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Power law IVIVC: An application of fractional kinetics for drug release and absorption

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ABSTRACT

Most correlations between *in vitro* and *in vivo* data (IVIVC) rely on linear relationships. However, non-linear IVIVC can be also observed, justified and validated. The purpose of the present work was the development of a methodology for power law IVIVC, which mirror power law kinetics under *in vitro* and *in vivo* conditions. Fractional calculus was used to justify power law kinetics for zero-order processes in disordered media. Power law kinetics was observed in a large number of *in vitro* data sets. When "zero-order" release and absorption is considered in terms of fractional calculus the following power law IVIVC between the fraction released F_r and the fraction absorbed F_a, is obtained: $F_a = \mu F_r^{\lambda} - \beta$, where μ is a constant related to the rate constants and the orders of the release/absorption kinetics, λ is the ratio of the orders of the kinetics under *in vitro* and *in vivo* conditions and β accounts for a time shift between the *in vitro* and *in vivo* processes; We used literature data to develop power law IVIVC and derive estimates for μ, λ and β; the simulated pharmacokinetic profiles using the *in vitro* release data and the IVIVC developed compared well with the actual *in vivo* data.

1. Introduction

Dissolution and release testing are integral components of the pharmaceutical product development process. They are used as quality control procedures in pharmaceutical production and as surrogates for *in vivo* bioavailability, and bioequivalence studies when *in vitro–in vivo* correlations have been established. Plausibly, considerable attention has been shown in the modelling of dissolution and release data (Macheras and Iliadis, 2006).

Classically, dissolution is described as a first-order process since the rate of dissolution is considered proportional to the difference between the instantaneous concentration C at time t, and the saturation solubility, C_s (Noyes and Whitney, 1897; Dokoumetzidis and Macheras, 2006).

The mathematical models commonly used to describe the kinetics of drug release from a large variety of devices are two simple expressions, the Higuchi law (Higuchi, 1961) and the power law (Peppas, 1985); the latter law states that

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released at infinity, k is an experimentally determined constant and n is an exponent that depends on the geometry of the system and related to the diffusional mechanisms. One should also add that both laws for $n = 0.5$ describe adequately the first 60% of drug release following pure Fickian diffusion (Ritger and Peppas, 1987; Kosmidis et al., 2003; Macheras and Iliadis, 2006). Also, zero-order release kinetics can be considered as a special case of the power law (it is called Case II transport for polymeric devices (Ritger and Peppas, 1987; Kosmidis et al., 2003)) and can be derived from the power law by placing $n = 1$:

$$\frac{M_t}{M_\infty} = k_0 t \tag{2}$$

where k_0 is a zero-order rate constant.

In the field of GI absorption analysis, most of research is based on the tank and tube models, which are accompanied with the assumptions of perfect mixing and homogeneous flow, respectively (Dressman and Fleisher, 1986; Sinko et al., 1991; Oh et al., 1993). In this context, first-order kinetics for immediate release formulations and zero-order kinetics for most of the extended release formulations are routinely used for the description of the absorption phase.

Various reports in the literature have attempted either to explore the inadequacy of the above models to describe experimental data and/or to provide a scientific basis for the empirically used

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approaches. For example, a fractal hypothesis (Rinaki et al., 2003), based on previous Monte Carlo simulation findings (Bunde et al., 1985), was used to interpret the perfect fit of the power law to the entire sets (and not only to 60%) of experimental drug release data. Similarly, in the field of GI absorption analysis a variety of unconventional input functions like a cube-root law (Cutler, 1978b), polynomials (Cutler, 1978a), multi-exponentials (Veng-Pedersen, 1980) and splines (Verotta, 1993) have been used successfully but empirically in deconvolution methods for the identification of the input function. Also, several pharmacokinetic strategies (Zhou, 2003) have been empirically used for the analysis of typical and atypical absorption profiles. Besides, GI absorption phenomena have been described using probabilistic and fractal approaches (Kalampokis et al., 1999a,b; Dokoumetzidis et al., 2005).

