New Frames of Reference for Mapping Drugs in the Four Classes of the BCS and BDDCS into Regions with Clear Boundaries

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The Biopharmaceutics Classification System (BCS), adopted by drug regulatory agencies for oral drug products approval, classify drug substances into four classes according to their aqueous solubility and epithelial membrane permeability. In a solubility-permeability frame of reference, drugs on the boundaries of the four regions depicting the four drug classes are problematic to classify. To remove the fuzziness in the boundaries of the solubility-permeability frame of reference, a dataset of 85 oral drugs from all four classes of BCS are mapped into new frames of references in which the coordinate axes are based on the rates of dissolution, systemic elimination (metabolism), and membrane permeation.
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Introduction

The Biopharmaceutics Classification System (BCS), introduced in 1995 by Amidon and his colleagues to classify drug substances into four classes, has been a valuable tool that facilitates oral drug product development and has had an increasing impact on regulatory practice. Because of its validity and vast applicability, BCS has been adopted by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the World Health Organization (WHO) to set bioavailability and bioequivalence standards in immediate-release (IR) oral drug products approval,[1–5] and has been the subject of extensive research in recent years.[6–10]

In BCS, drug substances are grouped in four classes, Class I: substances of high solubility and high permeability, Class II: substances of low solubility and high permeability, Class III: substances of high solubility and low permeability, and Class IV: substances of low solubility and low permeability, with solubility and permeability being aqueous solubility and intestinal membrane permeability, respectively.

The solubility* of a substance is equal to the highest concentration of the substance in solution in equilibrium with the concentration of the undissolved substance at a given temperature and pressure. When the drug substance is an active pharmaceutical ingredient (API) of a drug product administered orally, its solubility is determined, in addition to equilibrium between the concentration of the substance in solution and the concentration of the undissolved substance, by the interaction of the substance under investigation with other substances, other APIs, and excipients. A drug substance or an API is considered highly soluble when the highest dose strength is soluble in 250 mL or less of an aqueous medium with pH in the range 1–7.5, as per FDA. For EMA, "a drug substance is considered highly soluble if the highest single dose administered as immediate release formulation(s) is completely dissolved in 250 mL of buffers within the range of pH 1–6.8 at 37 ± 1°C." Finally, for WHO an API is considered highly soluble when the highest dose recommended by WHO (if the API appears on the WHO Model List of Essential Medicines) or highest dose strength available on the market as an oral solid dosage form (if the API does not appear on the WHO Model List of Essential Medicines) is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8. The pH-solubility profile of the API should be determined at 37 ± 1°C in aqueous media.

The intestinal membrane permeability of a drug is determined by several methods such as, (a) pharmacokinetic studies in human subjects, in conjunction with mass balance, and bioavailability studies, (b) *in vivo* or *in situ* intestinal perfusion in suitable animal models, (c) *in vitro* permeability methods using excise intestinal tissues, (d) permeation of suitable epithelial cells, for example, Caco-2 or TC-7 cells, and (e) *in silico* permeability determination. Intestinal permeability measurements are time consuming and are not routinely made. According to FDA guidance, "in the absence of evidence suggesting instability in the gastrointestinal tract (GIT), a drug substance is considered highly permeable when the extent of absorption in humans is determined to be equal or greater than 90% of an administered dose, based on mass balance or in

*The characterization of solubility as a thermodynamic property is rather unfortunate as thermodynamics deals with systems in equilibrium rather than in transition.

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comparison to intravenous reference dose." EMA defines that "complete absorption is considered to be established where measured extent of absorption is $\geq 85\%$ and it is generally related to high permeability. Reported bioequivalence between aqueous and solid formulations of a particular compound administered via the oral route may be supportive as it indicates that absorption limitations due to (immediate release) formulation characteristics may be considered negligible. Well performed in vitro permeability investigations including reference standards may also be considered supportive to in vivo data." According to WHO, when an API is absorbed to an extent of 85% or more, it is considered to be "highly permeable." The permeability criterion was relaxed from 90% in the FDA guidance to 85% in the WHO "multisource document." Some examples of APIs now included in BCS Class I that were previously considered to be in Class III are paracetamol, acetylsalicylic acid, allopurinol, lamivudine, and promethazine.[11]

The FDA has utilized the BCS into formulating guidelines for waivers of *in vivo* bioavailability (BA) and bioequivalence (BE) testing for IR solid dosage forms of drug in Class I, which are drugs of high solubility and high permeability. This type of drug, in addition to high solubility and high permeability, exhibits rapid dissolution. Thus, a decision for a waiver of *in vivo* BA/BE testing is made on three characteristics, solubility, a thermodynamic, or a thermostatic rather property, permeability, a transport property, and dissolution rate, a kinetic attribute. It has been mentioned earlier that permeability is associated with absorption, the rate of which also depends on several transport processes, including dissolution, absorption, membrane permeation, and elimination (metabolism or excretion), which determine the spatiotemporal evolution of the drug substance concentration in the GIT, when taken orally.

A basic premise of the BCS is that if two drug substances yield the same dissolution profiles along the GIT, they will result in the same plasma profile after oral administration. The drug substances that show similarity of their dissolution profiles are termed bioequivalent.[1] For IR solid oral dosage formulations for which similarity of concentration profiles in the GIT has been ensured, the API(s) of the substance under investigation and the comparator drug maybe listed in the WHO prequalification of medicines program (PQP) and expensive and time-consuming *in vivo* BA and BE studies are waived off in favor of *in vitro* dissolution studies. BCS provides biowaivers for Classes I, II, and III drug substances, under certain provisos.

