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Characterization and Dissolution Properties of Ketoprofen in Binary and Ternary Solid Dispersions with Polyethylene Glycol and Surfactants

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ABSTRACT The effect of incorporation of an anionic [sodium dodecyl sulfate (SDS) or dioctylsulfosuccinate (DSS)] or nonionic [Tween 60 (TW60)] surfactant on the properties of ketoprofen solid dispersions in polyethylene glycol 15000 (PEG) has been investigated. Physicochemical and morphological properties of the various solid systems were determined by differential scanning calorimetry, hot stage microscopy, X-ray powder diffraction analysis, and scanning electron microscopy. The results from dissolution studies, performed according to the USP 24 basket method, indicated that all ternary dispersed systems were significantly ($p<0.001$) more efficacious than the corresponding binary ones, by virtue of the additive wetting and solubilizing effect due to the presence of the surfactant. The relative effectiveness of the incorporated surfactant was in the same order as found in phase-solubility studies (i.e., SDS>DSS>TW60). With regard to the solid dispersion preparation method, coevaporated products always gave better results than the corresponding cofused ones; however, this effect was statistically significant ($p<0.001$) only in the initial phase of the dissolution process. The most effective solid dispersion was the 10-80-10 w/w drug-PEG-SDS ternary coevaporate, which allowed dissolution of 50% drug after only 6 min (in comparison with >120 min for drug alone and 17 min for the binary coevaporate) and dissolution of about 100% drug after 30 min (in comparison with >120 min for the binary coevaporate).

KEYWORDS Ketoprofen, Ternary solid dispersions, Polyethylene glycol, Surfactants, Sodium dodecyl sulfate

INTRODUCTION

Ketoprofen is a potent and safe nonsteroidal anti-inflammatory drug endowed with good analgesic properties, but its very low water solubility (0.13 mg mL^{-1} at 25°C) can give rise to formulation problems and limit its therapeutic applications and bioavailability.

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Among the numerous techniques investigated for enhancing the dissolution properties of poorly water-soluble drugs and hence, possibly, their bioavailability, solid dispersion in water-soluble carriers has attracted considerable interest and has often been successfully applied (Craig, 2002; Craig & Newton, 1992; Leuner & Dressman, 2000; Mura et al., 1996). The main factors claimed to explain the improved dissolution rates of solid-dispersed drugs include particle size decrease, reduction of aggregation and/or agglomeration phenomena, improved wettability, loss of crystallinity, and solubilizing effect of the carrier (Craig, 2002). Solid-dispersion strategy has been experimented also for ketoprofen, and various carriers have been tested (Margarit et al., 1994; Roger & Anderson, 1982; Sheen et al., 1995; Takayama et al., 1982). However, at present, no ketoprofen marketed products arising from this approach are available, probably because of the unsatisfactory performance of the studied systems.

Because of the limitations presented by classic solid dispersions, pharmaceutical formulators are constantly searching for new and more powerful methods to improve their efficiency and, consequently, applicability (Serajuddin, 1999). In particular, recent investigations have shown that formulation of ternary solid dispersions by using suitable carrier combinations or by adding an appropriate third component, such as a hydrophilic surfactant, can give rise to a further improvement in drug dissolution properties with respect to the corresponding binary systems (Cirri et al., 2004; Jachowicz et al., 2000; Mura et al., 1999; Serajuddin, 1999; Sjökvist et al., 1991; Vippagunta et al., 2002).

Therefore, we considered it worthy of interest to extend the studies aimed at improving the dissolution properties of ketoprofen through the formulation of ternary solid dispersions. Polyethylene glycol (PEG) was chosen as the hydrophilic carrier because of its frequent, proven, and effective use, whereas three different surfactants (i.e., sodium dodecyl sulfate, sodium dioctyl sulfosuccinate, and Tween 60) were tested as possible ternary components. The present work was then devoted to the development and characterization of solid dispersions of ketoprofen in PEG-surfactant systems, with the main objective of evaluating the role played by the presence and type of surfactant and by the system preparation method on the drug dissolution properties. Phase-solubility studies were performed to evaluate and compare the solubilizing efficacy of the various examined carrier combinations toward the drug. The dissolution behavior of the different solid systems was determined by means of the USP basket apparatus, whereas their physicochemical properties were investigated by differential scanning calorimetry, hot stage microscopy, X-ray powder diffractometry, and scanning electron microscopy.

MATERIALS AND METHODS

Materials

Ketoprofen (KETO) was supplied by Sigma-Aldrich Corp. (St. Louis, MO, USA) and polyethylene glycol 15000 (PEG) by Merck (Darmstadt, Germany). Tween 60 (TW60) (Merck) was selected as nonionic surfactant, sodium dioctyl sulfosuccinate (DSS) and sodium dodecyl sulfate (SDS) (Sigma-Aldrich Corp.) as anionic surfactants.

Preparation of Solid Dispersions

Binary (10–90 w/w drug-PEG) and ternary (10-80-10 w/w drug-PEG-surfactant) solid dispersions were prepared according to both the melting and solvent methods.