The common denominator of drug dissolution, release and absorption processes is the diffusional mechanism. In our previous work (Dokoumetzidis and Macheras, 2009) we proposed a unified theory based on fractional calculus (Hilfer, 2000; Sokolov et al., 2002) interpreting both classical kinetics in Euclidean media and non-classical kinetics in disordered media. Fractional calculus introduces derivatives and integrals of fractional order, e.g. half derivative, in order to describe anomalous diffusion data. Using fractional calculus we showed that a fractionalized zero-order release gives rise to power law kinetics (Dokoumetzidis and Macheras, 2009). This provides a physical interpretation of the empirically used power law for the description of the entire release curve.

Pharmaceutical scientists wish to develop validated *in vitro–in vivo* correlations (IVIVC) since product development is facilitated and bioequivalence studies are not needed (Emami, 2006). This quest in particular applies to extended release formulations and the FDA guidance pays considerable attention to all aspects of the internal and external validation of the IVIVC (FDA Guidance, 1997). In parallel, the FDA guidance specifies five correlation levels, which are related to the ability of the developed correlation to predict the concentration time profile of the formulation upon administration to humans. From the early days of IVIVC up to the most recent ones, a limited number of validated linear correlations have been reported (Humbert et al., 1994; Eddington et al., 1998; Mahayni et al., 2000; Takka et al., 2003; Emami, 2006). In all these studies, a linear relationship was established between an appropriate release characteristic and an *in vivo* bioavailability parameter. Besides, there are also several examples in the literature of either poor linear correlation (Lake et al., 1999; Varshosaz et al., 2000; Sreenivasa Rao et al., 2001; Al-Behaisi et al., 2002) or uncorrelated data (Eddington et al., 1998; Meyer et al., 1998; Mircioiu et al., 2005). Although most of the work on IVIVC is based on linear relationships both the USP and the FDA state that non-linear models are acceptable to describe the *in vitro–in vivo* relationship (FDA Guidance, 1997; USP XXIV, 2000; Young, 2006). In fact, various reports provide scientific evidence for predictive non-linear correlations (Polli et al., 1996; Dunne et al., 1997, 1999; Sirisuth et al., 2002; Corrigan et al., 2003; Parojčić et al., 2007). The best known non-linear models are the ones proposed by Polli et al. (1996) and Dunne et al. (1997, 1999). The former model assumes first-order dissolution and permeation and gives rise to a parabolic relationship when delayed *in vivo* dissolution is assumed. The work of Dunne et al. (1997, 1999), is based on considering the time at which a drug molecule enters solution (*in vitro* or *in vivo*) to be a random variable and correlates the *in vitro* and *in vivo* distributions using a proportional odds, proportional hazards or proportional reversed hazards model. Both approaches provide scientifically based non-linear models, in contrast to empirically used non-linear functions, such as sigmoid, Weibull, Higuchi, or Hixson–Crowell in IVIVC (Mendell-Harary et al., 1997).

In this study, we employ fractional calculus in order to develop non-linear IVIVC which mirror power law kinetics under *in vitro* and *in vivo* conditions. We also discuss the implications and the physical meaning of the power law in the light of fractional calculus. Finally, in order to test the predictive performance of the power law IVIVC, we simulate pharmacokinetic profiles considering as input rate the *in vitro* profile transformed through the established IVIVC, and compare them to the literature pharmacokinetic profiles.

2. Theory

2.1. Micro-environment dimensionality and agitation conditions in drug dissolution and release processes

The proper design of the *in vitro* dissolution setups for the study of drug dissolution from immediate and controlled release formulations are primarily limited by the knowledge of gastrointestinal lumen conditions. In an attempt to establish physiologically relevant test conditions *in vitro*, milk has been used as a food mimicking medium (Macheras et al., 1987; Macheras et al., 1989) and artificial fluids, simulating gastric and small intestinal conditions in the fasted and fed state have been developed (Dressman et al., 1998, 2007). Although all these media are more akin to the *in vivo* situation, the simulation of the *in vivo* hydrodynamics remains an insuperable obstacle (Dokoumetzidis and Macheras, 2008). For example, all *in vitro* setups cannot simulate the bidirectional movement of chyme and the segmental mixing under *in vivo* conditions. On the other hand, analysis based on computational fluid dynamics for the basket (USP Type I) and paddle (USP Type II) methods of dissolution (USP XXIV, 2000) revealed the chaotic aspects of hydrodynamics (D'Arcy et al., 2005, 2006). In parallel, even small changes in the flow rate of the medium in the official flow-through apparatus (USP Type IV) (USP XXIV, 2000) result in significant changes of drug dissolution profiles (Wu et al., 2004).

