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Fractional kinetics in drug absorption and disposition processes

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Abstract We explore the use of fractional order differential equations for the analysis of datasets of various drug processes that present anomalous kinetics, i.e. kinetics that are non-exponential and are typically described by power-laws. A fractional differential equation corresponds to a differential equation with a derivative of fractional order. The fractional equivalents of the "zero-" and "first-order" processes are derived. The fractional zero-order process is a power-law while the fractional first-order process is a Mittag–Leffler function. The latter behaves as a stretched exponential for early times and as a power-law for later times. Applications of these two basic results for drug dissolution/release and drug disposition are presented. The fractional model of dissolution is fitted successfully to datasets taken from literature of in vivo dissolution curves. Also, the proposed pharmacokinetic model is fitted to a dataset which exhibits power-law terminal phase. The Mittag–Leffler function describes well the data for small and large time scales and presents an advantage over empirical power-laws which go to infinity as time approaches zero. The proposed approach is compared conceptually with fractal kinetics, an alternative approach to describe datasets with non exponential kinetics. Fractional kinetics offers an elegant description of anomalous kinetics, with a valid scientific basis, since it has already been applied in problems of diffusion in other fields, and describes well the data.

Keywords Fractional kinetics · Anomalous kinetics · Power-law

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Introduction

Diffusion is one of the main mechanisms of various processes in living organisms and as such, plays an important role in the course of drugs in the body. Processes like membrane permeation, dissolution of solids and dispersion in cellular matrices are considered to be governed by diffusion. Diffusion is classically described by Fick's law and is based on the fact that a molecule makes a random walk, where its mean squared displacement is proportional to time. However, in the last few decades, strong experimental evidence has suggested that this is not always true and diffusional processes that deviate from this law have been observed. These are either faster (super-diffusion) or slower (sub-diffusion) than the classic case and the mean square displacement is a power of time, with exponent greater, or less than 1, respectively [1]. This type of diffusion gives rise to kinetics that are referred to as anomalous, to indicate the fact that deviate from the classic description [1]. Moreover, anomalous kinetics can also result from reaction-limited processes and long-time trapping. It is thought that anomalous kinetics introduces memory effects in the process that need to be accounted for to correctly describe it. A theory that describes such anomalous kinetics is the so called fractal kinetics [2] where explicit power functions of time, in the form of time-dependent coefficients, are used to account for the memory effects. In the pharmaceutical literature several datasets have been described by empirical power-laws [3], gamma functions [4] or fractal kinetics [5–9] and their use has been justified by the presence of anomalous diffusion. These include mainly pharmacokinetics of drugs that are distributed in deeper tissues [10] and bone seeking elements [7, 11]. Applications of fractal kinetics have also appeared in drug dissolution [12, 13].

An alternative theory to describe anomalous kinetics uses fractional calculus [14, 15], which introduces derivatives and integrals of fractional order, such as half or 3 quarters. Although fractional calculus was introduced by Leibniz more than 300 years ago, it is only within the last couple of decades that real-life applications have been explored [16–18]. It has been shown that differential equations with fractional derivatives describe experimental data of anomalous diffusion more accurately. In this work, we attempt to introduce these concepts in the pharmaceutical literature with two simple applications in drug dissolution and pharmacokinetics.

Theory

Fractional kinetics

Since expressions involving fractional derivatives have not been reported in the pharmaceutical literature before, a brief definition and two applications to the widely used zero- and first-order kinetics are given below.

Derivatives of integer order n, $d^n f(t)/dt^n$ of a function $f(t)$ are well defined. For a fractional order of differentiation a, where for simplicity we assume that $0 < a < 1$, the a-th derivative is defined through fractional integration and successive ordinary

differentiation. Fractional integration of order a is defined, according to the Riemann–Liouville integral [16]:

$$ {}_0D_x^{-a} f(t) = \frac{1}{\Gamma(a)} \int_0^t (t-\tau)^{a-1} f(\tau) d\tau $$

where $\Gamma(.)$ is the gamma function. Consequently, fractional differentiation is defined as:

$$ {}_0D_t^a f(t) = \frac{d}{dt} \left[\frac{1}{\Gamma(1-a)} \int_0^t \frac{f(\tau)}{(t-\tau)^a} d\tau \right] $$

