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Characterization study of a diclofenac salt by means of SEM and fractal analysis

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Abstract

In this paper, the morphological and surface characteristics of five samples from different batches of the same salt, diclofenac/*N*-(2-hydroxyethyl)pyrrolidine, were investigated using SEM descriptors and fractal dimensions. Two samples were crystallized from organic solvents; the others from water. This elementary difference is suitable to introduce differences in their behaviours. Salt particles obtained from organic solvents present cubic shapes and smooth surfaces. On the other hand, salt particles obtained from aqueous solutions exhibit irregular forms and rugged surfaces. Furthermore, solvent molecules are adsorbed on the particle surface during the synthesis process or become incorporated into the bulk. When these substances are subjected to thermal treatment, the solvent molecules are lost, causing a change in the external morphology of the particles. The fractal dimensions calculated from the slope of a Richardson plot were 1.14, 1.04, 1.09, 1.05 and 1.10. These results seem to indicate that the *D* values are not greatly affected by the mode of synthesis and solvent employed.

Keywords: Diclofenac/*N*-(2-hydroxyethyl)pyrrolidine; Crystallization mode; Size and shape descriptors; Surface geometry; Fractal dimension

1. Introduction

Optimization of a drug substance through the determination of some physical and chemical properties is required in the development of a stable, effective, safe and reproducible dosage form. Dissolution rate, pH-solubility profiles, pH-stability profiles, drug-excipient interactions, etc., are a few of these parameters. All these properties are the controlling factors of drug bioavailability together with the physical and chemical stability (Labhasetwar et al., 1993).

Thus, from a preformulation point of view, it is important to understand the process of dissolution of drugs and to know the factors governing it. The process of dissolution frequently precedes the absorption of drugs across biological membranes to reach the systemic circulation. Therefore, drugs of low aqueous solubility usually present problems in relation to their bioavailability (Florence and Attwood, 1988).

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On the other hand, it has been shown that particle size, particle morphology and surface area of drugs can influence significantly the dissolution process and, therefore, the absorption process. When the rate of dissolution is lower than the rate of absorption, the dissolution process becomes rate limiting (Romero et al., 1991).

In a previous paper (Fini et al., 1993a), we analyzed the influence of the salt-forming bases and demonstrated the role of apparently secondary aspects in the process. In this paper, we further restrict the field of interest dealing with five samples from different batches of the same salt, diclofenac/*N*-(2-hydroxyethyl)pyrrolidine, recently employed as a new chemical form for delivering the anti-inflammatory agent diclofenac (Fini et al., 1993b). Two samples were crystallized from organic solvents; the others from water. This simple difference was sufficient to introduce differences in the solution behaviour of the salt samples and in processing: the first ones, in fact, display a sobresaturation, while the others readily reach saturation (about 2% w/w) in water.

The different behaviour was considered to be due either to the bulk or to the surface properties of the samples. Therefore, we carried out a thermal treatment of the sample particles, with a parallel examination of the particles by scanning electron microscopy (SEM) and a detailed surface study by means of fractal analysis.

Moreover, as a continuing part of the fractal analysis applied successfully to a single diclofenac salt (Fernández-Hervás et al., 1994), the aim of this work was, using the concepts of fractal geometry, to describe the morphologies and to predict dissolution behaviours of different samples of the same salt. Thus, one of the main objectives was to investigate whether the process of synthesis and type of solvent would affect the morphological and surface characteristics of the final product, as reflected in the fractal dimension (D) and SEM parameters and to find possible correlations between D values and the shape parameters obtained by SEM.

2. Experimental

2.1. Materials

The salt diclofenac/*N*-(2-hydroxyethyl)pyrrolidine (DHEP) was a gift from IBSA (Lugano, Switzerland). The samples of the salt were from different production batches and also represent different modes of preparation and/or crystallization of the final material. Throughout the paper, the samples are referred to as DHEP 1–5. They were prepared as follows.

