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Characterization of modified paracetamol by means of SEM and fractal analysis

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Abstract

The morphological and surface characteristics of paracetamol and modified paracetamol particles are investigated in order to continue using scanning electronic microscopy (SEM) descriptors and fractal dimensions to characterize powder particles. The coating materials were different acrylic resins type Eudragit®. The size and shape parameters of modified products indicated that the particles form deviated from elongated form becoming much more rounded powder particles. This circumstance implied an improvement in the flow properties of the products on the basis of the rheological parameters obtained. The fractal dimensions calculated from the slope of Richardson plots were comprised between 1.00 and 1.16 indicating that the coating treatment did not affect the roughness characteristics of paracetamol particles transforming only the final shape characteristics. Some interesting relationships among some SEM descriptors have been found.

Keywords: Flow properties; Fractal dimension; Modified paracetamol; Paracetamol; Size and shape descriptors; Surface geometry

1. Introduction

All too often characterization of raw materials and products has been centered on aspects of chemical purity, with only passing attention being given to the physical properties of the solid (Brittain et al., 1991). Fundamental characteristics of drug crystals such as particle size and morphological surface are known depending on the chemical composition and the method of preparation and handling (Ramadan and Tawashi, 1990).

The behavior of bulk solids is clearly influenced by shape and surface characteristics of the parti-

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cles integrating a powder. Several operations in pharmaceutical technology, such as pulverization, screening, granulation and/or drying, are also strongly influenced by the morphological structure of the solids components (Thibert et al., 1988). The effects of morphological particle features on flow properties of materials, packing of powders and biopharmaceutical characteristics of the formulations elaborated are widely known (Romero and Rhodes, 1991).

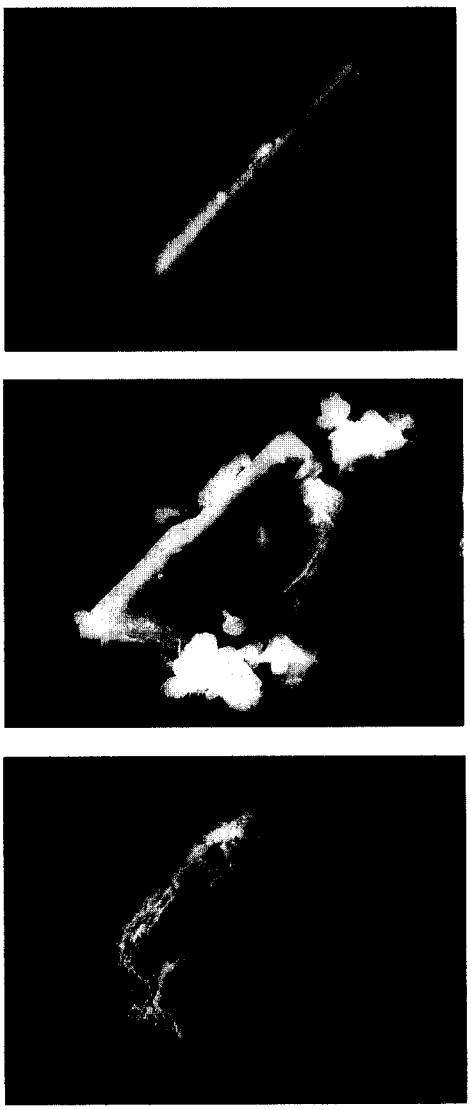

Fig. 1. Scanning electron micrographs of (a) commercial paracetamol; (b) modified paracetamol with Eudragit S 9%; and (c) modified paracetamol with Eudragit S 12%.

In a previous paper (Vela et al., 1995), we have described the rheological properties of paracetamol modified with different acrylic resins type Eudragit®. Paracetamol is a slightly water-soluble product with very poor flow and compressibility properties. A phase separation technique has allowed the poor flow properties and low compressibility of paracetamol to be changed, yielding a material, modified paracetamol, with improved flow properties. This modified paracetamol allowed the elaboration of tablets using a direct compression technique.

