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The power law can describe the 'entire' drug release curve from HPMC-based matrix tablets: a hypothesis

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Abstract

The purposes of this study were to (i) re-examine the relevance of Higuchi equation and the power law using both simulated and experimental release data in conjunction with the linearized, in terms of $t^{1/2}$, percent of drug release plots, (ii) demonstrate that the power law describes the entire drug release profile of several experimental data, and (iii) point out a physically based hypothesis for the successful use of power law in describing the entire drug release profile. Simulated data generated from the equation of power law were further analyzed using linear regression analysis in accord with the Higuchi equation. The analysis revealed that data generated from the equation of power law can be misinterpreted as obeying the Higuchi equation. The use of power law in describing the entire drug release curve from HPMC-based matrix tablets is validated by direct fit of power law equation to published data of other authors. A hypothesis based on the nonclassical diffusion of the solutes in the HPMC matrices is used to interpret the successful use of the power law in describing the entire release profile.

Keywords: Power law; Higuchi law; Drug release; Kinetics

1. Introduction

The release of drug from hydroxypropyl methylcellulose (HPMC)-based pharmaceutical systems has been given great interest over the last 20 years. These devices have been extensively used for the delivery of drugs over an extended period of time (Gurny and Peppas, 1990; Rydén and Edman, 1992; Colombo, 1993). Significant experimental and theoretical work has been performed to accurately model drug transport and reveal the mechanisms of drug release from these systems (Lee and Kim, 1991; Hariharan et al., 1994; Colombo et al., 1995,1996,2000; Ferrero et al., 2000). Despite the complexity of the phenomena involved, two well known approaches are used extensively and successfully for the analysis of drug release data in these systems (Higuchi, 1961; Korsmeyer et al., 1983; Siepmann and Peppas, 2001).

The first approach relies on the famous Higuchi equation, Eq. (1), (Higuchi, 1961)

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

where M_t and M_∞ are cumulative amounts of drug released at time t, and infinite time, respectively; and k is a constant reflecting formulation characteristics. According to Eq. (1), the fraction of drug released is proportional to the square root of time. The basic assumption for the derivation of Eq. (1), is that the initial concentration of the drug in the system, C_0, is

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much higher than drug solubility, C_s and diffusion is the sole mechanism of drug release (Higuchi, 1961). The same proportionality between the fraction of drug released and the square root of time can also be derived from Fick's second law of diffusion for thin films of thickness δ, under perfect sink conditions, uniform initial drug concentration with $C_0 < C_s$ and assuming constant diffusivities (Siepmann and Peppas, 2001)

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\delta^2}\right)^{1/2} \times \left\{\pi^{-1/2} + 2\sum_{m=1}^{\infty}(-1)^m \text{ierfc}\frac{m\delta}{2\sqrt{Dt}}\right\} \quad (2)$$

where D is the diffusivity of the drug within the matrix system, m is the axial coordinate through which diffusion occurs and ierfc is the integrated error function complement. The second term in the brackets of Eq. (2) vanishes at short times and thus, an accurate approximation of Eq. (2) can be written as follows

$$\frac{M_t}{M_\infty} = 4\left(\frac{Dt}{\delta^2}\right)^{1/2} = k'\sqrt{t} \quad (3)$$

where, $k' = 4D^{1/2}/\delta$. Thus, under substantially different conditions, those studied by Higuchi and those assumed above for the exact solution of Fick's second law, the same proportionality between the fraction of drug released and the square root of time can be derived as a short time approximation.

The second approach relies on the semi-empirical Eq. (4), used extensively and successfully for the analysis of the first 60% of the release curves (Colombo et al., 1995,1996; Ferrero et al., 2000; Bettini et al., 2001), proposed by Korsmeyer et al. (1983)

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

where k is the kinetic constant and n is an exponent characterizing the diffusional mechanism. Only in two cases of $n = 0.5$ (pure diffusion controlled drug release) and $n = 1$ (swelling-controlled drug release or Case II transport), Eq. (4) becomes physically realistic. Other values for n indicate anomalous transport kinetics (Ritger and Peppas, 1987), i.e. a combined mechanism of pure diffusion and Case II transport. As can be seen, the special case with $n = 0.5$ in Eq. (4) represents the Higuchi model (Siepmann and Peppas, 2000).