Class I drugs exhibit high absorption and solubility and the rate limiting step for absorption is dissolution, and, in case of very rapid dissolution, gastric emptying. Class II drugs have high absorption but low solubility, and drug dissolution is the rate limiting step for absorption, except in case of a very high dose number. Peptides and proteins constitute part of Class III and technologies handling such materials are on a rise now days. Finally, Class IV drugs exhibit a lot of problems for effective oral administration. Fortunately, extreme examples of these compounds are the exception rather than the rule and are rarely developed and reach the market, while the route of choice for administering such drugs is parenteral, with the formulation containing solubility enhancers.

In 2005, Wu and Benet[12] drew attention to drug elimination through metabolism or excretion, a transport process as important as dissolution, absorption and intestinal membrane permeation, and proposed, as a modification of BCS, the Biopharmaceutics Drug Disposition Classification System (BDDCS) which provides a very simple surrogate for intestinal membrane permeability. The basic concept of BDDCS was derived from observations that the great majority of BCS compounds with high permeability (Classes I and II) are primarily eliminated by metabolism, whereas the great majority of low permeability (Classes III and IV) are primarily eliminated unchanged into the urine and/or bile. Benet, Amidon, and several of their colleagues[13] proposed that "regulatory agencies add the extent of drug metabolism (i.e., $\geq$90% metabolized) as an alternate method for the extent of drug absorption (i.e., $\geq$90% absorbed) in defining Class I drugs suitable for a waiver of *in vivo* studies of bioequivalence."

The differences between BCS and BDDCS in terms of purpose and basis have been reviewed and analyzed in several articles.[13–15] The purpose of BCS is to facilitate biowaivers of *in vivo* bioequivalence studies for drugs that exhibit no significant intestinal absorption problems, while the purpose of BDDCS is to predict drug disposition of new molecular entities (NMEs) as well as potential drug–drug interactions for NMEs and drugs on the market with respect to the intestine and liver.

The work presented here aims at providing a unified frame of reference in terms of one-type characteristics, for example, all kinetic constants of rate processes, to better delineate the boundaries of the four classes in BCS.

Materials and Methods

Drug data base

A list of orally administered drugs from the literature that have been classified, based on their solubility and intestinal permeability, and have reached the market has been compiled and is presented in Table 1. The use of a larger dataset was not feasible due to more than one missing estimates for the used properties, especially for Class IV drugs. When more than one oral dose is used, the value from "Annex 8. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release" was used. In this list of 85 drugs, 60% are found to belong in the same BCS (Latin number) and BDDCS (Arabic number) class, according to literature. The remaining 40% are "problematic," as they seem to belong to more than one class or to different BCS and BDDCS classes, according to literature.

A mass balance model

Amidon and his colleagues, who introduced the BCS, from its early inception, utilized mass balance models with linear transfer kinetics[16,17,23–26] to rationalize drug classification into four classes. In the present work, the same approach as that of Amidon and his colleagues is followed to delineate the boundaries of the drug classes in BCS.

The physical model of the GIT adopted in the present work is shown in Figure 1. The oral dosage form with drug concentration c_0 enters the GIT when the stomach empties. Several mass-transfer processes, denoted by their rate constants, take place in the GIT. The oral dosage form undergoes dissolution (k_d) by the gastric fluids in the GIT lumen and the drug concentration reaches its bulk value c_g. The drug in the GIT lumen is adsorbed (k_a) onto the epithelial wall membrane, where its concentration reaches a value c_b, and undergoes degradation (k_l). The absorbed drug permeates (k_e) the epithelial membrane and enters the systemic circulation where the drug concentration reaches the value c_b. The drug in the plasma is

Table 1. Drug Data Base from the Literature and Their BCS and BDDCS Classification

Drug Substances	BCS Class[a]	BDDCS Class[b]
Caffeine	I	1
Chlorpheniramine	I	1
Desipramine	I	1
Dexamethasone	I	1
Estradiol	I	1
Metoprolol	I	1
Propranolol	I	1
Scopolamine	I	1
Imipramine	I	1
Nicotine	I	1
Timolol	I	1
Labetolol	I	1
Prazosin	I	1
Lidocaine	I	1
Sildenafil	I	1
Zidovudine	I, III	1
Ethosuximide	I, III	1
Theophylline	I, III, IV	1
Propylthiouracil	III, IV	1
Acetaminophen	III, IV	1
Acetylsalicylic acid	III, IV	1
Omeprazole	II	1
Chlorpromazine	II	1
Ketoprofen	II	1
Quinidine	III	1
Sumatriptan	III	1
Minoxidil	III	1
Disopyramide	I, III	1
Diazepam	I, II	1
Diltiazem	I, II	1
Verapanil	I, II	1
Carbamazepine	II	2
Griseofulvin	II	2
Indomethacine	II	2
Ibuprofen	II	2
Amprenavir	II	2
Naproxen	II	2
Phenytoin	II	2
Piroxicam	II	2
Praziquantel	II	2
Dipyridamole	II	2
Warfarin	II	2
Domperidone	II	2
Telmisartan	II	2
Citalopram	II	2
Lamotrigine	II	2
Nevirapine	II	2
Thiabendazole	II	2
Felodipine	II	2
Losartan	I, III	2
Glipizide	II, IV	2
Nelfinavir	II, IV	2
Ritonavir	II, IV	2
Sulfamethoxazole	II, IV	2
Sulfasalazine	II, IV	2
Saquinavir	I, III, IV	2
Ganciclovir	III	3
Ranitidine	III	3
Atenolol	III	3
Cimetidine	III	3
Erithromycin	III	3
Gabapentin	III	3
Enalaprilat	III	3
Cefadroxil	III	3
Lamivudine	III	3
Lisinopril	III	3
Pirenzepine	III	3
Lincomycin	III	3
Cephalexin	III	3
Cefradine	III	3
Cetirizine	III	3
Fexofenadine	III	3
Guanfacine	I	3
Sotalol	I	3
Clonidine	I	3
Amiloride	I	3
Hydrochlorothiazide	III, IV	3
Methotrexate	III, IV	3
Amoxicillin	I, III, IV	3
Sulpiride	IV	3
Chlorothiazide	IV	4
Furosemide	IV, II	4
Amphotericin B	IV	4
Ciprofloxacine	III, IV	3, 4
Acyclovir	III, IV	3, 4

[a]The BCS classification of the drug substances is from several bibliographic resources.[16–21]
[b]The BDDCS classification of the drug substances is from several bibliographic resources.[13,21,22]

subject to systemic elimination (k_{el}) which includes both metabolism and excretion of metabolites.

