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On the unphysical hypotheses in pharmacokinetics and oral drug absorption: Time to utilize instantaneous rate coefficients instead of rate constants

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ABSTRACT

This work aims to explore the unphysical assumptions associated with i) the homogeneity of the well mixed compartments of pharmacokinetics and ii) the diffusion limited model of drug dissolution. To this end, we i) tested the homogeneity hypothesis using Monte Carlo simulations for a reaction and a diffusional process that take place in Euclidean and fractal media, ii) re-considered the flip-flop kinetics assuming that the absorption rate for a one-compartment model is governed by an instantaneous rate coefficient instead of a rate constant, and, iii) re-considered the extent of drug absorption as a function of dose using an in vivo reaction limited model of drug dissolution with integer and non-integer stoichiometry values. We found that drug diffusional processes and reactions are slowed down in heterogeneous media and the environmental heterogeneity leads to increased fluctuations of the measurable quantities. Highly variable experimental literature data with measurements in intrathecal space and gastrointestinal fluids were explained accordingly. Next, by applying power law and Weibull input functions to a one-compartment model of disposition we show that the shape of concentration-time curves is highly dependent on the time exponent of the input functions. Realistic examples based on PK data of three compounds known to exhibit flip-flop kinetics are analyzed. The need to use time dependent coefficients instead of rate constants in PBPK modeling and virtual bioequivalence is underlined. Finally, the shape of the fraction absorbed as a function of dose plots, using an in vivo reaction limited model of drug dissolution were found to be dependent on the stoichiometry value and the solubility of drug. Ascending and descending limbs were observed for the higher stoichiometries (2.0 and 1.5) with the low solubility drug. In contrast, for the more soluble drug, a continuous increase of fraction absorbed as a function of dose is observed when the higher stoichiometries are used (2.0 and 1.5). For both drugs, the fraction absorbed for the lower values of stoichiometry (0.7 and 1.0) exhibit a non-dependency on dose profile. Our results give an insight into the complex picture of in vivo drug dissolution since diffusion-limited and reaction-limited processes seem to operate under in vivo conditions concurrently.

1. Introduction

The motto “Theory drives, experiment decides” is the basis for physicochemical-biological studies performed to understand nature's processes. The continuous scientific evolution through theory and experiment is found in the question of a student to Einstein and his notorious answer: “Student: Dr. Einstein, Aren't these the same questions as last year's [physics] final exam? Dr. Einstein: Yes; But this year the answers are different.” However, this continuous “theory-experiment” interaction can exhibit time gaps. Thus, the Higgs boson was predicted theoretically in 1964 and it was observed experimentally in 2012. In the same vein, the unrecognized assumption associated with the use of well stirred model, in predicting drug clearance and organ extraction ratio as well as in vitro - in vivo extrapolation (IVIVE) to predict in vivo clearance from in vitro measures of hepatic elimination was published in 2018 (Benet et al., 2018b) while the original article dealing with the clearance concepts in pharmacokinetics was published in 1973 (Rowland et al., 1973). Although there is an ongoing research and

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discussion (Benet et al., 2018a; Rowland and Pang, 2018) regarding the presented hypothesis, it is evident that in many cases there is a considerable time lag between theory and experimental evaluation.

Biopharmaceutical sciences are multidisciplinary; they rely on physical and chemical principles and study the biological impact of drugs in the treatment of diseases. Due to the complexity of in vivo drug processes, mathematical models are used to represent-describe the underlying physical–chemical-biological processes and phenomena. This approach allows the mathematical analysis of the model and estimation of the parameters involved e.g. absorption and elimination rate constants, which are useful for predictive purposes e.g. dosage regimen design. The development of a model is based on one or more hypotheses which rely on the operative mechanisms of the drug processes or phenomena. The validity of the used hypotheses is really crucial for the utility of the model and the subsequent theory-experiment justification. This is so since sometimes the model's hypotheses used are unphysical and the derived model parameter estimates are questionable or the experimental in vitro/in vivo set up does not agree with the theoretical hypotheses.

Traditionally, the models used in pharmacokinetics (PK) and pharmacodynamics (PD) rely on the *homogeneity* hypothesis i.e. the compartments in multi-compartmental PK/PD models are well mixed. Due to the complexity encountered in physiological systems, the homogeneous concepts and the associated classical first-order kinetics have been questioned. Thus, fractal or fractional kinetic models in biopharmaceutics and pharmacokinetics, which do not rely on homogeneous principles and well mixed media have been proposed (Kosmidis et al., 2003; Kosmidis et al., 2004; Dokoumetzidis and Macheras, 2009; Macheras and Iliadis, 2016; Sopasakis et al., 2018). In reality, the power law and the Weibull function which are used in a large number of experimental drug release, dissolution and absorption studies are based on fractal kinetics (Macheras and Dokoumetzidis, 2000). It has been proven that the power law corresponds to a zero-order process with a time dependent coefficient while the Weibull function describes a first-order process with a time dependent coefficient (Macheras and Dokoumetzidis, 2000). Thus, fractal kinetics approaches i.e. the power law and the Weibull function are used extensively but empirically in biopharmaceutics/pharmacokinetics. However, an extensively cited article on drug release kinetics, demonstrates that the time exponent of the Weibull function which originates from the prevailing fractal kinetics is associated with the drug release mechanism(s) in Euclidean or fractal media (Papadopoulou et al., 2006). In parallel, few experimental studies state explicitly that fractal or fractional kinetics govern the drug processes studied e.g. drug dissolution in biorelevant media (Niederquell and Kuentz, 2014) and drug absorption studies leading to non-linear IVIVC (Kytariolos et al., 2010).

Besides, a classical first-order relationship (Noyes and Whitney, 1897), which relies on the first Fick's law of diffusion, is used to describe the rate of drug dissolution since 1897. Several articles have questioned the hypotheses of the diffusion layer model of drug dissolution (Dokoumetzidis et al., 2008; Wang et al., 2012). Since this model has been used for the development of biopharmaceutic classification system (BCS) (Amidon et al., 1995), the regulatory (EMA, 2010; FDA, 2017) guidelines recommend specific criteria for the model parameters involved e.g. solubility.

In this work, we focus on the implications of unphysical hypotheses used in pharmacokinetics and oral drug absorption. To this end, we i) examine the homogeneity hypothesis using Monte Carlo simulations for a reaction and a diffusional process, which take place in Euclidean and fractal media, ii) re-consider the flip-flop kinetics assuming that an instantaneous rate coefficient and not a rate constant governs the input kinetics for a one-compartment model of drug disposition iii) re-consider the extent of drug absorption using an in vivo reaction limited model of drug dissolution with integer and non-integer stoichiometry values published recently (Macheras et al., 2018). We also underline the importance of non-classical kinetics for the emerging field of virtual bioequivalence.

