

Determination of fractal reaction dimension in dissolution studies

Georgia Valsami, Panos Macheras*

Laboratory of Biopharmaceutics and Pharmacokinetics, Department of Pharmacy, University of Athens, Panepistimiopolis, Athens 15771, Greece

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Abstract

The paper presents a method for the calculation of fractal reaction dimension, D_R , in dissolution studies of powdered substances with a given particle size distribution. An estimate for D_R can be directly obtained from dissolution experiments using the well known Hixson-Crowell equations in a modified form. The estimation is accomplished with a special computer program in BASIC which was developed and applied to simulated errorless and contaminated data with very good results. A practical demonstration of the method's usefulness was shown on experimental data taken from the literature.

Keywords: Dissolution; Fractal; Fractal dimension; Fractal reaction dimension

1. Introduction

The concept of fractals is innovative in the field of pharmaceutical sciences (Koch, 1993), although its use is widespread in the fields of chemistry (Amann and Gans, 1989), physics (Pietronero and Tassati, 1986) and physiology (West and Goldberger, 1987). According to Mandelbrot (1982), who introduced the term fractal, a system is fractally structured when one of its properties or quantities to be measured is, with certain limits, a function of the scale applied. As an example of fractal behaviour, the surface area, A , of an object is a multiple of the scale, e.g. a cm^2 and has a topological dimension $d_t = 2$; however, the measured surface area of an irregular and rough surface increases with decreasing scale size according to its special structure. This surface is termed 'fractal surface' (Koch, 1992) with a fractal dimension D lying between the topological and Euclidean dimensions, i.e. $2 <$

$D < 3$. In other words, D may be a fractional number. Furthermore, Farin and Avnir (1987, 1988) developed the concept of fractal reaction dimension D_R that is basically the effective fractal dimension of the object towards a reaction.

Based on the findings of Avnir's research group (Avnir, 1987; Farin and Avnir 1987, 1988; Farin et al., 1989) that the surfaces of most materials are fractal, Farin and Avnir (1992) were the first to use fractal geometry to determine effects of surface morphology on drug dissolution. The Hixson-Crowell cube root law equations (Hixson and Crowell, 1931) were appropriately modified (Farin and Avnir, 1992) to include surface roughness effects on the dissolution rate of drugs. Eq. 1 was derived for the general case of the entire time course of dissolution while Eq. 2 adheres to sink conditions (Farin and Avnir, 1992):

$$\frac{3}{D_R} (w^{-D_R/3} - w_0^{-D_R/3}) = kt \quad (1)$$

$$\left(\frac{3}{3-D_R}\right) (w_0^{(3-D_R)/3} - w^{(3-D_R)/3}) = w_e kt \quad (2)$$

* Corresponding author. Tel. (+30-1) 72 84 367/72 84 675-8; Fax (+30-1)-72 44191).

where w_e , w_0 , and w are the weight of the drug necessary to saturate the solution, the initial weight of the drug, and the weight of the drug after time t , respectively; k is the dissolution rate constant. Apparently, Eqs. 1 and 2 are valid as long as the value of D_R remains constant. However, two studies (Farin and Avnir, 1987; Fernandez Hervas et al., 1994) have shown that the value of D_R remains constant almost throughout the dissolution process.

According to Farin and Avnir (1987), an estimate for D_R can be obtained from the slope of a log-log plot of the initial rate of dissolution v versus the radius R of the various particle sizes tested. In reality, this kind of calculation is based on the fundamental proportionality (Farin and Avnir, 1987)

$$v \propto S \propto R^{D_R-3} \quad (3)$$

where S is the effective surface area for dissolution; obviously, by plotting $\log v$ as a function of $\log R$ a straight line with slope $D_R - 3$ is obtained. In reality, the proportionality in Eq. 3 between v and S is Wenzel's law (1777) for heterogeneous reactions which states that the larger the interface, the faster the reaction.

