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Characterization and compaction behaviour of nimesulide crystal forms

Piera Di Martino [a,*], Roberta Censi [a], Christine Barthélémy [b], Roberto Gobetto [c], Etienne Joiris [b], Admir Masic [c], Pascal Odou [b], Sante Martelli [a]

[a] *Laboratorio di Tecnica Farmaceutica, Dipartimento di Scienze Chimiche,Via S. Agostino, 62032 Camerino, Italy*
[b] *Laboratoire de Biopharmacie et Pharmacie Galénique, Faculté de Pharmacie, Université de Lille II, 59006 Lille, France*
[c] *Dipartimento di Chimica I.F.M., Università di Torino, Via P. Giuria 7, 10125 Torino, Italy*

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Abstract

Nimesulide is a typical nonsteroidal anti-inflammatory drug (NSAID), widely used in solid oral formulations. By crystallizing nimesulide from an ethanol solution a crystalline form was obtained, different from the reference sample, as confirmed by X-ray powder diffraction (XRPD), Differential Scanning Calorimetry (DSC) and solid cross polarization-magic angle spinning (^{13}C-CPMAS) NMR. Moreover, when crystallized from dioxane nimesulide forms a solvate. The solvate was characterized by XRPD, IR-spectrometry, DSC, thermo-gravimetric analysis (TGA) and by ^{13}C-CPMAS NMR. In particular, through this technique, the presence of several conformational isomers was demonstrated.

In addition to the physico-chemical characterization, the technological properties of nimesulide, namely densification and tableting, were evaluated. Contrarily to the other forms that are affected by capping phenomena at increasing compression pressures, the form obtained by desolvation of dioxane solvate has positive effect on tableting properties, increasing both compressibility and tabletability of nimesulide.

Keywords: Nimesulide; Polymorphism; Solvation; Tableting; Densification

1. Introduction

Drugs can exist in different crystalline forms. Formulators should appropriately take advantage of this when some unfavourable technological and biopharmaceutical properties of drugs must be improved. In the literature, there are many examples of the suitability of using one crystalline form rather than another one (Haleblian and McCrone, 1969; Joiris et al., 1998; Changquan and Grant, 2001; Rollinger et al., 2002; Bartolomei et al., 1999). However, a limit exists in the use of metastable forms because of their higher free energy (Hancock and Zografi, 1997) and reactivity than the stable form, with adverse effects on their physico-chemical stability.

Crystal modifications can also appear during the formulation phase, or even during the normal dosage form shelf-life. Changes in crystal form could be a consequence of some common technological process such as wet granulation (Otsuka et al., 1999), melting (Di Martino et al., 1997), spray drying (Di Martino et al., 2001), compression (Chan and Doelker, 1985), milling (Bauer-Brandl, 1996), that are required to produce the final dosage form. The possible incidence of these phenomena must be discovered and studied.

Therefore, the detection and the full characterization of all the possible polymorphs or solvates that can be formed are of paramount importance. In addition, the use of organic solvents, can give important problems on the residual solvent content, specially when they remain in high amount in the crystalline drug structure. Hence, solvent must be removed by desiccation and the efficacy of the process must be demonstrated.

The aim of this study is the elucidation of the changes in the crystalline form of nimesulide when crystallized from different solvents, and their impact on tableting properties. Nimesulide is a typical NSAID, widely used in solid oral formulations. It has analgesic, anti-inflammatory and antipyretic properties. It is an inhibitor of prostaglandin synthetase and of platelet aggregation (Moore and Harrington, 1974; Swingle and Moore, 1984).

* Corresponding author. Tel.: +39 0737 402215; fax: +39 0737 637345.
E-mail address: piera.dimartino@unicam.it (P. Di Martino).

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2. Materials and methods

2.1. Materials

Nimesulide was kindly supplied by A.C.R.A.F. (Ancona, Italy) and it will be identified as "reference". Solvents were all of analytical grade: ethanol (96%, v/v Panreac Quimica, Barcellona, Spain); acetone (Panreac Quimica); dioxane (Lab Scan, Dublin, Ireland); tetrahydrofuran (Panreac Quimica); dichlorometane (JT Baker, Deventer, Holland); trichloromethane (Normapur AR Prolabo, Fontenay/Bois, France).

2.2. Crystallization methods

Drug was dissolved in the solvent at 40 °C and the solution was allowed to cool spontaneously in an ice bath under stirring. Crystals were desiccated under an inhaler hood during one day at room temperature and afterwards preserved in presence of P_2O_5. For the technological study, the acicular crystals obtained from ethanol were gently broken. For all the samples, the 100–200 μm granulometric fraction was recovered by air-sieving the particles to remove the fines.