2.1.1. DHEP 1 and 2

29.4 g of acidic diclofenac were added to 100 ml of the appropriate solvent (ethanol for DHEP 1 and acetone-ethanol mixture 1:1 for DHEP 2). Under vigorous stirring, an equivalent amount of the base (*N*-(2-hydroxyethyl)pyrrolidine) was added portionwise. The system was heated to 40°C to favour the reaction and complete dissolution of the forming salt. The final solution was cooled to 10°C and a small amount of the salt was added as seed for crystallization. The solid precipitate was centrifuged, washed with pure solvent and dried under vacuum.

Table 1
Some physicochemical characteristics of DHEP salt

Salt	m.p. (°C)	Solubility (room temperature) (w/w)	Solvent content (w/w)	Moisture content (w/w)	Purity (%) [a]
DHEP 1	102.3	> 10 [b]	0.02	0.07	99.8
DHEP 2	100.2	> 10 [b]	0.007	0.34	99.8
DHEP 3	101.5	< 10	–	1.37	98.6
DHEP 4	100.9	< 10	–	1.22	99.3
DHEP 5	101.1	< 10	–	0.45	99.7

[a] HPLC after drying.
[b] Metastable and supersaturated solutions.

2.1.2. DHEP 3–5

8.7 g of the base (*N*-(2-hydroxyethyl)pyrrolidine) were added to 100 ml of water kept at 50°C; to this solution, 29.4 g of acidic diclofenac were then added portionwise under stirring. The pH of the system decreased to an almost neutral value. The remaining amount of base, necessary for complete neutralization of the diclofenac, was then added, avoiding an excessively high rise of pH. 1–2 g excess diclofenac were added and the system was allowed to stand for 15 min. The precipitate was filtered and the excess water was vacuum distilled until the volume was reduced to 50% of the starting value. The residual solution was cooled to 4°C for 6 h under continuous stirring. The precipitate was separated by centrifugation and dried under vacuum.

Table 1 lists some physicochemical characteristics of these salt samples.

2.2. Scanning electron microscopy

The shape and size of salt particles were examined under a scanning electron microscope (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 parameters of the solids was determined using an image analysis system connected to the microscope mentioned above. They are obtained, automatically, using a special computer program. This experimental method has been previously reported (Fernández-Hervás et al., 1994).

The following parameters were selected to characterize salt particles: area (A); perimeter (P); equivalent circle diameter (ECD) – this parameter is the diameter of the circle that has an area equal to the area of the particle:

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

shape factor (S) – this 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. It is defined as follows:

$$S = 4\pi\left[\mathrm{area}/(\mathrm{perimeter})^2\right]$$

maximum and minimum diameters (D_{max} and D_{min}); aspect ratio (a). 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 unity. 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.

2.3. Differential scanning calorimetry

Thermal analysis was performed on DHEP salts, using an automatic thermal analyzer system (Mettler FP80 HT Central Processor and Mettler FP85 TA Cell). The data processing system Mettler FP89 HT was connected to the thermal analyzer. Sealed and holed aluminum pans were used in the experiments for all the samples. Temperature calibrations were carried out using indium as a standard. An empty pan, sealed in the same way as the sample, was used as reference. All samples were run at a scanning rate of 10°C/min, from 40 to 300°C.

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 has been indicated in a previous paper (Fernández-Hervás et al., 1994).

3. Results and discussion

Diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt is a new non-steroidal anti-inflammatory salt derived from diclofenac acid (Fini et al., 1991). This salt also shows the phenomenon of self-aggregation, forming micelles with solubilization ability towards hydrophobic materials (Fini et al., 1994). This property plays an active role in the process of absorption, increasing the membrane permeability. The faster plasma level found, when DHEP is administered per os, can be associated to this weak detergency (Fini et al., 1991, 1992; Rabasco et al., 1992).

