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Fractal and reactive dimension of a diclofenac salt: effect of the experimental conditions

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Abstract

The characterization of five samples from different batches of the same salt, Diclofenac/N-(2-hydroxyethyl)pyrrolidine, was realized by means of fractal analysis. When the samples were subjected to weak heating, the fractal dimension of the surface obtained, before and after thermal treatment, suggest that no great modifications occurred on the particles surface. On the contrary, the analysis of reactive dimension toward dissolution, D_R, showed that much more reactive points appear on the particles surface after the heating process. Different values of D_R were obtained as result of changes in the composition of the dissolution medium.

Keywords: Diclofenac/N-(2-hydroxyethyl)pyrrolidine; Surface geometry; Fractal dimension; Reactive fractal dimension

1. Introduction

The formation of solvates or hydrates was clearly demonstrated in the case of diclofenac salts, depending on the crystallization solvent and the nature of the counterion (Fini et al., 1996). A thermal treatment, followed by a DSC analysis, allowed to obtain desolvated forms; a further random SEM analysis however showed, in same cases, changes concerning the shape parameter of the salts particles. A systematic examination was thus carried out also in term of fractal analysis to evaluate the differences before and after the thermal treatment of some samples of diclofenac salts that could be relevant concerning their behaviour toward dissolution.

The dissolution properties of a drug are essential in determining its bioavailability; moreover, the dissolution process depends on parameters of the dissolving solid particle such as surface morphology, degree of porosity, particle shape, etc. In this sense, it is very interesting to quantitatively analyze the degree of surface irregularity and roughness and their effects on the dissolution rate of drugs (Farin and Avnir, 1992), by means of the Fractal Geometry, that proposes a global parameter, the reactive dimension D_R, as the effective dimension of a substance toward a reaction inter-

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esting the surface of the particle (the dissolution process in our case) (Farin and Avnir, 1987). The concept of fractal dimension for reactivity is thus a useful mean of quantifying into a single parameter a set of properties, related to the morphology and surface of a particle, very difficult to quantify separately.

A previous report demonstrated the importance of microscopic particle properties, such as surface morphology and degree of porosity (summarized in the shape factor), over dissolution behaviour of these salts. In the case of 11 samples of a diclofenac salt obtained by crystallization from alcohol-type solvents or mixtures with triacetin (Fini et al., 1995a), an interesting inverse linear relationship was found between the efficiency of dissolution and the shape factor of the dissolving particles.

Moreover, the morphological and surface characteristics of five samples of different batches of the same salt diclofenac/N-(2-hydroxyethyl)pyrrolidine, investigated using SEM descriptors and surface fractal dimensions (D_S), indicated that D_S values are not greatly affected by the mode of preparation of the salts and solvent employed (Holgado et al., 1995).

As a continuing part of the fractal analysis applied successfully to diclofenac salts (Fernández-Hervás et al., 1994; Holgado et al., 1995; Fini et al., 1995a), the main objective of this work is to analyze and evaluate whether the different modes of preparations and thermal treatment would affect the dissolution behaviour of these samples of diclofenac salts, as reflected in their D_R values, determined before and after a thermal treatment; and also to determine which role plays the surface nature, when the dissolution medium changes from acid to basic one.

2. Experimental

2.1. Materials

The samples of the salt diclofenac/N-(2-hydroxyethyl)pyrrolidne (DHEP) were a gift from IBSA, (Lugano, Switzerland): they 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. The salt 1 was prepared mixing equivalent amount of acidic diclofenac and the organic base dissolved in acetone. The salt 2 was obtained as salt 1, using toluene. The salts 3, 4 and 5 were prepared suspending a given amount of acidic diclofenac in warm water under stirring, an equivalent amount of the base N(2-hydroxyethylpyrrolidine) dissolved in water was added and the stirring and temperature increased. The samples 3–5 differentiated for the experimental conditions (temperature of the final solution; degree of supersaturation), after precipitation. The salts 1', 2', 3', 4' and 5' were the same samples as 1–5 after a thermal treatment.

2.2. Thermal treatment

The different samples of DHEP 1–5 were subjected to thermal treatment in an oven (Selecta, model 204), at approximately 50°C for 1 day, obtaining the samples DHEP 1'–5'. The two different sets of samples underwent DSC to evaluate the presence of endothermic peaks due to the release of crystallization solvent. The sample 1 and 2 had a simple thermogram while the samples 3, 4 and 5 had an additional endothermic peak at temperature below 100°C. All the samples 1'–5' had simple thermograms with only the peak related to the melting of the salt.

2.3. Fractal analysis

The fractal dimension D_l of the particle contour of the two sets of samples was calculated from the slope of the Richardson plot (ln of perimeter length vs ln of step length), as it has been indicated in a previous paper (Fernández-Hervás et al., 1994). The approximation proposed by Farin and Avnir (1992) where $D_S = (D_l + 1)$ was used to calculate the fractal dimension of the surface. The fractal analysis was performed before and after the thermal treatment.

