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Influence of crystallization solvent and dissolution behaviour for a diclofenac salt

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Abstract

11 samples of diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt obtained by crystallization from alcohol-type solvents or mixtures with triacetin were analyzed by scanning electron microscopy and differential scanning calorimetry. Few differences were found concerning the size parameters of particles obtained from different solvents, while the shape parameters displayed major differences depending on the crystallization solvent. Most of the samples showed simple thermograms while in the case of those obtained from isopropanol and 1,3-butanediol, the presence of the solvent inside the mass of the crystals was recorded. Dissolution profiles were found to be different for all the samples (due also to different sizes of the dissolving particles). An interesting linear relationship was found between the efficiency of dissolution and the shape factor of the dissolving particles, suggesting the relevant importance of shape irregularity in affecting dissolution rate differences.

Keywords: Diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt; Scanning electron microscopy; Thermal analysis; Dissolution efficiency; Shape factor

1. Introduction

Knowledge of several physical and chemical properties of a drug is essential in the development of a stable, effective, safe and reproducible dosage form. These studies constitute the different steps to be carried out in the so-called preformulation program of a drug.

Many parameters such as crystal habit, chemical form, crystallization solvent, pH-solubility and pH-stability profiles, drug-excipient interactions, etc., are the main determinants of drug bioavailability from a solid dosage form together with physical and chemical stability.

Furthermore, all the aspects related to the performance of a dosage form of a drug can be modified by changes in manufacturing and synthetic processes. Particularly, the crystallinity is of significant importance. In fact, a modification in the crystallization conditions may affect the external appearance without altering the internal structure. Crystal habits influence many morphology characteristics, rheological and technophar-

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maceutical behaviours and, therefore, drug bioavailability from dosage forms. (Labhasetwar et al., 1993).

To carry out this type of study, we previously chose diclofenac as a reference of an acidic and poorly soluble drug, after examining the influence of the chemical form on the solubility in water and dissolution rate (Fini et al., 1994a). These parameters were also related to the morphology of the crystal powders and the structure of the salt forming bases as well as to characteristic cation-anion interactions (Holgado et al., 1995). Among the 30 salts examined, diclofenac/*N*-(2-hydroxyethyl)pyrrolidine salt, i.e., the most soluble in water, was examined with respect to its self-aggregation ability (Fini et al., 1991, 1994b) and solubility in a variety of non-aqueous or mixed solvents (Fini et al., 1994c). Crystals obtained from the saturated solution have been examined in this paper in order to evaluate the influence of the crystallization solvent on the precipitate morphology, particularly on the particle surface and related parameters. Moreover, since the diclofenac anion and *N*-(2-hydroxyethyl)pyrrolidine cation have in their molecules centers which behave as donor/acceptor of H-bonds, the interaction with solvent molecules cannot be without consequence on the nature of the crystal formed.

In a previous paper, the dissolution behaviour of DHEP in different solvents and binary solvent mixtures has been described (Fini et al., 1994b). In this article, our objectives were to investigate the process of recrystallization of DHEP from a series of solvents and binary solvent mixtures and to study the influence of the crystallization habit on the physicochemical and morphological characteristics and dissolution rates of the different samples of DHEP as previous steps of the preformulation program.

2. Materials and methods

2.1. Materials

The salt diclofenac/*N*-(2-hydroxyethyl)pyrrolidine (DHEP) was a gift from Ibsa, Lugano, Switzerland. The solvents used were PEG 200, PEG 400, 3-methyl-1-butanol, 2-propanol, 1,3-butanediol, 1,4-butanediol, 1-pentanol and glycerine triacetate (triacetin). Binary mixtures of triacetin and PEG 400 was used in different proportions: 10:90, 30:70, 50:50 and 70:30 by weight (Table 1). All the solvents were supplied by Fluka, Buchs, and were pure reagents.