However, the calculation of D_R from a $\log v - \log R$ plot requires the execution of a number of dissolution experiments with a variety of particles of well defined sizes and shape characteristics. Nonetheless, pharmaceutical powders are almost always 'polydisperse' (Carstensen, 1977); besides, multifractality may exist when a population of surface points can be divided into a number of sub-populations, each having a different reactivity towards the dissolution process (Stanley and Meakin, 1988; Carstensen and Francini, 1993). In addition, the fractal dimension of a series of granules or particles can exhibit inter-series variability in the connectivity (Gouyet, 1990) properties. Finally, violations of Wenzel's law are not unlikely to occur in diffusion controlled processes (Kopelman, 1988) like dissolution. For all these reasons, the particles of the different sizes can exhibit different fractal reaction dimensions. Accordingly, it would be more reliable to determine the fractal reaction dimension for each separate batch of particles. It is the purpose of this report to show that the calcula-

tion of D_R can be achieved directly from a dissolution run utilizing particles of a given size. This calculation does not require knowledge of either the surface or the radius of the particles and it is based on the assumption that the mass of the particles is related to the cube of the radius.

2. Theoretical

Eqs. 1 and 2 can be written more conveniently as Eqs. 4 and 5, respectively:

$$w^{-a} - w_0^{-a} = akt \quad (4)$$

$$w_0^b - w^b = bw_e kt \quad (5)$$

where $a = D_R/3$ and $b = (3 - D_R)/3$. As can be seen from Eqs. 4 and 5, on plotting the values of the left-hand side against time t , one can obtain the value of k from the slope of the straight line. In practice, this involves choosing a starting value for the fractal reaction dimension, D_R , e.g. 2 and, using an iterative method, searching for the linearity demanded by Eqs. 4 and 5 for the experimental data pairs (w, t) . When this has been found, one knows both values for k and D_R .

For this purpose a computer program in BASIC was constructed. The program requires the values of w_0 and w_e (only when Eq. 5 is used), an initial estimate and the range of values for D_R , and the experimental data pairs (w, t) . The program searches for the D_R value that best satisfies the linearity demanded by Eqs. 4 and 5, optimising the minimisation of SS (sum of squared discrepancies between the observed values and the values given by the model). At each iteration a new D_R value is selected using a step which is shortened as D_R approaches its optimum value. The program can be obtained from the authors upon request.

Simulation studies. Simulated data, both error-free and erroneous, were used to evaluate the proposed method. Error-free simulated data (w) were generated according to Eqs. 1 and 2, for various D_R values (1.7, 2.3, 2.5, 2.7) while the values 100 and 1000 were assigned for w_0 and w_e , respectively. The range of the independent vari-

able (t) values was also assigned. It was 0–100 in the case of Eq. 1 which describes the dissolution process when carried out under conditions which are allowed to develop up to saturation, and 0–10 in the case of Eq. 2, which adheres to sink conditions.

Erroneous simulated data, with various degrees of error, were generated by adding to each error-free w -value a pseudorandom normal variate of mean zero and relative standard deviation equal to 1–10% of the error-free value. Both error-free and erroneous simulated data were analysed according to the proposed method.

In order to get an idea about the deviation from linearity of the Hixson-Crowell plots when $D_R \neq 2$, the simulated error-free data (w, t) were also used for the construction of conventional Hixson-Crowell plots.

Dissolution studies. The proposed method was further applied to experimental dissolution data taken from the literature (Nobuyoshi and Nobutoshi, 1974; Carstensen and Mahendra, 1975). Both studies deal with the effect of particle size on the dissolution rate of sulfonamides (Nobuyoshi and Nobutoshi, 1974) and oxalic acid (Carstensen and Mahendra, 1975).

3. Results and discussion

Simulation studies. Figs. 1A and 1B are graphical representations of Eqs. 4 and 5, respectively, for error-free simulated data treated according to the proposed method. The y -values for each time point in Figs. 1A and 1B are based on the estimate for D_R derived from the computer analysis of data. In all cases, the calculated and theoretical D_R values were found to be identical. The estimated values for k were also almost identical to the theoretical value (1×10^{-3}), while the correlation coefficient is very close to unity in all cases studied.

The results from the analysis of erroneous simulated data according to Eqs. 4 and 5 are shown graphically in Fig. 2. Fig. 2A represents the dependence of the estimates for D_R and k on the percent error of data resembling the general case of the entire course of dissolution (Eq. 4).

