Review

DOI: 10.1002/minf.201000171

Computational-Regulatory Developments in the Prediction of Oral Drug Absorption

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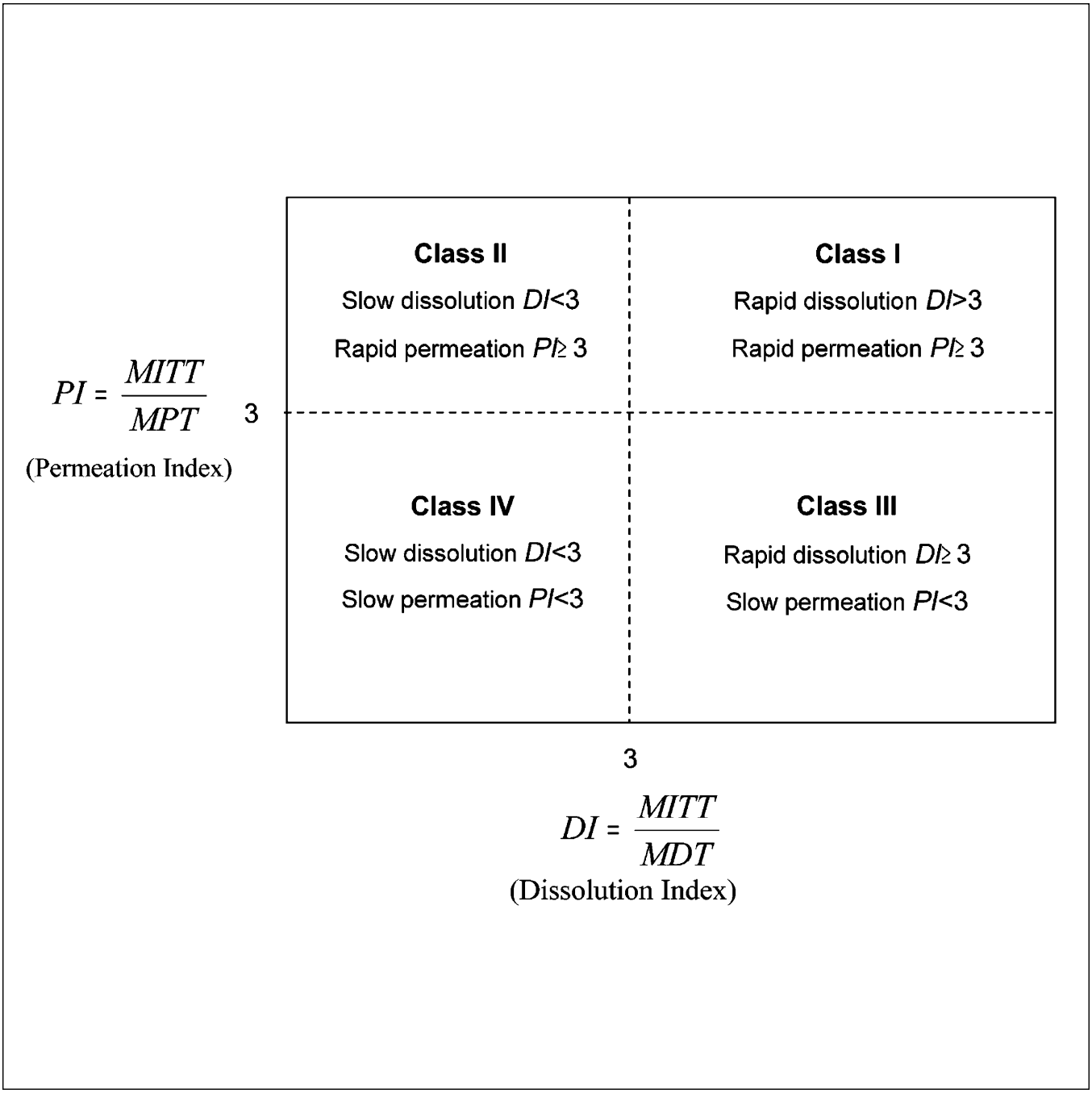
Presented at the 18th European Symposium on Quantitative Structure Activity Relationships, EuroQSAR 2010, Rhodes, Greece