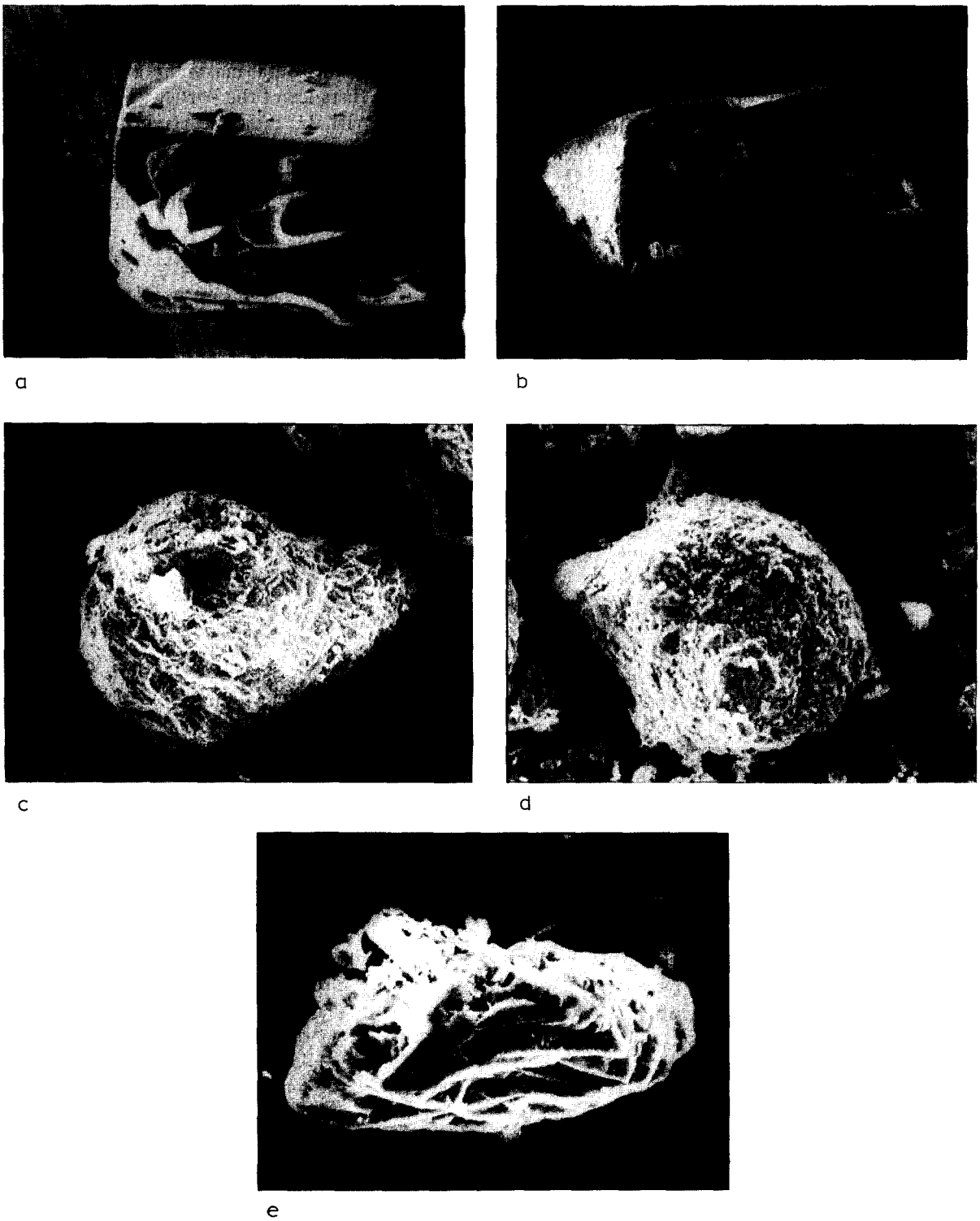

Fig. 1. Micrographs corresponding to DHEP samples: (a) DHEP 1, (b) DHEP 2, (c) DHEP 3, (d) DHEP 4, (e) DHEP 5.

