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Modelling and simulation in drug absorption processes

A. DOKOUMETZIDIS[1], G. VALSAMI[2], & P. MACHERAS[2]

[1]*University of Manchester, UK and* [2]*University of Athens, Greece*

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Abstract
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. Despite this complexity, various qualitative and quantitative approaches have been proposed for the estimation of oral drug absorption. These approaches are reviewed in this article with particular emphasis on drug dissolution modelling, dynamic systems for oral absorption and absorption models based on structure. The regulatory aspects of oral drug absorption and in particular the biopharmaceutic classification of drugs are also discussed. Models for drug dissolution and release describe adequately the *in vitro* data, and models for oral drug absorption provide reasonable results. The development of *in vitro–in vivo* correlations based on the official compendia specifications are facilitated using commercial computer packages.

Keywords: *Solubility, permeability, dissolution, intestinal transit, drug absorption*

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/pre-clinical development phase. Such a framework will certainly help regulatory agencies in developing scientifically based guidelines in accord with drug physicochemical properties for various aspects of oral drug absorption, for example dissolution, *in vitro–in vivo* correlations and biowaivers of bioequivalence studies.

Correspondence: P. Macheras, Laboratory of Biopharmaceutics and Pharmacokinetics, School of Pharmacy, University of Athens, Athens 15771, Greece. Tel: +030-210-7274026. Fax: +030-210-7274027. E-mail: macheras@pharm.uoa.gr

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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 (Macheras and Argyrakis 1997). Despite this complexity, various qualitative and quantitative approaches have been proposed for the estimation of oral drug absorption. The first section of this study deals with the processes of dissolution and release, while the following two focus on absorption models based on structure and the dynamical systems of oral drug absorption. The last section of this paper is devoted to the regulatory aspects of oral drug absorption and in particular to the biopharmaceutical classification of drugs.

Modelling of dissolution and release from solid drug formulations

Mathematical modelling of dissolution is necessary for successful oral absorption predictions, as dissolution is a dynamic, time-dependent process and cannot be characterized by a set of experimental values. *In vivo* dissolution models are based on mathematical models developed for *in vitro* dissolution data. However, purely empirical equations that have no physical meaning cannot be used for *in vivo* modelling because the parameters involved have no physical meaning and can take values only when fitted to dissolution data, which are not available *in vivo*. Only models that have a mechanistic or physical basis can be used as part of an absorption model. Their parameters may be determined *in vitro*, even when they are used under *in vivo* conditions, as these parameters have specific physical meaning.

The first model for *in vitro* dissolution data appeared in 1897, when Noyes and Whitney (1897) conducted the first dissolution experiments and noticed that the rate of dissolution is proportional to the difference between the instantaneous concentration, C, at time t, and the saturation solubility, C_s. These latter authors formulated the Noyes–Whitney law used extensively to model dissolution data, even today:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = k(C_s - C) \tag{1}$$

where k is a constant. The experiment configuration ensured that the surface of the materials was constant during dissolution. Noyes and Whitney attributed the mechanism of dissolution to a thin diffusion layer that is formed around the solid surface and through which the molecules diffuse to the bulk aqueous phase. The constant surface assumption was relaxed by Nernst (1904) and Brunner (1904).

More complex equations related to the diffusion layer dissolution model have appeared, with one of the most important contributions being the work of Levich (1962). More recently, Wang and Flanagan (1999) published a general, detailed model for spherical particles, taking into account explicitly the spherical geometry. The equations used for the diffusion layer model take simplified forms in sink conditions, for example the Hixson–Crowell cubic root equation (Hixson and Crowell 1931), which in general is not applicable under *in vivo* conditions.

Although the diffusion layer model, as expressed by the Noyes–Whitney and the Nernst–Brunner equations, is the most commonly used model today, several empirical equations are also used to model *in vitro* dissolution data. These equations, although they

lack a physical interpretation for the mechanism of the dissolution process, often offer better fits to the data. In 1972, Langenbucher published a report with the observation that when the quantity $-\ln(1-m)$ is plotted against time on a log-log plot, where m is the accumulated fraction of dissolved material, the curve looks linear, and one can then perform linear regression. This is equivalent to fitting a Weibull equation to the dissolution data:

$$m = 1 - \exp[-(t - T)^b/a] \tag{2}$$

where t is time, T is a lag time, a is a scale constant and b is a shape constant. The Weibull equation, because of its shape and flexibility, is one of the most commonly used equations to model *in vitro* dissolution data.

