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Research paper

Solid-state characterization and dissolution properties of Naproxen–Arginine–Hydroxypropyl-β-cyclodextrin ternary system

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Abstract

The effect of ternary complexation of naproxen, a poorly water soluble anti-inflammatory drug, with hydroxypropyl-β-cyclodextrin and the basic aminoacid L-arginine on the drug dissolution properties has been investigated. Equimolar binary (drug–cyclodextrin or drug–arginine) and ternary (drug–cyclodextrin–arginine) systems were prepared by blending, cogrinding, coevaporation, and characterized by differential scanning calorimetry, thermogravimetric analysis, FT-IR spectroscopy, X-ray diffractometry. The dissolution behavior of naproxen from the different products was evaluated by means of a continuous flow through method. The results of solid state studies indicated the presence of strong interactions between the components in ternary coevaporated and coground systems, which were both of totally amorphous nature. In contrast, the presence of either free drug or free arginine was detected when the third component (cyclodextrin or aminoacid) was physically mixed, respectively, to the drug–arginine binary system (as physical mixture, coevaporate, or coground product) or to the drug–cyclodextrin binary system (as physical mixture, coevaporate, or coground product). All ternary combinations were significantly ($P < 0.001$) more effective than the corresponding binary drug-cyclodextrin and drug–arginine systems in improving the naproxen dissolution rate. The best performance in this respect was given by the ternary coevaporate, with about 15 times increase in terms of both drug relative dissolution rate and dissolution efficiency. The synergistic effect of the simultaneous use of arginine and cyclodextrin on the dissolution rate of naproxen was attributed to the combined effects of inclusion in cyclodextrin and salt formation, as well as to a specific role played by arginine in this interaction.

Keywords: Hydroxypropyl-β-cyclodextrin; Naproxen; Arginine; Ternary system; Dissolution rate

1. Introduction

Cyclodextrins are powerful carriers for improving the therapeutic efficacy of drugs with poor solubility and/or stability problems, owing to their ability to amend these unfavourable properties through the formation of inclusion complexes [1–3]. However, the exploitation cyclodextrin properties in the pharmaceutical area is hindered by problems such as high molecular weight, rather high cost, relatively low water solubility, potential toxicity, etc. [4]. Strengthening the complexation and solubilization efficacy of cyclodextrins is a possible tool to reduce their workable amount in pharmaceutical formulations. Among the strategies proposed toward this aim, the addition of suitable auxiliary substances can be a valuable approach to increase the cyclodextrin solubilizing capacity [4–6]. It has been shown for example that certain low molecular weight acids or hydroxyacids can strongly enhance the cyclodextrin solubilizing power toward basic drugs, as a result of the combined effect of salt formation and inclusion complexation [7–11]. Likewise, the positive effects on drug solubility of ternary complexation involving an acidic drug, a basic additive and a cyclodextrin have been reported [12–14]. Pursuing our studies on naproxen–cyclodextrin binary systems [15] and a more recent study on the naproxen–hydroxypropyl-β-cyclodextrin–polyvinylpyrrolidone ternary system [16], we recently investigated the combined effect of hydroxypropyl-β-cyclodextrin and a series of

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aminoacids to test their effectiveness as ternary components on the enhancement of the drug aqueous solubility [17]. L-arginine, with the largest increase in the intrinsic solubility of naproxen and a peculiar synergistic effect when used in combination with hydroxypropyl-β-cyclodextrin, was the most efficacious of the tested aminoacids [17]. In the present work it seemed of interest to investigate in depth the role of L-arginine in improving the dissolution properties of naproxen. To this aim equimolar naproxen–hydroxypropyl-β-cyclodextrin–L-arginine combinations prepared by physical mixing, cogrinding under controlled experimental conditions, and coevaporation were tested for solid-state interaction using Differential Scanning Calorimetry, Thermogravimetric Analysis, X-ray powder diffractometry and FTIR spectroscopy. Parallel investigations were carried out on the ternary systems obtained by blending the third component with the drug–hydroxypropyl-β-cyclodextrin binary system (as physical mixture, coevaporate, or coground product) or the drug–L-arginine binary system (as physical mixture, coevaporate, or coground product). The effects of solid-state interaction in differently prepared ternary systems and in the binary systems containing naproxen were evaluated and compared in terms of drug dissolution properties (percent dissolved, dissolution efficiency, relative dissolution rate), which were determined using a continuous flow through apparatus.