2. Theory

2.1. Rate constants versus time dependent coefficients: focus on drug absorption

Let's consider the one compartment body model with first-order absorption and first-order elimination. The drug amount in the body, A_1 and the drug amount in the gastrointestinal tract A_0 as a function of time t are described by:

$$\frac{dA_0}{dt} = -k_a \bullet A_0, \quad A_0(0) = F \bullet D \tag{1}$$

$$\frac{dA_1}{dt} = k_a \bullet A_0 - k_{el} \bullet A_1, \quad A_1(0) = 0 \tag{2}$$

where V is the volume of distribution, F is the fraction of dose D absorbed, and k_a, k_{el} are the first-order rate constants for absorption and elimination respectively. For constant k_a, k_{el} the analytical solution of the differential equations gives the Bateman equation (Macheras et al., 1992)

$$C = \frac{FD}{V(k_a - k_{el})}(e^{-k_{el}t} - e^{-k_a t}) \tag{3}$$

Eq. (3) was the subject of the last paper of the late Edward Garret (Garrett, 1994) published in relation to flip-flop kinetics and the relative magnitude of rate constants (Bateman, 1908; Macheras et al., 1992).

Harry Bateman developed equations describing the abundances and activities in a decay chain as a function of time, based on the decay rates of isotopes. For the simple case of a chain of three isotopes, the corresponding Bateman equation reduces to Eq. (3). For drug absorption studies the derivation of Eq. (3) requires two hypotheses, i) the drug is in solution when administered i.e. there is no dissolution step involved and ii) the drug absorption is governed by a single rate constant, k_a. Although k_a strictly speaking corresponds to the drug's permeation step and is associated with the effective permeability of drug (Oh et al., 1993), countless PK and population PK analyses studies consider k_a as a ("hybrid") absorption rate constant. Needless to say that a single value for k_a prevailing throughout the gastrointestinal tract is an unphysical hypothesis too, given the site dependent character of drug permeation. Besides, a single permeability value is a poor predictor for the extent of absorption; this is one of the reasons for the use/replacement of permeability with the percent of metabolism (Wu and Benet, 2005) in the regulatory guidelines dealing with the BCS (EMA, 2010; FDA, 2017).

The hypothesis that drug absorption takes place from a homogenous drug solution in the gastrointestinal (GI) fluids and proceeds uniformly throughout the GI has been questioned in the literature long time ago (Macheras and Argyrakis, 1997). Thus, time dependent coefficients, k, based on fractal kinetics concepts were proposed (Kopelman, 1988; Macheras et al., 1996):

$$k_{a,Power} = k_1 t^{-h} \tag{4}$$

where k_1 is a constant expressed in $(time)^{-(1-h)}$ units, and the exponent h (unitless) is different than zero; time dependent coefficients have been used to express time dependency of many kinetic processes e.g. oral drug absorption (Macheras et al., 2018), enzymatic reactions (Kostylev and Wilson, 2013), decay drug curves (Macheras, 1996) and carrier mediated transport (Macheras, 1995). In this vein, functions with time exponents (power law and the Weibull function), have been used for the analysis of drug release and dissolution data (Macheras and Dokoumetzidis, 2000; Papadopoulou et al., 2006). During the last decade, another approach based on fractional calculus has been used to capture drug kinetic phenomena, which deviate from the classical exponential behavior driven by a rate constant (Dokoumetzidis and Macheras, 2009; Kosmidis and Macheras, 2018; Sopasakis et al., 2018).

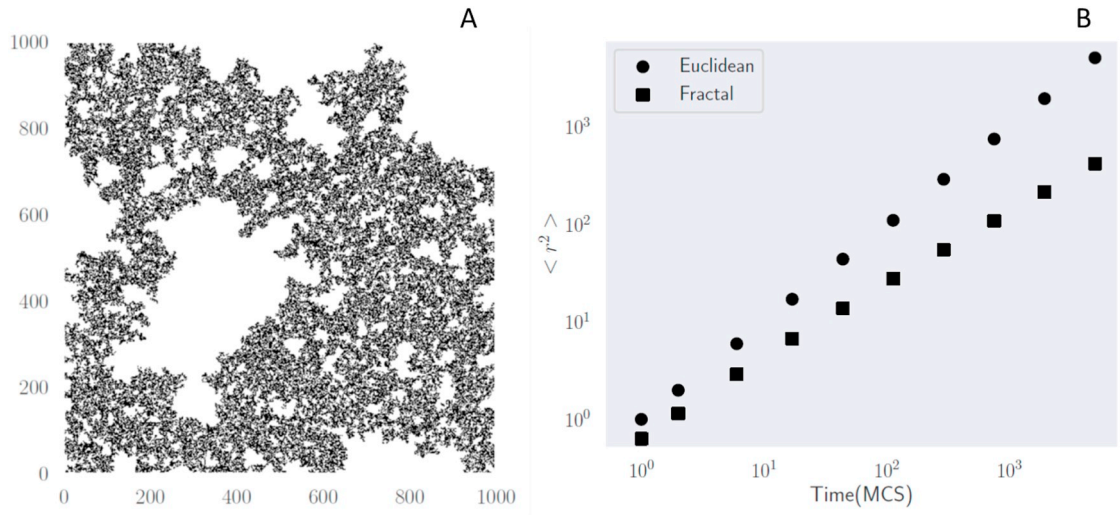

Fig. 1. (A) A picture of a percolation fractal embedded in a 1000 × 1000 square lattice. (B) Mean squared displacement as a function of time for a random walker moving on a normal square lattice (Euclidean) and on a percolation fractal (Fractal). Both axes are in logarithmic scale.

It is worthy to mention that the Mittag-Leffler function which naturally occurs as the solution of fractional order differential equations is closely related to the Weibull function.

2.2. Hypotheses for the drug dissolution mechanisms and their impact in biopharmaceutic classification of drugs

Since the early days of drug dissolution (Noyes and Whitney, 1897), the prevailing hypothesis for the dissolution mechanism was based on the diffusion layer model. The last review in the pharmaceutical literature dealing with the alternative hypothesis, namely, the reaction limited model of dissolution was published in 1967 (Higuchi, 1967). Criticisms for the unphysical hypotheses associated with the constancy of the diffusion layer model of dissolution throughout the dissolution process under in vitro and in vivo conditions have been reported in the literature e.g. (Dokoumetzidis et al., 2008; Wang et al., 2012). Recent studies demonstrate clearly that even under carefully controlled hydrodynamic conditions, the two dissolution mechanisms contribute to the dissolution of drug (Shekunov and Montgomery, 2016). According to the diffusion layer model of dissolution, the saturation solubility of drug drives the dissolution rate (Wang et al., 2012). This model was utilized for the development of BCS (Amidon et al., 1995) and therefore the saturation solubility of drug became the unique parameter for biopharmaceutic classification purposes in the relevant BCS guidelines (EMA, 2010; FDA, 2017). However, several concerns have been pointed out for i) the discrepancy between the dissolution-solubility criteria and the extent of absorption of the sparingly soluble nonsteroidal anti-inflammatory drugs (Yazdanian et al., 2004) ii) the dual BCS classification of soluble and insoluble drugs (Bergström et al., 2014) and iii) the binary character of the BCS (Macheras and Karalis, 2014). The in vivo reaction limited model of drug dissolution published recently (Macheras et al., 2018), opens a new dialogue for the proper consideration of the dissolution mechanisms hypotheses under the prism of biopharmaceutic classification of drugs.

