DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 1, pp. 65–74, 2004

RESEARCH PAPER

Characterization of Ibuproxam Binary and Ternary Dispersions with Hydrophilic Carriers

M. Cirri,[1,*] P. Mura,[1] A. M. Rabasco,[2] J. M. Ginés,[2] J. R. Moyano,[2] and M. L. Gònzalez-Rodrìguez[2]

[1]Dipartimento Scienze Farmaceutiche, Università di Firenze, Firenze, Italy
[2]Departamento Farmacia y Tecnología Farmacéutica, Universidad de Sevilla, Sevilla, Spain

ABSTRACT

This work investigates the possibility of increasing the dissolution properties of ibuproxam (a poorly water-soluble anti-inflammatory drug) using hydrophilic carriers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), or urea, alone or in combination. Phase-solubility studies showed that the carrier solubilizing power was in the order PEG>PVP>urea and evidenced a synergistic effect in drug solubility improvement when using carrier combinations. Binary and ternary systems, at 20/80 or 20/40/40 (w/w) drug/carrier(s) ratios, prepared by coevaporation of their ethanolic solutions or by cogrinding physical mixtures in a high-energy vibrational micromill, were characterized by differential scanning calorimetry (DSC), hot stage microscopy (HSM), and scanning electron microscopy (SEM) analyses. The results of dissolution tests (USP paddle method), in terms of Dissolution Efficiency, indicated that ternary systems were up to 35% more effective than the corresponding binary preparations and coevaporated products were up to 45% more efficacious than the corresponding coground ones. The IBUX-PEG-PVP coevaporated was the best product, allowing a more than three-times increase in Dissolution Efficiency with respect to drug alone; moreover, $t_{50\%}$ (>60 min for pure ibuproxam) was <10 min, and 90% dissolution was achieved after 30 min, whereas only 40% was obtained after 60 min for pure drug. The best performance of this system was attributed to a joined effect of the strong amorphizing power of PVP (as demonstrated by solid state analyses) with the high solubilizing efficacy of PEG (as emerged from phase-solubility studies). The drug dissolution rate from solid dispersions remained practically unchanged after one-year storage at room temperature in closed containers.

Key Words: Ibuproxam; Ternary solid dispersions; Coevaporation; Cogrinding; Hydrophilic carriers; Dissolution.

*Correspondence: M. Cirri, Dipartimento Scienze Farmaceutiche, Università di Firenze, Polo Scientifico Sesto Fiorentino, via U. Schiff, 6 50019 Sesto Fiorentino (FI), Italy; Fax: +39-055-4573671; E-mail: marzia.cirri@unifi.it.

DOI: 10.1081/DDC-120027513
0363-9045 (Print); 1520-5762 (Online)
Copyright © 2004 by Marcel Dekker, Inc.
www.dekker.com

ORDER REPRINTS

INTRODUCTION

Ibuproxam [(RS)-2-(4-isobutylphenyl)-propiohydroxamic acid] is a nonsteroidal anti-inflammatory agent endowed with good analgesic and antipyretic properties and elevated tolerability. However, its poor water-solubility (0.17 mg/mL at 25° C) can give rise both to formulation problems and low and variable bioavailability, thus hindering the full exploitation of its therapeutic properties.

The improvement of pharmaceutical and biological availability of hydrophobic drugs is still a major technological problem, and several approaches have been attempted in order to overcome this drawback. Among the strategies investigated for enhancing the dissolution properties of poorly water-soluble drugs, the solid dispersion technique in hydrophilic carriers has often been successfully applied.[1–4] The principal factors claimed to explain the improved dissolution rates of solid-dispersed drugs include particle size decrease, reduction of aggregation and/or agglomeration phenomena, solubilizing effect of the carrier, improved wettability, and loss of crystallinity.[5] However, despite the number of the studies on this subject, the mechanisms by which dissolution enhancement occurs are still not fully understood.[6] Recent investigations showed that formulation of ternary solid dispersions using suited combinations of carriers can give rise to further enhancement in drug dissolution properties with respect to the corresponding binary systems.[7–9]

Cogrinding in the presence of suitable additives is another possible approach to improve drug dissolution properties.[10–14] Particle size reduction and drug amorphization occurring during the mechanical treatment seem to be the principal factors responsible for the enhanced dissolution behavior.[15]

Earlier investigations aimed at improving ibuproxam dissolution properties through complexation with natural cyclodextrins indicated that β-cyclodextrin was the tailored partner for the drug, showing by far both the highest complexing and solubilizing properties.[16] However, it is known that the application of β-cyclodextrin in the pharmaceutical field is limited by its rather low aqueous solubility (18 mg/mL at 25° C).

Therefore, in the present work it was considered worthy of interest to extend our studies and investigate the possibility of improving ibuproxam dissolution properties by solid dispersion or cogrinding techniques with hydrophilic carriers such as polyvinylpyrrolidone (PVP) polyethylene glycol (PEG), or urea. The effectiveness of using these carriers in combinations was also tested, in order to evaluate a possible synergistic effect. Phase-solubility studies were performed to investigate the drug-carrier interactions in solution, whereas differential scanning calorimetry (DSC), x-ray powder diffractometry, hot stage microscopy (HSM), and scanning electron microscopy (SEM) analyses were used to characterize the solid state of the various drug-carrier(s) solid systems, and the USP 24 paddle method was used to test their dissolution properties. The effect of one-year storage at room temperature on drug dissolution behavior was also evaluated.

