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Commentary

On the Heterogeneity of Drug Dissolution and Release

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Drug dissolution phenomena were studied extensively during the last four decades since drug development, quality, and the *in vivo* performance of the marketed drug product are heavily dependent on the dissolution of drug and/or the drug product (1–3). A variety of empirical or semi-empirical models have been used to describe drug dissolution or release from formulations. All present models rely on classical kinetics and describe the amount of drug dissolved or released as an exponential function of time (4–7). One suggestion invokes an analogy with processes which are governed by time dependent rate coefficients (8). Here we approach this idea theoretically and experimentally, presenting evidence of a common mechanism for two widely used equations to describe drug dissolution or release. We re-interpreted, in terms of the heterogeneity of the reaction and/or diffusion space topology, the conventional parameters of the current models using experimental data from *in vitro* studies. Data from *in vivo* studies indicate that a time dependent rate coefficient governing dissolution kinetics operates in the gastrointestinal (GI) tract too. These observations provide a physically based interpretation for one of the major sources of high variability of the sparingly soluble drugs and imply the need to reconsider the current as well as the proposed changes for the assessment of bioequivalence studies for sparingly soluble, highly variable drugs.

Analysis of dissolution-release data. The first quantitative study of the dissolution process was published (9) in 1897 by Noyes and Whitney. Using water as a dissolution medium, they rotated cylinders of benzoic acid and lead chloride and analyzed the resulting solutions at various time points. They found that the rate (dC/dt) of change of concentration (C) of dissolved substances was proportional to the difference between the saturation solubility (C_s) of the substances and the concentration existing at any time t. Using K as a proportionality constant, this can be expressed as:

$$\frac{dC}{dt} = K(C_s - C) \tag{1}$$

Later on, Eq. 1 was modified (10,11) and expressed in terms of the dissolved amount of drug, m, at time t:

$$\frac{dm}{dt} = \frac{A \cdot D}{V \cdot \delta}(C_s - C) \tag{2}$$

where A is the effective surface area of the solid, D is the diffusion coefficient of the substance, δ is the effective diffusion boundary layer thickness adjacent to the dissolving surface and V is the volume of the dissolution medium. The integrated form of Eq. 2 is the most useful for practical purposes:

$$m = \frac{C_s}{V}(1 - \exp(-Kt)) \tag{3}$$

where

$$K = A \cdot D/\delta \tag{4}$$

Eq. 3 has a classical exponential form concaving downwards throughout the time course of the process approaching the plateau level C_s/V asymptotically. Although Eq. 3 has been used widely, it has been proven inadequate in modeling either S-shaped experimental data or data with a steeper initial slope. Therefore, a more general function, based on the Weibull distribution (12), was proposed (5) and applied (5,13) empirically but successfully in all types of dissolution curves:

$$M = 1 - \exp(-\alpha t^{\beta}) \tag{5}$$

where M is the accumulated fraction of the material in solution at time t, α is a scale parameter and β is a shape parameter which characterizes the curve as either typical exponential ($\beta = 1$), S-shaped ($\beta > 1$) or exponential with a steeper initial slope ($\beta < 1$). It is also worthy to mention that a gamma distribution function proposed (7) recently for modeling *in vitro* dissolution profiles implies a relevant type of time dependency for the amount of drug dissolved.

In parallel, the assessment of drug release from controlled release devices is accomplished routinely by the empirical Eq. 6 introduced in early eighties (6):

$$M = K_1 t^n \tag{6}$$

where K_1 is a kinetic constant characteristic of the drug/polymer system and n is an exponent taking values greater than 0.5 which characterize the diffusional mechanism of drug release. For example, when a $t^{-0.5}$ dependence of the drug release rate on time is found, a Fickian diffusion mechanism is justified. This specific case, is also referred as the Higuchi model (4). Eq. 6 has been derived as a simplification of more complex

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solutions while the actual geometry and the boundary conditions considered influence the final form of the equation (14,15). However, Eq. 6 is used extensively for the analysis of release data and is usually applied to the initial portion of the curve ($M \leq 0.6$).

Time dependent rate coefficients govern dissolution and release. The empirical derivation of equations 5 and 6 and their similarity (both equations contain exponents in the time variable) along with their extensive application and success in modeling dissolution or release data prompted us to reexamine if a common scientific basis exists. Since this type of time dependency is encountered in processes taking place in disordered media (8), we tested this hypothesis for dissolution and release phenomena. It is also worthy to mention that Elkoshi (16) in his work on variability of dissolution data has pointed out that the Weibull rate parameter may be time dependent.