Fusion Method

KETO (10% w/w) was added under stirring to the melted carrier (60–64°C) and mixed until a homogeneous system was obtained. In ternary systems, the surfactant (10% w/w) was dissolved in the melted carrier prior to the addition of KETO. The melts were quickly cooled and solidified on an ice-bath.

Solvent Method

The binary or ternary mixture of the components was dissolved in ethanol 95%, followed by the evaporation of the solvent using a rotary evaporator.

Each solid product was sieved to obtain the 75- to 150-μm granulometric fraction. For comparison purposes, the 10–90 w/w drug-PEG physical mixture was also prepared by simple blending of the previously sieved (75–150 μm) components.

Solubility Studies

Solubility studies of KETO were carried out to evaluate the possible solubilizing effect of the carrier by adding an excess of drug (50 mg) to 10 mL of aqueous solutions containing increasing concentrations of PEG 15000 (0–10% w/v) with or without the presence of 1.5% w/v of surfactant (SLS, DSS, TW60) in sealed glass containers maintained under magnetic stirring at constant temperature (25°C) until equilibrium (5 days). Drug concentration was spectrometrically determined at 260 nm (model U-2000, Hitachi, Tokyo, Japan).

Differential Scanning Calorimetry (DSC)

DSC analyses were performed with a Mettler TA4000 system, equipped with a DSC 25 cell, on 3- to 5-mg samples (Mettler M3 microbalance) in Al pans with perforated lids at the heating rate of $10°C \cdot min^{-1}$ in the 30–200°C temperature range under static air atmosphere.

Hot Stage Microscopy (HSM)

HSM assays were performed by using an Olympus BH-2 microscope fitted with a Mettler FP-82 hot stage. Each sample (5–10 mg) was placed on the sample stage and heated in the 30–200°C temperature range at a rate of 5–1°C min^{-1}.

X-Ray Powder Diffractometry

X-ray powder diffraction patterns were obtained over the 5–30° 2Θ range by using a Bruker D8-Advance Powder Diffractometer, equipped with a Debye–Scherrer transmission θ–θ geometry (Cu Kα radiation). The Sol-X® solid state Si(Li) was used as detector and C/Ni Goebel–Spiegel mirrors in the incident beam were used as monochromator. The scan rate was 0.02° s^{-1}.

Scanning Electron Microscopy (SEM)

SEM analysis was carried out by using a Philips XL-30 scanning electron microscope. Prior to analysis, samples were gold sputter-coated to render them electrically conductive.

Dissolution Test

Disssolution studies were performed according to the USP 24 basket method (model D-6, Turu Grau, Barcelona, Spain), by adding 25 mg of KETO or KETO equivalent to 500 mL of artificial gastric medium (HCl solution, pH 1.2) thermostated at 37±0.5°C. The basket rotation speed was 50 rpm. Concentration of dissolved drug was monitored through spectrophotometric assay at 260 nm as mentioned above. Each test was performed in triplicate (C.V.<3%). Dissolution efficiency (D.E.) was calculated from the area under the dissolution curve at time t and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975).

One-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls multiple-comparison test (Graph Pad Prism, Version 3) was used to evaluate the effect of both the solid-dispersion preparation method and the presence and type of surfactant on the drug D.E. and percent dissolved.

RESULTS AND DISCUSSION

Phase-Solubility Studies

Solubility studies revealed a linear increase of drug solubility in the presence of increasing surfactant or carrier concentration (Fig. 1). Analogous results have been found for this same carrier and several other

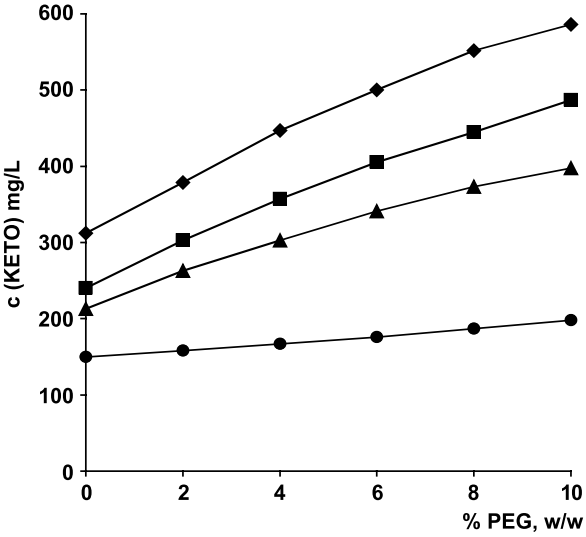

FIGURE 1 Ketoprofen (KETO) Phase-Solubility Diagrams in Aqueous Solutions at 25°C in the Presence of PEG without (●) or with 1.5% w/v of Tween 60 (▲), Sodium Dioctyl Sulfosuccinate (■) or Sodium Dodecyl Sulfate (◆).

kinds of drugs and have been attributed to the probable formation of weak soluble complexes (Cirri et al., 2004; Corrigan & Timoney, 1976; Mura et al., 1996; Najib & Suleiman, 1989). In particular, the formation of intermolecular hydrogen bonds between the carboxyl group of KETO and the ether oxygen of the polymer, which could concur to explain the enhanced KETO solubility in the presence of PEG, have been recently proven (Schachter et al., 2004).

