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# Use of fractal geometry on the characterization of particles morphology: Application to the diclofenac hydroxyethylpirrolidine salt

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**Abstract**

This paper describes the use of fractal geometry in the study of the morphology and the dissolution behavior of diclofenac-hydroxyethylpyrrolidine salt. Using an image analysis system based on Fourier analysis of contours, size and shape descriptors characterizing the particle were determined. Fractal dimension ($D$) using the Richardson plot and reactive dimension ($D_R$) were also evaluated. The relation found between $D$ and $D_R$ reflects a dissolution process strongly influenced by the size particle. Furthermore, the efficiency of the dissolution process can be increased by controlling the geometrical parameters of the salt.

*Key words:* Fractal geometry; Size and shape descriptors; Surface geometry; Fractal dimension; Reactive dimension

## 1. Introduction

The dissolution properties of a drug are decisive in determining its bioavailability. It has commonly been believed that only substances in the molecularly dispersed form, i.e., in solution, are transported across the intestinal wall and absorbed into the systemic circulation. It has been observed that the rate of absorption of many slightly soluble drugs from gastro-intestinal tract is limited by the rate of dissolution of the drug substance. Therefore, the particle size of a drug is important, if the substance in question has a low solubility (Florence and Attwood, 1988).

In addition to this factor, the dissolution process is determined by a variety of other properties of the drug particles such as surface morphology, degree of porosity, surface area, particle shape and diffusion constant of the dissolved material. On the other hand, the degree of surface irregularity and roughness can produce some effects on

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the dissolution rate of drugs (Farin and Avnir, 1992).

It is known that fractal geometry is a mathematical tool used to describe the surface morphology and the degree of surface irregularity of a particle (Mandelbrot, 1984). The fractal concept of Mandelbrot describes the surface of particles in terms of 'fractal surface', with a characteristic parameter referred to as the fractal dimension ($D$). Fractal analysis relies on the fact that the perimeter of a silhouette edge is dependent on the step length with which we measure it. Thus, the smaller the step length, the larger is the perimeter measured, because more details of the structure are taken into account (Thibert et al., 1988). So, the fractal dimension of particle contours is used to characterize the surface roughness. This relationship is given by Mandelbrot's classical expression (Mandelbrot, 1984):

$$L_\delta = k \cdot \delta^{1-D}$$

where $D$ is the fractal dimension, $\delta$ denotes the step length and $L_\delta$ is the perimeter estimated with step length $\delta$. An ideal fractal structure should produce a linear plot at all resolutions, when ln $L_\delta$ is plotted against ln $\delta$. The slope of this straight line is $S$, where $S = 1 - D$ (Thibert et al., 1988). $D$ is the fractal dimension and represents the degree of irregularity of the particle surface. The more irregular and wiggly a substance is, the higher the value of $D$ (Farin and Avnir, 1987).

As has been indicated above, the parameter $D$ reflects the morphology of the particle surface, but this surface need not coincide with the reactive surface which participates actively in the dissolution process (Avnir et al., 1984). To distinguish between the total geometric morphology of the surface, represented by $D$, and the morphology of the active surface, another parameter designated the reactive dimension and denoted by $D_R$ is considered.

The method used to calculate $D_R$ is based on the very old Wenzel law (Kopelman, 1989). Generally, this law establishes that the larger the particle surface, the highest dissolution rate is:

$$v = R^{D_R - 3}$$

where $D_R$ is the reactive dimension, $v$ denotes the dissolution rate and $R$ is the particle size. Analogously, $D_R$ can be calculated plotting ln $v$ vs ln $R$.

Useful information on dissolution processes can be obtained if $D_R$ can be elucidated and, furthermore, if it is possible to compare both types of dimensions, $D$ and $D_R$. Commonly, the surface area of the particle is used as a characterizing parameter for pharmaceutical powders. However, bioavailability considerations seem to suggest that the reactive surface, described by $D_R$, is of greater relevance (Farin and Avnir, 1987). The concept of fractal dimension for reactivity is thus a useful means of quantifying with a single parameter a set of properties that are very difficult to quantify separately.

The particular purpose of this work was to apply fractal analysis to the diclofenac-hydroxyethylpirrolidine salt and to correlate the fractal dimension ($D$) and the reactive dimension ($D_R$) with the shape parameters obtained by scanning electron microscopy and with the dissolution behavior. Furthermore, it was of interest to determine the relation between both dimensions, since it can reflect the mechanism of the dissolution process.

