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# On the use of the Weibull function for the discernment of drug release mechanisms

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**Abstract**

Previous findings from our group based on Monte Carlo simulations indicated that Fickian drug release from Euclidian or fractal matrices can be described with the Weibull function. In this study, the entire drug release kinetics of various published data and experimental data from commercial or prepared controlled release formulations of diltiazem and diclofenac are analyzed using the Weibull function. The exponent of time $b$ of the Weibull function is linearly related to the exponent $n$ of the power law derived from the analysis of the first 60% of the release curves. The value of the exponent $b$ is an indicator of the mechanism of transport of a drug through the polymer matrix. Estimates for $b \leq 0.75$ indicate Fickian diffusion in either fractal or Euclidian spaces while a combined mechanism (Fickian diffusion and Case II transport) is associated with $b$ values in the range $0.75 < b < 1$. For values of $b$ higher than 1, the drug transport follows a complex release mechanism.


*Keywords:* Weibull function; Power law; Drug release; Mechanism; Controlled release

## 1. Introduction

The modeling of drug release from delivery systems is important for the understanding and the elucidation of the transport mechanisms. Basically, the mathematical expressions used to describe the kinetics of drug release and the discernment of the release mechanisms are the Higuchi law (Higuchi, 1961) and the Peppas equation or the so-called power law (Ritger and Peppas, 1987; Siepmann and Peppas, 2001). The first approach relies on Eq. (1), which indicates that the fraction of drug released is proportional to the square root of time:

$$\frac{M_t}{M_\infty} = k\sqrt{t} \tag{1}$$

where $k$ is a constant reflecting formulation characteristics, and $M_t$ and $M_\infty$ are cumulative amounts of drug released at time $t$ and infinite time, respectively. The second approach is based on the semi-empirical Eq. (2):

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where $k$ is the kinetic constant and $n$ is an exponent characterizing the diffusional mechanism. When pure diffusion is the controlling release mechanism, $n = 0.5$ and Eq. (2) collapses to Eq. (1). Moreover, Eq. (2) also becomes physically realistic for $n = 1$ since drug release follows swelling controlled release or Case II transport (Siepmann and Peppas, 2001). Both Eqs. (1) and (2) are short time approximations (Siepmann and Peppas, 2001; Kosmidis et al., 2003a) of complex exact relationships and therefore their use is confined for the description of the first 60% of the release curve.

Another alternative for the description of release profiles is based on the empirical use of the Weibull function

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

where $a$ and $b$ are constants. Although this function is frequently applied to the analysis of dissolution and release studies (Van Vooren et al., 2001; Adams et al., 2002; Costa et al., 2003; Koester et al., 2004; Varma et al., 2005), its empirical use has

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been criticized (Costa and Sousa Lobo, 2001a). The criticism is focused on: (i) the lack of a kinetic basis for its use and (ii) the non-physical nature of its parameters (Costa and Sousa Lobo, 2001a). Besides, various attempts have been made to improve its performance (Schreiner et al., 2005) and validate its use (Macheras and Dokoumetzides, 2000; Elkoshi, 1997; Lansky and Weiss, 2003).

Recently, Monte Carlo simulation techniques were used for the study of Fickian diffusion of drug release both in Euclidian and fractal spaces (Kosmidis et al., 2003b,c). It was found that Eq. (3) describes nicely in both cases the entire drug release curve when the drug release mechanism is Fickian diffusion. In the case of release from Euclidian matrices studied by Kosmidis et al. (2003b), the value of the exponent $b$ was found to be in the range 0.69–0.75. In the case of release from the two-dimensional percolation fractal (Kosmidis et al., 2003c) with fractal dimension $d_f = 91/48$ the values of $b$ ranged from 0.35 to 0.39. It was shown that the Weibull function arises from the creation of a concentration gradient near the releasing boundaries of the Euclidian matrix (Kosmidis et al., 2003b) or because of the "fractal kinetics" behavior associated with the fractal geometry of the environment (Kosmidis et al., 2003c). The lower value of $b$ in the percolation cluster reflects the slowing down of the diffusion process in the disordered medium. These Monte Carlo simulation results are apparently pointing to a universal law since the Weibull model provides a simple physical connection between the model parameters and the system geometry. Note that Eq. (3) can be approximated by a power law when the product $\alpha t^b$ is small. This is evident from a simple series expansion of the exponential term in the right hand side of Eq. (3) (Kosmidis et al., 2003b).