Due to the approximate character of Eqs. (1), (3) and (4), their use is confined to the description of the first 60% of the release curve. Besides, the use of Eq. (4) for the description of the entire release curve has not been reported and/or justified so far. These observations prompted us to (i) re-examine the relevance of Eqs. (1) and (4) using both simulated and experimental data in the light of the linearized, in terms of $t^{1/2}$, release plots, (ii) demonstrate that Eq. (4) describes the entire drug release profile from several HPMC-based matrix tablets, and (iii) point out a physically based hypothesis for the capability of Eq. (4) to describe the entire drug release profile.

2. Materials and methods

2.1. Simulations

Simulated data were generated from Eq. (4) using values for n and k ranging from 0.4 to 0.65 and from 0.05 to 0.5, respectively. The range of n values in the neighborhood of the Higuchi exponent 0.5 which is the theoretical value for a diffusion controlled release process. Besides, values of n in the range of 0.4–0.65 are frequently quoted in literature for the discernment of drug release mechanisms (pure diffusion, anomalous transport and combination) from HPMC matrix devices of different geometries (Ritger and Peppas, 1987). The values assigned to k are similar to the estimates derived when Eq. (1) is fitted to drug release data whereas time is expressed in hours and k in $h^{-1/2}$ units. The constraint $M_t/M_\infty \leq 1$ was used for each set generated from Eq. (4). The duration of the simulated release experiment was arbitrarily set equal to 8 ($t \leq 8$). Therefore, the number of the simulated data generated from Eq. (4) varied according to the specific value assigned to k using in all cases a constant time step, 0.01. The pairs of data (M_t/M_∞, t) generated from Eq. (4) were further analyzed using linear regression analysis in accord with Eq. (1) (M_t/M_∞ versus $t^{1/2}$).

2.2. Experimental data

The use of Eq. (4) in describing drug release data from HPMC-based matrix tablets with $M_t/M_\infty >$ 60% is validated by direct fit of Eq. (4) to published

data of other authors (Ford et al., 1987; Pham and Lee, 1994; Sung et al., 1996; Bettini et al., 2001; Siepmann et al., 2002). Data were obtained by digitization of the points from enlargements of published figures. Release curves are frequently plotted as percent release versus $t^{1/2}$, but for curve fitting, the digitizing software (Windows Paint) in combination with SigmaPlot 5.0 was allowed to transform the data back to classical time units. Best-fit parameter values for k and n were obtained with SigmaPlot 5.0 program.

3. Results and discussion

3.1. Simulations

Table 1 shows the results of linear regression analysis (M_t/M_∞ versus $t^{1/2}$) for the data generated from Eq. (4). As expected, the theoretically correct sets of data ($n = 0.5$) exhibited ideal behaviour (intercept = 0, $R^2 = 1$). Judging from the R^2 values in conjunction with the number of data points utilized in regression, all other sets of data with $n \neq 0.5$ are also described nicely. It is also worthy to mention that the positive intercepts were very close to zero and only in two cases ($k = 0.4$, $n = 0.4$; $k = 0.5$, $n = 0.4$) were found to be in the range 0.10–0.11. In parallel, the negative intercepts found, were very close to the origin of the axes. A typical example of a set with a negative y-intercept is shown in Fig. 1.