2.3. Physical characterization

Nimesulide was studied by using the Differential Scanning Calorimetry (DSC, Pyris 1, Perkin-Elmer, Co. Norwalk, USA). The apparatus was equipped with an ethanol cooling system circulating in a refrigerator (Cryostat F4-Q, Haake Q, Karlsruhe, Germany). A dry purge of nitrogen gas (20 ml/min) was used for all runs. DSC was calibrated for temperature and heat flow using samples of pure indium and zinc standards. Sample mass was about 5–10 mg and aluminium open, perforated or closed pans were used. Each run was performed in triplicate from 0 to 180 °C at a heating rate of 10 °C/min.

Weight loss during heating was evaluated by TG Mettler TA 3000, equipped with a microbalance M3 (Mettler Toledo, Greifensee, Switzerland). The temperature range was from 25 to 160 °C at a heating rate of 10 °C/min, under dry nitrogen atmosphere.

The X-ray powder diffraction (XRPD) study was carried out to characterize nimesulide samples by using a Philips PW 1730 (Holland) X-ray generator for Cu Kα radiation (λ = 1.54178 Å). The goniometer supply was a Philips PW 1373 and the channel control a Philips PW 1390. The data were collected in the continuous scan mode using a step size of 0.01° 2θ. The scanned range was 2°–45° (2θ).

IR spectra were recorded between 4000 and 750 cm^{-1} (Perkin-Elmer 1600 Series FT-IR, Norwolk, USA). Each sample was mixed with KBr (FT-IR grade, Aldrich, Stenheim, Germany) and compressed at 70 kN with a Perkin-Elmer hydraulic press.

High-resolution ^{13}C solid state spectra were performed with a Jeol GSE 270 (6.34 T) spectrometer operating at 67.9 MHz, equipped with a Doty XC5 probe. The spectra were recorded at a spinning rate in the range 6–10 kHz under conditions of ^{1}H–^{13}C cross polarization, high power proton decoupling and magic angle spinning. The 90° pulse was 5.50 μs and the contact pulse was 5 ms. The line broadening was set to be 10 Hz satellite transitions. The spectra were collected after 400 scans using a recycle delay of 10 s. Cylindrical 6 mm o.d. zirconium rotors with sample volume of 120 μl were employed. For all samples, the magic angle was carefully adjusted from the ^{79}Br MAS spectrum of KBr by minimizing the line width of the spinning side band satellite transitions.

Gas phase chromatography (GC) (for dioxane and ethanol) was performed on a Shimadzu GC 14 B Chromatograph fitted with a Flame Ionisation Detector and a CR-6A Shimadzu integrator; packed column Porapack Super Q (Alltech, France), mesh range 80/100, length 6 ft, diameter 1/8 in. Carrier gas was anhydrous nitrogen (40 ml/min); injector: 210 °C; detector: 240 °C. Standard solutions were injected to validate the method (linearity, specificity, repeatability). Assay solutions were obtained by a microdistillation of 5 ml of absolute ethanol (for dioxane determination) or ethyl acetate (for ethanol determination) containing 100 mg of nimesulide crystals to be analysed. The following conditions were used:

- for dioxane: column temperature: isotherm at 170 °C. Injection: 10 μl. Retention times: ethanol 0.83 min.; dioxane: 7.5 min.
- for ethanol: column temperature: isotherm at 170 °C. Injection 5 μl. Retention times: ethanol 1.1 min, ethyl acetate: 4 min.

2.4. Technological properties

Crystal morphology of native particles was determined by using a scanning electron microscope (SEM, Stereoscan 360, Cambridge Instruments, Cambridge, United Kingdom). Samples were mounted on a metal stub with a double-sided adhesive tape and then covered under vacuum with a gold layer of 200 Å of thickness using a metallizator (Balzer MED 010, Liecktenstein).

The compression study was carried out on a high tech. mini rotary press (Ronchi, Piccola 10, Italy) equipped with a computerized control system to detect and analyse force-signals (pressing force and ejection force) and with 10 flat 11.28 mm-diameter punches. Because the sample quantities were small, they were introduced manually into only one die. Die and punches were prelubricated with a 1% magnesium stearate suspension (A.C.E.F., Italy) in ethanol 96% (v/v) (PRS, Panreac, Spain). The powder mass was progressively increased and the force at the upper punch was recorded. The results for each compression force were the mean of five measurements.

Results are expressed as tabletability (Joiris et al., 1998), i.e. the capacity of different materials to be transformed into tablets of specified strength under the effect of compression pressure and as compressibility (Joiris et al., 1998), which is the ability of a material to undergo a reduction in volume as a result of an applied pressure. Thickness and diameter of intact ejected tablets were measured with a manual micrometer (Mitutoyo, Japan) immediately after ejection. Tablet porosity was calculated from tablet dimensions, mass and apparent particle density. This last

parameter was measured by using a helium pycnometer (AccuPyc 1330, Micromeritics, Norcross, USA) with a cell of 10 cm^3. Results were the mean of 10 measurements. Crushing force was measured immediately after compression with a tablet strength tester (Erweka, type TBH30, Germany). Tensile strength Q (Fell and Newton, 1970) was calculated according to Eq. (1):

$$Q = \frac{2H}{\pi \times d \times t} \quad (1)$$

where H is the tablet crushing strength, d the diameter and t is the thickness of the tablet.