molecular informatics

Abstract: Early prediction of human intestinal absorption is important in selection of potential orally administered drugs. Various computational models for prediction of the fraction of dose absorbed, *Fa*, have been developed. In 1989, a sigmoidal relationship between *Fa* and drug absorption potential was shown. Since then various physicochemical descriptors of molecules (lipophilicity, polar surface area, hydrogen bond descriptors) have been found to correlate with human intestinal absorption and various attempts in estimating *Fa* have been reported. Most studies rely on the presupposition that *Fa* is mainly dependent on drug's solubility, which drives the dissolution rate in the gastrointestinal (GI) fluids, and the rate of passive drug transport across the intestinal membrane. In the same vein, the biopharmaceutics classification system (BCS) and the relevant FDA guideline classify drugs in four categories according to their aqueous solubility and permeability. However, the biopharmaceutics drug disposition classification system (BDDCS) revealed the poor predictability of permeability estimates for *Fa* and the major role of transporters for GI uptake of drugs. The role of solubility in the reaction limited model of dissolution and the ubiquitous presence of supersaturated solubility-dissolution phenomena in the GI lumen, call for a more physiologically relevant consideration of GI absorption.

Keywords: Oral drug absorption · Drug absorption · BCS FDA Guideline · Bioavailability

1 Introduction

The understanding and the prediction of oral drug absorption are of great interest for pharmaceutical drug development. The establishment of a comprehensive framework in which the physicochemical properties of drug candidates are quantitatively related to the extent of oral drug absorption will accelerate the screening of drug candidates in the discovery/preclinical development phase. Such a framework will certainly help regulatory agencies in developing scientifically based guidelines in accord with drugs physicochemical properties for various aspects of oral drug absorption e.g. dissolution, in vitro – in vivo correlations, waivers of bioequivalence studies.

However, the complex interrelationships among drug properties and processes in the gastrointestinal (GI) tract make the prediction of oral drug absorption a difficult task. In reality, drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors, and physiological variables including regional permeability differences, pH, luminal and mucosal enzymes, and intestinal motility, among others.[1–3] Accordingly, drug processes in the GI tract are characterised by high intra- and inter-subject variability which is inherently associated with the dynamics of the processes. Therefore, "rough estimates" rather than "predictions" of oral drug absorption, can be made. Despite this complexity, various qualitative and quantitative approaches have been proposed for the estimation of oral drug absorption.[1,2]

1.1 Fundamental Concepts in Oral Drug Absorption

Oral intake is one of the most important routes of drug administration, since it is most convenient for patients and results in high therapy compliance. Compounds intended for oral administration must have adequate biopharmaceutical properties in order to achieve therapeutic concentrations at their site of action. Oral drug absorption is a complex process dependent upon various drug properties as well as on physiological aspects of the gastrointestinal (GI) tract.[3] The most important factors influencing the rate and extent of intestinal drug absorption can be classified as: a) physicochemical (aqueous solubility, molecular size, aggregation/complexation, charge (pKa), H-bonding potential, hydrophobicity, crystal lattice energy), b) physiological (gastric emptying, intestinal motility, intestinal pH, membrane permeability, intestinal content composition, disease state), c) formulation (dosage form, absorption enhancers, drug release), d) biochemical (metabolism, efflux transporters, active uptake transporters).

It should be mentioned however, that in early stages of drug discovery process the medicinal chemist has only the molecular structure, which can be used to calculate various descriptors and further applied to e.g. predict solubility, permeability, absorption, etc. It is only in later stages of drug development where also experimental solubility and permeability data may be available.

1.2 Factors Influencing Oral Bioavailability

Oral bioavailability is mainly dependent on three factors: the fraction of dose absorbed (F_a); the fraction of drug escaped from metabolism in the gut wall (F_g); and the fraction of drug escaped from hepatic metabolism (F_h). Hence, the oral bioavailability of a drug is mainly a function of effective permeability (P_{eff}) across the intestinal mucosa, dissolution and solubility characteristics in the gastrointestinal (GI) fluids and metabolic stability.[3] One should also add the importance of drug transporters in influencing the pharmacokinetics of orally dosed drugs. This is particularly so for drugs with low solubility and/or dissolution rate. Although the discovery of

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Pgp dates back to 1976,[4] the role of transporters in oral drug absorption has become increasingly evident during the last decade.[5] Drug transporters in both the gut and the liver can help control access of drugs to systemic circulation by dictating the amount of drug that enters the body from the gut lumen and influencing how much drug escapes first pass metabolism in both gut and liver.[5]