These observations prompted us to use Eq. (3) for the analysis of the entire set of experimental data of controlled release formulations in conjunction with the classical analysis based on Eq. (2) for the first 60% of the release curve. To this end, the entire drug release kinetics of commercially available or prepared controlled release formulations of diltiazem and diclofenac was studied. In addition, published release data for a variety of drugs were re-examined using Eqs. (2) and (3) in order to set up a theoretical basis for the discernment of release mechanisms using Eq. (3).

## 2. Materials and methods

### 2.1. Materials

Hydroxypropylmethylcellulose (Metolose 90 SH 4000, Metolose 90 SH 4000SR, Metolose 90 SH 15000, Metolose 90 SH 100000SR, Shin Etsu) was used as a polymeric excipient. Diclofenac sodium (Sigma Chemical Co.) and Diltiazem hydrochloride (ELPEN) were used as model drugs. Magnesium stearate (BDH) was used as a lubricant.

### 2.2. Manufacture of tablets

Diclofenac sodium was mixed with hydroxypropylmethylcellulose and with 1% of magnesium stearate for 15 min in a powder mixer (WAB Turbula type T2F). Diltiazem hydrochloride was mixed with hydroxypropylmethylcellulose and with 1% of magnesium stearate for 15 min in a powder mixer (WAB Turbula type T2F). The composition of the tablets is shown in Table 1.

Table 1
Composition of the prepared controlled release formulations

| | Polymer | Polymer ratio | Model drug |
|---|---|---|---|
| A | Metolose 90 SH 4000SR | 1:3 | Diclofenac sodium |
| B | Metolose 90 SH 4000 | 1:3 | Diclofenac sodium |
| C | Metolose 90 SH 15000 | 1:3 | Diclofenac sodium |
| D | Metolose 90 SH 4000SR | 1:4 | Diclofenac sodium |
| E | Metolose 90 SH 4000 | 1:4 | Diclofenac sodium |
| F | Metolose 90 SH 15000 | 1:4 | Diclofenac sodium |
| G | Metolose 90 SH 100000SR | 1:4 | Diclofenac sodium |
| H | Metolose 90 SH 4000SR | 2:3 | Diltiazem hydrochloride |
| I | Metolose 90 SH 4000 | 2:3 | Diltiazem hydrochloride |

Tablets were directly compressed on a single punch tablet machine (Carver 3393) using 9 mm flat faced punch and die. The pressure was ranged from 3 to 7 MPa and applied for 20 s. Each tablet weighed 200 mg.

Commercial products were also tested in the study: Vurdon® 100 mg diclofenac sodium (Help), Tildiem® 120 mg diltiazem hydrochloride (Sanofi Synthelabo), Elvesil® 120 mg diltiazem hydrochloride (Biomedica).

### 2.3. Drug release studies

Tablets of each formulation were subjected to dissolution studies at $37 \pm 0.5\,^{\circ}C$ using the USP apparatus II—paddle method (Pharma Test type PTW SIII) at a stirring rate of 100 rpm. 900 ml of deionized water was used as a dissolution medium. 5 ml of dissolution samples were withdrawn every 30 min and were immediately replaced with an equal volume of deionized water to maintain a constant total volume. Samples were filtered via a syringe fitted with a membrane filter (RC, 17 mm, 45 um) and assayed by UV–vis spectrophotometer at 276 and 244 nm for diclofenac and diltiazem, respectively.