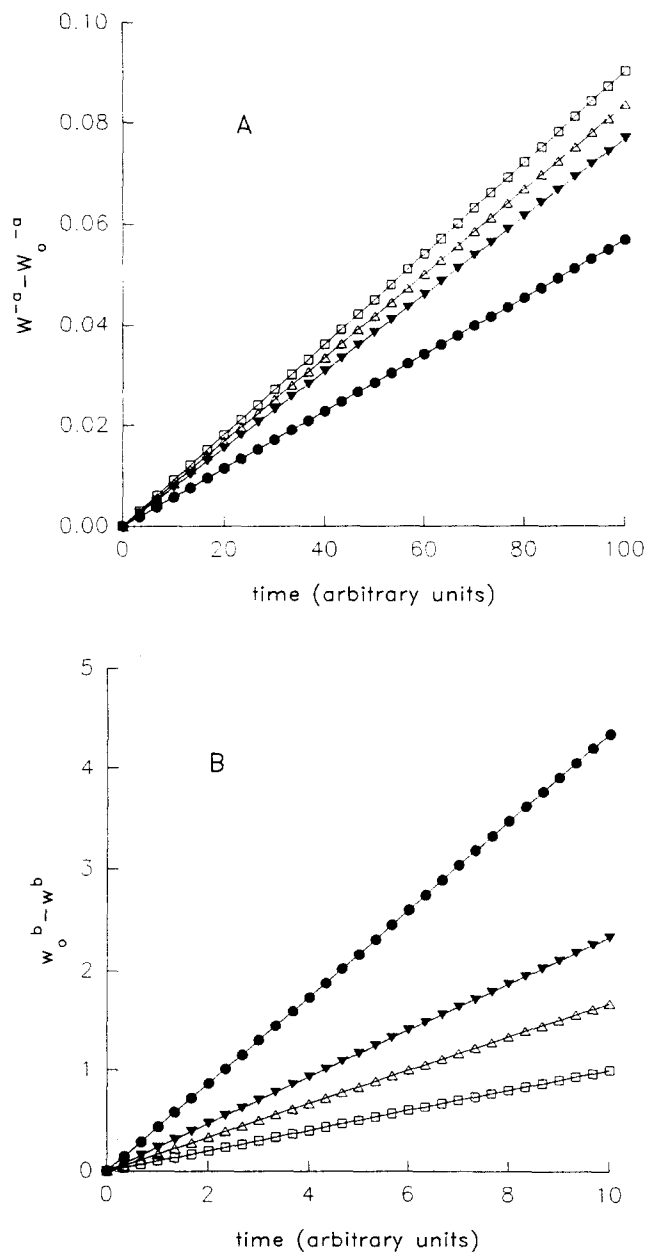


Fig. 1. Graphical representations of (A) Eq. 4 and (B) Eq. 5 for error-free simulated data treated according to the proposed method. The calculated and theoretical D_R and k -values were found to be identical ($k_{\text{theoretical}} = 1 \times 10^{-3}$). Key: (●) $D_R = 1.7$; (▼) $D_R = 2.3$; (△) $D_R = 2.5$; (□) $D_R = 2.7$.

The almost zero slope of the graph reflects the ability of the proposed method to give valid estimates of the parameters under conditions of experimental error. A similar plot for erroneous simulated data resembling dissolution under sink conditions is shown in Fig. 2B. The larger scatter-

