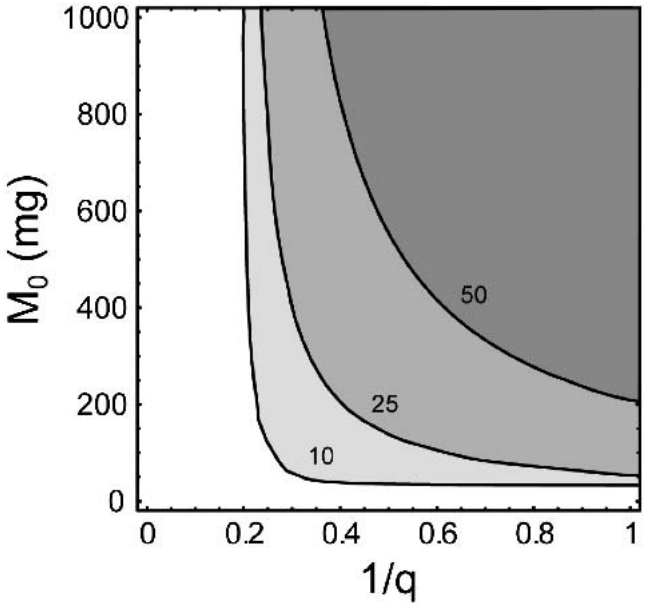

Fig. 1. Plot of dose, M_0, versus the dimensionless solubility/dose ratio, $1/q$. The curves indicate 90% absorption for three radius sizes 10, 25, and 50μm assuming $P_{eff} = 1.2 \times 10^{-2}$ cm/min. Since the assigned value to P_{eff} corresponds to the upper boundary limit [expressed in apparent permeability values (14)] of the borderline permeability region of QBCS (10), compounds of category II of QBCS exhibiting complete absorption are located in the shaded areas.

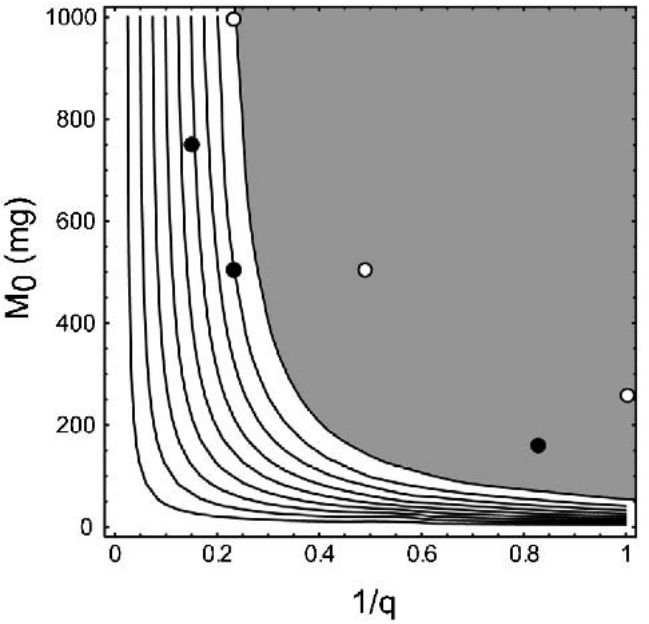

Fig. 2. Plot of dose, M_0, versus the dimensionless solubility/dose ratio, $1/q$. The curves indicate stepwise increase of 10% of absorption from left to right (range 10–90%) for parameter values $r_0 = 25$ μm and $P_{eff} = 1.2 \times 10^{-2}$ cm/min. The open circles denote a drug administered in doses 250, 500, 1000 mg with solubility 1 mg/ml while the black dots denote a drug administered in doses 150, 500, 750 mg with solubility 0.5 mg/ml. Drugs located in the shaded region are fully absorbed ($F > 0.90$) Class II drugs.

examples administered in doses (250, 500, 1000 mg) and (150, 500, 750 mg) with solubility 1 and 0.5 mg/ml, respectively; common values for the particle radius, $r_0 = 25$ μm and the effective permeability, $P_{eff} = 1.2 \times 10^{-2}$ cm/min for both drugs/formulations were considered. As it can be seen only the lower dose of 150 mg of the lower solubility drug can be completely absorbed while all three doses of the more soluble drug exhibit complete (250 and 500 mg) or almost complete (1000 mg) absorption, Fig. 2.