The utilization of the Weibull equation is routinely done on an empirical basis, but a physical interpretation for its use to model dissolution data has also been given (Macheras and Dokoumetzidis 2000) in the context of fractal kinetics (Kopelman 1989). Assuming that instead of the time constant k in equation 1, a time-dependent instantaneous rate coefficient governs the dissolution rate under non-homogeneous conditions, then k can be replaced by:

$$k = k_1 t^{-h} (t \neq 0) \tag{3}$$

where k_1 is a constant not dependent on time with units $(\text{time})^{h-1}$, and h is a pure number. Equation 3 has been used in chemical kinetics to characterize phenomena that take place under dimensional constraints or understirred conditions (Kopelman 1988). In dissolution studies it is used to account for the time dependency of the dissolution rate, as a result of changes in the conditions during the dissolution process, i.e. the reduction of the effective surface area, and/or the non-homogeneous hydrodynamic conditions affecting the thickness of the diffusion layer and diffusion coefficient. Using equation 3 for replacing k in equation 1, changing the concentration variable to amount and integrating the resulting equation, one obtains the Weibull equation, equation 2, for $a = k_1/(1-h)$ and $b = 1-h$. For $h = 0$ then $b = 1$ and the Weibull equation collapses to the Noyes–Whitney equation. The exponent h can be considered as a measure of heterogeneity in the sense that the further away it is from zero, the further away the dissolution kinetics are from the ideal homogenous case described by the Noyes–Whitney equation.

An important parameter in drug dissolution is the dose:solubility ratio, as this determines whether the initial drug quantity will reach saturation, leaving some undissolved quantity, or dissolve entirely. To model correctly these two cases, branched versions of the Noyes–Whitney and the Weibull equations have been considered (Dokoumetzidis et al. 2006). Expressing the equation as a fraction of dose dissolved, Φ, the branched Weibull equation has the form

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

where q is the dimensionless dose:solubility ratio equal to Dose/(C_s V), C_s is the 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 Noyes–Whitney is obtained from equation 4 by letting $b = 1$. The branched versions of the dissolution models allow, in principle, the estimation of solubility even when the data do not reach saturation (Dokoumetzidis et al. 2006).

For a considerable proportion of compounds, controlled release formulations are developed, when the immediate release formulations are not appropriate. Reasons for that

include a short half-life of the drug, a narrow therapeutic index, site-dependent absorption and marketing benefits. The basic performance requirement of controlled release systems is that they release drug *in vivo*, according to a predictable rate and the principal release mechanism for these systems is diffusion. The mathematical modelling of drug release from diffusion-controlled systems relies on the Higuchi model published in 1961. Later on, Peppas (1985) introduced a semi-empirical equation (the so-called power law) to describe drug release from polymeric devices.

Apart from the Peppas equation, the Weibull equation has also been used for modelling data from sustained release formulations. This has been investigated using Monte Carlo simulation methods of the release process (Kosmidis et al. 2003a, 2003b). Unlike *in vitro* dissolution profiles, a release time profile determined *in vitro* can usually be used *in vivo* too, even when described by empirical equations, as these systems are made to release the drug at a consistently specific rate.

Dynamical systems for oral drug absorption

Transit through the GI tract, including gastric emptying, is a particularly important element of the overall variability observed in drug absorption. Like dissolution, gut transit is a time-dependent, dynamic process and, therefore, can only be accurately characterized by full mathematical modelling. In general, the drug follows the movement of the intestinal fluids which is more rapid in the beginning of the small intestine and slows down as it approaches the colon. Also, the fluids move slower near the walls of the lumen and the flow is more rapid near the axis of the lumen, a fact that contributes significantly to the axial dispersion of material along the lumen. The other important factor for the dispersion is the intestinal motility. Food has an important impact on the transit profile of the GI contents, as well as their composition. The presence of food particularly influences gastric emptying and generally increases the transit time through the intestinal lumen. Experimentally, GI transit has been studied by non-invasive techniques, such as gamma-scintigraphy (Digenis et al. 1990; Kelly et al. 2003), non-absorbable tracers (Sawamoto et al. 1997) and magnetic resonance imaging (Weitschies et al. 1994). These latter techniques offer valuable information and assist the building of detailed models for GI drug transit and absorption.