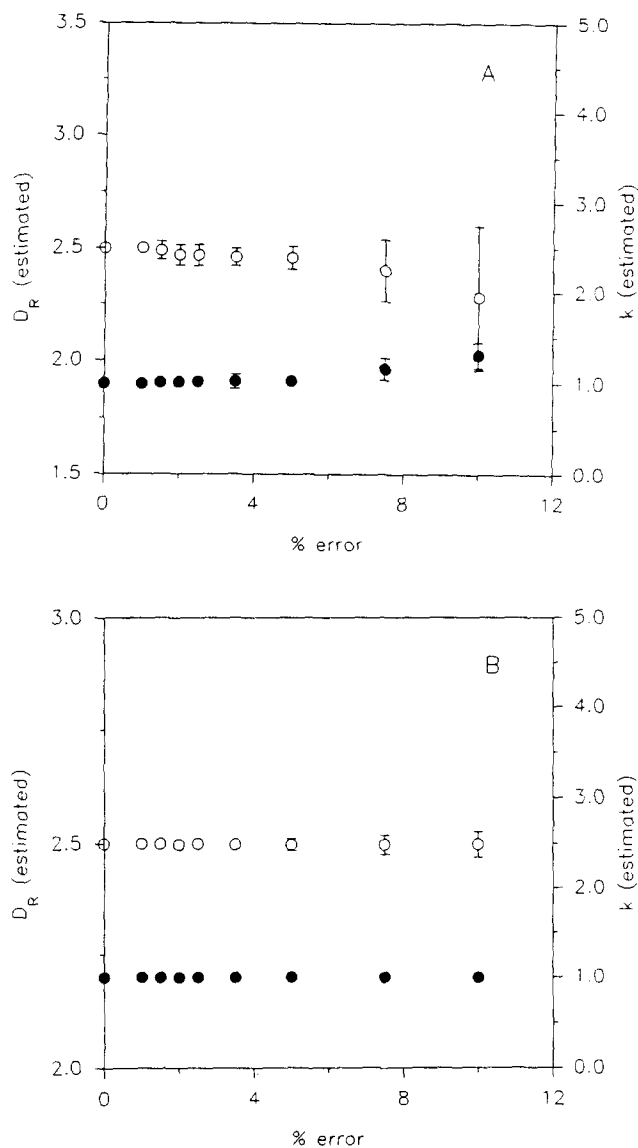


Fig. 2. Dependence of the estimates for D_R and k on the percent error of data resembling: (A) the general case of the entire course of dissolution (Eq. 4); (B) dissolution under sink conditions (Eq. 5). Key: (○) D_R ; (●) k .

ing of the parameter estimates in Fig. 2A than in Fig. 2B originates, probably, from different propagation of error between Eqs. 4 and 5, since the error added on the values of the dependent variable, w , is the same in both cases.

Figs. 3A and 3B are graphical representations of the Hixson-Crowell equations for the same error-free simulated data. It should be recalled that Eqs. 4 and 5 collapse to the Hixson-Crowell equations by substituting $D_R = 2$. The degree of deviation of the graph from linearity becomes

