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Research Paper

Analysis of Dissolution Data Using Modified Versions of Noyes–Whitney Equation and the Weibull Function

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Purpose. The aim of the study is to develop modified, branched versions of the Noyes–Whitney and the Weibull equations, including explicitly the solubility/dose parameter, for the analysis of dissolution data, which reach the plateau either at infinite or finite time.
Methods. The modified Weibull function is applied to the analysis of experimental and literature dissolution data. To demonstrate the usefulness of the mathematical models, two model drugs are used: one highly soluble, metoprolol, and one relatively insoluble, ibuprofen.
Results. The models were fitted successfully to the data performing better compared with their classic versions. The advantages of the use of the models presented are several. They fit better to a large range of datasets, especially for fast dissolution curves that reach complete dissolution at a finite time. Also, the modified Weibull presented can be derived from differential equations, and it has a physical meaning as opposed to the purely empirical character of the original Weibull equation. The exponent of the Weibull equation can be attributed to the heterogeneity of the process and can be explained by fractal kinetics concepts. Also, the solubility/dose ratio is present explicitly as a parameter and allows to obtain estimates of the solubility even when the dissolution data do not reach the solubility level.
Conclusion. The use of the developed branched equations gives better fittings and specific physical meaning to the dissolution parameters. Also, the findings underline the fact that even in the simplest, first-order case, the speed of the dissolution process depends on the dose, a fact of great importance in biopharmaceutic classification for regulatory purposes.

KEY WORDS: dissolution; Noyes–Whitney law; solubility; Weibull function.

INTRODUCTION

Classically, drug dissolution is considered to be governed by the Noyes–Whitney equation (1), where the dissolution rate is proportional to the difference of dissolved drug concentration C at time t from the solubility level C_s in a first-order manner:

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

where k is the dissolution rate constant. This means that the dissolution profile, obtained upon integration of Eq. (1), is exponential reaching the plateau value C_s at infinite time:

$$C = C_s[1 - \exp(-kt)] \tag{2}$$

Obviously, this approach cannot be used to describe numerous dissolution data, which deviate from first-order kinetics, e.g., when the entire dose is dissolved and the plateau value is reached at finite time. Although several other models of dissolution, either derived by extension of the Noyes–Whitney equation or based on different reasoning, have been proposed (2), the concept of first-order kinetics is still prevailing in dissolution studies despite the limited practical use of Eq. (2) for the analysis of dissolution data.

An empirical equation described by Weibull (3) in 1951 was adopted in dissolution studies more than 30 years ago (4):

$$\frac{M_t}{M_\infty} = 1 - e^{-at^b} \tag{3}$$

where M_t is the accumulated mass dissolved at time t and M_∞ is the mass dissolved at infinite time, whereas a is a scale parameter and b is a shape parameter. Equation (3) has been applied extensively and successfully in the analysis of a great number of dissolution studies (5–7). Because of the empirical use of the Weibull function in dissolution studies, criticism ranging from the lack of a kinetic basis for its use to the nonphysical nature of the parameters has been reported (8,9).

In this study, we focus on the proper use of the Noyes–Whitney and Weibull equations for the analysis of dissolution data using branched versions of them, which reach plateau either at infinite or finite time. The modified Weibull function is applied to the analysis of experimental

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and literature dissolution data. Two model drugs are used, one highly soluble (metoprolol) and one relatively insoluble (ibuprofen), to demonstrate the advantages of the mathematical models presented.

THEORY

A Branched Version of the Noyes–Whitney Equation. Classically, the Noyes–Whitney equation [Eq. (1)] is expressed in terms of concentration and implies the use of an adequate amount of drug in order for the drug concentration to reach the saturation level C_s. This premise does not apply always in practice because drugs are used in miscellaneous doses, whereas their solubility values in the different solubility media differ remarkably. A more physically relevant version of Eq. (1) can be obtained (10) if one multiplies both sides of Eq. (1) by V/M_0 (volume of the dissolution medium/dose):

$$\frac{d\Phi}{dt} = k\left(\frac{1}{q} - \Phi\right) \tag{4}$$

where Φ is the fraction of drug dose dissolved and $q = M_0/VC_s$ is the dose/solubility ratio expressed as a dimensionless quantity because the volume of the dissolution medium is taken into account. Equation (4) leads to Eq. (5) when $q \geq 1$:

$$\Phi = \frac{1}{q}\left(1 - e^{-kt}\right) \tag{5}$$

which means that only a portion of the dose is dissolved and the drug reaches the saturation level $1/q$.