All aforementioned observations indicate that the prevailing hydrodynamic conditions in the micro-environment of solid particles during drug dissolution or release differ considerably not only between the *in vitro* setups and the *in vivo* conditions but also among the official dissolution tests. Plausibly, the critical steps of drug dissolution and release, namely, solid–solvent reaction at the interface, the diffusion of the solute in the diffusion layer or in the matrix of the delivery system are highly affected by the agitation conditions leading to setup-dependent dissolution or release profiles. Similarly, the heterogeneous *in vivo* conditions (Weitschies et al., 2005) are not only indicative of the large difference between *in vitro* and *in vivo* hydrodynamics but also of a subject-dependent *in vivo* dissolution or release profile. From a kinetic point of view, one can argue that the dimensionality of the space in the solid–liquid interface is unknown under *in vitro* and *in vivo* conditions and varies considerably among *in vitro* apparatuses and subjects.

In the following sections we model drug release and absorption assuming that these processes take place in disordered media (either *in vitro* or *in vivo*) of unknown dimensionality by employing fractional calculus formalism.

2.2. Zero-order fractional release

Following the work of Dokoumetzidis and Macheras (2009), the fractionalized zero-order release differential equation can be written as:

$$\frac{d^{\alpha}M}{dt^{\alpha}} = k_{0,f} \tag{3}$$

where $d^{\alpha}M/dt^{\alpha}$ stands for the Caputo fractional derivative of non-integer order α, M is the amount of released drug at time t

and $k_{0,f}$ is the fractional zero-order rate constant expressed in amount/(time)$^{\alpha}$ units. Eq. (3) upon integration gives Eq. (4):

$$M = \frac{k_{0,f}}{\Gamma(\alpha+1)} t^{\alpha} \tag{4}$$

where $\Gamma(x)$ is the gamma function. Eq. (4) reveals that the change of M as a function of time follows a power law when zero-order release is considered in non-integer dimensions. Eq. (4) can be expressed in terms of the fraction of dose released F as follows:

$$F = \frac{k'_{0,f}}{\Gamma(\alpha+1)} t^{\alpha} \tag{5}$$

where $k'_{0,f}$ is the fractional zero-order release rate constant expressed in (time)$^{-\alpha}$ units.

2.3. Modeling in vitro and in vivo datasets

Eq. (5) was fitted to datasets taken from the literature (Cedillo-Ramírez et al., 2006; AlKhatib et al., 2008), where model parameters $k'_{0,f}$ and α were estimated. Data points were obtained by digitizing scanned images of the published plots. All fittings were performed with MATLAB using the subroutine "lsqnonlin".

2.4. Development of power law IVIVC

In our work, we focus on level A IVIVC, since it is the highest level of correlation and provides the most information. The following approach was applied to the literature data. Data points were obtained by digitizing scanned images of the published plots. Initially, Eq. (5) was fitted to the *in vitro* data and the deconvolved *in vivo* data. Subsequently, a direct relationship of fraction absorbed *in vivo* (F_a) versus fraction released *in vitro* (F_r) was derived and fitted to the data sets.