The mass balance equations that describe the fate of the drug from the oral dosage forms in Figure 1 read as follows

$$V_g\left(\frac{\partial c_g}{\partial t}+\frac{UA_{gc}}{V_g}\frac{\partial c_g}{\partial x}\right)=k'_d A_{ap}(c_s-c_g)-P_{ap}A_gA_g-UA_{gc}c_g \quad (1)$$

in GIT lumen

$$V_e\frac{dC_e}{dt}=k'_a c_g A_e-P_e A_{ex}(c_e-c_b) \text{ in epithelial membrane} \quad (2)$$

$$V_b\left(\frac{\partial c_b}{\partial t}+\frac{U_b A_{bc}}{V_g}\frac{\partial c_b}{\partial x}\right)=P_e A_b(c_e-c_b)-U_b A_{bc}c_b \quad \text{in plasma} \quad (3)$$

where U and U_b are the axial velocity flow of the liquid in the GIT lumen and in the blood vessels of a layer attached to the epithelium membrane, respectively, c_g is the drug concentration in the GIT lumen in g/L, c_s the drug saturation solubility in g/L, c_e the concentration of the drug, absorbed on the epithelium membrane, in g/L, and c_b the drug concentration in plasma in g/L. A_g, A_{gc}, and V_g are the GIT lumen surface area, its cross-sectional surface area, and its volume, respectively; A_e, A_{ex}, and V_e are the epithelial membrane surface area on the side of GIT, the same surface area on the side of blood-vessel layer, and the epithelial membrane volume, respectively; and A_b, A_{bc}, and V_b are the blood-vessel layer surface area on the side of the epithelial membrane, its cross-sectional surface area, and its volume, respectively.

The above mass balance system leads to

$$\frac{dC_g}{dt}=k_d(c_s-c_g)-k_a c_g-k_l c_g \text{ in GIT lumen} \quad (1')$$

$$\frac{dC_e}{dt}=K_a c_g-k_e(c_e-c_b) \text{ in epithelial membrane} \quad (2')$$

$$\frac{dC_b}{dt}=K_e(c_e-c_b)-k_{el}c_b \text{ in plasma} \quad (3')$$

The rate constants of the various processes are determined as follows. Dissolution is modeled according to Noyes–Whitney stagnant diffusion layer,[27] and its rate constant is given by

$$k_d=DA_{dp}/h_{dl}V_g \ \left(s^{-1}\right) \quad (4)$$

where D is the drug diffusivity in water (cm^2/s), A_{dp} the surface area of the drug particle, h_{dl} the thickness of the stagnant

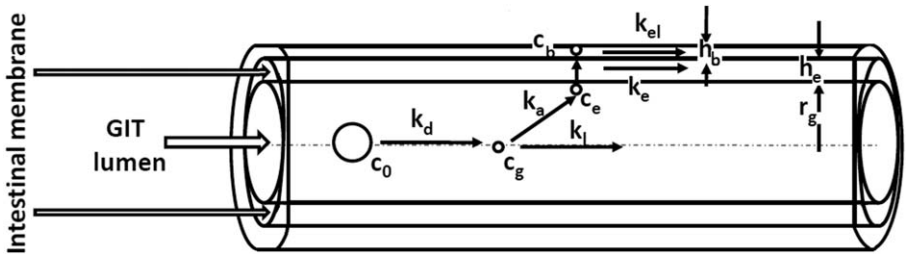

Figure 1. The fate of a drug from its oral dosage form.

diffusion layer, and V_g the volume of liquid in the GIT. The drug diffusivity, D, is estimated either from the Stokes–Einstein equation[28]

$$D = kT/f \tag{5a}$$

where k is the Boltzmann constant, T the temperature, and f the drag coefficient which for a spherical molecule is $f = 6\pi r_m \mu$ (r_m is the hydrodynamic radius of the molecule and μ is the viscosity of the fluid), or from the empirical relation[29]

$$\log D = -4.131 - 0.4531\ \log \mathrm{MW} \tag{5b}$$

where MW is the molecular weight of the drug.[30] The drug particle is assumed to be spherical with radius $r_{dp} = 2.5 \times 10^{-3}$ cm, the diffusion layer thickness is $h_{dl} = 2 \times 10^{-3}$ cm, and the liquid volume in the GIT lumen $V_g = 0.25$ l.[17,18] From Eq. 1–1′, $k_d = 4k'_d\, r_{dp}^2/r_g^2 L$, with L the GIT lumen length.[6]

The adsorption rate constant is given by

$$k_a = P_{ap} A_g / V_g = 2P_{ap}/r_g \quad (\mathrm{s}^{-1}) \tag{6}$$

where P_{ap} is the apparent permeability in cm/s,[17,31–33] and $r_g = 1$ cm is intestinal tube radius.[6,17,18]

The rate constant of elimination in the GIT lumen is estimated from

$$k_l = \frac{U}{L} = \frac{7}{t_{si}} \quad (\mathrm{s}^{-1}) \tag{7}$$

where, $t_{si} = 11{,}952$ s is the mean small intestinal transit time.[24]

The rate constant of epithelial membrane permeation is given by

$$k_e = P_e \left(\frac{1}{r_g} + \frac{1}{h_e} \right) \tag{8}$$

where $P_e = K_{o/w} D/h_e$ in cm/s is the epithelial wall membrane permeability in cm/s, $K_{o/w}$ is the octanol/water partition coefficient,[18,30] $h_e = 1.5 \times 10^{-3}$ cm is the epithelial wall thickness.[18,34,35] Also, $K_a = k_a r_g/2h_e$.