On the other hand, fractal geometry is a mathematical tool used to describe the surface morphology and the degree of surface irregularity of a particle (Mandelbrot, 1984; Graf, 1991). The fractal concept of Mandelbrot describes the surface of particles in terms of 'fractal surface', with a characteristic parameter named 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 is, the larger the perimeter measured is, 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):

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

where, D is the fractal dimension, δ is the step length and L_δ is the perimeter estimated with step length δ. An ideal fractal structure should pro-

Table 1
Size and shape descriptors of particles of commercial paracetamol

	Mean	e
A (μm^2)	646.59	104.32
P (μm)	142.61	10.95
S	0.39	0.033
D_{max} (μm)	59.27	4.52
D_{min} (μm)	31.75	3.59
a	1.92	0.19

Mean values and standard errors; $n = 20$.

Table 2
Size parameters and shape descriptors of particles of the indicated products

	6% E		9% E		12% E	
	Mean	e	Mean	e	Mean	e
A (mm^2)	20812.0	5499.7	17745.7	2421.7	9124.2	1841.4
P (mm)	947.035	112.366	855.258	72.009	614.05	84.621
S	0.267	0.018	0.324	0.043	0.317	0.031
D_{max} (mm)	242.337	30.082	229.868	20.068	201.03	41.577
D_{min} (mm)	145.129	16.961	140.304	10.421	102.14	10.207
a	1.553	0.102	1.639	0.154	1.654	0.166

Mean values and standard errors; $n = 20$.

duce a linear plot at all resolutions, when ln L_δ is plotted against ln δ. The slope of this straight line is S, where $S = 1 - D$. D is the fractal dimension and represents the degree of irregularity of the particle surface with a value between 1 and 2. The more irregular and wiggly a substance is, the higher the value of D is (Farin and Avnir, 1987). A complete and extensive review of the principal Fractal Geometry concepts and their applications in the pharmaceutical field has been recently realized (Fini et al., 1996).

In this study, a scanning electron microscope (SEM) connected to an image processor is used to obtain, automatically, a wide variety of parameters describing the shape and granulometric characteristics of the powder particles. This method offers numerous advantages over other methods (optical microscopy): automatic and more accurate measurements, saving a great amount of time and yielding into more reliable conclusions from the results with a smaller number of observations (Paraira et al., 1994).

So, the main purpose of this work is to describe the morphological characteristics of paracetamol and modified paracetamol with 6, 9 and 12% of different type of Eudragit® using a SEM technique and the fractal analysis to find a correlation among the fractal dimension (D), descriptors obtained by SEM and rheological properties of all these products. This study will ensure a better understanding, from a rigorous morphological point of view, of the improvement obtained in the rheological properties and the possibility of elaborating tablets by means of direct compression.

Recently, our research group has successfully applied the fractal analysis to the characterization of particles morphology of diclofenac–hydroxyethylpirrolidine (Fernández-Hervás et al., 1994; Fini et al., 1995; Holgado et al., 1995a) and modified lactoses (Holgado et al., 1995b). On the basis of these results, we consider it particularly interesting to characterize and quantify the particles shape of drugs and excipients due to the need of pharmaceutical industry to find methods for rapidly characterizing and validating solid products, especially when high speed automatized production chains are used (Bergeron et al., 1986; Ramadan and Tawashi, 1991).

2. Experimental procedures

2.1. Materials

Paracetamol (Acofarma, Tarrasa, Barcelona, Spain) was used as a model drug. Eudragit® E 12.5%, L 12.5% and S 12.5% (Industrias Sintéticas Curtex, Barcelona, Spain) were chosen as coating acrylic resins.

2.2. Paracetamol treatment

Paracetamol was treated at three different percentages (6, 9 and 12% w/w of dry substance) of the three indicated polymers, using a phase separation technique involving evaporation of the solvent present in the systems (Vela et al., 1995). Suspensions of paracetamol in ethanol were prepared and

Table 3
Size parameters and shape descriptors of particles of the indicated products

	6% L		9% L		12% L	
	Mean	e	Mean	e	Mean	e
A (mm^2)	1306.9	163.2	2911.2	220.08	46.58	1.377
P (mm)	164.15	13.72	236.16	10.972	353.7	42.83
S	0.6087	0.031	0.6505	0.0228	0.419	0.034
D_{max} (mm)	53.808	3.517	82.167	3.3036	121.7	17.1
D_{min} (mm)	37.664	3.131	56.679	2.7495	65.36	7.821
a	0.9106	0.068	1.015	0.0714	1.866	0.127