The presence of surfactant markedly strengthened the solubilizing power of PEG toward the drug. Based on the slopes of the respective solubility curves, assumed as an index of the relative solubilizing power, the effectiveness of the tested surfactants varied in the order SDS>DSS>TW60. Thus, the solubilizing efficiency was higher for the anionic surfactants than for the nonionic one.

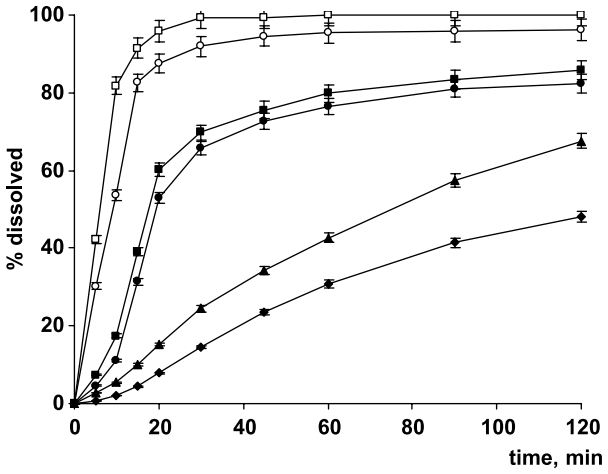

FIGURE 2 **Dissolution Curves of Ketoprofen (KETO) Alone (◆) or from its 10/90 w/w Binary Physical Mixture (▲), Cofused (●), and Coevaporated (■) Products with PEG or from 10/80/10 w/w Ternary Cofused (○) and Coevaporated (□) Products with PEG and Sodium Dodecyl Sulfate (Mean of Three Experiments; C.V.<3%).**

Dissolution Studies

The results of dissolution tests in terms of dissolution efficiency and percent drug dissolved at 10, 30, and 120 min, time to dissolve 50% drug, and relative dissolution rate at 5 min are collected in Table 1, whereas the mean dissolution curves of KETO and of some representative binary and ternary systems with PEG and surfactant (SDS) are presented in Fig. 2. As is evident at a glance, all the systems exhibited faster dissolution rates than KETO alone. The significant ($p<0.001$) improvement of drug dissolution properties obtained from the simple physical mixture with the hydrophilic polymer can be explained by the wetting and solubilizing properties of PEG. Binary solid dispersions were significantly ($p<0.001$) more effective in both dissolution efficiency and percent of dissolved drug than the corresponding physical mixture, and allowed a reduction of $t_{50\%}$ from 75 min to 17 or 20 min for coevaporated and cofused products, respectively. Drug particle size decrease, reduction of aggregation phenomena among the hydrophobic drug particles, and increase in the effective surface area owing to the more intimate contact and fine dispersion into the hydrophilic carrier can be the principal causes for the improved performance of KETO in solid-dispersed systems. Moreover, as confirmed by subsequent solid state studies, a loss of drug crystallinity as a consequence of its almost complete molecular dispersion in the polymer obtained by both coevaporation and cofusion methods, together with a concomitant reduction of PEG crystallinity, further concur to explain the enhanced dissolution properties of KETO in such systems. Coevaporated products showed an initial significantly ($p<0.001$) higher dissolution rate than the cofused ones, but both the percent dissolved and D.E. values at 120 min were no longer statistically different ($p>0.05$).

All ternary systems revealed significantly ($p<0.001$) better dissolution properties than the corresponding binary ones. Micellar solubilization phenomena can be excluded, because the final surfactant concentration in the dissolution medium (0.005% w/v) was in all cases below their respective critical micelle concentration (Mukerjee & Mysels, 1971; Sjökvist et al., 1991), which is, for example, between 0.1 and 0.2% w/v for SDS. Therefore, the observed effect can be attributed to the additive solubilizing effect of the surfactant in the microenvironment surrounding the dissolving drug particles, together with its favorable influence on improving drug wettability and spreadability by decreasing the interfacial tension between drug particles and dissolution medium (Sheen et al., 1995). As for the influence of the surfactant type, their effectiveness was in the same rank order as found in phase-solubility studies (i.e., SDS>DSS>TW60). Thus, such a relationship could be particularly useful for a preliminary screening to select the most suitable surfactant for incorporation in solid dispersions to increase the drug dissolution properties. Also in the case of ternary systems, coevaporated products gave better results than

TABLE 1 **Dissolution Parameters of Ketoprofen (KETO) Alone or from Its Physical Mixture (P.M.), Cofused (COF), or Coevaporated (COE) Products with PEG or PEG-Surfactant [Sodium Dodecyl Sulfate (SDS); Sodium Dioctylsulfosuccinate (DSS); Tween 60 (TW60)] in Percent Dissolved (PD) and Dissolution Efficiency (DE) at 10, 30, and 120 min, Time to Dissolve 50% Drug ($t_{50\%}$), and Relative Dissolution Rate (rdr) at 5 min**