Using Eq. (5) and assuming that drug release is the limiting step for oral absorption, the fraction of dose released, F, either *in vitro* (F_r) or *in vivo* (F_a), can be expressed as follows:

$$F = kt^{\alpha} \tag{6}$$

where k equals $k'_{0,f}/\Gamma(a+1)$. Assigning the symbols (k_1, α_1) and (k_2, α_2) to the *in vitro* and *in vivo* conditions, respectively and solving the *in vitro* version of Eq. (6) in terms of t and substituting to its *in vivo* counterpart, we obtain:

$$F_a = k_2 \left(\frac{F_r}{k_1}\right)^{\alpha_2/\alpha_1} \tag{7}$$

Eq. (7) can be further simplified as follows:

$$F_a = \mu F_r{}^{\lambda} \tag{8}$$

where $\lambda = \alpha_2/\alpha_1$ and $\mu = k_2/k_1{}^{\alpha_2/\alpha_1}$. Finally, we can incorporate a y-intercept constant β, which accounts for a time shift between the *in vitro* and *in vivo* processes

$$F_a = \mu F_r^{\lambda} - \beta \tag{9}$$

Eq. (9) can be applied to the *in vitro* and *in vivo* data of extended release formulations, which usually follow a zero-order or power law pattern. The exponent λ represents a similarity factor between the *in vitro* and *in vivo* conditions. It is obvious that when $\lambda = 1$, Eq. (9) is linear and additionally when $\beta = 0$ the line passes through the origin of the axes, i.e. the *in vitro* and *in vivo* profiles superimpose. However, when $\lambda \neq 1$ a non-linear relationship arises, with the degree of non-linearity being proportional to the ratio of α_2 and α_1. In all cases, Eq. (9) can be fitted to experimental F_r, F_a data to derive estimates for μ, λ and β.

In order to simulate blood concentrations using as information an *in vitro* dataset, we can consider the convolution of the input rate derived from the *in vitro* dataset, the IVIVC and the exponential impulse response function, $\exp(-k_e \cdot t)$ where k_e is the elimination rate constant. To calculate the input rate, we can use the values of the *in vitro* fraction released, converted to the corresponding *in vivo* values using the IVIVC relationship of Eq. (9). We can then calculate a piecewise constant rate of input and use it for convolution, to calculate the concentration in the blood. The final integrated equation which gives the blood concentration C_b at any time t, given the *in vitro* data points $F_{r,j}$ at the corresponding times τ_j, the pharmacokinetic parameters k_e and the volume of distribution, V, and the IVIVC parameters μ and λ, is the following:

$$C_b(t) = \frac{\text{Dose}}{V} \sum_{j=1}^{m-1} \frac{\mu(F_{r,j+1}^{\lambda} - F_{r,j}^{\lambda})}{k_e(\tau_{j+1} - \tau_j)} \left(e^{-k_e(t-\tau_{j+1})H(t-\tau_{j+1})} - e^{-k_e(t-\tau_j)H(t-\tau_j)}\right) \tag{10}$$

where m is total number of available *in vitro* data points and $H(x)$ is the step function which takes the value 1 for $x \geq 0$ and 0 for $x < 0$.

3. Results

3.1. Dissolution and release

Zero-order kinetics (Eq. (2)) is often a desirable feature for controlled release formulations and it has been justified in several cases (Mandal et al., 2007). Also, the extensive and successful use of the power law (Eq. (1)) for the estimation of the exponent n, which can be related to the release mechanisms, is routinely based on the analysis of the initial 60% of the release data because of the approximate character of Eq. (1) (Siepmann and Peppas, 2001; Kosmidis et al., 2003). However, it is not uncommon to see the entire set (up to 100% release) of experimental data obeying the power law (Rinaki et al., 2003). Numerous experimental data were recently published in the literature (Cedillo-Ramírez et al., 2006; AlKhatib et al., 2008), after the first publication for this not uncommon kinetic behavior and its interpretation using a fractal hypothesis (Rinaki et al., 2003). This kinetic behavior is in full agreement with Eqs. (4) and (5), which describe a "ballistic" exit (zero-order kinetics) in a disordered medium.

