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European Journal of Pharmaceutics and Biopharmaceutics 60 (2005) 99–111
European Journal of Pharmaceutics and Biopharmaceutics
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Research paper

Diclofenac salts, II. Solid dispersions in PEG6000 and Gelucire 50/13

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Received 12 February 2004; accepted in revised form 19 November 2004
Available online 13 January 2005

Abstract

A number of systems were prepared at five compositions (5, 10, 20, 30 and 40% w/w) of diclofenac/*N*-(2-hydroxyethyl) pyrrolidine salt and acidic diclofenac in PEG6000 and Gelucire 50/13, as physical mixtures and as solid dispersions. Powder X-ray diffractograms for the systems examined show shifted and normal peaks, suggesting that the drug is present inside the samples in different physical states. Differential scanning calorimetry does not offer important information, since drug solubility into the carriers increases with temperature and thermograms show only the melting point peak of the carriers. Hot-stage microscopy examination explains that, in high concentration samples, the drug is present either dissolved into the carriers, or precipitated as microcrystals, or undissolved crystals of larger size. Gelucire 50/13 allows the formation of larger crystals than PEG, using both the chemical forms of the drug. The release percentage of the drug from PEG6000/acidic diclofenac reaches 50% after few minutes in the most favourable case and appears to be dependent on the composition of the samples: the more diclofenac is present as dissolved in the pre-treated samples, the higher is the release. The optimum composition was found in the range of 5–10% w/w.

Keywords: Diclofenac/-(2-hydroxyethyl) pyrrolidine and acidic diclofenac; PEG6000 and Gelucire 50/13; Solid dispersions; SEM; XRD; HSM and DSC; Dissolution profiles

1. Introduction

Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. They have been consequently objects of numerous researches to improve this behaviour. Among common NSAIDs, diclofenac, a potent anti-inflammatory drug of this class, is one of the least soluble compounds. Even though present as sodium and potassium salt [1] since long time in commercial formulations, the problem of its solubility seems not yet solved: in fact new salt forms, such as those with diethylamine and *N*-(2-hydroxyethyl) pyrrolidine (DHEP) have been recently prepared for pharmaceutical topical forms and other diclofenac salts were prepared and examined for their physical and chemical properties [2–5].

Recent papers outlined new problems, which can be encountered with the chemical form of the salts (hydration/dehydration; polymorphism; instability) [1,2]. It appeared therefore interesting to examine the possibility of increasing either the solubility of a soluble salt or to obtain comparable results, but using the parent compound diclofenac, through the formation of a solid dispersion with a hydrophilic carrier: the main purpose of the transformation is to obtain an increment of dissolution rate and bioavailability without the formation of a salt. A second aim was to take advantage of the solubility of DHEP in many organic solvents [6] and to try to prepare solid dispersion in both PEG and Gelucire, coupling the hydrophilicity of the salt form together with that of the excipient.

Several carriers have been employed in preparing solid dispersion and among those frequently used are PEGs, PVP, sugar or urea [7]. PEG polymers are widely used for their low melting point, low toxicity, wide drug compatibility and hydrophilicity [7–13]. Recently a new class of compounds, Gelucires, have been proposed [14] with different melting

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doi:10.1016/j.ejpb.2004.11.005

point and HLB, suitable to the same purpose. In this study, we prepared and characterized three systems of solid dispersion: acidic diclofenac in PEG6000 and Gelucire 50/13 and *N*-(2-hydroxyethyl) pyrrolidine diclofenac salt in Gelucire 50/13 of varying compositions. The choice of this particular salt of diclofenac was related to its possible solubility into the carriers, since it was previously reported [6] that this salt was found soluble at interesting levels in a variety of hydrophilic and lipid solvents. Physical analysis, such as powder X-ray diffractometry (XRD), differential scanning calorimetry (DSC), hot-stage microscopy (HSM) were performed to elucidate the structure of the dispersion, to detect possible drug:carrier interactions and to evaluate the validity of this pharmaceutical form to improve the solution behaviour of the active agent.

The paper is preliminary to the choice of the best couple chemical form/carrier for the preparation of microspheres, using a novel ultrasound-assisted atomizer, associated to an innovative method to control the solidification temperature of the final microspheres [15]. This study parallels that of the salt formation concerning diclofenac with the common aim to increase solubility and thus availability, without any chemical modification: the formation of a salt often creates unforeseen problems in stability and behaviour of the final chemical form [1,16].

2. Experimental

2.1. Materials

Acidic diclofenac was of pharmaceutical grade sample, gift from Farchemia (Bergamo, Italy). Its thermogram fits that of a commercial sample (m.p. 170 °C). Diclofenac/*N*-(2-hydroxyethyl) pyrrolidine was a gift from IBSA (Lugano, Switzerland): m.p. 106–107 °C.

PEG6000 was a commercial sample, purchased by Montplet & Esteban S.A. (Barcelona, Spain) and was of the highest purity available (m.p. 60 °C).

Gelucire 50/13 was a gift by Gattefossé (France) and has m.p. 50 °C and HLB 13.

2.2. Preparation of the physical mixtures

Physical mixtures were prepared mixing diclofenac and its salt with PEG6000 or Gelucire 50/13 in order to obtain five formulations containing 5, 10, 20, 30 and 40% w/w in active agent.

2.3. Preparation of the solid dispersions

Five grams of each physical mixture were melt in a porcelain plate with a gradual increasing of the temperature (10 °C min^{-1}) up to a value necessary for the complete melting. At about 10 °C above the melting temperature of the carrier, the systems containing 5, 10 and 20% w/w of diclofenac were transparent and limpid; at the same temperature samples containing 30 and 40% of diclofenac were heterogeneous and opaque, where suspended diclofenac particles were visible. These last systems, however, turned homogeneous at increasing temperature, because dissolution of the drug is complete at these temperature.

The systems thus prepared were placed in a freezer at −20 °C for 24 h and then crushed while the samples were at this temperature; milled and sieved at room temperature; powders having 200 μm size were used for further tests.

2.4. X-ray diffraction (XRD)

A Philips PW1130/90 apparatus, using Cu Kα radiation filtered by Ni (36 kg; 26 nD), was employed. The samples were analysed in the range of $2\theta = 3–65°$ with a scanning rate $2\theta = 10°$ min^{-1}. Figs. 1–3 show the results obtained for the systems acidic diclofenac/PEG6000 and Fig. 4 shows the results for the system DHEP/Gelucire 50/13.

2.5. Scanning electron microscopy (SEM)

SEM images were taken by a Philips XL30 microscope: samples were previously sputter-coated with a gold layer in order to make them conductive (Fig. 5).

2.6. Differential scanning calorimetry (DSC)

Thermograms were obtained by a Mettler equipment (FP 80HT control unit, FP 85TA cell furnace and FP 89 control software). Samples of about 10 mg were accurately weighed and analysed in pierced Al crucibles in the range of 40–300 °C, at a heating rate of 10 °C min^{-1} (Figs. 6 and 7).

2.7. Thermomicroscopy (HSM)

Hot-stage microscopy was carried out by means of a hot plate Mettler FP 82HT, coupled to an optical microscopy Olympus BH-2, equipped with a photographic recorder (Olympus C-35AD-4). A control unit Mettler FP 80HT was used to control the heating rate of the hot plate in the range of 25–300 °C, with a scan rate of 1 °C min^{-1} in the proximity of the most interesting thermal events (Figs. 8–11).

2.8. Dissolution rate studies

Dissolution profiles were obtained using a USP 25 paddle method (Turu-Grau mod. D-6 apparatus), evaluating 10 mg of pure diclofenac—as reference—or equivalent amounts of each sample.

The dissolution medium was 500 ml of bidistilled water at 37 ± 1 °C at 50 rpm; withdrawals were obtained at presetted times and the drug concentration was measured spectrophotometrically at $\lambda = 276$ nm (Fig. 12).