This is the Riemann–Liouville definition of the fractional derivative. We can notice that the fractional integration, is basically a convolution integral between the function and a power-law of time, i.e. ${}_0D_x^{-a} f(t) = t^{a-1} * f(t)$, where the star "*" denotes convolution, accounting for the memory effects of the studied process. The fractional derivatives have properties that are not intuitive and take some time to get used to, for example, the half derivative of a constant λ in respect to x, does not vanish and instead is $\lambda/\sqrt{\pi \cdot x}$. The left-side index "0" of the D operator, denotes the lower end of the integration which in this case has been assumed to be zero. However, alternative lower bounds can be considered leading to different definitions of the fractional derivative with slightly different properties. An alternative lower bound which has been considered is "$-\infty$" and is referred to as the Wyel definition [15], which accounts for the entire "history" of the studied function, and is considered preferable in some applications. In fact one of the disadvantages of the definition with the "0" lower bound is that when used in differential equations it gives rise to initial conditions that involve the fractional integral of the function and are difficult to interpret physically. This is one of the reasons the Wyel definition has been introduced, but this definition may not be very practical for most applications either, as it involves an initial condition at time $-\infty$. An alternative definition of the fractional derivative which is referred to as the Caputo definition is preferable for most physical processes as it involves explicitly the initial condition at time zero. The definition is:

$$ {}_0^C D_t^a f(t) = \frac{1}{\Gamma(1-a)} \int_0^t \frac{f'(\tau)}{(t-\tau)^a} d\tau $$

where the upper-left index "C" stands for Caputo and the prime denotes classic differentiation. This definition for the fractional derivative, apart from the more familiar initial conditions, gives rise to more familiar properties, one of them being that the Caputo derivative of a constant is in fact zero as usual. The different definitions of the fractional derivative give different results but these are not contradicting, since they apply for different conditions and it is a matter of choosing

the appropriate one for each specific application. All definitions collapse to the usual derivative for integer values of the order of differentiation. For a nice introduction to fractional calculus and various applications in physics the article of Sekolov et al. [14] is recommended, while the review by Magin [16] gives more details and also some biologically oriented applications. More rigorous, but still addressed to the applied scientist is the book by Podlubny [15].

The fractional versions of the most commonly encountered in pharmaceutical literature types of kinetics are presented below and take the form of fractional order ordinary differential equations. The solutions of this type of equations are usually pursued by appropriate versions of the Laplace transform [15], since the Laplace transform of the ${}_0D_t^{-a}$ operator has the simple form $L\left\{{}_0D_t^{-a}f(t);s\right\} = s^{-a}F(s)$. Throughout this presentation, we are considering the Caputo version of the fractional derivative for the reasons already explained.

Zero-order kinetics

The classical zero-order kinetics equation, where the rate of change of quantity X, expressed in mass units, is considered to be constant and equal to k_0, expressed in mass/time units, is given by:

$$\frac{dX}{dt} = k_0$$

Its solution is a linear function of time and when the initial condition is zero, it has the form:

$$X = k_0 t$$

The fractional expression for the zero-order kinetics equation can be obtained by replacing the derivative of order 1 by a derivative of fractional order a:

$$\frac{d^a X}{dt^a} = k_{0f}$$

where k_{0f} is a constant with units (mass)/(time)^a. The solution of this equation for initial condition $X(0) = 0$ is a power law [15].

$$X = \frac{k_{0f}}{\Gamma(a+1)} t^a \tag{1}$$

First-order kinetics

The first-order differential equation, where the rate of change of quantity X is proportional to its current value, is given by:

$$\frac{dX}{dt} = -k_1 X$$

Its solution by considering an initial condition of $X(0) = X_0$ is given by the classical equation of exponential relaxation:

$$X = X_0 \exp(-k_1 \cdot t)$$

In fractional terms, however, the first-order equation can be written by replacing the derivative of order 1 by a fractional one,

$$\frac{d^a X}{dt^a} = -k_{1f} X \tag{2}$$

where k_{1f} is a constant with $(\text{time})^{-a}$ units. The solution of this equation can be found in most books or papers of the fast growing literature on fractional calculus [14, 16] and for initial condition $X(0) = X_0$ it has the form:

$$X = X_0 E_a\left(-k_{1f} \cdot t^a\right) \tag{3}$$

where $E_a(x)$ is a Mittag–Leffler function [15] which is defined as

$$E_a(x) = \sum_{k=0}^{\infty} \frac{x^k}{\Gamma(a \cdot k + 1)}. \tag{4}$$

The function $E_a(x)$ is a generalization of the exponential function and it collapses to the exponential when $a = 1$, i.e. $E_1(x) = exp(x)$.