MATERIALS AND METHODS

Materials

Ibuproxam (IBUX) was kindly provided by Laporte Organics Francis (Caronno Pertusella, Varese, Italy). Polyvinylpyrrolidone K30 (PVP), polyethylene glycol 4000 (PEG), and urea were obtained from Sigma Chemical Co. St. Louis, USA. All solvents used were of analytical grade.

Preparation of Solid Dispersions

The IBUX solid dispersions were prepared by coevaporation, according to the solvent method as follows. Mixtures at different drug/carrier(s) ratios [20/80 or 20/40/40 (w/w)] were dissolved in ethanol and then the solvent was removed using a rotary evaporator. The resulting solid mass was then sieved to obtain the 75–150 μm granulometric fraction.

Preparation of Ground Systems

The 20/80 or 20/40/40 (w/w) ground mixtures of drug and carrier(s) were prepared by cogrinding the corresponding blends in a vibrational mill (Mixer Mill Type MM 200, Retsch, GmbH, Düsseldorf, Germany) for 60 minutes at a frequency of 24 Hz. Grinding jars of 12 cm^3 volume and stainless steel balls of 9 and 12 mm diameter were used. The total weight of each sample was about 1 g. Physical mixtures at the same ratios were prepared for comparison purposes by simple blending in a mortar. Each solid product was sieved and the 75–150 μm granulometric sieve fraction was used for following studies.

Solubility and Phase Solubility Studies

Solubility measurements of IBUX were performed by adding excess amounts of drug to 10 mL of water

Copyright © Marcel Dekker, Inc. All rights reserved.

ORDER REPRINTS

containing a fixed amount of carrier (12% w/v) or carriers mixture (6%+6% w/v) in sealed glass containers. The suspensions were magnetically stirred at 37° ± 0.5° C. Phase-solubility studies were carried out by adding excess amounts of drug to 10 mL of aqueous solution containing increasing amounts of each carrier (0–20% w/v), in sealed glass containers stirred at 37° ± 0.5° C. In both series of experiments, when equilibrium was reached (2 days), the solutions were filtered through a 0.45 μm membrane filter and spectrophotometrically assayed for drug concentration at λ_{max} = 221 nm (Perkin Elmer, Boston, USA Lambda2 spectrophotometer). Each experiment was performed in triplicate (coefficient of variation C.V. < 2%). The results were statistically analysed (Unpaired t-test, Minitab Release 10xtra statistical software) in order to evaluate the significance of the observed differences.

Differential Scanning Calorimetry (DSC)

The DSC analysis was performed with a Mettler TA4000 apparatus equipped with a DSC 25 cell. Samples of 5–10 mg were scanned in pierced aluminum pans at a heating rate of 10° C min^{-1} from 30 to 200° C under static air. The instrument was calibrated using Indium (melting point, 156.61° C; enthalpy of fusion, 28.71 $J.g^{-1}$).

Hot Stage Microscopy (HSM)

Additional information on the thermal behavior of solid systems was obtained from their visual examination by hot stage microscopy. Analysis was performed using an Olympus BH-2 microscope fitted with a Mettler FP-82 hot-stage. A total of 5–10 mg of each sample 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 Diffraction

X-ray powder diffraction patterns were obtained at room temperature with a Philips PW 1130 diffractometer (Co Kα radiation), at a scan rate of 2° min^{-1} over the 5–30 2θ range.

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy was used to characterize the solid state of the various solid systems. Analyses were carried out using a Philips XL-30 scanning electron microscope. Prior to examination, samples were gold sputter-coated to render them electrically conductive.

Dissolution Tests

Dissolution studies were performed according to the USP 24 paddle method (Sotax AT7 Apparatus), by adding sample amounts equivalent to 50 mg of drug to 1000 mL of twice-distilled water thermostated at 37° C ± 0.5° C. The paddle rotation speed was 70 rpm. Concentration of dissolved drug was monitored through spectrophotometric assay at 221 nm (Perkin–Elmer Lambda2 spectrophotometer). The results presented are mean values of four determinations (C.V. < 1.5%). Dissolution Efficiency (DE) 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.[17] Unpaired t-test (Minitab Release 10xtra statistical software) was used to evaluate the effect of both the binary system preparation method and the carrier type on the drug DE.