The underlying reason for a region of fully absorbed drugs in category II of the QBCS, shown in Figs. 1 and 2, originates from the dynamic character of the dissolution-uptake processes. A global measure of the interplay between dissolution and uptake can be seen in Fig. 3, which shows the mean dissolution time, (MDT) in the intestines as a function of the effective permeability for a Class II drug [$(1/q) = 0.2$]. As a matter of fact, the uptake of drug promotes indirectly the dissolution of drug and this is reflected on the value of MDT. This parameter is calculated as the area under the curve (AUC) of the time profile of the undissolved fraction of dose in the intestinal lumen. Clearly, the MDT value is reduced as effective permeability increases, Fig. 3. Needless to say that the MDT would be infinite for this particular drug [$(1/q) = 0.2$] if dissolution was considered in a closed system ($P_{eff} = 0$) (11). The plot of Fig. 3 verifies this observation since $MDT \to \infty$ as $P_{eff} \to 0$.

Figure 4 shows the classification of the NSAIDs, reported by Yazdanian *et al.* (7) and listed in Table I, in the solubility/dose ratio ($1/q$) apparent permeability (P_{app}) plane of the QBCS (10). The four plots of Fig. 4 correspond to solubility data at pH 1.2, 5.0, 7.4, and fed-state–simulated intestinal fluid at pH 5.0 and indicate that i) all NSAIDs are highly permeable since most of them lie above the horizontal line or in the upper part of the borderline region of permeability, and ii) as pH increases from 1.2 to 7.4, the NSAIDs move from Class II to Class I (the nomenclature of Classes in BCS according to the FDA guidance (4) and QBCS (10) is identical in terms of the dose/solubility classification). Figure 4 demonstrates that with the exception of ibuprofen (no. 9),

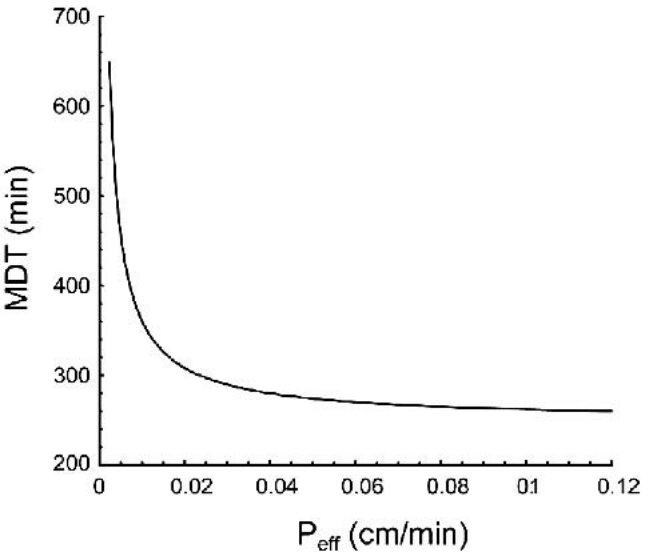

Fig. 3. The mean dissolution time (MDT) in the intestines as a function of P_{eff} for parameter values: $M_0 = 10$ mg, $(1/q) = 0.2$, and $r_0 = 10$ μm. MDT is calculated as the area under the curve of the undissolved fraction of dose using the integral, $MDT = \int_0^\infty (r_p/r_0)^3 dt$ in conjunction with Eqs. 5 and 6.