The rate constant of systemic elimination is given by[36,37]

$$k_{el} = (U_b\ A_{bc})/V_b = \ln 2/t_{1/2,p} \tag{9}$$

where $t_{1/2,p}$ is the plasma elimination half time in s.[30] Also, $K_e = k_e r_g h_e / r_e h_b$, where h_b is the blood-vessel layer thickness.

Because the mean GIT emptying time or mean degradation time, $t_l = 1/k_l = 1080$ s,[38] is much greater than the dissolution, $t_d = 1/k_d$, or diffusion time, $t_D = r_l^2/D \approx 0.4$ s $\approx t_d$, and the mean adsorption time, $t_a = 1/k_a$, and the former is smaller than the latter, dissolution seems to be the rate-controlling process in the lumen of GIT. By similar reasoning, permeation of the epithelial membrane and systemic elimination seem to be the rate-controlling processes in the epithelium of GIT and the blood-vessel layer, respectively.

The various processes that the oral drug dosage form undergoes are modeled as linear terms in the mass balance equations. To this end, the rate of drug absorption is $k_a c_g$, the rate of drug degradation in GIT $k_l c_g$, the epithelial membrane permeation rate $k_e(c_e - c_b)$, the rate of systemic elimination $k_{el} c_b$, and the dissolution rate $k_d(c_s - c_g)$. It can be seen that drug solubility enters into the driving force, thus determining the extent and not the rate of dissolution. The assumption of linear rate expressions is an approximation.

Equations 1′–3′ are linear and can be easily solved with initial conditions

$$t = 0 \quad c_g = c_0, \quad c_e = c_b = 0 \tag{10}$$

where c_0 is the oral drug dosage form concentration in g/L. It is obvious that the drug dosage strength like its solubility does not affect the rate of the various mass-transfer processes.

Equations 1′–3′ can be formulated into a system of equations of the form

$$d\mathbf{c}/dt = \mathbf{A}\mathbf{c} + \mathbf{b} \tag{11}$$

where the matrix of coefficients or transfer matrix, $\mathbf{A}$, has the form: $\mathbf{A} = \begin{bmatrix} -(k_d + k_a + k_l) & 0 & 0 \\ K_a & -k_e & 0 \\ 0 & K_e & -k_{el} \end{bmatrix}$

The eigenvalues of $\mathbf{A}$ are

$$\lambda_1 = -k_e, \quad \lambda_2 = -k_{el}, \quad \lambda_3 = -(k_d + k_a + k_l) \tag{12}$$

These eigenvalues provide a set of three independent modes and can be made into axes of a Cartesian coordinate system onto which the various drugs are marked.

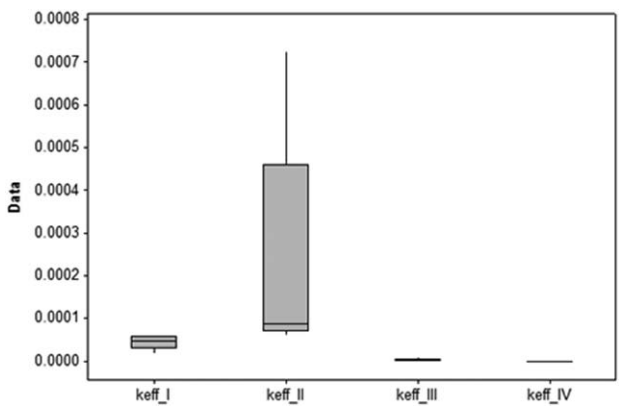

Figure 2. Box plot of k_{eff} values of oral dosage drugs that belong to the same BCS and BDDCS class according to bibliography.

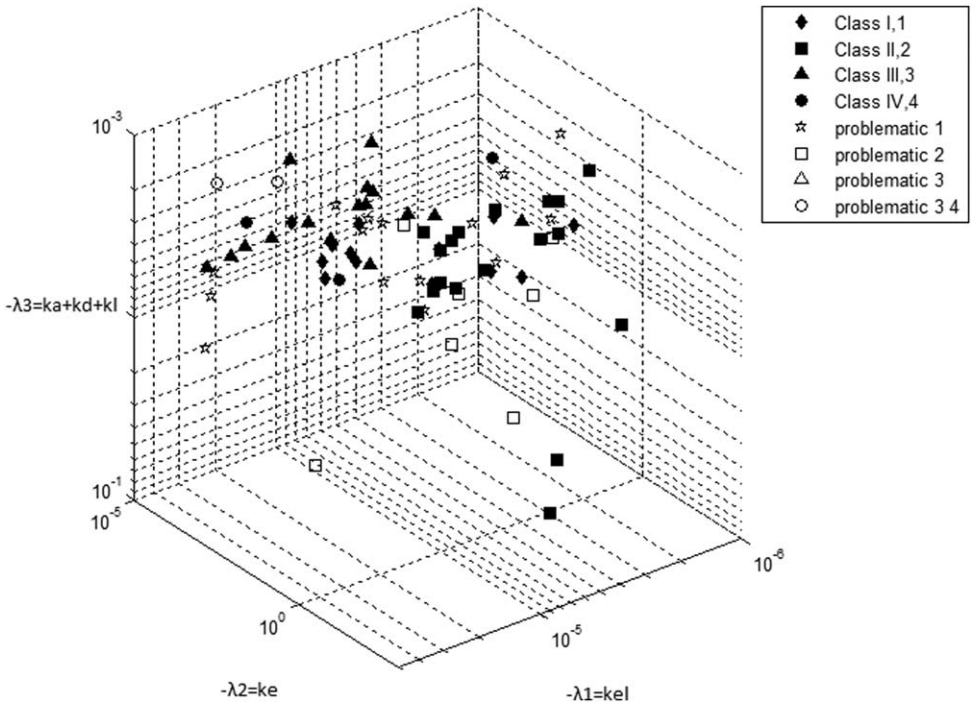

Figure 3. Orthogonal coordinate system based on eigenvalues of coefficient matrix A and drugs of list in Table 1.