RESULTS AND DISCUSSION

Phase-Solubility Studies

Phase-solubility diagrams showed a linear increase of drug solubility with an increase of the concentration of each examined carrier. Analogous results have been found for these same carriers and several other kinds of drugs and have been attributed to the probable formation of weak soluble complexes.[18–22] On the other hand, the enhancement of the drug solubility in the aqueous carrier solution could be equally well explained by the cosolvent effect of the carrier.[23] It has been found that hydrophilic carriers mainly interact with drug molecules by electrostatic bonds (ion-to-ion, ion-to-dipole, and dipole-to-dipole bonds), even though other types of forces, such as van der Waals forces and hydrogen bonds, can frequently play a role in the drug-carrier interaction.[24] The PEG showed the highest solubilizing power, with a more than three-fold increase of drug intrinsic solubility in the presence of 20% carrier (Fig. 1A). The slopes of straight line relationships, assumed as indicative of the relative solubilizing efficiency,[25] showed that the solubilizing power of PEG was 1.2-fold higher than that of PVP ($P < 0.005$) and 1.4-fold higher than that of urea ($P < 0.001$). The effectiveness of using these carriers simultaneously was also tested, to evaluate a possible synergistic effect. Solubility studies of IBUX in binary and ternary systems indicated that 1:1 (w/w) PEG-PVP or PEG-urea combinations were significantly more effective ($P < 0.001$) in improving drug solubility than the corresponding carriers used at the same total concentration, but separately (Fig. 1B). Therefore, to

Copyright © Marcel Dekker, Inc. All rights reserved.

ORDER REPRINTS

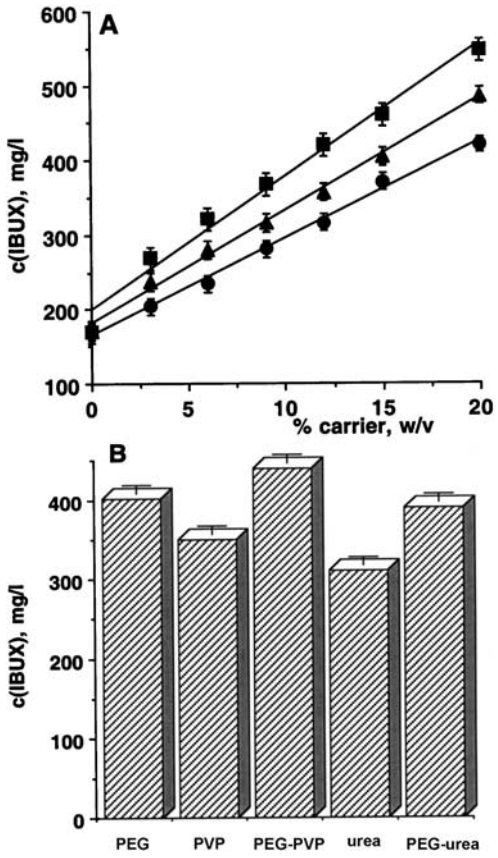

Figure 1. A) Ibuproxam (IBUX) phase-solubility diagrams in aqueous solutions at 37° C in the presence of PEG (■), PVP (▲), or urea (●). B) Aqueous solubilities of ibuproxam (IBUX) at 37° C in the presence of 12% (w/v) of PEG, PVP, or urea or their combinations (6+6% w/v).

better evaluate the greater efficacy of carrier combinations, binary and ternary solid systems were prepared, by both coevaporating or cogrinding methods, at 20/80 or 20/40/40 (w/w) drug-to-carrier(s) ratio.

Solid-State Studies

The thermal curves of IBUX in binary and ternary solid systems obtained by cogrinding and coevaporating methods with PVP, PEG, and urea are illustrated in Fig. 2, together with those of pure drug and carriers and their physical mixtures. The DSC curve of IBUX was typical of a crystalline anhydrous substance, exhibiting a sharp endothermal peak due to its melting process, followed by an intense exothermal effect attributable to the drug thermal decomposition. At a scan rate of 10° C min^{-1}, the observed melting peak temperature was 126.3° ± 0.3° C (three runs) with an apparent heat of fusion of 128.4±4.2 $J.g^{-1}$, whereas the exothermal effect was peaked at 165.3° ± 0.5° C. A large endothermal effect, in the 70–140° C range, associated with water loss, was recorded for amorphous PVP,[26] while the DSC profiles of PEG 4000 and urea presented a single sharp endothermal peak due to the carrier melting, at 60.4° C and 139.0° C, respectively.

A different thermal behavior was observed for the various drug-carrier(s) combinations, depending on both the nature of the carrier and the sample preparation method. The DSC analysis revealed the absence of strong drug-carrier solid-state interactions in systems with urea, where both drug and excipient melting peaks were always present, regardless of the method of sample preparation. The slight reduction in temperature and intensity of drug melting endotherm, observed in coground and particularly in coevaporated product, can be ascribed to a partial loss of drug crystallinity as a consequence of the sample preparation technique. On the contrary, complete disappearance of the drug melting peak was observed in all binary systems with PVP, including simple blend, indicating marked solid-state interactions with this carrier. This behavior, analogous to that previously observed for mixtures with PVP of naproxen[26] or ibuproxam,[27] was not due to a pharmaceutical incompatibility. In fact, it can be explained by the formation of crystalline microaggregates of the drug and their high dispersion within the polymeric amorphous matrix occurring during simple mixing, up to probable achievement of total drug amorphization as a consequence of cogrinding or coevaporation treatments.[27] X-ray diffraction analysis confirmed this hypothesis, showing the total disapperance of the characteristic diffraction peaks of IBUX crystals in its coground and coevaporated products with the amorphous polymer, indicating complete drug amorphization (Fig. 3). Moreover and interestingly, DSC analysis (Fig. 2) showed that the peak temperature of the PVP dehydration endotherm was gradually lowered and its enthalpy parallely decreased, passing from the pure substance to the physical mixture, coground, or coevaporated products with the drug, thus revealing that the polymer dehydration process was affected by drug-polymer interactions. It has been hypothesized that analogous surface phenomena are involved in both water-PVP and drug-PVP solid-state interactions.[28] The complete disappearence of IBUX melting peak was observed in all combinations with PEG as well. In this case, the phenomenon, already observed in solid dispersions of other drugs with this same polymer,[28–30] was attributable to the drug dissolution in the melted carrier before reaching its fusion temperature[27] and therefore, not indicative of a pharmaceutical incompatibility.

