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Ternary systems of naproxen with hydroxypropyl-β-cyclodextrin and aminoacids

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Abstract

The purpose of the present study was to investigate the combined effect of hydroxypropyl-β-cyclodextrin and different aminoacids (L-lysine, LYS; L-valine, VAL; L-iso-leucine, LEU; and L-arginine, ARG) on the solubility of naproxen, a poorly water-soluble anti-inflammatory drug. Aqueous solubilities of naproxen in binary and ternary systems with hydroxypropyl-β-cyclodextrin and each aminoacid were determined. The pH was measured in all solubility studies and its role on drug solubility variation was evaluated. Arginine was the most effective aminoacid in improving drug solubility and the only one which showed a synergistic effect when used in combination with hydroxypropyl-β-cyclodextrin. In contrast, some reduction with respect to the theoretical drug solubility (i.e. the sum of the solubilities in the presence of cyclodextrin and aminoacid separately) was observed in ternary combinations with the other aminoacids. This occurred also in the case of lysine, despite the higher solubility of its ternary system in comparison with the binary cyclodextrin complex at pH 7. Phase-solubility experiments showed that the ternary system with arginine (pH ≈ 7) exhibited a stability constant 3.6 times higher and was about 5.5 times more effective in improving drug solubility than the binary complex in buffered (pH ≈ 7) aqueous solutions. These results demonstrated that the high increase in the drug solubility shown by ternary systems with arginine was not simply due to a favorable pH change but to multicomponent complex formation. Solid products of naproxen with hydroxypropyl-β-cyclodextrin, and/or arginine, prepared by different methods, were characterized by Differential Scanning Calorimetry (DSC), Hot Stage Microscopy (HSM) and Scanning Electron Microscopy (SEM).

Keywords: Naproxen; Hydroxypropyl-β-cyclodextrin; Solubilization; Aminoacids; Arginine; Multicomponent complexes

1. Introduction

Cyclodextrins have received increasing interest in the pharmaceutical field because of their ability to favorably modify physical, chemical and biological properties of a number of hydrophobic drug molecules through the formation of inclusion complexes (Duchêne, 1987; Szejli, 1988; Uekama et al., 1998). However, due to various reasons (such as their high molecular weight, relatively low water solubility and possible parenteral toxicity), the amount of cyclodextrins that can be used in most pharmaceutical formulations is limited (Loftsson and Brewster, 1996). Therefore, in order to be able to reduce the amount of cyclodextrins necessary to obtain the desired drug solubilizing and/or stabilizing effect, it is important to find effective methods to adequately improve their performance. Among the different approaches undertaken with this aim, recent works showed that the addition of suitable auxiliary substances can

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significantly increase the cyclodextrin solubilizing and complexing abilities by multicomponent complex formation (Loftsson and Brewster, 1996). For instance, it was shown that the addition of small amounts of a suitable water-soluble polymer to a drug-cyclodextrin system can improve the performance of the cyclodextrin (Loftsson et al., 1994; Ganzerli et al., 1996; Loftsson et al., 1996). The combined use of cosolvent and cyclodextrins positively influenced the solubility of nonpolar solutes (Li et al., 1999; Muñoz de la Pena et al., 1991). On the other hand, the influence of hydroxyacids in intensifying the cyclodextrin solubilizing power toward basic drugs can be seen as a result of the combined effects of salt formation and inclusion complexation (Redenti et al., 2000; Mura et al., 2001a). Ternary complexation involving salt formation was also reported for acidic drugs (Redenti et al., 2001; Vikmon et al., 1999; Piel et al., 1997).