From a review of the literature, only a few applications of fractal geometry to the study of drugs have been found (Avnir et al., 1984; Kocova et al., 1993). Nevertheless, some investigations about this subject have been developed using excipients and other substances (Bergeron et al., 1986; Thibert et al., 1988; Ramadan and Tawashi, 1991; Cartilier and Tawashi, 1993). For this reason, we consider it particularly interesting to characterize solid drugs based on the analysis of individual particles and quantifying the particle shape due to the need of the pharmaceutical industry to find methods for rapidly characterizing and validation solid drugs (Bergeron et al., 1986).

In previous papers (Fini et al., 1991, 1992), we have reported that the diclofenac-hydroxyethylpirrolidine salt (Fig. 1) is more soluble and dissolves more rapidly than the corresponding diclofenac free acid and sodium forms. On the other hand, we have recently verified in a prefor-

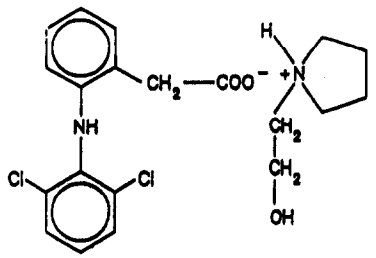

Fig. 1. Physicochemical properties of diclofenac-hydroxyethylpyrrolidine salt: molecular weight = 411.32, melting point = 101–102°C, solubility (25°C) = 18.92 mg/ml, partition coefficient = 8.32.

mulation program that this salt presents the best physicochemical characteristics in comparison with other counterions, either inorganic cations or organic bases (Fernández-Hervás, 1993).

## 2. Experimental

### 2.1. Materials

The salt used in this investigation, diclofenac-hydroxyethylpyrrolidine (DHEP), was a gift from IBSA (Lugano, Switzerland).

### 2.2. Scanning electron microscopy

The shape and size of salt particles were examined using a scanning electron microscope (Philips, XL30). A very thin coat of carbon was applied to each sample, which was examined at different magnifications and a number of micrographs were taken of each sample.

### 2.3. Image analysis

Size and shape analysis of the solids was carried out using an image analysis system based on Fourier descriptors. They are obtained using a special computer program which is based on obtaining the coordinates $(x,y)$ of the particle boundary through the digitization of the particle image. The coordinates are then used to calculate a set of invariant shape descriptors.

Table 1
Parameters obtained by using Fourier contour analysis and fractal analysis techniques

| Technique | Characteristic | Parameter | Symbol |
|---|---|---|---|
| Fourier contour analysis | size | diameter | $d$ |
| | | area | $A$ |
| | | perimeter | $P$ |
| | | equivalent circle diameter | ECD |
| | shape | shape factor | $S$ |
| | | maximum horizontal distance | $X_{max}$ |
| | | maximum vertical distance | $Y_{max}$ |
| | | aspect ratio | $a$ |
| | | projection $X$ | Proj $X$ |
| | | projection $Y$ | Proj $Y$ |
| Fractal analysis | surface geometry | fractal dimension | $D$ |

Table 1 lists the information obtained in terms of size (mean diameter, area, perimeter and equivalent circle diameter) and shape parameters (shape factor, maximum horizontal distance, maximum vertical distance, aspect ratio, projection in the horizontal direction and projection in the vertical direction) that describe the micromorphology of isolated particles.

#### 2.3.1. Equivalent circle diameter (ECD)

This parameter is the diameter of the circle that has an area equal to that of the particle:

$$\text{ECD} = 2 \cdot \sqrt{(\text{area}/\pi)}$$

#### 2.3.2. Shape factor

The shape factor provides information about the elongation of the particle. For a circular particle the shape factor is unity, while for all other particles the shape factor is lower than 1:

$$\text{Shape factor} = 4\pi\left[\text{area}/(\text{perimeter})^2\right]$$

#### 2.3.3. Maximum horizontal and vertical distances

These refer to the maximum horizontal and vertical distances between two points on the boundary of the particle on horizontal and vertical lines, respectively.