The percentage of drug released from the tablet in a 10-h period of time was determined. All studies were conducted in triplicate for each bunch of tablets and mean values were obtained.

### 2.4. Analysis of dissolution data and model fitting

Drug release kinetics was analyzed by plotting the mean release data versus time. Estimates for $b$ were derived by fitting Eq. (3) to the entire set of data; estimates for $n$ were derived by fitting Eq. (2) to the first 60% of release curve. Eqs. (2) and (3) were similarly fitted to literature data obtained by digitations of the points from the published figures. In all cases the SigmaPlot 5.0 program was used.

## 3. Results and discussion

Successful fittings were obtained when Eq. (3) was fitted to the entire release curve of the prepared, commercial formu-

Table 2
Estimates for $n$ and $b$ derived form the fitting of Eqs. (2) and (3), respectively, to release data

| Formulation/reference | $n$ (S.E.) | $R^2$ ($N$)[a] | $b$ (S.E.) | $R^2$ ($N$)[a] |
|---|---|---|---|---|
| A | 0.851 ± 0.029 | 0.995 (9) | 1.40 ± 0.076 | 0.98 (20) |
| B | 0.7942 ± 0.0099 | 0.9993 (10) | 1.32 ± 0.063 | 0.98 (20) |
| C | 0.871 ± 0.012 | 0.9992 (10) | 1.35 ± 0.050 | 0.99 (20) |
| D | 0.926 ± 0.012 | 0.9994 (8) | 1.6 ± 0.11 | 0.98 (20) |
| E | 0.900 ± 0.018 | 0.999 (9) | 1.53 ± 0.093 | 0.98 (20) |
| F | 0.862 ± 0.011 | 0.9993 (10) | 1.41 ± 0.065 | 0.99 (20) |
| G | 0.769 ± 0.014 | 0.997 (14) | 1.25 ± 0.072 | 0.97 (20) |
| H | 0.6377 ± 0.0083 | 0.9993 (8) | 0.965 ± 0.028 | 0.992 (20) |
| I | 0.610 ± 0.012 | 0.998 (9) | 0.942 ± 0.034 | 0.99 (20) |
| Vurdon® | 0.535 ± 0.040 | 0.9997 (9) | 0.911 ± 0.041 | 0.98 (20) |
| Tildiem® | 1.04 ± 0.038 | 0.995 (10) | 1.57 ± 0.056 | 0.993 (20) |
| Elvesil® | 0.538 ± 0.019 | 0.995 (8) | 0.788 ± 0.017 | 0.995 (20) |
| (Bettini et al., 1995)[b] | 0.329 ± 0.085 | 0.96 (4) | 0.646 ± 0.052 | 0.98 (12) |
| (Bettini et al., 1995)[c] | 0.397 ± 0.015 | 0.9995 (4) | 0.698 ± 0.026 | 0.998 (10) |
| (Picker, 1999)[d] | 0.928 ± 0.028 | 0.995 (11) | 1.32 ± 0.054 | 0.99 (14) |
| (Picker, 1999)[e] | 0.775 ± 0.021 | 0.98 (10) | 1.21 ± 0.087 | 0.98 (14) |
| (Picker, 1999)[f] | 0.845 ± 0.043 | 0.992 (8) | 1.35 ± 0.064 | 0.99 (14) |
| (Picker, 1999)[g] | 0.952 ± 0.054 | 0.98 (11) | 1.33 ± 0.046 | 0.994 (16) |
| (Korsmeyer et al., 1983)[h] | 0.652 ± 0.030 | 0.990 (9) | 1.19 ± 0.076 | 0.97 (17) |
| (Ferrero et al., 2000)[i] | 1.09 ± 0.026 | 0.997 (9) | 1.59 ± 0.070 | 0.992 (13) |
| (Sujja-areevath et al., 1996)[j] | 0.900 ± 0.044 | 0.996 (7) | 1.17 ± 0.022 | 0.998 (20) |
| (Sung et al., 1996)[k] | 0.676 ± 0.035 | 0.99991 (10) | 1.04 ± 0.045 | 0.991 (15) |
| (Sung et al., 1996)[l] | 0.6197 ± 0.0086 | 0.9997 (7) | 1.07 ± 0.059 | 0.99 (15) |
| (Sung et al., 1996)[m] | 0.6476 ± 0.0051 | 0.9998 (8) | 1.05 ± 0.050 | 0.99 (15) |
| (Siepmann et al., 2002)[n] | 0.649 ± 0.018 | 0.998 (8) | 0.894 ± 0.021 | 0.998 (13) |
| (Siepmann et al., 2002)[o] | 0.7527 ± 0.0065 | 0.998 (5) | 1.13 ± 0.058 | 0.994 (13) |
| (Siepmann et al., 2002)[p] | 0.727 ± 0.022 | 0.998 (9) | 1.02 ± 0.028 | 0.997 (14) |
| (Bettini et al., 2001)[q] | 0.6184 ± 0.0032 | 0.99996 (6) | 0.944 ± 0.034 | 0.995 (10) |
| (Bettini et al., 2001)[r] | 0.670 ± 0.024 | 0.997 (8) | 0.997 ± 0.039 | 0.994 (13) |
| (Bettini et al., 2001)[s] | 0.623 ± 0.080 | 0.998 (22) | 1.01 ± 0.035 | 0.99 (38) |
| (Ford et al., 1987)[t] | 0.5715 ± 0.0083 | 0.998 (18) | 0.896 ± 0.042 | 0.98 (25) |
| (Ford et al., 1987)[u] | 0.704 ± 0.017 | 0.995 (16) | 1.06 ± 0.040 | 0.99 (23) |
| (Juarez et al., 2001)[v] | 0.467 ± 0.037 | 0.99 (4) | 0.732 ± 0.053 | 0.99 (6) |
| (Juarez et al., 2001)[w] | 0.4455 ± 0.0093 | 0.999 (7) | 0.662 ± 0.037 | 0.991 (9) |