Table 1
Results of linear regression (M_t/M_∞ vs. $t^{1/2}$) for data generated from Eq. (4)

k	n	Intercept	Slope	R^2	N[a]
0.05	0.40	0.01287	0.03668	0.9970	800
	0.45	0.006719	0.04305	0.9993	800
	0.50	0[b]	0.05	1	800
	0.55	−0.005760	0.05760	0.9994	800
	0.60	−0.01545	0.06571	0.9976	800
	0.65	−0.02436	0.07501	0.9950	800
0.3	0.40	0.0772	0.02201	0.9970	800
	0.45	0.04031	0.2583	0.9993	800
	0.50	0[b]	0.3	1	800
	0.55	−0.04418	0.3456	0.9994	800
	0.60	−0.08866	0.3925	0.9976	743
	0.65	−0.1258	0.4349	0.9949	637
0.4	0.40	0.1030	0.2935	0.9970	800
	0.45	0.05270	0.3451	0.9993	766
	0.50	0[b]	0.4	1	625
	0.55	−0.04676	0.4513	0.9994	529
	0.60	−0.08829	0.4987	0.9976	460
	0.65	−0.1253	0.5422	0.9948	409
0.5	0.40	0.1117	0.3800	0.9969	565
	0.45	0.05243	0.4424	0.9993	466
	0.50	0[b]	0.5	1	400
	0.55	−0.04649	0.5525	0.9993	352
	0.60	−0.0878	0.6002	0.9975	317
	0.65	−0.1245	0.6432	0.9947	290

[a] Number of data points utilized in regression.
[b] Estimates not statistically significant different from zero were derived.

These observations indicate that almost the entire set of data listed in Table 1 and generated from Eq. (4) can be misinterpreted as obeying Eq. (1). Under real experimental conditions the discernment of kinetics is even more difficult when linear regression of M_t/M_∞ versus $t^{1/2}$ is applied. This is so, if one takes into account (i) the small number of data points available, (ii) the constraint for the percent of drug released applied, $M_t/M_\infty \leq 0.60$, (iii) the experimental error of data points, (iv) the high variability or lack of data points at the early stages of the experiment, and (v) the possible presence of a lag-time. In addition, the square root transformation of the time data changes the distribution and variances of the errors. Therefore, it is advisable to fit Eq. (4) to experimental data using nonlinear regression.

The overall conclusion of the simulation study is that release data should not be analyzed using Eq. (2). Instead, it is advisable to fit Eq. (4) to data points complying with the constraint $M_t/M_\infty \leq 0.60$. Conclusions concerning the release mechanisms can be based on the estimates for n and statistical properties of the regression line (Ritger and Peppas, 1987). In Section 3.2 we pose the question of the possible use of Eq. (4) for the analysis of release data exceeding the 0.6 limit for M_t/M_∞.

3.2. Experimental data

Ford et al. (1987) studied the release of several drugs among of which were theophylline, tetracycline and diazepam from matrices containing HPMC in different HPMC:drug ratios. The authors fitted Eq. (1) to data points of various linear parts of the Higuchi plots. We re-analyzed all available data using Eq. (4) and the results are quoted in Table 2. As can be seen, Eq. (4) describes nicely all data sets analyzed while

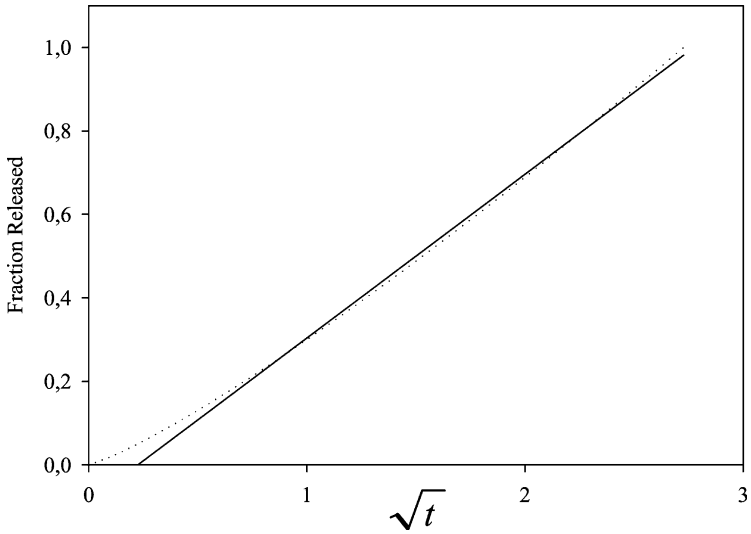

Fig. 1. A typical example of fitting (solid line) Eq. (1) to data (dotted line) generated from Eq. (4) using $k = 0.30$ and $n = 0.60$.