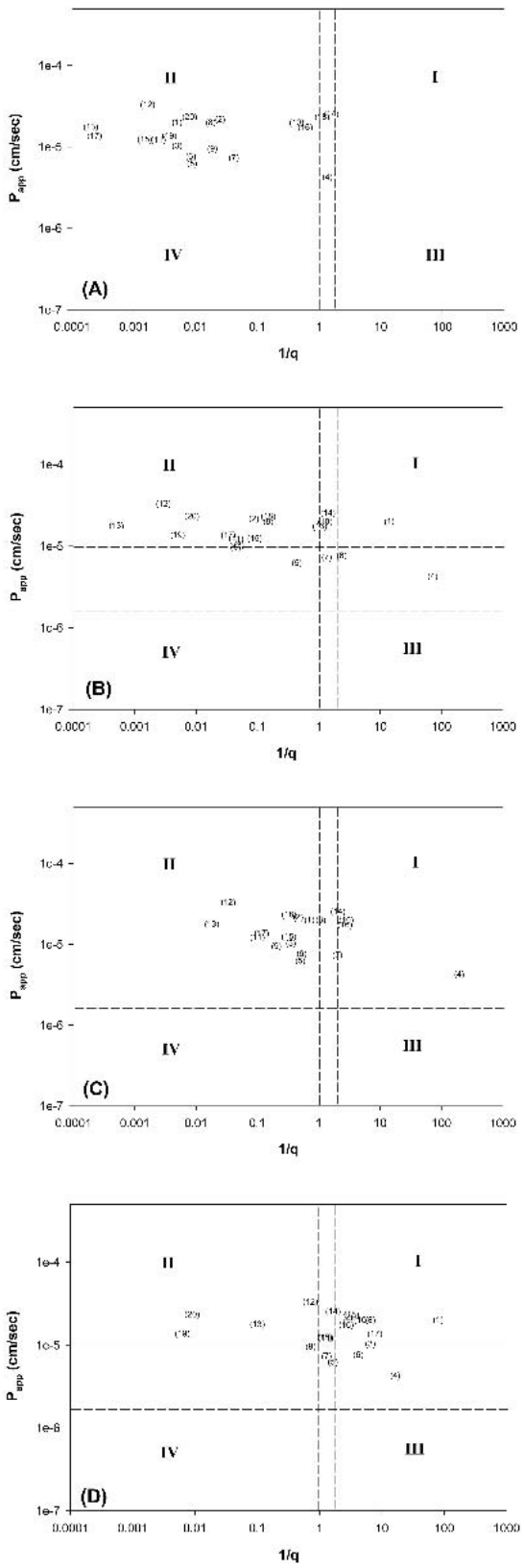

Fig. 4. The classification of drugs (7) listed in Table I in the (solubility/dose ratio, apparent permeability) plane of the QBCS (10). Solubility values for the calculation of *1/q* values correspond to pH 1.2 (A), pH 5.0 (B), fed-state–simulated intestinal fluid, pH 5.0 (C), and pH 7.4 (D). The roman numerals (I–IV) denote the four drug classes (10).

Table I. Dose and Human Bioavailability Data of NSAIDs (Ref. 7)

No.	Drug	Highest dose (mg)	% Human bioavailability
1	Diclofenac	50	54
2	Etodolac	400	>80
3	Indomethacin	50	98
4	Ketorolac	20	100
5	Sulindac	200	88
6	Tolmetin	600	>90
7	Fenoprofen	600	85
8	Flurbiprofen	100	92
9	Ibuprofen	800	>80
10	Ketoprofen	75	100
11	Naproxen	500	99
12	Oxaprozin	600	95–100
13	Mefenamic acid	250	Rapidly absorbed
14	Acetylsalicylic acid	975	68 (unchanged drug)
15	Diflunisal	500	90
16	Salicylic acid	750	100
17	Meloxicam	15	89
18	Piroxicam	20	Rapidly absorbed
19	Celecoxib	200	—
20	Rofecoxib	25	93

oxaprozin (no. 12), mefenamic acid (no. 13), and the two nonacidic NSAIDs [celecoxib (no. 19) and rofecoxib (no. 20)], the remaining compounds can be classified as Class I drugs relative to solubility at pH 7.4, (Fig. 4D). This observation is in full agreement with the findings of Yazdanian *et al.* (7).