Dynamic mathematical models describing intestinal transit are basically of three different types:

- Tank models, where the GI tract is considered to be a single well-stirred compartment.
- Compartmental transit models, where the intestinal tract is modelled by a series of compartments.
- Dispersion models, where a continuous tube including transport and dispersion is employed.

The mixing tank model is the simplest model that can describe the absorption process. It consists of a compartment where dissolution and absorption take place. Typically, a first-order decrease of drug due to transit out of the intestinal tank is considered (Dressman and Fleisher 1986). An alternative one-compartment absorption model is based on a microscopic mass balance approach and implements transit as a time constraint, after which absorption stops, assuming that the end of the intestinal transit has been reached (Sinko et al. 1991; Oh et al. 1993), The latter approach, despite its simplicity, is quite

adequate for a qualitative description and has been the basis for the definition of the key parameter of dissolution number *Dn* (Oh et al. 1993) and for the formulation of the Biopharmaceutics Classification System (BCS; Amidon et al. 1995).

The compartmental transit models were introduced in the mid-1990s by Yu et al. (1996) and also by Grass (1997). Yu et al.'s model is referred to as the Compartmental Absorption Transit (CAT) model and comprises a number of compartments in series which act as delay elements, but specific physiological meaning is given to each one of them, corresponding to intestinal regions. It has been reported (Yu et al. 1996) that seven compartments for the small intestine is the best choice for this model. For immediate release formulations, gastric emptying is modelled as a first- or zero-order transit process from the stomach compartment to the first intestinal compartment. The dissolution and release processes can be incorporated as well in the above formulation by considering more than one drug concentration, corresponding to the unreleased, the undissolved and the dissolved molecules of drug (Yu and Amidon 1999). In a later modification of the CAT model, referred to as Advanced CAT, the transit rate constants are scaled accordingly to correspond to realistic flows of the actual segments of the intestinal tube, therefore taking larger values for the upper compartments (Agoram et al. 2001). This latter model also incorporates a number of additional processes, such as release, dissolution, precipitation, gut metabolism, influx and efflux transport in the enterocytes and other features, and in its complete form is the basis of the commercial software package GastroPlus™ (Simulations Plus, available online at: http://www/simulations-plus.com/products/gastro_plus.html).

An alternative to the compartmental mathematical description is the dispersion model (Ni et al. 1980). In this model, a tube is considered and within it a continuous concentration spatial profile. The time evolution of the spatial profile of the concentration, $C(z,t)$, is described mathematically by a partial differential equation (PDE), incorporating dispersion and transport of the form:

$$\frac{\partial C(z,\,t)}{\partial t} = \alpha \frac{\partial^2 C(z,\,t)}{\partial z^2} - \beta \frac{\partial C(z,\,t)}{\partial z} - \gamma C(z,\,t) \tag{5}$$

where α is the dispersion coefficient, mainly due to geometrical dispersion, β corresponds to the velocity of the intestinal fluid and $\gamma = 2P_{eff}/R$ is the drug absorption rate constant, expressed in terms of effective permeability, P_{eff} and the radius of the intestine, R. Equation 5 needs appropriate initial profile and boundary conditions to be fully defined and, for some special cases, has analytical solutions (Ni et al. 1980), otherwise it can be solved numerically. Again, concentrations for two species can be considered for the undissolved and the dissolved drug molecules (Macheras and Illiadis 2006). The dispersion model may include spatially varying β and γ to implement the downstream slowing down of the fluid and also regionally varying permeability, yielding a very component-rich behaviour (Figure 1; Macheras and Illiadis 2006).

Also, in 2003, Willmann et al. presented a drug absorption model for the rat which has some flavour of the dispersion model; and in 2004 they extended the same model for humans too (Willmann et al. 2003, 2004). In this model a continuous drug concentration profile is considered inside a tube which is described by a Gaussian function with a transiently moving centre and varying width, thus mimicking the dispersion and transport phenomena in the tube. This model evolved to be a part of the commercial, physiologically based, pharmacokinetic simulation software PK-Sim® (Bayer Technology Services, http://www.pk-sim.com).