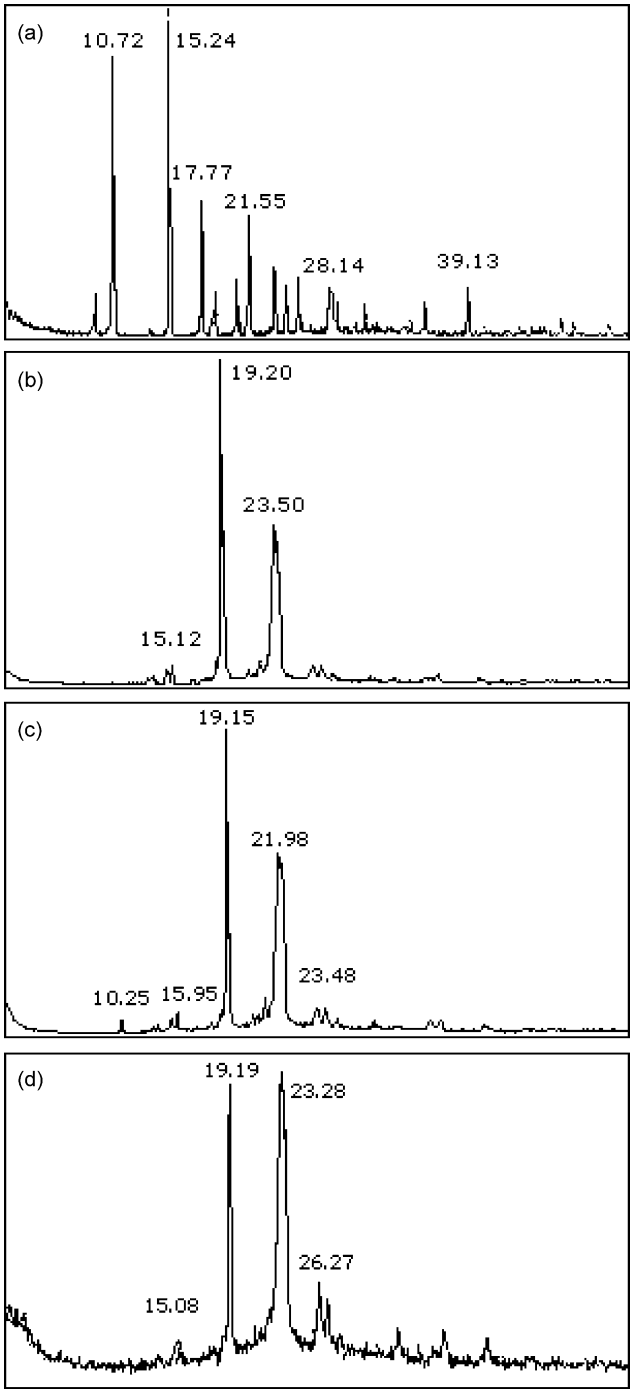

Fig. 1. XRD diffractograms for the system acidic diclofenac/PEG6000: (a) diclofenac; (b) PEG6000; (c) 5% w/w physical mixture; (d) 5% w/w solid dispersion.

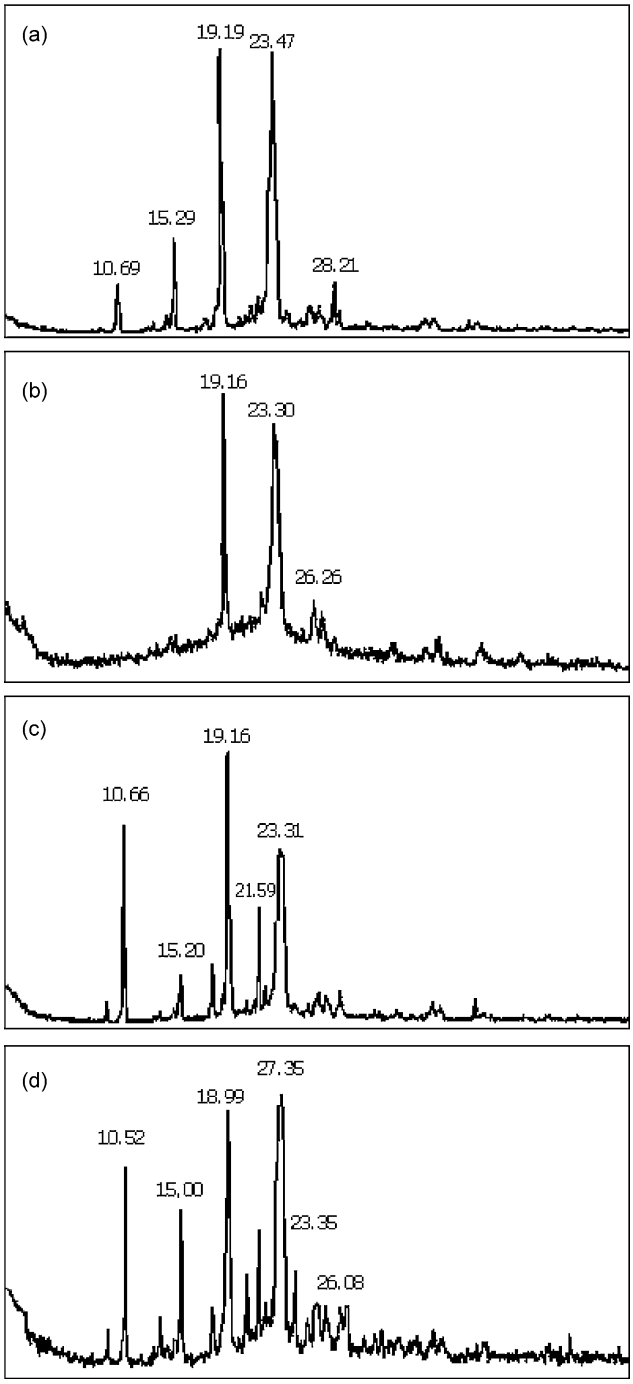

Fig. 2. XRD diffractograms for the system acidic diclofenac/PEG6000: (a) 10% w/w physical mixture; (b) 10% w/w solid dispersion; (c) 20% w/w physical mixture; (d) 20% w/w solid dispersion.

3. Results and discussion

Physical evaluations were carried out for all the three systems: here we report and discuss only the most interesting aspects for each formulation.

XRD diffractograms of the powders for the systems acidic diclofenac/PEG6000 are shown in Figs. 1a–d, 2a–d and 3a–d. Fig. 1a and b show XRD diffractograms of pure diclofenac and PEG6000, respectively. Most significant peaks are at $2\theta = 10.72$; 15.30; 17.17; 21.55 and 28.14° for diclofenac; and $2\theta = 15.12$; 19.20 and 23.50° for PEG6000 and employed to identify each component in the physical mixtures and in the solid dispersions. In the case of the physical mixtures, diffractograms are simply the sum of those of pure components and no interaction could be detected between them; the intensity of the peaks reflects

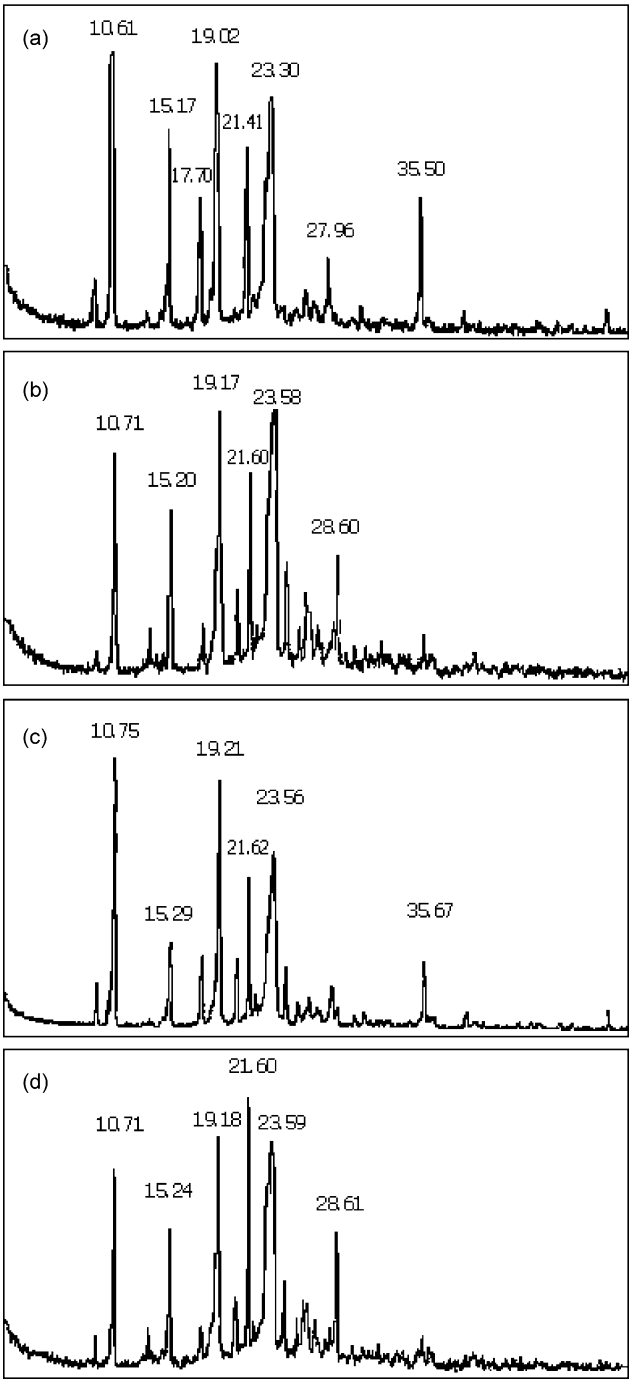

Fig. 3. XRD diffractograms for the system acidic diclofenac/PEG6000: (a) 30% w/w physical mixture; (b) 30% w/w solid dispersion; (c) 40% w/w physical mixture; (d) 40% w/w solid dispersion.