3. Materials and methods

Our work is based on modeling and simulation. All simulations and fitting work was based on Matlab R2016b. The following three areas were explored.

3.1. Diffusional processes and reactions in homogenous-heterogeneous media

The drastic effect of the heterogeneity of the medium becomes clear in the computational study of diffusive processes. Such processes are studied by using the random walk model (Bunde et al., 1985; Weiss, 2005; Bunde and Havlin, 2012; Bunde and Havlin, 2013). In this work diffusional processes were examined in homogeneous as well as on heterogeneous (fractal) environments. For the homogeneous case, an empty square lattice was used initially where a random walker is placed at a randomly chosen lattice site. Then the walker performs random walks, i.e. moves to one of its four nearest neighbors with equal probability. At each step position of the walker is monitored. When the walker completes a predetermined number of steps process is repeated starting from a new lattice site. The main quantity of interest is the mean squared displacement of the walker as a function of time. Means are calculated as averages of the different realizations of the random walk and the time is proportional to the number of steps performed. Thus, the time unit is one Monte Carlo Step (MCS) as it is commonly done in Monte Carlo simulations of diffusion processes (Bunde et al., 1985; Bunde and Havlin, 2012). For the heterogeneous case, random walks on the famous percolation fractal were studied (see Fig. 1A, for an example of such a fractal surface).

In order to simulate the cases of systems of particles that diffuse and react in fractal substrates, the reaction of type $A + B \rightarrow 0$ was examined by mean of Monte Carlo simulations on homogeneous and fractal spaces. For the homogeneous space, simulations we start with a square lattice where we place particles of type A or B with probability 0.5 for each particle. Thus, our initial configuration is that of a square lattice that is a random mixture of A and B particles with no empty sites. Due to the randomness in the choice of particle types, the initial number of A particles is approximately –but not exactly- equal to that of the B particles. Then, we randomly select a particle and move it, according to the random walk model, to one of its four nearest neighbors. If the target site is occupied by a particle of the same type as the chosen one, the movement is aborted as we assume excluded volume interactions between particles of the same type. If the target site is occupied by a particle of a different type then both particles are removed from the system, simulating an $A + B \rightarrow 0$ reaction. Finally, if the target site is empty then the selected particle moves to the target site. After each particle selection, the time is incremented by 1/N where N is equal to the number of particles present in the system. Thus, onetime unit (MCS) in this case corresponds to the time interval where all particles in the

system have on average the chance to move once. This is a rather common convention in Monte Carlo simulations of reaction-diffusion systems. We monitor the system for a long period of time until one of the particle times is completely eliminated. Then we repeat our simulations starting from a different initial configuration and average our results for statistical purposes. For the heterogeneous case the simulation method is similar to the above, the difference being that now the A and B particles initially occupy the sites of a randomly generated percolation fractal and that they perform random walks and reactions on this restricted fractal geometry. In both cases, the quantity of interest is the average total number of particles < N > present in the system as a function of time.

3.2. Flip-flop kinetics with time varying absorption rate coefficient

Flip-flop kinetics occur when the rate constant of absorption is slower than the rate constant of elimination ($k_a < k_{el}$). For the simple one compartment model case, the concentration of the drug in the body after oral administration is explained with the Bateman function previously shown (Eq. (1)). In the representative simulations shown in this work regarding flip-flop kinetics, dynamics are tested under scenarios where the absorption rate is time-dependent either following a power function similar to that of Eq. (4) or a Weibull distribution function shown in Eq. (5) (Piotrovskii, 1987).

$$Fraction\ of\ drug\ absorbed = 1 - e^{-\left(\frac{t}{alpha}\right)^{beta}} \tag{5}$$

The absorption rate coefficient resulting from a case where the absorbed drug follows a Weibull distribution is:

$$k_{a,Weibull} = \frac{beta}{alpha} \cdot \left(\frac{t}{alpha}\right)^{beta-1} \tag{6}$$

For the simulations shown in Figs. (4)–(6), random values of parameters were chosen so to satisfy flip-flop kinetics ($k_a < k_{el}$). The parameters used were: $k_a = 0.3$, $k_{el} = 0.5$, $k_1 = 0.3$, $alpha = 1$, $V = 1$ and $D = 10$. The time exponents h and beta are taking values from 0.1 to 0.9.

3.3. Classical or fractal kinetics in a reaction-limited in vivo model of drug dissolution

A series of simulations were carried out using the in vivo reaction limited model of drug dissolution published recently (Macheras et al., 2018). Two drugs with different solubilities were considered, 1 and 0.05 mg/ml. The values were chosen so as to represent compounds of relatively low solubility where we believe that the current theory needs to be revisited. 1 mg/ml is considered the lower limit of soluble compounds and 0.05 mg/ml indicates sparingly soluble/low solubility compounds. Soluble compounds are outside of the focus of this work. The fraction of dose absorbed was calculated as a function of drug dose assuming integer and non-integer values for the stoichiometry (a) of drug dissolution/reaction, namely, 0.7, 1.0, 1.5 and 2.0. The following values were assigned to the model parameters, $k_{-1} = 0.050\ min^{-1}$, $k_1^* = 0.005\ mg^{1-\alpha}\ min^{-1}$, $P_{eff} = 0.001$ cm/min while the simulation time (mean intestinal transit time) was set equal to 199 min (Macheras et al., 2018).

4. Results

4.1. Diffusional processes and reactions in homogenous-heterogeneous media

Fig. 1A shows a picture of a percolation fractal embedded in a 1000 × 1000 square lattice. Fig. 1B is a double logarithmic plot of the mean squared displacement of the random walker as a function of time

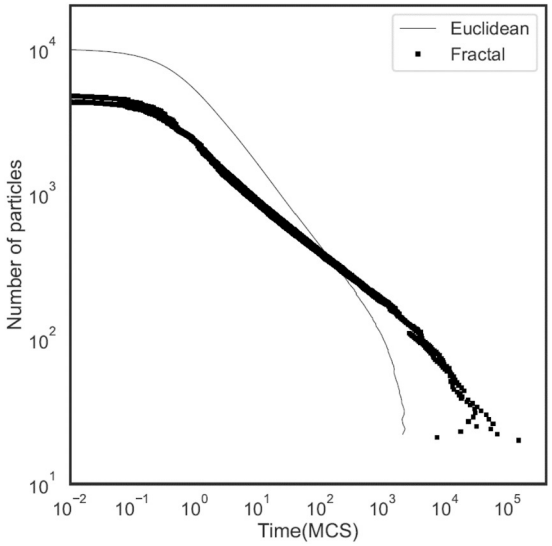

Fig. 2. Mean number of particles versus time for the reaction A + B → 0, particles move and react on a square lattice with L = 100 (dots) and on percolation fractals embedded in the previous lattice (squares). Both axes are in logarithmic scale.

for the Euclidean (homogenous case) as well as the fractal case. In both cases we observe straight lines with different slopes. This is in agreement with the well-known theoretical results (Bunde and Havlin, 2012; Bunde and Havlin, 2013) and of considerable importance for diffusive processes (see Discussion).