Mean values and standard errors; $n = 20$.

stirred in a magnetoagitator (SBS, Mod. A-06) for 5 min at a constant temperature of 40°C. Then the required volumes of each Eudragit® were added to obtain the desired coating proportions: 6, 9 and 12% of dry resin. Most of the solvent was removed by decreasing the pressure of the system using a water pump. Powders were dried in an oven at 45°C for 12 h. The resulting products were crushed until all the particles were smaller than 500 μm, selecting the 50–500 μm granulometric fraction.

2.3. Image processing system

The shape and size of paracetamol particles were examined using a SEM (Philips, XL30). A very thin coat of carbon was applied to each sample, which was examined at different magnification and some micrographs were taken of each sample.

Size and shape analysis of the solids was determined using an image analysis system connected to the microscope above mentioned. They are obtained, automatically, using a special computer program which is based on obtaining a pixel matrix of the particle boundary by the digitization of the particle image. This pixel matrix, allowing a spatial resolution expressed in micrometers, is then used to calculate a set of size and shape descriptors.

The following parameters were selected to describe the micromorphology of isolated particles: maximum and minimum diameters, area, perimeter, shape factor and aspect ratio.

2.3.1. Shape factor

It provides information about the elongation of the particle. For a circular particle, the shape factor is 1; for all other particles, the shape factor is smaller than 1.

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

Table 4
Size parameters and shape descriptors of particles of the indicated products

	6% S		9% S		12% S	
	Mean	e	Mean	e	Mean	e
A (mm^2)	40337.7	6482.20	4359.09	787.769	19822.6	2486.15
P (mm)	1103.29	131.621	294.627	26.9469	594.01	46.6497
S	0.4490	0.0580	5.9550	5.3385	0.6992	0.0302
D_{max} (mm)	309.109	27.1331	103.219	9.7153	206.378	14.2734
D_{min} (mm)	206.878	19.1700	69.3390	6.6210	140.987	10.1374
a	1.2610	0.1538	1.2590	0.1231	1.05583	0.11036

Mean values and standard errors; $n = 20$.

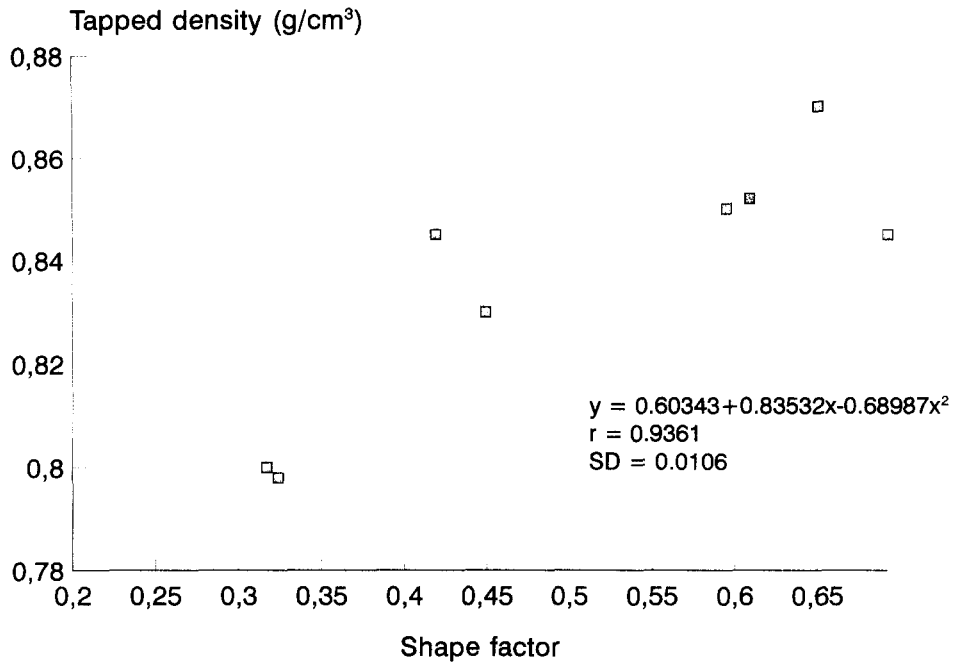

Fig. 2. Relationship between shape factor and tapped density.