[a] Number of data points.
[b] Fig. 6a, 10 mol% MAA.
[c] Fig. 6a, 80 mol % MAA.
[d] Fig. 5a, GP 911 NF.
[e] Fig. 5a, GP 812 NF.
[f] Fig. 5b, GP 911 NF.
[g] Fig. 5b, GP 812 NF.
[h] Fig. 1, KCl/ polyviol.
[i] Fig. 2, NaCMC.
[j] Fig. 4, 3 mm diameter.
[k] Fig 2a, 50:47.
[l] Fig. 2a, 20:77.
[m] Fig. 2a, 35:62.
[n] Fig. 7a 4:4 mm diameter.
[o] Fig. 6a, 1 mm diameter.
[p] Fig. 5a, 1.3 mm diameter.
[q] Fig. 1, BPP.
[r] Fig. 1, DCN.
[s] Fig. 3, BPP.
[t] Fig. 2, 45 mg HPMC.
[u] Fig. 1, 60 mg HPMC.
[v] Fig. 2.
[w] Fig. 5.

lations as well as to literature data. Two typical examples of successful fittings using Eq. (3) are shown in Figs. 1 and 2. Similarly, successful fittings were obtained when Eq. (2) was fitted to the first 60% of the release curve of these formulations (Figs. 1 and 2). An overview of the derived estimates for $b$ and $n$ from the fitting of Eqs. (2) and (3) to the data of the prepared and commercial formulations as well as to the literature data is listed in Table 2. The values of the standard errors and

