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COMMENTARY

The Changing Face of the Rate Concept in Biopharmaceutical Sciences: From Classical to Fractal and Finally to Fractional

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INTRODUCTION

The time course of drug in the body is dynamic. A large number of processes, based on fundamental physicochemical principles, are involved from the initial disintegration of the tablet and the dissolution of the active ingredient, to the pharmacological effect of drug. However, irrespective of the detailed characteristics, the common and most principal component of the underlying mechanism of numerous drug processes is diffusion. The diffusion of molecules at the microscopic level results in the observed "flux" at the macroscopic level and further to the " rate" of the process, which is the crux of the matter for the present commentary.

A PRELUDE IN REGULAR DIFFUSION

Since diffusion is the random migration of molecules or small particles arising from motion due to thermal energy, the analysis of the diffusive spreading usually relies on the one-, two- or three-dimension random walk models (1). For the purposes of the present work, two striking properties are of major importance in classical diffusion. The first is that the root mean square displacement of a walker (particle or molecule) $<z^2(t)>$ is proportional to the square root of time, t:

$$< z^2(t) > \propto t \tag{1}$$

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where z is a spatial coordinate. The second property is that the net flux is proportional to the gradient of the concentration function (at z and t):

$$\mathcal{J}(z,t) = -D\frac{\partial C(z,t)}{\partial z} \tag{2}$$

This is Fick's first law of diffusion, which states that the net flux, $\mathcal{J}(z, t)$, is proportional to the gradient of the concentration function, $C(z, t)$, where D is the diffusion coefficient. The minus sign in Eq. 2 indicates that the flow occurs from the concentrated to the dilute region of the solution.

CLASSICAL FIRST-ORDER PROCESSES

Classical biopharmaceutic, pharmacokinetic and pharmacodynamic processes mostly rely on Eq. 2. For example, the flux is the flow $\dot{q}(t)$of the material between two regions (L, R) of different concentrations C_L and C_R ($C_L > C_R$) through a membrane of surface S and thickness δ; the flow $\dot{q}(t)$ can be written using Eq. 2 approximating the concentration gradient by differences:

$$\dot{q}(t) = R_{LR} = \frac{D'S}{\delta}[C_L(t) - C_R(t)]$$
$$= P \cdot S[C_L(t) - C_R(t)] \tag{3}$$

where R_{LR} is the transfer rate of the material, D' is a modified diffusion coefficient, for restricted diffusion inside the membrane, and the parameter $P = D'/\delta$ characterizes the diffusing ability of a given solute for a given membrane, and is called permeability with dimensions length × time^{-1}. Equation 3 reveals the first-order character of the transfer rate. Under sink conditions ($C_L >> C_R$), Eq. 3 can be

simplified to a zero-order relationship:

$$\dot{q}(t) = R_{LR} = \frac{D'A}{\delta} C_L(t) = P \cdot S \cdot C_L(t) \quad (4)$$

All permeation studies dealing with transcellular passive diffusion are based either on Eq. 3 or 4 to get an estimate for *P*. In the same vein, the Noyes-Whitney law in dissolution studies (2) as well as most of the rate expressions used in absorption, distribution and excretion of drugs in pharmacokinetics follow the first-order pattern (1) (Fig. 1).

FROM THE LAW OF MASS ACTION TO FRACTAL KINETICS

In chemical kinetics, we are interested in the time-dependences of the concentrations of the reactants and products. However, the rate equations we use in chemical kinetics presuppose that the reactions are really reaction-limited. This means that the typical time needed for the reactants to reach each other in the reaction space (diffusion time, t_{diff}) is much shorter than the typical time needed for the two chemical species to react when placed in close proximity (reaction time t_{reac}). Under these conditions ($t_{reac} > t_{diff}$), the rate of the reaction is proportional to the global concentrations of the reactant species (law of mass action). Accordingly, there is an extensive use of the classical rate equations based on the law of mass action in protein binding studies, drug-receptor, drug-enzyme, and drug-carrier interactions in the various fields of drug research (1).

For diffusion-limited reactions ($t_{reac} < t_{diff}$), the transport properties of the reactants determine the kinetics. In this case, the kinetics are largely influenced by local fluctuations in the concentration of the reactants, since the concept of global concentrations is meaningless. Most importantly, the kinetics are sensitive to the peculiarities of the diffusion process, which may be anomalous if the medium is of low dimensionality (fractal or disordered). The hallmark of anomalous diffusion is that the mean square displacement of particle or molecule follows the pattern

$$< z^2(t) > \propto t^{2/d_w} \quad (5)$$

where d_w is the fractal dimension of the random walk and its value is usually $d_w > 2$ (1). The exponent d_w arises from the obstacles of the structure, i.e., the diffusional propagation is hindered by geometric heterogeneity. Equation 5 links the propagation of the diffusion front to the structure of the medium, and it recovers also the classical law of regular diffusion when $d_w = 2$ (see Eq. 1).

The drastic and unexpected consequences of nonclassical kinetics of diffusion limited reactions are called fractal kinetics (3). Due to dimensional or topological constraints, the position of the reactants is not re-randomized as a function of time. This results in segregation of the species while correlations begin to develop between the reactants' positions, and depletion zones around each reactant steadily grow with time, which subsequently has a profound effect on the rate of the reaction. In fact, the rate constant k of the reaction is no longer "constant," but depends on the growth of this depletion zone and, consequently, is time dependent

$$k(t) = kt^{-h} (t > t_0) \quad (6)$$

where $k(t)$ is the instantaneous rate coefficient, since it depends on time t, and h is the fractal kinetics exponent ($0 \leq h < 1$). The switching time t_0 depends on experimental conditions and indicates that the value of $k(t)$ crosses over from a constant regime at short times, $t < t_0$, to a power law decrease at longer times, $t > t_0$, Fig. 1.