For the densification study, powders were compressed on an instrumented Frogerais OA single punch tablet machine (Frogerais, France) equipped with 11.3 mm flat-faced punches, by introducing manually 390 mg samples into the prelubricated die, according to Lefèbvre et al. (1989). Five cycles were performed for all substances, corresponding to a maximal punch pressure of about 125 MPa. For a single compression cycle, both compression pressures on the upper and lower punches and the displacement of the upper punch were measured and recorded at a frequency of 4000 Hz. Correction of displacement transducer data for machine looseness and punch deformation were carried out according to Juslin and Paronen (1980).

Pressure transmission through the powder bed in the die was estimated by comparing the maximal compression pressures on the upper and lower punches. The transmission coefficient corresponds to the ratio of lower punch and upper punch pressure values.

The densification behaviour of powders was studied using Heckel's (1961) Eq. (2)

$$\ln\frac{1}{1-D} = KP + A \quad (2)$$

where D is the relative density of the compressed powder bed at the applied pressure P. K is the slope of the straight linear portion of the Heckel plot and the reciprocal of K is the mean yield pressure (P_Y). The constant A is the sum of two densification terms, as expressed by the Eq. (3):

$$A = \ln\left(\frac{1}{1-D'_0}\right) + B' \quad (3)$$

According to Doelker (1994), D'_0 corresponds to the relative density of the powder at the moment when the last recorded applied pressure is still nil, and B' is the densification due to particle fragmentation. Constants A and B' can be expressed as relative densities using both the Eqs. (4) and (5):

$$D_A = 1 - e^{-A} \quad (4)$$

$$D'_B = D_A - D'_0 \quad (5)$$

Heckel's profiles were established from single compression cycles of tablets compressed approximately at 100 MPa. Parameters P_Y, D_A, D'_0, D'_B were calculated using a precompression pressure value of 1.5 MPa. Several methods were described to select a linear region of the Heckel function in order to determine Heckel constants. According to Paronen and Ilkka (1996), a range of measurement points, with the highest linear regression coefficient, was selected. This corresponds to a value in the range 50–100 MPa for all the samples. Each value is a mean of five measurements.

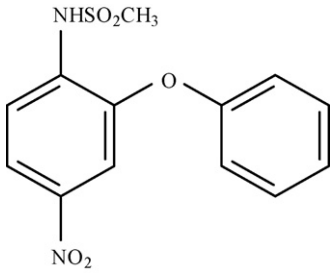

Fig. 1. Nimesulide molecular structure.

Elastic recovery (ER) was calculated according to Armstrong and Haines-Nutt (1974) Eq. (6):

$$ER = \left[\frac{(t_2 - t_1)}{t_1}\right] \times 100 \quad (6)$$

where t_1 is the minimal thickness of the powder bed in the die and t_2 is the thickness of the recovered tablet.

3. Results and discussion

3.1. Crystallization of nimesulide from different solvents

The molecular structure of nimesulide, 4-Nitro-2-phenoxymethanesulfonanilide, $C_{13}H_{12}N_2O_5S$, is given in Fig. 1. In a previous work, Kapoor et al. (1998) demonstrated that by crystallizing nimesulide in presence of different organic solvents, some physical properties were affected, such as melting point, solubility and dissolution rate, leading to suppose that several polymorphic forms of nimesulide were obtained. Thus, in the present study, nimesulide was crystallized from different solvents, selected according to their polarity and nimesulide solubility (ethanol, acetone, dioxane, THF, dichloromethane, trichloromethane). Crystals were analysed by XRDP, the best and fastest technique for evaluation of crystallographic differences. Interreticular distances of samples obtained from acetone, trichloromethane, dichloromethane and THF are identical to that of reference sample. On the contrary, differences in the interplanar spacing were observed for samples obtained from ethanol and dioxane. The corresponding XRPD patterns are represented in Fig. 2. The related results are discussed below.