For systems of particles that diffuse and react on fractal substrates we expect a profound slowing down of the reactions in fractals as compared to homogeneous spaces. To confirm this hypothesis, we examine by mean of Monte Carlo simulations a reaction of type A + B → 0 on homogeneous as well as on fractal spaces as described in Materials and methods.

Fig. 2 shows Monte Carlo simulation results of a system of A and B particles which diffuse and react following the A + B → 0 reaction rule. More specifically, Fig. 2 presents the mean number of particles as a function of time for particles move and react on a square lattice with L = 100 (dots) and on percolation fractals embedded in the previous lattice (squares). Notice that, in agreement to our intuition obtained from the study of random walks on fractals, the reaction slows down considerably when the environment is disordered. Despite that initially the number of A and B particles is less than that in the homogeneous, the time it takes for the system to become practically empty is larger by > 2 order of magnitude in the heterogeneous case.

In addition to the reaction slow-down, there is another important aspect characteristic of reactions on heterogeneous environments. The environmental heterogeneity leads to increased fluctuations of the measurable quantities. To demonstrate that Fig. 3 shows the standard deviation (SD) of the number of particles N present in the system as a function of time for the above described Euclidean (dots) and fractal (squares) reaction cases.

At all times the standard deviation for the A + B → 0 reaction on a fractal is considerable higher (notice that the plot is in log scale) than the same reaction on the homogeneous environment.

4.2. Flip-flop kinetics with time varying absorption rate coefficient

Fig. 4 shows simulations of the one compartment model that retains power-model dependent absorption rate coefficients (Eq. (4)) with varying exponent's h values. The absorption time coefficient used to solve Eq. (1) was therefore $k_{a,\ Power} = k_1 t^{-h}$. In Fig. 4A the dotted line represents the oral PK when k_a is constant. Solid lines are the profiles representing oral PKs with time-dependent absorption rate coefficients

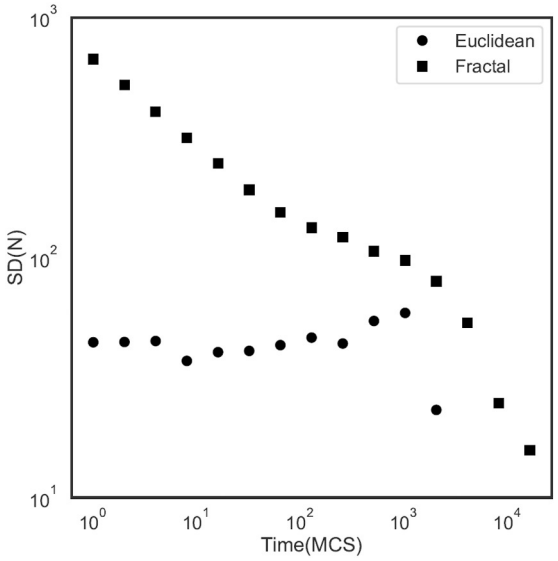

Fig. 3. Standard deviation SD (N) of the number of particles as a function of time for the reaction A + B → 0. A square lattice with L = 100 (dots) has been used for the Euclidean case and percolation fractals embedded in the previous lattice (squares) for the fractal case. Both axes are in logarithmic scale.

with gradually increasing exponents *h*. Gradually higher exponent values lead not only to higher C_{max} but also to a change of the shape of the curve that retains a steeper drop for higher *h* values. The time of the C_{max} (t_{max}) is gradually decreasing. In Fig. 4B, the time profiles of $k_{a,Power}$ are shown for the different *h* values with corresponding shading to Fig. 4A. As the *h* increases the rate of $k_{a,Power}$ decrease is increasing as it is shown by the gradually steeper drop of the curves.

Next, time dependency mediated by a Weibull distribution (Eq. (6)) was modelled. Similar to Fig. 4, Fig. 5 shows simulations of the one compartment model that retains absorption rates resulting from a Weibull distribution with varying exponent's *beta* values. Again, the dotted line of Fig. 5A represents the oral PK when $k_{a,Weibull}$ is constant and equal to k_a. Gradually shaded solid lines, are simulations with gradually increasing exponents' *beta*. Larger exponents lead to higher C_{max} and a change of the steepness of the curve. In contrast with the power model and Fig. 4, the t_{max} increases for gradually higher time exponent values. Fig. 5B shows the time profiles of $k_{a,Weibull}$ for the different *beta* values. As *beta* value increases, $k_{a,Weibull}$ becomes constant to gradually larger times.

The time when $k_{a,Power}$ or $k_{a,Weibull}$ becomes equal to k_{el} in the simulations shown in Figs. 4 and 5 was further calculated. Fig. 6 x-axis shows the exponent value (*h* or *beta*) and the y-axis the time when $k_{a,Power}$ or $k_{a,Weibull}$ is equal to k_{el}. For the sake of clearance the curves were plotted in log-y axis. The two curves retain similar patterns with higher exponents resulting in larger times where $k_{a,Power}$ or $k_{a,Weibul}$ become equal to k_{el}. However, the Weibull model seems to maintain a more exponential increase that in log-linear axes this translates to a straight line.

Finally, Fig. 7 shows the fitting of the Eqs. (1)–(2) retaining either constant or time-dependent absorption rate coefficients (e.g. power, Weibull) for three compounds known to exhibit flip-flop kinetics (Garrison et al., 2015). Fig. 7 show the experimental data of Pravastatin (Singhvi et al., 1990) (Fig. 7A), Levovirin (Lin et al., 2003) (Fig. 7E), and Cefuroxime (Fig. 7I) along with the resulting fits using constant or time dependent absorption coefficients. For the data sets E and I all approaches resulted in acceptable fits judging from the R^2 values. However, the data set E exhibits flip–flop kinetics regardless the constant or time-dependent character of the input parameter. In contrast, the data set I follows classical flip-flop kinetics if constant values for the rate constants are assumed (panel J) while for both time-dependent approaches the input rate coefficient is higher than the elimination rate constant throughout the time course of drug in the body (panels K and L). For the data set A, the fit using the Weibull input rate coefficient is superior to the other two approaches ($R^2_{constant}$ = 0.888, R^2_{power} = 0.881, $R^2_{Weibull}$ = 0.998). This is due to the rapid increase of the input rate coefficient during the absorption phase of drug shown in Panel D.