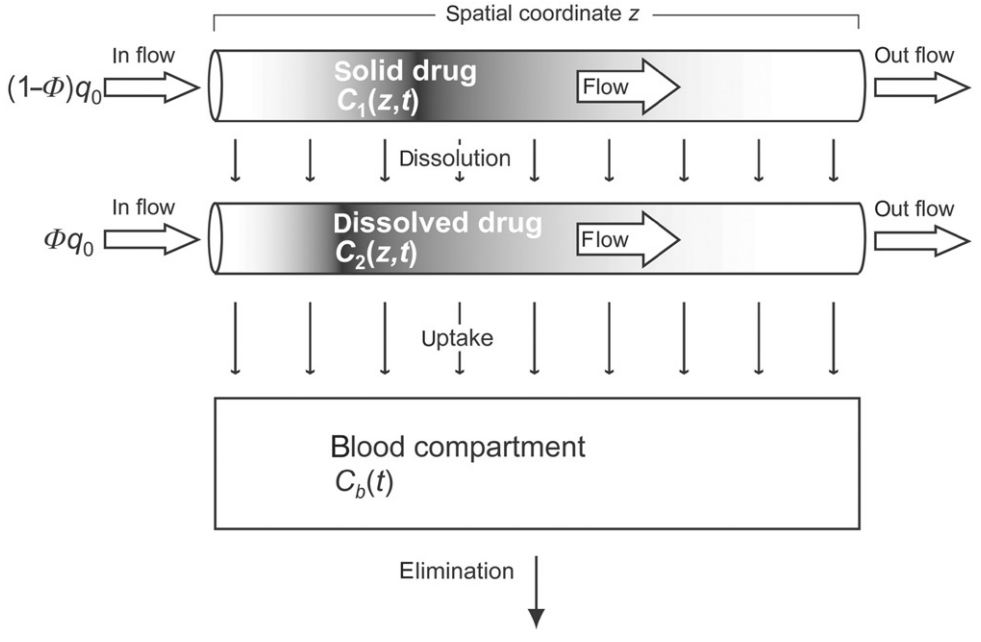

Figure 1. A dispersion model that incorporates spatial heterogeneity for the gastrointestinal absorption process. q_0 denotes the administered dose and ϕ is the fraction of dose dissolved in the stomach. $C_1(z,t)$, $C_2(z,t)$ are the spatio-temporal profiles of the undissolved and dissolved drug concentrations, respectively, where z is the axial coordinate, while $C_b(t)$ is the drug concentration in the general circulation. (Reprinted from Macheras and Iliadis 2006, with permission from Springer).

Other attempts to model drug transit in the intestinal lumen, include Monte Carlo simulations. Kalampokis et al. (1999a, 1999b) have presented a GI drug absorption model, where the drug flow in the small intestine was simulated with a biased random walk model, and probabilistic concepts were used to describe the dissolution and uptake processes.

The integrated absorption models that have appeared in the recent years, have become parts of whole body ADME simulation software packages. These models use *in vitro*, *in vivo* and/or *in silico* information as input and have exhibited reasonable results for predicting oral absorption. In general, modelling of passively absorbed drugs is more successful than the actively transported, as it is simpler and the factors involved have been studied more extensively. Despite the fact that predictions are not perfect, they are still quite useful as they help with identification of absorption problems as early as possible in the drug development pipeline.

Absorption models based on structure

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' (Lipinski et al. 1997), 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

Although various computational approaches for the prediction of intestinal drug permeability and solubility have been reported (Stenberg et al. 2002), recent computer-based absorption models use 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' (Bergstrom et al. 2003), Abraham molecular descriptors (Zhao et al. 2001, 2002), and a variety of structural descriptors with neural networks (Turner et al. 2004) have shown to be determinants of oral drug absorption.