Results

One of the most discussed transport properties of drugs is the effective intestinal membrane permeability.[6,39] In the mass balance model presented earlier, as $P_{\text{eff}} = P_{\text{ap}} P_w/(P_{\text{ap}} + P_{\text{w}})$,[6] the respective effective membrane permeation rate constant, k_{eff}, is related to absorption and membrane permeation rate constants in the form

$$\frac{1}{k_{\text{eff}}} = \frac{1}{k_{\text{a}}} + \frac{1}{k_{\text{e}}} \tag{13}$$

Figure 2 depicts the box plots of k_{eff} values of oral dosage drugs that belong to the same BCS and BDDCS class (about 60% of the drugs listed in Table 1). This figure shows that Class I and II drugs show a higher effective adsorption rate and Class II drugs are distinguished from drugs of the other classes as they take effective membrane permeation rate values over a much greater range than the rest.

Figure 3 presents a three-dimensional (3-D) frame of reference with orthogonal coordinate axes named after the eigenvalues of the coefficient matrix in Eq. 11, together with the

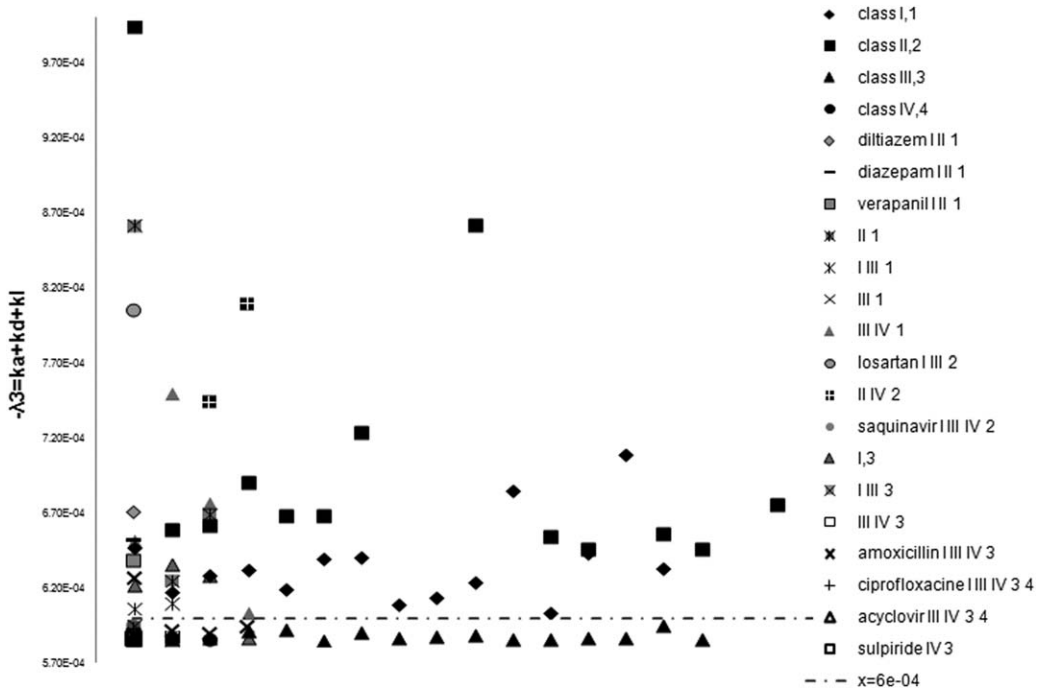

Figure 4. Drugs of list in Table 1 on the $(-\lambda_1, -\lambda_3)$ plane.

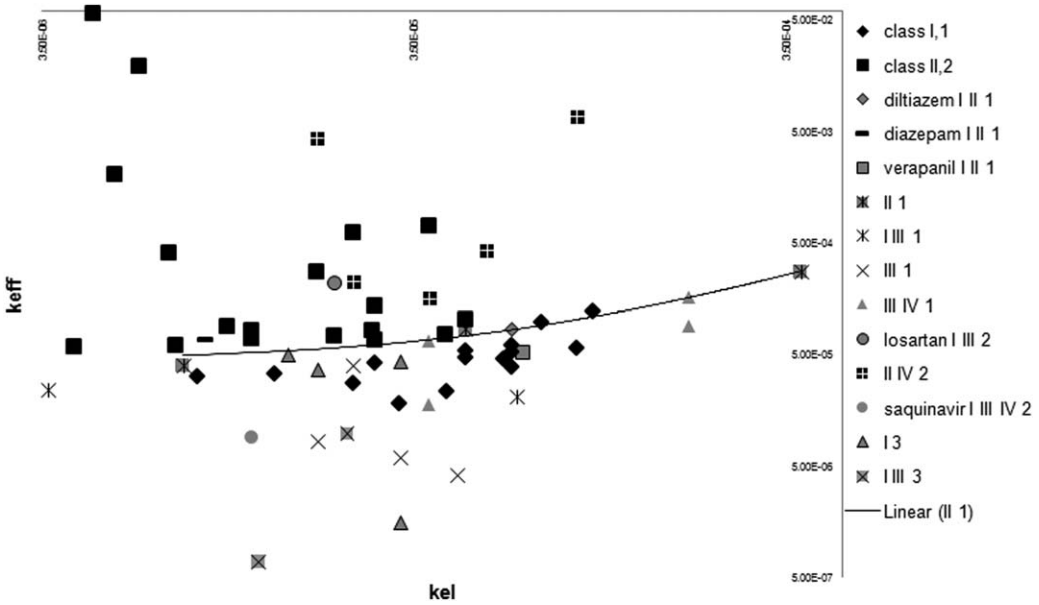

Figure 5. Separation of Classes I,1 and II,2 in plot with axis k_{eff} and k_{el} (logarithmic scale).