The validity of Eq. 3 relies on Fick's first law of diffusion and presupposes that all terms comprising K in Eq. 4 remain constant throughout the process. However, the drug surface area of either powders or immediate release formulations is decreasing as dissolution proceeds. In fact, a dramatic reduction of the surface area is observed whenever the dose number, which in this case is the drug mass divided by the volume of the dissolution medium and the drug's solubility, is less than 10. This problem has been realized over the years and equations which take into account the diminution of the surface area have been published e.g. Hixson-Crowell (17) and its modifications (18–20). Although these approaches (17–20) demonstrate the important role of the drug materials surface and its morphology on dictating the dissolution profile, they still suffer from limitations regarding the shape and size distribution of particles, the conditions (sink or not) as well as the assumptions for the constancy of the diffusion layer thickness δ and drug's diffusivity D throughout the process. In reality, the parameters δ and D cannot be considered constant during the entire course of the dissolution process when polydisperse powders are used and/or an initial phase of poor de-aggregation of granules or poor wetting of formulation is encountered.

The basic theory of chemical kinetics originates from the work of Smoluchowski (21) at the turn of the century. He showed that for homogeneous reactions in three dimensional systems the rate constant is proportional to the diffusion coefficient (Eq. 4), i.e., both D and K are time independent. However, this is not true for lower dimensions (8). Since drug release from controlled release formulations takes place at interfaces of different phases (liquid-solid boundaries), homogeneous conditions may not prevail during the entire course of the process in the effective diffusion boundary layer adjacent to the dissolving surface. Similarly, the release of a drug from a polymer matrix or its diffusion through a polymer membrane depends drastically on the geometrical characteristics of the materials (22).

For the reasoning delineated above both for immediate and controlled release formulations, the validity of use of a classical rate constant, K, in Eq. 1 is questionable; it stands to reason that a time dependent instantaneous rate coefficient k to govern both dissolution and release under nonhomogeneous conditions, can be conceived (8):

$$k = k_1 t^{-h} \quad (t \neq 0) \tag{7}$$

where k_1 is a constant not dependent on time with units $(\text{time})^{h-1}$ and h is a pure number. Eq. 7 is used in chemical kinetics to describe phenomena which take place under dimensional constrains or understirred conditions (8). It is used here to describe the time dependency of the dissolution rate which originates from the change of the parameters involved in Eq. 4 during the dissolution process i.e. the reduction of the effective surface area, A, and/or the nonhomogeneous hydrodynamic conditions affecting δ and D.

Using Eq. 7 for replacing K in the fundamental Eq. 1, changing the concentration variable to amount and integrating the resulting equation, one obtains (see Appendix):

$$M = 1 - \exp\left(-\frac{k_1}{1-h} t^{1-h}\right) \tag{8}$$

Eq. 8 is identical to the Weibull equation (5) for $a = k_1/(1-h)$ and $\beta = 1 - h$. Besides, Eq. 8 collapses to the "homogeneous" Eq. 3 when $h = 0$.

Relying again on Eq. 1, assuming sink conditions ($C_s >> C$), utilizing Eq. 7 to replace K in Eq. 1, and applying the same approach as above, one obtains (see Appendix):

$$M = \frac{k_1}{1-h} t^{1-h} \tag{9}$$

which is identical to equation (6) for $K_1 = k_1/(1-h)$ and $n = 1 - h$. Also, Eq. 9 can be considered as a rough approximation of Eq. 8 at early times since the former can be obtained form the latter if one uses a one-Taylor series expansion for the exponential term of Eq. 8. This reveals the interrelationship of the empirically used Eqs. 5 and 6 and explains the well known fact (6) that Eq. 6 can only describe the initial portion of the release curve ($M \leq 0.6$). It should be noted that the derivation of Eqs. 8 and 9 requires $h < 1$. This should be taken into account whenever these equations are applied to real data.