Since most of the drugs are classified in Class II relative to solubility values in buffer or fed state simulated intestinal fluid both at pH 5.0, (Figs. 4B and 4C), a series of simulations based on Eqs 5, 6, and 8 were carried out to examine whether or not the extensive absorption, Table I, of the NSAIDs can be explained. To this end, these experimental data are coplotted in Fig. 5 with the curves generated from Eqs 5, 6, and 8 assuming $F = 0.90$, radius sizes 10 and 25 μm, and assigning $P_{eff} = 2.0 \times 10^{-2}$ cm/min which corresponds (14) to the mean ($P_{app} = 1.68 \times 10^{-5}$ cm/s) of the apparent permeability values of the NSAIDs (7). Visual inspection of the plot based on the solubility at pH 5.0, Fig. 5A, reveals that only the absorption of sulindac (no. 5, $F = 0.88$) can be explained by the generated curve adhering to 25 μm while flurbiprofen (no. 8, $F = 0.92$) lies very close to the theoretical line of 10 μm.

On the contrary, the extensive absorption of tolmetin (no. 6, $F > 0.90$), sulindac (no. 5, $F = 0.88$), etodolac (no. 2, $F > 0.80$), diflunisal (no. 15, $F = 0.90$), ibuprofen (no. 9, $F > 0.80$), using the corresponding doses listed in Table I, can be explained on the basis of the solubility data in fed state simulated intestinal fluid at pH 5.0 in conjunction with the curve generated assigning $r_o = 25$ μm, Fig. 5B; also, the curve generated from $r_o = 10$ μm and the solubility in the biorelevant medium of indomethacin (no. 3) and piroxicam (no. 18) interpret their extensive absorption. Although naproxen (no. 11, $F = 0.99$) lies very close and meloxicam (no. 17, $F = 0.89$) in the neighborhood of the theoretical line of 10 μm, oxaprozin (no.12, $F = 0.95$ to 1.0) is located far away from the simulated curve of 10 μm, Fig. 5B. Special caution is required for the interpretation of diclofenac (no. 1, $F = 0.54$) which lies between the theoretical curves of 10 and 25 μm in Fig. 5B.