Furthermore, the solubility value of DHEP in 1-octanol was higher than that determined in water. The progressive decrease in electrical conductivity of DHEP solutions of the same concentrations in solvents of decreasing dielectric constant suggested that the salt is present in 1-octanol as ion pairs. Ion association is promoted by internal H-bonds involving the N-H imino group of the diclofenac anion and the hydroxy group of the cation and produces species that have properties almost identical to those of uncharged compounds and can therefore dissolve or distribute into poorly polar solvents. This peculiar behaviour of DHEP appears suitable for the dermal absorption of the active principle diclofenac from topical forms (Fini et al., 1993b).

All these properties were studied using a very pure sample of DHEP. During this study, we occasionally observed that DHEP (and other diclofenac salts) crystals tended to contain solvent molecules, demonstrated by an endothermic peak at low temperature (60–70°C), before melting, in thermograms. Moreover, it emerged that DHEP samples crystallized from organic solvents resulted in supersaturated solutions in water, slowly evolving to equilibrium; in contrast, with samples prepared directly in water or crystallized from water, saturation was soon achieved. Therefore, on the basis of these results and in order to explain this behaviour, further studies based on the SEM technique, before and after simple thermal treatment, and fractal dimension study were carried out on various samples of DHEP obtained in different ways and with diverse times of production.

Fig. 1 shows the micrographs corresponding to the indicated samples. As can be observed, salt particles obtained from organic solvents (DHEP 1 and 2) present cubic shapes and smooth surfaces. On the other hand, salt particles resulting from aqueous solutions (DHEP 3–5) exhibit irregular forms and rugged surfaces.

In relation to the SEM parameters, Table 2 shows, as an example, data obtained for 20 particles corresponding to DHEP 3 and Table 3 lists the mean values corresponding to all of the samples. Considering the size parameters (area, perimeter, ECD, minimum and maximum diameters), small differences have been found between them although a previous sieving was not processed. DHEP 1 appears to present the most homogeneous particle size (low values of SD). In contrast, the highest variability is presented by DHEP 3.

Table 2
Size and shape descriptors of DHEP 3 particles

Particle no.	A (mm^2)	P (mm)	ECD (mm)	S	D_{min} (mm)	D_{max} (mm)	a
1	0.1603	1.6930	0.4518	0.70	0.4140	0.5731	1.23
2	0.0320	0.0863	0.2020	0.54	0.2083	0.2482	0.86
3	0.0522	1.3037	0.2578	0.39	0.2490	0.3629	1.11
4	0.1065	1.5077	0.3683	0.59	0.3502	0.4567	0.87
5	0.1038	1.6064	0.3636	0.51	0.3832	0.4696	0.92
6	0.4653	6.6070	0.7697	0.13	0.8553	1.1169	1.08
7	0.0945	1.3296	0.3468	0.67	0.3209	0.4429	0.90
8	0.0672	1.1677	0.2925	0.62	0.2360	0.4218	1.35
9	0.0744	1.1738	0.3077	0.68	0.3012	0.3339	0.88
10	0.0911	1.5871	0.3406	0.45	0.3601	0.4103	0.97
11	0.2389	3.5246	0.5516	0.24	0.5904	0.6726	0.85
12	0.1381	1.6966	0.4193	0.60	0.4448	0.5269	0.94
13	0.3235	2.6740	0.6418	0.57	0.5840	0.8502	1.14
14	0.1188	1.9682	0.3889	0.39	0.3863	0.5711	0.55
15	0.0729	1.4518	0.3047	0.43	0.3293	0.5069	0.73
16	0.1064	3.3002	0.3681	0.12	0.4454	0.5962	1.39
17	0.1631	1.7111	0.4557	0.70	0.4502	0.5485	1.09
18	0.1926	1.9440	0.4952	0.64	0.4155	0.6746	0.91