4.3. Classical or fractal kinetics in a reaction-limited in vivo model of drug dissolution

Although dissolution drug research has been based exclusively on the diffusion layer model, several approaches based on a reaction-limited concept, suitable for in vitro studies, have been published (Dokoumetzidis and Macheras, 1997; Lánsky and Weiss, 1999; Valsami et al., 1999; Dokoumetzidis et al., 2008; Charkoftaki et al., 2011).

In this work we utilize an in vivo reaction limited model of dissolution (Macheras et al., 2018) to study the effect of the stoichiometry value of the dissolution/reaction on the fraction of dose absorbed. Both integer (1.0 and 2.0) and non-integer (07. 1.5) stoichiometry (α) values

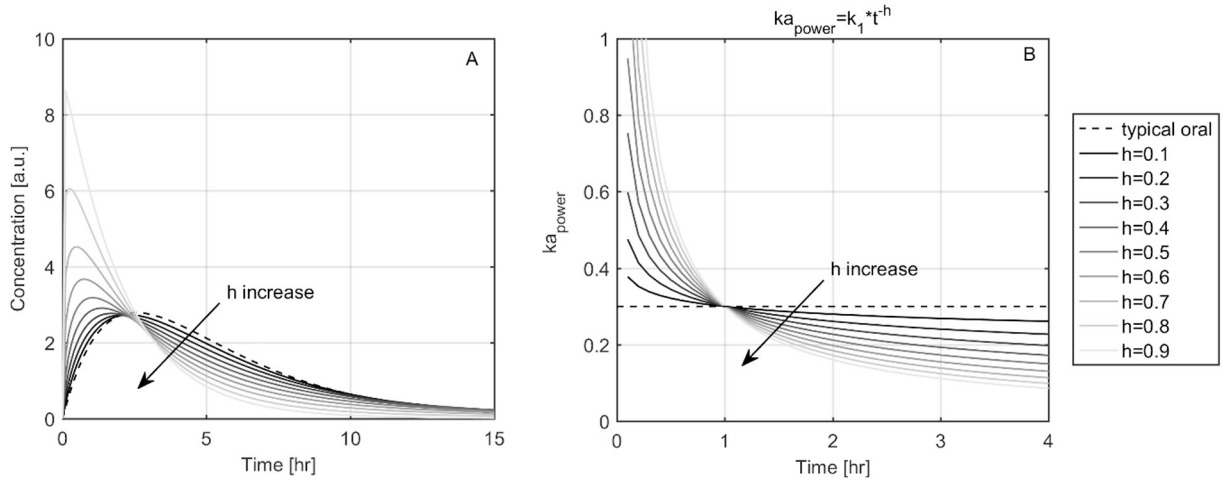

Fig. 4. PK responses and $k_{a,Power}$ profiles for a hypothetical one compartment model for the case of typical oral, and oral with a time-dependent absorption rate resembling a power model (Eq. (4)). A: Concentration versus time profile of typical oral (dotted line), and oral with a power model like absorption rate (black to light grey). Power model was assumed to retain the form $k_{a,\ Power} = k_1 t^{-h}$. B: The time profile of $k_{a,Power}$ for the different scenarios tested. The horizontal line corresponds to $k_a = 0.3$.

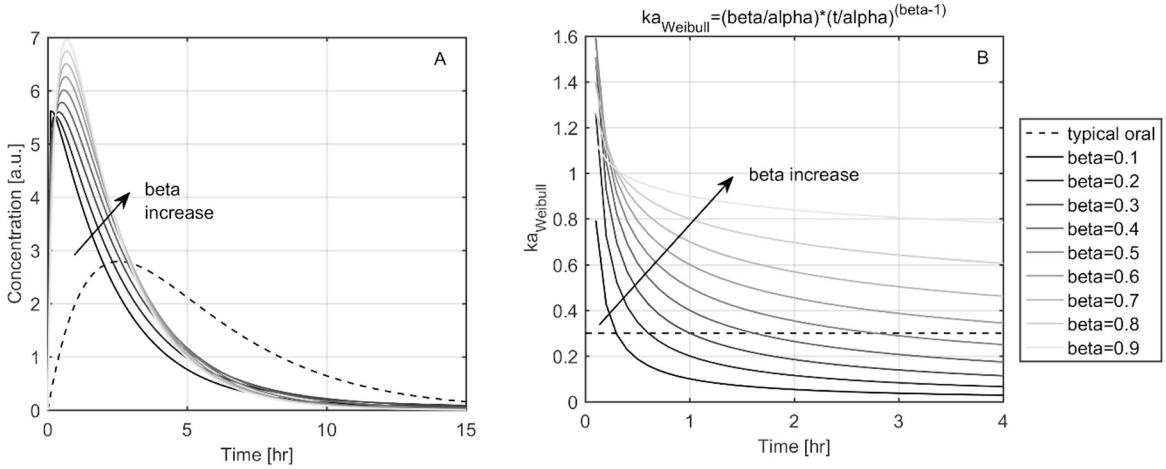

Fig. 5. PK responses and $k_{a,Weibull}$ profiles for a hypothetical one compartment model for the case of typical oral, and oral with a time-dependent absorption rate resembling a Weibull model (Eq. (6)). A: Concentration versus time profile of typical oral (dotted line), and oral with a Weibull model like absorption rate (black to light grey). Weibull model was assumed to retain the form $k_{a,Weibull} = \frac{beta}{alpha} \bullet \left(\frac{t}{alpha}\right)^{beta-1}$. The time profile of $k_{a,Weibull}$ for the different scenarios tested. The horizontal line corresponds to $k_a = 0.3$.

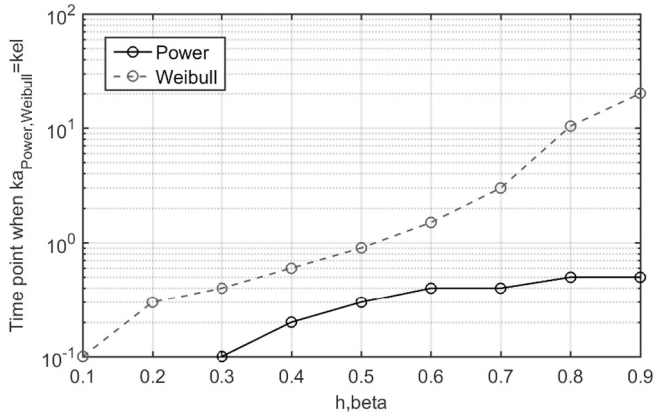

Fig. 6. Time where $k_{a,Power}$ or $k_{a,Weibull}$ becomes equal to k_{el} versus the different exponent values for the case of the power (h) and Weibull model (beta).

were examined. The results are shown in Figs. 7 and 8 for a sparingly soluble (0.05 mg/ml) and a relatively soluble (1 mg/ml) compound, respectively. The plots do not exhibit a "bilinear-saturation type" shape which is the typical behavior of the saturation solubility driven diffusion limited dissolution models (Charkoftaki et al., 2012).