Sample	PD10	PD30	PD120	DE10	DE60	DE120	$t_{50\%}$ (min)	rdr
KETO	2.0	14.6	48.0	0.8	5.6	26.8	>120	1
PM KETO-PEG	5.4	24.4	67.6	2.7	10.9	38.7	75	4.7
COE KETO-PEG	17.4	69.8	85.8	8.0	37.3	69.4	17	24.7
COF KETO-PEG	11.2	65.8	82.4	5.1	32.2	65.5	20	12.3
COE KETO-PEG-SDS	81.8	99.4	100	28.5	74.5	93.5	6	70.3
COF KETO-PEG-SDS	53.6	92.0	96.2	17.4	62.9	87.0	9	50.3
COE KETO-PEG-DSS	65.2	94.4	98.6	13.3	68.0	89.9	8	61.0
COF KETO-PEG-DSS	36.4	85.4	93.4	41.5	51.8	81.3	12	27.7
COE KETO-PEG-TW60	44.2	88.6	94.8	34.6	53.7	83.6	11	40.0
COF KETO-PEG-TW60	28.2	78.4	89.8	11.2	45.6	75.7	14	21.0

the corresponding cofused ones and, as observed for binary dispersions, this effect was particularly marked in the first phase of the dissolution process. In particular, the rdr (relative dissolution rate) values at 5 min for coevaporated systems were about twice as much as the corresponding cofused systems (Table 1). Moreover, clearly significant differences ($p<0.001$) were observed after 10 min among all the percent dissolved and D.E. values. However, the differences in the dissolution performance of the various ternary systems tended to become gradually less evident with time, and after 120 min no more statistically significant differences ($p>0.05$) were found between cofused and coevaporated products for a given ternary system nor between products containing SDS or DSS.

Solid-State Studies

In the attempt to shed light on the different dissolution behavior shown by the various examined

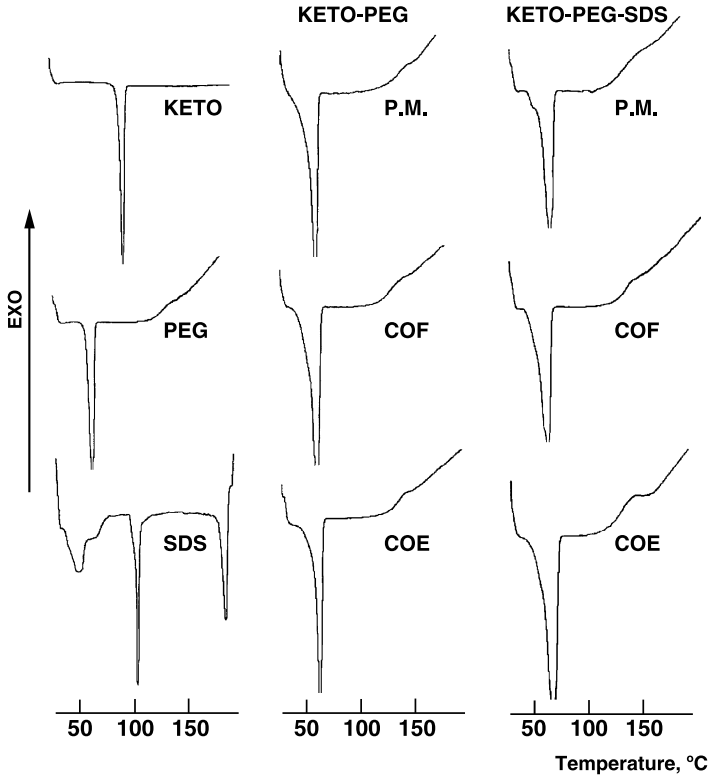

FIGURE 3 **DSC Curves of Pure Ketoprofen (KETO), PEG, and Sodium Dodecyl Sulfate (SDS) and their Binary (10/90 w/w) and Ternary (10/80/10 w/w) Physical Mixtures (P.M.), Cofused (COF), and Coevaporated (COE) Products.**

systems, and, in particular, on the better performance of SDS-containing products, adequate solid-state studies were performed on selected samples.

The thermal curves of pure components and of some selected binary and ternary solid dispersions are shown in Fig. 3. The thermal curves of KETO and PEG indicate their crystalline and anhydrous nature, exhibiting only one endothermic peak corresponding, respectively, to the melting of the drug (95.7°C, ΔH 110.2 J/g) and of the polymer (at 63.9°C, ΔH 187.2 J/g); at higher temperatures (>110°C), in the case of PEG an exothermic peak was observed, which appeared as a positive deviation from the baseline. The DSC curve of SDS showed one broad endothermal effect ranging between 50 and 70°C, due to a dehydration process, followed by a sharp peak at 107.3°C and another peak at 188.2°C, due to decomposition phenomena (Sjökvist et al., 1991). The DSS thermal curve (not shown) exhibited a very broad and irregular endothermal band between 50 and 150°C, typical of an amorphous hydrated product. The thermal curve of TW60 cannot be recorded within the selected temperature range, because it is liquid at ambient temperature. The thermal behavior of all the binary and ternary solid dispersions was very similar and did not differ from that of the simple physical mixture. In fact, all the systems, independent of the presence and type of surfactant, always displayed only one endothermal effect, peaked at around 60°C due to the polymer fusion, whereas drug and surfactant (if present) endothermal effects were absent. The lack of the drug-melting endotherm suggested that it dissolved into the melted PEG during heating. Hot stage microscopy analysis, performed to support this hypothesis, made it possible to exclude the disappearance of KETO-melting peak as being due to its amorphization. In fact, it was possible to observe, both in cofused and in coevaporated systems, the presence of drug crystals, which, starting from a temperature of about 60–62°C, gradually dissolved in the melted carrier, up to the achievement of complete dissolution at about 70°C (Fig. 4). This phenomenon is not exclusive of KETO, but it has been reported for other drugs dispersed in PEGs (Cirri et al., 2004; Mura et al., 1996; Veiga et al., 1993). Ternary systems showed a very similar thermal behavior, with the exception of cofused and coevaporated products containing SDS, where particles of surfactants were still visible up to 80°C and appeared totally dissolved in the melted polymer only at about 97°C (Fig. 4).