Hydroxypropyl-β-cyclodextrin (HPβCd) is the most accepted representative of the hydroxyalkylated β-cyclodextrin derivatives, in virtue of its high water solubility and solubilizing power, low cost and low toxicity. We previously showed that both complexing and solubilizing power of HPβCd toward naproxen (NAP), a very poorly water-soluble (0.027 mg ml^{-1} at 25 °C) nonsteroidal anti-inflammatory drug, can be significantly improved by addition of a small amount of polyvinylpyrrolidone (Mura et al., 2001b). Therefore, it seemed of interest to extend our studies on the multicomponent technology as a strategy for improving the cyclodextrin solubilizing power and to investigate the combined effect of HPβCd and a series of aminoacids (L-lysine, LYS; L-valine, VAL; L-iso-leucine, LEU; or L-arginine, ARG), selected to test their effectiveness as possible ternary components, on the enhancement of NAP aqueous solubility. The use of aminoacids for multicomponent complex formation with acidic drugs appears of special interest, due to their potential ability to simultaneously interact with both the drug, via electrostatic interactions, and cyclodextrin, via hydrogen bonding. Moreover, their effectiveness as suitable salt-forming agents for acidic drugs has been demonstrated (Morris et al., 1994; Berge et al., 1977; Laveneziana et al., 1996).

The solubilizing efficiency of each ternary system was compared with that of the corresponding drug-cyclodextrin and drug-aminoacid systems, with the object of choosing the most effective third component. The pH was determined in all solubility studies and its role in drug solubility variation was taken into account. Phase-solubility experiments were then performed to investigate the interaction of NAP with HPβCd, alone or in the presence of the selected aminoacid. Drug-HPβCd complexation was studied also in aqueous solutions buffered at the same pH of the ternary system aqueous solution, in order to separately evaluate the role of pH and ternary complexation on drug solubility improvement. Solid binary and ternary systems of NAP with HPβCd and the selected aminoacid, prepared by different techniques, were characterized by Differential Scanning Calorimetry (DSC), Hot Stage Microscopy (HSM), and Scanning Electron Microscopy (SEM), in order to examine the amorphous or crystalline state of the drug in the various combinations and to investigate possible solid-state interactions among the components.

2. Materials and methods

2.1. Materials

NAP, LYS, VAL, LEU, and ARG were from Sigma (St. Louis, MO, USA). HPβCd average molar substitution 0.9 (average molecular weight 1475.5) was a gift from Wacker-Chemie GmbH (München, Germany).

2.2. Solubility studies

Solubility measurements of NAP and its equimolar mixtures with the different aminoacids, equimolar complexes with HPβCd and equimolar drug-Cd-aminoacid systems were carried out by adding an excess amount of drug (320 mg) or each product (always containing 320 mg of drug) to 10 ml aqueous solutions in sealed glass containers magnetically stirred (500 rpm) at constant temperature (25 ± 0.5 °C). Aliquots of 0.5 ml were periodically withdrawn with a syringe-filter (pore size 0.45 μm), and, after suitable dilution, assayed for drug concentration by second derivative ultraviolet spectroscopy (Mura et al., 2001b) (Perkin-Elmer mod.552S, Norwalk, CT, USA) until equilibrium was reached (48 h). The presence

Table 1
Solubility of NAP in aqueous solution at 25 °C, alone or in the presence of aminoacids (VAL, LEU, ARG, LYS) and/or HPβCd

Sample	NAP solubility (mg ml^{-1})	pH at equilibrium	NAP alone solubility (mg ml^{-1}) at the same pH
NAP alone	0.027	4.85	0.027
NAP + VAL	0.18	5.06	0.038
NAP + LEU	0.19	5.14	0.045
NAP + ARG	14.5	7.30	2.90
NAP + LYS	12.1	7.14	2.60
NAP + HPβCd	5.50	4.45	0.026
NAP + HPβCd (phosphate buffer pH 7)	11.3	6.98	2.20
NAP + VAL + HPβCd	5.36	4.15	0.024
NAP + LEU + HPβCd	5.38	4.19	0.024
NAP + ARG + HPβCd	29.5	6.90	2.20
NAP + LYS + HPβCd	16.0	6.58	1.40

The aqueous solubility of the drug alone, at the different pH values, is also reported.

of cyclodextrin and/or aminoacid did not interfere with the assay. The pH at equilibrium was checked in all the suspensions (see Table 1) and its role in drug solubility variation was taken into account. Each test was repeated four times (coefficient of variation C.V. < 3%).