The solution of Eq. 2 basically means that the fractional derivative of order a of the function $E_a(x^a)$ is itself a function of the same form, exactly like the classic derivative of an exponential is also an exponential. It also makes sense to restrict a to values $0 < a \leq 1$, since for values of a larger than 1 the solution of Eq. 2 is non-monotonous and negative values for X appear.

From these elementary equations the basic relations for the time evolution in drug dissolution and drug disposition can be formulated, with the assumption of diffusion of drug species taking place in heterogeneous space. Two examples are considered, namely, drug release or dissolution and drug disposition.

Drug release or dissolution

For the two processes of interest, we assume that under homogeneous conditions, mostly found in vitro, a zero-order differential equation describes the release kinetics while dissolution kinetics follows the classical first-order Noyes–Whitney equation [19]. Due to the heterogeneous structure and function of the GI tract [20], one can argue that the dissolution or release of drug takes place in a disordered, under stirred medium of unknown dimensionality. Since diffusion is the principal mechanism for both processes, fractional derivatives can be used to describe the kinetics under the heterogeneous in vivo conditions. The fractional derivative of zero-order release can be written as:

$$\frac{d^a C}{dt^a} = k_{0f} \tag{5}$$

where k_{0f} is the rate constant with units (concentration)/$(\text{time})^a$. The fractional form of the Noyes–Whitney equation, using the notation of Ref. [21] for the concentration term can be written as follows:

$$\frac{d^a(C_s - C)}{dt^a} = -k_d(C_s - C) \tag{6}$$

where C is the drug concentration in the GI fluids, C_s is the saturation solubility, t is time, k_d is a rate constant with units $(\text{time})^{-a}$ and $0 < a \leq 1$. Equations 5 and 6 upon integration give Eqs. 7 and 8, respectively

$$C = \frac{k_{0f}}{\Gamma(a+1)} t^a, \tag{7}$$

$$C = C_S(1 - E_a(-k_d \cdot t^a)) \tag{8}$$

where $\Gamma(x)$ is the gamma function and $E_a(x)$ is the Mittag–Leffler function, Eq. 4. It is worth mentioning that power-laws like Eq. 7 have been used extensively to describe drug release [19, 22, 23]. Also, as we will see further on, Eq. 8, behaves as a Weibull function for small times, a function used extensively to model drug dissolution curves [19, 24], and for larger times it behaves as a power-law.

Pharmacokinetics

In the simplest pharmacokinetic relationship, the iv bolus injection with first-order elimination, in a one compartment model, the drug concentration, C, follows the common expression

$$\frac{dC}{dt} = -k_{el}C$$

where k_{el} is the elimination rate constant. The fractional version of this equation can be written as

$$\frac{d^aC}{dt^a} = -k_{1f} \cdot C \tag{9}$$

where k_{1f} is a constant with units $(\text{time})^{-a}$. The solution of Eq. 9, as already mentioned, can be written as:

$$C = C_0 E_a\left(-k_{1f} \cdot t^a\right) \quad \text{for} \quad a \leq 1 \tag{10}$$

where C_0 is the ratio (dose)/(apparent volume of distribution). This equation for small times behaves as a stretched exponential, i.e. $\sim \exp(-k_{1f} \cdot t^a)$, as we will see further on, while for large values of time as a power-law. It is therefore a good candidate to describe various datasets exhibiting power-law-like kinetics due to the slow diffusion of the drug in deeper tissues.

Equation 9 is a relationship for the simplest case of fractional kinetics. It accounts for the anomalous diffusion process, which may be considered to be the limiting step of the entire kinetics. Classic clearance may be considered not to be the limiting process here and is absent from the equation. More complex cases can be devised including systems of fractional differential equations, although the analytical solution in these cases may not be available. However, algorithms for the numerical solution of fractional differential equations exist [15]. Fractional

calculus is a live area of research in Mathematics and progress in made continuously, motivated also by the increasing number of applications.