Equations 8 and 9 signify the time dependent character of the rate coefficient governing the processes. These observations reveal that the parameters β and n of Eqs. 5 and 6, respectively, can be interpreted in terms of the heterogeneity of the corresponding processes. For example an S-shaped dissolution curve with $\beta > 1$ (Eq. 5) for an immediate release formulation can be now interpreted as an heterogeneous dissolution process ($h < 0$, Eq. 9) whose rate increases with time during the upwards concaving initial limb of the curve and decreases after the point of inflection. This kind of behavior can be associated with an initial poor deaggregation or poor wetting. In this context, Table 1 presents values for h using β and n estimates derived from dissolution and release studies reported in literature. The examples listed in Table 1, from a plethora of data available in literature, indicate that the rate of release is monotonically decreasing with time ($0 < h < 1$) while the rate of dissolution can be either monotonically decreasing ($0 < h < 1$) or increasing initially and decreasing afterwards ($h < 0$). Homogeneous conditions ($h \approx 0$) were found in only one of the seventeen examples considered. These observations provide an indirect, physically based interpretation for the superiority of the Weibull function over other approaches (13) for the analysis of dissolution data.

In vivo considerations. Since heterogeneous conditions both in terms of hydrodynamics and composition prevail in the GI tract (24), the aforementioned analysis is also valid for the *in vivo* drug dissolution. In addition, the parameters D, C_s, V, and δ are also influenced by the conditions in the GI tract such

as surfactants in gastric juice and bile, viscosity of lumenal contents, motility patterns, pH, food components, secretions and coadministered fluids (25). Thus, it is very difficult to conceive, under *in vivo* conditions, of a physical situation where the proportionality constant K (Eq. 4) remains constant and Eq. 3 is valid, where the parameters A, D, C_S, V and δ change in time. Again, a time dependent instantaneous rate coefficient k (Eq. 7) would be more appropriate.

In vivo dissolution has been primarily studied by indirect methods such as deconvolution of plasma concentration-time profiles of the drug (26–29). Table I shows estimates for h derived from fittings of Eqs. 8 or 9 to *in vivo* dissolution profiles determined indirectly in dogs and humans and reported in literature. The estimates for h indicate that they are not only drug dependent but also formulation and subject dependent. Homogeneous conditions ($h \approx 0$) were justified in only two of the nineteen data sets examined. It can be anticipated that the heterogeneous picture would be even more patent if more *in vivo* dissolution profiles for class II and IV (31) sparingly soluble drugs were available for analysis. Unfortunately, data for this kind of drugs are missing since deconvolution presupposes intravenous administration to determine the unit impulse response. The sporadical empirical use of the Weibull function to describe GI absorption data (32,33) is an additional indirect

Table I. Estimates for h Obtained from In Vitro and In Vivo Studies

Drug or substance	Formulation[a]	Medium	Species (subject)	h	R^{2b}	Ref
In vitro						
Acetylsalicylic acid	Bufferin-A	H_2O pH 7.5	—	−0.18[c]	NR	5
Acetylsalicylic acid	Bufferin-B	0.01 N HCl	—	0.18[c]	NR	5
Acetylsalicylic acid	Bufferin-C	0.1 N HCl	—	0.28[c]	NR	5
Acetylsalicylic acid	Bufferin-D	H_2O pH 7.5	—	0.01 [c]	NR	5
Acetylsalicylic acid	Bufferin-E	0.01 N HCl	—	0.31[c]	NR	5
Acetylsalicylic acid	Bufferin-F	0.1 N HCl	—	0.35[c]	NR	5
Diltiazem HCl	Tablet-"REF"	H_2O	—	−0.144[c]	NR	13
Diltiazem HCl	Tablet-"MM"	H_2O	—	−0.167[c]	NR	13
Diltiazem HCl	Tablet-"mm"	H_2O	—	−0.085[c]	NR	13
KCl	Tablet-polyviol	H_2O	—	0.400 [d]	0.984	6
Phenylpropanolamine HCl	Tablet-polyviol	A. g. j.[e]	—	0.400 [d]	0.999	6
Phenylpropanolamine HCl	Tablet-polyvanol	A. g. j.[e]	—	0.442 [d]	0.997	6
Bovine serum albumin	Tablet-polyvanol	A. g. j.[e]	—	0.533 [d]	0.976	6
Carbofuran	StX_1	H_2O	—	0.36 [d]	0.996	23
Carbofuran	StX_2	H_2O	—	0.44 [d]	0.994	23
Carbofuran	StX_3	H_2O	—	0.43 [d]	0.992	23
Carbofuran	StX_4	H_2O	—	0.41 [d]	0.994	23
In vivo						
Ibuprofen	Capsule D	—	Human (1)	0.113 [f]	0.998	26
Ibuprofen	Tablet E	—	Human (1)	0.106 [f]	0.998	26
Ibuprofen	Capsule C	—	Human (5)	0.333 [f]	0.983	26
Ibuprofen	Tablet E	—	Human (10)	0.081 [f]	0.999	26
Ibuprofen	Tablet E	—	Human (14)	0.106 [f]	0.995	26
Carbamazepine[g]	Suspension	—	Human (1)	−0.041[f]	1	30
Carbamazepine[g]	Suspension	—	Human (2)	−1.660[f]	0.997	30
Theophylline	Capsule (FT-1)	—	Dog	−0.425[f]	0.997	28
Theophylline	Capsule (FT-2)	—	Dog	−0.265[f]	0.991	28
Theophylline	Capsule (FT-3)	—	Dog	0.602 [h]	0.949	28
Theophylline	Capsule (FT-4)	—	Dog	0.296 [f]	0.947	28
Flucytosine	Capsule (CCR)	—	Dog	0.034 [f]	0.984	29
Remoxipride	Microcapsules	—	Human (A)	−0.309[f]	0.954	27
Remoxipride	Microcapsules	—	Human (B)	0.146 [f]	0.975	27
Remoxipride	Microcapsules	—	Human (C)	0.170 [f]	0.946	27
Remoxipride	Microcapsules	—	Human (D)	0.126 [f]	0.975	27
Remoxipride	Microcapsules	—	Human (E)	0.160 [f]	0.994	27
Remoxipride	Microcapsules	—	Human (G)	0.304 [f]	0.997	27
Remoxipride	Microcapsules	—	Human (H)	0.135 [f]	0.997	27

