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MiniReview

Modeling and Monte Carlo Simulations in Oral Drug Absorption

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Abstract: Drug dissolution, release and uptake are the principal components of oral drug absorption. All these processes take place in the complex milieu of the gastrointestinal tract and they are influenced by physiological (e.g. intestinal pH, transit time) and physicochemical factors (e.g. dose, particle size, solubility, permeability). Due to the enormous complexity issues involved, the models developed for drug dissolution and release attempt to capture their heterogeneous features. Hence, Monte Carlo simulations and population methods have been utilized since both dissolution and release processes are considered as time evolution of a population of drug molecules moving irreversibly from the solid state to the solution. Additionally, mathematical models have been proposed to determine the effect of the physicochemical properties, solubility/dose ratio and permeability on the extent of absorption for regulatory purposes, e.g. biopharmaceutics classification. The regulatory oriented approaches are based on the tube model of the intestinal lumen and apart from the drug's physicochemical properties, take into account the formulation parameters the dose and the particle size.

Modern drug design not only focuses on the pharmacological activity of a compound but also considers its ability to be absorbed and to reach its site of action. The development of tools capable of predicting the fraction of dose absorbed or bioavailability, would therefore enhance our ability to develop viable drugs. However, oral drug absorption is affected by both drug properties and the physiology of the gastrointestinal tract including drug dissolution or release from the dosage form, the manner in which drug interacts with the aqueous environment and the membrane, and irreversible removal by first-pass organs such as the intestine and liver. Thus, the factors that influence the absorption of drug from the gastrointestinal tract can be divided into physiological factors (intestinal pH, transit time, gastrointestinal motility, luminal metabolism, blood flow, endogenous substances, such as bile salts, transporters and exogenous substances such as nutrients) and physicochemical factors (dose, particle size, solubility, partition coefficient, dissociation constant, chemical stability, etc.).

Despite the complexity and heterogeneity of gastrointestinal drug absorption, a variety of models have recently been developed for the study of either one single or all the participating processes in oral drug absorption. The former group of models is of exploratory nature while the latter group focuses on the prediction of intestinal absorption. The models rely on Monte Carlo simulations, population approaches, systems of difference or differential equations and principles of fractal geometry or fractal kinetics. These recent developments in this field of research are itemized in the following three sections under the subheadings i) Monte Carlo simulations in drug release ii) novel approaches in drug dissolution and iii) predictive models of oral drug absorption.

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Monte Carlo simulations in drug release

This technique has only recently been used in order to study the problem of drug release giving illuminating results. The Monte Carlo method comes in many flavours and is used in many different ways, from numerical integration to Bayesian inference and decision theory, which all share in common the utilization of random numbers, wherefrom its name. One of its uses is Monte Carlo simulation, which is a computational technique for the solution of physical problems of statistical nature (Landau & Binder 2000). In a Monte Carlo simulation one attempts to follow the "time dependence" of a system for which change is supposed to be stochastic instead of deterministic, modeling this randomness by random numbers generated during the simulation. Using a different sequence of random numbers will produce similar (with a "statistical error") but not identical results. It is mainly used to monitor the time evolution of a physical system with a large number of components by

drawing random numbers in order to determine the future state of each component in microscopic level. A large number of "computer experiments" are performed and averages are calculated that characterize observable quantities, determining the macroscopic state of the system. Until recently the modeling of drug release was primarily mathematical modeling using differential equations (Ritger & Peppas 1987a&b; Siepmann & Peppas 2000). Only recently some attempts have been made to introduce Monte Carlo technique in the study of drug release problems.

The problem of particle release from a matrix is the central point in studying drug release from delivery systems. The basic question posed is how do the drug molecules escape from a tablet or capsule that is taken orally and how are they delivered to the gastrointestinal tract. The release mechanism is dependent on the device used, and thus there is no single answer to the above question. In some cases the drug device disintegrates instantly and the entire quantity of solid drug particles becomes available for dissolution in the gastrointestinal fluids. On the other hand, for controlled release formulations several mechanisms can be envisaged.