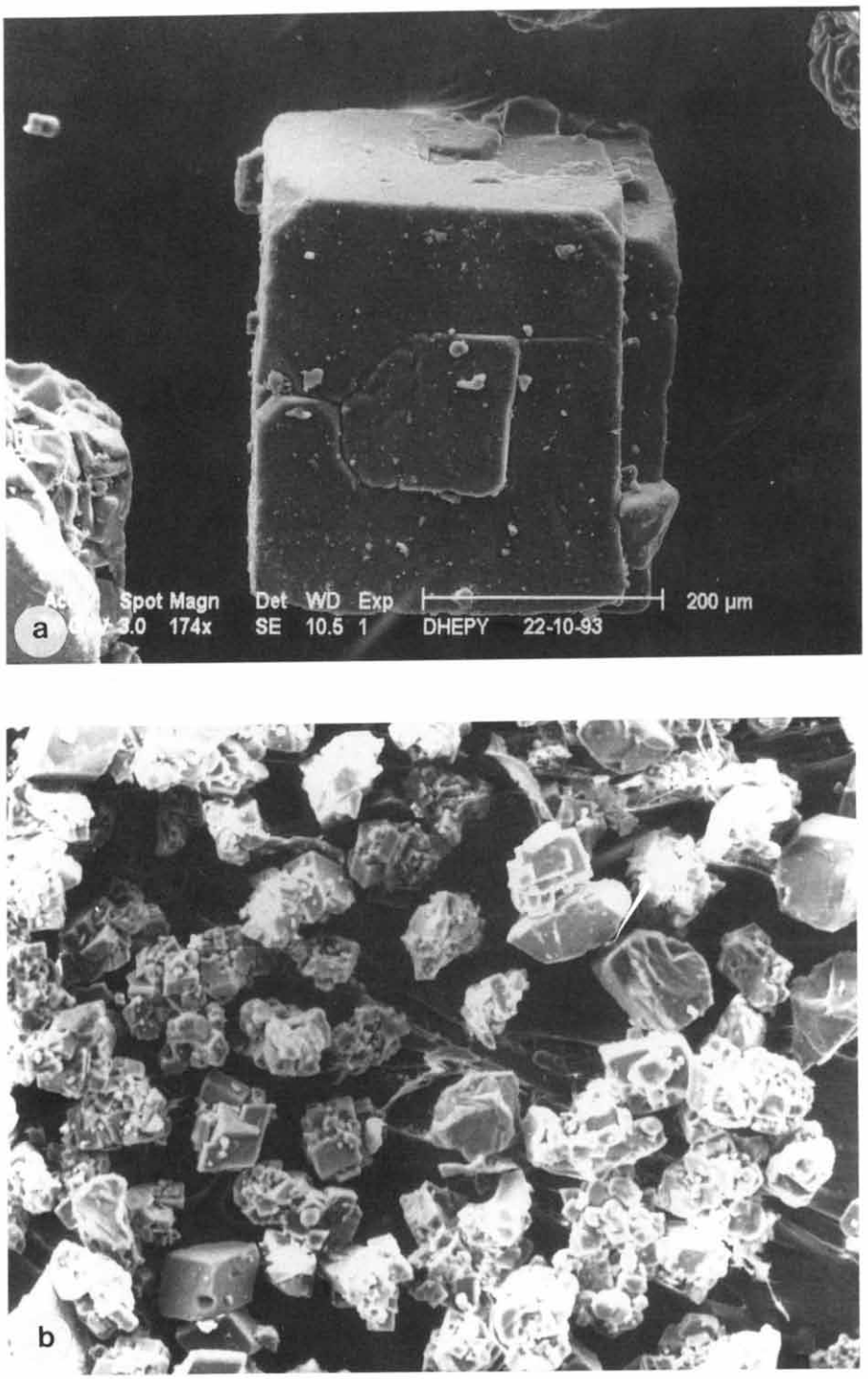


Fig. 2. Scanning electron micrographs of: (a) DHEP, 250–300 $\mu$m; (b) DHEP, 175–200 $\mu$m.

*2.3.4. Aspect ratio*

The aspect ratio is the ratio of the horizontal maximum and vertical maximum distances of the particle. For a round or a square particle, the aspect ratio is unity. For those elongated in the $x$-direction the ratio is larger than unity. Particles elongated in the $y$-direction have an aspect ratio lower than unity.

*2.3.5. Projections in the horizontal and vertical direction*

These parameters are the maximum distances (the range) of all boundary points projected onto the $x$- and $y$-axes, respectively.