2. Materials and methods

2.1. Materials

Naproxen (NAP) ((S)-(+)-6-methoxy-α-methyl-2-naphthalenacetic acid) from Sigma Chemical Company (St Louis, MO, USA) was recrystallized twice from ethanol. Hydroxypropyl-β-cyclodextrin (HPβCD) with an average degree of substitution per anhydroglucose unit of 0.9 was kindly provided by Wacker Chemie GmbH (München 70, G). L-arginine (ARG) was obtained from Sigma Chemical Company (St Louis, MO, USA). The individual components were sieved and the 75–150 μm granulometric fractions used for the preparation of solid systems. All other reagents were of analytical grade.

2.2. Preparation of solid systems

NAP-HPβCD, NAP-ARG and NAP-HPβCD-ARG equimolar mixtures were prepared by blending the respective components, NAP (2.30 g), HPβCD (14.00 g) and ARG (1.74 g), in a Turbula apparatus (Turbula mixer TA 2, Willy A. Bachofen Maschinenfabrik, Switzerland) for 15 min.

Coground products were prepared by milling 500 mg of binary or ternary mixtures in a a high energy vibrational mill (Mixer Mill Type MM 200, Retsch, GmbH, Düsserdolf, Germany) for 60 min at 24 Hz. Grinding jars (volume 12 cm^3) and stainless steel balls (9 and 12 mm diameter) were used. Ternary systems were also prepared by simple blending of the third component (ARG or HPβCD), respectively, with the NAP-HPβCD or NAP-ARG coground binary system.

NAP-HPβCD, NAP-ARG and NAP-HPβCD-ARG equimolar coevaporated products were prepared by adding suitable volumes of aqueous solutions of HPβCD and/or ARG to ethanol-water solutions (1:1 v/v) of NAP and evaporating the resulting solutions in a rotary evaporator at 60 °C under vacuum. The solid residue was dried at room temperature for 24 h. Ternary systems were also prepared by blending an equimolar amount of the third component, ARG or HPβCD, respectively, with the NAP-HPβCD or NAP-ARG coevaporated system.

Sieved products (75–150 μm) were used for all subsequent studies.

2.3. Differential scanning calorimetry (DSC)

DSC analyses were carried out using a Q 1000 DSC (Q™ series) (TA Instruments) equipped with a Tzero cell and a refrigerating cooling system and utilizing the advanced Tzero™ technology. Weighed samples (1.5–3 mg, Mettler M3 microbalance) were scanned in covered Al pans under dry nitrogen purge (50 ml min^{-1}) at 10 K min^{-1} between 30 and 300 °C. The Universal Analysis 2000 software was used to calculate extrapolated onset temperature, peak temperature and enthalpy value for each thermal event.

2.4. Thermogravimetric analysis (TGA)

Mass losses were recorded with a Mettler TA 4000 apparatus equipped with a TG 50 cell at the heating rate of 10 K min^{-1} on 7–11 mg samples in covered alumina crucibles in the 30–300 °C temperature range under dry nitrogen purge (50 ml min^{-1}).

2.5. X-ray powder diffraction (XRPD)

X-ray powder diffraction patterns were taken at ambient temperature and were obtained with a Philips PW 1130 diffractometer (Cu Kα radiation) over the 10–50 2Θ range at a scan rate of 1° min^{-1}.

2.6. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were obtained as Nujol mulls using a Perkin-Elmer Mod. 1600 apparatus (resolution 4 cm^{-1}).

2.7. Dissolution rate studies

Dissolution studies were carried out using a continuous flow through cell system, to maintain laminar flow and physiological sink conditions throughout the test. The equipment used was a Sotax CE1 Flow Through Cell (USP Apparatus 4), equipped with a 3252 Flow Cell unit

specially designed for powders (Sotax AG, Switzerland). The dissolution medium (pH ≈ 6 unbuffered water deareated by ultrasonication) was pumped to the cell via the Sotax CY1 piston pump at a flow rate of 8 ml min^{-1}. The temperature of the flow cell was kept constant at 37 ± 0.5 °C. A bed of about 600 mg glass beads ($\phi = 1$ mm) was laid in the bottom of the cell and 60 mg of NAP or NAP equivalent were put into the dissolution chamber. Millipore AP25 filters (Millipore, USA) were used to filter the eluate which was continuously collected (open method). Samples were withdrawn every 5 min up to 60 min and spectrometrically analyzed for drug concentration using a UV/VIS Spectrophotometer Shimadzu UV-1601 at 274 nm by a second derivative ultraviolet absorption method [10]. The cumulative amount of drug dissolved as a function of time was calculated [18]. Each test was repeated at least three times (coefficient of variation CV < 2.5%).