To calculate the reactive dimension to dissolution, the following five fractions of DHEP samples were obtained by sieving (Retsch, type

Vibro): 350–250 μm, 250–200 μm, 200–175 μm, 175–100 μm and 100–50 μm. Each sieving fraction was subjected to a dissolution assay in the USP XXIII 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. Dissolution of samples was detected by the increase in conductance of the dissolution medium (λ-λ_o), λ_o being the initial conductance of the starting solution) using a digital conductivitymeter (Crison, model Micro CM-2201) linked to a chart recorder and an IBM-compatible personal computer. The system provides one conductivity datum per s. Twenty micrograms of each sample was used in the dissolution rate measurements, ensuring sink conditions.

The dissolution profiles have been obtained plotting the amount dissolved at each time versus time; the amodelistic parameter, dissolution efficiency (E_d) (Salvadó et al., 1987), was then calculated for each fraction. The reactive dimension D_R, for the dissolution process was calculated from the slope of the plot of ln E_d versus ln particle size.

3. Results and discussion

DSC revealed that samples 3, 4 and 5, as obtained from the preparation of salt, contained an endothermal peak that is absent in the thermogram of the same samples after weak heating: this was attributed to the fact that original samples were hydrates and, after the treatment, solvent molecules were lost. This aspect was previously discussed elsewhere (Holgado et al., 1995).

The size and shape analysis for each sample were carried out on the salt before and after thermal treatment. The geometrical parameters obtained from SEM examination revealed mainly that the shape factor, after thermal treatment, achieved values close to the unity for those samples prepared in aqueous solution, indicating that the loss of residual solvent process undergone by these samples modify their dimensions and yields particles with more regular and uniform shapes. Therefore, the area values also decreased, indicating a more compact structures for these same samples.

Despite these geometrical differences within the same sets, both before and after the treatment, the fractal analysis yielded fractal dimension of surface (D_S) values very similar: 2.14, 2.04, 2.09, 2.05 and 2.10, suggesting that this paramenter is little affected by the experimental conditions used for the preparation of the salts.

Furthermore, the same parameter D_S has been calculated after the thermal process, obtaining: 2.10, 2.07, 2.08, 2.13 and 2.05 for DHEP 1', 2', 3', 4' and 5', respectively (Table 1): that is, no significant difference between the corresponding D_S values for the samples before the thermal treatment.

Comparing these values of D_S with the SEM descriptors calculated previously (Holgado et al., 1995) for samples subjected to thermal treatment, no relationship between both variables have been found. The shape of the particles changes when the solvent molecules are lost, but this circumstance does not imply a transformation in the roughness or irregularity of the particle surface, because the D_S values persist unalterate. This demonstrates that solvent molecules are not simply adsorbed at the surface; their lost involves proportional reduction of the dimension of the particle and the surface is interested only to a limited extent, as confirmed by the fractal dimension of the surface. Moreover, preliminar ther-

Table 1
Regression values obtained from Richardson plots (n = 5)

Product	D_S	$r_{x,y}$	F	P
DHEP 1*	2.14	0.9552	41.719	0.0030
DHEP 2	2.04	0.9297	19.129	0.0221
DHEP 3	2.09	0.9596	34.876	0.0097
DHEP 4	2.05	0.9977	659.904	0.0001
DHEP 5	2.10	0.9843	93.372	0.0024
DHEP 1'	2.10	0.9869	112.677	0.0018
DHEP 2'	2.07	0.9023	13.141	0.0361
DHEP 3'	2.08	0.9868	111.580	0.0018
DHEP 4'	2.13	0.9249	17.760	0.0244
DHEP 5'	2.05	0.9626	37.924	0.0086

*Symbols are as follows: 1 and 1' samples on the same batch before (1) and after (1') a thermal treatment.

D_S, fractal surface dimension of the particles of given batch.

Table 2
Regression values obtained in the D_R study ($n = 5$)

Product	D_R	$r_{x,y}$	F	P
DHEP 1	2.76	0.8973	16.530	0.0153
DHEP 2	2.80	0.9865	145.416	0.0003
DHEP 3	2.68	0.9906	209.018	0.0001
DHEP 4	2.77	0.9946	367.853	<0.0001
DHEP 5	2.65	0.9902	201.413	0.0001
DHEP 1'	2.92	0.9152	15.469	0.0293
DHEP 2'	2.89	0.9746	56.597	0.0049
DHEP 3'	2.86	0.9775	64.453	0.0040
DHEP 4'	2.92	0.8627	8.734	0.0598
DHEP 5'	2.99	0.9291	18.923	0.0224

Symbols as in Table 1. D_R, reactive fractal dimension to dissolution.

mogravimetric result (Fini et al., 1995b) indicate that the amount of water present in the crystal is small and, consequently, also the changes related to dehydration are limited.