Recently, Yalkowsky et al. (2006) proposed the 'rule of unity' to predict the absorption efficiency of orally administered drugs that are passively transported. The rule of unity is a theoretically based semi-empirical relationship that relies on the absorption potential concept (Dressmann et al. 1985; Macheras and Symillides 1989). It has been applied to passive human absorption data and has been shown to be a good indicator of the absorption of orally administered drugs. According to the 'rule of unity', drugs with absorption values that correspond to more than 50% of the dose are classified as 'well absorbed', while those with absorption values that correspond to less than 50% of the dose are classified as 'poorly absorbed'.

More recently, Linnankofski et al. (2006) developed models for predicting oral drug absorption kinetics by correlating human intestinal absorption rate constants (k_a) with the physicochemistry of passively absorbed drugs. The k_a values of 22 passively absorbed drugs were derived from human plasma concentration–time profiles using deconvolution analysis, an approach that provides more information about the kinetics of absorption through the entire intestine rather than the jejunal perfusion system, which measures P_{eff} in only a 10-cm segment of the jejunum. The derived k_a values fitted an ideal sigmoidal relationship prevailing between a parameter describing the kinetics of oral absorption and the fraction of dose absorbed. The multivariate PLS analysis applied to establish the relationships between log k_a values and simple computed molecular descriptors, revealed that the most important parameters describing log k_a were polar surface area, number of hydrogen bond donors and log D, at a physiologically relevant pH value. A combination of two or three of these descriptors permitted the prediction of passive intestinal absorption kinetics in humans.

Regulatory aspects of oral drug absorption: Biopharmaceutic classification of drugs

Amidon and co-workers (Oh et al. 1993) made an elegant analysis of a drug dissolution and absorption model for water-insoluble compounds and indicated very clearly that the key

parameters controlling drug absorption are three dimensionless numbers: an absorption number, a dissolution number and a dose number representing the fundamental processes of membrane permeation, drug dissolution and dose, respectively. The development of the Biopharmaceutics Classification System (BCS) (Amidon et al. 1995) was mainly based on these findings (Oh et al. 1993); however, only permeability and solubility were considered as the key underlying parameters controlling drug absorption. Accordingly, drugs were divided into four high/low solubility–permeability classes (Amidon et al. 1995). Although the dose was not included directly into the actual classification (Amidon et al. 1995), a drug is defined as highly soluble in the FDA guidance on the biowaiver of *in vivo* bioavailability and bioequivalence (FDA Guidance for Industry 8/2000) 'when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0−7.5'. In addition, both in the original BCS article as well as in the FDA's guideline, the dose is considered indirectly in the additional dissolution specifications for rapidly dissolving immediate release formulations, i.e. no less than 85% of the dose is dissolved within 30 min (FDA Guidance for Industry 8/2000).

Recently, Rinaki et al. (2003b) 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 (Rinaki et al. 2003a). The QBCS uses a solubility:dose ratio ($1/q$) vs. permeability plane with scientifically, physiologically based cut-off values for compound classification (Figure 2); q is the dimensionless dose/solubility ratio equal to Dose/(C_sV).

More specifically, classification according to QBCS is based on the tube model of the intestinal lumen (Figure 3) that places particular emphasis on the mean time for dissolution, *MDT* (or mean time for saturation, *MDTs*, when the entire dose is not dissolved), and uptake (mean absorption time, *MAT*) of drug in relation to the mean intestinal

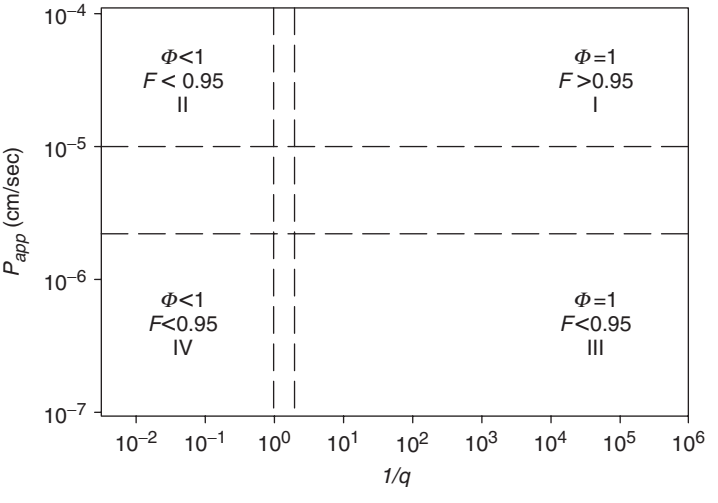

Figure 2. The solubility: Dose ratio ($1/q$), apparent permeability (P_{app}) plane with the specific cut-off points used for drug classification according to the Quantitative Biopharmaceutic Classification System (QBCS). Each class of the QBCS can be characterized on the basis of the anticipated values for the fraction of dose absorbed, F, and the fraction of dose dissolved, ϕ, at the end of the dissolution process; $1/q$ is the dimensionless solubility/dose ratio, equal to $C_sV/Dose$). (Reprinted from Macheras and Iliadis 2006, with permission from Springer).