2.3. Phase-solubility studies

Excess amounts of NAP or NAP-ARG equimolar combination were added to 10 ml of unbuffered aqueous solutions containing increasing concentrations of HPβCd in the 0–25 mM concentration range. The suspensions were magnetically stirred at 25 ± 0.5 °C, and, periodically, filtered aliquots were spectrometrically assayed for drug concentration according to the same procedure followed in Section 2.2, until equilibrium was reached (48 h). The pH at equilibrium was 4.8–4.4 and 6.9–7.0 for binary and ternary systems, respectively. Each test was performed in triplicate (C.V. < 3%). Analogous phase-solubility studies were also performed, under the same experimental conditions, on NAP-HPβCd binary systems in pH 7 phosphate buffer solutions (i.e. the same pH shown by unbuffered aqueous solutions of NAP-ARG combinations with HPβCd). The apparent 1:1 stability constants of the complexes were calculated from the slope of the straight portion of the phase-solubility diagrams (Higuchi and Connors, 1965).

2.4. Preparation of solid systems

Equimolar binary (NAP-HPβCD, NAP-ARG) and ternary (NAP-HPβCD-ARG) systems were prepared from previously sieved (75–150 μm) individual components by: (a) 15 min tumble mixing (physical mixture, PM); (b) 60 min grinding in a micro-vibrational mill (Retsch, GmbH, Düsseldorf, Germany) (coground mixture, GR); (c) coevaporation of water–ethanol solutions of the PM in a rotary evaporator at 60 °C (coevaporated systems, COE). Each solid product was sieved and the 75–150 μm granulometric sieve fraction used for the following tests.

2.5. DSC

DSC analysis was performed with a Q 1000 DSC (Q^{TM} series) (TA Instruments) equipped with a Tzero cell and a refrigerating system, utilizing the advanced Tzero^{TM} technology. Weighed samples (2–3 mg, Mettler M3 microbalance) were scanned in covered aluminium pans under dry nitrogen purge (50 ml min^{-1}) at a scan rate of 10 °C min^{-1} over a temperature range of 30–300 °C.

2.6. HSM

HSM assays were performed using a Olympus BH-2 microscope fitted with a Mettler FP-82 hot-stage. A small amount of sample was placed on the sample

stage and heated in the 30–300 °C temperature range at a rate of 5–1 K min^{-1}.

2.7. SEM

SEM analysis was performed using a Philips XL-30 SEM. Before examination, samples were gold-sputter coated to render them electrically conductive.

3. Results and discussion

3.1. Solubility studies

Solubility studies of NAP in binary and ternary equimolar systems with HPβCd and each aminoacid in water at 25 °C showed that ARG and LYS were the most effective of the examined aminoacids in improving NAP solubility, reasonably in accordance with their stronger basic character and the acidic nature of the drug (Table 1). When the aminoacids were used in combination with HPβCd, a clear synergistic effect on NAP solubility enhancement was found in ternary systems with ARG. In fact, by dividing the drug solubility in the NAP-HPβCd-ARG ternary system (value in the second column of Table 1) by the solubility of drug alone at the same pH (pH ≈ 7) (value in the fourth column of Table 1), a 13.4-fold increase was found, whereas in the case of NAP-HPβCd binary system at pH 7, the corresponding increase was only 5.1-fold. Moreover, the drug solubility in the ternary system was higher than the one calculated by adding the solubilities in the presence of Cd (at the same pH ≈ 7) and aminoacid separately. On the contrary, some reduction with respect to the theoretical calculated drug solubility was observed in the ternary combinations with the other aminoacids. This occurred also in the case of LYS, despite the higher solubility of the ternary NAP-HPβCd-LYS system in comparison with the NAP-HPβCd binary one at pH 7. This effect could be explained by the weak pH-lowering always observed when is HPβCd added to the NAP-aminoacid systems, but it might also be due to a possible competitive effect for inclusion into the Cd cavity. In fact, cyclodextrin complexation with aminoacids has been reported (Bao-Yun et al., 2001).

The synergistic effect in drug solubility improvement exhibited by ARG in ternary systems with HPβCd seems to indicate a specific involvement of ARG in the molecular assembly of a ternary complex, probably by establishing electrostatic interactions with the carboxylic group of NAP and hydrogen bonds with the hydroxyl groups of HPβCd. On the basis of these results, the ternary system with ARG was selected for further investigations.