*2.4. Fractal analysis*

The fractal dimension of a particle contour was calculated from the slope of the Richardson plot (ln of perimeter length vs ln of step length) as indicated above (Thibert et al., 1988; Ramadan and Tawashi, 1991).

To calculate the reactive dimension of DHEP, the following six fractions were obtained by sieving (Retsch, type Vibro): 250–300, 200–250, 175–200, 125–175, 100–125 and 75–100 $\mu$m. Each sample was subjected to a dissolution assay in the USP XXII basket apparatus (Turu Grau, model D-6), using 500 ml of purified water at 37 ± 0.5°C. The rotational speed was kept constant at 50 rpm. 2 ml samples were withdrawn at various time intervals and analyzed, without dilution, using a UV spectrophotometer (Hitachi, model U-2000) ($\lambda$ = 276 nm). Once the dissolution profiles had been obtained, the amodelistic parameter, dissolution efficiency ($E_d$) (Salvado et al., 1987), was then calculated for each fraction. The reactive dimension was calculated from the slope of the plot of ln $E_d$ vs ln size particle.

## 3. Results and discussion

As an example, Fig. 2 shows SEM micrographs illustrating the shape and surface of different sieve fractions of DHEP. Smooth surfaces in the single particles are evident.

Table 2
Size parameters of DHEP particles

| Number of particle | $A$ ($\mu m^2$) | $P$ ($\mu$m) | ECD ($\mu$m) | $d$ ($\mu$m) |
|---|---|---|---|---|
| 1 | 25769.06 | 675.18 | 181.14 | 199.01 |
| 2 | 24989.99 | 685.47 | 178.38 | 183.30 |
| 3 | 28945.24 | 688.44 | 191.97 | 204.51 |
| 4 | 28615.64 | 705.64 | 190.88 | 210.49 |
| 5 | 26188.55 | 688.71 | 182.60 | 185.53 |
| 6 | 27686.76 | 617.41 | 187.75 | 187.23 |
| 7 | 28046.32 | 754.47 | 188.97 | 197.43 |
| 8 | 26338.37 | 686.88 | 183.13 | 195.80 |
| 9 | 29784.24 | 676.86 | 194.74 | 199.43 |
| 10 | 25739.09 | 786.03 | 181.03 | 185.91 |
| 11 | 23761.47 | 626.59 | 173.94 | 192.77 |
| 12 | 23821.40 | 690.29 | 174.16 | 179.09 |

To determine the size and shape characteristics and the fractal dimension of DHEP, the 175–200 $\mu$m sieve fraction was used. The assay was carried out employing 12 particles.

The size characteristics of the samples are listed in Table 2. Table 3 lists the shape characteristics of DHEP obtained.

The aspect ratio (Table 3) yields values close to unity, since the lengths of the crystal edges are similar, being evident in the cubic structure of the salt particles shown by the SEM pictures. The mean value obtained for the aspect ratio was 1.006 (standard error = 0.089), indicative of reduced deviation from the perfect shape of a cube. This circumstance is also demonstrated with the data corresponding to the $x$ and $y$ projections in

Table 3
Shape descriptors of DHEP particles

| Number of particles | $X_{max}$ ($\mu$m) | $Y_{max}$ ($\mu$m) | $a$ | Proj $X$ ($\mu$m) | Proj $Y$ ($\mu$m) | $S$ |
|---|---|---|---|---|---|---|
| 1 | 163.65 | 235.83 | 0.69 | 169.49 | 251.21 | 0.71 |
| 2 | 169.49 | 205.07 | 0.83 | 175.54 | 215.33 | 0.67 |
| 3 | 157.80 | 235.83 | 0.67 | 157.80 | 251.21 | 0.77 |
| 4 | 169.49 | 225.58 | 0.75 | 192.87 | 235.83 | 0.72 |
| 5 | 204.56 | 184.57 | 1.11 | 216.25 | 189.69 | 0.69 |
| 6 | 181.18 | 184.57 | 0.98 | 192.87 | 194.82 | 0.91 |
| 7 | 210.40 | 210.20 | 1.00 | 216.25 | 215.33 | 0.62 |
| 8 | 233.78 | 153.80 | 1.52 | 245.47 | 184.57 | 0.70 |
| 9 | 210.40 | 174.51 | 1.21 | 210.40 | 210.20 | 0.82 |
| 10 | 239.63 | 169.18 | 1.42 | 239.63 | 174.31 | 0.52 |
| 11 | 146.11 | 220.45 | 0.66 | 181.18 | 220.45 | 0.76 |
| 12 | 204.56 | 153.80 | 1.33 | 204.56 | 158.93 | 0.63 |