transit time, *MITT*. The dynamic character of the processes involved in intestinal drug absorption implies that a proper biopharmaceutical classification of drugs can be based on fundamental drug properties, which determine or are associated with the global kinetic characteristics of the drug processes, *MDT* (or *MDTs*) and *MAT*, taking into account the time domain of the physiological restriction, *MITT* (Figure 3).

For dissolution classification purposes, the dimensionless dose:solubility ratio $q = \text{Dose}/(C_s V)$ for the particular drug formulation, which was recently shown to be dependent on *MDT* when the entire dose is dissolved ($q \leq 1$), or *MDTs* when the entire dose is not dissolved ($q > 1$; Rinaki et al. 2003a), is considered.

For permeability classification purposes the experimental values of the apparent permeability, P_{app}, for drug transport in Caco-2 monolayers, which have been shown to model adequately the drug transport *in vivo*, are used. In addition, a cut-off point for highly permeable drugs, $P_{app} = 10^{-5}$ cm/s, ensuring fraction of drug absorbed > 0.95, has been established. In line with the recent data of Bergstrom et al. (2003) and Sun et al. (2002) regarding the cut-off limit of permeability, the values for permeability classification purposes from 2×10^{-6} to 10^{-5} cm/s for P_{app} as a boundary region of highly permeable drugs for complete absorption, are used. A large number of drugs were classified into the four explicitly defined quartiles of the permeability-solubility:dose ratio plane and the borderline region (Figure 2). In general, the classification results were found to be in accord with the experimental observations in regard to the fraction of dose absorbed (Rinaki et al. 2003b).

An application of QBCS for the identification of biowaivers among class II drugs was recently reported (Rinaki et al. 2004), where the dynamics of the two consecutive drug processes, dissolution and wall permeation, are considered in the time domain of the physiologic transit time. Analysis relies on the tube model of the intestinal lumen

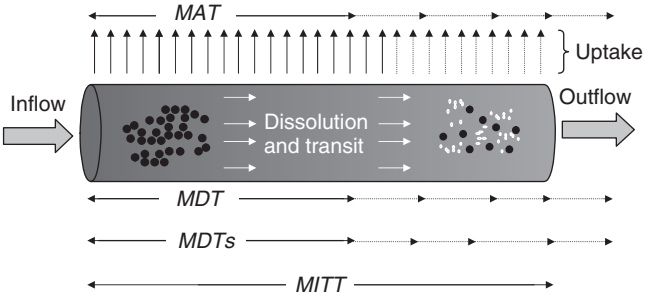

Figure 3. A schematic of absorption processes in the intestine. The black dots represent drug solid particles and the white dots represent dissolved drug species. Drug dissolution in the intestinal fluids and permeation of the intestinal wall are consecutive first-order processes, which take place in the time domain of the mean intestinal transit time (*MITT*) imposed by the physiology. When the entire dose can be dissolved in the intestinal contents the mean dissolution time (*MDT*) refers to the dissolution process of the entire dose. When only a fraction of dose can be dissolved in the intestinal contents, the mean dissolution time for saturation (*MDTs*) refers to the dissolution process of the fraction of dose dissolved, ϕ. If the entire dose is dissolved prior to its arrival at the end of the tube then the fraction of dose dissolved, ϕ is equal to one, otherwise $\phi < 1$. The mean absorption time (*MAT*) refers to the permeation process. The positioning of the right end pinpoints of the arrows associated with *MDT*, *MDTs* and *MAT* indicate that each of them can be smaller, higher or equal to *MITT*. (Reprinted from Rinaki et al. 2003b, with permission from Springer).

used by Oh et al. (1993) for the development of BCS (Amidon et al. 1995). 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 as follows:

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

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

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, F at the end of the tube, similar to that used in the study of Oh et al. (1993) was also considered:

$$F = \frac{M_0 - M_{solid} - M_{dissolved}}{M_0} \tag{8}$$

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:

$$F = 1 - \left(\frac{r_p}{r_0}\right)^3 - \Phi \tag{9}$$

where r_p, and Φ in Equation 9 refer to their values at $t = MITT$.