According to the classical mechanism the escape route of drug molecules from the release device is through Fickian diffusion before the device is dissolved. For detailed studies of this model, see for example Siepmann & Peppas (2001) and Ritger & Peppas (1987a&b). This model has also been studied by means of Monte Carlo simulations (Kosmidis *et al.* 2003a). The basic assumption of the model is that the number of particles N inside the release device obeys the differential equation

$$\frac{dN}{dt} = -a\, f(t) N \tag{1}$$

where $f(t)$ is a function of t and a is a proportionality constant. A plausible assumption for the form of $f(t)$ is that of a power law and hence the above differential equation will have the solution

$$N = N_0\, exp(-\alpha\, t^b) \tag{2}$$

Monte Carlo simulations have verified that the Weibull function (Eq. 2) describes nicely the drug release curve when the drug release mechanism is Fickian diffusion (fig. 1). Monte Carlo simulations were further used to determine the connection of parameters α, b with the geometry of the release device. The simulation results have shown that both parameters are independent of the initial drug concentration of the release device, but they depend on the ratio N_{leak}/N_{total}, where N_{leak} is the number of leak sites and N_{total} the total number of sites of the simulated system. More specifically α is strongly depended on the specific surface of the matrix and b has two contributions. The most significant is the one resulting from the particle interactions and their ability to move inside the matrix, and a weaker contribution from the specific surface. In this case the value of exponent b was found to be $b \approx 0.70$, for large devices.

A second possibility is that the release devise, as it is immersed in the gastrointestinal tract fluids, it is penetrated by these fluids, creating areas of high diffusivity. Thus, the drug molecules can escape from the release device through diffusion from these high diffusivity "channels". Now, the dominant release mechanism is diffusion, but in a complex disordered medium. The same is true when the polymer inside the release device is assuming a configuration resembling a disordered medium. This is a model proposed for hydroxypropylmethylcellulose matrices (Bonny & Leuenberger 1991). This last interesting possibility was first studied by Bunde *et al.* (1985) and recently by Kosmidis at al (2003b). Despite earlier results indicating that fractal release rates were described by power laws, extensive com-

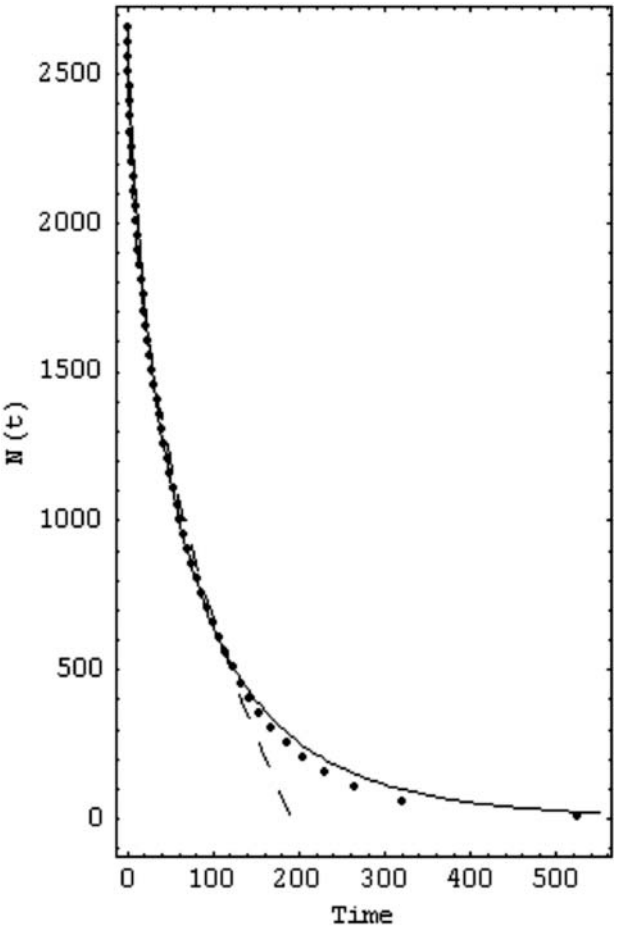

Fig. 1. Release curves from a cylindrical device with axial and radial release. The interior of the cylinder is considered to be Euclidean. The plot shows the number of particles inside a cylinder as a function of time expressed in Monte Carlo Steps (MCS).