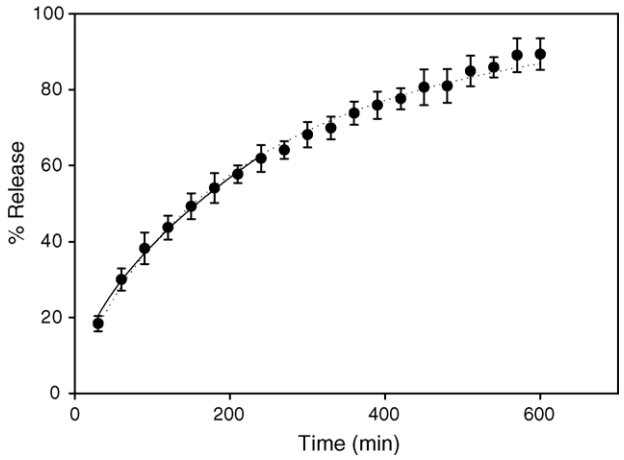


Fig. 1. Fittings of Eq. (2) (solid line) and Eq. (3) (dotted line) to release data of Elvesil®. Fitting results are shown in Table 2.

the correlation coefficients of the nonlinear regressions listed in Table 2 are indicative of the good fittings of Eqs. (2) and (3) to the corresponding data.

In Fig. 3 the estimates derived for $b$ are plotted versus the estimates for $n$ for all data analyzed. The linear relationship established indicates not only the mathematical relevance of the exponents $b$ and $n$ of Eqs. (2) and (3), but also the physical connection of the models parameters and the release mechanism. For example, the equation derived from the linear regression analysis of $b$ and $n$ values, if solved for $n = 0.45$, which indicates pure diffusion controlled release from cylinders (Ritger and Peppas, 1987), yields $b = 0.74$, which lies in the range 0.69–0.75 of the theoretically anticipated values for Fickian diffusion observed by Kosmidis et al. (2003b) in the Monte Carlo simulations. It is interesting to note that the three estimates for $n$, 0.397, 0.4455, 0.467 (Table 2) in the proximity of the theoretical value $n = 0.45$ correspond to $b$ values 0.698, 0.662, 0.732, respectively which lie either in or very close to the theoretical range 0.69–0.75 (Kosmidis et al., 2003b). These differences are obviously related to the multiple sources of experimental errors, the uncertainty of the estimates for both parameters as well as to the different specific surface (Kosmidis et al., 2003b) of the formulations examined. Also, values for $n$ higher than 0.5, which are indicative of anomalous transport (combined mechanism of pure diffusion and Case II transport) correspond to $b$ values higher than 0.80, which were not observed in the Monte Carlo simulations based on pure Fickian diffusion (Kosmidis et al., 2003b,c).

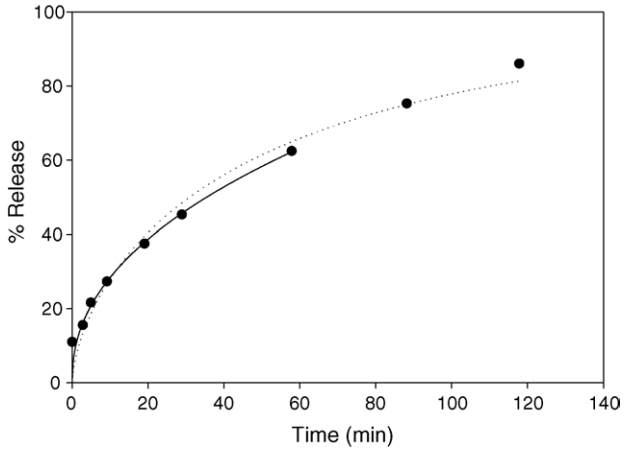


Fig. 2. Fittings of Eq. (2) (solid line) and Eq. (3) (dotted line) to literature release data (Juarez et al., 2001, Fig. 5). Fitting results are shown in Table 2.