Table 1
DHEP samples and crystallization solvents

Sample no.	Solvent/solvent mixture
1	triacetin/PEG 400 (10:90)
2	triacetin/PEG 400 (30:70)
3	triacetin/PEG 400 (50:50)
4	triacetin/PEG 400 (70:30)
5	1,3-butanediol
6	1,4-butanediol
7	3-methyl-1-butanol
8	1-pentanol
9	2-propanol
10	PEG 200
11	PEG 400

2.2. Preparation of the samples

100 mg of the salt were added to 1 g of each solvent or binary mixture; the system was heated in water bath up to 50° C for 5 min and then kept at 25° C for 24 h. In the absence of precipitate, a further 100 mg of the salt were added and the procedure repeated until a precipitate was formed on cooling. The systems were allowed to equilibrate for months: crystals grow slowly, showing smooth surfaces and globular forms. Finally, they were isolated and washed with diethyl ether.

2.3. Scanning electron microscopy

The shape and size of salt particles were examined by scanning electron microscopy (Philips, XL30). A very thin coat of carbon was applied to each sample, which was examined at different magnifications and some micrographs were taken of each sample. Size and shape parameters of the solids were 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 previously been reported (Fernández-Hervás et al., 1994).

The following parameters were selected to characterize the salt particles: area (A); perimeter (P); shape factor (S; this parameter 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),

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

maximum and minimum diameters, (D_{max} and D_{min}); and 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 one and particles elongated in the y-direction have an aspect ratio smaller than unity.

Six crystals of each sample were employed to accomplish all the measurements.

2.4. Thermal analysis

Differential scanning calorimetry (DSC) analysis was used to determine the thermal behaviour of DHEP salts. DSC thermograms were obtained using an automatic thermal analyzer system (Mettler FP80 HT Central Processor and Mettler FP85 TA Cell). A data processing system (Mettler FP89 HT) was connected to the thermal analyzer. Sealed and holed aluminium pans were used in the experiments for all the samples. Temperature calibrations were performed using indium as a standard. An empty pan, sealed in the same way as the sample, was used as a reference. All samples were run at a scanning rate of 10° C/min, from 40 to 200° C.

2.5. Dissolution rate

The dissolution profiles of different DHEP samples were determined using the rotating basket apparatus of USP XXII (Turu Grau, model D-6). The dissolution medium was 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, using a digital conductivity meter (Crison, model micro CM-2201) linked to a chart recorder and an IBM-compatible personal computer. The system provides one conductivity datum per s. An isolated crystal of each sample was used in the dissolution rate measurements.

3. Results and discussion

The salt diclofenac/*N*-(2-hydroxyethyl)pyrrolidine (DHEP), a new chemical form of the NSAID diclofenac, has recently become available

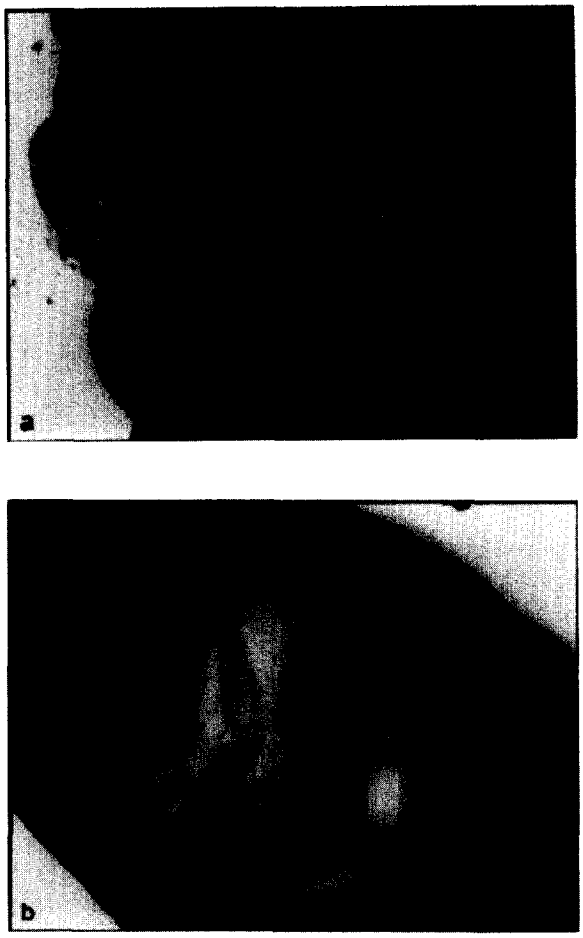

Fig. 1. Microphotographs of DHEP crystals obtained from triacetin/PEG 400. (a) 70:30; (b) 10:90 w/w.