[a] Characterization as reported in the original paper.
[b] Correlation coefficient; NR denotes not reported.
[c] Estimate derived from the reported β value using $h = 1 - \beta$ (Eq. 8).
[d] Estimate derived from the reported n value using $h = 1 - n$ (Eq. 9).
[e] Artificial gastric juice.
[f] Estimate derived by fitting Eq. 8 to the reported in vivo dissolution profiles.
[g] Dissolution profile obtained directly.
[h] Estimate derived by fitting Eq. 9 to the reported in vivo dissolution profiles.

indication that dissolution in the GI tract takes place under heterogeneous conditions. It should be also noted that the relevance between fractal processes which are described with power time laws and the Weibull distribution has been also discovered for other physical processes (34).

The above observations provide explicit evidence that time dependent rate coefficients govern the dissolution process under *in vivo* conditions. Plausibly, one should expect a dramatic effect of the space topology of drug dissolution on the plasma concentration-time curves of bioavailability and bioequivalence studies for poorly soluble drugs. This effect can be modeled using a hypothetical drug which follows one-compartment model disposition with first-order absorption and elimination while its dissolution in the GI tract is governed by a time dependent rate coefficient. Figure 1 shows the profiles (amount in plasma versus time in arbitrary units) for a variety of values assigned to the time exponent, *h*. The large differences observed, underline the importance of this time dependency in regard to the assessment of bioavailability and bioequivalence studies in particular for sparingly soluble drugs. Thus, one of the major sources of variability for poorly soluble drugs (35) can be associated with the time dependent character of the rate coefficient which governs drug dissolution under *in vivo* conditions (24), as exemplified in Fig. 1. Based on these findings, the failure of *in vitro-in vivo* correlations for drugs of low permeability and solubility (class IV) (31) can be also interpreted. This failure is not only due, as usually stated, to our inability to reconstruct the *in vivo* conditions but it is also associated with the different characteristics of the time depended rate coefficients governing dissolution under *in vitro* and *in vivo* conditions. For example, the initial conditions i.e. the initial rapture of the formulation and the initial placement of the drug particles in the GI tract which cannot neither fixed or controlled as being subject-time dependent are very important kinetically (8) and enhance significantly both the intra- and inter-subject variability. Moreover, the experimentally measured parameters C_{max}, t_{max}, and *AUC* are dependent on the topology of dissolution-release and they are in essence "time depended", Fig. 1. Current pharmacokinetic models and the relevant statistical methodologies of bioequivalence studies do not consider any time dependency in the pharmacokinetic parameters. These remarks should be taken into account in view of the movement in progress towards the replacement of average with individual bioequivalence by Food and Drug Administration (36,37). It is advisable therefore to carry out more research in order to understand fully the heterogeneous character of drug dissolution under *in vivo* conditions which is the major source of variability for poorly soluble drugs (35). These experimental data can be further used to develop and evaluate appropriate bioequivalence criteria and statistical methodologies for highly variable drugs.