Table 4
Study of correlation between shape parameters (in all cases, $n = 12$)

| | |
|---|---|
| Proj $X = -0.68724$ Proj $Y + 343.459$ | $r = 0.7407$<br>$F = 12.1525$<br>$P = 0.0059$ |
| Proj $X = 0.83703 X_{max} + 41.0045$ | $r = 0.9374$<br>$F = 72.4322$<br>$P < 0.0001$ |
| Proj $X = -0.710527 Y_{max} + 339.510$ | $r = 0.7886$<br>$F = 16.4505$<br>$P = 0.0023$ |
| Proj $Y = -0.702874 X_{max} + 30.6784$ | $r = 0.7333$<br>$F = 11.6311$<br>$P < 0.0001$ |
| Proj $Y = 0.906743 Y_{max} + 30.6784$ | $r = 0.9338$<br>$F = 68.1375$<br>$P < 0.0001$ |
| $Y_{max} = -0.804738 X_{max} + 349.740$ | $r = 0.8152$<br>$F = 19.8121$<br>$P = 0.0012$ |

comparison with the maximum $x$ and maximum $y$ values obtained.

The shape factor parameter is used to measure object complexity, namely, contour complexity (Ramadan and Tawashi, 1991). The shape factor data obtained for the analyzed particles yielded values less than unity, demonstrating little variation in the particles' silhouette.

Table 4 lists the most important correlation parameters obtained in this study. On the basis of the results obtained, we can conclude that a close correlation between the shape parameters has been found, revealing useful information about the shape of these salt particles.

### 3.1. Fractal contour analysis

The fractal dimension calculated from the slope of the Richardson plot was 1.14 (see Table 5) as shown in Fig. 3. To calculate the fractal dimension of the surface ($D_s$), the approximation proposed by Farin and Avnir (1992) is used. In this case, $D_s = D_l + 1$ and then $D_s$ yields a value of 2.14. The degree of irregularity is given by $D$, the result obtained indicating a small rugged particle, as $D_s$ is between 2 and 3 (Thibert et al., 1988). In relation to this concept, Farin and Avnir (1989) state that $D \approx 2$ refers to the classical assumption of smooth and flat areas of the particles.

Table 5
Regression parameters obtained in the $D$ study

Coefficient of determination: 0.9125
Multiple correlation coefficient: 0.9552
Estimated constant term: 7.5564
Standard error of estimate: 0.06313

| Source of variance | D.F. | Sum of squares | Mean of squares | $F$ test | Probability |
|---|---|---|---|---|---|
| Regression | 1 | 0.166295 | 0.166295 | 41.7186 | 0.0030 |
| Residuals | 4 | 0.015944 | 0.003986 | | |
| Total | 5 | 0.182240 | | | |

Regression coefficient −0.1357
Standard coefficient −0.9552
Standard error 0.02100
$T$ −6.4590
Probability 0.0030

All the results are in agreement with the shape parameters and SEM pictures indicated above. Therefore, it clearly appears that fractal analysis is a useful tool for not only characterizing the irregularity of the surfaces, but also for correlating this fractal parameter with the physical description of pharmaceutical solids. The size and shape descriptors obtained above, in combination with the fractal dimension, will provide preformulation assays with a solid technique for the appro-

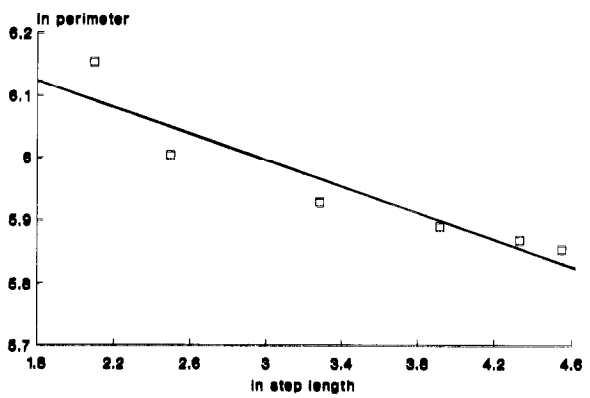


Fig. 3. Plot of ln of the perimeter as a function of ln of the step length.