5. Discussion

5.1. Diffusional processes and reactions in homogenous-heterogeneous media

The linear relationship between the displacement of the random walker and time shown in Fig. 1 along with the different slopes maintained are in well agreement with known theoretical results (Bunde and Havlin, 2012; Bunde and Havlin, 2013). Fig. 1B deciphers that the mean squared displacement $< r^2 > \sim t$ is proportional to time in the homogeneous case and scales sub-linearly with time (e.g. $< r^2 > \sim t^{dw}$ with $d_w < 1$) in the fractal case. This is of paramount importance for diffusive processes since in the two dimensional case, the mean surface explored by a random walker can be approximated by the expression $< S > \sim 4\pi < r^2 >$. This implies that the fraction *Sr* of the area explored by a walker of a fractal over the area explored by a Euclidean walker is proportional to $t^{dw} - 1$ and, since $d_w - 1$ is always a negative number, this fraction *Sr* becomes negligible after some time t. This again implicates that random walkers on fractal surfaces may not be efficient in exploring their surroundings and this is of profound importance as it ultimately indicates that the homogeneity hypothesis may not be always valid. Therefore, in cases of systems of particles that diffuse and react in fractal substrates a profound slowing down of the reactions is expected in fractals compared to homogeneous spaces.

Fig. 2 shows, in agreement to intuition obtained from the study of random walks on fractals, that the reaction slows down considerably when the environment is disordered. Despite that the number of A and B particles is less than that in the homogeneous initially, the time it takes for the system to become practically empty is larger by > 2 orders of magnitude in the heterogeneous case. Fig. 3 confirms that at all times, the standard deviation for the $A + B \rightarrow 0$ reaction on a fractal is considerable higher (log-scale plot) than the same reaction on the homogeneous environment. Such effects can explain experimental observations for drug measurements in heterogeneous media, namely, the intrathecal space and gastrointestinal aspirates exhibiting enormous variability (Clarysse et al., 2009; Kuttler et al., 2010). According to Kuttler et al. (2010), "the intrathecal space does not behave as a well-mixed volume and that measuring concentration in the CSF after injection to support a classical pharmacokinetic approach may not provide any meaningful data for analysis". In the second case (Clarysse et al., 2009), outliers are present in 14 sets (out of 15) of measurements in the gastrointestinal fluids; again, the heterogeneity of the medium (space) and/or the inherent property of time dependency of fractal kinetics are a plausible explanation of such a variability. Needless to say that the high variability of published data in various disciplines of biosciences can be associated with the phenomena described above.

5.2. Flip-flop kinetics with time varying absorption rate coefficients: implications for PBPK modeling and virtual bioequivalence

Drug absorption is a complex process that is affected by various factors such as presystemic metabolism, physiology of the gastrointestinal tract (GIT), disease state etc. In pharmacokinetic analysis, many times drug absorption is assumed first-order despite the fact that there are numerous cases of atypical drug absorption profiles that first-order absorption kinetics fail to satisfactorily describe (Zhou, 2003). Recent works have stressed out the various complications that may arise underlining the need to develop and apply new methodologies for non-linear in vitro in vivo correlations (e.g. use of fractional kinetics) (Kytariolos et al., 2010).