The fittings of Eq. (5) to a large number of experimental data sets (data not shown) covering the 0–100% release range (Cedillo-Ramírez et al., 2006; AlKhatib et al., 2008) were highly successful with a high degree of correlation (R^2: 0.9717–0.9999). This proves that the entire release curve can be described as a zero-order fractional process, i.e. a power law. Furthermore, the estimates derived for α are indicative of the degree of disorderliness of the release process (Metzler and Klafter, 2000). Theoretically, the closer to unity, the less disordered the system is; for $\alpha = 1$ a linear increase of concentration with time is observed (typical zero-order release). The estimates for α ranged from 0.4462 to 0.7215 and were very close to the values of exponent n of Eq. (1) obtained from the fittings to the power law, as reported in the literature (Cedillo-Ramírez et al., 2006; AlKhatib et al., 2008). In general, Eq. (5) can be successfully be fitted to every dataset obeying power law kinetics to get an estimate for α, which indicates the degree of disorderliness of the release process.

3.2. IVIVC

The simulated IVIVC shows that when the exponent α has different values *in vitro* and *in vivo* ($\lambda \neq 1$), non-linear relationships are possible (Fig. 1A and B). The degree of deviation from linearity is proportional to the difference of the time exponents a_1 and a_2 which reflect the difference of the conditions between the two

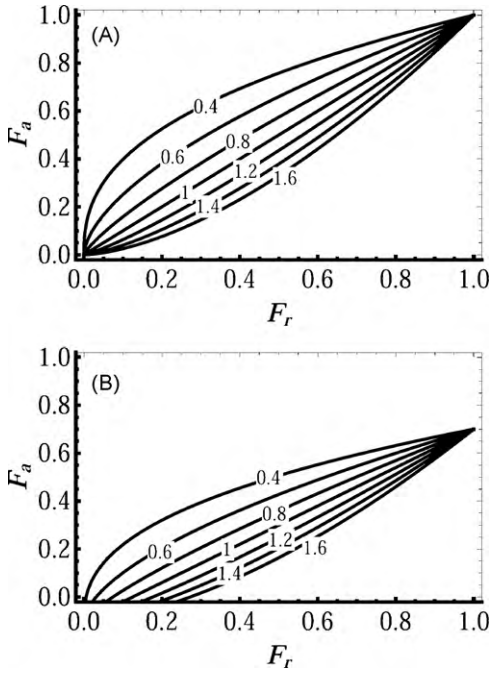

Fig. 1. Simulated IVIVC using Eq. (9) for $\lambda = 0.4–1.6$ in the case of $\mu = 1$ and $\beta = 0$ (A) and $\mu = 0.8$ and $\beta = 0.1$ (B).

environments (Fig. 1A). By introducing the *y*-intercept constant β, the simulated IVIVCs become more realistic, as shown in Fig. 1B.

In general, the shape of IVIVC curves of Fig. 1A and B resemble the corresponding non-linear IVIVC curves reported in the literature. The direct fittings of the F_r and F_a versus time curves using Eq. (5) in the case of a previously published article (Dutta et al., 2005) indicate a difference of α values between the *in vitro* and *in vivo* conditions (Fig. 2A and B). It is expected that a non-linear relationship should be more appropriate than a linear one. By direct fitting of Eq. (9) to the F_a versus F_r data of the abovementioned article (Dutta et al., 2005), we obtained a non-linear relationship (Fig. 3A). The estimates derived for λ, μ and β are listed in Table 1. It should be noted that the authors used a linear approach to correlate the data, but the non-linear fit seems more appropriate, since it provides a higher level of correlation (R^2: 0.9659 linear versus 0.9940 non-linear) with more randomly distributed residuals.