3.2. Phase-solubility studies

Phase-solubility studies of NAP in binary and ternary systems with HPβCd and ARG were then performed to obtain more information about the drug solubilization mechanism and the multicomponent complex formation. Solubility diagrams obtained by adding increasing amounts of HPβCd to excess amounts of NAP or NAP-ARG equimolar mixture were both of A_L type according to the Higuchi classification (Higuchi and Connors, 1965), showing a linear increase of drug solubility, indicative of the formation of soluble complexes (Fig. 1). The ratio between the slopes of the phase-solubility curves of the ternary and binary systems ($S_{T\,pH\approx7}/S_{B\,pH\approx4.5}$), assumed as an index of the relative solubilizing

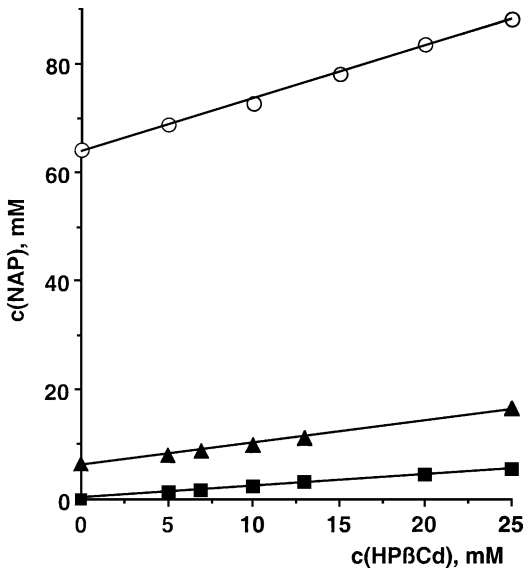

Fig. 1. Phase-solubility diagrams at 25 °C of NAP in the presence of increasing amounts of HPβCD in pH 7 buffered solution (▲) or in unbuffered aqueous solutions without (■) (pH ≈ 4.5) or with (○) (pH ≈ 7) arginine (ARG).

efficiency, was 4.8, thus confirming the greater effectiveness of the ternary system. However, a clear decrease of drug-HPβCd interaction was observed, as indicated by the sharp reduction of the stability constant value which passed from 2080 M^{-1} for the binary complex to 360 M^{-1} for the ternary one. The reduced affinity for the Cd cavity can be explained on the basis of the higher initial drug solubility, due to the salt formation, and to the reduced affinity for the apolar Cd cavity as a consequence of drug increased ionization in the presence of the basic aminoacid (pH ≈ 7) (Krishnamoorthy and Mitra, 1996), analogously to that found with basic drugs in the presence of hydroxyacids (Mura et al., 2001a,b). However, this effect was largely counterbalanced by the about 17-fold drug solubility increase obtained in the ternary system in comparison with the corresponding binary complex in aqueous unbuffered solution (pH 4.5).