drugs from the list in Table 1 that are classified the same in both BCS and BDDCS, marked by color filled shapes, as well as the "problematic" drugs that belong to different BCS and BDDCS classes, marked by unfilled shapes. In this figure, the boundaries that separate Classes I,1 and II,2 from Classes III,3 and IV,4 are well distinguished. This is shown better in Figure 4, where the limit of $-\lambda_3 = 6 \times 10^{-4}\ s^{-1}$ separates drugs in Classes I,1 and II,2 from those in Classes III,3 and IV,4. Regarding the so called "problematic" drugs, the BDDCS seems to be rather determining their classification.

Once Classes I,1 and II,2 are separated from Classes III,3 and IV,4, further discrimination can be observed on marking the same drugs on plots with coordinate axis k_{el} and k_{eff} (Figures 5 and 6). In Figure 5, Classes I,1 and II,2 are obviously separated, with the "problematic" drugs of BCS Class II and BDDCS Class 1 forming a boundary between Classes I,1 and II,2. Similarly, in Figure 6, Classes III,3 and IV,4 are clearly separated, while the "problematic" drugs of both classes seem to belong to Class III,3.

A principal component analysis (PCA) for the above classification with independent variables, the ratios of the rate constants, k_d/k_{eff}, k_a/k_{eff}, and k_{el}/k_{eff}, shows that the significant variables for classification are k_d/k_{eff} and k_{el}/k_{eff}, accounting for 55.6% of the total data variation. A two-dimensional (2-D) frame of reference with orthogonal coordinate axes named after k_d/k_{eff} and k_{el}/k_{eff} and the same as before in the 3-D frame reference drugs mapped is shown in Figure 7, where the influence of the dissolution, systemic elimination, and effective permeability on the drug classification is presented simultaneously. Here, all the classes are clearly distinguished and the "problematic" drugs are positioned in the neighborhood of class boundaries, with a tendency to belong to their class determined as in BDDCS.

To verify the class separation shown in Figure 7, a Cluster Analysis, first, for drugs that belong to the same BCS and

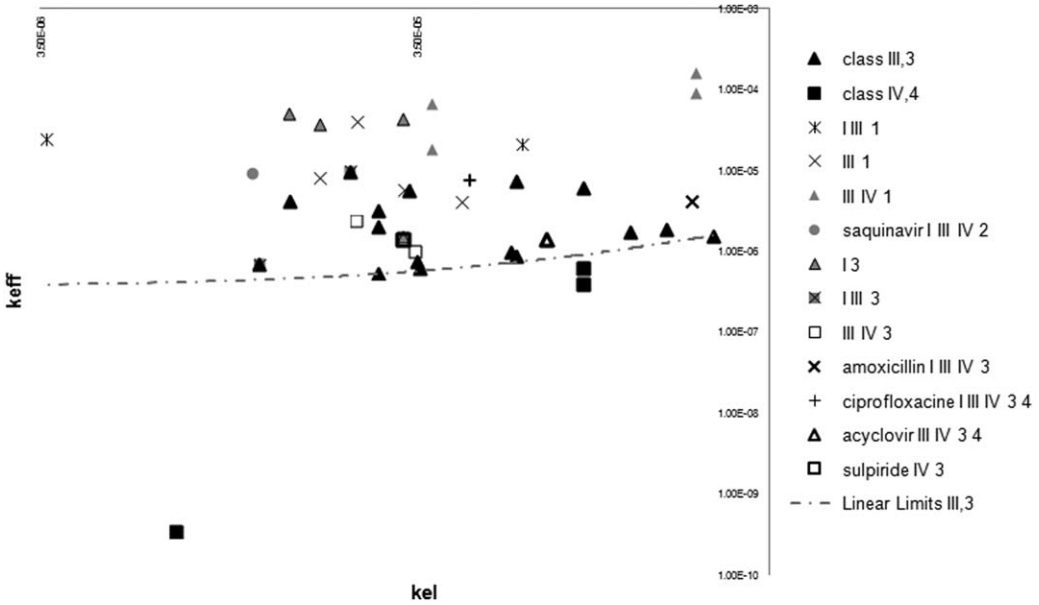

Figure 6. Separation of Classes III,3 and IV,4 in plot with axis k_{eff} and k_{el} (logarithmic scale).