the estimates for the exponent n are, in all cases, significantly different from 0.5. Most importantly, Eq. (4) fits nicely to five sets of data (rows 1, 2, 5–7; Table 2) whereas the last datum point exceeds the usual constraint 0.6 for M_t/M_∞. A typical example of a successful fitting is shown in Fig. 2. In addition, the estimates for n of theophylline and tetracycline are quite similar, and in some cases statistically equivalent, with the estimates derived from data fulfilling the constraint $M_t/M_\infty \leq 0.6$, Table 2. The results for diazepam listed in Table 2 indicate zero-order kinetics; however, the data points belong only to the initial part of the release curve and definite conclusion for the entire release profile cannot be justified.

In another study, Sung et al. (1996) used the value of exponent n derived from fittings of Eq. (4) to the first 60% of data, to evaluate the mechanism(s) of drug release from HPMC matrices. We fitted Eq. (4)

Table 2
Parameter estimates derived from the fitting of Eq. (4) to experimental data reported by Ford et al. (1987)

	k (S.E.)	n (S.E.)	R^2	Percentage release of last time point
Theophyline				
60 mg HPMC	0.0101 (0.0006)	0.6906 (0.0105)	0.9974	92
90 mg HPMC	0.0061 (0.0003)	0.7252 (0.0071)	0.9989	73
180 mg HPMC	0.0060 (0.0003)	0.6976 (0.0077)	0.9986	59
270 mg HPMC	0.0049 (0.0003)	0.7094 (0.0111)	0.9973	52
Tetracycline				
45 mg HPMC	0.0153 (0.0008)	0.6133 (0.0088)	0.9973	92
60 mg HPMC	0.0183 (0.0008)	0.5595 (0.0068)	0.9980	76
90 mg HPMC	0.0185 (0.0009)	0.5302 (0.0076)	0.9972	65
180 mg HPMC	0.0092 (0.0008)	0.6065 (0.0140)	0.9929	54
270 mg HPMC	0.0065 (0.0007)	0.6316 (0.0169)	0.9906	46
Diazepam				
50 mg HPMC	0.0007 (0.0000)	0.9482 (0.0040)	0.9998	37
61.5 mg HPMC	0.0007 (0.0000)	0.9362 (0.00092)	0.9991	31
200 mg HPMC	0.0014 (0.0001)	0.7951 (0.0141)	0.9975	24

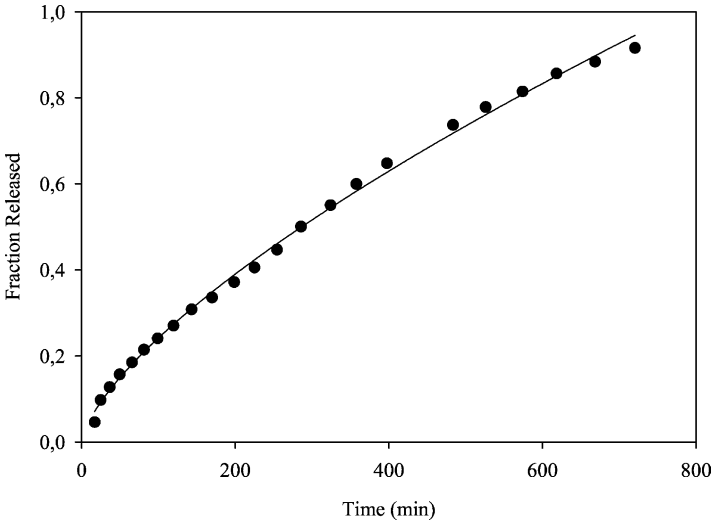

Fig. 2. A typical example of fitting (solid line) Eq. (4) to experimental data quoted in Table 2 (theophylline/60 mg HPMC).

to the entire sets of data and the fitting results obtained are presented in Fig. 3. In all three cases, the fittings were excellent utilizing all available data points. It is worthy to mention that a considerable number of data points of all sets analyzed were lying beyond the limit 0.60 for M_t/M_∞, Fig. 3. For fitting purposes, only the first time point exhibiting 100% drug release from the matrices containing HPMC K100LV was utilized in regression, Fig. 3C. The estimates for the exponent n are in the range 0.64–0.71.