2 The Evolution of GI Drug Absorption Analysis

2.1 1985–2000: The Road to BCS and the BCS FDA Guideline

In 1985, Amidon and co-workers, using a pseudoequilibrium model, made a major step in the theoretical analysis of oral drug absorption when solubility and dose were taken into account for the estimation of the absorption potential (AP) of a drug, apart from the pH-partition hypothesis parameters (lipophilicity, and degree of ionization).[6] The first approach for a biopharmaceutical drug classification was published four years later. In this study[7] the estimate of the drug's 'absorption potential' was used for the biopharmaceutic classification of drugs in three categories.[7] However, the microscopic tube model based on mass balance considerations published in 1993 can be considered as a landmark in the history of oral drug absorption since it revealed the three fundamental parameters, namely, "dissolution", "dose" and "absorption" numbers, which control the extent of oral drug absorption.[8] In fact, "Dissolution number" corresponds to the ratio of the "Mean Intestinal Transit Time (MITT)" to the "Mean Dissolution Time (MDT)" of drug particles, while "Dose number" correspond to the ratio of the "Dose" to the product of "Drug Solubility" with the "volume of intestinal fluids", and "Absorption number"

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corresponds to the ratio of "MITT" to the drug's "Mean Absorption Time (MAT)". As a matter of fact, two differential equations, expressed in dimensionless variables, were used to describe the dissolution of drug particles and the uptake of the dissolved drug. Based on this analysis, drug dissolution follows the diffusion layer model and therefore, saturation solubility is the driving force of the dissolution rate, while drug permeation follows passive diffusion and therefore, permeability is the governing parameter of the uptake. This work enabled Amidon et al.[9] to develop in 1995 a Biopharmaceutics Classification System (BCS). According to BCS a substance is classified on the basis of its aqueous solubility and intestinal permeability; thus, four drug classes were defined i.e., high solubility/high permeability (Class I), low solubility/high permeability (Class II), high solubility/low permeability (Class III), low solubility/low permeability (Class IV) (Figure 1). The properties of drug substance were combined with the dissolution characteristics of the drug product and predictions with regard to the in vitro–in vivo correlations for each of the drug classes were pointed out. The FDA guidance[10] on BCS issued in 2000 provides regulatory benefit for highly permeable drugs that are formulated in rapidly dissolving solid immediate release formulations. 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" while a drug product is defined as rapidly dissolving when no less than 85% of the dose is dissolved within 30 min using USP Apparatus I at 100 rpm in a volume of 900 mL in 0.1 N HCl, as well as in pH 4.5 and 6.8 buffers. For new and generic drugs that fulfil the high permeability-high solubility-rapid dissolution requirements (i.e BCS Class I drugs), a waiver of in vivo bioequivalence study can be granted according to the relevant FDA guidance,[10] eliminating therefore, unnecessary drug exposure to healthy subjects and reducing drug production cost without affecting the quality of public health standard.[11]

In parallel, computer-based models, based on calculated molecular descriptors have been developed to predict the extent of absorption from chemical structure in order to facilitate the lead optimization in the drug discovery process. Basically, the physicochemical descriptors of drug molecules can be useful for predicting absorption for passively absorbed drugs. Since dissolution is the rate-limiting step for sparingly soluble drugs, while permeability becomes rate-controlling if the drug is polar, computer-based models are based on molecular descriptors related to the important drug properties including solubility and permeability across the intestinal epithelium.

A rapid popular screen for compounds likely to be poorly absorbed is Lipinski's "rule of 5",[12] which states that poor absorption of a compound is more likely when its structure is characterized by:

- molecular mass >500,
- log$P>5$
- more than 5 H-bond donors expressed as the sum of OHs and NHs, and
- more than 10 H-bond acceptors expressed as the sum of Ns and Os
- substrates for biological transporters are exceptions from these rules
- two alerts indicate limited permeability or solubility

Although various computational approaches for the prediction of intestinal drug permeability and solubility have been reported,[13] recent computer-based absorption models utilize a large number of topological, electronic, and geometric descriptors in an effort to take both aqueous drug solubility and permeability into account. Thus, descriptors of "partitioned total surface areas (PTSA)",[14] molecular descriptors such as *C*log*P*, molecular polar surface area, number of hydrogen acceptors and donors and Abraham molecular descriptors,[15,16] and a variety of structural descriptors with neural networks[17] have shown to be determinants of oral drug absorption. PTSA was found to satisfy both drug solubility and permeability for BCS calculations.[14] Good relationships were found between absorption and Abraham molecular descriptors or *C*log*P*. The developed absorption models accurately predicted BCS class I, III and IV compounds while absorption of BCS class II compounds was overpredicted because dissolution is the rate-limiting step of absorption.[15,16] Turner et al.,[17] used radial basis function artificial neural networks and theoretical descriptors to develop a quantitative structure–pharmacokinetic relationship (QSPkR) for structurally diverse drug compounds. The developed QSPkR model[17] did not require experimental parameters but relied on theoretical information generated from drug structure. Successful predictions were made for compounds exhibiting high bioavailability, as well as compounds with poor bioavailability but good absorption. The descriptors in the optimum model could potentially provide useful information regarding structural properties required to develop compounds with adequate bioavailability characteristics, while it may be also used for the preliminary evaluation of the bioavailability of potential drug candidates without performing expensive laboratory experiments.