"Flip-flop" kinetics is an example situation where the rate limiting

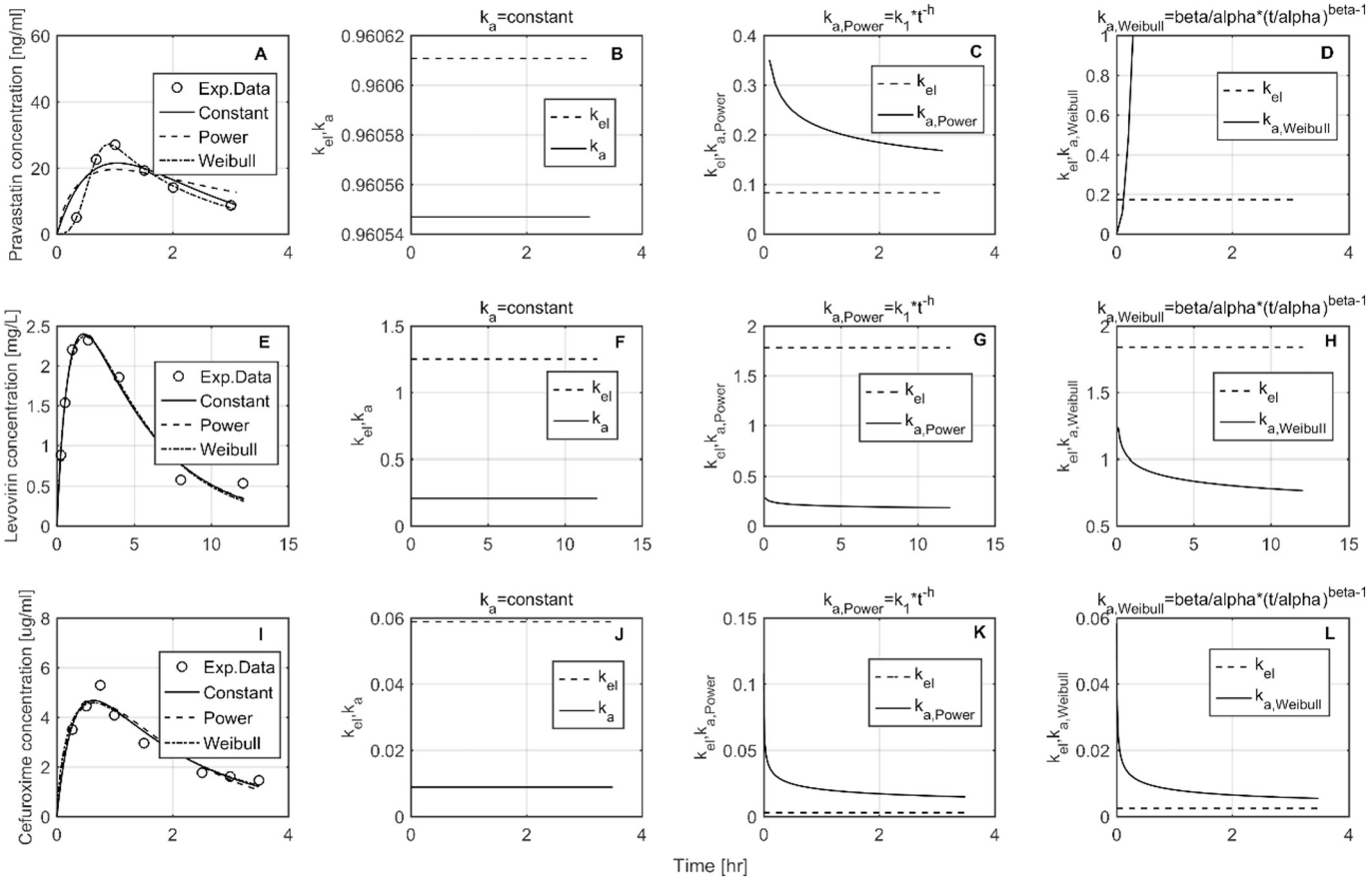

Fig. 7. Evaluation of time-dependent absorption rate coefficients in three compounds maintaining flip-flop kinetics (Pravastatin, Levovirin, Cefuroxime). A: PK data of Pravastatin (Singhvi et al., 1990) along with the fitting of Bateman function using an absorption rate constant (solid line), and absorption coefficients based on power (dotted line), and Weibull models (dash dot line). B–D: k_a and k_{el} resulted from the fitting using an absorption rate constant (B), power model (C), and Weibull function (D). E: PK data of Levovirin (Lin et al., 2003) along with the fitting of Bateman function using an absorption rate constant (solid line), and absorption coefficients based on power (dotted line), and Weibull models (dash dot line). F–H: k_a and k_{el} resulted from the fitting using an absorption rate constant (F), power model (G), and Weibull function (H). I: PK data of Cefuroxime (Ruiz-Carretero et al., 2000) along with the fitting of Bateman function using an absorption rate constant (solid line), and absorption coefficients based on power (dotted line), and Weibull models (dash dot line). G–L: k_a and k_{el} resulted from the fitting using an absorption rate constant (G), power model (K), and Weibull function (L).

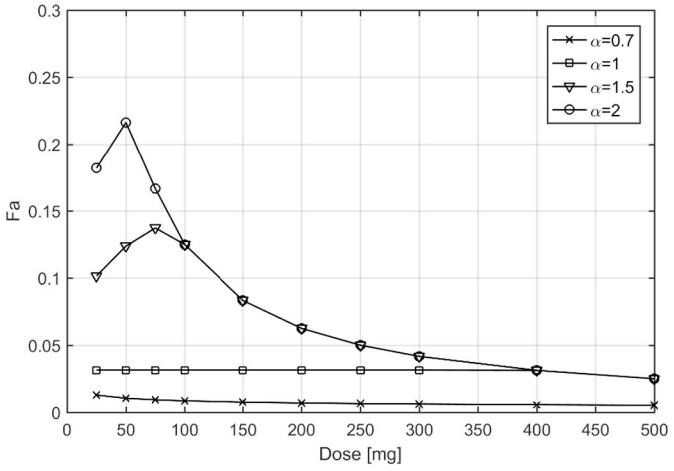

Fig. 8. Fraction of dose absorbed as a function of dose using the reaction limited in vivo drug dissolution model (Macheras et al., 2018). Key: $k_{-1} = 0.050\,\text{min}^{-1}$, $k_1^* = 0.005\,\text{mg}^{1-\alpha}\text{min}^{-1}$, $C_s = 0.05$ mg/ml, $P_{eff} = 0.001$ cm/min. The time runs for 199 min.

step is the absorption process ($k_a < k_{el}$) and lack of comparison between oral and IV PK data of the drug, may lead to an inappropriate absorption model and misspecification of the PK parameters. Furthermore, site dependence of permeability, time-dependent gastric emptying and change of pH in the GIT (Langguth et al., 1994), confer a strong time-dependency to the absorption rate that makes modeling efforts more demanding. Of note, absorptive and efflux transporters may play important role in the disposition of drugs maintaining flip-flop kinetics as many of those are substrates of these transporters as it was recently shown (Garrison et al., 2015). In order to address the complications that may arise in similar situations, in this work we evaluate the PK profiles of a simple one compartment model characterizing flip-flop kinetics and retain a time dependent absorption rate.

The transit, dissolution, and uptake of drug under the heterogeneous GIT conditions can resemble fractal kinetics where the time dependency of the rate coefficient is expressed by Eq. (4) (Kopelman, 1988; Macheras et al., 1996). In this work we evaluate the PK of this power like absorption rate dynamic through simple one compartment model simulations maintaining flip flop kinetics. Compared to the typical first-order absorption profile (Fig. 4A dot line), power like absorption retain different C_{max} and t_{max} along with different steepness of the curves for varying time exponent values (h). This is due to the $k_{a,Power}$ curvature shown in Fig. 4B that for high h values the drop of k_a is more abrupt. As h increases, the C_{max} increases and the t_{max} decreases reaching almost zero. The later phase of the PK follows the profile of $k_{a,Power}$ and reaches the levels of the typical constant absorption rate profile to gradually larger times.

The Weibull distribution has long been used in order to describe in

vitro dissolution profiles as well as in vivo absorption processes (Christensen et al., 1980; Piotrovskii, 1987; Smith et al., 1993). The advantage of the Weibull distribution is that it can characterize profiles retaining either typical exponential, S-shaped or exponential with a steeper initial slope depending on the value of the Weibull's exponent (Eq. (5)). For the parameters used in this work, the absorption rate profiles resulting from the Weibull distribution are shown in Fig. 5B. Fig. 5A shows the resulting PK profiles under a flip-flop kinetics scenario. Similar to the simple power model shown in Fig. 4, gradually higher time exponent values (*beta*) leads to higher C_{max}. However, in contrast with the power model, for the case of Weibull function the higher beta values lead to increased t_{max} times. Comparing the responses of the one compartment model under scenarios of power like or Weibull distribution like absorption rates in Fig. 6, the Weibull function appears to reaches levels where $k_{a,Weibull}$ is equal to k_{el} in an exponential manner.

The analysis of real data (Fig. 7) obeying flip flop kinetics using functions with a time dependent coefficient, allows a re-consideration of oral absorption kinetics. It seems likely a time dependent coefficient is more physically relevant for the input rate of the complex oral drug absorption processes. The superiority of the Weibull like absorption rate coefficient is most likely associated with the time dependent characteristics of first-order, passive drug absorption processes (Macheras and Dokoumetzidis, 2000). Despite the extensive empirical use of the Weibull function in pharmacokinetics, this is the first time whereas the Weibull function is applied to actual experimental oral PK data in the realm of fractal kinetics. We are currently working in revisiting oral drug absorption analysis. One of our major concerns is the unphysical characteristics of the current flip flop analysis i.e. the maintenance for infinite time ($\exp(-k_a t) < \exp(-k_{el} t)$ in Eq. (3)) of the absorption process; this is not physiologically sound.