3.1.1. Physical characterization of nimesulide crystallized in dioxane

In Fig. 2, the XRPD patterns of the sample crystallized in dioxane are compared to that of reference nimesulide, and several differences in interreticular distances between the two structures are highly evident. During the DSC study, the presence of a large endotherm at approximately 343.15 ± 0.48 K extrapolated onset temperature was observed (Fig. 3a). The thermo-gravimetric analysis (TGA) allowed to attribute this

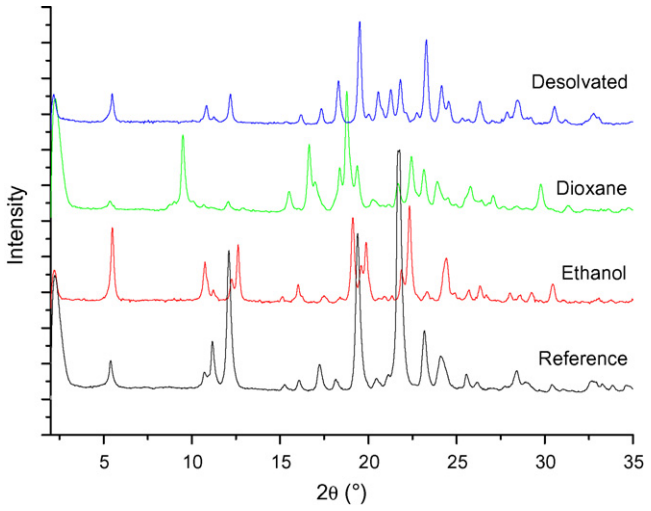

Fig. 2. XRPD of reference nimesulide, nimesulide crystallized from ethanol, nimesulide crystallized from dioxane and nimesulide crystallized from dioxane and then desiccated.

behaviour to a desolvation process (Fig. 3b). The calculation of the solvent weight loss led to establish a nimesulide:dioxane ratio of 4:1. Dioxane content in solvated nimesulide, evaluated by GC, was of 57921 ± 889 ppm, approximately corresponding to 5% (w/w). In order to confirm the dioxane solvate formation, the sample was heated at 70 °C for 1 h in a ventilated oven. The XRPD of the desiccated sample, reported in Fig. 2, shows the reversion of the solvated nimesulide structure to that of the reference one. Some differences in peak intensities can be pointed out and in particular the peak at about 22° (2θ) which represents the 100% in the reference sample is strongly reduced in the desolvated one. After this thermal treatement, desolvation was not yet observed by both DSC and TGA and the dioxane content determined by GC was <75 ppm.

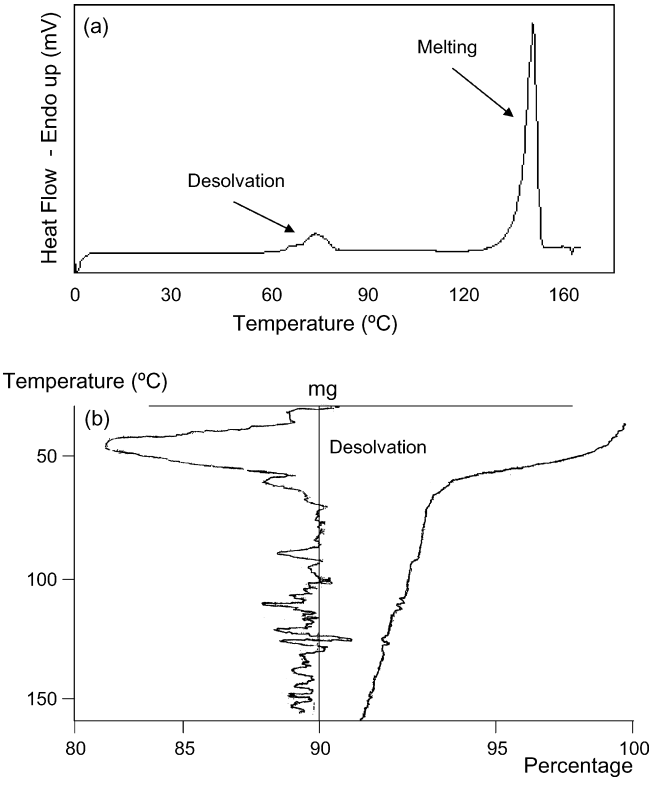

Fig. 3. Thermal analysis of nimesulide crystallized in dioxane: (a) DSC thermal analysis (heating rate 10 °C/min) and (b) TGA thermal analysis (heating rate 10 °C/min).

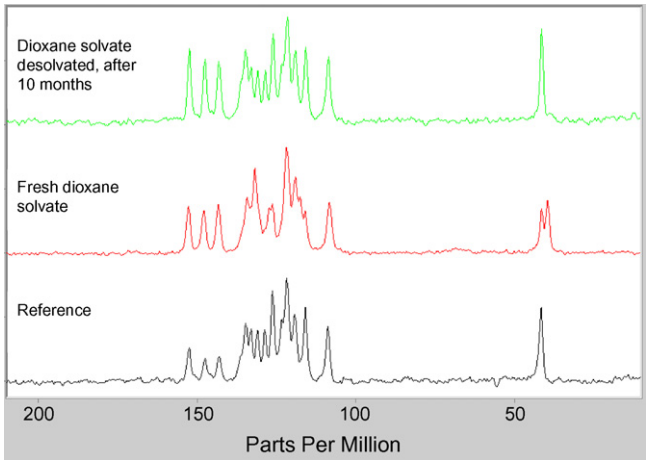

Fig. 4. ^{13}C CPMAS NMR spectra of reference nimesulide, nimesulide crystallized from dioxane and immediately analysed, and nimesulide crystallized from dioxane and analysed after 10 months.