Copyright © Marcel Dekker, Inc. All rights reserved.

ORDER REPRINTS

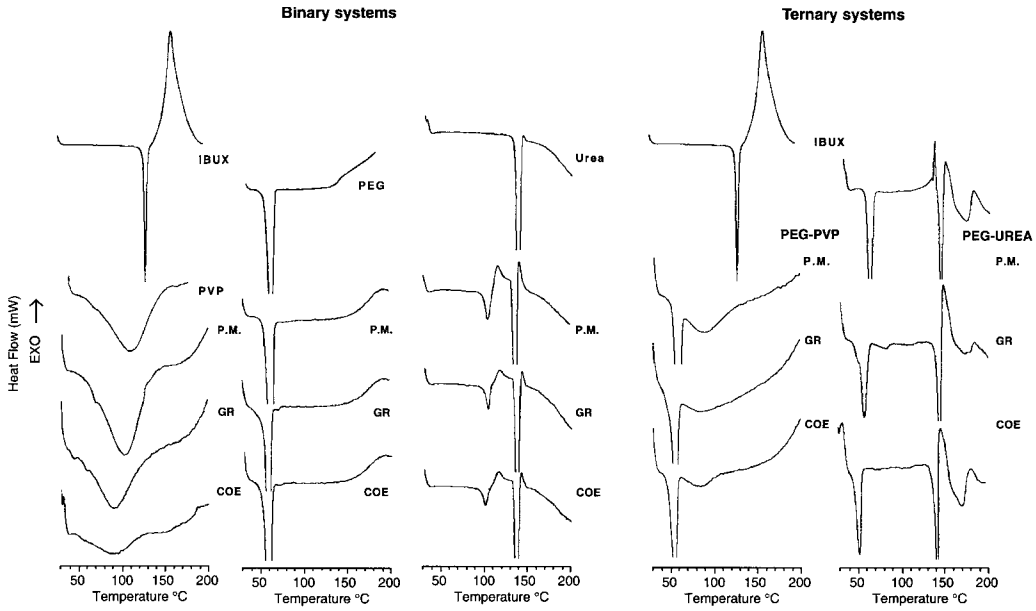

Figure 2. DSC curves of pure ibuproxam (IBUX) and carriers and their binary (20/80 w/w) and ternary (20/40/40 w/w) physical mixtures (PM), coground (GR), and coevaporated (COE) products.

All IBUX-PEG-PVP ternary systems exhibited an endothermal peak at 60° C due to the PEG fusion, followed by a broad endothermal effect corresponding to the PVP dehydration, whereas, as expected, no IBUX thermal effects were detectable, as a consequence of the combined solubilizing and amorphizing effects towards the drug due to the simultaneous presence of both PEG and PVP. Even the IBUX-PEG-urea systems presented the total disappearence of the drug melting peak, only exhibiting two endothermal peaks at 60° C and 139° C, due to the fusion of PEG and urea, respectively. Drug dissolution in the melted PEG, as above explained, is responsible for the disappearance of IBUX melting peak.

Hot stage microscopy analysis (Fig. 4) supported the interpretation of DSC results, making it possible to detect the melting process of characteristic drug polyhedric crystals in all binary systems with urea (thus confirming the absence of solid-state drug carrier interactions), and to observe the gradual dissolution of drug crystals in the melted carrier in all combinations with PEG. The same phenomenon was observed also in ternary systems with PEG-PVP or PEG-urea even though it was less clearly appreciable, due to the presence of the particle of the second carrier. Binary coevaporated and coground products with PVP substantially appeared as homogenous glassy systems. The emergence of water present in the polymer, observed in the range from 70° to 120° C, made system behavior monitoring more difficult in this temperature range.

The morphologies of pure drug and carriers and their combinations were investigated by SEM analysis. Fig. 5 shows some selected representative samples. The IBUX crystals appeared as fine needles with smooth surfaces, partially agglomerated in bundles. The PEG 4000 exhibited crystalline agglomerates of rather irregular size and shape, whereas urea consisted of sticklike crystals. Spheroidal particles of various sizes with some concavities and cracking on their surface were revealed for PVP K30. The results of SEM analysis of solid systems prepared both by coevaporating and cogrinding methods were consistent with DSC

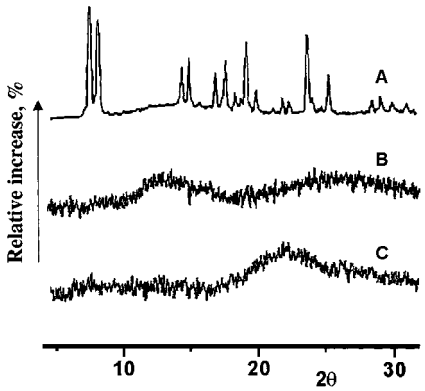

Figure 3. Powder x-ray diffraction patterns of pure ibuproxam (A) and PVP (B) and their 20/80 w/w coevaporated product (C).