Results and discussion

Plots of Eqs. 1 and 3 for various values of a are shown in Fig. 1a, b, respectively. In the special case of classical diffusion, $a = 1$, Eqs. 1 and 3 provide the linear and mono-exponential increase or decrease with time, of zero- and first-order kinetics, respectively, while for different values of a, the curves deviate from the special case. In Fig. 2, a plot of Eq. 3 is shown in log–log scale together with a stretched exponential function and a power-law function for $a = 1/2$. One can observe from the figure that for $a < 1$ and small values of time, Eq. 3 overlaps with the stretched exponential function while for large values of time it follows the power-law.

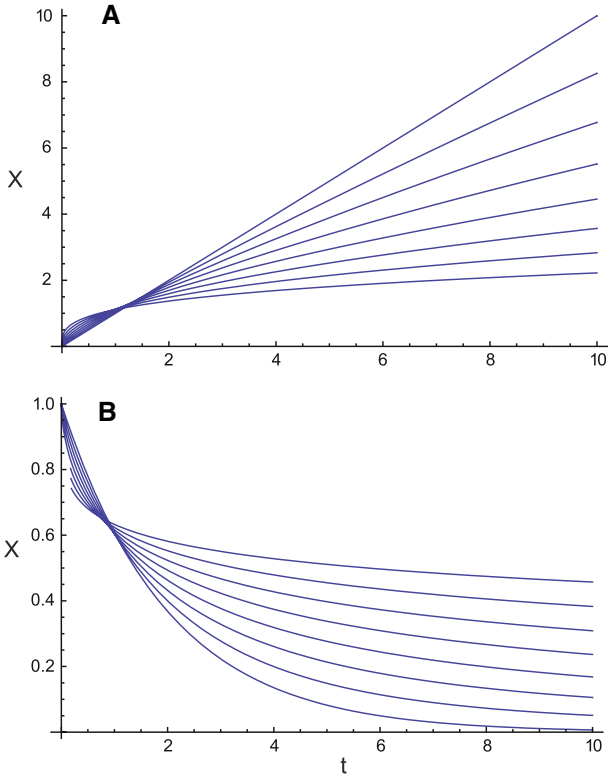

Fig. 1 **a** Plot of the Eq. 1 for $k_{0f} = 1$ and various values for a, from $a = 0.3$ to $a = 1$ (*top straight line*). **b** Plot of the Eq. 3 for $X_0 = 1$, $k_{1f} = 0.5$ and various values of a, from $a = 0.3$ to $a = 1$ which is the exponential function $\exp(-0.5t)$ (*bottom curve*)

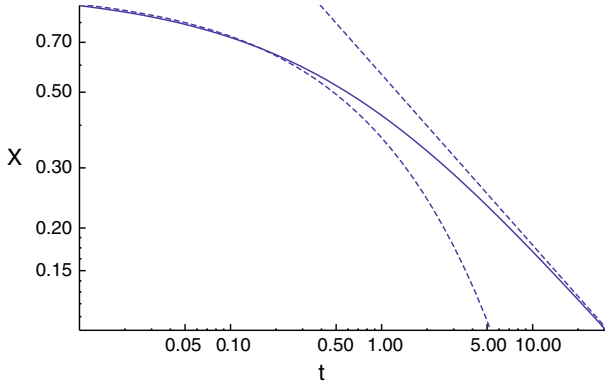

Fig. 2 Log-log plot of Eq. 3 for $a = 0.5$ (*middle curve*), the stretched exponential function $\exp(-t^{0.5})$ (*bottom curve*) and the power function $t^{-0.5}/\Gamma(0.5)$, (*top curve*). Equation 3 starts close to the stretched exponential and finishes close to the power function