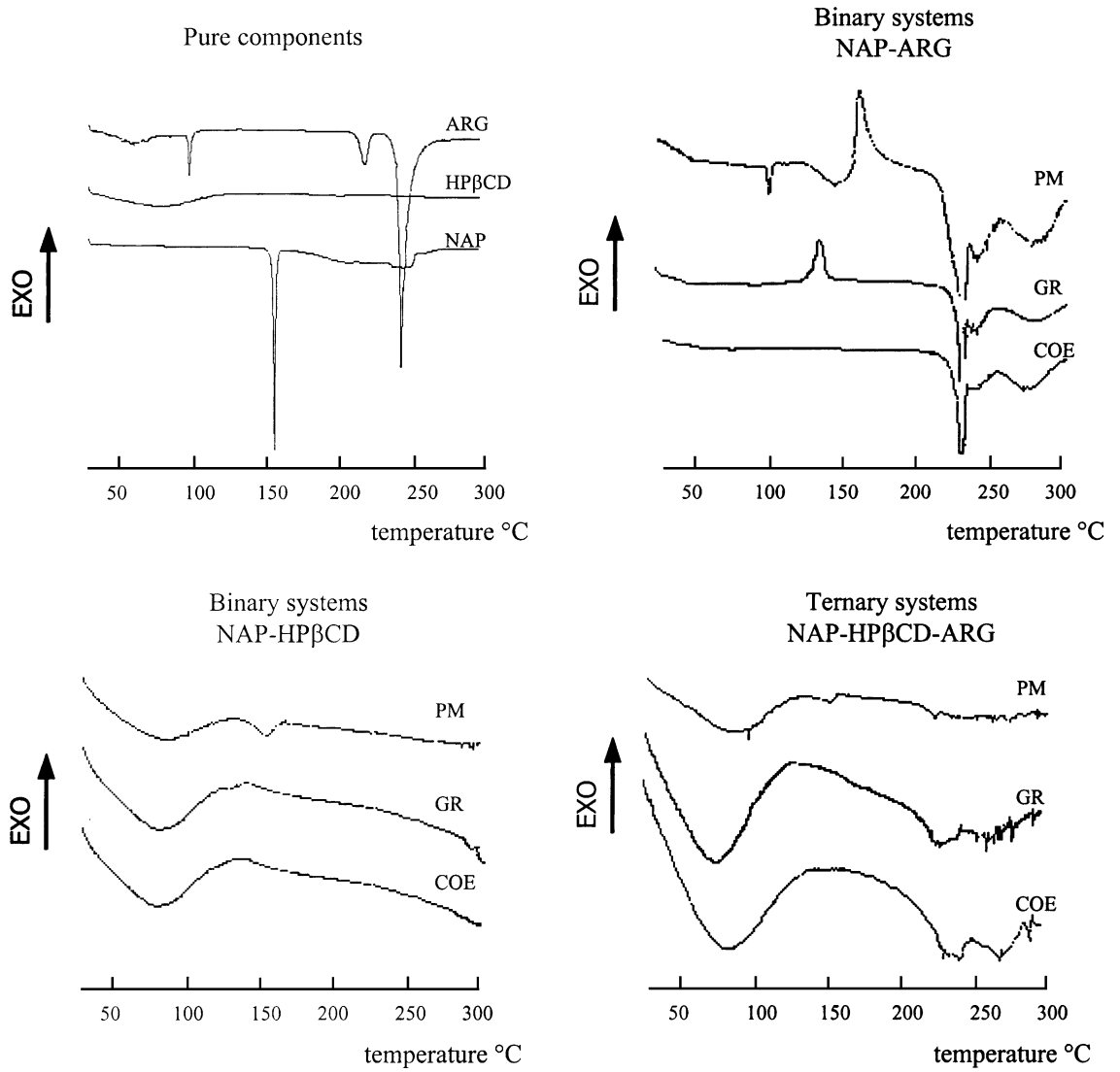

Fig. 2. DSC curves of: pure components (NAP, ARG, HPβCD) and of binary and ternary equimolar physical mixture (PM), coground (GR) and coevaporated (COE) products of NAP with ARG and/or HPβCD.

Moreover, the multicomponent complex with ARG exhibited a 11.5-fold improvement in drug solubility with respect to the NAP-HPβCd-PVP multicomponent system (Mura et al., 2001b).

Phase-solubility experiments were also performed on NAP-HPβCd binary systems in aqueous pH 7 phosphate buffer solution (i.e. about the same pH of the ternary system aqueous solution in the presence of ARG), in order to evaluate the effect on cyclodextrin solubilizing efficiency towards NAP due to the simple pH variation. As expected, as a consequence of drug ionization (Loftsson et al., 1993), the stability constant of the NAP-HPβCd complex strongly decreased falling to $100\,M^{-1}$. This effect was clearly more marked than that observed for the ternary complex, even though the pH of the complexation media