This type of kinetics where the rate of the process (reaction) is governed by a time-dependent coefficient has found many applications (4). Processes like dissolution and release, which are based on diffusion principles, have been modeled with this type of kinetics (5). Moreover, time-dependent coefficients have been used to explain the pharmacokinetics of calcium (6) and mibefradil (7–9). The heterogeneous character of the drug processes in the gastrointestinal lumen (10,11) has also been analyzed with fractal and fractal kinetics principles (12), and this has led to the development of the heterogeneous tube model for the gastrointestinal absorption (13,14). Besides, fractal concepts coupled with diffusion dispersion principles have been used for the development of a fully physiological recirculatory model (15,16), while fractal kinetics have been applied to the study of elimination processes (17).

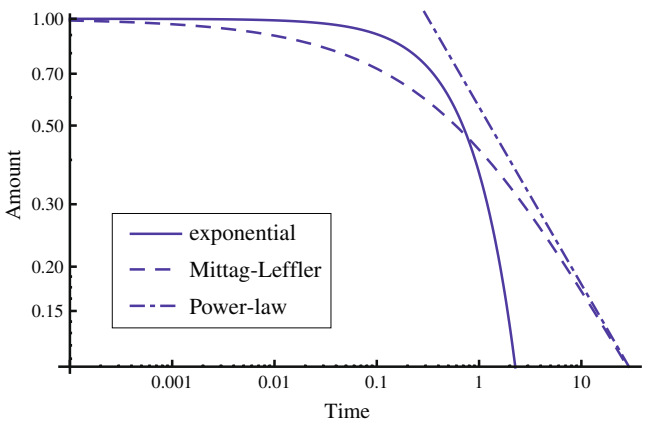

Fig. 1 Three types of kinetics: simple exponential decline (*solid line*), power-law decline (*dot-dash*), and Mittalg-Leffler kinetics (*dashed*). Note that ML converges to the power-law profile for long times.

FRACTIONAL KINETICS

An alternative way to describe mathematically anomalous diffusion and diffusion in constrained and fractal topologies

is by the use of fractional calculus (18). Fractional calculus studies derivatives and integrals of fractional order. A fractional integral is a convolution integral of the integrated function and a kernel which has the form of a power function. Fractional derivatives are defined by differentiating fractional integrals (18).

Differential equations built with fractional derivatives (FDEs) can describe anomalous kinetics without introducing time-dependent coefficients as in fractal kinetics. The presence of the convolution of a function with a power law of time introduces memory effects essential in the description of anomalous diffusion. Simple FDEs give rise to solutions commonly used in pharmaceutical sciences. The simplest FDE describes a constant fractional rate of order $0<\alpha<1$, i.e.

$$D_t^{\alpha} A(t) = k_0 \text{ with } A(0) = 0 \tag{7}$$

where the operator D_t^{α} stands for the Riemann-Liouville fractional derivative of order α with respect to t for the function $A(t)$, and k_0 is a constant. Equation 8 gives rise to the power law of time commonly used in pharmaceutics (18), i.e.

$$A(t) = \frac{k_0}{\Gamma(\alpha+1)} t^{\alpha} \tag{8}$$

where Γ is the gamma function. Also, the FDE describing a proportional fractional rate, i.e.

$$D_t^{\alpha} A(t) = -k_1 A(t), \text{ with } A(0) = A_0 \tag{9}$$

where k_1 is a constant, gives rise to the so called Mittag-Leffler (ML) function of order α denoted as $E_{\alpha}(x)$, which is a fractional generalization of the exponential function (18).

$$A(t) = A_0 E_{\alpha}(-k_1 t^{\alpha}) \tag{10}$$

An ML function behaves as a stretched exponential for small times, but as a power law for large times and, hence, is capable of describing datasets which have a power law terminal phase but without blowing up at time zero as the plain power law does, e.g. in pharmacokinetics (18) (Fig. 1).

It is common when working with fractional calculus to construct models by "fractionalizing" ordinary, well-established models. Although it may be straightforward to fractionalize simple systems described by one ODE, by changing the order of the derivative of the ODE, e.g. Eqs. 7 and 9, when working with more complex models described by systems of ODEs, such as multi-compartmental models in pharmacokinetics, care needs to be taken so that the final fractional equations are consistent with each other and the desired properties, such as mass balance, are maintained (19). However, it is possible to construct fractional models of arbitrary structure with mixed fractional orders coexisting (20). Another aspect to consider is the lack of analytical solutions for the more complex fractional models. This makes the employment of numerical methods necessary in order to simulate with these fractional models. Fortunately, an increasing number of numerical methods for linear (20) or even non-linear systems (21) have been developed in the last few years. Also, as fractional calculus and its applications is a growing field of active research, the relevant literature is expected to grow both for theory and methodology, as well as applications. In pharmaceutical sciences, fractional calculus is considered to be a promising new tool, and the relevant applications are growing rapidly (18–20, 22, 23).

Fractal and fractional kinetics are used to model datasets that depart from the classic exponential kinetics. The signature of this anomalous kinetics is power-law time profiles. This type of kinetics has been known even before the development of the theoretical tools discussed in this manuscript, and empirically based power functions have been used to model this type of kinetics in the past (24, 25).

While the classic representations of rate are applicable under homogeneous conditions where classic diffusion dominates, in heterogeneous confined topologies, fractal concepts need to be introduced to account for anomalous diffusion and memory effects. These effectively introduce time-varying properties for the system. A more elaborate and appealing way to represent these non-classic rates is by fractional calculus, where the phenomena of anomalous diffusion are described naturally, as fractional generalizations of classic laws, without introducing explicit time dependence.

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