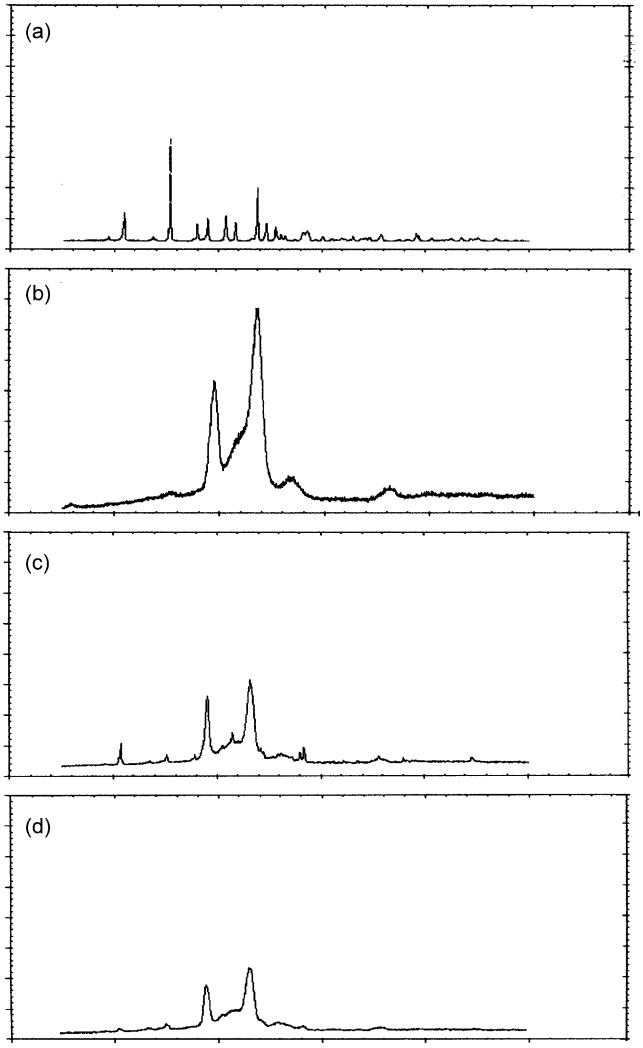

Fig. 4. XRD diffractograms for the system acidic diclofenac/Gelucire 50/13: (a) acidic diclofenac; (b) Gelucire 50/13; (c) 10% w/w physical mixture; (d) 10% w/w solid dispersion.

their mutual concentration (Figs. 1c, 2a,c, 3a and c). In the case of solid dispersions, at 5 and 10% w/w (Figs. 1d and 2b), the baseline is a little irregular, while the peaks of the drug are practically not appreciated, especially at low 2θ values. It could be attributed to the destruction of its crystal lattice, because of progressive amorphization or dissolution into the carrier. The peaks associated to the carrier are not shifted with respect to the physical mixture, so it can be hypothesised the formation of an insertion-type solid, where drug molecules find place inside the structure of the carrier without, or with a limited, deformation of the original crystal structure. This is common in mixtures of polymeric carriers with small amounts of low molecular weight drugs [17].

In the XRD diffractogram of the 20% w/w solid dispersion (Fig. 2d), peaks, which can be attributed to diclofenac, are shifted with respect to the values measured in the physical mixture of the same composition (Fig. 2c).

From these results it emerges that, up 10% w/w composition, the drug is completely dissolved into the carrier, while, starting from 20% w/w diclofenac, the system appears oversaturated and pure drug crystals are present inside the solid dispersion. Therefore, systems containing 30 and 40% w/w of diclofenac do not differ from this last one: the XRD diffractograms of the solid

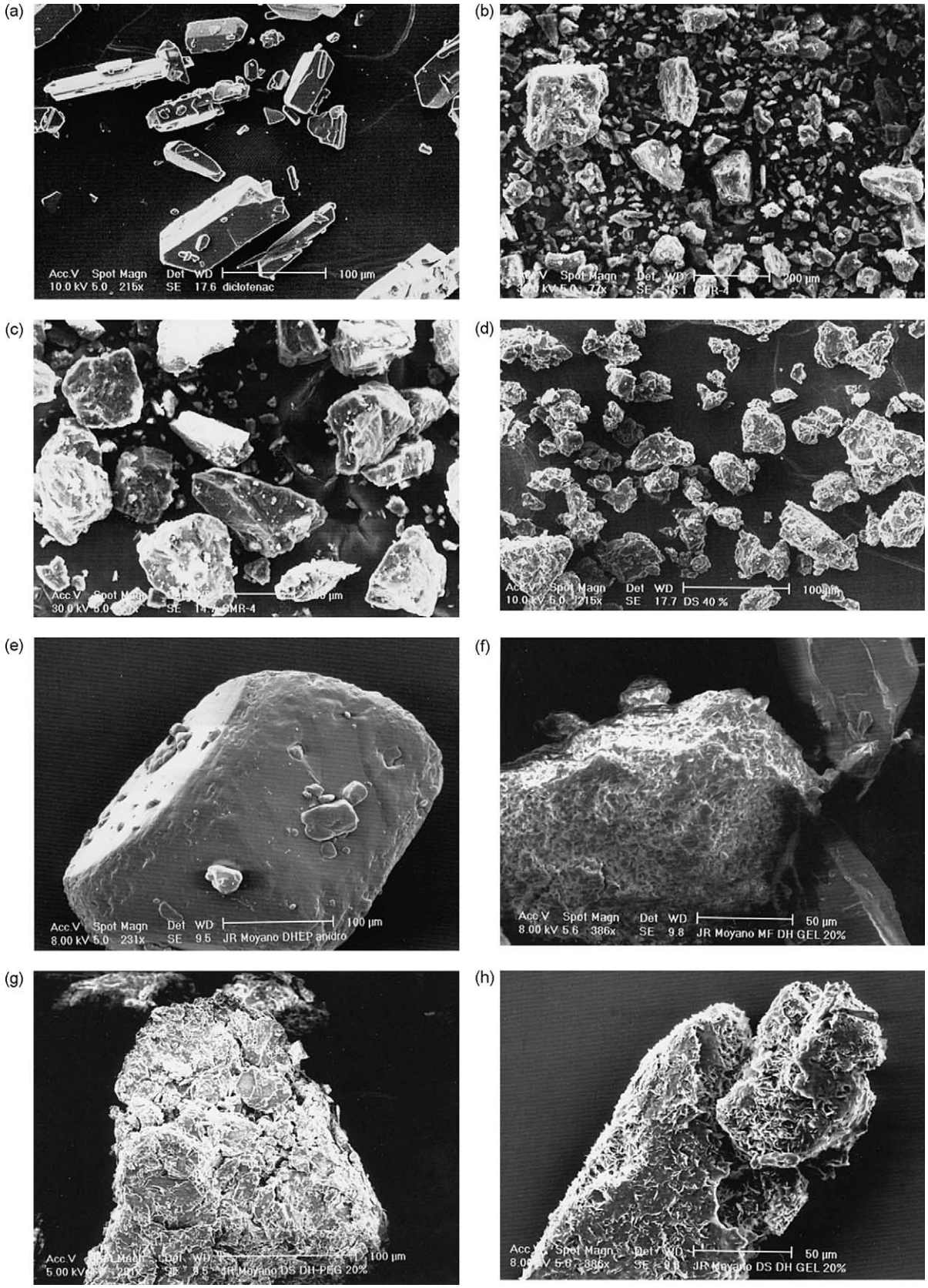

Fig. 5. SEM powder micrographs for some system acidic diclofenac/PEG6000: (a) acidic diclofenac; (b) PEG6000; (c) 5% w/w solid dispersion; (d) 20% w/w solid dispersion. SEM powder micrographs for some system DHEP/Gelucire 50/13: (e) diclofenac/*N*-(2-hydroxyethyl) pyrrolidine (DHEP); (f) 5% w/w physical mixture; (g) 5% w/w solid dispersion; (h) 20% w/w solid dispersion.