However, when $M_0 < C_sV$, i.e., when $q < 1$, which means that the entire dose is eventually dissolved, the dissolution follows the usual exponential form only until it reaches the value $\Phi = 1$, i.e., 100% of the drug is dissolved, in a finite time T and thereafter continues flat, so:

$$\Phi = \begin{cases} \frac{1}{q}\left(1 - e^{-kt}\right) & \text{for } t < T(\Phi < 1) \\ 1 & \text{for } t \geq T \end{cases} \tag{6}$$

where

$$T = -\frac{\ln(1-q)}{k} \tag{7}$$

is the time when dissolution terminates. In several situations, a lag time τ is present, and this has been subtracted from time t in Eqs. (5)–(7).

A Modified Version of the Weibull Function. The Noyes–Whitney equation [Eq. (1)] is characterized by the condition that a positive constant, the dissolution rate constant k, governs the rate of dissolution throughout the process. This fundamental premise has been questioned in literature, and models with time-dependent rate coefficients have been reported (11–13) as more physically relevant. This reasoning is associated with various time-dependent phenomena, which take place as dissolution proceeds including lack of stirring in the microenvironment of drug particles, surfaces with irregular boundaries, decrease of the surface area, and reduction of the diffusion layer of the drug particles with time. A choice of a power law, time dependency of the dissolution rate coefficient, is a reasonable one and can be justified in the context of fractal kinetics (14).

Therefore, letting the dissolution rate coefficient be $k = k_1t^{-h}$ and replacing in Eq. (4), we end up with

$$\frac{d\Phi}{dt} = k_1t^{-h}\left(\frac{1}{q} - \Phi\right) \tag{8}$$

where k_1 is a constant with $(\text{time})^{h-1}$ units and h is a dimensionless constant. It can be shown (13) that solving Eq. (8) and replacing $a = k_1/(1-h)$ and $b = 1-h$, a modified version of the Weibull function can be derived. However, again, we have to consider two cases:

For $q \geq 1$, the solution is

$$\Phi = \frac{1}{q}\left(1 - e^{-at^b}\right) \tag{9}$$

which describes a dissolution curve that reaches asymptotically the saturation level $1/q$ because only a portion of the drug dose is dissolved.

When $q < 1$, the solution takes a branched form like before, exhibiting a Weibull approach to $\Phi = 1$ in finite time T and flat thereafter:

$$\Phi = \begin{cases} \frac{1}{q}\left(1 - e^{-at^b}\right) & \textit{for } t < T(\Phi < 1) \\ 1 & \textit{for } t \geq T \end{cases} \tag{10}$$

where

$$T = \left(-\frac{\ln(1-q)}{a}\right)^{\frac{1}{b}} \tag{11}$$

is the time that $\Phi = 1$.

In several situations, a lag time τ is present, and this has been subtracted from time t in Eqs. (8)–(11).

Therefore, we derived a modified version of the Weibull function, which is used extensively in dissolution curve fitting, and also attribute a physical meaning instead of using it empirically. Also, the modified Weibull, unlike the standard version, includes explicitly the solubility/dose parameter and is capable of following dissolution curves that have not reached saturation.

It should be noted that the classical form of the Weibull function [Eq. (3)] is equivalent to the physically relevant modified versions Eqs. (9) and (10). This is so because $M_t/M_\infty = \Phi$ when $M_\infty = M_0$, whereas $M_t/M_\infty = q\Phi$ when $M_\infty = C_sV < M_0$.

Mean Dissolution Time for Eqs. (2), (6), and (10). One of the main features of the first-order dissolution kinetics on the basis of Eq. (1) is that the mean dissolution time (MDT) is equal to the reciprocal of the dissolution rate constant (15):

$$MDT = 1/k \tag{12}$$

This result has been used extensively, but as we have already mentioned, this is very rarely correct, because the first-order kinetics very rarely applies throughout the dissolution

process. This can be verified by quoting the MDT for Eq. (6) (10):

$$\mathrm{MDT} = \int_0^\infty (1-\Phi)dt = \int_0^{-\frac{\ln(1-q)}{k}} \left(1-\frac{1}{q}\left(1-e^{-kt}\right)\right)dt = \frac{q-(q-1)\ln(1-q)}{kq} \quad (13)$$

which shows that the result MDT = $1/k$ is valid only in the special case of $q = 1$. Thus, for Noyes–Whitney-type kinetics, when $q < 1$, MDT depends also on q and not only on k.