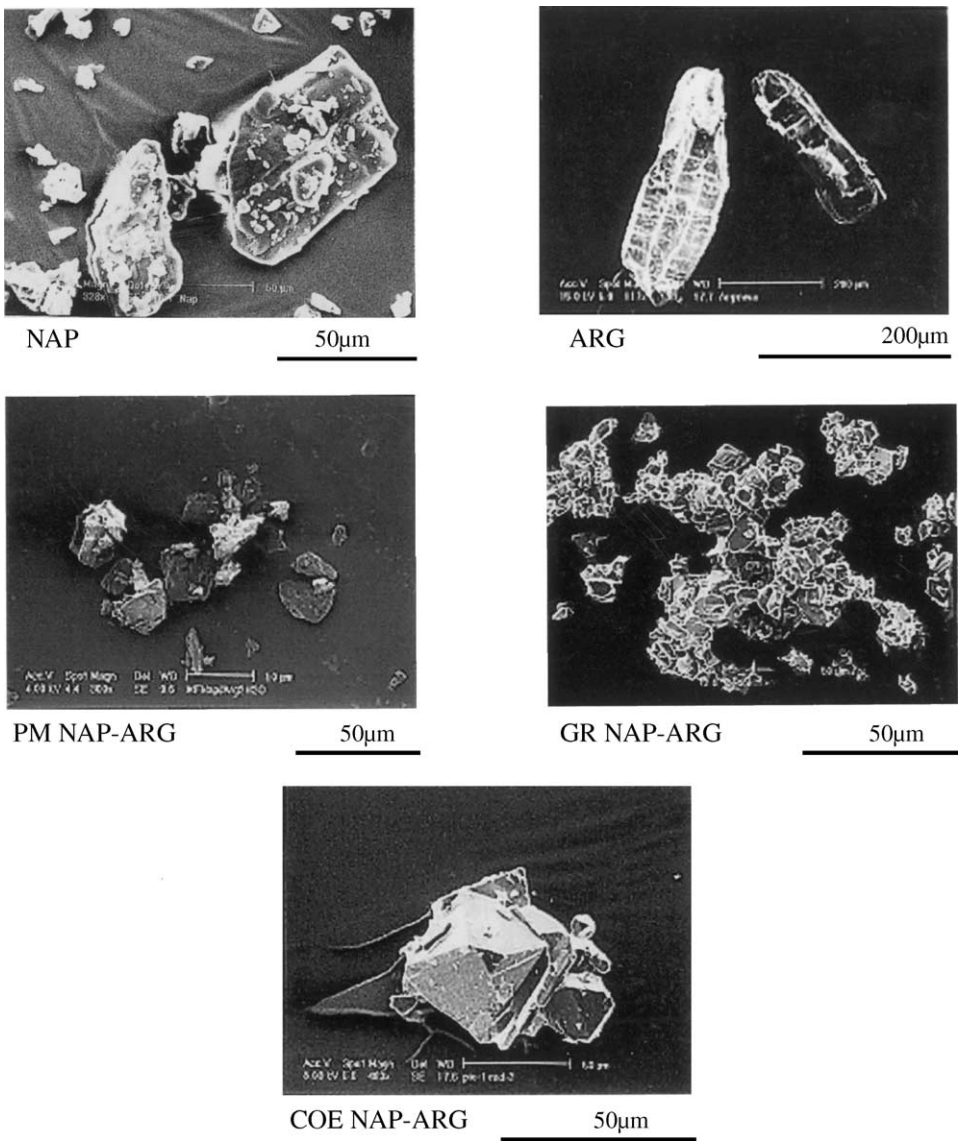

Fig. 3. Scanning electron micrographs of NAP, ARG and their equimolar physical mixture (PM), coground (GR) and coevaporated (COE) products.

was practically the same. Moreover, the concomitant increase in drug solubility with respect to that in aqueous unbuffered solution (pH 4.5) was only 3 times (in comparison with the 17 times increase given by the ternary system), and the relative solubilizing efficiency, calculated by the ratio between the slopes of the phase-solubility curves ($S_{B\,pH\approx7}/S_{B\,pH\approx4.5}$), was only 1.9. Finally, the relative solubilizing efficiency of the ternary system with respect to the binary one at the same pH ($S_{T\,pH\approx7}/S_{B\,pH\approx7}$) was 2.4. All these findings confirm the important role of ARG in the drug solubilizing process by ternary complexation. It can be hypothesized that multicomponent complex formation can take place by exploiting the specific interaction of the aminoacid counterion with the hydrogen bond system of the host (Steiner et al., 1995). The better performance of the NAP-HPβCd-ARG complex will allow reduction in the amount of Cd needed to solubilize