We concluded that a dioxane solvate form was obtained. The solvation by dioxane promotes only slight modifications on the nimesulide crystal form, but these are sufficient to induce changes in crystallographic parameters. According to Allen et al. (1978), who suggested that low desolvation temperatures involve a weak molecule–solvent interaction, the relatively low desolvation temperature confirms that no strong bonds participate of nimesulide–dioxane interaction. In fact, the possible hydrogen bond between the hydrogen of the sulfonamidic group and the oxygen of the dioxane molecule seems not to be present, as demonstrated by the absence of a large band at 3800 cm^{-1} in the IR spectra. Another important behaviour is the relative stability of the solvated form. In fact, by XRPD it was possible to follow the progressive conversion of the solvated form to the desolvated form at ambient conditions, with its complete transformation after 10 months. In order to confirm these results a ^{13}C-CPMAS NMR was recorded (Fig. 4). By comparing the number and the shape of the resonances between the reference nimesulide and the nimesulide crystallized in dioxane, the presence of several new resonances was noted. In particular, in addition to the typical peaks present in the reference spectra, a new signal in the methyl region at δ = 39.5 ppm and several others in the aromatic region (100–140 ppm) were observed in the spectra of the nimesulide crystallized in dioxane. These data corroborate the hypothesis that a metastable form is obtained in the case of crystallization in dioxane, with a crystal structure, which closely resembles that of the final product, as also suggested by the fact that after 10 months the structure of nimesulide from dioxane is completely reversed to that of reference nimesulide. The lack of the presence of dioxane peaks in the NMR spectra (normally found at 26.5, 66.9 and 94.2 ppm) can be explained by the low percentage of the solvent in the crys-

tal structure. On the basis of the NMR data it is not possible to completely elucidate the structure of the metastable product obtained by crystallization in dioxane. Nevertheless double resonance for the methyl group is a clear indication of a new conformational arrangement of the nimesulide molecule, probably stabilized by different intermolecular hydrogen bonds and van der Waals interactions.

Thus, it is possible to conclude that the solvation by dioxane slightly modifies the nimesulide crystallographic structure and promotes conformational changes in the molecule.

3.1.2. *Physical characterization of product crystallized in ethanol*

The XRPD patterns for nimesulide obtained by crystallization from ethanol are compared to the reference sample and to the drug recrystallized from dioxane in Fig. 2. Differences in the interreticular distances of the peaks can be observed, suggesting differences in their crystallographic structures. The XRPD patterns correspond to those reported by Bergese et al. (2003).

In the present report, the attempts to attribute the X-ray powder patterns to a specific crystallographic lattice were not successful. This is due to the fact that the present pattern results from the co-existence of two different crystallographic structures. In fact, in nimesulide crystallized from ethanol the presence of a mixture of the two polymorphic forms was already pointed out by Bergese et al. (2001, 2003).

Because the DSC, carried out at the commonly used heating rate of 10 K/min, showed a slightly splitted endothermic peak, the sample recrystallized from ethanol was subjected to additional DSC heating rates (Fig. 5). Slower heating rates, particularly 0.5 and 1.0 K/min, allowed to evidence the presence of an additional small endotherm, with an onset temperature depending from the heating rate: at a 0.5 K/min heating rate the extrapolated onset melting temperature is 418.95 ± 0.50 K; whereas at higher heating rate the temperature progressively approaches that of the stable form (420.65 ± 0.75 K). These temperature values are well superimposable to those reported by Bergese et al. (2003). Thus, it is possible to conclude that the first small endotherm, corresponding to the melting of a metastable form, is followed by a quite pronounced crystallization exotherm and by the stable form melting endotherm. Also on the basis of the preliminary remarks obtained from the XRPD data, it is possible to assume the presence of a mixture of two different polymorphic forms in the sample crystallized from ethanol. The ethanol content, evaluated by GC, was 723 ± 16 ppm. In Fig. 6, CPMAS ^{13}C NMR spectrum of nimesulide obtained by recrystallization from ethanol is compared to the reference sample. The former shows slightly broader peaks while the number of resonances is smaller with respect to the reference sample.

The existence of two polymorphic forms observed by the DSC and XRPD cannot be detected by solid state NMR. This is probably due to similar chemical environments of the different carbon atoms and/or the low content of one of the forms as detected by DSC.

3.2. *Influence of polymorphism and pseudo-polymorphism on technological properties of nimesulide*

SEM photomicrographs of different native samples are given in Fig. 7. The reference crystals appear such as quite isodimensional irregular particles, with rather smooth angles. Crystals obtained from ethanol appear as needle-like particles, while those from dioxane are similar to the reference crystals and their desolvation process does not affect crystal habit.