The MDT derived from Eq. (10) is:

$$MDT = \frac{1}{bqa^{\frac{1}{b}}} \times \left[b(q-1)(-\ln(1-q))^{\frac{1}{b}} - \Gamma\left(\frac{1}{b}, -\ln(1-q)\right) + \Gamma\left(\frac{1}{b}\right)\right] \quad (14)$$

where $\Gamma(\cdot)$ is the complete gamma function and $\Gamma(\cdot,\cdot)$ is the incomplete gamma function. Equation (14) reveals that MDT depends on q, a, and b and collapses to Eq. (13) when $b = 1$.

For the classic Weibull function [Eq. (3)], i.e., for $q = 1$, the MDT is

$$MDT = a^{-\frac{1}{b}}\,\Gamma\left(\frac{1}{b}+1\right) \quad (15)$$

Note that one cannot directly substitute $q = 1$ in Eq. (14) to derive Eq. (15).

Finally, it should be noted that when the entire dose cannot be dissolved, the MDT is infinite. In this case, one can use the mean saturation time MDT_s as a meaningful time metric for the portion of dose dissolved and is given by (10):

$$MDT_s = \frac{\int_0^\infty (1/q-\Phi)dt}{1/q} \quad (16)$$

For both Noyes–Whitney and Weibull equations, Eq. (16) simplifies to the respective expressions of MDT for $q > 1$, i.e., Eq. (12) for Noyes–Whitney and Eq. (15) for Weibull.

METHODS

To demonstrate the usefulness of the mathematical models presented in the previous section, two model drugs were used: one highly soluble (metoprolol) and one relatively insoluble (ibuprofen). The dissolution data of metoprolol were taken from literature (16); thus, the dissolution data of "fast," "medium," and "slow" formulations containing 100 mg metoprolol tartrate were analyzed. The metoprolol data, as well as the data of ibuprofen described in Experimental Data that follows, were fitted with the modified Weibull [Eq. (9) or (10)] and the simple Weibull [Eq. (3)]. The branched equations were fitted only to the data below the plateau level ($\Phi < 1$) to derive estimates for the model parameters. The rest of the data (values equal to the plateau level) were ignored because this portion of the dissolution curve is assumed to be described by the second branch, which is trivial and does not contain any parameters. Also, the MDT values were calculated and compared with the estimates of the graphical method. The graphical method uses the trapezoidal rule to estimate the area between the fraction dissolved-time curve and the plateau level (ABC), and then the MDT is given by that area divided by the plateau level Φ_∞:

$$MDT = \frac{ABC}{\Phi_\infty} \quad (17)$$

EXPERIMENTAL DATA

Ibuprofen Dissolution

Dissolution testing was performed on two tablet formulations of 200- and 600-mg ibuprofen (Brufen 200 mg, lot # 4C 22 and Brufen 600 mg, lot # 4C 105) from Vianex SA (Maroussi, Greece). Appropriate corrections based on the actual content in ibuprofen of the tablets (200 or 600 mg) were made following the United States Pharmacopeia analytical procedure (17). Also, dissolution testing was performed on formulations containing 50-mg ibuprofen, derived from 200-mg tablets. Particularly, a 200-mg tablet was initially cut into two pieces, and one of these pieces was further cut in two parts. The actual content in ibuprofen of the quarter of the 200-mg tablet used in the dissolution runs was determined by subtracting the content of the unused parts from the average content of the 200-mg tablets (17).

Studies were conducted on three tablets of each formulation. Dissolution was tested with the paddle method at 50 rpm. The medium used was 900 ml of acetate buffer, pH 4.5. Dissolution samples for Brufen 600-mg tablets were collected at 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, 120, 150, and 180 min. Brufen 200 mg in acetate buffer was sampled at identical times plus at 135, 165, 210, 240, 270, 300, 330, and 360 min. Fifty-milligram formulations were sampled at 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 330, 360, and 420 min. Samples were assayed by UV spectrophotometer at 221 nm.