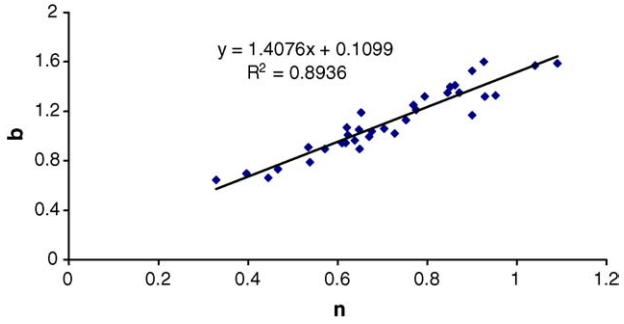


Fig. 3. Linear regression of the estimates for $b$ versus the estimates for $n$.

It is very well known that classical linear regression analysis is inappropriate when the independent variable $x$ is subject to experimental error. Because both $b$ and $n$ are estimates accompanied by their uncertainties, we performed linear regression based on geometric mean functional relationship approach, which does not require any assumptions concerning the absence of errors in either of the variables (Valsami and Macheras, 1995; Sprent and Dolby, 1980). The linear equation derived was $y = 1.489x + 0.0516$, $R^2 = 0.893$, which for $n = 0.45$ gives $b = 0.72$. Again, this value of $b$ lies in the range 0.69–0.75; thus, both regression analyses resulted in roughly identical results.

Due to the successful use of the Weibull function in the analysis of the entire release profile when drug release follows pure Fickian diffusion, the problem related to the successful description of the entire release curve of several controlled release formulations using Eq. (2) (Rinaki et al., 2003a) was re-considered. The hypothesis of non-classical diffusion (Rinaki et al., 2003a) based on a power law derived from simulation studies in fractal spaces reported by Bunde et al. (1985) was not verified in the recent detailed Monte Carlo simulations in the same fractal spaces (Kosmidis et al., 2003c). As mentioned previously, Eq. (3) can be approximated by a power law when the product $\alpha t^b$ is small. Because of this relevance of the Weibull function with the power law, one can argue that the description of the entire release curve with Eq. (2) is indicative of a combined release mechanism. Simulated pseudo-data were used to substantiate this argument assuming that the release obeys exclusively Fickian diffusion up to time $t = 90$ (arbitrary units) while for $t > 90$ a Case II transport starts to operate too; this scenario can be modeled using Eq. (4):

$$\frac{M_t}{M_\infty} = 1 - \exp(-0.05t^{0.70}) + f(t) \quad (4)$$

where

$$f(t) = 0 \quad \text{for } t < 90$$

$$f(t) = 0.04(t - 90)^{0.89} \quad \text{for } t > 90$$

Also, Eq. (5) was used to simulate concurrent release mechanisms of Fickian diffusion and Case II transport by assigning $f(t) = 0.04t^{0.89}$ throughout the release process.

$$\frac{M_t}{M_\infty} = 1 - \exp(-0.05t^{0.70}) + 0.04t^{0.89} \quad (5)$$

Pseudo-data generated from Eqs. (4) and (5) are plotted in Fig. 4(a and b) along with the fitted curves.

$$\frac{M_t}{M_\infty} = 0.046t^{0.59} \quad (6)$$

$$\frac{M_t}{M_\infty} = 0.07t^{0.55} \quad (7)$$

The nice fittings of Eqs. (6) and (7) to the release data generated from Eqs. (4) and (5), respectively, verify the argument that the power law can describe the entire set of release data following combined release mechanisms. In this context, we performed a nonlinear fitting of the power law to the entire release curve of six data sets quoted in Table 2 (H, I, Vurdon®, Siepmann et al., 2002([n]), Bettini et al., 2001([q]), Ford et al., 1987([t]) with $b$ values in the range 0.894–0.965. In all cases nice fittings were obtained ($R^2$ range 0.98–0.999) and $n$ values in the range 0.50–0.61. These results are in close agreement with the simulation findings for $n$ values in Eqs. (6) and (7). It can be concluded therefore that $b$ values in the range of 0.75–1.0 and $n$ values in the range of 0.50–0.60 derived from the analysis of the entire set of data using the Weibull function and the power law, respectively, are indicative of a combined release mechanism.