in different pharmaceutical forms. The solubility of this salt has been measured in 28 solvents and 28 binary mixtures, to simulate the different conditions either of pharmaceutical technology (e.g., hydroalcoholic solutions) or the physiological environment (lipid membranes). A variety of behaviours was demonstrated for this salt in the different solvents: self-aggregation in water with solubilizing ability, ion-pair formation in 1-octanol – unexpected for an ionic compound, high solubility in lipid-like and low dielectric constant solvents. While the solubility in triacetin is 1.4% w/w, PEG/triacetin mixtures can contain more than 10% w/w salt, even in the presence of a high percentage of the lipid component.

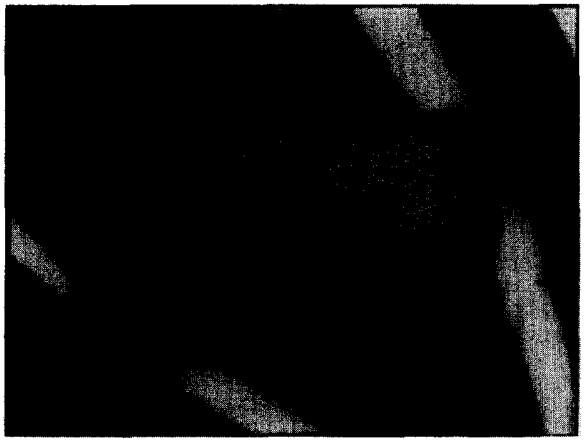

Fig. 2. Microphotographs of DHEP crystals obtained from: (a) 1,4-butanediol; (b) 2-propanol.

Fig. 3. Microphotographs of DHEP crystals obtained from: (a) PEG 200; (b) PEG 400.

Therefore, the salt samples recrystallized from solvents and binary solvent mixtures (Table 1) were then studied from a morphological point of view. They were obtained from alcohol-type solvents or mixtures with a lipid-like solvent (triacetin). The dissolution behaviour will subsequently be explained on the basis of the shape and morphological descriptors.

Fig. 1–3 show the micrographs corresponding to the indicated samples. Due to the fact that particles were prepared by slow evaporation of the solvent, their dimensions were larger than usual, although of irregular form, with rounded edges and smooth faces. As can be observed, salt particles obtained from triacetin/PEG 400 mix-

Table 2
Mean values (± SD) of SEM descriptors corresponding to the indicated samples

Sample	A (mm^2)	P (mm)	S	D_{max} (mm)	D_{min} (mm)	a
1	12.44 ± 1.08	31.03 ± 2.03	0.26 ± 0.02	5.33 ± 0.11	4.46 ± 0.23	0.76 ± 0.01
2	22.12 ± 1.79	37.68 ± 1.98	0.50 ± 0.01	6.66 ± 0.31	5.15 ± 0.36	1.39 ± 0.06
3	17.93 ± 1.54	25.01 ± 1.54	0.36 ± 0.01	5.50 ± 0.26	4.52 ± 0.25	0.77 ± 0.02
4	13.16 ± 1.21	18.37 ± 0.96	0.19 ± 0.02	5.53 ± 0.37	3.52 ± 0.19	1.49 ± 0.35
5	34.62 ± 1.41	34.03 ± 1.73	0.78 ± 0.01	8.18 ± 0.41	6.38 ± 0.46	0.90 ± 0.02
6	20.18 ± 1.33	19.71 ± 1.01	0.45 ± 0.02	6.57 ± 0.38	5.24 ± 0.29	1.39 ± 0.33
7	18.90 ± 1.13	20.73 ± 1.31	0.25 ± 0.02	5.49 ± 0.25	5.18 ± 0.38	1.07 ± 0.24
8	23.33 ± 0.04	17.25 ± 0.20	0.49 ± 0.03	2.49 ± 0.08	1.79 ± 0.07	1.32 ± 0.16
9	22.59 ± 0.01	17.94 ± 0.34	0.62 ± 0.02	2.23 ± 0.07	1.85 ± 0.06	1.12 ± 0.17
10	32.28 ± 1.73	30.52 ± 2.07	0.84 ± 0.01	8.08 ± 0.07	6.47 ± 0.28	1.09 ± 0.21
11	58.53 ± 1.44	38.02 ± 2.19	0.51 ± 0.02	11.28 ± 0.88	7.80 ± 0.33	1.14 ± 0.13