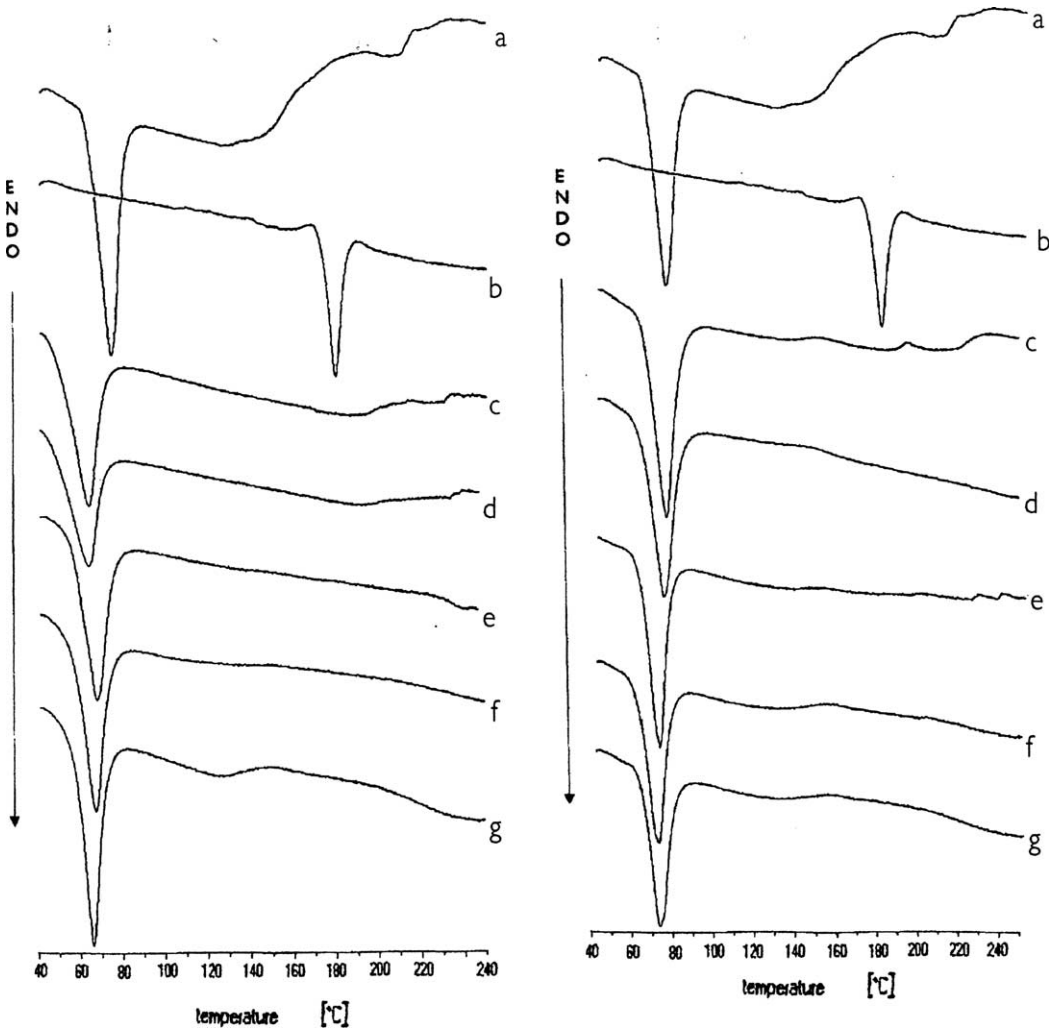

Fig. 6. DSC thermograms for: (a) PEG6000; (b) acidic diclofenac; for physical mixtures (left) and solid dispersions (right): (c) 5% w/w; (d) 10% w/w; (e) 20% w/w; (f) 30% w/w; (g) 40% w/w.

dispersion (Fig. 3b and d) overlap those of the respective physical mixtures (Fig. 3a and c).

XRD results for the systems acidic diclofenac/Gelucire 50/13 are reported in Fig. 4a–d only for the 10% w/w composition and reflect what observed for the previous formulations: the formation of a solid dispersion destroys almost completely the crystallinity of the drug and represents a suitable modification for improving its availability. Further studies as a function of time shall indicate the stability of this situation.

From SEM micrographs it can be appreciated the homogeneity of the solid dispersions, being impossible to distinguish the presence of diclofenac crystals (Fig. 5a) among PEG particles (Fig. 5b), whose shape is the same independent of the system considered. Fig. 5c shows a 5% w/w, while Fig. 5d shows a 20% w/w solid dispersion of acidic diclofenac in PEG6000. The salt morphology (Fig. 5e) is recognizable when in physical mixture with Gelucire 50/13 (Fig. 5f), while in solid dispersions the morphology of the excipient dominates (Fig. 5g and h: 5 and 20% w/w solid dispersion of the salt in Gelucire 50/13, respectively).

Fig. 6 reports the thermograms of the PEG physical mixtures and solid dispersions containing acidic diclofenac: Fig. 6a and b are the thermograms of pure PEG6000 and pure diclofenac; Fig. 6c–g (left) shows the thermograms of the physical mixtures; while Fig. 6c–g of the right part refers to thermograms of the corresponding solid dispersions. Thermal profiles of both physical mixtures and solid dispersions exhibited a single endothermic peak at about 60 °C, for all the samples, corresponding to the fusion of the carrier: no peak was present associated to the melting of the drug. Each binary sample exhibited substantially the same thermal behaviour. Differently to other systems, such as for instance ibuprofen–PEG10000 [18], the indomethacin–PEG6000 system produces only one-peak thermogram up to 40% w/w composition, while peaks related to the fusion of both polymorphs I and II appear at 80% w/w

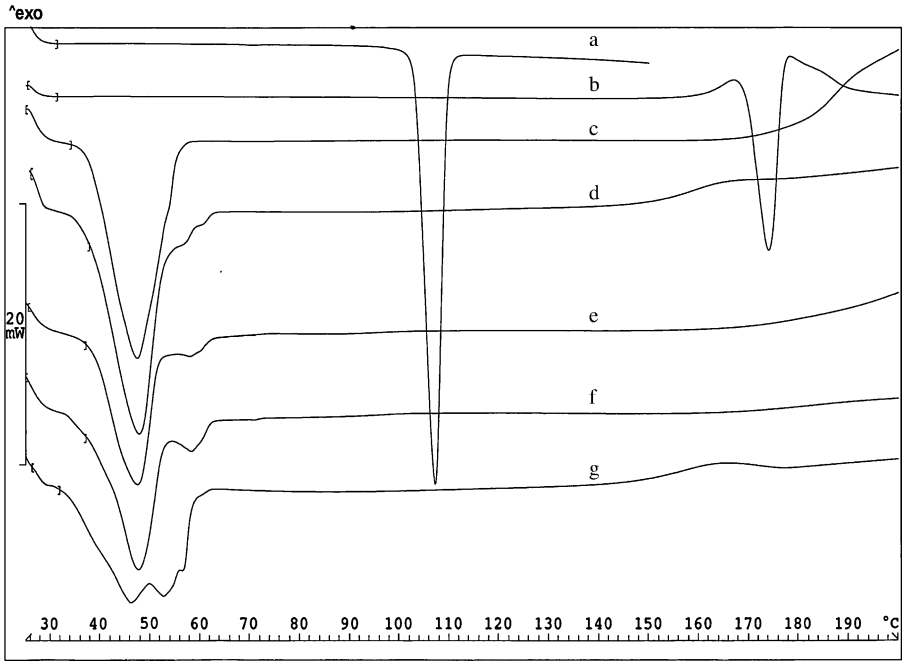

Fig. 7. DSC thermograms for some system acidic diclofenac/Gelucire 50/13 and for some system DHEP/Gelucire 50/13: (a) DHEP; (b) acidic diclofenac; (c) 10% w/w acidic diclofenac/Gelucire 50/13 physical mixture; (d) 10% w/w DHEP/Gelucire 50/13 physical mixture; (e) 10% w/w acidic diclofenac/Gelucire 50/13 solid dispersion; (f) 10% w/w DHEP/Gelucire 50/13 solid dispersion; (g) pure Gelucire 50/13.

indomethacin composition [19]. We can hypothesise that during the scanning of the temperature the solid drug (when present) dissolves into the molten PEG6000, starting from 60 °C and is no more present in its undissolved form inside the systems, when the melting temperature of diclofenac is reached. Evidently, at least at high temperature, present systems are far from saturation, even at 40% w/w of diclofenac, and no signal indicates the presence of solid diclofenac when its melting is reached. However, thermomicroscopy (see below) indicates that in the temperature range between the melting temperature of the carrier and that of the drug, drug crystals are still present as a consequence of the recrystallization on cooling, after the preparation of the solid dispersions.