Drug dissolution

In drug dissolution the classic Noyes–Whitney law does not always provide good fits to the data while alternative functions such as the Weibull function may perform better [19]. Equation 8 for small times behaves as a Weibull (stretched exponential) while for large times as power-law and therefore, it may be appropriate for the description of dissolution data. To investigate this, we fitted a version of Eq. 8 to seven datasets of in vivo dissolution data, which have been produced by deconvolution of plasma data of remoxipride capsules (100 mg), taken from literature [25]. A lag-time parameter, t_{lag}, was introduced and the model was expressed as fraction of dose dissolved, Φ:

$$\Phi = \mathrm{F} \cdot \left[1 - E_a\left(-k_d \cdot \left(t - t_{lag}\right)^a\right)\right] \tag{11}$$

where F is a parameter corresponding to the plateau of the dissolution curve or the final fraction dissolved. The analysis was done in MATLAB using the subroutine "lsqnonlin" while for the calculation of the Mittag–Leffler function, the subroutine "MLF" by Podlubny and Kacenak, was used [26]. The parameter estimates and their standard errors are shown in Table 1. Figure 3 shows the fits of the model to the data and visual inspection reveals that this is adequate. R^2 values are also included in Table 1 and seem to be close to the unit. Also, from Table 1, we can see that the parameter a, which corresponds to the order of the process, is in some cases significantly smaller than 1, suggesting that for these datasets heterogeneous conditions prevail, while for some cases the estimate of a is close to 1 indicating that these processes can effectively be described by a simple exponential and therefore correspond to classic kinetics.

A benefit of describing the data with the fractional equation is that it is a simple, elegant representation which corresponds to a mathematical generalisation of a commonly used equation. Further, it has a solid scientific basis which has been demonstrated in a wide range of applications across different disciplines. The

Table 1 Estimated parameters of Eq. 11 when fitted to the datasets from Ref. [25]

Dataset	F	a	k_d (hours^{-a})	t_{lag} (hours)	R^2
A	0.884 (0.062)	0.929 (0.233)	0.750 (0.382)	1.251 (0.639)	0.986
B	0.860 (0.056)	0.960 (0.191)	0.734 (0.182)	0.856 (0.079)	0.975
C	1.356 (1.574)	0.672 (0.900)	0.349 (0.206)	1.578 (1.463)	0.946
D	0.871 (0.025)	0.975 (0.071)	0.620 (0.057)	0.889 (0.074)	0.993
E	0.868 (0.013)	0.916 (0.034)	0.733 (0.026)	0.898 (0.019)	0.998
G	1.011 (0.073)	0.649 (0.263)	1.432 (0.498)	1.353 (0.380)	0.997
H	0.980 (0.008)	0.946 (0.024)	1.000 (0.029)	0.923 (0.011)	0.999

The numbers in parentheses are the standard errors. The letters correspond to the dataset names in the original paper. Goodness of fit R^2 values are also included

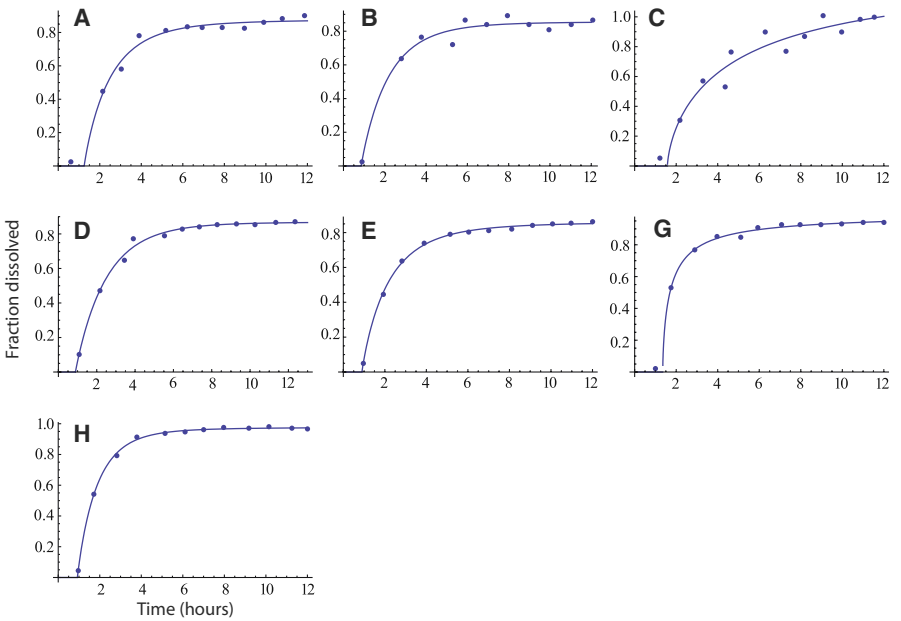

Fig. 3 Seven plots corresponding to the datasets of in vivo dissolution of remoxipride capsules, produced by deconvolution, from Ref. [25], together with the fitted curves of Eq. 11 (*the letters correspond to the ones in the original paper*). The best fit parameter values for Eq. 11 are shown in Table 1