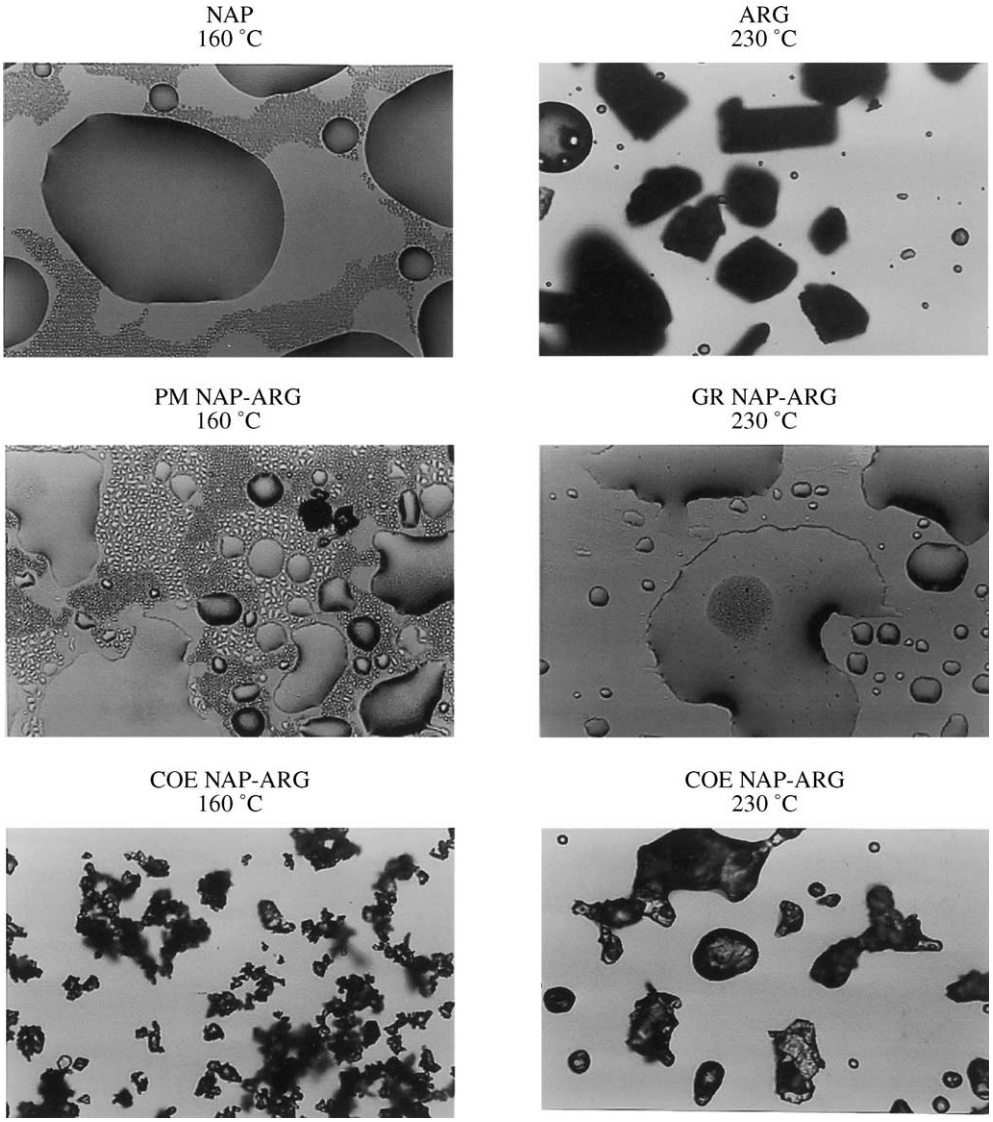

Fig. 4. Photomicrographs of NAP, ARG and equimolar NAP-ARG PM, coground (GR) and coevaporated (COE) products taken during HSM analysis.

a given amount of the drug (Redenti et al., 2001) and, moreover, it could be suitably utilized to formulate fast-dissolving NAP solid dosage forms (Moore et al., 2000). Therefore, it was considered worthy of interest to prepare and adequately characterize solid ternary systems.