One-way analysis of variance (ANOVA) followed by the Student–Newman–Keuls multiple comparison test (Graph Pad Prism, Version 3) was used to compare the effect of using NAP-HPβCd or NAP-ARG or NAP-ARG-HPβCd systems and of their preparation method in terms of drug dissolution efficiency [19], percent of drug dissolved at a given time and relative dissolution rate (ratio between the drug amount dissolved from a given system at a given time and that dissolved at the same time from NAP alone).

3. Results and discussion

3.1. Solid-state studies

3.1.1. X-ray diffractometry

X-ray powder diffraction patterns of pure components and various binary and ternary solid systems are collected in Fig. 1. Spectra of both NAP and ARG showed several intense diffraction peaks, which indicate their crystalline state, whereas a flat pattern, typical of amorphous substances, was shown by HPβCD. As for NAP-ARG binary systems, the pattern of the physical mixture was the simple superposition of those of the pure components, whereas a clear loss of crystallinity was observed in the coground system; on the contrary the coevaporate pattern indicated the formation of a new crystalline phase attributable to the salt formed between ARG and NAP. In contrast, a strong reduction of drug crystallinity was observed in its physical mixture with HPβCD, and almost completely amorphous patterns were shown by both coground and coevaporated systems. As for the ternary systems, only a few of the most intense diffraction effects of

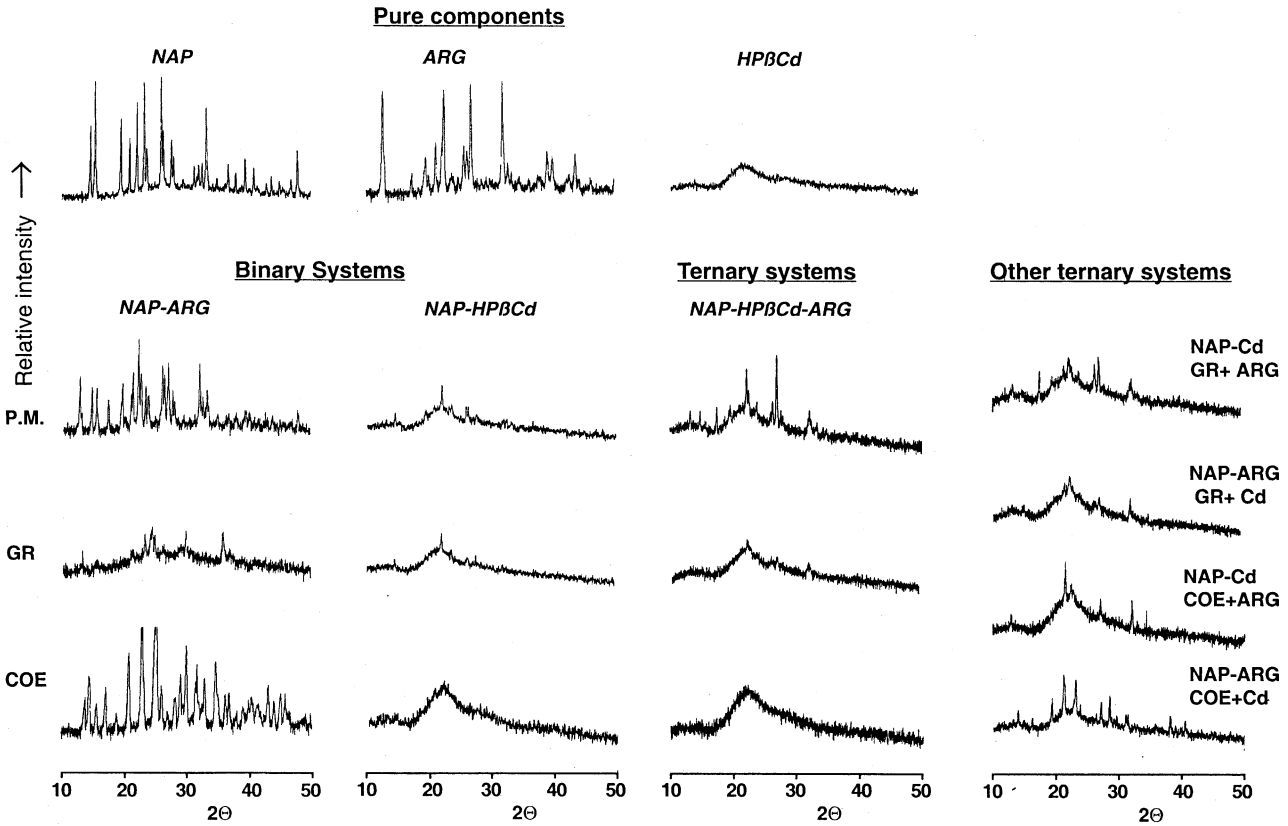

Fig. 1. X-ray powder diffraction patterns of individual components and binary (NAP-ARG, NAP-HPβCD) and ternary (NAP-ARG-HPβCD) physical mixtures (P.M.), coground (GR) and coevaporated (COE) systems; other ternary systems: physical mixtures of ARG with NAP-HPβCD coground (GR) and coevaporated (COE) systems; physical mixtures of HPβCD with NAP-ARG coground (GR) or coevaporated (COE) systems.