2.3.2. Maximum horizontal and vertical diameters

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

2.3.3. Aspect ratio

The aspect ratio is the ratio of the horizontal maximum and the vertical maximum distance of the particle. For a round or a square particle, the aspect ratio is 1. For those elongated in the X direction the ratio is larger than 1. Particles elongated in the Y direction have an aspect ratio smaller than 1.

The assay were carried out employing 20 isolated particles.

2.4. Fractal analysis

The fractal dimension of a particle was calculated from the slope of the Richardson plot (ln of perimeter length vs. ln of step length) as has been indicated above (Thibert et al., 1988).

3. Results and discussion

3.1. Morphological analysis of paracetamol—rheological properties

As an example, Fig. 1 shows the SEM micrographs illustrating the shape and surface characteristics of commercial paracetamol (Fig. 1(a)) and an example of modified paracetamol with Eudragit® S 9% (Fig. 1(b)) and 12% (Fig. 1(c)).

The size characteristics and shape descriptors of the samples are shown in Tables 1–4. The rheological parameters have been previously reported (Vela et al., 1995). They showed that all the rheological parameters of the modified products have been improved by using the coating technique. Flow rate and angle of repose values could not be determined for commercial paracetamol because its rheological characteristics were very poor.

In relation to size parameters, great differences between commercial paracetamol and modified paracetamols are evident. For example, the values of D_{max} and D_{min} exhibited by commercial parac-

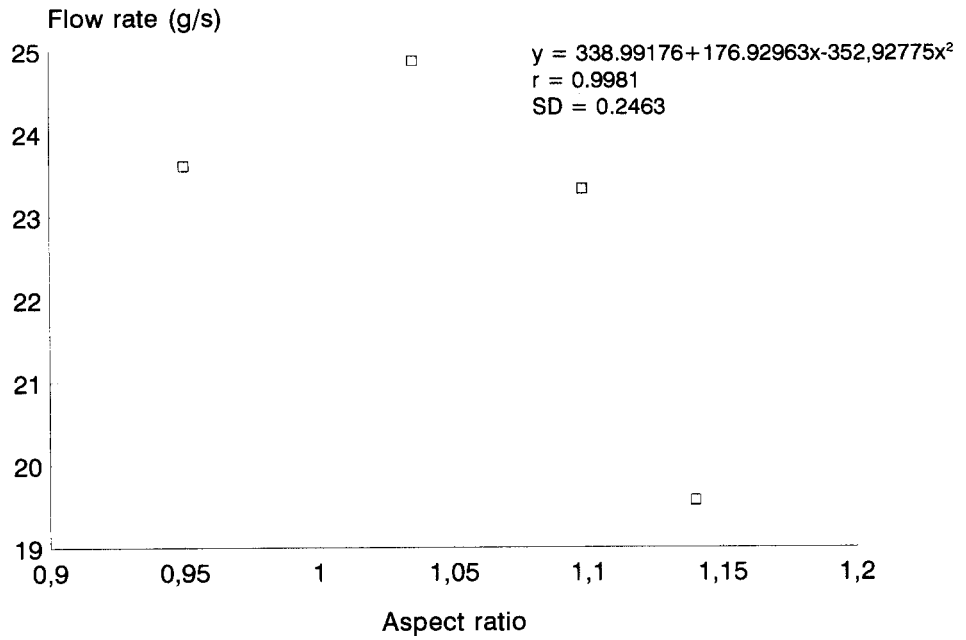

Fig. 3. Relationship between aspect ratio and flow rate.

etamol are indicative of the elongated and acicular form of their particles: D_{max} value is almost twice that of D_{min} value. On the contrary, for the modified products the differences between both parameters are minor indicating a deviation from acicular forms of particles. In this case, size parameters did not offer much more information over the improvement of the physical characteristics of commercial paracetamol particles, so shape parameters were considered.