The fitting results, Figs. 1, 2 and 4 and the correlation developed between $b$ and $n$ estimates, Fig. 3 allow one to infer that the $b$ values derived from the fitting of Eq. (3) to the entire drug release curve data can characterize the release mechanism. Table 3 summarizes the diffusional mechanism in connection with the specific $b$ values of the Weibull function found in the experimental and simulation work of this study as well as in the Monte Carlo simulations of the previous studies (Kosmidis et al., 2003b,c). According to the remarks quoted in Table 3, for values of $b$ lower than 0.75 the release follows Fickian diffusion either in Euclidian ($0.69 < b < 0.75$) or fractal space, $b < 0.69$.

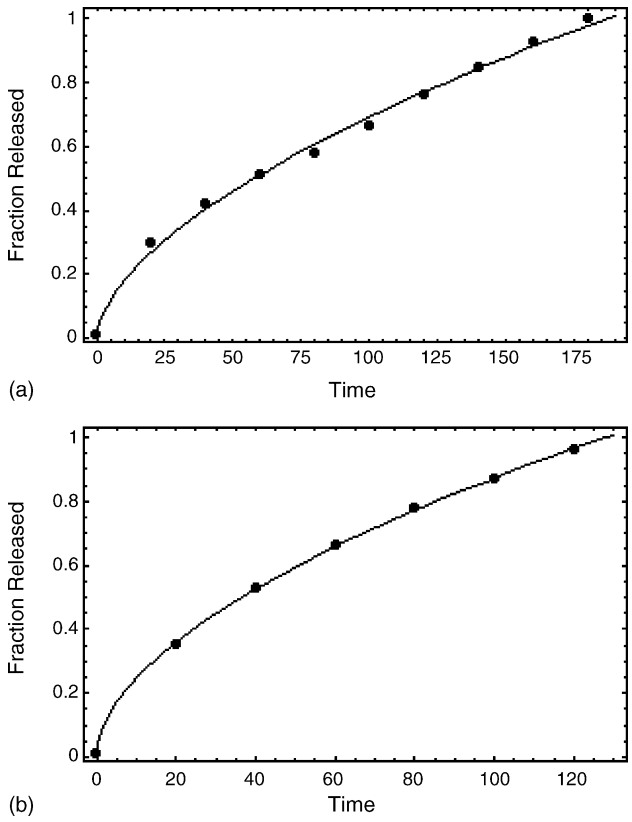


Fig. 4. (a) Points are simulation data produced using Eq. (4). The solid line is the fitting of the power law Eq. (6) to data. Best fitting parameters are $k = 0.046$ for the proportionality constant and $n = 0.59$ for the exponent. (b) Points are simulation data produced using Eq. (5). The solid line is the fitting of the power law Eq. (6) to data. Best fitting parameters are $k = 0.070$ for the proportionality constant and $n = 0.55$ for the exponent.

For Fickian diffusion the increase of $b$ reflects the decrease of the disorder of the medium. It is well known, that diffusion in a disordered medium has several interesting properties different from those observed in an ordered environment (Bunde et al., 1985 and refs therein).

Values of $b$ in the range 0.75–1.0 indicate a combined mechanism which is frequently encountered in release studies. For these cases, additional confirmation can be obtained when the

Table 3
Exponent b of the Weibull function using the entire set of data and mechanism of diffusional release

| $b$ | Release mechanism—remarks |
|---|---|
| $b < 0.35$ | Not found in simulation (Kosmidis et al., 2003b,c) and the experimental results. May occur in highly disordered spaces much different than the percolation cluster. |
| $b \sim 0.35$–$0.39$ | Diffusion in fractal substrate morphologically similar to the percolation cluster (Kosmidis et al., 2003c) |
| $0.39 < b < 0.69$ | Diffusion in fractal or disordered substrate different from the percolation cluster[a] |
| $b \sim 0.69$–$0.75$ | Diffusion in normal Euclidian space (Kosmidis et al., 2003b) |
| $0.75 < b < 1$ | Diffusion in normal Euclidian substrate with contribution of another release mechanism[b] |
| $b = 1$ | First order release obeying Fick's first law of diffusion; the rate constant $a$ of Eq. 3 controls the release kinetics and the dimensionless solubility/dose ratio determines the final fraction of dose dissolved (Rinaki et al., 2003b) |
| $b > 1$ | Sigmoid curve indicative of complex release mechanism[c] |