a. Dotted line: Monte Carlo simulation results for cylinder with height 21 sites and diameter 21 sites. Number of drug molecules N_0=2657
b. Thin solid line: Fitting results using the Weibull model. Plot of curve $N=N_0$. Exp$(-\alpha\, t^b)$ N_0=2657, α=0.0049, b=0.72
c. Dashed Line: Fitting results using the power law model. Plot of curve $N=N_0$. $(1-k\, t^n)$ N_0=2657, k=0.094, n=0.45. (Power law fitting)

The Weibull function describes simulation data more accurately till the end of the release. From Kosmidis *et al.* (2003a) reproduced with permission of the copyright owner.

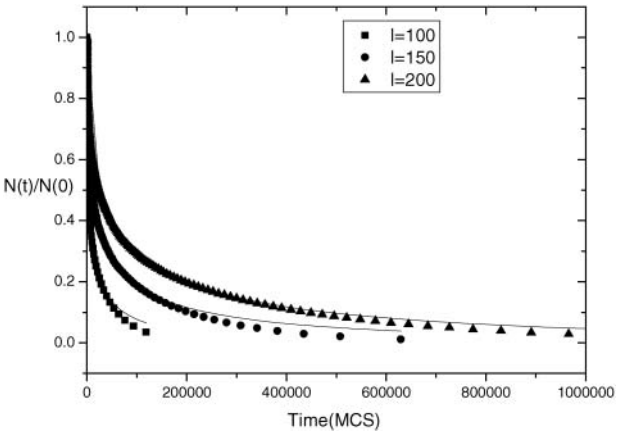

Fig. 2. Release curves from percolation fractals embedded in lattices of size 100×100, 150×150 and 200×200, respectively. The plot shows the number of particles (normalized) remaining in the percolation fractal as a function of time expressed in Monte Carlo Steps (MCS) for the above mentioned lattice sizes. $N(t)$ is the number of particles that remain in the fractal at time t, and N_0 is the initial number of particles. Monte Carlo Simulation results are represented by points. The solid lines represent the results of non-linear fitting with a Weibull function $N=N_0$. Exp$(-\alpha\ t^b)$. From Kosmidis *et al.* (2003b) reproduced with permission of the copyright owner.

puter simulation results as well as application of the fractal kinetics theory have shown that the stretched exponential, (Eq. 2), is a more proper description, but with a different (lower) value for the exponent b (fig. 2).

Of course, in realistic situations for controlled release formulations, it is expected that the above mechanisms co-exist simultaneously. This fact usually complicates the analysis of experimental data. In such cases Monte Carlo simulations may be particularly useful.

A different application of Monte Carlo method to drug release modeling was published by Siepmann *et al.* (2002). In this work, Monte Carlo method is used for the numerical solution of a partial differential equation model.

Novel approaches in drug dissolution

Fractals (Bassingthwaighte *et al.* 1994) are geometrical objects with infinite detail and possess the property of self similarity. Other than their mathematical applications, fractal concepts have been applied in a lot of disciplines when the presence of non-standard geometry, e.g. non-smooth surfaces plays an important role. The use of fractal concepts in drug dissolution first appeared in Farin & Avnir (1992). In this work the classical Noyes-Whitney equation and the Hixson-Crowell cubic root law were extended and modified to include surface roughness effects on the dissolution rate of drugs. An application of the results of this study appeared in Valsami & Macheras (1995), where a method for the calculation of fractal reaction dimension, in dissolution studies of powdered substances, is presented. The method was applied to simulated errorless and contaminated data with very good results, as well as on experimental data taken from the literature. In 2000, Macheras & Dokoumetzidis presented models of dissolution and release which generalized the classical models by replacing the rate constants of the latter by power functions of time, in the same rationale discussed above for Eq. 1, deriving the well-known empirically used Weibull equation (a stretched exponential function similar to Eq. 2, Langenbucher (1972) and the power law (Ritger & Peppas 1987a&b). The models were fitted to experimental profiles and departure from the classical case (expressed by the value of the exponent of the power function of time), gave a measure of heterogeneity of the dissolution or release process. This approach gives a physical interpretation to the great success of Weibull and power law functions for the description of dissolution and release data. Also, the power law type rate coefficients can be physically interpreted by fractal kinetics (Kopelman 1988), due to the heterogeneous nature of the understirred dissolution medium. Fractal kinetics is a concept that first appeared in chemical kinetics to describe the kinetics of chemical reactions which are considered to take place in non-homogeneous, distorted, spaces and are closely related to fractal geometry mentioned above.