Considering shape parameters, it is interesting to emphasize shape factor (S) and aspect ratio (a) data obtained for modified substances. The shape factor is used to measure object complexity, namely, contour complexity (Ramadan and Tawashi, 1991). The S data obtained yielded similar values and smaller than unity, except for particles modified with Eudragit® E, that present the lowest values for this parameter. This circumstance suggests that particles modified with Eudragit® L and S, although not being completely circular particles, have regular contours. On the other hand, aspect ratio values of modified samples are always lower than one of commercial paracetamol, indicating the rounding of paracetamol particles by the application of the polymer coating. In this case, aspect ratio data corresponding to paracetamol particles modified with Eudragit® E offer again the worst results in comparison with Eudragit® L and S.

Therefore, it can be concluded that the application of the coating process on paracetamol particles modifies the shape of their particles, transforming the acicular and elongated form in rounded shape, by depositing the Eudragit® small particles on the drug surface. It does not seem to have great influences on the type and percentages of polymer used and on the size and shape descriptors values, although Eudragit® L and S seem to offer the best results as it will be confirmed later. This coating treatment only affects the external form of the particles but does not imply a change in the roughness of the surface particles as it will be seen in the discussion of the fractal dimension results.

This situation is consistent with the rheological parameters obtained for the modified products. Some interesting relationships have been found between S and a data and the rheological parameters. As an example, Fig. 2 shows the relationship

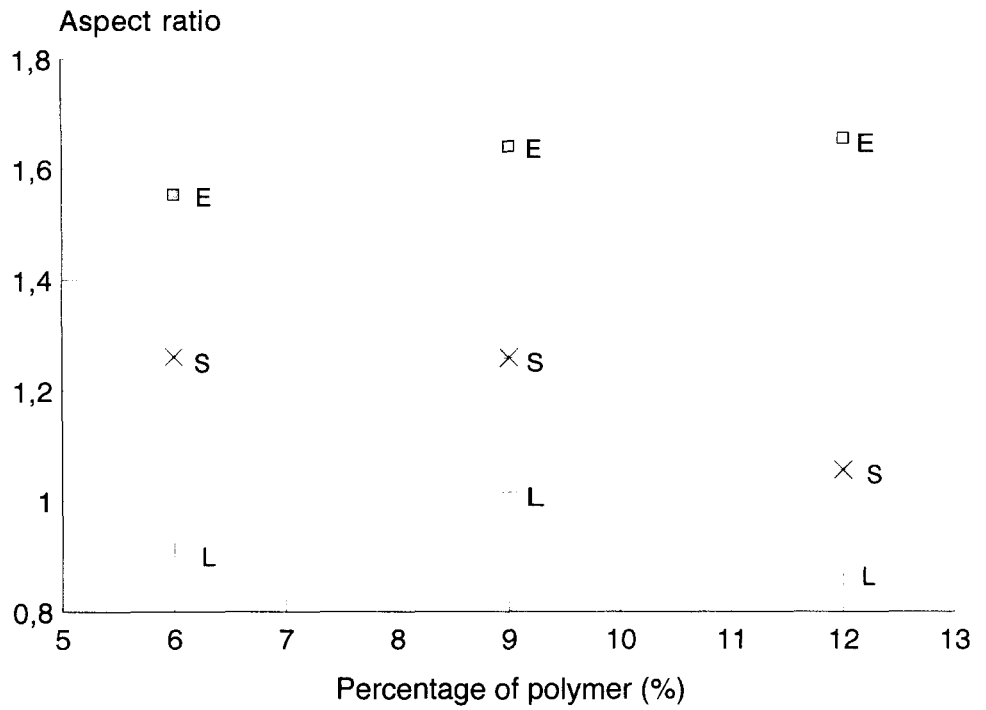

Fig. 4. Relationship between aspect ratio and percentage of polymer.

between shape factor and tapped density. As it can be seen, the relationship established is parabolic-type. Other parabolic relationships were also found: aspect ratio-shape factor ($r = 0.9311$), aspect ratio-flow rate ($r = 0.8112$) and aspect ratio-tapped density ($r = 0.9322$). Similar results have been previously found for modified lactoses (Holgado et al., 1995b). In this occasion a very good parabolic relationship was found between aspect ratio and flow rate (Fig. 3). Therefore, in the case of paracetamol, there will be maximum flow rate or tapped density values that can be defined on the basis of the shape factor or aspect ratio parameters. Hence, considering a determined product and by means of knowing shape factor or aspect ratio values, the maximum flow rate or tapped density can be calculated and would reach a constant value for this type of substance.