2.2 2000–2010: The Meta-BCS Period

2.2.1 Theoretical and Experimental Concerns for Dissolution

Dissolution research started to develop more than a century ago.[18,19] The dissolution process of a solid drug is mainly described by Equation 1, the so-called Noyes–Whitney equation[20] and its modified form of Nernst and Brunner:[21,22]

$$dC/dt = k(C_s - C) \quad (1)$$

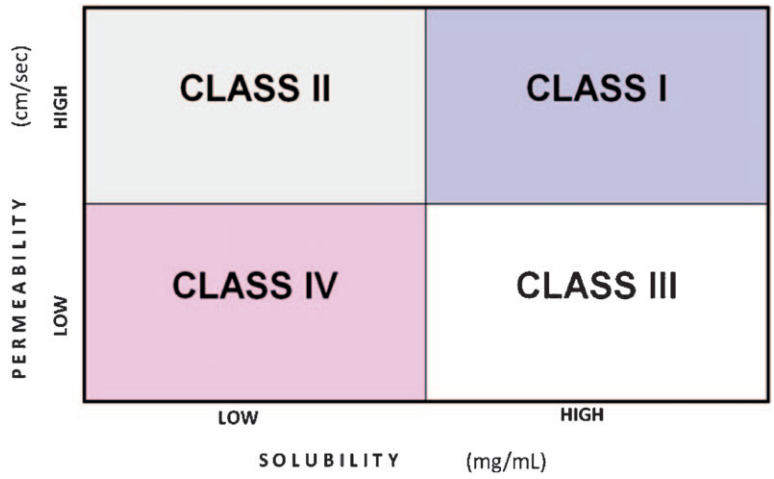

Figure 1. The BCS plane according to which a drug substance is classified to one of four classed according to its aqueous solubility and permeability characteristics.

where k is the dissolution rate constant, C_S is the saturation solubility of drug and C is the concentration of drug in the bulk fluid at time t. Equation 1 relies on the diffusion layer model which assumes that a thin diffusion layer is formed around the solid particles surface, through which the dissolved drug molecules diffuse to the bulk aqueous medium. However, dissolution is a classical heterogeneous process since it takes place on the solid–liquid phase boundaries.[23] All heterogeneous processes involve several steps. In fact, the dissolution of a solid in an aqueous solution is considered to take place in two steps: (i) a reaction at the solid–liquid interface (interfacial transport) and (ii) transfer of the dissolved species through the diffusion layer to the bulk aqueous phase.[1,2,18,19] The slower of these steps exercises a dominating influence upon the rate of dissolution. Accordingly, Equation 1 is used to describe drug dissolution when the rate of diffusion of the species is much slower than the reaction at the solid-liquid interface. The extensive use of Equation 1 in biopharmaceutics is associated with its mathematical simplicity and the governing role of saturation solubility in the rate of drug dissolution.

The Importance of Hydrodynamics in Drug Dissolution

Equation 1 represents a theoretically sound expression only for diffusional flow in a static medium but it should be regarded as purely empirical when applied to a medium in motion.[19,23] This prompted Levich[23] to develop the theory of the so called convective diffusion of solute in liquids and derived relationships for the thickness of the diffusion layer and the agitation rate of the rotating disk apparatus.[24] In parallel, a series of fluid dynamic models[25] rely on diffusion principles and the assumption of the unstirred fluid layer, too. Most of the studies dealing with the diffusion layer model are performed in the rotating disk device where the surface area and the hydrodynamic conditions are perfectly controlled. The results of these studies clearly demonstrate the predominant role and effect of agitation conditions on the rate of drug dissolution. However, these results cannot be extrapolated to the official dissolution tests as recent studies based on computational fluid dynamics revealed the complexity of the fluid flow in these systems.[26–28] In addition, dissolution results in various official dissolution tests differ because of the differences in agitation rate. Moreover, the variable and heterogeneous conditions and volume content of the gastrointestinal fluid[2,29] are extremely dissimilar if compared with the flow of liquid in the rotating disk device.