Gelucire 50/13 shows a complex endotherm, due to the fusion of the product: the peak at about 45 °C being dominant over other three peaks [20]. This is related to the fact that it is formed by a mixture of low melting components, rather than a single compound. The thermal behaviour of both physical mixtures and solid dispersions of the drug (acid and salt) in Gelucire 50/13 (Fig. 7a–f) did not differ from those of the system in PEG6000, indicating the ease of dissolution of both compounds examined into the molten mass of both carriers and are not discussed in details.

Thermomicroscopy offers better results to interpret the thermal behaviour of the samples [21]. At thermomicroscope, acidic diclofenac crystals display prismatic morphology (Fig. 8a) that progressively converts into liquid vesicles in the range of 165–180 °C, where melting occurs: the molten material turns black at higher temperatures. At the same examination, PEG6000 contains irregularly shaped particles that start to melt at about 60 °C: the melt is quite stable up to 200 °C and, on cooling, solidifies and the solid recovers its crystallinity. A deviation of the thermogram baseline in this temperature range suggests, however, that the polymer somewhat decomposes on heating.

All the samples of the solid dispersions, before heating, appear as irregular and opaque particles, apparently homogeneous, where it is difficult to differentiate the single components (Fig. 5c and d); this aspect was encountered also in the case of physical mixtures, where diclofenac (acid or salt) closely adhere to the carrier particles. On heating the physical mixtures, the first thermal event observed is the melting of the carrier (Fig. 8b–f): the liquid droplets are transparent and allow visualisation of drug crystals, which maintain their morphology. HSM can also differentiate a solid dispersion from a physical mixture. In the case of the system acidic diclofenac/PEG6000, Fig. 8b shows that a 5% solid dispersion is completely melted at 60 °C, while, at the same temperature, a physical mixture still contains crystals (Fig. 8c). The differences are also more marked in the case of the 10% systems: the physical mixture needs a higher temperature to contain diclofenac completely dissolved; at 60 °C a number of diclofenac crystals are still visible in the physical mixture (Fig. 8e), while completely limpid and molten system appears in Fig. 8d at the same temperature. At 65 °C, a 10% w/w physical mixture still contains undissolved drug crystals (Fig. 8f). At 60 °C, a 20% w/w solid dispersion contains only microcrystals (Fig. 9a), while physical mixture of the same composition contains much more crystals (Fig. 9b), whose morphology and size are

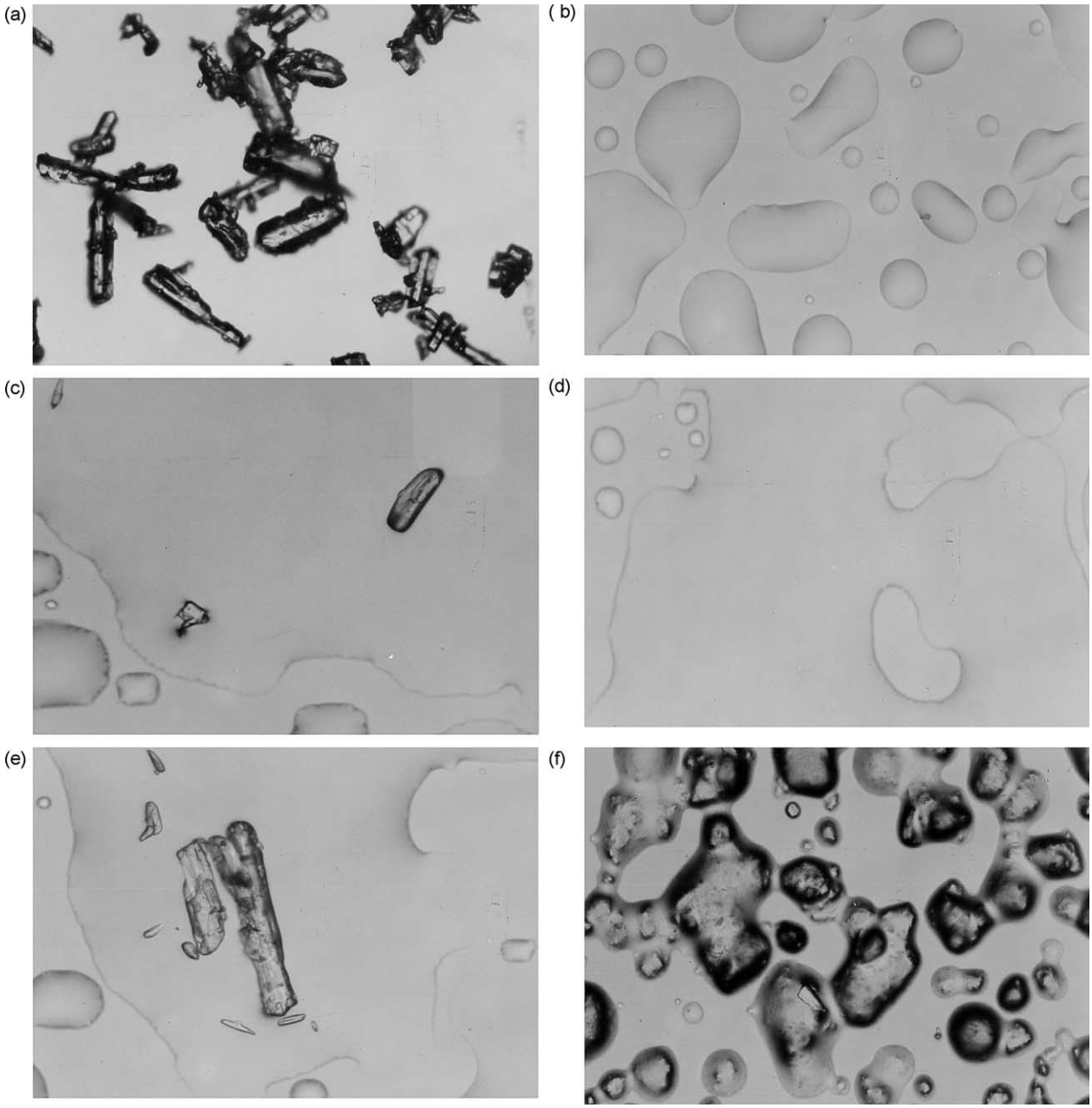

Fig. 8. HSM photographs for acidic diclofenac/PEG6000 systems: (a) acidic diclofenac at 150 °C (before melting); (b) 5% w/w solid dispersion at 60 °C; (c) 5% w/w physical mixture at 60 °C; (d) 10% w/w solid dispersion at 60 °C; (e) 10% w/w physical mixture at 60 °C; (f) 10% w/w physical mixture at 65 °C.

those of the starting diclofenac: crystallisation during the rapid cooling produced a decrease of the particle size. In 40% w/w solid dispersion, crystals of different size are visible inside the drop of molten PEG at 60 °C (Fig. 9c), while diclofenac crystals of the same physical mixture maintain their morphology despite the higher temperature of the observation (Fig. 9d). The higher content of the drug prolonged the period of diclofenac dissolution into PEG6000: at 130 °C, crystals of higher size are not yet dissolved at this high temperature (Fig. 9e) in the solid dispersion: the amount of undissolved drug is even higher in the physical mixture and crystals can be observed also at high temperature (Fig. 9f). Practically, the same was observed in the case of the 30% w/w systems.