Copyright © Marcel Dekker, Inc. All rights reserved.

ORDER REPRINTS

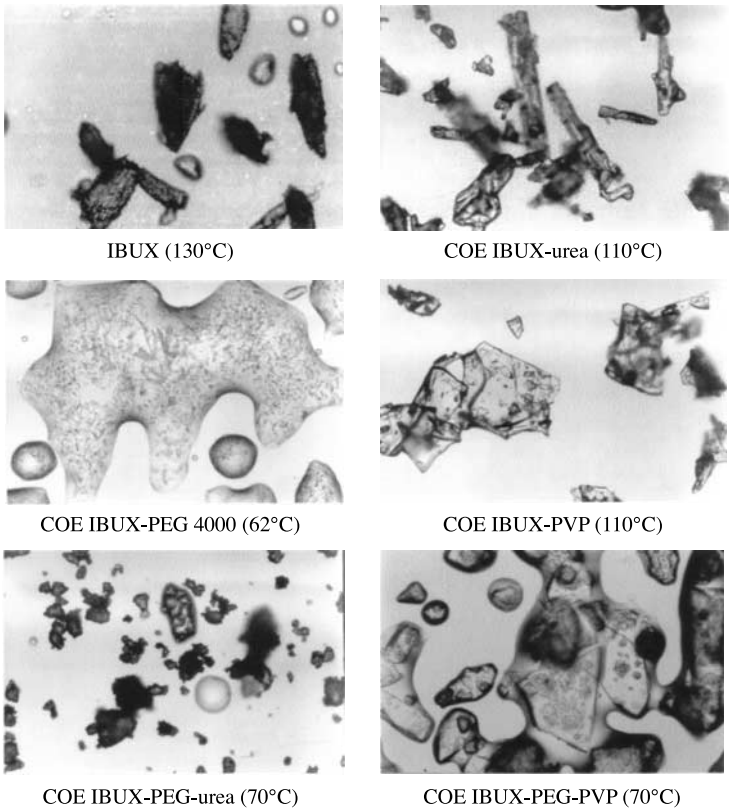

Figure 4. Photomicrographs of ibuproxam (IBUX) and its binary (20/80 w/w) and ternary (20/40/40 w/w) coevaporated (COE) and coground (GR) products with PEG, PVP, and urea taken during HSM analysis.

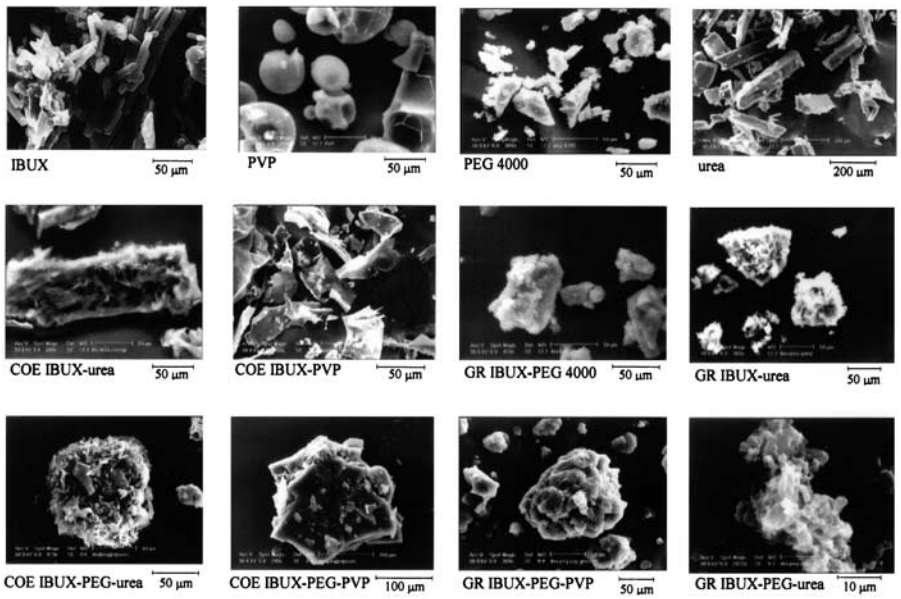

Figure 5. Scanning electron micrographs of pure ibuproxam (IBUX) and carriers and their binary (20/80 w/w) and ternary (20/40/40 w/w) coevaporated (COE) and coground (GR) products.

Copyright © Marcel Dekker, Inc. All rights reserved.