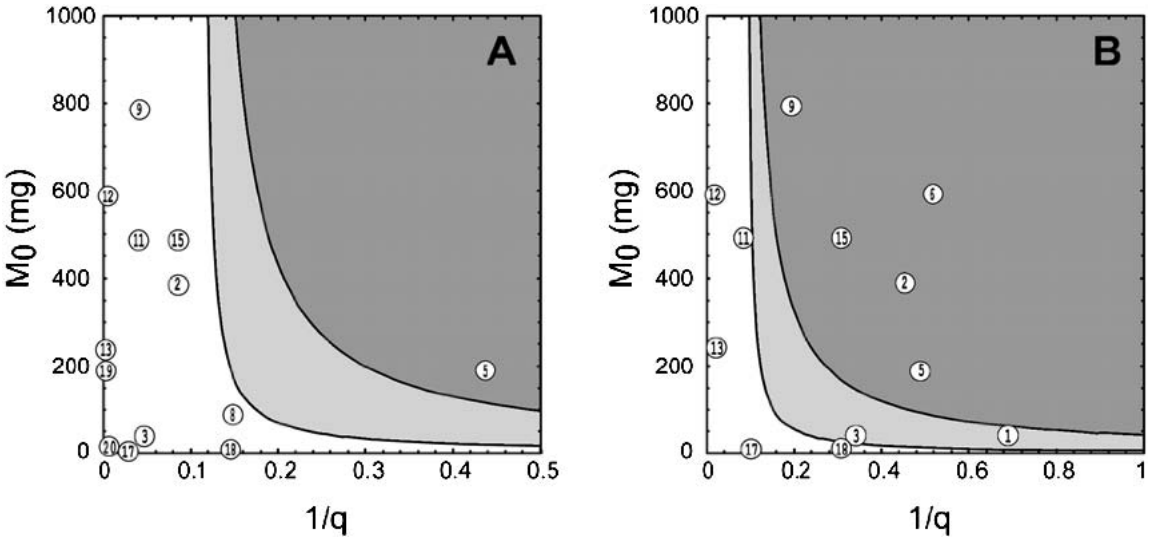

Fig. 5. Plot of M_0 versus $(1/q)$, for the experimental data classified in Class II, of Figs. 4B and 4C. The curves denote 90% absorption for two particle sizes (from left to right 10 and 25 μm) assigning $P_{eff} = 2 \times 10^{-2}$ cm/min which corresponds (14) to the mean, $P_{app} = 1.6 \times 10^{-5}$ cm/s of the Caco-2 permeability values of the data (7). Drugs located in the shaded regions are fully absorbed ($F > 0.90$) Class II drugs. Key: Fig 4B Class II data (A); Fig 4C Class II data (B).

Some reports suggest that diclofenac undergoes first-pass metabolism ($F = 0.60$) while some others refer to absolute bioavailability, 0.90 (15). Explicit data for the extent of absorption of mefenamic acid (no. 13), Fig. 5B, are not reported (7) while solubility data in fed-state–simulated intestinal fluid at pH 5.0 for the two nonacidic NSAIDs, celecoxib (no. 19) and rofecoxib (no. 20) have not been measured (7).

Overall, the extensive absorption and the solubility data in the biorelevant medium of the NSAIDs nos. 2, 3, 5, 6, 9, 15, and 18 in conjunction with the simulated curves of M_0 versus $1/q$ plot, Fig. 5B, substantiate the view that biowaivers can be found among Class II drugs. Relying on a global consideration of solubility data in all media studied (7), one can also anticipate that solubility data of NSAIDs in, for example, pH 6.0 would also lead to similar results, that is, Class II classification and justified extensive absorption on the basis of M_0 versus $1/q$ plot. Therefore, this work does not support the proposal for solubility measurements at pH > 5 for acidic drugs (7) but rather points out the importance of the dynamic nature of the absorption processes for those drugs classified in Class II. It should be also noted that a conservative approach was used in the present work for the interpretation of the NSAIDs' extensive absorption, Table I. In fact, only the highest doses of drugs were analyzed while the duration of absorption was restricted to the mean intestinal transit time, 199 min (13), that is, absorption from stomach or large intestine was not taken into account. Besides, the lower value for the volume of the intestinal content, 250 ml (6,7,10) was used in the simulations. This means that drugs like naproxen (no. 11) and meloxicam (no. 17) in Fig. 5B would also be interpreted if higher values of the two physiologic parameters for time and volume had used.

CONCLUSIONS

One of the most significant results of the present work is the elucidation of the relationships between the fraction of dose absorbed and dose for drugs with low solubility/dose ratio, (1/q)<1. The graphs in Fig. 2 unveil that passively absorbed drugs with low dimensionless solubility/dose ratio, [(1/q) <1], used in various doses, exhibit dose-dependent absorption of non-Michaelian type. Obviously, this does not apply for drugs/formulations with (1/q) >1 since Class I drugs are fully absorbed while for Class III drugs, absorption is permeability- and not solubility/dose ratio-limited. Thus, the value of 1/q is not only critically important for biopharmaceutic classification purposes (10) but also plays a key role in determining the extent of absorption and whether or not absorption of passively absorbed drugs exhibits dose dependency in the range of doses used. These results shed light on the old problem of the non-linear oral absorption produced by the low solubility/dose ratio of drug compound (16–18).

The dynamic model developed and the analysis presented highlights the importance of the parameters dose, solubility/dose ratio, particle size and effective permeability, P_{eff} for drug intestinal absorption phenomena. An estimate for the latter parameter can be derived from the correlations developed (14) between effective permeability, P_{eff}, values determined in humans and the Caco-2 system. This means that the relationships of these meaningful parameters with the fraction of dose absorbed for drugs with low solubility/dose ratio, [(1/q) < 1], can be used as a guidance for the formulation scientist in the development phase. Moreover, these relationships set up the theoretical basis for identifying biowaivers among Class II drugs in the framework of the QBCS (10). Consequently, consideration should be given to the dynamic aspects of intestinal absorption for biopharmaceutic drug classification.

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