If the maximum values of the curve $S = -6.098 + 12\,611a - 5.841a^2$ are calculated, the results are the following: $a = 1.08$ and $S = 0.71$. This means that with this treatment technique, a good improvement in the shape of paracetamol particles has been achieved as the initial parameters of commercial paracetamol were $a = 1.92$ and $S = 0.39$. So, knowing the best values for a and S and using the other parabolic relationships, it is possible to calculate the best values for tapped density and flow rate.

Following the same procedure, the maximum values obtained for the other parabolic relationships are: shape factor-tapped density: $S = 0.61$, $TD = 0.86$; aspect ratio-tapped density: $a = 0.93$,

Table 5
Fractal dimension values of the indicated products

Products	Fractal dimesions		
Paracetamol	1.12 ± 0.03		
	6%	9%	12%
Paracetamol L	1.14 ± 0.03	1.17 ± 0.04	1.05 ± 0.01
Paracetamol E	1.13 ± 0.02	1.00 ± 0.12	1.06 ± 0.01
Paracetamol S	1.04 ± 0.01	1.12 ± 0.02	1.06 ± 0.01

Mean values and standard errors.

TD = 0.85; aspect ratio-flow rate: $a = 1.5$; FR = 11.49.

So, it is possible to conclude that the optimum values for tapped density and flow rate that can be obtained with this treatment are closed to 0.85 and 11.49, respectively.

In the case of modified lactoses (Holgado et al., 1995b) the maximum values obtained for aspect ratio and flow rate were 1.02 and 25.08, respectively. There is a clear difference between the behavior of lactose and paracetamol as with lactose a better value for aspect ratio and a high flow rate is obtained. This situation can be explained on the basis of the particle size used in each assay. For paracetamol, a wide granulometric fraction was used (50–500 μm) while for lactose the granulometric fraction employed was more narrow (150–400 μm). It is well known the primordial role developed by the factor 'particle size' in the rheological properties of a bulk solid.

On the other hand, no clear relationship between size and shape parameters and type and percentage of polymer has been found. As an example, Fig. 4 shows the relationship between aspect ratio and percentage of polymer showing that for each proportion of polymer (6, 9 and 12%) the same sequence is observed: the best results for this parameter are obtained with Eudragit® L and S as is indicated above.

3.2. Fractal analysis

Table 5 shows the values of fractal dimension obtained for commercial paracetamol and modified paracetamol. As can be seen, data are very similar in all the cases. No relationship between fractal dimension values and type or percentage of polymer can be observed. This signifies that the treatment realized onto the commercial paracetamol particles has not been successful in changing the roughness characteristics of the particles surface. The treatment only has modified the shape parameters (aspect ratio and shape factor) as has been indicated above. These same results have been obtained with other substances: several diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt samples showed similar fractal dimension values. They were not greatly affected by the mode of synthesis and solvent employed in their preparation (Holgado et al., 1995a). In the other case, different samples of commercial lactose were modified with diverse acrylic resins type Eudragit® (Holgado et al., 1995b) obtaining also similar results which were consistent with shape parameters and flow properties.

So, in conclusion, the improvement achieved in the rheological characteristics of commercial paracetamol that allowed tablets to be obtained by direct compression, has been obtained by means of modifications experimented in the shape of paracetamol particles: the particles of polymer have occupied the surface of paracetamol particles, rounded them and decreased their elongated shape but without affecting the regularity of the surface as has been illustrated by the fractal dimension values obtained.

Further studies will be carried out in order to calculate the reactive fractal dimension of commercial and modified paracetamol that enables the explanation of dissolution behaviors of the elaborated tablets containing these products. The reactive fractal dimension, as a parameter measuring the surface, which participates actively in the dissolution process, is of vital importance in order to understand and explain the dissolution process of any substance as is indicated by Farin and Avnir (1987).

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