In 1997 a population growth model was developed by Dokoumetzidis & Macheras for describing drug dissolution which does not require the assumptions of time continuity and Fick's law of diffusion, and which can be applied to both homogeneous and heterogeneous media. The mass dissolved is considered to be described by a discrete time, difference equation, specifying successive "generations". Thus, the dissolution process is considered as time evolution of a population of the drug molecules moving irreversibly from the solid state to the solution. The model was fitted successfully to experimental danazol data, as well as the prediction of fraction of dose absorbed for highly permeable drugs. The population growth model of dissolution (Dokoumetzidis & Macheras 1997) has also been used for the analysis of supersaturated dissolution data of phenytoin and nifedipine (Valsami *et al.* 1999).

The continuous analogue of the discrete population growth model of dissolution (Dokoumetzidis & Macheras 1997), using an ordinary differential equation instead of a discrete differential equation, was published by Lansky & Weiss (1999). In this model, instead of assuming a constant fractional dissolution rate, as in the classical first-order model, it is considered that the fractional dissolution rate is a decreasing function of the dissolved amount controlled by the dose/solubility ratio. The model was successfully fitted to data and the main conclusion was that the mean dissolution time is affected by the dose/solubility ratio. In a successive paper Lansky & Weiss (2001) investigated new models characterizing dissolution data utilizing two approaches: consideration of heterogeneous materials and randomly time-varying conditions. In the former, the heterogeneity of the dissolving substance was considered to introduce variation of the fractional dissolution rate, with the result that the heterogeneity, with the same mean properties, slows down the dissolution with respect to the homogeneous case. In the latter approach, the fractional dissolution rate was considered to