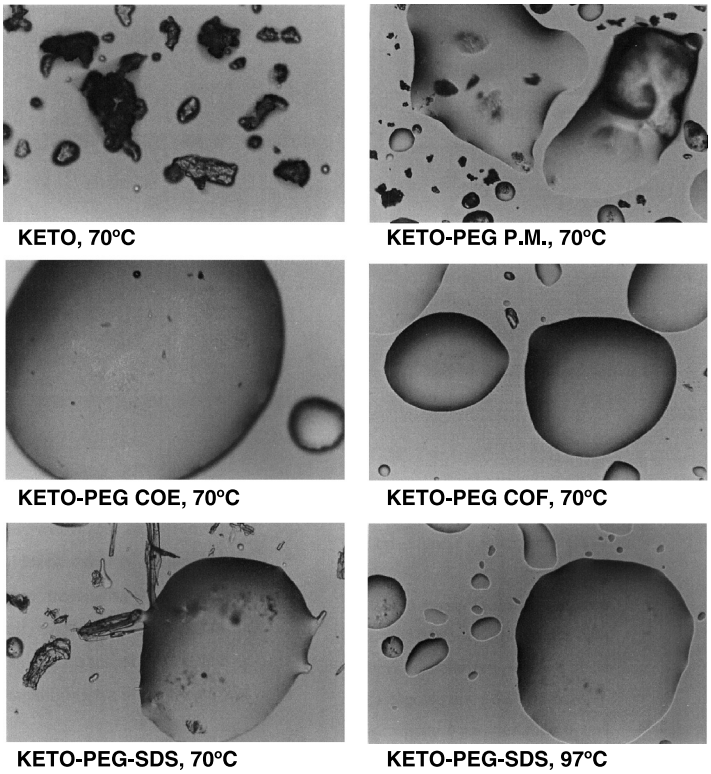

FIGURE 4 **Photomicrographs of Crystals of Ketoprofen (KETO) and its 10/90 w/w Binary Physical Mixture (P.M.), Coevaporated (COE), and Cofused (COF) Products with PEG, and 10/80/10 w/w Ternary KETO-PEG-SDS (Sodium Dodecyl Sulfate), Taken During HSM Analysis.**

TABLE 2 **Thermal Parameters of the Melting Endotherm of PEG Alone or in Its Physical Mixture (P.M.), Cofused (COF), or Coevaporated (COE) Products with Ketoprofen (KETO) or KETO-Surfactant [Sodium Dodecyl Sulfate (SDS); Sodium Dioctylsulfosuccinate (DSS); Tween 60 (TW60)]**

Sample	T_{Onset} (°C)	T_{peak} (°C)	T_{Endset} (°C)	ΔH_{fus} (J/g)	ΔT_{Onset} (°C)	ΔT_{peak} (°C)	$\Delta\,\Delta H$ (J/g)
PEG	61.1	64.8	68.3	185.0	—	—	—
P.M. KETO-PEG	59.5	63.2	66.9	187.6	−1.6	−1.6	+2.6
COF KETO-PEG	57.0	62.8	67.9	175.3	−4.1	−2.0	−9.7
COE KETO-PEG	56.7	63.7	67.5	165.6	−4.4	−1.1	−19.4
P.M. KETO-PEG SDS	59.1	64.5	69.3	180.2	−2.0	−0.3	−4.8
COF KETO-PEG-SDS	54.8	63.1	67.8	163.8	−6.3	−1.7	−21.2
COE KETO-PEG-SDS	51.6	62.8	69.8	145.5	−9.5	−2.0	−39.5
COF KETO-PEG-DSS	52.7	63.5	66.6	155.9	−8.4	−1.3	−29.1
COE KETO-PEG-DSS	52.1	62.4	69.3	139.7	−9.0	−2.4	−45.3
COF KETO-PEG-TW60	51.9	62.6	64.3	143.2	−9.2	−1.8	−41.8
COE KETO-PEG-TW60	51.2	61.7	65.4	124.1	−9.9	−3.1	−60.9

On the other hand, by carefully examining the DSC curves of the various investigated systems (Fig. 3), some interesting differences can be pointed out in the features of the polymer melting endotherm, whose main characterizing parameters are collected in Table 2. As can be observed, no important variations in the polymer-melting temperature and related enthalpy were detected in binary and ternary physical mixtures in comparison with pure PEG. By contrast, a lowering of the onset temperatures and a concomitant reduction in enthalpy of the PEG fusion endotherm were recorded in solid dispersions, the effect being more evident for ternary than for binary systems, and for coevaporated than for cofused products. Such a decrease in the heat of fusion value can be due to a decrease in PEG crystallinity, resulting in an increased dissolution rate (Sjökvist et al., 1991). Therefore, these results suggest that the drug, particularly when in