Composition of Dissolution Medium

The advances on oral drug absorption prediction attracted the obvious interest of scientists in the importance of dissolution tests as predictors of oral absorption of Class II drugs. One of the avenues followed in this field of research is the study of the solubility and dissolution properties of poorly soluble drugs in either food-mimicking media, e.g. milk[30,31] or biorelevant media.[31–33] Alternatively, human aspirates were used to study drug solubility and dissolution in the gastrointestinal tract.[34–37] Although most of the lipophilic drugs were found to be more soluble in milk than in aqueous media,[30,31] the solubility of danazol and felodipine in HCl under- or over-estimates their intragastric solubilities, respectively.[34,35] Overall, the solubility data in human gastric aspirates have high intra- and inter-subject variability[34] while the solubilizing capacity of human intestinal fluids in the fed state is strongly time-dependent.[37] This type of variability is inherently associated with the dynamics of the processes in the gastrointestinal tract, which cannot be mimicked under in vitro conditions, and is one of the reasons for the failure of IVIVC.[38]

The Problem of Dose

It should be noted that dissolution specifications of the FDA guidance are not correlated with the drug's solubility/dose ratio, which has been shown to control the rate of drug dissolution.[39] It was Lansky and Weis[40] who raised a question on this issue for the first time in 1999, and soon after dose was incorporated explicitly into the fundamental relationships used routinely in dissolution.[39,41] The Noyes–Whitney equation (Equation 1) was modified taking into account the dose and the volume of the dissolution medium;[39,41] thus Equation 1 was expressed in terms of the fraction of dose dissolved, Φ:

$$d\Phi/dt = k(q^{-1} - \Phi) \quad (2)$$

where k is the dissolution rate constant and q is the dimensionless dose/aqueous solubility (C_s) ratio since the volume of the dissolution medium, V has been taken into account ($q = \text{dose}/C_s \cdot V$).[39] Equation 2 reveals that $1/q$ is the primary parameter for the rate of drug dissolution in terms of Φ; this was one of the reasons justifying the recent use of $1/q$ in the quantitative-BCS.[42] In addition, the value of $1/q$ determines the final fraction of dose dissolved while, when the entire dose is dissolved ($q \leq 1$), the Mean Dissolution Time (*MDT*) is dependent on q as follows:

$$MDT = [q - (q-1)\ \ln(1-q)]/kq \quad (3)$$

When the entire dose is not dissolved ($q > 1$), the Mean Dissolution Time for saturation is $MDT_s = k^{-1}$.[37] To model correctly these two cases, a branched version of the Noyes–Whitney equation has been considered.[41] Expressing the equation as fraction of dose dissolved, Φ, the branched Noyes-Whitney equation has the form

$$\Phi = \begin{cases} \frac{1}{q}(1 - e^{-a \cdot t}) & \text{for} \quad t < T \quad (\Phi < 1) \\ 1 & \text{for} \quad t \geq T \end{cases} \quad (4)$$

where q is the dimensionless dose/solubility ratio equal to Dose/(C_s V), C_s is the saturation solubility and T is the time where the entire quantity of the initial dose has been dissolved; V is the volume of the dissolution medium. The branched version of the dissolution model allows, in principle, the estimation of solubility even when the data do not reach saturation.[41]

Reaction Limited Model in Drug Dissolution

Recently, the concept of the so called 'interfacial barrier model' or 'reaction-limited model' of dissolution was reviewed.[43] The limited use of this model in drug dissolution is due to the prevalence of the rotating disk apparatus in the mechanistically driven dissolution studies. The fully controlled hydrodynamic conditions of the rotating disk experiments favour the predominance of the slower step, namely, the diffusion of dissolved drug molecules over the interfacial transport. Even the reactive terms in diffusion-convective equations used in rotating disk experiments are considered instantaneous and ignored. However, as it was mentioned above, the hydrodynamics and accordingly the drug's dissolution mechanism(s) in the rotating disk device are different from the various official dissolution apparatuses as well as the gastrointestinal lumen.