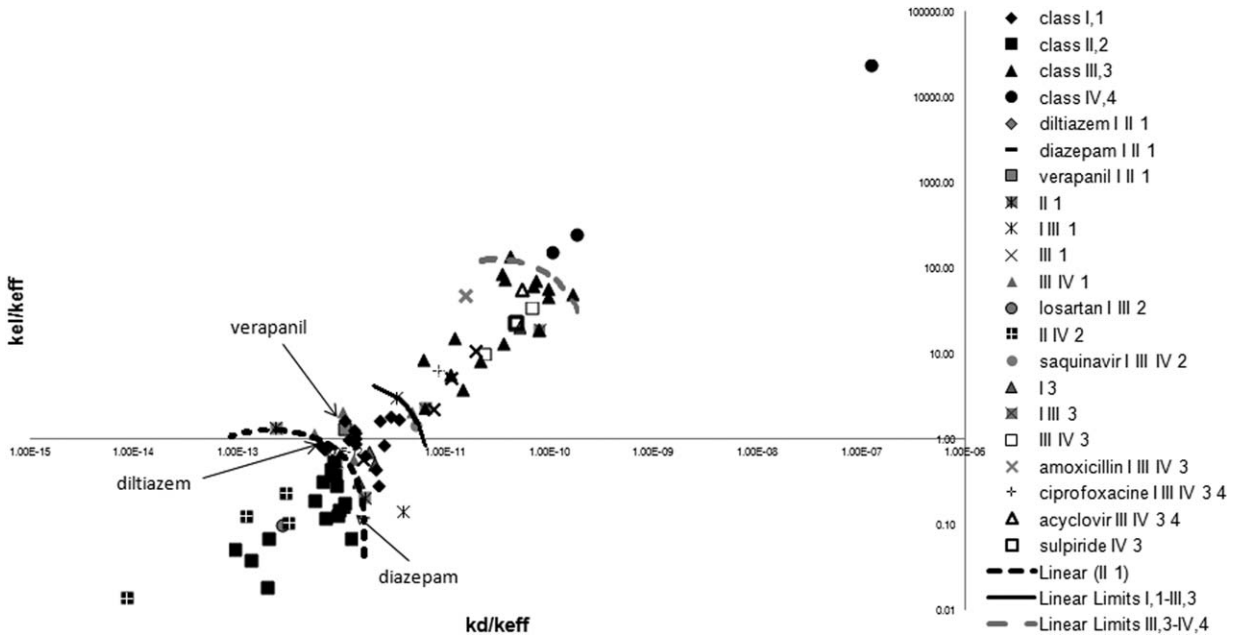

Figure 7. Separation of BCS and BDDCS classes in a plot with axis k_{el}/k_{eff} and k_d/k_{eff} (logarithmic scale).

BDDCS class.[19] Clustering is carried out with commercially available software Minitab. With hierarchical clustering and the hypothesis that the groups are initially not known, six clusters are observed, as shown in the resulting dendrogram (Figure 8), with a Euclidean distance measure and Ward's linkage that tends to produce clusters with similar numbers of observations, even though it is rather sensitive to outliers. The results in this figure seem to be well correlated with Figure 7 and the following clusters are recognized: Cluster 1 with 6 drugs that clearly belong to Class II,2 in the down left corner of Figure 7, Cluster 2 with the remaining 12 drugs of Class II,2, in the proximity of Class I,1, Cluster 3 with 16 drugs of Class I,1 plus cetirizine that belongs in Class III,3, in the proximity of Class I,1, Cluster 4 with 6 drugs of Class III,3, in the proximity of Class I,1, and Cluster 5 with the rest of Class III,3 drugs. Drugs of Class IV,4 seem to be contained in Cluster 5 due to their close location with Class III,3, except for amphotericin B that is clearly separated in the top right corner of Figure 7 and forms the last Cluster 6 in Figure 8.

After these clusters are identified, cluster K-Means analysis is utilized to locate "problematic" drugs on the dendogram. Their cluster partition seems to verify Figure 7. For most of these drugs, BDDCS seems to be more important for their cluster separation, except for chloropromazine that lies in the limits of Classes I,1 and II,2 (Clusters 2 and 3, respectively), disopyramide that belongs to Class III,3, in the proximity of Class I,1 (Cluster 4), diazepam that belongs to Class II,2 in the proximity of Class I,1 (Cluster 2), and saquinavir, guanfacine, sotalol, and clonidine that belong to Class I,1 (Cluster 3).

Discussion

The BCS, in which drugs in oral solid dosage form are grouped together into four classes, based on their aqueous solubility and intestinal membrane permeability, is a regulatory tool developed to enable waivers of expensive and time-consuming *in-vivo* bioavailability (BA)/bioequivalence (BE) testing in favor of *in vitro* dissolution testing for IR drugs. The original criteria for BCS, solubility, and membrane permeability were heterogeneous in nature, a thermodynamic or rather thermostatic property the former and a transport property the latter. It became soon apparent that it was not solubility but dissolution rate rather together with membrane permeation rate (permeability) that determines the fate of the drug in the

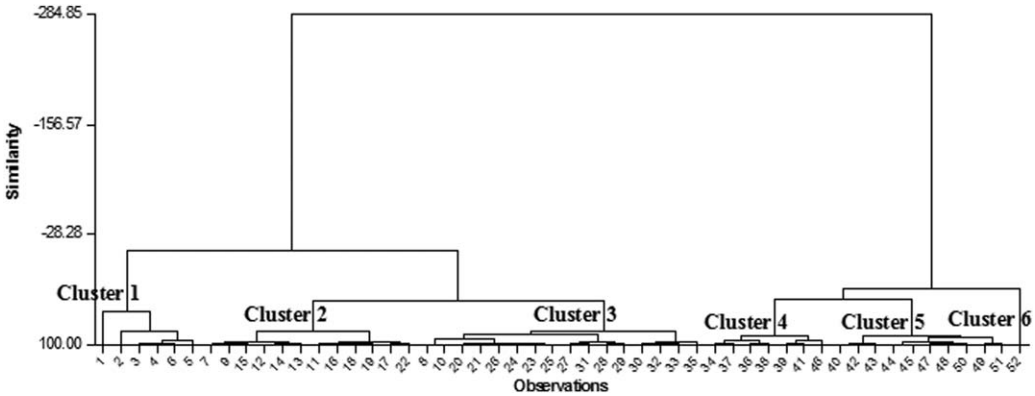

Figure 8. Dendogram of clusters of drugs in database selected from literature (the reference numbers of the drugs are presented in Table 2).