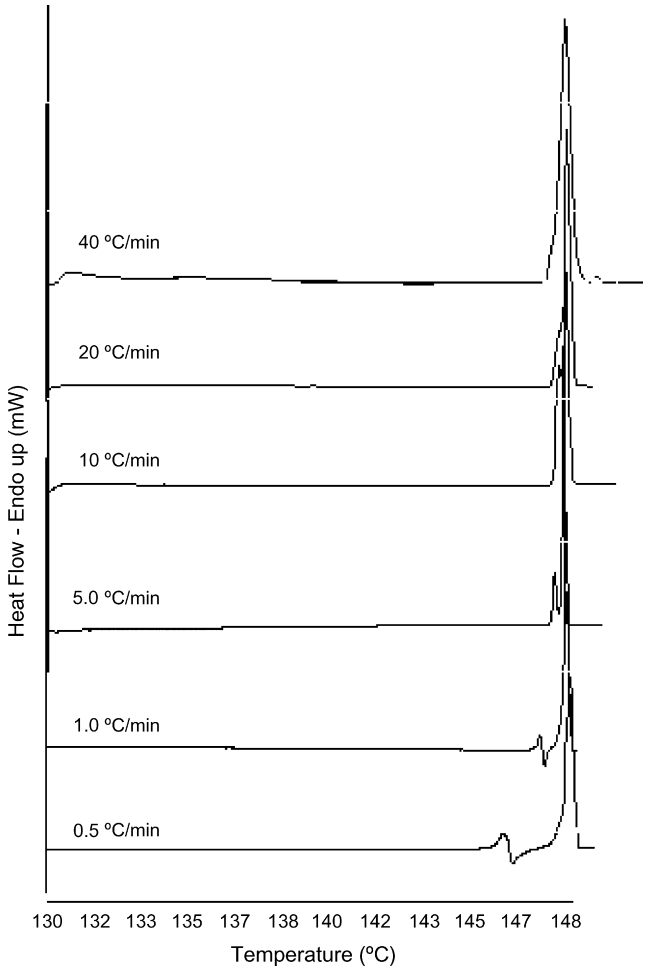

Fig. 5. DSC thermal analysis of nimesulide crystallized in ethanol. Scans were performed at different heating rates.

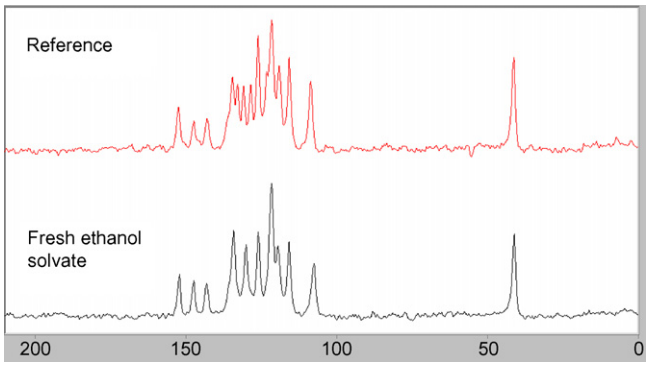

Fig. 6. CPMAS ^{13}C NMR spectra recorded at 67.9 MHz for nimesulide reference sample and nimesulide crystallized from ethanol solution.