tures present the most irregular forms and rugged surfaces. In contrast, the salt obtained from 1,4-butanediol shows parallelepiped-shaped and smooth surfaces.

In relation to the SEM parameters, Table 2 lists the mean values corresponding to the indicated samples. Considering the size parameters (area, perimeter, minimum and maximum diameters), only minor differences were found among them.

Concerning the shape parameters (shape factor and aspect ratio), major differences can be observed. In the case of the shape factor, no relationship between this parameter and the type of recrystallization solvent was established. The importance of this parameter in relation to the dissolution rate will be commented upon later. In relation to the aspect ratio values, a general form of behaviour was not found. The most extreme case corresponds to the sample obtained from triacetin/PEG 400 mixture (70:30). This result indicates that crystals are apparently elongated in the x-direction.

The thermal study revealed a very similar behaviour for all the samples. Some thermograms of these samples are shown in Fig. 4a and b. Apparently, there are no significant changes in melting point values. It is interesting to emphasize the

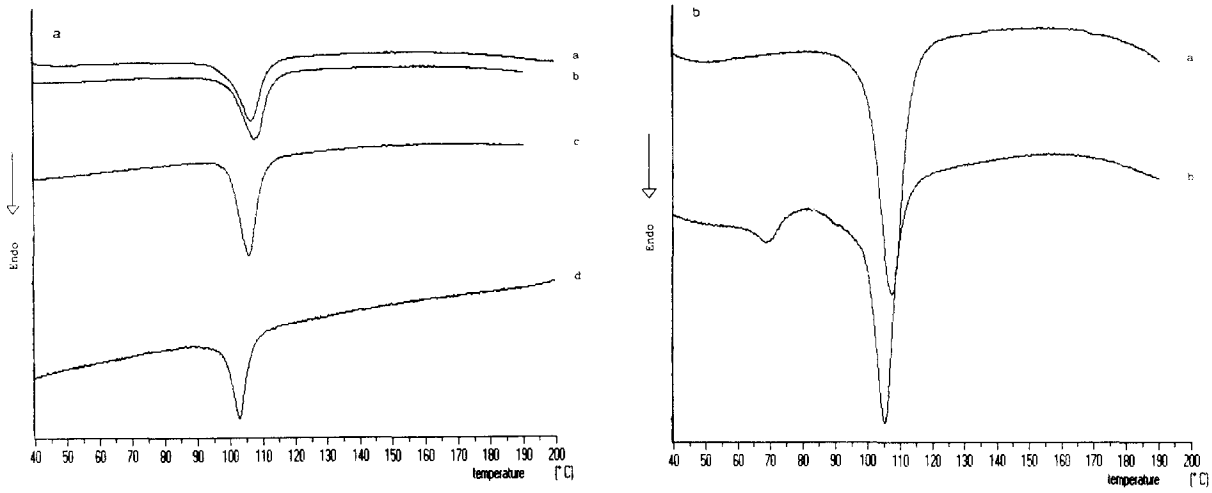

Fig. 4. Thermograms of the samples obtained from: (a) triacetin/PEG 400, 30:70; (b) 1,4-butanediol; (c) PEG 400; (d) triacetin/PEG 400, 70:30. (b) Thermograms of the samples obtained from: (a) triacetin/PEG 400, 10:90; (b) 1,3-butanediol.