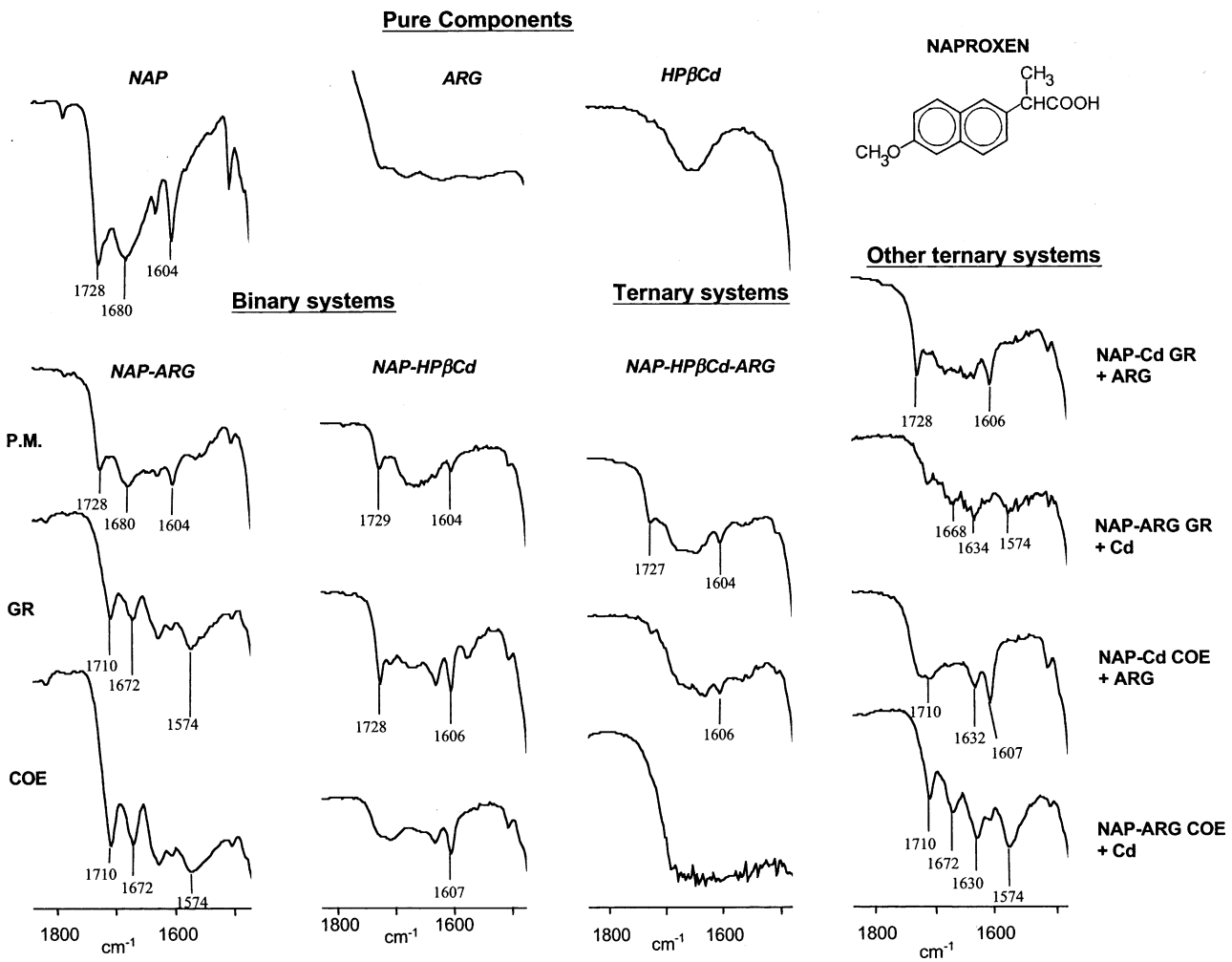

Fig. 2. FTIR spectra of individual components and binary (NAP-ARG, NAP-HPβCD) and ternary (NAP-ARG-HPβCD) physical mixtures (P.M.), coground (GR) and coevaporated (COE) systems; other ternary systems: physical mixtures of ARG with NAP-HPβCD coground (GR) and coevaporated (COE) systems; physical mixtures of HPβCD with NAP-ARG coground (GR) or coevaporated (COE) systems.