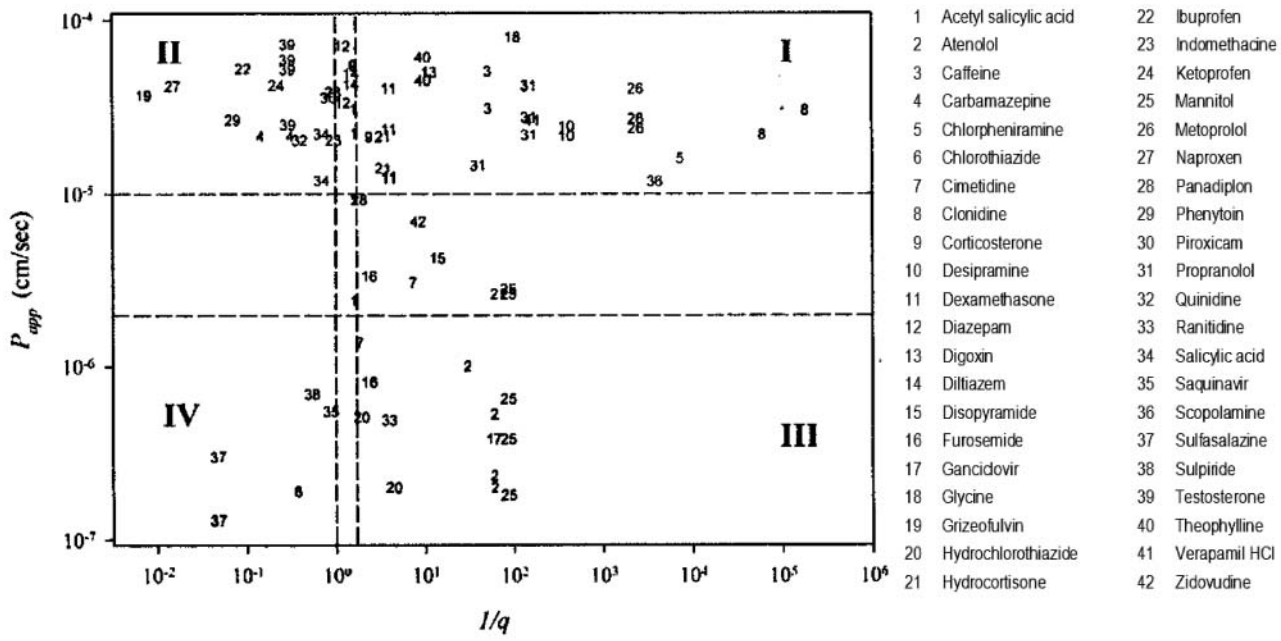

Fig. 3. The classification of 42 drugs in the (solubility/dose ratio, apparent permeability) plane for the QBCS. The dashed lines refer to the cutoff points of the four classes. From Rinaki *et al.* (2003b) reproduced with permission of the copyright owner.

evolve randomly, allowing dissolution to be a stochastic process, which permits predictions about the role of the stochastic fluctuations of the dissolution rate, and establishing the boundaries for the dissolution profiles. Also, Lansky & Weiss (2003) proposed a classification of dissolution profiles in terms of a novel measure of heterogeneity. Dissolution profiles were compared to the classical first-order model, which was considered to be the homogeneous case. A measure called Kullback-Leibler information distance was proposed for measuring similarity between the first-order model and other common descriptors of dissolution. It was applied successfully in simulated and experimental data, and was proposed to be a measure of heterogeneity in dissolution profiles.

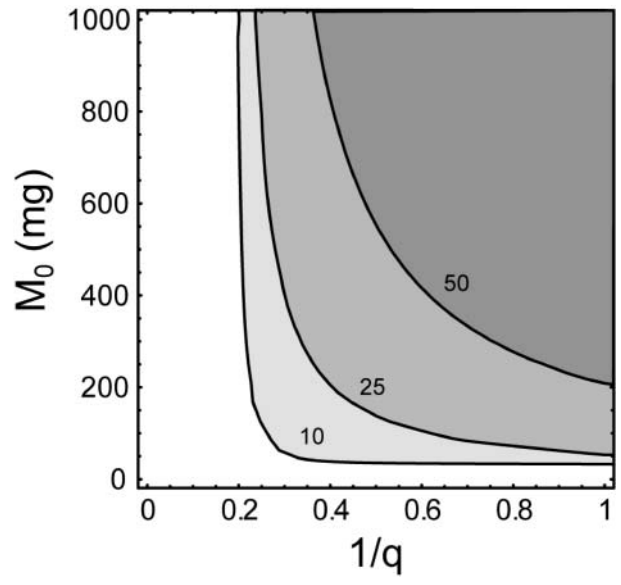

Fig. 4. Plot of dose, M_0 versus the dimensionless solubility/dose ratio, $1/q$. The curves indicate 90% absorption for three radii sizes, 10, 25, and 50 μm assuming $Peff=1.2\times10^{-2}$ cm/min. Since the assigned value to P_{eff} corresponds to the upper boundary limit (expressed in apparent permeability values (fig. 3)) of the borderline permeability region of QBCS, compounds of category II of QBCS exhibiting complete absorption are located in the shaded areas. From Rinaki *et al.* (2004) reproduced with permission of the copyright owner.