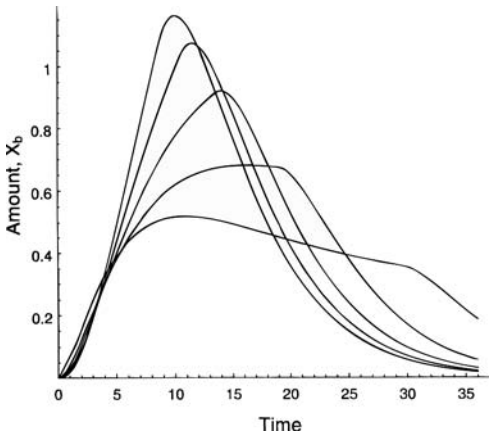

Fig. 1 Amount of drug in the body *versus* time, for a drug following one-compartment model disposition assuming that dissolution is governed by a time dependent rate coefficient, *k*, (Eq. 7). The graphs were derived from numerical solution of the following system of differential equations describing the changes of the dissolved amount, X_g, in the GI tract and the absorbed amount, X_b, in the body:

$$\frac{dX_g}{dt} = k_1 t^{-h} (X_s - X_g) - K_a X_g \quad \text{and} \quad \frac{dX_b}{dt} = K_a X_g - K_e X_b$$

where X_s is the amount of drug corresponding to the saturation solubility in the GI, K_a, and K_e are the input, elimination rate constants, respectively. The following values in arbitrary units were assigned to the parameters: $X_s = 5$, $K_a = 0.3$, $K_e = 0.2$, $k_1 = 0.05$, h (from top to bottom referring to the ascending limbs of the curves): -0.4, -0.2, 0, 0.2, 0.4.

APPENDIX

Derivation of Eq. 8

Multiplying both sides of Eq. 1 by V, expressing the resulting equation in terms of amount ($VdC = dm$, $C \cdot V = m$, $C_s V = m_\infty$) and using the rate coefficient k from Eq. 7 to replace K, one obtains:

$$\frac{dm}{dt} = k_1 t^{-h} (m_\infty - m)$$

Integrating

$$\int_0^m \frac{dm}{m_\infty - m} = k_1 \int_\tau^t t^{-h}\, dt$$

$$\ln \frac{m_\infty}{m_\infty - m} = \frac{k_1}{1-h} (t^{1-h} - \tau^{1-h})$$

$$\frac{m_\infty}{m_\infty - m} = \exp\left[\frac{k_1}{1-h} (t^{1-h} - \tau^{1-h})\right]$$

$$m = m_\infty \left\{1 - \exp\left[-\frac{k_1}{1-h} (t^{1-h} - \tau^{1-h})\right]\right\}$$

Taking the limit as τ approaches to zero, for $h < 1$ we get Eq. 8:

$$\frac{m}{m_\infty} \equiv M = 1 - \exp\left[-\frac{k_1}{1-h} t^{1-h}\right]$$

Derivation of Eq. 9

Assuming sink conditions ($C_s << C$) for Eq. 1, multiplying both sides of Eq. 1 by *V*, expressing the resulting equation in terms of amount ($VdC = dm$, $C_s V = m_\infty$) and using the rate coefficient k from Eq. 7 to replace K, one obtains:

$$\frac{dm}{dt} = k_1 t^{-h} m_\infty$$

Integrating

$$\frac{1}{m_\infty}\int_0^m dm = k_1 \int_\tau^t t^{-h}\, dt$$

$$\frac{m}{m_\infty} = \frac{k_1}{1-h}\,(t^{1-h} - \tau^{1-h})$$

Taking the limit as τ approaches to zero, for $h < 1$ we get Eq. 9:

$$\frac{m}{m_\infty} \equiv M = \frac{k_1}{1-h}\, t^{1-h}$$

NOTE

Recently, Lansky and Weiss published an article (*Pharm. Res*, **16**:1470–1476 (1999)) presenting a model in which the fractional dissolution rate is not constant but a decreasing function of the amount dissolved.

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