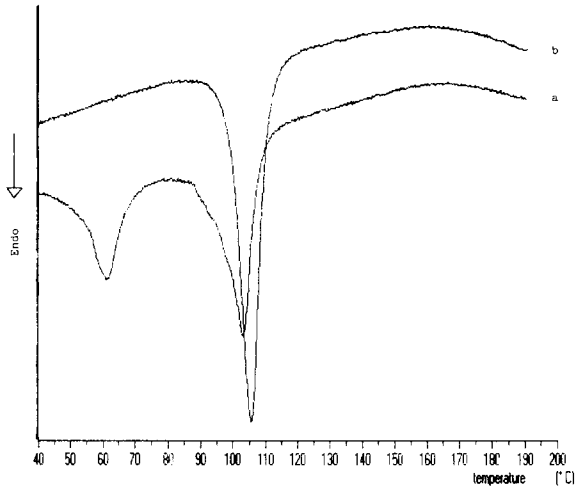

Fig. 5. Thermograms of the samples obtained from 2-propanol: (a) before and (b) after thermal treatment (40° C, 3 days).

thermogram corresponding to the sample obtained from 1,3-butanediol presenting an additional endothermic peak, approximately between 65 and 70° C, corresponding, perhaps, to the solvent.

When these samples were subjected to thermal treatment in an oven (Selecta model 204), 40° C for approx. 3 days, the new thermograms did not demonstrate these endotherms. As an example, Fig. 5 shows this circumstance for DHEP 9. Therefore, it can be assumed that solvent molecules become associated to the crystal during the recrystallization process and are lost after heating of the samples. Further investigations will be carried out in order to determine whether solvent molecules are only adsorbed on the particle surface or incorporated into the bulk. Thus, it should be possible to gain knowledge on the formation of potential solvates.

Table 3
Dissolution efficiency corresponding to the indicated samples

Sample	E_d (%)
DHEP 1	58.80
DHEP 2	33.11
DHEP 3	47.56
DHEP 4	64.38
DHEP 5	20.53
DHEP 6	48.24
DHEP 7	72.49
DHEP 8	47.43
DHEP 9	44.36
DHEP 10	21.12
DHEP 11	32.03

Fig. 6–8 show the dissolution profiles of the studied samples. The dissolution efficiency was calculated as amodelistic parameter in order to evaluate the dissolution process (Table 3). As can be observed, the highest values of E_d are achieved by those samples presenting the most irregular shapes, i.e., lower shape factor values.

No relationship was observed between the E_d

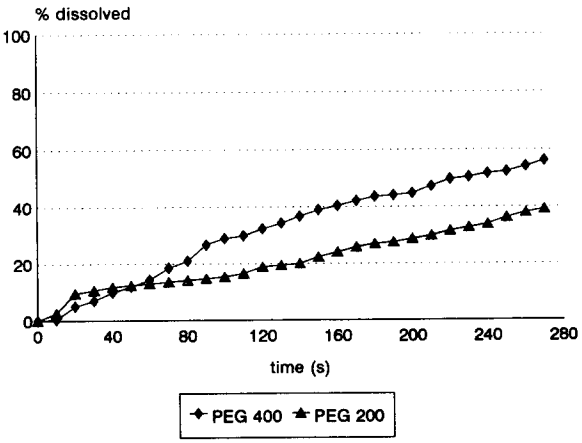

Fig. 6. Dissolution profiles for the DHEP samples indicated.

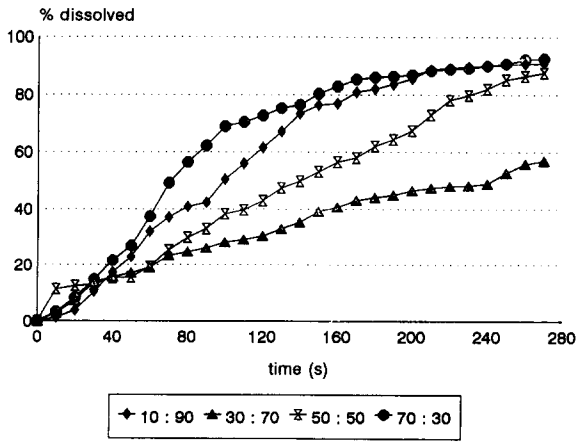

Fig. 7. Dissolution profiles for the DHEP samples obtained from diverse triacetin/PEG 400 mixtures.