Most observations parallel those carried out on the systems containing acidic diclofenac/Gelucire 50/13 (Fig. 10a–f) or DHEP/Gelucire 50/13 (Fig. 11a–f). In these cases, two important aspects emerged, being the same the composition: (1) sizes of the dispersed acid particles in Gelucire 50/13 are larger than those present in PEG at the same temperature. Probably the lower crystalline nature of Gelucire with respect to PEG, on cooling, allows

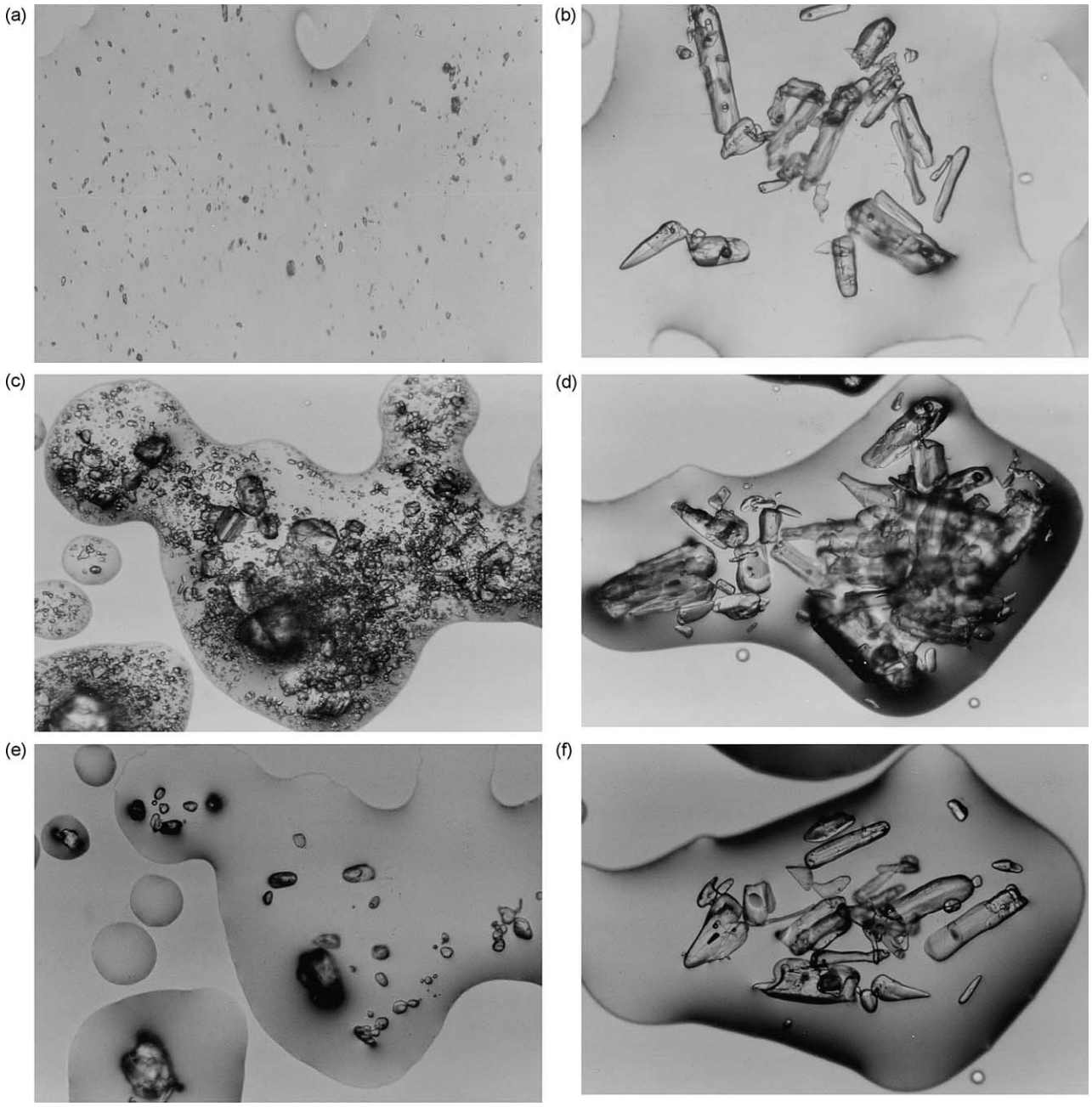

Fig. 9. HSM photographs for acidic diclofenac/PEG6000 systems: (a) 20% w/w solid dispersion at 60 °C; (b) 20% w/w physical mixture at 60 °C; (c) 40% w/w solid dispersion at 60 °C; (d) 40% w/w physical mixture at 70 °C; (e) 40% w/w solid dispersion at 130 °C; (f) 40% w/w physical mixture at 130 °C.

a more rapid increase of the size of diclofenac crystals, favouring the diffusive processes accompanying the crystal growth; (2) the salt, that is an ionic compound, displays an interesting solubility in Gelucire 50/13, that is a lipid carrier: however, since DHEP melts at 106 °C and decomposes above melting temperature [16], its stability after the preparation of the solid dispersion must be assessed. This aspect, together with a higher stability of the acid at the temperature used in preparing the samples, suggested not to consider further here the DHEP/Gelucire 50/13 systems and therefore dissolution tests were carried out only for the systems acid/PEG. However, systems containing Gelucire 50/13 remain interesting, because of the surfactant properties of this carrier and systems containing diclofenac/Gelucire 50/13 are currently studied to prepare microspheres by a novel ultrasound assisted spray-congealing technique [22,23].

These results confirm the importance of a solid dispersion over a physical mixture and document the change in size and morphology of the re-precipitated