The classical Noyes–Whitney relationship was explained using Boltzman's thermodynamic principles as early as in 1933.[44] However, a well founded mathematical model for reaction-limited dissolution has not been proposed until recently. During the last decade, three reaction-limited approaches which do not rely on premises of diffusion principles were reported.[43,45,40] The most recent of these approaches[41] is based on the bidirectional chemical reaction of the undissolved drug species with the free solvent molecules yielding the dissolved species of drug complex with solvent:

$$s + nw \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} c \quad (5)$$

The rate of dissolution is driven by the concentration of undissolved species [s] and the saturation solubility corresponds to the concentration when the reaction equilibrium is reached. In that work,[43] the model equation developed was applied successfully to dissolution data sets measured in official apparatuses. Also, the governing role of the saturation solubility in the dissolution process associated with the diffusion layer model was not verified.[43] This observation underlines the importance and the potential of application of reaction-limited approaches in the simulation of oral drug absorption where classical diffusion principles are not applicable due to the heterogeneous composition and structure-function of the gastrointestinal tract.[2,29]

2.2.2 Theoretical and Experimental Concerns for Solubility

The limited use of the FDA guideline for biowaiver was recently attributed to the conservatism of the BCS solubility and dissolution criteria.[46] Furthermore, the "high solubility" definition criteria of the BCS based FDA guidance have been found very conservative for a great number of non-steroidal anti-inflamatory drugs which exhibit extensive absorption.[47] In a simulation study, most of these results were explained using a dynamic dissolution-permeation model in the GI tract.[48] The kinetics of the two consecutive drug processes dissolution and wall permeation are considered in the time domain of the physiologic transit time. This analysis relies on the tube model of the intestinal lumen utilized by Oh et al.[8] for the development of BCS.[9] 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 equations of drug dissolution-uptake in the intestines is expressed in terms of the fraction of dose dissolved as follows:

$$\frac{dr_p}{dt} = \begin{cases} -\frac{D}{\rho}\frac{M_0}{V_0 r_p}\left(\frac{1}{q} - \Phi\right) & \text{if} \quad r_p > 0 \\ 0 & \text{if} \quad r_p = 0 \end{cases} \tag{6}$$

$$\frac{d\Phi}{dt} = \frac{3D}{\rho V_0}\frac{r_p M_0}{r_0^3}\left(\frac{1}{q} - \Phi\right) - \frac{2P_{eff}}{R}\Phi \tag{7}$$

where Φ is the fraction of dose dissolved, D is the diffusion coefficient of the drug, M_0 is the dose, ρ is the density of the solid drug, R is the radius of the intestinal lumen, N_0 is the number of drug particles in the dose, V_0 is the luminal volume, r_0 is the initial radius of the spherical drug particles, r_p is the radius of the spherical drug particles, and P_{eff} is the effective permeability of the drug.

A mass balance equation for the fraction of dose absorbed, *Fa* at the end of the tube, similar to that used in the study of Oh et al.[8] was also considered:

$$Fa = (M_0 - M_{solid} - M_{dissolved})/M_0 \tag{8}$$

where M_{solid} and $M_{dissolved}$ denote the mass of the undissolved and dissolved drug, respectively at the end of the intestine. Equation 8 simplifies to Equation 9:

$$Fa = 1 - (r_p/r_0)^3 - \Phi \tag{9}$$

where r_p, and Φ in Equation 9 refer to their values at $t =$ *MITT* (Mean Intestinal Transit Time).

One of the most significant results of this work[48] was the elucidation of the relationships between the fraction of dose absorbed and dose for drugs with low solubility/dose ratio, $(1/q) < 1$. It was shown 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 whereas 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[42] but also plays a key role in determining the extent of absorption. Besides, passively absorbed drugs can exhibit "dose dependency" in the range of doses utilized.

Recent studies dealing with kinetic solubility and supersaturated phenomena[49,50] place particular emphasis on the relevance of supersaturated solubility with the biopharmaceutic classification of drugs. Moreover, supersaturated solubilities are frequently found in studies measuring drug concentrations in human aspirates[51,52] while the subsequent precipitation of drug has been the subject of several studies.[53,54] Recently, a study[55] of the effect of supersaturation on oral drug absorption revealed that formulation technology that can induce supersaturation may be of great assistance to the successful development of poorly water-soluble drugs. In the same vein, stable supersaturated milk based formulations of NSAIDs were prepared with satisfactory in vivo performance.[56]

As the dissolution process in the biopharmaceutical classification system article has been modelled with a modified form of the Noyes-Whitney equation,[20–22] the dominant role of the aqueous solubility has been mirrored in the classification and the biopharmaceutical classification system guideline.[10] However, our knowledge of the exact dissolution mechanisms under in vivo conditions is limited; thus, dissolution-based instead of solubility-based classifications have been proposed for new molecular entities[57,58] and