values and the nature of the crystallization solvent or experimental parameters, such as the surface area of the particles or other SEM parameters. As observed previously in the case of this salt (Fernández-Hervás et al., 1994), fractal analysis revealed the presence of irregularities on the surface that can affect the process of dissolution besides the usual parameters contained in the Noyes-Whitney equation. It is therefore possible that, in the case of different samples of the same compound, the fractal structure of the dissolving surface accounts for the E_d values. Without carrying out a time-consuming fractal analysis, the shape factor can be used here as an indicator. In fact, the shape factor relates the surface area of the particle to the extension of the peripherical border: a value of 1 is typical of a circular particle; it follows that a shape factor value lower than 1 is indicative of particles with increasing irregularity in contour. The relationship between the shape factor and E_d is shown in Fig. 9 as being roughly inversely linear. This circumstance demonstrates the importance of novel microscopic particle properties, such as surface morphology and degree of porosity, summarized in the shape factor, beside classical parameters, such as the surface area and particle dimension and shape to analyze the dissolution data.

The effects of surface irregularity and roughness on the dissolution rate of drugs and, obviously, on their bioavailability from solid dosage

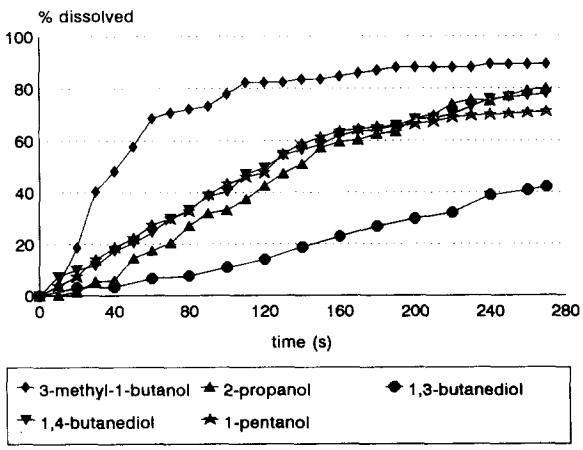

Fig. 8. Dissolution profiles for the DHEP samples indicated.

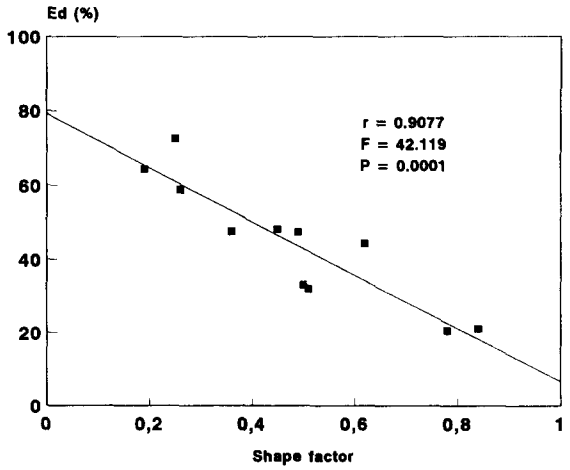

Fig. 9. Inverse linear relationship between efficiency of dissolution and shape factor.

forms (Farin and Avnir, 1992) are well known. The obtained results indicate that the efficiency of a dissolution process can be increased by controlling the geometrical parameters of the pharmaceutical powders (Farin and Avnir, 1987) and, therefore, the routes to achieve them, such as the nature of the crystallization solvent, the degree of saturation and the temperature of the starting solution and the rate of cooling during crystallization.

On the other hand, it is important to emphasize the usefulness of these SEM parameters as a new tool to interpret the dissolution behaviour of drugs. Applying an image processor to the electronic microscope, a rapid and effective method to determine easily the crystal morphology has been achieved. This method offers a series of variables estimating the morphological characteristics of particles, meaning more reliable conclusions and saving a considerable amount of time.

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