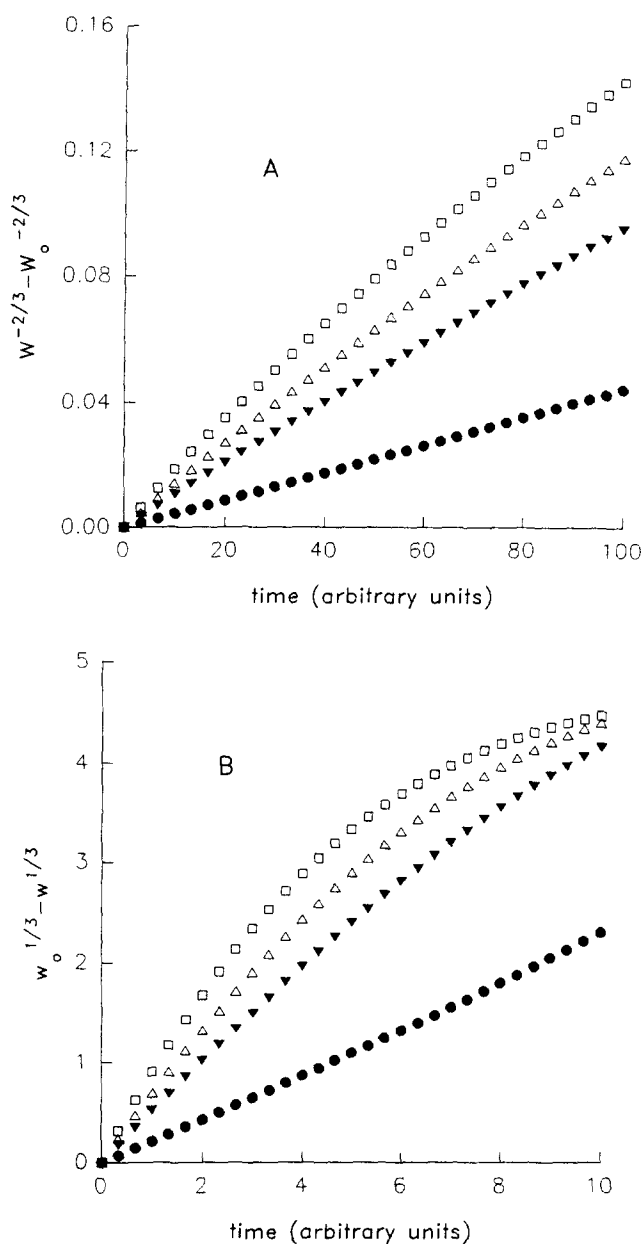


Fig. 3. Graphical representations of the Hixson-Crowell equations for error-free simulated data resembling: (A) the general case of the entire course of dissolution; (B) dissolution under sink conditions, when $D_R \neq 2$. Key: (●) $D_R = 1.7$; (▼) $D_R = 2.3$; (△) $D_R = 2.5$; (□) $D_R = 2.7$.

more pronounced as the value of D_R deviates from 2. The more intense deviation from linearity is observed in cases of dissolution under sink conditions (Eq. 5). This is associated with the value of the exponent of the dependent variable. For a given D_R value, the relative deviation of the exponent $b = (3 - D_R)/3$ in Eq. 5 from the

value of $1/3$ is greater than that of the exponent $a = D_R/3$ in Eq. 4 from the value of $2/3$.

Dissolution studies. Nobuyoshi and Nobutoshi (1974) have studied the effect of particle size on the dissolution rate of sulphadiazine. A re-analysis of their data was performed utilizing our proposed method. The results are shown in Fig. 4. The estimates for D_R were found to be 2.09, 1.97 and 1.90 (mean 1.99 ± 0.1) for the drug particle sizes 132, 186 and 332 μm , respectively. In all cases, a smooth surface is revealed since the dimension of the surface is ≈ 2 . However, this observation is not unexpected if one takes into account the linear Hixson-Crowell plots reported by the authors (Nobuyoshi and Nobutoshi, 1974) in conjunction with the results presented in Fig. 3. Thus, dissolution occurs only at the outer exposed regions of the drug crystal since only the outer portions of the drug surface are accessible to the solvent molecules.

The second set of experimental data concerns the dissolution of oxalic acid dihydrate crystals of log-normal particle-size distribution (Carstensen and Mahendra, 1975). The authors found a biphasic Hixson-Crowell plot with an initial linear part up to a critical time t_c which corresponds to

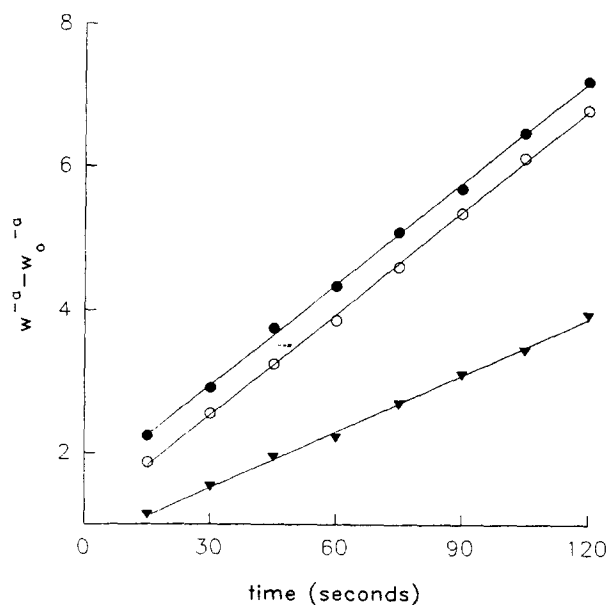


Fig. 4. Graphical representation of Eq. 4 for data taken from Nobuyoshi and Nobutoshi (1974), reanalysed according to the proposed method. Key: particle size (○) 132 μm ; (●) 186 μm ; (▼) 332 μm .

the dissolution of the particles of the smallest diameter. Beyond this point, the cube root plot changes slope. The analysis of the data according to the proposed method, using Eq. 5, was performed by segmenting the data as suggested in the study (Carstensen and Mahendra, 1975). The first four points, which correspond to the dissolution of the smallest particles were analyzed separately from the last five points which correspond to the dissolution of the particles with the greater diameter. For the first four points a value of D_R equal to 3.0 was determined, while for the last five points the estimate for D_R was found to be 2.16. The results obtained are shown in Fig. 5.