Table 3
Mean values of size and shape descriptors corresponding to the indicated salts

Parameters	DHEP 1			DHEP 2			DHEP 3			DHEP 4			DHEP 5		
	Mean	SD	*e*	Mean	SD	*e*	Mean	SD	*e*	Mean	SD	*e*	Mean	SD	*e*
A (mm^2)	0.0267	0.0021	$6E-4$	0.2385	0.1334	0.0357	0.1433	0.1081	0.0254	0.0825	0.0467	0.0134	0.0356	0.0240	0.0054
P (mm)	0.6900	0.0461	0.0133	2.2378	0.7229	0.1932	2.0610	1.3365	0.3150	1.4458	0.4490	0.1296	1.0253	0.4931	0.1103
ECD (mm)	0.1841	0.0069	0.0020	0.5300	0.1498	0.0400	0.4070	0.1395	0.0329	0.3142	0.1033	0.0298	0.2008	0.0713	0.0159
S	0.7100	0.1004	0.0290	0.5836	0.1404	0.0375	0.4983	0.1848	0.0435	0.4708	0.1352	0.0390	0.4440	0.1596	0.0356
D_{min} (mm)	0.1718	0.0150	0.0043	0.5757	0.1332	0.0356	0.4068	0.1525	0.0359	0.3058	0.0994	0.0287	0.1924	0.0720	0.0160
D_{max} (mm)	0.2373	0.0159	0.0046	0.6507	0.1749	0.0467	0.5435	0.2000	0.0472	0.4067	0.1272	0.0367	0.3060	0.1191	0.0266
a	1.0142	0.3048	0.0880	0.9878	0.3964	0.1059	0.9872	0.2098	0.0494	1.0542	0.3384	0.0977	1.4590	0.5201	0.1163

Considering the shape parameters (shape factor and aspect ratio), major differences can be observed. In the case of the shape factor, DHEP 1 and 2 displayed S values closer to unity than those salts prepared in aqueous solution. This circumstance seems to indicate that the salts synthesized from organic solvents present regular shapes and small variability in particle silhouette (see Fig. 1), while DHEP 3–5 particles exhibit major complexity.

On the other hand, the aspect ratio data obtained show similar values, close to unity, also indicating regular forms for all these salts. The unique exception was presented by DHEP 5, demonstrating an aspect ratio value of 1.46. This result indicates that these particles are probably elongated in the x-direction. Therefore, it can be conclude that DHEP 5 particles showed a significant irregularity in shape and contour in order of the S values and data obtained for this salt.

It is interesting to emphasize the thermal behaviour of these salts. All the thermograms obtained showed endotherms, close to 60°C, corresponding to the loss of solvent molecules. As an example, Fig. 2 shows the thermogram corresponding to DHEP 5. When these salts were subjected to thermal treatment in an oven (Selecta model 204), at approx. 50°C for 3 days, the new thermograms did not show those endotherms. Thus, it can be assumed that solvent molecules adsorbed on the particle surface during the process of synthesis or incorporated into the bulk are lost after heating the samples. The loss of solvent molecules is accompanied by a change in the external morphology of the particles.

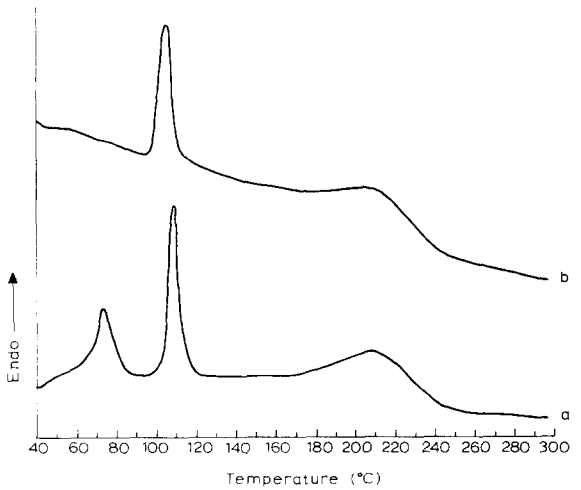

Fig. 2. Thermograms corresponding to DHEP 5: (a) before thermal treatment; (b) after thermal treatment.