Table 6
Regression parameters obtained in the $D_R$ study

Coefficient of determination 0.8052
Estimated constant term 5.0915
Multiple correlation coefficient 0.8973
Standard error of eststimate 0.05292

| Source of variance | D.F. | Sum of squares | Mean of squares | $F$ test | Probability |
|---|---|---|---|---|---|
| Regression | 1 | 0.046299 | 0.046299 | 16.5300 | 0.0153 |
| Residuals | 4 | 0.011204 | 0.002801 | | |
| Total | 5 | 0.057504 | | | |

Regression coefficient −0.2359
Standard coefficient −0.8973
Standard error 0.05802
$T$ −4.0657
Probability 0.0153

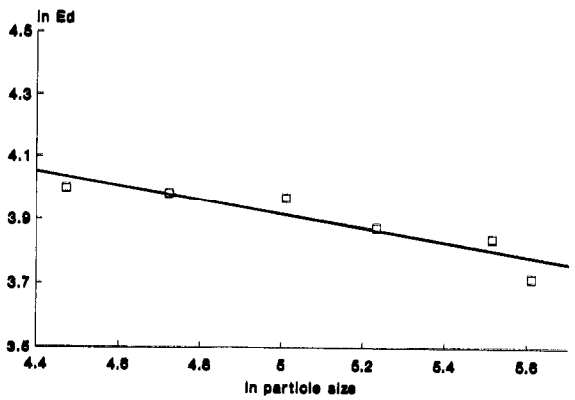


Fig. 4. Plot of ln of $E_d$ as a function of ln of particle size.

priate selection of materials and for the detection of undesirable properties related to shape-surface characteristics.

As indicated above, to calculate $D_R$ different granulometric fractions were selected. The same morphology of the salt particles has been observed (Fig. 2), hence, it is possible to affirm that, in this case, the basic property of self-similarity of fractal objects is evident. This symmetry feature indicates that upon determined technological transformations of the system (milling, size reduction), the surface geometric irregularities do not change and the system is invariant (Pfeifer and Obert, 1989).

By the other hand, the value obtained for $D_R$ was 2.76 (see Table 6) as shown in Fig. 4. As demonstrated above, $D_R$ can be interpreted as the effective fractal dimension of a particle towards the dissolution process. The result $D_R > D$ reveals that, in spite of the smooth surfaces presented by the salt particles, there are reactive surface sites which have been manifested during the dissolution process. The differences found between both type of $D$ would involve a great variability in the geometric surface in comparison to the reactive surface. We believe that this circumstance is due to the fact that the particles are constituted by an agglomeration of cubes and, then, there are fissures and cracks which compose the boundary particle which cannot be measured by the Richardson method. Therefore, the 'real' surface exposed to the dissolution medium can be considered more irregular than that offered by a single particle.

With respect to the relation $D_R > D$, Farin and Avnir (1987) suggest that this phenomenon can be governed by either roughening or trapping effects. In the first case, the morphology of the surface may change during the dissolution process. In the second, reactive sites may be trapped in cracks and narrows pores. This last event is not considered in this case, because DHEP particles do not present porous surfaces as shown by the SEM pictures.

Consequently, to study this particular situation, $D_R$ was calculated at predetermined time periods. Table 7 lists the $D_R$ values obtained at 10, 20, 30, 40 and 120 min, the reactive surface morphology remaining constant during the assay at either the beginning or ending of the dissolution process. In relation to these results, it is possible to affirm that the dissolution behavior of DHEP cannot be related to the roughening phenomenon because the reactive surface offered to

Table 7
$D_R$ values obtained as a function of time

| Time (min) | $D_R$ | $F$ | $p$ |
|---|---|---|---|
| 10 | 2.74 ± 0.053 | 22.697 | 0.0089 |
| 20 | 2.75 ± 0.058 | 17.792 | 0.0135 |
| 30 | 2.76 ± 0.064 | 13.433 | 0.0215 |
| 40 | 2.76 ± 0.057 | 17.770 | 0.0135 |
| 120 | 2.76 ± 0.058 | 16.530 | 0.0153 |

the dissolution medium changes in magnitude but not in morphology. Thus, surface-reaction dissolution produced surface fractals.

From the above, the results of this study suggest that shape descriptors and fractal dimensions ($D$ and $D_R$), depicting the morphological and surface characteristics of an object, could be used for the description of the particle surface geometry and of the identification of different behaviors during dissolution processes.

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