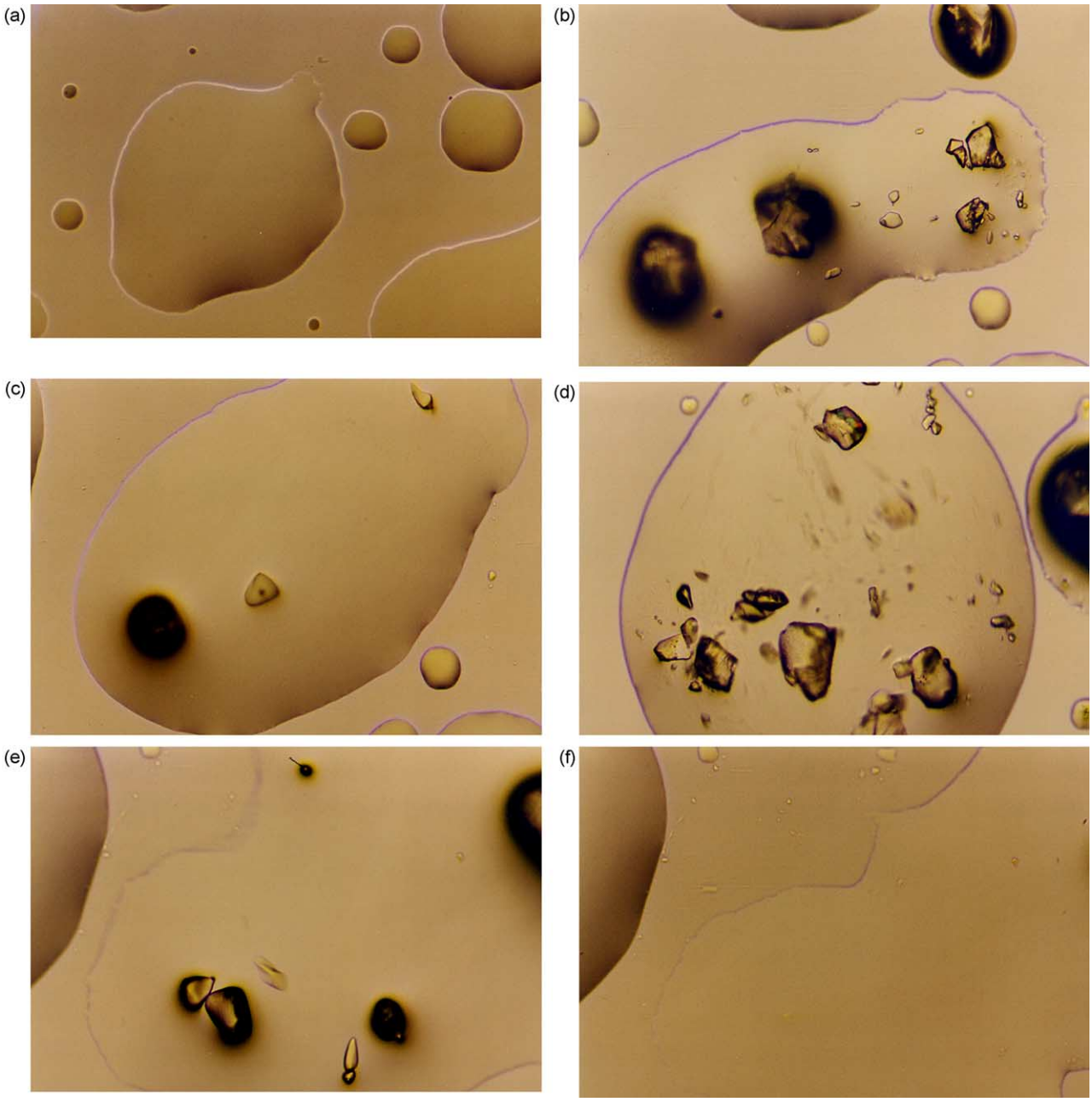

Fig. 10. HSM photographs for the DHEP/Gelucire 50/13 solid dispersions: (a) 5% w/w at 55 °C; (b) 10% w/w at 55 °C; (c) 10% w/w at 80 °C; (d) 20% w/w at 55 °C; (e) 20% w/w at 80 °C; (f) 20% w/w at 90 °C.

crystals of the drug inside the solid dispersion with respect to the starting physical mixture. It can be hypothesised that, where a large oversaturation occurs (during the preparation of the solid dispersion, heating was continued up to complete dissolution of the drug), the formation of crystal seeds is easier and a too large oversaturation in the solid phase can be prevented; differently to what observed in the 5 and 10% w/w solid dispersion. In these last cases, a lower oversaturation could prevent complete crystallisation in short period of time thus forming a metastable system, which only slowly evolves to equilibrium. This can explain differences observed in the percent release (see below), in term of amount dissolved diclofenac or of size of its precipitated crystals.

The complexity of the systems (e.g. dissolved and undissolved or precipitated drug, particles of different size) is reflected by the dissolution and release profiles of the active agent. Fig. 12 shows the dissolution profiles for physical mixtures and solid dispersions, respectively. The fact that physical mixtures offer practically overlapping dissolution profiles confirms, as above suggested, that the systems need a preliminary modification in order to display

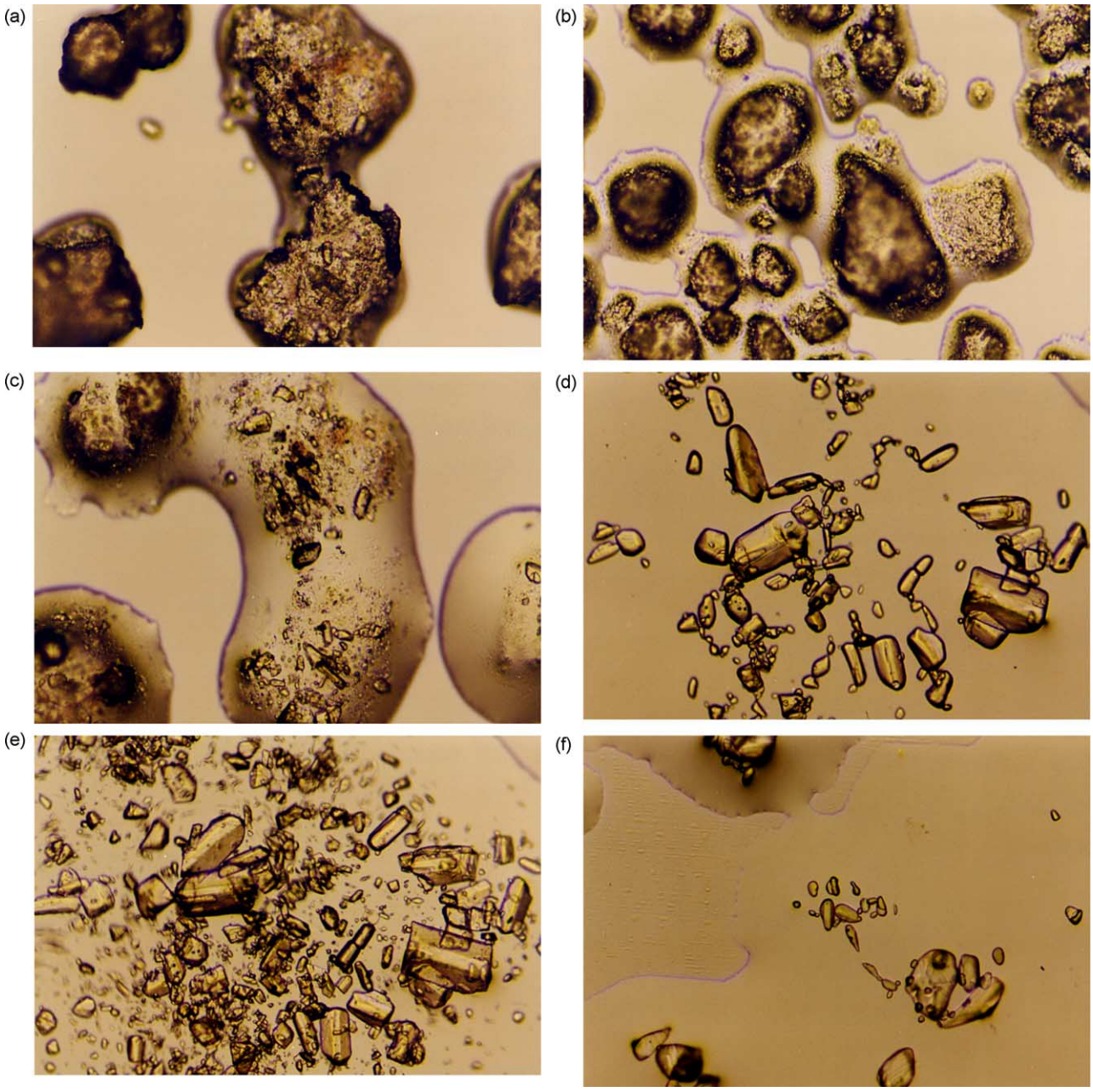

Fig. 11. HSM photographs for the acidic diclofenac/Gelucire 50/13 solid dispersions at 50 °C: (a) 5% w/w; (b) 10% w/w; (c) 20% w/w; (d) 30% w/w; (e) 40% w/w; (f) 40% w/w at 140 °C.

their potentialities. In the physical mixtures, only fair interactions exist between the drug and the carrier and the dissolution enhancement with respect to pure drug is slight. However, it can be appreciated that the higher is the diclofenac content, the higher is the release of the drug, even though differences are very limited and the overall dissolution represents about 10% of the starting material in the most favourable case.

Larger changes occurred in the case of the preparation of solid dispersions by melting and a considerable improvement compared to physical mixtures is obtained when diclofenac is formulated as solid dispersion in PEG6000: in these cases, the presence of dissolved diclofenac or its precipitation as microcrystals of reduced size or a partial amorphization of the solid drug permit achieving different levels of saturation and solubility of diclofenac into PEG and promote dissolution. The 5 and 10% w/w solid dispersions display the best performance, according also to all previously reported suggestions, that is in these systems diclofenac is not present as a separate phase after the preparation of solid dispersions. The dissolution profiles indicate that the release of the drug is practically immediate,

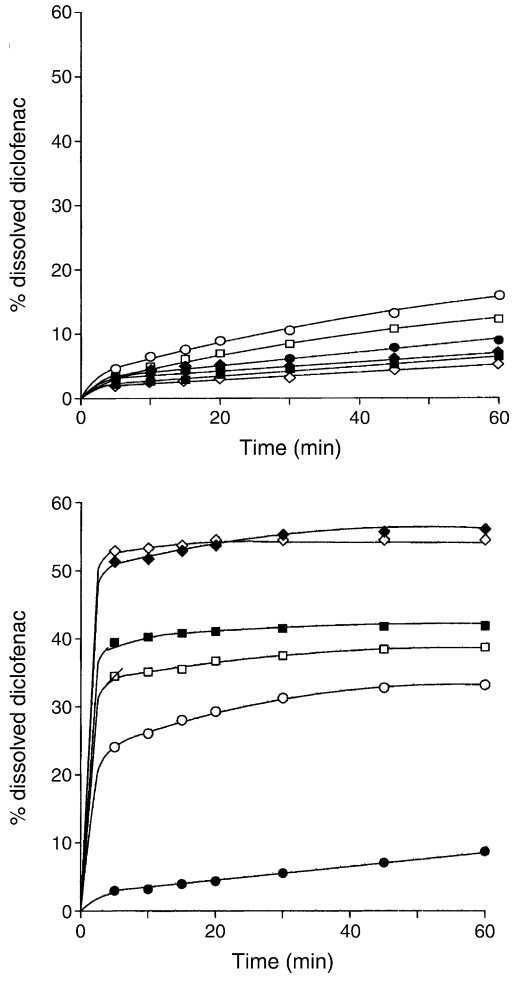

Fig. 12. Dissolution profiles for the acidic diclofenac/Gelucire 50/13 (physical mixtures—above; solid dispersions—below): ●, acidic diclofenac; ♦, 5% w/w; ◇, 10% w/w; ■, 20% w/w; □, 30% w/w; ○, 40% w/w.