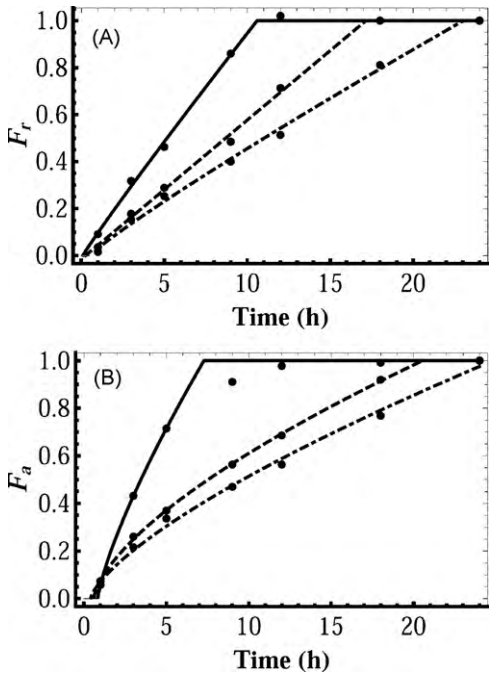

Fig. 2. Fitting of Eq. (6) to *in vitro* released (A) and *in vivo* absorbed (B) data from the literature (Dutta et al., 2005) for fast (solid line), medium (dashed line) and slow (dashed-dot line) formulations.

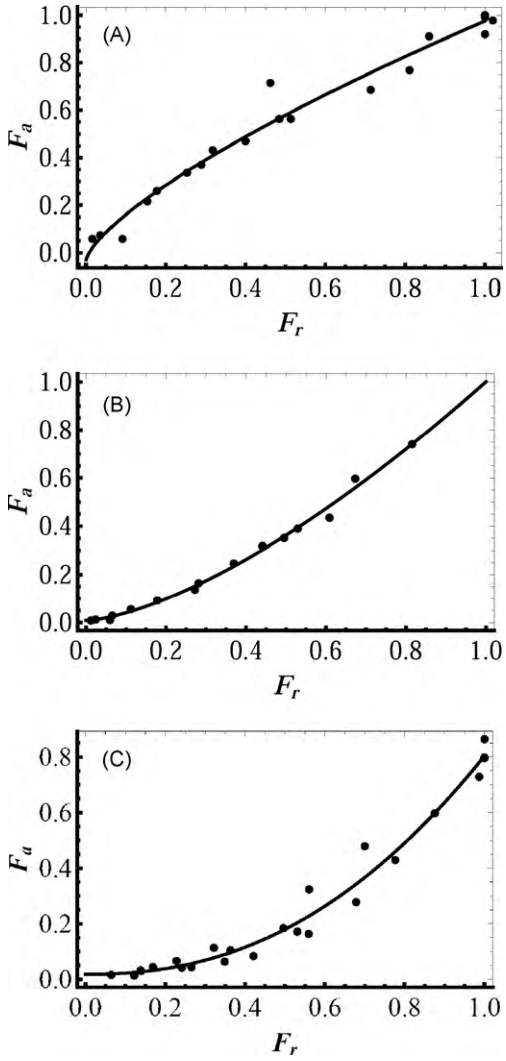

Fig. 3. Fitting of Eq. (9) to IVIVC curves from the literature data: (A) Dutta et al. (2005), (B) Ravishankar et al. (2006) and (C) Corrigan et al. (2003). The parameter estimates derived from the fittings are listed in Table 1.

The comparison of the simulated pharmacokinetic profiles using the *in vitro* data and the IVIVC relationship, to the real pharmacokinetic profiles of the corresponding formulations found in (Dutta et al., 2005), i.e. an internal validation procedure, was performed by convolution using Eq. (10) (Fig. 4). As can be seen the generated curves describe adequately the experimental *C*, *t* profiles.

The same methodology was applied to datasets from other articles (Corrigan et al., 2003; Ravishankar et al., 2006), where non-linear IVIVC have been established. Our alternative approach utilizing Eq. (9) produced similar results (Table 1 and Fig. 3B and C).

Table 1
Parameter estimates after fitting Eq. (9) to the literature data.

Reference	Estimates (S.E.)			R^2
	λ	μ	β	
Dutta et al. (2005)	0.7236 (0.0920)	1.0050 (0.0580)	0.0294 (0.0586)	0.9940
Ravishankar et al. (2006)	1.4868 (0.0795)	0.9931 (0.0311)	−0.0084 (0.0103)	0.9970
Corrigan et al. (2003)	2.2804 (0.2048)	0.7856 (0.0267)	0.0184 (0.0187)	0.9881