ORDER REPRINTS

and HSM findings. The presence of small drug crystals uniformly and finely dispersed or adhered to the carrier surface was clearly detectable in all its binary combinations with PEG and urea. On the contrary, the characteristic IBUX crystals, dispersed or adhered to the surface of spherical particles of PVP, were detectable only in physical mixtures, whereas the original morphology of both drug and carrier disappeared in coevaporated and coground systems, which appeared as aggregates of glassy flakes, making it impossible to differentiate the two components. All ternary coground and coevaporated systems appeared as substantially amorphous agglomerates. Moreover, SEM examination evidenced the higher homogeneity of coevaporated products and the particular disposition of coground products to form more compact agglomerates, reasonably ascribed to the production, during the mechanical treatment, of electrostatic charges (whose presence on their surface sometimes hindered SEM analysis of these samples).

Dissolution Studies

Dissolution studies were carried out in order to determine the improvement in dissolution rate of IBUX obtained in the various binary and ternary systems and to evaluate the influence of both the type of carrier and the sample preparation method. The results of the dissolution tests are shown in Fig. 6 and summarized in Table 1 in terms of time necessary to dissolve 50% drug, relative dissolution rate at 5 min, percent drug dissolved at 30 min, and Dissolution Efficiency at 60 min. The slight but statistically significant ($P < 0.001$) improvement of IBUX dissolution from physical mixtures as compared with the pure drug is most likely due to the ability of the carrier to enhance the wettability of the hydrophobic drug and also to a possible microenvironmental, solubilizing effect. A remarkable increase of IBUX dissolution properties with respect to the physical mixtures was obtained from the corresponding dispersions prepared both by cogrinding and coevaporating techniques. The sample treatment, by reducing the drug crystal dimensions and by increasing the drug-carrier contact surface, favored a more complete drug dispersion in the hydrophilic carrier matrix, and then a greater interaction. Systems with PVP exhibited significantly better ($P < 0.001$) dissolution properties than the corresponding ones with urea and with PEG, in spite of the higher solubilizing power towards the drug of this latter carrier. This finding is probably attributable to the high amorphizing properties of PVP, as emerged from solid-state studies.

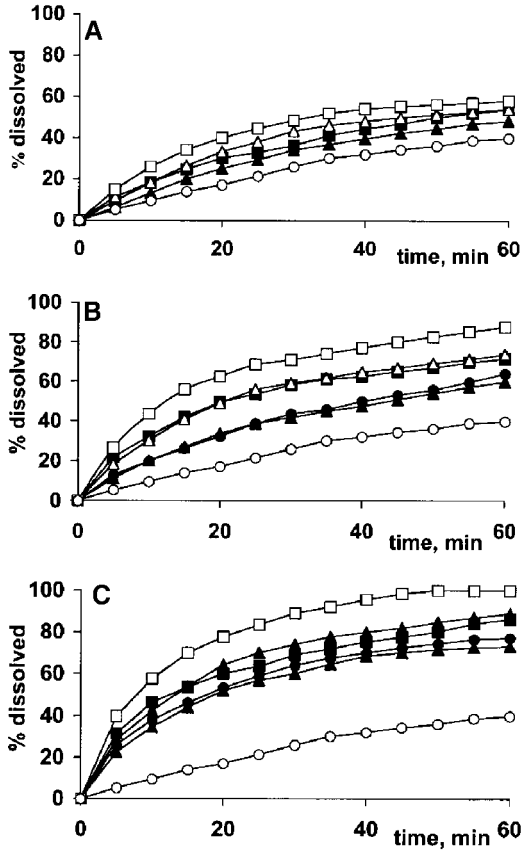

Figure 6. Dissolution curves of ibuproxam (IBUX) alone (○) and from its binary (20/80 w/w) and ternary (20/40/40 w/w) physical mixtures (A), coground (B), and coevaporated (C) products with PEG (●), PVP (■), urea (▲), PEG-PVP (□), and PEG-urea (△) (mean of four experiments, coefficient of variation CV < 1.5%, error bars omitted for the sake of clarity).

Results of dissolution tests also pointed out the influence of the method used in the solid systems preparation, indicating that coevaporation was always clearly more effective than cogrinding ($P < 0.001$) in improving drug dissolution properties. This effect could be explained by the observed marked tendency of coground products to form compact agglomerates and by the presence of electrostatic charges on the surface (as evidenced from SEM analysis), which could give rise to worse wettability. Finally, regardless of the sample preparation method, dissolution tests revealed the better performance of ternary systems with respect to the corresponding binary ones ($P < 0.001$), thus confirming the synergistic effect found in solubility studies. In particular, the best system was the IBUX-PVP-PEG coevaporated one, the only one

Copyright © Marcel Dekker, Inc. All rights reserved.

ORDER REPRINTS

Table 1. Dissolution parameters of ibuproxam (IBUX) alone and from its physical mixtures (PM), coground (GR), and coevaporated (COE) products with urea, PEG, and PVP (standard deviations in brackets).