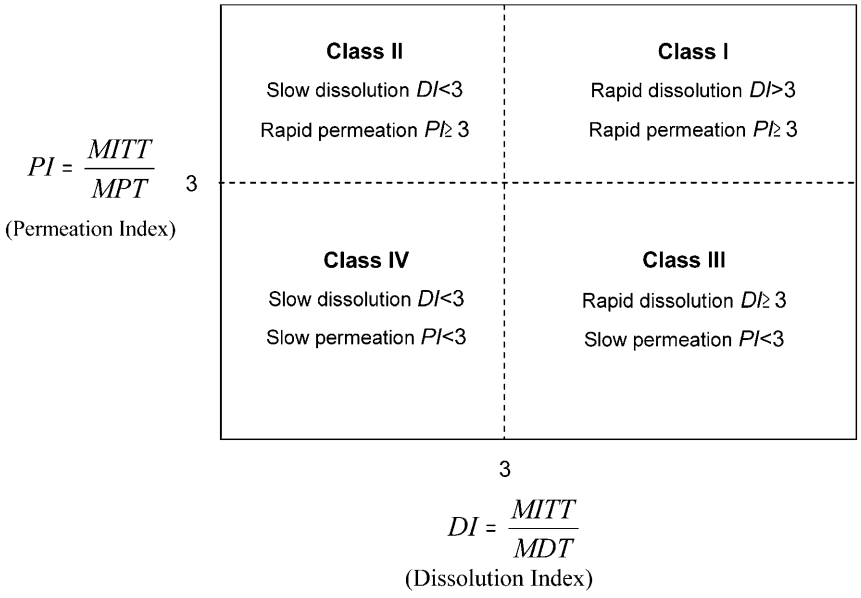

Figure 2. The biopharmaceutics classification system for marketed-drugs (BCS-MD) as put forth by Papadopoulou et al.[57]

marketed drugs.[57] In this vein, model-independent dissolution criteria such as mean dissolution time[57] (Figure 2) and intrinsic dissolution rate (IDR)[58] have been proposed for dissolution classification. Furthermore, the recent work of Avdeef and co-workers made great progress in this field since they developed a novel approach for measuring IDR of very small quantities of compounds introduced as powders to buffered solutions.[59,60] Using almost 10000-fold less material, these IDR measurements may possibly serve as a surrogate for the BCS solubility/dissolution classification in early stages of drug development.[59,60] In the same vein, in a modified physiological BSC introduced recently,[61] the importance of investigating solubility and dissolution under physiologically relevant conditions in all stages of the drug discovery process to push suitable compounds forward, to select proper formulations and to reduce the risk of food effects, was postulated.[61]

2.3 2005–2010: The Introduction of BDDCS and the Transporters Era

After the publication of the FDA guidance on BCS,[10] Professor Leslie Banet questioned in several talks the ability of permeability estimates to predict the extent of drug absorption. These concerns lead to the development of the so called Biopharmaceutic Drug Disposition Classification System (BDDCS)[62] (Figure 3). BDDCS extends the BCS to include drug elimination and the effects of efflux and transporters on oral drug absorption.[62] The authors suggest that this modified version of BCS is useful in predicting overall drug disposition when transporter-enzyme interplay will yield clinically significant effects, the direction, mechanism and importance of food effects, and the transporter effects on post-absorption systemic drug concentration following oral and intravenous dosing. They also suggest that drug classification according to BDDCS using elimination criteria, may expand the number of Class I biowaivers while it provides predictability of drug disposition profiles for drugs of Classes II, III and IV.

It should be mentioned however, that depending on the dose administered, transporters may be fully saturated. In this case, drug physicochemical properties are prevailing to drug absorption. As already mentioned, passively absorbed drugs with low dimensionless solubility/dose ratio, ($(1/q) < 1$) used in various doses, exhibit "dose dependent absorption" of non-Michaelian type and therefore, the value of $1/q$ is not only critically important for biopharmaceutic classification purposes[42] but also plays a key role in determining the extent of absorption. Only for drugs given in small doses transporter efflux and gut wall metabolism may become absorption-limiting. However, the criteria proposed to define "$\geq 90\%$ metabolized" as an alternative method for the extent of absorption for Class I biowaivers take this into account.[63,64] According to the European Medicines Agency (EMA)[64] "Following a single oral dose to humans, administered at the highest dose strength, mass balance of Phase 1 oxidative and Phase 2 conjugative drug metabilites in the urine and feces, account for $\geq 90\%$ of the dose administered". This is the strictest definition since for an orally administered drug to be $\geq 90\%$ metabolized by Phase 1 and Phase 2 processes it is obviously that the drug must be absorbed extensively.[63,64]