Solubility Studies: Ibuprofen

An excess of ibuprofen powder (5 mg) was added to flasks containing 10 ml of pH 4.5 acetate buffer. Three flasks were placed in a temperature-controlled bath at 37°C under constant shaking rate of 160 rpm. Samples were filtered through a 0.45-μm membrane filter and, after being diluted with pH 4.5 acetate buffer, were assayed by UV spectrophotometer at 221 nm.

RESULTS AND DISCUSSION

In Figs. 1 and 2, profiles of dissolution curves using the analytical solutions of Eqs. (6) and (10), respectively, are shown for various values of the q parameter exhibiting the

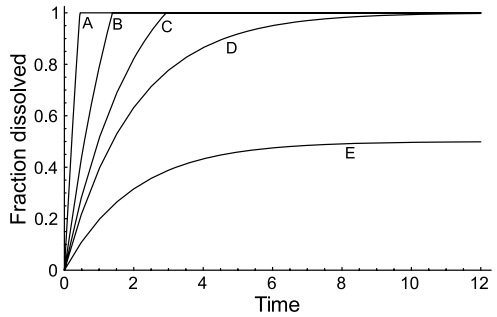

Fig. 1. Theoretical profiles generated with the branched Noyes–Whitney [Eq. (6)] for $a = 0.5$ and $1/q = 5$, 2, 1.3, 1, and 0.5 for curves A, B, C, D, and E, respectively.

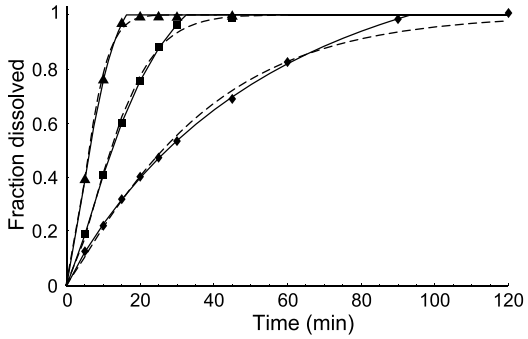

Fig. 3. Dissolution profiles from Polli *et al.* (16), fitted with the modified Weibull [Eq. (10)] (solid) and the simple Weibull [Eq. (3)] (dashed). Key according to Polli *et al.* notation: (▲) fast, (■) medium, (◆) slow.

various qualitatively different cases for $q > 1$, $q < 1$, and the marginal case where $q = 1$. All curves in Figs. 1 and 2 resemble those routinely observed in dissolution studies. Also, note that profiles A, B, C, and D of Figs. 1 and 2 clearly exhibit different MDTs that depend on the dose, whereas profile E has infinite MDT as the drug never dissolves entirely, and one may only derive a MDT_s instead of a MDT estimate.

Equations (3), (9), and (10) were fitted to the various dissolution profiles described in Methods to exhibit the usefulness of the introduced formulae. Figure 3 shows the metoprolol literature data (16) together with the fitted curves of Eq. (10) and the simple Weibull [Eq. (3)]. Visual inspection reveals that the fitting with the modified Weibull [Eq. (10)] is superior to the simple Weibull [Eq. (3)] following better the features of the data, including the sigmoid start and the abrupt end of the dissolution process in finite time. The parameter estimates are presented in Table I. For the modified Weibull, also estimates for the parameter q are available, which makes the estimated parameters three, and therefore, one needs at least three points before the 100% dissolution level to fit the model and determine all the parameters. As we can see in Table I, the parameter estimates of the simple and the branched Weibull are quite different even when the curve looks similar visually. According to the theoretical aspects of the model, parameter q corresponds to the dose/solubility ratio; however, in this case, because the solubility is very high, in the order of 1000 mg/ml (16), clearly, the estimated value is not correct. There are other factors that control the dissolution rate and shape the dissolution curve, such as the surface area of the drug particles and the intrinsic dissolution rate constant, and it is impossible to extrapolate the curve to the true value of solubility by using data that reach only a small fraction (by a factor of 10,000) of this high level of solubility. However, as we will see with the case of ibuprofen, the solubility level can be predicted by Eq. (10), when its value is low enough to be a major factor for the dissolution process, even when the data never reach the solubility level.