One of the most significant results of this work (Rinaki et al. 2004) 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 for the first time 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 (Rinaki et al. 2003) 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 utilized.

The dynamic model developed and the analysis presented (Rinaki et al. 2004) 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 (Sun et al. 2002) 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 (Rinaki et al. 2003). Consequently, consideration should be given to the dynamic aspects of intestinal absorption for biopharmaceutical drug classification.

Recently, Kortejarvi, Urti and Yliperttula (2007) used a pharmacokinetic simulation model to evaluate current biowaiver criteria for BCS class I drugs and to explore whether biowaivers can be found among BCS class II–IV drugs. Gastrointestinal tract parameters and drug-related parameters were combined with the CAT model (Yu et al. 1996) to study the effects of formulation types and different rates of dissolution and gastric emptying on drug concentration in plasma. Simulated C_{max} and AUC values of solid dosage forms were compared with the respective values for oral solution. According to the results (Kortejarvi et al. 2007), BCS class III drugs and slowly eliminating BCS class I drugs are better biowaiver candidates than rapidly eliminating BCS class I drugs, for which 10–25% difference in C_{max} values were observed.

A modified version of BCS was also developed recently, namely the Biopharmaceutics Drug Disposition Classification System (BDDCS), which extends the BCS to include drug elimination and the effects of efflux and transporters on oral drug absorption (Wu and Benet 2005). These latter 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 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.

Some practical applications of this area of research are particularly useful for regulatory submissions, since the development and possible role of *in vitro–in vivo* correlation (IVIVC) is discussed both in US Pharmacopeia (USP 29) and in a number of FDA guidances (09/1997a,b, 10/1997, 08/2000, 10/2000). IVIVC is defined as 'a predictive mathematical model describing the relationship between an *in vitro* property (usually the rate and extent of dissolution or release) and a relevant *in vivo* release response, for example plasma concentration or amount of drug absorbed'. Four types of IVIVC have been described in FDA guidances, namely levels A, B, C and multiple level C. Level A correlation describes the relationship between the entire *in vitro* dissolution time course and the *in vivo* response time course. Since level A is the most informative IVIVC, the approach to setting upper and lower dissolution specifications using this type of correlation is described in FDA guidance (1997a). The software PDx-IVIVC was developed for the prediction of plasma concentration curves for formulations at the upper and lower dissolution specifications (http://globomax.net/products/pdx_ivivc.cfm).

Conclusions

The various qualitative and quantitative approaches for the estimation of oral drug absorption have been reviewed in this article with particular emphasis on drug dissolution modelling, dynamic systems for oral absorption and absorption models based on structure. Mathematical modelling of dissolution is important for successful oral drug absorption predictions. However, only models that have mechanistic or physical basis can be used as part of an absorption model. The Weibull function used in the modelling of drug dissolution and release was shown to have a physical basis. Dynamic mathematical

models describing simultaneously the intestinal transit and absorption processes should be applied in order to have accurate predictions for drug absorption. These models are useful tools as part of commercially available whole body models. Computer-based models, based on calculated molecular descriptors are useful to predict the extent of absorption from chemical structure in order to facilitate the lead optimization in the drug discovery process. Regarding the regulatory aspects of oral drug absorption, the dose should be taken into account for the biopharmaceutic drug classification since the solubility/dose ratio was proved to be the key parameter for solubility classification, inextricably linked to the dynamic characteristics of the dissolution process. Owing to the dynamic nature of dissolution-uptake processes, biowaivers can be also found in class II. Also, using elimination criteria may expand the number of class I biowaivers and provide predictability of drug disposition profiles for drugs of classes II, III and IV. Finally, the development of IVIVC in accord with the official compendia specifications is facilitated using computer packages.

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