The capability of the power law to describe the entire release curve was also validated in additional studies dealing with drug release from HPMC matrices (Pham and Lee, 1994; Bettini et al., 2001; Siepmann and Peppas, 2001). Figs. 4–6 show the fittings of Eq. (4) to the experimental data along with the estimates derived for k and n. In all cases, the entire release profile was analyzed and the fitting results are very good.

3.3. A hypothesis

It is very well known that because of the approximate character of Eq. (4) its use in drug release studies is confined to the first 60% of the release curve. For this particular reason, most of the published fractional drug release–time plots are not extended beyond the 0.60 release boundary. Our results provide explicit evidence that the power law Eq. (4) can describe the entire release profile of several drug release studies from HPMC-based delivery systems, Figs. 2–6, Table 2. To the best of our knowledge, the only relevant application of the power law for the analysis of the entire dissolution or release curves, was empirically proposed by Flaig (1974). Undoubtedly, an explanation associated with the classical theories of drug release cannot be pointed out. However, a release mechanism based on the nonclassical diffusion of the solute within the polymeric system can be postulated to interpret these findings. Nonclassical diffusion is encountered in disorder media whereas time dependent diffusion coefficients govern the diffusion process (Havlin and Ben Avraham, 1987; Kopelman, 1988). The topology of the disordered medium is the principal factor determining the diffusion of solute at the microscopic level. The fundamental law of physics which applies to well stirred, homogeneous systems dictates that the mean square displacement of the walker, $\langle x^2 \rangle$ in the random walk model is proportional to time (Ben-Avraham and Havlin, 2000a)

$$\langle x^2 \rangle \propto t \tag{5}$$

However, in disordered systems, $\langle x^2 \rangle$ is not proportional to time (Ben-Avraham and Havlin, 2000b)