heterogeneous conditions that the fractional approach applies to, are of particular importance under in vivo conditions, in the gastrointestinal system. Ideally, one could envisage that the degree of heterogeneity is described by parameter a and therefore, the same drug formulation will give different values under different conditions, i.e. in vivo *versus* in vitro. In this case, an IVIVC approach could employ these new equations to establish a valid correlation.

Pharmacokinetics

As already mentioned, in pharmacokinetics several drugs are known to follow distribution kinetics that deviate from the linear compartmental approach and are best described by power-laws. This is attributed physically to slow diffusion in deeper tissue spaces and the bone. Indeed, important such examples are bone seeking elements like calcium [7], plutonium [11], strontium [27], etc. However, another known example of a drug which follows power-law kinetics is amiodarone [4, 10]. Fractional kinetics allows an alternative description of the anomalous kinetics of such drugs. We analysed, using Eq. 10, amiodarone data taken from literature [10], in order to demonstrate that this approach can describe datasets that follow power-law kinetics. In Fig. 4 semi-log and log–log plots of the data together with the best fit of Eq. 10 are shown. Also the estimates for the parameter values were as follows: $a = 0.84$ (0.012), $k_{1f} = 5.49$ (1.06) days^{-a}, $C_0 = 5.49$ (0.89) ng/ml, where the

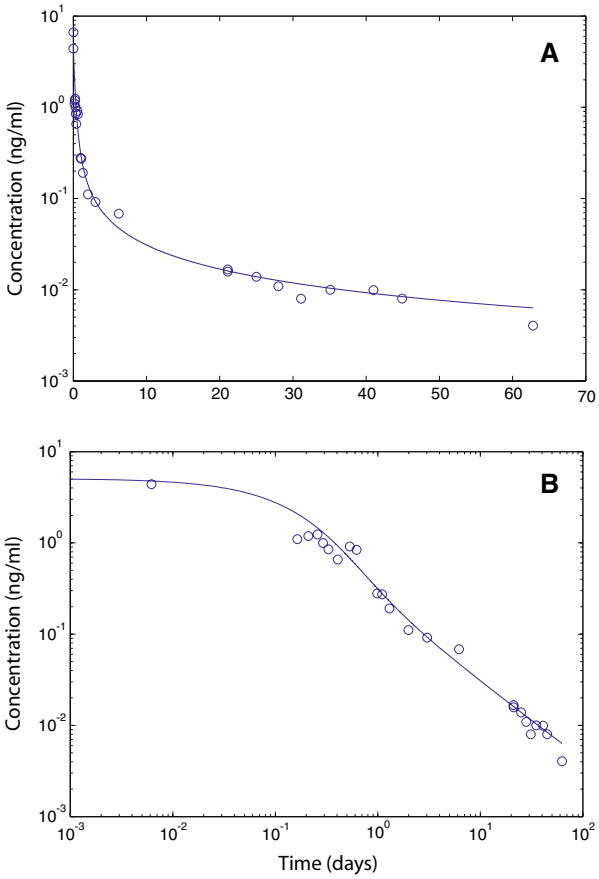

Fig. 4 Semi-log (**a**) and Log–log (**b**) plots of the amiodarone kinetic data from Ref. [10], together with the fitted curve of Eq. 10