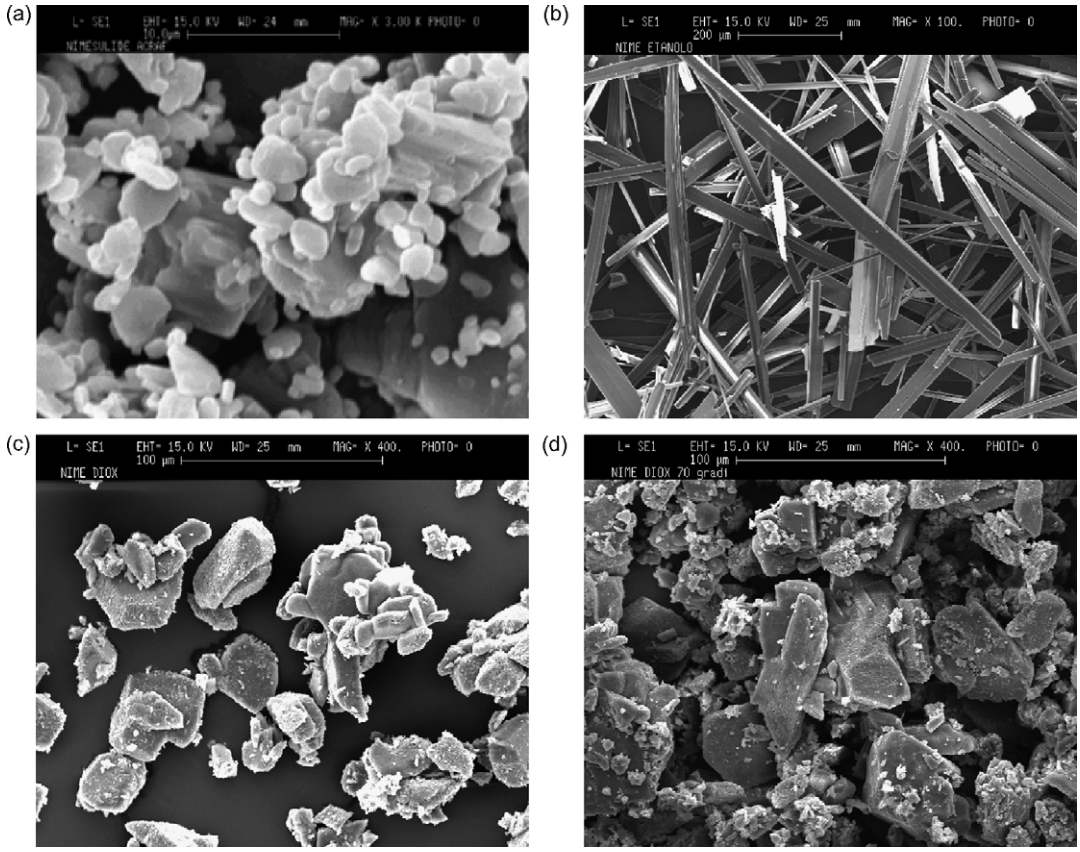

Fig. 7. SEM microphotographs of nimesulide bulk samples: (a) nimesulide reference; (b) nimesulide crystallized in ethanol; (c) nimesulide crystallized in dioxane and (d) nimesulide crystallized in dioxane and then desolvated at 70 °C for 1 h.

Tableting properties of nimesulide samples are given in Fig. 8. Nimesulide reference shows a quite good tabletability until about 150 MPa and the tablet tensile strength increases proportionally with the compression pressure applied. Capping signs clearly appear above 150 MPa, as demonstrated by the strong decrease in tablet tensile strength (Fig. 8a) and by constant tablet porosity with increasing compression pressure (Fig. 8b). Nimesulide recrystallized in ethanol shows poorer tableting properties. In spite of its tablet tensile strength higher than reference nimesulide at lower compression pressures, capping drastically appears even at about 100 MPa (Fig. 8a), as can be explained by the compressibility (Fig. 8b). Nimesulide crystallized in dioxane shows the poorest tabletability, as demonstrated by the lowest tablet tensile strength (Fig. 8a) and by the highest tablet porosity (Fig. 8b). However, its capping appears less clearly than with previous samples. Completely different is tableting behaviour of nimesulide crystallized from dioxane and then desolvated. During the entire considered compression pressure range, it always shows the best tabletability (Fig. 8a), and no capping occurs, as also shown by its ability to reduce its volume in the considered compression pressure range (Fig. 8b).

Results of the Heckel's analysis are reported on Table 1. They show only small differences among all products, the greatest being found between the reference and the three other samples. Under compression, reference nimesulide exhibits the greatest particle slippage ($D'_0 = 0.634 \pm 0.003$), but a minor particle fragmentation tendency ($D'_B = 0.095 \pm 0.003$). Additionally, the densification process by particle deformation is poorer than in the other samples, as supported by the highest mean yield pressure value ($P_Y = 93.7 \pm 0.9$). The poor tableting properties (low tablet tensile strength and high porosity) can be a consequence of the densification behaviour, but they can be also related to a poor particle–particle interaction during the consolidation phase. In conclusion, its densification behaviour is typical for a quite rigid material and differences with the other products should be ascribed to differences in crystallographic properties (monoclinic/pseudo-orthorhombic form).

The three other samples are characterized by a higher fragmentation tendency that reduces differences in original particle size and shape. This is accompanied by a somewhat better deformability, but greater elastic recovery (greater visco-elastic component). Apparently, due to the very small differences among all these products, these considerations are insufficient to explain the capping tendency at higher compression pressures and differences in tabletability. It is possible that differences in tabletability are related not to differences in densification behaviour, but rather to differences in bonds involved in the structure consolidation. In fact, the particles obtained from dioxane and then desiccated, which exhibit a far higher tabletability and no capping tendency, have Heckel parameters similar than nimesulide samples obtained from both ethanol and dioxane. The better tabletability of a desolvated material is not unusual. It has been previously described by Fachaux et al. (1995), that in the case of paracetamol recrystallized in dioxane and sub-

Table 1
Heckel's parameters obtained from single compression cycles and total elastic recovery