The value of D_R for the smallest particles, 3.0, indicates that dissolution occurs at equal rates from all the bulk of the particles (Farin and Avnir, 1992). According to Farin and Avnir (1992) the first-order decay equation:

$$-\frac{dw}{dt} = kw_e w \quad (6)$$

is obtained from the fractal form of the Noyes-

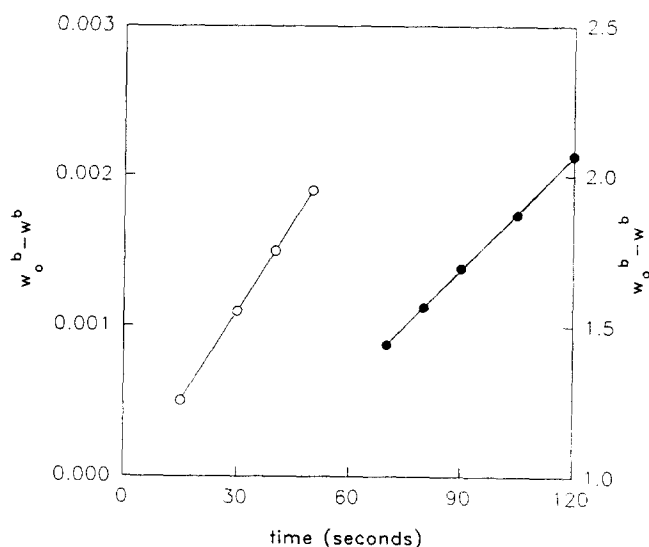


Fig. 5. Graphical representation of Eq. 5 for data taken from Carstensen and Mahendra (1975), reanalysed according to the proposed method, segmented as suggested by the authors. Key: (○) analysis of the first four points (left-hand side ordinate), which correspond to the dissolution of the smallest particles and (●) analysis of the last five points (right-hand side ordinate) which correspond to the dissolution of the particles with the greater diameter.

Whitney equation adhering to dissolution under sink conditions (Farin and Avnir, 1992):

$$-\frac{dw}{dt} = kw_e w^{D_R/3} \quad (7)$$

after substitution for $D_R = 3$. The estimate for $D_R = 3.0$ for the dissolution of the smallest particles of the oxalic acid dihydrate powder fits nicely to the above interpretation. It should be mentioned, however, that the Hixson-Crowell plot for $D_R = 3$ is not linear (see Fig. 3). This discrepancy is attributed to the fact that the four data points correspond to the initial part of the curved Hixson-Crowell plot when $D_R = 3$.

The value for D_R , 2.16, estimated from the analysis of the last five data points, could be related with the value of the surface fractal dimension, D , of the greater particles of the oxalic acid powder. Since the whole spectrum of relation between D and D_R is possible (Avnir, 1994) and the value of D is not known, it is rather difficult to distinguish between a $D_R < D$, a $D_R > D$ or a $D_R = D$ case. However, a $D_R < D$ case seems to be unlikely to occur since oxalic acid is not a sparingly soluble substance (Farin and Avnir, 1992). If this is a valid hypothesis then it is more reasonable to argue that a $D_R \approx D$ case operates. In fact, the estimated value for D_R , 2.16, is quite close to 2, and indicates a classical Wenzel's law situation where all surface oxalic acid molecules participate in the dissolution process. On the other hand, special circumstances may yield $D_R > D$ (Farin and Avnir, 1987; Avnir, 1994). If this is the case, then the determined D_R value indicates roughening of the substance surface characterized by cracks, defects and narrow pores.

In conclusion, the present approach adds to the conventional analysis based on Hixson-Crowell plots. Thus, non linear Hixson-Crowell plots can be explained on the basis of surface irregularity as shown in Fig. 3, while an estimate for D_R can be obtained from a single set of experimental dissolution data utilising a simple computer program. The knowledge of D_R , if coupled with an estimate for D , can provide information on the mechanism of dissolution of drugs. It is hoped that the present approach of the estimation of D_R

will facilitate the application of fractal geometry (Farin and Avnir, 1992; Avnir, 1994) to dissolution studies.

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