As has been indicated above, DHEP salts subjected to thermal treatment in an oven can lose their solvent content. Fig. 3 shows micrographs of the salts after thermal treatment: the reduction in the particle dimensions and the more compact and packed aspect of the substances are evident.

The size and shape analysis was also carried out on the salts subjected to thermal treatment in order to investigate the influence of loss of solvent molecules on the morphological characteristics. The results obtained are shown in Table 4. More pronounced differences can be appreciated in relation to the S data. The S values are significantly increased for those salts synthesized in aqueous solution, indicating that the dehydration process undergone by these salts can modify their structures, yielding particles with more regular and uniform shapes (see Fig. 3). On the other hand, the area values also decreased, indicating a more compacted and dense structure for the salts after the heating process.

DHEP 1 displays a different behaviour from that of the other samples. All the size and shape parameters of this salt increased after the thermal treatment. This aspect is still under examination and will not be discussed here.

The SEM optical analysis, despite the microscopic level observation, does not account for the degree of surface irregularity and roughness, therefore, the particle surface was also analyzed in term of fractal geometry. In fact, according to Farin and Avnir (1987), the course of a heterogeneous chemical reaction, such as the dissolution process, is the result of a complex interplay between aspects of the chemistry and surface characteristics of particles.

Taking into account the degrees of surface irregularity and roughness, it can be possible to predict their effects on the dissolution rate of drugs and, therefore, on the biopharmaceutical behaviour of the elaborated formulations. The