	Reference	Ethanol	Dioxane	Dioxane-desolvated
Apparent particle density (g cm^{-3})	1.477 ± 0.003	1.476 ± 0.001	1.440 ± 0.004	1.4403 ± 0.003
D'_0 (at 1.5 MPa)	0.634 ± 0.003	0.566 ± 0.007	0.513 ± 0.005	0.509 ± 0.002
D_A	0.730 ± 0.001	0.729 ± 0.001	0.662 ± 0.001	0.663 ± 0.002
D'_B ($D_A - D'_0$)	0.095 ± 0.003	0.163 ± 0.008	0.149 ± 0.004	0.154 ± 0.003
P_Y	93.7 ± 0.9	79.0 ± 1.1	79.2 ± 0.9	79.2 ± 0.8
Elastic recovery (%)	1.48 ± 0.15	2.21 ± 0.17	2.15 ± 0.36	1.96 ± 0.25

Values are the mean of five determinations and 95% confidence intervals are indicated.

sequently desolvated, the solvent removal could leave a porous structure, suitable for compression. In the present study, authors suggest that the presence of one dioxane molecule every four nimesulide molecules promotes slight changes in the crystallographic structure (from monoclinic pseudo-orthorhombic to monoclinic form) and that desiccation promotes complete structure reversion (from monoclinic to monoclinic pseudo-orthorhombic form). This structure modification is accompanied by an important decrease of the peak intensity in the desolvated sample (Fig. 2), leading to an irregular structure more favourable to compression.

The product obtained from ethanol has moderate densification properties, due to particle fragmentation but, at the same time, an important elastic recovery. It seems that the deformation behaviour is due to a certain elastic component which is very important at higher compression pressures, and not offset by the contemporary establishment of strong bonds.

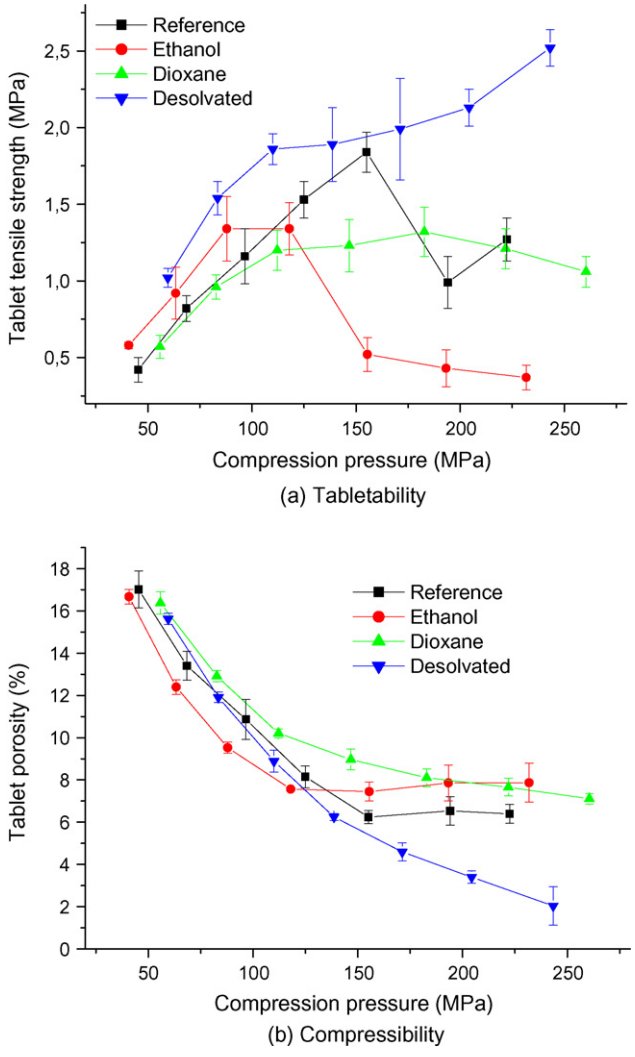

Fig. 8. Compression behaviour study of nimesulide samples: (a) tabletability and (b) compressibility.

4. Conclusion

Information recovered by several physico-chemical analyses such as XRPD, ^{13}C NMR CPMAS, DSC and TGA reveal that crystallization in solvents such as dioxane or ethanol leads to crystallographic changes. Crystallographic modifications were accompanied by differences in tableting properties. In particular, nimesulide crystallized in dioxane showed after desiccation the best tabletability and compressibility. Considering that, due to capping problems, nimesulide tablets must be produced by a granulation procedure, the possibility to obtain a directly compressible form could be an important tool, not only for technological reasons, but also because of the very poor water solubility of the drug. In fact, tablets obtained by direct compression generally disintegrate faster than tablets obtained by a granulation process, leading to an improvement in drug bioavailability. This aspect will be considered in depth in a further publication. In addition, considering the important modifications that could be involved during crystallization processes, particular care must be taken to control crystalline modifications during technological processes.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2007.05.009.

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