numbers in brackets correspond to the standard errors of the estimates. Visual inspection of Fig. 4 reveals that the fit is adequate, which is expectable as amiodarone data are known to follow anomalous kinetics. This is clearer in the log–log plot (Fig. 4b) where the terminal phase is well described by a straight line. But as opposed to the simple power-law that goes to infinity when time approaches zero, the Mittag–Leffler function describes the initial part of the curve too. Also as before, we can see that the value of parameter a, that gives the best fit to the data is significantly different to 1. Of course it is wrong to compare the goodness of fit of this approach with the one-compartment classical model as one would use a multi-compartmental model to fit this dataset. But in the classic compartmental approach the solution always gives rise to a sum of exponentials, the slower of which survives for large times and shapes the terminal decay, so the behaviour is always exponential. The difference with power-law kinetics is that it is always slower than any exponential kinetics, regardless of how large the half-life is. This is because in power-law kinetics there is no constant half-life and the concentration is halved in ever increasing time intervals. Using multi-compartmental kinetics to account for power-law kinetics would give rise to a high number of compartments that would increase with the time-span of the data. So for longer times, one would need more compartments, i.e. more exponential phases to describe the data. The power-law kinetics and more specifically the Mittag–Leffler kinetics accounts for that, with a simple solution that contains a small number of parameters. Power-law kinetics, when present, have important clinical implications, including infinite AUC and accumulation without reaching a steady state. Also a clearance value (Dose/AUC) may not be a meaningful parameter to describe the elimination of drug from the body since the rate limiting process is the anomalous diffusion.

The present approach provides an alternative to empirical power-laws [3] or other methods suggested to study this type of data [10, 11]. An advantage of the Mittag–Leffler function of the simple power-law is that while the power-law becomes infinite as time approaches zero, Eq. 10 behaves as a stretched exponential when time approaches zero and as power-law for large times, describing the data correctly in all time scales. It presents an elegant formulation with physical relevance and builds on the simple compartmental analysis of the classical pharmacokinetics. Beyond this simple example, presented here, more complex models can be formulated with this approach but these probably require the utilisation of numerical methods for the solution of the system as an analytical solution may not be tractable.

Comparison of fractional and fractal kinetics

The approach of the fractal kinetics, as introduced by Kopelman in chemical reaction kinetics [2], and then applied also in pharmaceutical topics [5–9, 12, 13] addresses the same issue of anomalous kinetics in heterogeneous media. It is tempting to compare it with the concepts of fractional kinetics, in terms of the formulation of equations and their solutions.

In fractal kinetics a first-order process is expressed using a time dependant rate coefficient $K(t)$

$$\frac{dX(t)}{dt} = -K(t)X(t) \tag{12}$$

The coefficient usually takes the form of a power function

$$K(t) = b \cdot t^{-h} \tag{13}$$

The power time function is considered to account for the memory effects of such a process. The solution of Eq. 12 for the initial condition $X(0) = X_0$ is a stretched exponential function.

$$X(t) = X_0 exp\left[-\frac{b}{1-h}t^{1-h}\right] \tag{14}$$

On the other hand, if we represent the memory effects of the process following anomalous kinetics, by an equation which includes the convolution of the studied function with a time varying function, we have:

$$\frac{dX(t)}{dt} = -K(t) * X(t) \tag{15}$$

where the star symbol "*" stands for the convolution operator and

$$K(t) * X(t) = \int_0^t K(t-\tau)X(\tau)d\tau$$

Then if we let the kernel $K(t)$ of the memory integral to be a power function similar to Eq. 13, namely,

$$K(t) = k_{1f} \cdot t^{a-2} \quad \text{with} \quad 0 < a < 2$$

we can derive a first-order fractional differential equation, where in this case the fractional derivative follows the Riemann–Liouville definition. This equation has for solution a Mittag–Leffler function [15].

So there is a resemblance of the two approaches, as far as the formulation of the equations is concerned (Eqs. 12 and 15). However, the main difference is the explicit presence of the memory effects in the fractional approach through the convolution integral, while in the fractal approach the memory effects are introduced through the time dependant coefficients. These memory effects play a key role in anomalous kinetics. The results (solutions) of the two approaches are also similar, as we have discussed above, i.e. Mittag–Leffler versus stretched exponential, but not identical.

Conclusions

Fractional kinetics offers an elegant description of anomalous kinetics, i.e. non-exponential terminal phases, the presence of which has been acknowledged in pharmaceutical literature extensively. Giving first a small introduction on the subject, we presented two applications, on drug dissolution and the

pharmacokinetics of amiodarone. The approach offers simplicity, a valid scientific basis, since it has already been applied in problems of diffusion in physics and biology. It introduces the Mittag–Leffler function which describes well the data in all time scales unlike the empirical power-laws which describe the data only for large times. Despite the mathematical difficulties, we believe that fractional kinetics is an interesting approach for the toolbox of the pharmaceutical scientist.

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