Predictive models of oral drug absorption

The complexity and heterogeneity of gastrointestinal drug absorption is very well known (Macheras & Argyrakis 1997). Two major approaches have been formulated in the modelling of the drug absorption processes involved in the complex milieu of the gastrointestinal tract. The first one is the simplified description of the observed profiles, using ordinary differential equations or even empirical algebraic equations, where the heterogeneity is either ignored, or included indirectly. These approaches, despite their simplicity, offer a reasonable qualitative description, and are often used to support development of industry regulations (FDA 2000). The most important example is the development of Biopharmaceutics Classification System (BCS) (Amidon *et al.* 1995) which was based on a simple homogeneous "first-order" model for dissolution and uptake (Oh *et al.* 1993), but included the key features of these processes. On the other hand, there is a second approach that tries to describe in more detail the complexity of the processes taking place in the intestinal lumen, using either compartmental analysis, i.e. systems of several differential equations (Yu *et al.*

1996; Grass 1997; Agoram *et al.* 2001), dispersion systems with partial differential equations (Ni *et al.* 1980; Dokoumetzidis & Macheras 2003; Willmann *et al.* 2003), or Monte Carlo simulations (Kalampokis *et al.* 1999a&b). In these approaches the heterogeneity is accounted for explicitly and mathematical models are built that include several parameters, which are sometimes difficult to estimate, due to the lack of data from within the intestinal lumen. In spite of this, there has been significant success with some of these approaches that has even led to the development of commercial computer software like GastroPlus™ (Simulations Plus Inc. Lancaster, CA, USA, http://www.simulations-plus.com/) and iDEA pkEXPRESS™ (LION bioscience AG, Heidelberg, Germany, http://www.lionbioscience.com/). With the further development of non-invasive techniques, more data from within the region of interest will be available, and there is certainly great future in these approaches. Here however, we will focus mainly on recent developments in the simplified or empirical description of oral drug absorption and the relevant regulatory aspects.

The key role of dose/solubility in drug dissolution using the classic first order dissolution model was demonstrated by Rinaki *et al.* (2003a). They investigated the relationship between mean dissolution time (MDT) and dose/solubility ratio, in the same vein as Lansky & Weiss (1999). The findings were applied to *in vitro* and *in vivo* data taken from literature and exhibit that mean dissolution time of a drug depends on dose/solubility ratio, even when the model considered is the simplest possible. The realization of the central role of dose/solubility ratio in drug dissolution prompted the introduction of the Quantitative Biopharmaceutics Classification System (QBCS) (Rinaki *et al.* 2003b). In full analogy with the BCS (Amidon *et al.* 1995), the QBCS classifies drugs into four categories based on their permeability (P_{app}) and solubility/dose ratio (1/q) values defining appropriate cutoff points. For category I (high P_{app}, high 1/q), complete absorption is anticipated, whereas categories II (high P_{app}, low 1/q) and III (low P_{app} , high 1/q) exhibit dose/solubility ratio- and permeability-limited absorption, respectively. For category IV (low P_{app}, low 1/q), both permeability and dose/solubility ratio are controlling drug absorption. The QBCS was also applied to a set of 42 drugs, which were classified into the four categories giving predictions of intestinal drug absorption in accord with the experimental observations (fig. 3).

Also, a recent work by Rinaki *et al.* (2004), focuses in identifying biowaivers among Class II drugs in the framework of QBCS. In this study, using simulations based on a dynamical system of drug absorption, complete absorption for Class II drugs was observed for regions of the fundamental parameters, which define oral drug absorption in humans, namely: i) the formulation-related factors, dose, particle radius size and ii) the drug-related properties, dimensionless solubility/dose ratio (1/q) and effective permeability (fig. 4). Non-steroidal anti-inflammatory drugs (NSAIDs) were employed to illustrate the application of the approach in identifying biowaivers among the NSAIDs.

Conclusions

Monte Carlo simulation techniques can be used to describe problems of drug release both in Euclidean and fractal spaces. The results received are pointing to a universal release law given by the Weibull function. This finding substantiates the use of the Weibull function in kinetic studies of drug release. Both the classic and the continuous population growth of dissolution models indicate that the fundamental parameter of dissolution, the mean dissolution time, depends on the dose/solubility ratio. This relationship provides the theoretical basis for the use of dose/solubility ratio for biopharmaceutical classification purposes. Finally, some Class II drugs of BCS (Amidon *et al.* 1995) can exhibit complete absorption due the dynamics of drug absorption processes.

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