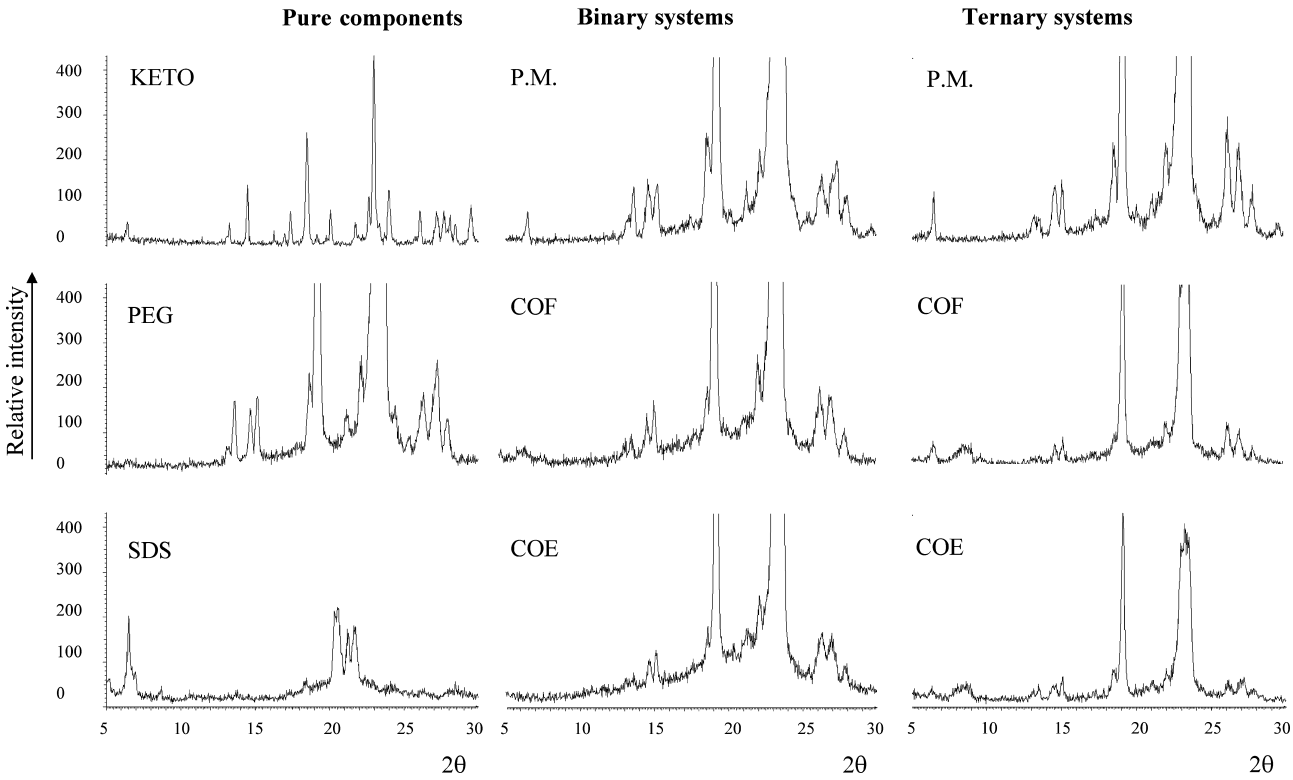

FIGURE 5 **Powder X-ray Diffraction Patterns of Pure Ketoprofen (KETO), PEG, and Sodium Dodecyl Sulfate (SDS) and of Binary (KETO-PEG 10/80 w/w), or Ternary (KETO-PEG-SDS 10/80/10 w/w) Physical Mixture (P.M.), Cofused (COF), and Coevaporated (COE) Products.**

mixture with the surfactant, has an amorphizing effect on the polymer, likely due to hampering of PEG recrystallization in solid-dispersed systems because of the presence of drug and surfactant in the blend during the cooling or coevaporation processes.

These results only partially explain the different dissolution performance of the various examined systems, indicating the greater role played by the nature of the surfactant than by the amorphization degree of the system in affecting the drug dissolution properties. In fact, the decrease of PEG fusion enthalpy in the ternary systems with the three considered surfactants was in the order TW60>DSS>SDS; this was in agreement with the liquid, amorphous semisolid, and crystalline nature, respectively, of these surfactants, but it was exactly in the opposite order with respect to their effectiveness in improving drug solubility and dissolution properties.