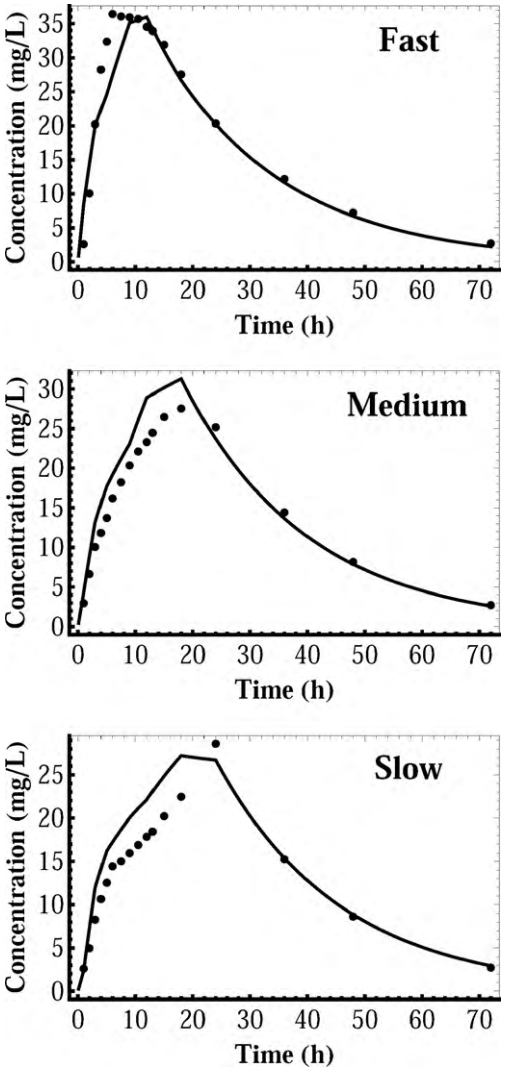

Fig. 4. Observed versus predicted plasma concentration–time profiles. The symbols represent the mean observation values reported in the literature (Dutta et al., 2005) and the lines represent the power law IVIVC model predicted plasma-time profiles.

4. Discussion

Previous studies in this field of research interpreted the heterogeneous character of drug release, and dissolution using time dependent coefficients (Macheras and Dokoumetzidis, 2000). However, the proposition of the power law for zero-order kinetics in lower dimensions using fractional kinetics principles offers a better insight in the mechanisms of drug release phenomena. The axiomatic derivation of the power law as the fractional analogue of the zero-order kinetics, substantiates the use of the power law for the entire span of release originally introduced by Bunde et al. (1985) using Monte Carlo simulations. In fact, the routine use of the power law for the analysis of the first 60% of data (Ritger and Peppas, 1987; Kosmidis et al., 2003; Macheras and Iliadis, 2006) can be now extended to the entire set (100%) of data. The two approaches can be used complementary to each other since the first approach (60% of data) interprets the diffusional mechanism(s) involved while the second approach (100% of data) gives a global view of the disorderliness of the system based on the deviation from unity of the estimate for α (Metzler and Klafter, 2000).

Fractional calculus provides a unified basis for the analysis of the diverse and heterogeneous processes of drug release, dissolution and absorption. This is so since all these processes are inherently heterogeneous and fractional calculus can tackle their common denominator, namely, the underlying anomalous diffusion.

In the field of IVIVC, fractional calculus provides a scientific basis for the analysis of non-linear relationships. Using fractional derivatives, power law kinetics can be the result of zero-order processes in disordered media. Our analysis shows that this case leads to a power law relationship between F_a and F_r, Eq. (9), while a linear relationship is still possible in the special case where $\lambda = 1$. This work provides a new insight in the field of IVIVC, since it makes possible the development and validation of non-linear relationships, instead of trying to linearize the plots by modifying and optimizing the dissolution conditions.

Finally, this work can be added to the long list of applications of fractional calculus in biomedical sciences and especially pharmacokinetics which has been growing recently (Magin, 2004; Li et al., 2007; Magin et al., 2007; Jiang and Xu, 2009; Li et al., 2009; Pereira, 2009; Popovic et al., 2010; Verotta, 2010a, 2010b; Dokoumetzidis et al., 2010).

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