We applied the Fractal Geometry to quantify the surface which participates actively in the dissolution process and determined a reactive dimension (D_R) for the particles of both sets of samples. Two clear aspects can be drawn from the results reported in Table 2: (a) In all of the cases, D_R values of the samples subjected to thermal treatment are higher than those corresponding to samples without treatment; and (b) the same relationship $D_R > D_S$ have been found for all the samples.

The first observation seems to indicate that the loss of the solvent molecules change the behaviour of the samples toward the dissolution medium originating much more reactive surfaces. This is in accord with the well known phenomenon that anhydrous forms dissolve more rapidly that the hydrate ones (Florence and Attwood, 1988). Moreover, this aspect can be related also to the decrease of the surface area of the particles observed (Holgado et al., 1995). In fact, the SEM study revealed that salt particles with minor size and more compact aspect yielded higher values of dissolution rate, reported in terms of dissolution efficiency. To this respect, a marked dependence between the dissolution efficiency values and shape factor values was observed for different samples of the salt diclofenac/N-(2-hydroxyethyl)pyrrolidine crystallized from different solvents (Fini et al., 1995a).

In relation to the second point, the $D_R > D_S$ reveals that, in spite of the smooth external surface, suggested by the D_S values, before and after heating process, the salt particles possess reactive surface sites which manifest during the dissolution process. This same behaviour was reported in a previous paper dealing with the fractal dimension of the diclofenac hydroxyethyl pyrrolidine salt (Fernández-Hervás et al., 1994). At the present, it can be concluded that either the relationship between D_R and D_S is independent of mode and solvent employed in the process of the preparation of the salt or that some peculiar mechanism is operating inside the solution in driving dissolution of this salt more efficiently than expected: in fact, as previously reported, this salt in aqueous solution displays colloidal properties, originates supersaturation and possible self-aggregation (Fini et al., 1994). These phenomena can alter the dissolution process.

The importance of the dissolution medium in modifying the environment around the dissolving particle, actively interacting with particle surface, was evident when the pH of the medium was changed from almost neutral to acidic and alkaline values. Change of pH in the two media actually means change of the dominant cation in the solution, namely H^+ ion in acid medium and Na^+ ion in basic medium. In this case, an interexchange between the bulk solution and the dissolving particle surface can occur, causing modifications. Two different mediums with extreme pH values were selected: pH = 3.0 and pH = 10.0 which were obtained after adding of a determined volume of 0.1 N HCl and 0.1 N NaOH to 500 mL of purified water, respectively. In this case, althoug the initial conductance of dissolution media was high, the conductivitymeter used in the assay had sufficient sensitivity to detect little increases in the conductance medium, due to the dissolution of the salt.

In the acidic medium, the diclofenac anion can be protonated forming the poorly soluble acidic diclofenac on the surface as well as in the solution: the different in solubility between this form

Table 3
Ed values obtained at different pH values as a function of the granulometric fraction considered

Granulometric fractions (μm)	E_d (%) (Acidic medium)	E_d (%) (Basic medium)
250–350	75.44	50.45
200–250	89.85	91.45
175–200	92.95	93.81
100–175	95.71	94.24
50–100	99.66	86.78

and the DHEP salt is dramatic. Acidic diclofenac is 8 μM soluble versus 46 μM for the DHEP salt. This suggest the possibility that a poorly soluble layer is deposited on the surface of the salt, slowing down the dissolution process. However since each run was followed for 2 h, this represents a time sufficient for a almost complete dissolution, as suggested by the high E_d values obtained in most cases (Table 3). It must be noted moreover that, even though in these conditions the solubility of acidic diclofenac was not overcome, the approach of the saturation level could affect the sink conditions and probably the global process in terms of E_d.

In the solution rich of sodium ion, on the contrary, dissolution does not appear to be modified according to the fact that the Na^+ and HEP salts of diclofenac have close solubility values (30 and 46 μM): the interexchange on the particle surface (it any, in these conditions) does not affect the E_d value.

As a consequence, the D_R value in alkaline medium does not differ from that determined in water, while it is higher than that at low pH at each range of particle size considered (Table 4).

Table 4
Regression values obtained in the D_R study for DHEP at different conditions

DHEP 4	acidic conditions (pH = 3.0)	basic conditions (pH = 10.0)
D_R	2.58	2.83
$r_{x,y}$	0.7967	0.8492
F	5.2200	7.7570
P	0.1065	0.0687

When the relatively high particle size is considered, it can be observed the E_d in acidic medium is reduced. In fact, at each range of particle size considered, the differences observed between both E_d values are lower when the particle size decreases. So, it can be concluded that at high particle sizes, the nature of dissolution medium acts as predominant factor in the dissolution process while at low particle sizes this factor does not seem to exert any influence.

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