The results of X-ray diffraction studies were in good agreement with those of HSM and DSC analyses. Despite a covering and/or partial masking by the polymer diffraction peaks of most KETO crystallinity peaks, some of these, such as in particular those at 6.5°, 17°, 20°, and 29.5° 2 θ, were sufficiently distinguishable in the XRD spectrum of the binary physical mixture (Fig. 5). In the ternary mixture with SDS, the further interference with some peaks of the surfactant (at 6.5° and 20° 2 θ) made identification of residual crystalline drug more difficult. An almost complete loss of drug crystallinity (with respect to the corresponding physical mixtures) was observed in all solid dispersions. Only in binary cofused dispersions might there be a detectable small amount of very little crystallites of KETO (weak and broad peak at 6.5° 2 θ). Because of the low amount of drug in the systems and the strong interference of PEG bands, it was not possible to obtain accurate quantitative data of the drug residual crystallinity. The superimposition of the spectra of binary with ternary systems or of cofused with coevaporated ones revealed a lower general crystallinity degree of the ternary compared with the binary systems, as well as of the coevaporated compared with the cofused products, as demonstrated by a reduction of the intensity and number of crystallinity peaks of the corresponding spectra. This was particularly evident for the characteristic peaks of

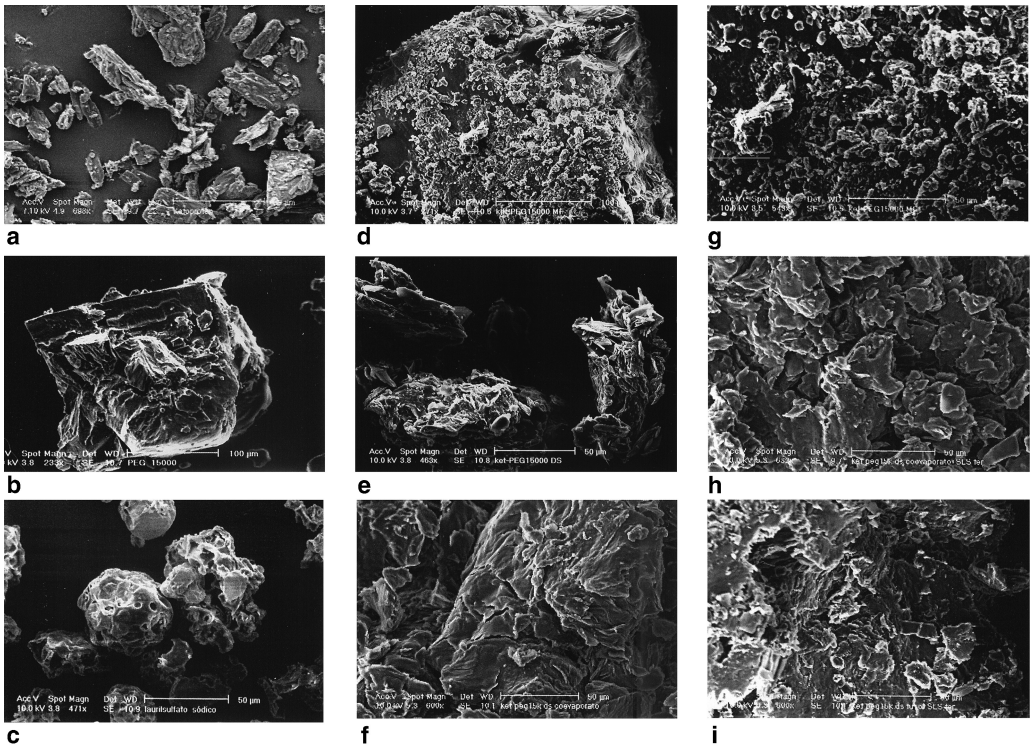

FIGURE 6 **Scanning Electron Micrographs of Pure Ketoprofen (KETO) (a), PEG (b), and Sodium Dodecyl Sulfate (SDS) (c); KETO-PEG 10/80 w/w Physical Mixture (d), Cofused (e), and Coevaporated (f) Products; KETO-PEG-SDS 10/80/10 w/w Physical Mixture (g), Cofused (h), and Coevaporated (i) Products.**

PEG, indicating an evident lower crystallinity and/or the presence of smaller crystallites of the polymer in coevaporated than in cofused products.

These results, in accordance with those of DSC analysis, could concur to explain, on the basis of the different amorphization degrees exhibited by the systems, the better dissolution effectiveness shown by coevaporated than cofused products (the composition of the system being the same).

Finally, scanning electron microscopy analysis demonstrated the higher degree of drug dispersion obtained in both binary and ternary solid dispersions, which appear as totally homogeneous systems, in comparison with the corresponding physical mixture, where, by contrast, it was still possible to detect the KETO crystals dispersed on the carrier particle surface (Fig. 6). No differences were observed in the morphology of cofused or coevaporated products, indicating that both techniques were effective in producing highly homogeneous partially amorphous dispersed systems.