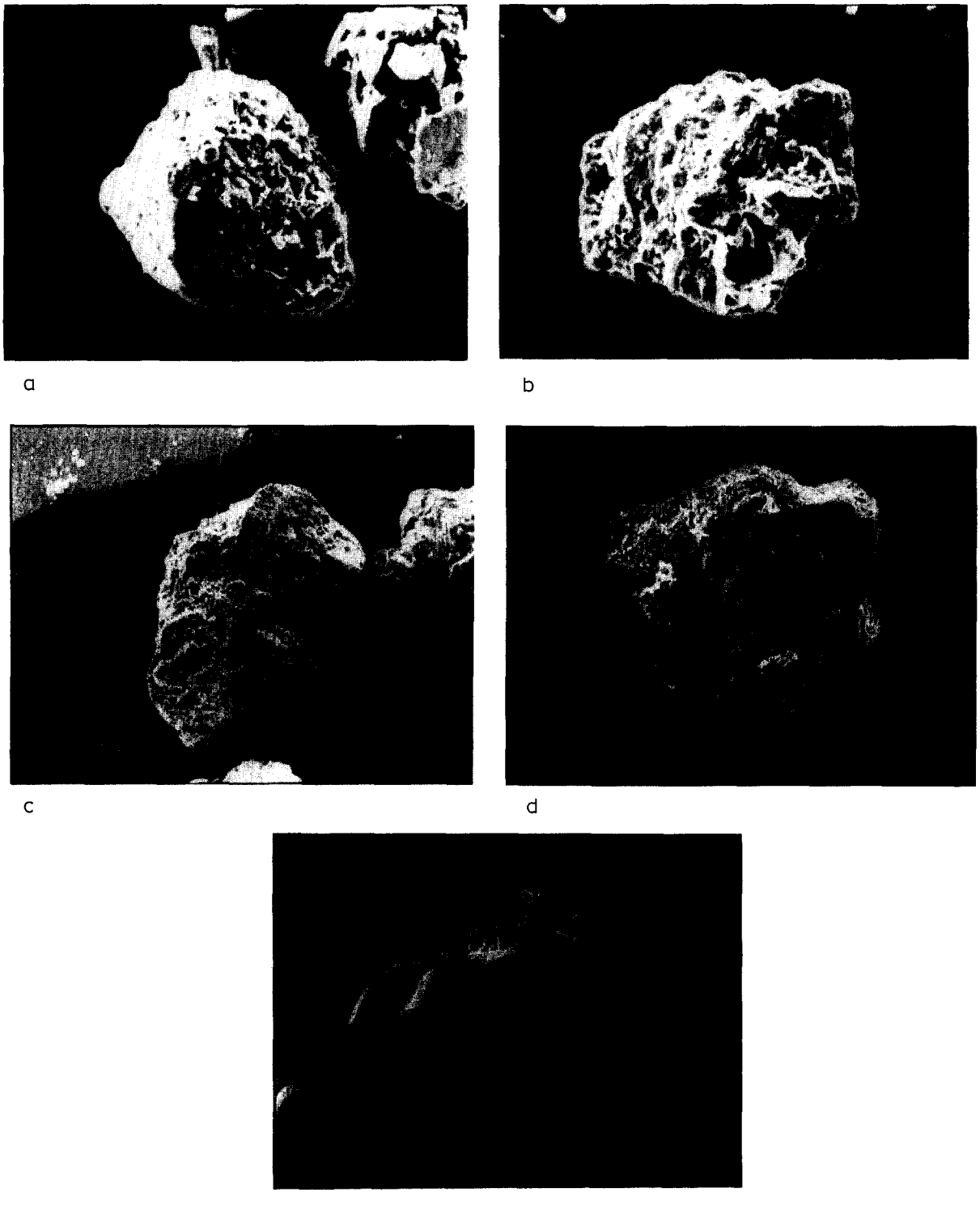

Fig. 3. Micrographs corresponding to DHEP samples after thermal treatment: (a) DHEP 1, (b) DHEP 2, (c) DHEP 3, (d) DHEP 4, (e) DHEP 5.

Table 4
Mean values of size and shape descriptors of the samples subjected to thermal treatments

Parameters	DHEP1′			DHEP2′			DHEP3′			DHEP4′			DHEP5′		
	Mean	SD	*e*	Mean	SD	*e*	Mean	SD	*e*	Mean	SD	*e*	Mean	SD	*e*
A (mm^2)	0.1400	0.0463	0.0120	0.1107	0.0461	0.0119	0.0907	0.0519	0.0138	0.1154	0.0720	0.0217	0.0923	0.0453	0.0126
P (mm)	1.7460	0.3899	0.1007	1.3887	0.3908	0.1008	1.2121	0.3582	0.0957	1.3873	0.4308	0.1299	1.1830	0.3139	0.0871
ECD (mm)	0.4147	0.0794	0.0205	0.3953	0.1342	0.0346	0.3279	0.0964	0.0257	0.3718	0.1054	0.0318	0.3338	0.0793	0.0220
S	0.5833	0.1450	0.0374	0.7333	0.1351	0.0348	0.7386	0.1330	0.0355	0.7209	0.0928	0.0279	0.7969	0.0770	0.0214
D_{min} (mm)	0.4700	0.0907	0.0234	0.4260	0.0978	0.0253	0.3329	0.0967	0.0258	0.3818	0.1073	0.0323	0.3323	0.0918	0.0255
D_{max} (mm)	0.5180	0.0984	0.0254	0.4607	0.0951	0.0245	0.3729	0.1233	0.0329	0.4454	0.1431	0.0432	0.3692	0.0978	0.0271
a	0.9907	0.2238	0.0577	1.156	0.3007	0.0776	0.9971	0.2646	0.0707	1.1200	0.3181	0.0959	1.0346	0.2507	0.0695

mathematical tool used to quantify the surface properties is fractal geometry (Mandelbrot, 1984; Farin and Avnir, 1988, 1992). The basic approach of this theory is to describe quantitatively a complex geometry of an object if the object is symmetric to transformation of scale.