Sample		$t_{50\%}$[a]	Rel. diss. rate[b]	DP_{30}[c]	DE_{60}[d]
IBUX	–	>60	–	26.0±0.4	23.1±0.5
IBUX-urea (20/80 w/w)	PM	≈60	1.2	34.1±0.5	29.8±0.6
	GR	45	2.1	41.8±0.6	37.0±0.7
	COE	≈20	4.3	60.0±0.9	53.2±0.9
IBUX-PEG (20/80 w/w)	PM	≈60	1.6	34.4±0.5	30.9±0.6
	GR	<40	2.5	43.6±0.6	39.5±0.8
	COE	<20	4.9	64.0±0.9	57.6±1.0
IBUX-PVP (20/80 w/w)	PM	50	1.8	36.2±0.5	33.7±0.7
	GR	≈20	4.2	58.3±0.8	51.4±0.9
	COE	<15	6.0	69.0±1.0	63.0±1.2
IBUX-PEG-urea (20/40/40 w/w)	PM	≈45	2.1	43.4±0.6	36.7±0.7
	GR	≈20	3.5	59.2±0.8	52.6±1.1
	COE	<15	5.4	74.0±1.1	65.3±1.3
IBUX-PEG-PVP (20/40/40 w/w)	PM	≈30	2.8	48.5±0.7	41.9±0.9
	GR	<15	5.0	70.9±1.0	63.7±1.3
	COE	<10	7.5	90.0±1.3	78.3±1.5

[a]Time (min) to dissolve 50% drug.
[b]Ratio between amount of drug dissolved from a drug-carrier system and from drug alone at 5 min.
[c]Percent of drug dissolved after 30 min.
[d]Dissolution Efficiency area under the dissolution curve at 60 min expressed as % of the area of the rectangle described by 100% dissolution in the same time.

which allowed 100% dissolved drug to be reached after 50 minutes.

Finally, it is important to emphasize that all binary and ternary products did not show significant changes in their dissolution properties or in their thermal behavior after one year storage at room temperature in closed amber-glass containers.

CONCLUSION

All the examined carriers were effective, even though to different degrees, in improving drug dissolution properties. Despite the highest solubilizing power of PEG towards IBUX shown by phase-solubility studies, binary combinations with PVP exhibited better dissolution performance, indicating that the marked amorphizing power of this polymer plays an important role in enhancing drug dissolution.

The importance of the suitable selection of the system preparation method for optimizing drug dissolution improvement has been demonstrated. In fact, coevaporation allowed the obtainment of more homogeneous systems with drug Dissolution Efficiency values from 25% to 45% higher than those obtained by cogrinding. Moreover, ternary solid dispersions obtained by coevaporation exhibited drug Dissolution Efficiency values from 25% to 35% higher than the corresponding binary preparations, showing a synergistic effect of carrier combinations in improving drug dissolution properties. In particular, the IBUX-PEG-PVP combination was the best system, allowing reduction of $t_{50\%}$ (>60 min for IBUX) to <10 min, with a 7.5-fold improvement of dissolution rate as compared to pure drug. The best performance of this system is attributable to the combined effect of the high amorphizing power of PVP with the great solubilizing efficacy of PEG. The dissolution behavior of this product was comparable to that previously observed for the IBUX-β-cyclodextrin inclusion complex obtained by spray-drying or sealed-heating techniques.[16]

Therefore, considering that the selected drug-to-carrier(s) w/w ratio (20/80) is similar to that of the previously prepared equimolar IBUX-β-cyclodextrin complex, and since potential problems related to the relatively low water solubility of β-cyclodextrin are avoided, solid dispersion by coevaporation of IBUX in

Copyright © Marcel Dekker, Inc. All rights reserved.

ORDER REPRINTS

the PVP-PEG combination appears as a more attractive and economic technique than cyclodextrin complexation for improving IBUX dissolution performance.

ACKNOWLEDGMENT

Financial support from Ministero Università Ricerca Scientifica Tecnologica is gratefully acknowledged.