CONCLUSION

Binary solid dispersion of KETO in PEG was effective in improving the drug dissolution properties in both percent of drug dissolved and dissolution efficiency ($p<0.001$). However, the addition of a surfactant when preparing the PEG-KETO solid dispersions significantly improved KETO dissolution properties in comparison with the simple binary product ($p<0.001$). In particular, ternary dispersions exhibited a dramatic increase in relative drug dissolution rate at 5 min, which passed from 24.7 for binary coevaporate to 62 or 70 for ternary coevaporates with DSS or SDS, respectively. An analogous increase was also observed for percent drug dissolved and D.E. at 10 min, whose values in the case of ternary dispersions were from 2.6 to 4.8 times higher than those of the corresponding binary ones (see Table 1). The most effective system was the 10-80-10 w/w KETO-PEG-SDS ternary coevaporate, which allowed achievement of 50% dissolved drug after only 6 min (in comparison with >120 min for drug alone and 17 min for the binary coevaporate) and about 100% dissolved after 30 min (in comparison with >120 min for the binary coevaporate). The greater efficacy of SDS, compared with the other examined surfactants, could be attributed to both its higher hydrophilic character and its stronger solubilizing ability, as found in phase-solubility studies, despite its lower amorphizing power, whereas the better performance shown by coevaporated than cofused systems seemed to be attributable to their higher amorphization degree.

Therefore, the KETO-PEG-SDS coevaporate appears to be the most suitable product for developing fast-release formulations of the drug, which could be particularly useful in the treatment of clinical conditions requiring quick pain relief.

ACKNOWLEDGMENTS

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REFERENCES

Cirri, M., Mura, P., Rabasco, A. M., Ginés, J. M., Moyano, J. R., & González-Rodríguez, M. L. (2004). Characterization of ibuproxam binary and ternary dispersions with hydrophilic carriers. *Drug Development and Industrial Pharmacy*, *30*, 65–74.

Corrigan, O. I., & Timoney, R. F. (1976). The influence of polyethylene glycols on the dissolution properties of hydroflumetiazide. *Pharmaceutica Acta Helvetiae*, *51*, 268–271.

Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, *231*, 131–144.

Craig, D. Q. M., & Newton, J. M. (1992). The dissolution of nortriptyline.HCl from polyethylene glycol solid dispersions. *International Journal of Pharmaceutics*, *78*, 175–182.

Jachowicz, R., Nürnberg, E., Pieszczek, B., Kluczykowska, B., & Maciejewska, A. (2000). Solid dispersion of ketoprofen in pellets. *International Journal of Pharmaceutics*, *206*, 13–21.

Khan, K. A. (1975). The concept of dissolution efficiency. *Journal of Pharmacy and Pharmacology*, *27*, 48–49.

Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutical Sciences*, *50*, 47–60.

Margarit, M. V., Rodriguez, I. C., & Cerezo, A. (1994). Physical characteristics and dissolution kinetics of solid dispersions of ketoprofen on polyethylene glycol 6000. *International Journal of Pharmaceutics*, *108*, 101–107.

Mukerjee, P., & Mysels, K. J. (1971). *Critical Micelle Concentrations of Aqueous Surfactant Systems*. Washington, DC: National Standard Reference Data Series, National Bureau of Standards.

Mura, P., Manderioli, A., Bramanti, G., & Ceccarelli, L. (1996). The properties of solid dispersions of naproxen in various polyethylene glycols. *Drug Development and Industrial Pharmacy*, *22*, 909–916.

Mura, P., Faucci, M. T., Manderioli, A., & Bramanti, G. (1999). Thermal behavior and dissolution properties of naproxen from binary and ternary solid dispersions. *Drug Development and Industrial Pharmacy*, *25*, 257–264.

Najib, N. M., & Suleiman, M. S. (1989). Characterization of a diflunisal polyethylene glycol solid dispersion system. *International Journal of Pharmaceutics*, *51*, 225–232.

Roger, J. A., & Anderson, A. J. (1982). Physical characteristic and

dissolution profiles of ketoprofen-urea solid dispersion. *Pharmaceutica Acta Helvetiae*, *57*, 276–282.

Schachter, D. M., Xiong, J., & Tirol, G. C. (2004). Solid state NMR perspective of drug-polymer solid solutions: a model system base on poly(ethylene oxide). *International Journal of Pharmaceutics*, *281*, 89–101.

Serajuddin, A. T. M. (1999). Solid dispersions of poorly-water-soluble drugs: early premises, subsequent problems and recent breakthroughs. *Journal of Pharmaceutical Sciences*, *88*, 1058–1066.

Sheen, P. C., Khetarpal, V. K., Cariola, M. C., & Rowlings, C. E. (1995). Formulation studies of a poorly water-soluble drug in solid dispersions to improve bioavailability. *International Journal of Pharmaceutics*, *118*, 221–227.

Sjökvist, E., Nystrom, C., & Alden, M. (1991). Physicochemical aspects of drug release. The effect of sodium dodecylsulphate additions on the structure and dissolution of a drug in solid dispersions. *International Journal of Pharmaceutics*, *68*, 53–62.

Takayama, K., Nambu, N., & Nagai, T. (1982). Factors affecting the dissolution of ketoprofen from solid dispersions in various water-soluble polymers. *Chemical and Pharmaceutical Bulletin*, *3*, 3013–3019.

Veiga, M. D., Bernad, M. J., & Escobar, C. (1993). Thermal behaviour of drugs from binary and ternary system. *International Journal of Pharmaceutics*, *89*, 119–124.

Vippagunta, S. R., Maul, K. A., Tallavajhala, S., & Grant, D. J. W. (2002). Solid-state characterization of nifedipine solid dispersions. *International Journal of Pharmaceutics*, *236*, 111–123.