Modeling and simulation can play an important role in every stage of Quality by Design (QbD) based drug development (Zhang et al., 2011). Apart from evaluating PK profiles of parent drug and metabolites, simulation based approaches may be advantageous to assess the potential outcome of different scenarios in bioequivalence studies. Recently it was shown that virtual bioequivalence studies can successfully reproduce results of healthy volunteers and importantly indicate future studies that can be of interest and extra caution (Doki et al., 2017). In an effort to best address the multiple physiology-based differences such studies entail, there is an extensive use of physiologically based pharmacokinetic (PBPK) modeling where relevant knowledge regarding the population of interest can be incorporated. For this reason, there are numerous softwares used with integrated physiology-related information including ADMEWORKS DDI Simulator (www.fqs.pl/en/chemistry/products/admeworks-ddi-simulator), CLOEPK (www.cyprotex.com/insilico/physiological_modelling/cloe-pk), GastroPlus (www.simulations-plus.com), PK-Sim (www.open-systems-pharmacology.org), and Simcyp (www.certara.com). The common ground in different PBPK approaches is the inclusion of both drug-specific and organism-specific parameters based on which someone can test different drugs on the same physiology (e.g. renally impaired individuals) or the same drug to different populations (e.g. Asian) (Mavroudis et al., 2018). Due to the high complexity of human physiology and GIT, as well as the formulation related parameters that many times are not well defined, frequently, PBPK models integrate indirect relationships (e.g. Weibull function) to explain the dissolution of the compound in the organism. Based on this, introduction of more complicated models of absorption (e.g. fractal kinetics) can be used for a better explanation of the absorption processes.

5.3. Classical or fractal kinetics in a reaction-limited in vivo model of drug dissolution

In all cases studied the low values of the fraction absorbed in Figs. 8 and 9 are linked with the relatively high k_{-1} value (backward constant) assigned in comparison with the dissolution/rate constant (Macheras et al., 2018). In other words, drug precipitation operated throughout

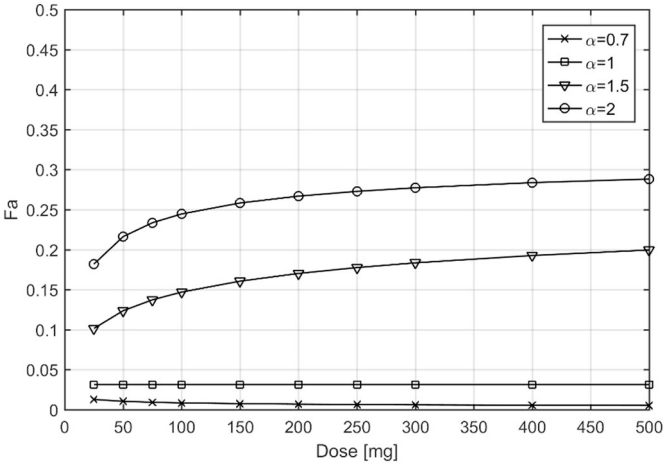

Fig. 9. Fraction of dose absorbed as a function of dose using the reaction limited in vivo drug dissolution model (Macheras et al., 2018). Key: $k_{-1} = 0.050\ min^{-1}$, $k_1^* = 0.005\ mg^{1-\alpha} min^{-1}$, $C_s = 1.0$ mg/ml, $P_{eff} = 0.001$ cm/min. The time runs for 199 min.

the dissolution/reaction process. One can see remarkable differences in the fraction absorbed as a function of dose plots (Figs. 8 and 9) for a sparingly soluble (0.05 mg/ml) and a soluble (1 mg/ml) compound, respectively. The graphs of Fig. 8 exhibit ascending and descending limbs for the higher stoichiometries (2.0 and 1.5). On the contrary, for the highly soluble drug (1 mg/ml) a continuous increase of fraction absorbed is observed when the higher stoichiometries are used (2.0 and 1.5), Fig. 9. For both drugs, the fraction absorbed for the lower values of stoichiometry (0.7 and 1.0) exhibit a non-dependent on dose profile, Figs. 8 and 9. Also, the fraction of dose absorbed is higher for the stoichiometry integer values than the lower fractal value i.e. (2.0 versus 1.5) and (1.0 versus 0.7). This is in accordance with the results of Figs. 1B and 3 since the value of stoichiometry controls the reaction rate of drug dissolution process. Although, these results differ from the typical behavior of the saturation solubility driven diffusion limited dissolution models (Charkoftaki et al., 2012), there are many unresolved scientific factors regarding the effect of dose on fraction absorbed or bioavailability in the literature. The complex picture of dissolution, supersaturation, precipitation, re-dissolution processes and phenomena as a function of dose has been studied recently (Vertzoni et al., 2011; Psachoulias et al., 2012; Kourentas et al., 2016; Kourentas et al., 2018). Due to the inherent complexity, poor predictions can be made for the effect of dose on the extent of absorption. This is so since the drug properties are also important not only for the processes mentioned above but also for the dissolution mechanisms prevailing under in vivo conditions. In fact, Shekunov and Montgomery (2016) have shown that the two dissolution mechanisms i.e. diffusion limited and reaction limited, take place concurrently and their relative contribution depend on drug properties. This can also have implications for the biopharmaceutical classification of drugs if a reaction limited dissolution model is considered (Macheras et al., 2018). However, it is not currently possible to dissect out experimentally the relative importance of diffusion and reaction kinetics for the in vivo dissolution kinetics. Needless to say that an in silico/in vivo dissolution model based on the two dissolution mechanisms is highly desirable. Additional in vitro dissolution studies focusing on the discernment and contribution of the dissolution mechanisms to the overall dissolution are required (Shekunov and Montgomery, 2016). These data if coupled with drug's physicochemical properties or molecular descriptors will facilitate a “bottom up” approach and help the PBPK modeler to go beyond the diffusion layer model to improve the prediction of drug absorption.

6. Conclusions

Through the use of Monte Carlo simulations applied to diffusional and reaction processes in Euclidean and fractal spaces, our work revealed that the processes are slowed down in heterogeneous media; besides, the environmental heterogeneity leads to increased fluctuations of the measurable quantities. These findings can explain high variability in measurements in understirred biomedia (intrathecal space, gastrointestinal fluids). Along the same lines, introduction of time-dependent absorption rate coefficients in theoretical models simulating flip-flop kinetics showed that the simulated concentration-time profiles resemble the classical *C-t* curves but the exact shape of the curve is dependent on the value of the time exponent of the input function (e.g. Power law, Weibull function). Fitting of PK data further underlined that the rate limiting process (absorption vs elimination) is time dependent and as such identification of flip-flop behavior can be misinterpreted. Finally, the profile of the fraction of dose absorbed as a function of dose, using a reaction limited model for the in vivo drug dissolution and assuming different stoichiometries, revealed i) that the shape of the profile is affected by the solubility of drug and the stoichiometry of the dissolution/reaction, and ii) that higher profiles are observed for higher stoichiometries i.e. 2.0 versus 1.5 and 1.0 versus 0.7.

These results indicate that is time to incorporate fractal kinetics in various processes associated with PBPK modeling and virtual bioequivalence. More applications can be envisaged in the area of PKPD population approaches in the not too distant future.

Acknowledgments

One of us (P. Macheras) dedicates this work to the memory of Cpt George Baltadoros who offered his life to our Country; he died on 1st April 2018.

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