[a] These values were not observed in Monte Carlo simulation results (Kosmidis et al., 2003b,c). It is, however, plausible to assume this possibility as there has to be a cross-over from fractal to Euclidian dimension. In fact, values of $b$ were found to be equal to 0.61–0.62 in our preliminary simulation release studies in a 2D diffusion limited aggregation (DLA) fractal.

[b] In this case, the power law can describe the entire set of data of a combined release mechanism (see text).

[c] The rate of release increases up to the inflection point and thereafter declines.

power law can describe the entire set of data. The specific case of $b = 1$ is compatible with first-order release, whereas the concentration gradient in the dissolution medium drives the rate of release (Rinaki et al., 2003b). Finally, when $b > 1$ the sigmoid shape of the Weibull function indicates that a complex mechanism governs the release process. This is so since the rate of release does not change monotonically. In fact, the release rate initially increases nonlinearly up to the inflection point and thereafter decreases asymptotically.

Based on the remarks of Table 3, it seems that regardless of the type of the hydroxypropylmethyl cellulose polymer used and its content in the tablet with respect to the active substance, all the prepared diclofenac formulations (A–G, Table 2) exhibit a complex release mechanism; this results from the estimates of *b* for the formulations A–G of Table 2, which were found to be higher than 1. It seems likely that the dissolution process of the relatively insoluble diclofenac plays a role in the release kinetics along with other release mechanisms. Conversely, a combined release mechanism for the freely water soluble diltiazem for the prepared formulations H and I in Table 2, can be justified since the estimates for *b* are 0.965 and 0.942, respectively. This can be attributed to the hydrophilic nature of diltiazem, which allows the drug to have a favorable interaction with the aqueous dissolution medium.

Moreover, the difference observed between the dissolution profile of diclofenac and that of diltiazem could partly be due to the relevant amount of the polymer used in the formulations of these drugs (entries A and H, B and I, Table 1). In the case of diltiazem, where the relevant amount of the drug in the tablet formulation with respect to Metolose is 2:3 (entry H, Table 1), the value of *b* is 0.965, indicative of diffusion controlled mechanism with contribution of another release pathway. On the other hand, in the analogous formulation of diclofenac sodium (entry A, Table 1), where a higher amount of polymer with respect to the drug is present in the tablet preparation, the *b* value is 1.40 and this corresponds to a sigmoid curve, which is indicative of a complex release mechanism. The above trend was also observed in the cases of recipes I and B; the values of *b* in these cases are 0.942 and 1.32, respectively.

Finally, it should be noted that the Weibull function has been used for the kinetic analysis of release from a variety of diltiazem formulations (Costa, 2001; Costa and Sousa Lobo, 2001b; Costa and Sousa Lobo, 2001c; Sathe and Venitz, 2003). However, no one of these studies provides a hint for the release mechanism(s) of diltiazem in relation to the estimates of the Weibull parameters.

## 4. Conclusion

Overall, this study provides experimental evidence for the successful use of the Weibull function in drug release studies. Although the Weibull function has been used empirically for the analysis of release kinetics (Bonferoni et al., 1998; Lin and Cham, 1996; Antal et al., 1997; Van Vooren et al., 2001; Adams et al., 2002; Costa et al., 2003; Koester et al., 2004; Varma et al., 2005), the results of the present study provide a link between the values of *b* and the diffusional mechanisms of the release.

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