Recently in silico methods were applied to automatically classify drugs according to BDDCS.[65] Computational models were developed and utilised to predict BDDCS class for new compounds from molecular structure using available molecular descriptors and software.[65] The authors pointed out that these in silico approaches could aid the pharmaceutical industry in speeding drugs to the patient and reducing costs. This could have significant applications in drug discovery to identify molecules that may have future developability issues.[65]

BDDCS was also recently used in classifying the permeability of marketed drugs.[63] As mentioned above, the extent of drug metabolism ($\geq 90\%$ metabolized) is used as an alternative method in defining Class I marketed drugs suitable for a waiver of in vivo studies of bioequivalence. This approach was also included in the recently released guideline of the European Medicines Agency on the investigation for bioequivalence, as an alternative for measurement of the extent of absorption for BCS-based biowaiver applications.[64] In their recent work, Benet and Larregieu[66] stated that although US Food and Drug Administration (FDA)-approved Biopharmaceutics Classification System (BCS) Class I drugs are designated as high-permeability drugs, in fact, the criterion utilized is high extent of absorption. This ambiguity should be eliminated, and the FDA criterion should explicitly be stated as $\geq 90\%$ absorption based on absolute bioavailability or mass balance.

Heterogeneous Biophysical Characteristics of GI Absorption

The mathematical models used for the analysis of GI absorption e.g. the microscopic tube model rely on classical

Figure 3. Biopharmaceutics Drug Disposition Classification System (BDDCS) as put forth by Wu and Benet.[62]

principles e.g. homogeneous flow. In reality all these models do not represent the heterogeneous structure and function of the GI system. However, several attempts have been made to understand the biophysical characteristics of GI drug absorption, as well as the effect of the complex *in vivo* dynamics and the interplay of the various factors on drug absorption processes. Towards this end, in the recent study of Sugano[67] the effect of Aqueous Boundary Layers (ABL) to oral absorption of a drug is discussed. Oral drug absorption is affected by several ABLs, which the drug have to pass through in order to be bioavailable i.e ABLs on drug particles and the intestinal surface which affect dissolution and permeation rates of the drug.[67] ABLs are discussed based on the fluid dynamic theory, since it can provide insights into the essence of mass transfer (dissolution and permeation of a drug) and improve the experimental design and computational simulation of oral absorption. The authors point out that the ABL hinders the measurement of membrane permeability (P_m) when P_m is close or higher than the ABL permeability (P_{ABL}), since it exists ubiquitously adjacent to the membrane. Therefore, it is necessary to remove the effect of the ABL to obtain an appropriate quantitative structure permeability relationship (QSPR).[67,68] This point has been overlooked in much QSPR literature and Caco-2 permeability is used regardless of the rate limiting step of apparent permeability. However, when the ABL was removed, the P_{app} value reached above 0.1 cm/s,[67,69] while after removal of the ABL and correction for the pH partition theory, a linear free energy relationship can be observed rather than nonlinear relationship which makes QSPR straightforward.[67]

The concept of complex dynamics of in vivo drug dissolution in GI tract and membrane transport is also discussed in the paper of Sugano.[67] It should be mentioned however that fractal kinetics was applied to describe carrier mediated drug transport by Macheras as early as in 1995[70] while, in 1997 Macheras and Argyrakis[3] pointed out the need to consider heterogeneity in GI drug absorption. This type of studies have indicated that when fractal kinetics operates, time dependent coefficients and not rate constants govern the complex processes in the GI tract. Extensive work has been performed in this field the last decade.[38,71,72] In addition, the interplay of various factors, such as cytochrome P450 enzymes and P_{gp} transporters, pH microclimate and P_{gp}-transporters, concentration dependence of Pgp substrates permeability, on GI drug absorption has been extensively discussed.[73–75]

3 Epilogue

Our ignorance about the exact dissolution mechanisms operating under in vitro and in vivo conditions points to the use of model independent parameters e.g. Mean Dissolution Time, for biopharmaceutic classification purposes. Furthermore, supersaturated solubility data of sparingly soluble drugs are more physiologically relevant for biopharmaceutic classification purposes and solubility-dissolution studies can be carried out towards this end. Finally, incorporation of recent scientific understanding regarding intestinal wall permeability (*transporters, transporter-enzyme interplay*) is absolutely necessary to improve the predictability of GI theoretical models.

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Received: November 25, 2010
Accepted: January 24, 2011
Published online: March 17, 2011