reaching after a few minutes a steady concentration in solution. These values can be considered as the solubility level of diclofenac originated by the dissolution of different amount of hydrophilic PEG6000, and are proportional to the relative amount of diclofenac actually dissolved in the solid dispersions of different composition: while systems (5 and 10%), where the drug is present as completely dissolved into PEG, show a six-fold increment of the solubility of acidic diclofenac in the same conditions; systems, which are heterogeneous for the presence of undissolved or re-precipitated crystals, show a lower solubility. The level reached with 40% w/w solid dispersion can be taken as the solubility (20×10^{-6} M) of diclofenac in water at 37 °C (with a possible small overestimation, due to uncertainty of equilibrium achievement in this short period of observation): the small amount of PEG in the solution should not affect too much this value. This value agrees with an increment due to higher temperature with respect to the value found at 25 °C [24] and suggests the influence of PEG in promoting a faster dissolution rate with respect to pure diclofenac, which after 60 min. did not demonstrate to reach a plateau of saturation.

4. Conclusions

- Solid-state studies did not indicate chemical decomposition of the components (drug and excipient), showing compatibility and formation of homogeneous systems up to 10% w/w composition. PEG allows a better solubilization of diclofenac and its derivative than Gelucire 50/13.
- DSC data suggest that diclofenac and its salt can dissolve into the carriers up to 20% w/w concentration at temperature above the carrier melting point.
- HSM technique is more efficient than DSC in evidencing differences among the samples, showing the presence of macrocrystals in the solid dispersions together with microcrystals, or dissolution of diclofenac at higher temperature. Sizes of the drug crystals on cooling are higher in Gelucire 50/13 than in PEG.
- XRD analysis confirms HSM results, suggesting that the drug:carrier composition alter the crystallinity of the samples.
- Poorly soluble diclofenac improves its dissolution, when coupled with PEG6000.
- The preparation of a solid dispersion can represent an alternative to the salt forms to improve solubility of diclofenac and is preliminar to its formulation as microspheres from a novel ultrasound assisted atomizer with an innovative control of the temperature.

Acknowledgements

This paper was partly supported by Italy/Spain Integrated Action Funds and MURST (ex-40%) Funds.

References

[1] A. Fini, M. Garuti, G. Fazio, J. Alvarez-Fuentes, M.A. Holgado, Diclofenac salts. I. Fractal and thermal analysis of sodium and potassium diclofenac salts, J. Pharm. Sci. 90 (2001) 2049–2057.
[2] K.M. O'Connor, O.I. Corrigan, Comparison of the physicochemical properties of the *N*-(2-hydroxyethyl) pyrrolidine, diethylamine and sodium salt forms of diclofenac, Int. J. Pharm. 222 (2001) 281–293.
[3] M.J. Fernandez-Hervas, M.A. Holgado, A.M. Rabasco, A. Fini, Comportamiento en disolucion de diferentes sales de diclofenaco: estudio de solubilidad, Ind. Farmaceutica 3 (1995) 83–87.
[4] A. Fini, G. Fazio, M.J. Fernandez-Hervas, M.A. Holgado, A.M. Rabasco, Factors governing the dissolution of diclofenac salts, Eur. J. Pharm. Sci. 4 (1996) 231–238.
[5] A. Fini, G. Feroci, G. Fazio, M.J. Fernandez-Hervas, M.A. Holgado, A.M. Rabasco, Effects of the counterions on the properties of diclofenac salts, Int. J. Pharm. Adv. 1 (1996) 269–284.

[6] A. Fini, G. Fazio, I. Rapaport, A.M. Rabasco, Comportamento in soluzione di alcuni sali del diclofenac, Acta Technol. Leg. Med. V (1994) 13–26.
[7] C. Leuner, J. Dressman, Improving drug solubility for oral delivery using solid dispersion, Eur. J. Pharm. Biopharm. 50 (2000) 47–60.
[8] W.L. Chiou, S. Riegelman, Pharmaceutical applications of solid dispersion systems, J. Pharm. Sci. 60 (1971) 1281–1302.
[9] D.Q.M. Craig, Polyethylene glycols and drug release, Drug Dev. Ind. Pharm. 16 (1990) 2501–2527.
[10] A.H. Goldberg, M. Gibaldi, J.L. Kanig, M. Mayersohn, Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. IV. Chloramphenicol-urea system, J. Pharm. Sci. 55 (1966) 581–583.
[11] C.W. Lin, T.M. Cham, Effect of particle size on the available surface area of nifedipine from nifedipine-polyethylene glycol 6000 solid dispersions, Int. J. Pharm. 127 (1996) 261–272.
[12] L.S. Taylor, G. Zografi, Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions, Pharm. Res. 14 (1997) 1691–1698.
[13] D.Q.M. Craig, The mechanism of drug release from solid dispersions in water soluble polymers, Int. J. Pharm. 231 (2002) 131–144.
[14] D.Q.M. Craig, The physical characterisation of Gelucire 50/13, in: Gattefossé (Ed.), Bullettin Technique Gattefossé, No. 89, Saint Priest, Cedex, France, 1996, pp. 39–50.
[15] A. Fini, C. Cavallari, B. Luppi, L. Rodriguez, Characterization of indomethacin/stearic acid microsphere prepared by a ultrasound assisted spray-congealing process, J. Control. Release, work in progress.
[16] M.T. Ledwige, S.M. Draper, D.J. Wilcock, O.I. Corrigan, Physico-chemical characterization of diclofenac *N*-(2-hydroxyethyl) pyrrolidine: anhydrate and dihydrate crystalline forms, J. Pharm. Sci. 85 (1996) 16–21.
[17] J. Kreuter, Feste dispersionen, in: J. Kreuter, C.-D. Herzfeldt (Eds.), Grundlagen der Arzneiformenlehre Galenik, 2, Springer, Frankfurt am Main, 1999, pp. 262–274.
[18] G.M. Khan, Z. Jiabi, Preparation, characterization and evaluation of physicochemical properties of different crystalline forms of ibuprofen, Drug Dev. Ind. Pharm. 24 (1998) 455–462.
[19] J.L. Ford, M.H. Rubinstein, Phase equilibria and dissolution rate of indomethacin–polyethylene glycol 6000 solid dispersions, Pharm. Acta Helv. 53 (1978) 93–98.
[20] N. Khan, D.Q.M. Craig, The influence of drug incorporation on the structure and release properties of solid dispersion in lipid matrices, J. Control. Release 93 (2003) 355–368.
[21] J.M. Ginés, M.D. Veiga, M.J. Arias, A.M. Rabasco, Elaboration and thermal study of interaction between cinnarizine and gelucire 53/10 physical mixtures and solid dispersions, Int. J. Pharm. 126 (1995) 287–291.
[22] N. Passerini, B. Perissutti, M. Moneghini, D. Voinovich, B. Albertini, C. Cavallari, L. Rodriguez, Characterization of carbamazepine gelucire 50/13 microparticles prepared by spray-congealing process using ultrasounds, J. Pharm. Sci. 91 (2002) 699–707.
[23] C. Cavallari, L. Rodriguez, B. Albertini, N. Passerini, F. Rosetti, A. Fini, Thermal and fractal analysis of diclofenac/Gelucie micro particles obtained by ultrasound assisted automisation. J. Pharm. Sci. accepted for publication. 2004.
[24] A. Chiarini, A. Tartarini, A. Fini, pH-Solubility relationship and partition coefficients for some anti-inflammatory arylaliphatic acids, Arch. Pharm. (Weinheim) 317 (1984) 268–273.