$$\langle x^2 \rangle \propto t^{2/D_w} \tag{6}$$

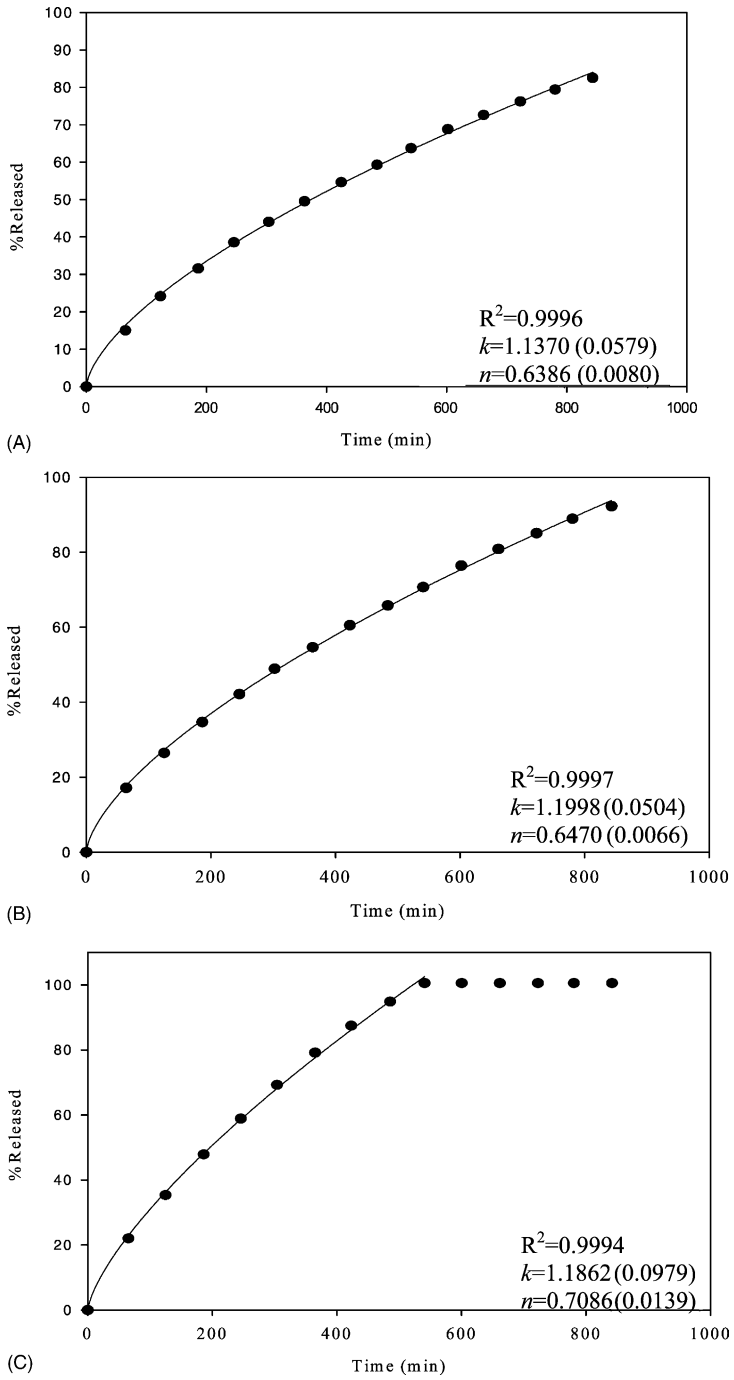

Fig. 3. Fittings of Eq. (4) to the entire sets of adinazolam mesylate release data (Sung et al., 1996) from HPMC matrices of different viscosities. (A) HPMC K4M, (B) HPMC K15M, and (C) HPMC K100LV.

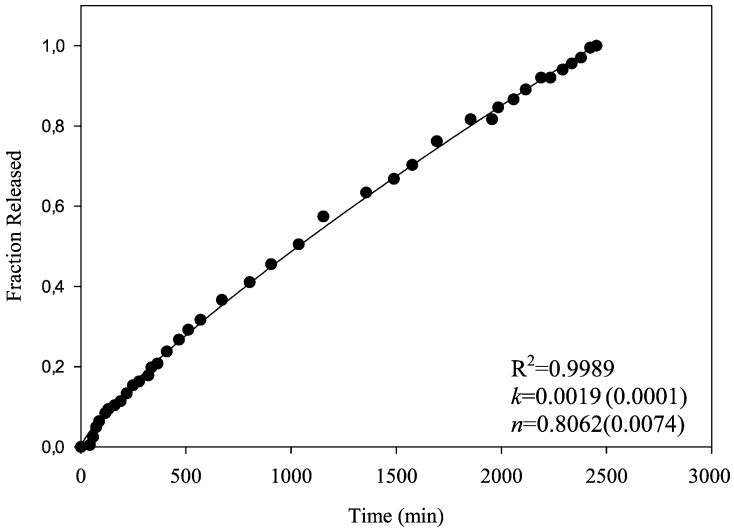

Fig. 4. Fitting of Eq. (4) to the entire set of fluoresceine release data from HPMC matrices (Pham and Lee, 1994).

where $D_w \neq 2$ is the fractal walk dimension of the walker (Avnir, 1989). The net result of this property is that scaling laws (power laws) like Eq. (4) are associated with the kinetics of the processes (Ben-Avraham and Havlin, 2000a,b). This kinetic behaviour has been validated in simulation studies of drug release in fractal matrices (Bunde et al., 1985). Also, the percolation model (Leuenberger et al., 1987) which is in essence a disordered medium has been used to model HPMC matrices (Bonny and Leuenberger, 1991). In parallel, nonclassical diffusion on percolation clusters is a well validated mechanism (Ben-Avraham and Havlin, 2000c). It seems likely that the spatiotemporal variation in porosity of the dynamically swelling polymer is close enough to the percolation threshold for nonclassical diffusion effects to impinge on release kinetics.