REFERENCES

1. Sheen, P.C.; Khetarpal, V.K.; Cariola, C.M.; Rowlings, C.E. Formulation studies of a poorly water-soluble drug in solid dispersions to improve bioavailability. Int. J. Pharm. **1995**, *118*, 221–227.
2. Mura, P.; Manderioli, A.; Bramanti, G.; Ceccarelli, L. The properties of solid dispersions of naproxen in various polyethylene glycols. Drug Dev. Ind. Pharm. **1996**, *22* (9,10), 909–916.
3. Kai, T.; Akiyama, Y.; Nomura, S.; Sato, M. Oral absorption improvement of poorly soluble drug using solid dispersion technique. Chem. Pharm. Bull. **1996**, *44*, 568–571.
4. Leuner, C.; Dressman, J. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Sci. **2000**, *50*, 47–60.
5. Corrigan, O.I. Mechanisms of dissolution of fast release solid dispersions. Drug Dev. Ind. Pharm. **1985**, *11* (2,3), 697–724.
6. Craig, D.Q.M. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int. J. Pharm. **2002**, *231*, 131–144.
7. Mura, P.; Faucci, M.T.; Manderioli, A.; Bramanti, G.; Parrini, P. Thermal behavior and dissolution properties of naproxen from binary and ternary solid dispersions. Drug Dev. Ind. Pharm. **1999**, *25* (3), 257–264.
8. Jachowicz, R.; Nürnberg, E.; Pieszczek, B.; Kluczykowska, B.; Maciejewska, A. Solid dispersion of ketoprofen in pellets. Int. J. Pharm. **2000**, *206*, 13–21.
9. Vippagunta, S.R.; Maul, K.A.; Tallavajhala, S.; Grant, D.J.W. Solid-state characterization of nifedipine solid dispersions. Int. J. Pharm. **2002**, *236*, 111–123.
10. Otsuka, M.; Matsuda, Y. Effect of cogrinding with various kinds of surfactants on the dissolution behavior of phenytoin. J. Pharm. Sci. **1995**, *84*, 1434–1437.
11. Shin, S.C.; Oh, I.J.; Lee, Y.B.; Choi, H.K.; Choi, J.S. Enhanced dissolution of furosemide by coprecipitating or cogrinding with crospovidone. Int. J. Pharm. **1998**, *175*, 17–24.
12. Sugimoto, M.; Okagaki, T.; Narisawa, S.; Koida, Y.; Nakajima, K. Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water-soluble polymer. Int. J. Pharm. **1998**, *160*, 11–19.
13. Mura, P.; Faucci, M.T.; Parrini, P.L. Effects of grinding with microcrystalline cellulose and cyclodextrins on the ketoprofen physicochemical properties. Drug Dev. Ind. Pharm. **2001**, *27* (2), 119–128.
14. Mura, P.; Cirri, M.; Faucci, M.T.; Ginès-Dorado, J.M.; Bettinetti, G.P. Investigation of the effects of grinding and co-grinding on physicochemical properties of glisentide. J. Pharm. Biomed. Anal. **2002**, *30*, 227–237.
15. Nakai, Y. Molecular behavior of medicinals in ground mixtures with microcrystalline cellulose and cyclodextrins. Drug Dev. Ind. Pharm. **1986**, *12* (7), 1017–1039.
16. Mura, P.; Adragna, E.; Rabasco, A.M.; Moyano, J.R.; Pérez, J.I.; Arias, M.J.; Ginés, J.M. Effects of the host cavity size and the preparation method on the physicochemical properties of ibuproxam-cyclodextrin systems. Drug Dev. Ind. Pharm. **1999**, *25* (3), 279–287.
17. Khan, K.A. The concept of dissolution efficiency. J. Pharm. Pharmacol. **1975**, *27*, 48–49.
18. Higuchi, T.; Connors, K.A. Phase-solubility techniques. Adv. Anal. Chem. Instrum. **1965**, *4*, 117–212.
19. Shahjahan, M.; Enever, R.P. Investigation of the nature of the interaction of nitrofurazone with urea. Int. J. Pharm. **1992**, *82*, 229–232.
20. Sekikawa, H.; Nakano, M.; Arita, T. Inhibitory effects of polyvinylpyrrolidone on the crystallization of drugs. Chem. Pharm. Bull. **1978**, *26* (1), 118–126.
21. Corrigan, O.I.; Timoney, R.F. The influence of polyethylene glycols on the dissolution properties of hydroflumetiazide. Pharm. Acta Helv. **1976**, *51* (9), 268–271.
22. Ford, J.L. The current status of solid dispersions. Pharm. Acta Helv. **1986**, *61* (3), 69–88.
23. Chiou, W.L. Pharmaceutical applications of solid dispersions systems: x-ray diffraction and aqueous solubility studies on griseofulvine-polyethylene glycol 6000 systems. J. Pharm. Sci. **1977**, *66* (7), 989–991.

Copyright © Marcel Dekker, Inc. All rights reserved.

ORDER REPRINTS

24. Rácz, I. Physicochemical interactions encountered in the course of drug product preparation. In *Drug Formulation*; Wiley J and Sons: New York, 1989; 212–242.
25. Najib, N.M.; Suleiman, M.S. Characterization of diflunisal-polyethylene glycol solid dispersions systems. Int. J. Pharm. **1989**, *51*, 225–232.
26. Bettinetti, G.P.; Mura, P. Dissolution properties of naproxen in combinations with polyvinylpyrrolidone. Drug Dev. Ind. Pharm. **1994**, *20* (8), 1353–1366.
27. Mura, P.; Faucci, M.T.; Manderioli, A.; Bramanti, G.; Ceccarelli, L. Compatibility study between ibuproxam and pharmaceutical excipients using differential scanning calorimetry, hot-stage microscopy and scanning electron microscopy. J. Pharm. Biomed. Anal. **1998**, *18*, 151–163.
28. Bettinetti, G.P.; Bruni, G.; Giordano, F.; Mura, P. Thermal analysis of the dehydration process of cross-linked polyvinylpyrrolidone and its mixtures with naproxen. Drug Dev. Ind. Pharm. **1994**, *20* 14), 2215–2225.
29. Veiga, M.D.; Bernad, M.J.; Escobar, C. Thermal behavior of drugs from binary and ternary systems. Int. J. Pharm. **1993**, *89*, 119–124.
30. Veiga, M.D.; Diaz, P.; Ginés, J.M.; Rabasco, A.M. Preparation and evaluation of mequitazine/PEG 600 binary systems. Pharmazie **1994**, *49*, 906–909.

Copyright © Marcel Dekker, Inc. All rights reserved.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

Copyright of Drug Development & Industrial Pharmacy is the property of Marcel Dekker Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

Copyright of Drug Development & Industrial Pharmacy is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.