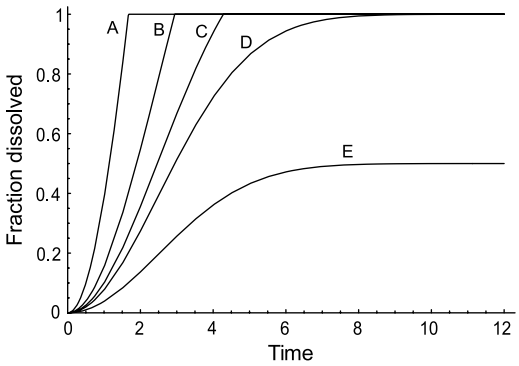

Fig. 2. Theoretical profiles generated with the branched Weibull [Eq. (10)] for $a = 0.08$, $b = 2$, and $1/q = 5$, 2, 1.3, 1, and 0.5 for curves A, B, C, D, and E, respectively.

The exponential, Noyes–Whitney equation is a special case of the Weibull equation for $b = 1$. This means that the "slow" dissolution curve having $b = 0.927$, quite close to 1, can be well approximated by the branched Noyes–Whitney equation [Eq. (6)]; however, for the other two curves, this statement does not hold (Table I).

In Table II, characteristic times of dissolution are presented for the literature datasets analyzed. These include the MDT, estimated both theoretically, using Eq. (14), which is the MDT of the branched Weibull [Eq. (10)], and Eq. (15), which is the MDT of the classic Weibull [Eq. (3)], as well as graphically using Eq. (17). Also, the total dissolution time T is reported using Eq. (11), which is a much simpler formula than the one of the MDT. As we can see from Table II, the classic Weibull [Eq. (3)] tends to overestimate the MDT [calculated by Eq. (15)] in some instances because it fails to follow the sharp corner at the end of the dissolution process. In fact, the classic Weibull [Eq. (3)] assumes that dissolution continues asymptotically forever. However, the difference can be negligible in some cases depending on the data. The total dissolution time T or the time when dissolution concludes is another parameter reported in Table II. This is only available with the branched Weibull [Eq. (10)] and not with the classic one [Eq. (3)] where the equivalent time is infinite. This time is useful because it gives a time scale for the dissolution process and is calculated much more easily than the MDT. It cannot replace the MDT for a general picture of the dissolution rate but still can give an upper conservative but meaningful limit for the dissolution process.

In Fig. 4, the dissolution curves of 50, 200, and 600 mg of ibuprofen are shown together with the fitted models. For the curves of 200 and 600 mg of ibuprofen, Eq. (9) was used, as the profiles reach final levels of $\Phi < 1$. However, for the case

Table I. Parameter Estimates (SD in Parentheses) of the Modified [Eq. (10)] and the Simple Weibull [Eq. (3)] Equations, from the Fitting of Metoprolol Data Taken from Literature (16)

	Modified Weibull [Eq. (10)]			Simple Weibull [Eq. (3)]	
	a	*b*	1/*q*	*a*	*b*
Fast	0.045 (–)	1.39 (–)	1.11 (–)	0.035 (0.0056)	1.62 (0.074)
Medium	0.023 (0.00062)	1.27 (0.016)	1.16 (0.016)	0.017 (0.0032)	1.48 (0.066)
Slow	0.024 (0.0007)	0.927 (0.018)	1.24 (0.035)	0.018 (0.0032)	1.12 (0.052)

of the curve of 50-mg ibuprofen, Eq. (10) was used, as it reaches full dissolution ($\Phi = 1$). Visual inspection of Fig. 4 shows adequate fitting of all three curves. In Table III, the parameter estimates of the fittings are presented. Again, parameter $1/q$ was estimated, which has the physical meaning of the solubility/dose ratio. In the fourth column of Table III, the values of solubility that correspond to the values of $1/q$ estimated by the model, the dose, and the volume of the dissolution medium are reported, calculated by

$$C_s = \frac{M_0}{V}\frac{1}{q} \tag{18}$$

The solubility values of ibuprofen in pH 4.5 acetate buffer quoted in Table III are similar and are in reasonable agreement with the experimental value found in the solubility studies [0.0945 (0.0018) mg/ml]. Therefore, the model is capable of estimating ibuprofen solubility, even when the data do not reach the solubility level because of the dose being too small, e.g., 50 mg. Also, from Table III, we can see that in all cases, the exponent b is quite different from unity, suggesting that the Noyes–Whitney model, which forces b to be 1, would not be appropriate. In the last two columns of Table III, the MDT for 50 mg and the MDT_s for 200 and 600 mg are calculated. The MDT for 200 and 600 mg is infinite because they correspond to the case of $q > 1$, where a fraction of the drug is never dissolved.