3.3. Solid-state studies

The DSC curves of pure components and various binary and ternary systems are presented in Fig. 2. The NAP thermal profile ($T_{fus} = 156.8 \pm 0.2\,^{\circ}C$, $\Delta H_{fus} = 142.5 \pm 1.3\,J\,g^{-1}$) indicated its crystalline anhydrous state. A dehydration endothermic band between 50 and 150 °C (7% as mass fraction by TGA), was observed for the amorphous HPβCd. The ARG thermal curve showed a dehydration effect at 99 °C (3.8% as mass fraction by TGA), followed by melting ($T_{fus} = 222.2 \pm 0.3\,^{\circ}C$, $\Delta H_{fus} = 64.3 \pm 0.5\,J\,g^{-1}$) and immediately afterwards by a decomposition phenomenon. The thermal curves of NAP-HPβCd systems showed a marked broadening and reduction in intensity of NAP fusion endotherm when passing from PM to coground product up to its disappearance in the coevaporated one, indicative of complete drug amorphization and/or inclusion complexation (Mura et al., 1995). The thermal behavior of NAP-ARG systems strongly depended on their preparation method. The DSC profile of the PM showed in succession the dehydration endotherm of ARG at 99 °C, a broad melting phenomenon (104–135 °C), an exothermic effect at 158 °C, attributed to salt formation, and then a sharp endothermic peak at 230 °C, due to salt melting, followed by decomposition phenomena. The more intimate contact between the components, obtained by cogrinding, favored interaction and salt formation during the DSC scan, as indicated by the exothermic effect at 138 °C, followed by an endothermic peak at 230 °C corresponding to the salt melting. The DSC curve of the coevaporated product only showed the salt melting peak at 230 °C. As for the ternary products, the PM showed the broad endothermic cyclodextrin dehydration band (70–130 °C) followed by two very slight endothermic peaks due to melting of noninteracted NAP (150 °C) and NAP-ARG salt (230 °C), respectively, and finally by decomposition bands. In ternary coevaporated and coground products these melting effects disappeared and only the endothermic effects due to dehydration (50–160 °C) and decomposition (250–300 °C) were observed, indicating complete interaction between the components.

The particular behavior of NAP-ARG systems required further investigations which were performed by SEM analysis (Fig. 3). Drug and ARG crystals were well detectable in the PM, whereas the formation of amorphous aggregates was observed in the coground system, where it was no more possible to differentiate the two components. Coevaporated products appeared as polyhedric crystals, different from the original morphology of both drug and ARG, indicating the presence of a new crystalline phase, as a consequence of salt formation.

HSM analysis (Fig. 4) confirmed the results of DSC and SEM analyses, showing the presence in coevaporated product of crystals morphologically different from those of NAP and ARG, due to the formation of the salt which melted at about 230 °C. On the contrary, melting of NAP (at 155 °C) and ARG (at 220 °C) crystals was detected in physical and coground mixtures, even though a further melting phenomenon (due to the fusion of salt formed during sample heating) was observed at 230 °C.

4. Conclusion

The study demonstrated the possibility of significantly improving the dissolution performance of NAP by simultaneous complexation with cyclodextrin and salt formation. The importance of proper selection of the most suitable counterion to adequately improve the cyclodextrin-solubilizing efficiency has been pointed out. ARG was the best candidate, among the tested aminoacids, for increasing NAP solubility and the only one which showed a synergistic effect when used in combination with HPβCd. Multicomponent complex formation was obtained by simultaneously exploiting salt formation and interaction of the aminoacid with the hydrogen bond system of the host.

Phase-solubility experiments demonstrated that the ternary system with ARG (pH ≈ 7) exhibited a stability constant 3.6 times higher than the binary complex in buffered (pH ≈ 7) aqueous solutions and the drug solubility improvement obtained in the ternary system in the presence of 25 mM HPβCd was about 5.5 times higher than that in the binary system, both at pH 7.

These results confirmed that the strong increase in the drug solubility shown by ternary systems with ARG was not simply due to a favorable pH change of the solution.

Solid-state analyses demonstrated that coevaporation technique was suitable for obtaining solid homogeneous equimolar NAP-HPβCd-ARG complexes. These systems could be useful for formulating fast-dissolving drug solid dosage forms able to assure rapid onset of analgesic action and improved bioavailability, since NAP absorption is not hindered by poor membrane permeability (Amidon et al., 1995). Moreover, the use of the aminoacid as counterion should reduce the burning sensation and bitter taste given by cyclodextrin complexes of NSAIDs sodium salts when dissolved in water (Redenti et al., 2001).

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