These observations, if coupled with our simulation results as well as the concerns raised for the linearity

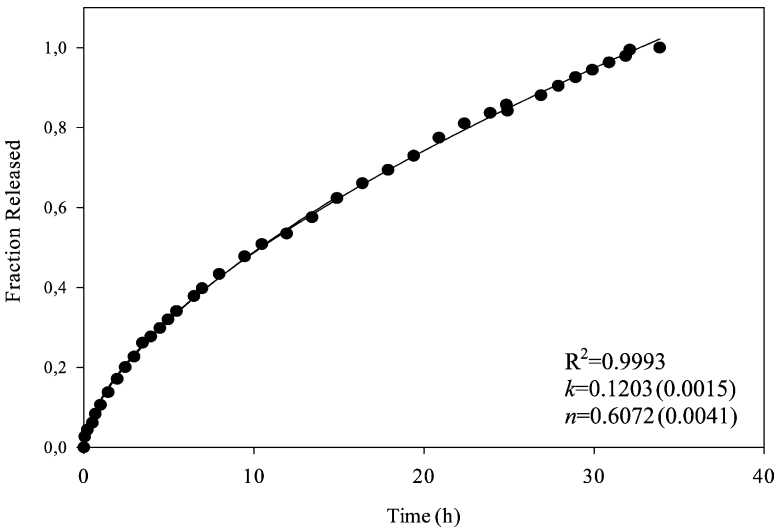

Fig. 5. Fitting of Eq. (4) to the entire set of buflomedil pyridoxal release data from HPMC matrices (Bettini et al., 2001).

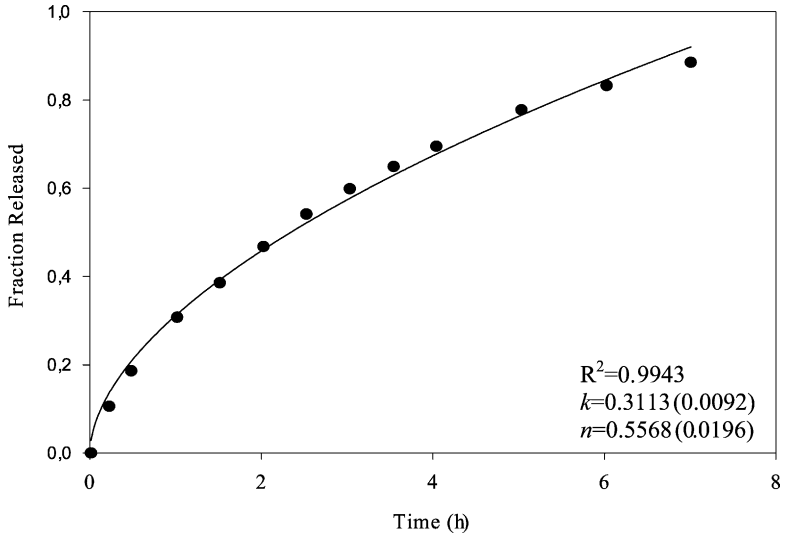

Fig. 6. A typical example of fitting Eq. (4) to chlorpheniramine maleate release data from HPMC K15M matrix tablets (tablet height 4 mm; tablet height:tablet radius ratio 1:1) (Siepmann et al., 2002).

of Higuchi plots far beyond the theoretical limitations (Skoug et al., 1991), substantiate the view that nonclassical diffusion can be a physically based mechanism for the release of drug from HPMC matrices whenever Eq. (4) suits nicely to the entire release curve. Needless to say, that more studies are required to elucidate and validate the postulate of nonclassical diffusion in drug release studies from HPMC-based matrices.

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