The fractal concept describes the surface of particles in terms of the 'fractal surface', with a characteristic parameter called 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, since 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, δ denotes the step length and L_δ is the perimeter estimated with step length δ. An ideal fractal structure should produce a linear plot at all resolutions, when ln L_δ is plotted against ln δ. The slope of this straight line is S, where $S = 1 - D$ (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, the higher is the value of D (Farin and Avnir, 1987).

At the same time, a scanning electron microscope connected to an image processor was used in this study 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 techniques (optical microscopy): automatic and more accurate measurements, the saving of a great amount of time and the yielding of more reliable conclusions from the results with a smaller number of observations, mainly (Paraira et al., 1994).

The fractal dimensions calculated from the slope of the Richardson plot were 1.04, 1.09, 1.05 and 1.10 for DHEP 2, 3, 4 and 5, respectively (see Table 4). Table 5 lists the regression values obtained for Richardson plots of all these salts. If the approximation proposed by Farin and Avnir (1992) is used, then D_s (fractal dimension of surface) would yield values of 2.04, 2.09, 2.05 and 2.10. These values are not markedly different from that exhibited by DHEP 1 (2.14), previously reported (Fernández-Hervás et al., 1994). Farin and Avnir (1989) state that $D_s \approx 2$ refers to the classical assumption of smooth and flat areas of the particles.

Therefore, the results appear to indicate that the D values are not greatly affected by the mode of synthesis and solvent employed. On the other hand, these same results are consistent with neither the surface aspect nor shape parameters obtained by SEM. Hence, it is necessary to confirm these differences in shape and surface characteristics using other techniques to calculate the fractal dimension, as the degree of surface irregularity and roughness can produce important and significant effects on the dissolution rate of these salts and, therefore, on their bioavailability when included in dosage forms.

4. Conclusions

The present results suggest that different behaviour in solution of these samples of DHEP can be attributed both to bulk and surface pa-

Table 5
Regression values obtained from Richardson plots (standard errors in brackets)

Product	n	Slope	Constant term	r_{xy}	F	P
DHEP 1	5	−0.1357 (0.0210)	7.5564 (0.0631)	0.9552	41.7186	0.0030
DHEP 2	5	−0.0356 (0.0081)	8.0092 (0.0132)	0.9297	19.1288	0.0221
DHEP 3	5	−0.0904 (0.0153)	7.1782 (0.0279)	0.9596	34.8759	0.0097
DHEP 4	5	−0.0567 (0.0022)	7.7880 (0.0051)	0.9977	659.904	0.0001
DHEP 5	5	−0.1087 (0.0112)	6.9920 (0.0210)	0.9843	93.3717	0.0024

rameters of the particles. Weak and prolonged heating modifies the form and dimensions of particles, suggesting that the release of solvent molecules influences not only the external surface (as moisture) but also the internal structure. This is not surprising due to the presence of hydrophilic centers in the anion (N-H imino group) and cation (hydroxy group) capable of forming hydrogen bonds with water (or solvent) molecules.

From these results, it is not clear whether the solvent participates in the crystal packing. More accurate analysis (e.g., diffractometry or thermogravimetry) is needed to highlight the role of the solvent as well as to define better the fractal dimension, using different techniques, such as the physisorption of an N_2 monolayer using the BET equation to analyze the change in apparent surface area of the solid as a function of particle size. This method has some advantages: it is easier to obtain a wide range of particle size than to use a wide range of step lengths to measure the perimeter of particles, so a wide range of self-similarity may be detected; adsorption of only one type of molecule is necessary. Further investigations employing this technique will be carried out to confirm the assumptions proposed in this work.

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