Table 2. Drugs Data Base, BCS, and BDDCS Classification and Cluster Partition[a]

Basic Class No.	Drug Substances	BCS	BDDCS	Cluster K-Means Partition
1	Warfarin	II	2	1
2	Citalopram	II	2	1
3	Praziquantel	II	2	1
4	Thiabendazole	II	2	1
5	Carbamazepine	II	2	1
6	Dipyridamole	II	2	1
7	Phenytoin	II	2	2
8	Lidocaine	I	1	3
9	Amprenavir	II	2	2
10	Timolol	I	1	3
11	Felodipine	II	2	2
12	Ibuprofen	II	2	2
13	Indomethacine	II	2	2
14	Domperidone	II	2	2
15	Griseofulvin	II	2	2
16	Telmisartan	II	2	2
17	Piroxicam	II	2	2
18	Naproxen	II	2	2
19	Lamotrigine	II	2	2
20	Prazosin	I	1	3
21	Sildenafil	I	1	3
22	Nevirapine	II	2	2
23	Dexamethasone	I	1	3
24	Propranolol	I	1	3
25	Metoprolol	I	1	3
26	Caffeine	I	1	3
27	Desipramine	I	1	3
28	Estradiol	I	1	3
29	Chlorpheniramine	I	1	3
30	Nicotine	I	1	3
31	Imipramine	I	1	3
32	Scopolamine	I	1	3
33	Labetolol	I	1	3
34	Erithromycin	III	3	4
35	Cetirizine	III	3	3
36	Enalaprilat	III	3	4
37	Cimetidine	III	3	4
38	Lisinopril	III	3	4
39	Lamivudine	III	3	4
40	Cephalexin	III	3	5
41	Atenolol	III	3	4
42	Cefadroxil	III	3	5
43	Cefradine	III	3	5
44	Ranitidine	III	3	5
45	Pirenzepine	III	3	5
46	Fexofenadine	III	3	4
47	Lincomycin	III	3	5
48	Ganciclovir	III	3	5
49	Furosemide	IV, II	4	5
50	Gabapentin	III	3	5
51	Chlorothiazide	IV	4	5
52	Amphotericin B	IV	4	6
#	Zidovudine	I, III	1	3
#	Ethosuximide	I, III	1	3
#	Theophylline	I, III, IV	1	3
#	Propylthiouracil	III, IV	1	3
#	Acetaminophen	III, IV	1	3
#	Acetylsalicylic acid	III, IV	1	3
#	Omeprazole	II	1	3
#	Chlorpromazine	II	1	2
#	Ketoprofen	II	1	3
#	Quinidine	III	1	3
#	Sumatriptan	III	1	4
#	Minoxidil	III	1	4
#	Disopyramide	I, III	1	4
#	Diazepam	I, II	1	2
#	Diltiazem	I, II	1	3
#	Verapanil	I, II	1	3
#	Losartan	I, III	2	2
#	Glipizide	II, IV	2	1
#	Nelfinavir	II, IV	2	2
#	Ritonavir	II, IV	2	2
#	Sulfamethoxazole	II, IV	2	2

TABLE 2. *Continued*

Basic Class No.	Drug Substances	BCS	BDDCS	Cluster K-Means Partition
#	Sulfasalazine	II, IV	2	1
#	Saquinavir	I, III, IV	2	3
#	Guanfacine	I	3	3
#	Sotalol	I	3	3
#	Clonidine	I	3	3
#	Amiloride	I	3	5
#	Hydrochlorothiazide	III, IV	3	5
#	Methotrexate	III, IV	3	4
#	Amoxicillin	I, III, IV	3	5
#	Sulpiride	IV	3	5
#	Ciprofloxacine	III, IV	3,4	4
#	Acyclovir	III, IV	3,4	5

[a]The "Basic Class No." refers to drugs with the same BCS and BDDCS classification. The "problematic" drugs are presented with # symbol.

GIT. As it happens, Class I high solubility and high permeability drugs exhibit also rapid dissolution. Permeability, on the other hand, is not an easily measured property. In the BCS adopted by FDA, drug absorption on the epithelial GIT wall was correlated with permeability in the sense that absorption equal or greater than 90% of an administered drug indicates high drug membrane permeability. Later, BDDCS, a modified BCS, offered another rate process, systemic elimination, as an alternate surrogate for permeability.

In this work, two new frames of reference were proposed for mapping orally delivered-drug in the four drug classes of the BCS and BDDCS. A list of 85 drugs that have reached the market and have been classified in BCS and BDDCS in various literature sources was compiled and the drugs from this list were mapped in a 3-D frame of reference with orthogonal coordinate axes the eigenvalues of the coefficient matrix in the system of mass balance equations for the drug, with the eigenvalues being all rate constants of the various processes in GIT. A PCA with independent variables, the ratios of dissolution, absorption, and systemic elimination to effective membrane permeation rate constants showed that the significant variables for this classification were the ratios of dissolution and systemic elimination to effective membrane permeation rate constants, respectively. A 2-D frame of reference with orthogonal coordinate axes the aforementioned ratios was constructed and the same drugs from the 3-D frame of reference were mapped in the new frame of reference.

In both 3-D and 2-D frames of reference proposed here, the four drug classes of BCS and BDDCS were mapped into regions with boundaries that are clear and distinct. In these plots, the so-called "problematic" drugs, that is, drugs that are classified differently in BCS and BDDCS are placed in classes that are suggested by BDDCS.

Conclusion

Two new frames of reference are proposed for mapping the four classes of orally delivered drugs of BCS and BDDCS, which are based on drug aqueous solubility and intestinal membrane permeability.

One of the frames of reference is 3-D with orthogonal coordinate axes the eigenvalues of the system of mass balance equations for the drug in the lumen and the epithelium of the GIT, and in the adjacent plasma, specifically representing the basic rate constants of drug dissolution, adsorption, degradation, membrane permeation, and systemic elimination.

The other frame of reference is 2-D with orthogonal coordinate axes the ratios of dissolution and systemic elimination to effective membrane permeation rate constants. These three processes, by comparison of their characteristic times, seem to be the rate-controlling processes in the GIT lumen, the plasma in the layer adjacent to the epithelium, and the epithelium.

In both proposed frames of reference, the boundaries of the regions, into which the four drug classes of BCS and BDDCS are mapped, are clear and distinct, while the same boundaries in the original aqueous solubility-membrane permeability frame of reference.

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