The advantages of the use of the modified Weibull equation presented here are several. They fit better to a large range of datasets, especially for fast dissolution curves that reach complete dissolution. These curves often exhibit an abrupt end when they reach complete dissolution, which is not captured by models that do not have a branched structure. Also, the modified Weibull presented has a physical meaning as opposed to the purely empirical character of the original Weibull equation and can be derived from differential equations. The exponent of the Weibull equation can be attributed to the heterogeneity of the process and can be explained by fractal kinetics concepts (13,14), with $b = 1$ corresponding to the homogeneous case (15) and collapses to the Noyes–Whitney equation. Parameter q corresponds to the dose/solubility ratio and allows one to obtain estimates of the solubility even when the data do not reach that level.

A major conclusion revealed by the use of the branched versions of the Weibull and the Noyes–Whitney equations is related with the MDTs and the fact that these depend on the dose, even in the simple case of the Noyes–Whitney equation, as shown in Figs. 1 and 2. This is in contrary to the common belief that the dissolution process, being first order, depends only on the dissolution rate constant [Eq. (12)]. The fact that the dissolution time depends on the dose has great importance in the bioavailability of drugs (18), as dissolution is a key factor together with permeability of the intestinal wall. This also underlines the need to include the dose explicitly in biopharmaceutic classification for regulatory purposes (18,19). Also, because of the nature of the models presented and the fact that dissolution takes a finite time when the dose is small enough and does not continue forever asymptotically, the time T when dissolution ends may be used as a useful time scale of the dissolution process, instead of the MDT.

In conclusion, the use of the branched equations developed gives better fittings and specific physical meaning to the parameters. Also, this work underlines the fact that

Table II. MDT for the Metoprolol Data in (16), Estimated by Various Equations and Total Dissolution Time, T

	MDT [Eq. (14)] (min)	MDT [Eq. (15)] (min)	MDT [Eq. (17)] (min)	*T* (min)
Fast	6.81	6.98	7.032	16.28
Medium	13.43	13.92	13.32	32.52
Slow	32.88	34.93	32.56	93.48

MDT = mean dissolution time.

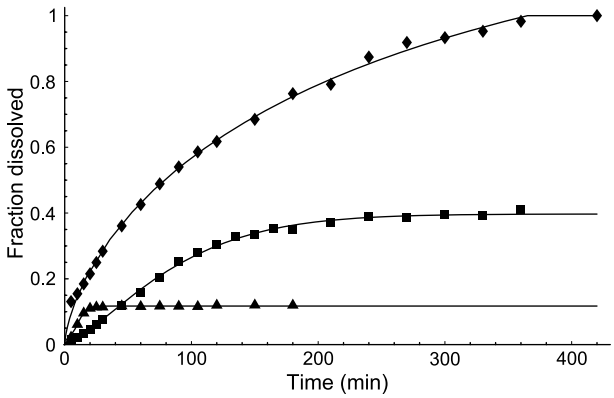

Fig. 4. Dissolution profiles of ibuprofen tablets, fitted with the modified Weibull [Eqs. (9) and (10)]. Key: (◆) 50 mg fitted with Eq. (10), (■) 200 mg fitted with Eq. (9), and (▲) 600 mg fitted with Eq. (9).

Table III. Parameter (SD in Parentheses), Solubility Estimates, and MDT Values (or MDT_s where Applicable) Derived from the Fitting of the Modified Weibull [Eqs. (9) and (10)] to Ibuprofen Dissolution Data

	a	*b*	1/*q*	Solubility (mg/ml)	MDT (min)	MDT_s (min)
600 mg	0.0096 (0.0019)	1.89 (0.083)	0.117 (0.00061)	0.078	∞	10.36
200 mg	0.0020 (0.00031)	1.36 (0.035)	0.396 (0.0034)	0.088	∞	88.37
50 mg	0.0231 (0.0012)	0.67 (0.026)	1.423 (0.11)	0.079	111.56	–

even in the simplest, first-order case, the speed of the dissolution process depends on the dose, a fact of great importance in biopharmaceutic classification for regulatory purposes. Finally, this work demonstrates the physical relevance between the Noyes–Whitney equation and the Weibull function. It can be anticipated that the methodology developed can be used for the analysis of dissolution data in both research and regulatory settings.

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