NAP, emerging from the amorphous profile of HPβCD, can be seen in the physical mixture and they totally disappeared after cogrinding or coevaporation of the mixture. Finally, the spectra of ternary systems obtained by adding ARG to the NAP-CD coground or coevaporated systems, or by adding HPβCD to the NAP-ARG coground and coevaporated mixtures were actually the weighted superposition of the spectra of their respective components.

3.1.2. IR Spectroscopy

FTIR spectra recorded in the 1500–1800 cm^{-1} spectral region for the pure components and their differently prepared binary and ternary combinations are shown in Fig. 2. The typical quartet of bands of NAP carbonyl stretching between 1727 cm^{-1} and 1604 cm^{-1}, was still discernable and did not show any shift in any binary and ternary physical mixtures, even though it was partially masked by the HPβCD band. On the contrary, both binary NAP-ARG coground and coevaporated products exhibited marked spectral changes with respect to the physical mixture, as a probable consequence of salt formation. As for NAP-HPβCD systems, while the coground product spectrum was similar to that of the physical mixture, a change was observed in that of the coevaporated one, with disappearance of the band at 1728 cm^{-1}. Similar spectral changes have been observed by other authors for NAP-βCd colyophilized systems and explained by the dissociation of the intermolecular hydrogen bonds of NAP through inclusion complexation [20]. A single broad, irregular band was observed for coground and even so for coevaporated ternary systems, as a consequence of strong interactions between the components. On the contrary, the spectra of systems obtained by blending the third component to the binary coground or coevaporated products were substantially the superposition of those of their respective components.

3.1.3. Thermal analysis

The DSC and TGA curves of pure components and their various combinations are presented in Figs. 3 and 4,

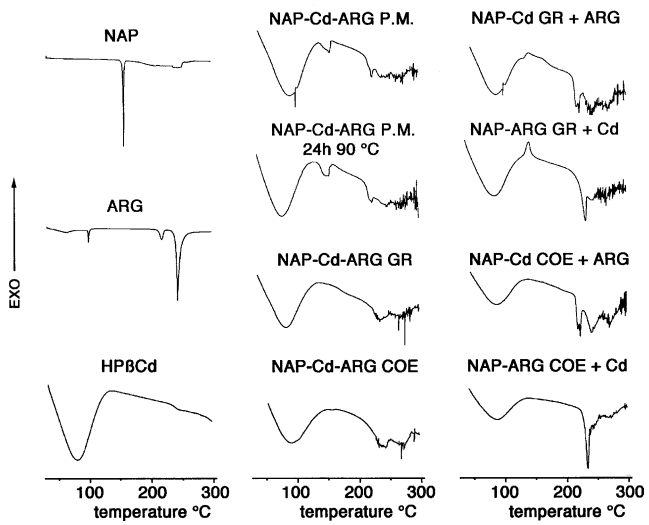

Fig. 3. DSC curves of individual components and NAP-ARG-HPβCD physical mixtures (P.M.), coground (GR) and coevaporated (COE) systems; other ternary systems: physical mixtures of ARG with NAP-HPβCD coground (GR) and coevaporated (COE) systems; physical mixtures of HPβCD with NAP-ARG coground (GR) or coevaporated (COE) systems.

respectively. DSC analysis indicated the crystalline anhydrous state of NAP ($T_{onset} = 155.7 \pm 0.1$ °C, $T_{peak} = 156.4 \pm 0.2$ °C, $\Delta H_{fus} = 142.3 \pm 1.4$ J g^{-1} (4 runs)) and TGA its incipient decomposition at 169 °C. The DSC profile of ARG showed three distinct endotherms peaking at 98, 220 and 244 °C, which were attributed, on the basis of TGA results, respectively to water loss from a small portion of ARG.2H_2O present in the sample, melting with decomposition of anhydrous ARG, and total decomposition of the melt. The DSC curve of HPβCD was typical of an amorphous substance with loosely bound water (3.55% by weight by TGA).

The thermal behaviour of NAP-ARG and NAP-HPβCD binary systems, previously characterized by DSC analysis [17], was further investigated by TGA. Mass losses between 35 and 100 °C due to the aminoacid water escape and with $T_{onset} = 208$ °C due to thermal decomposition were detected for NAP-ARG physical mixture. By contrast, as a consequence of the sample treatment, the dehydration effect was absent in both coground and coevaporated products. A water loss of 3.48% by weight was detected for the NAP-HPβCD physical mixture, due to Cd dehydration. A similar

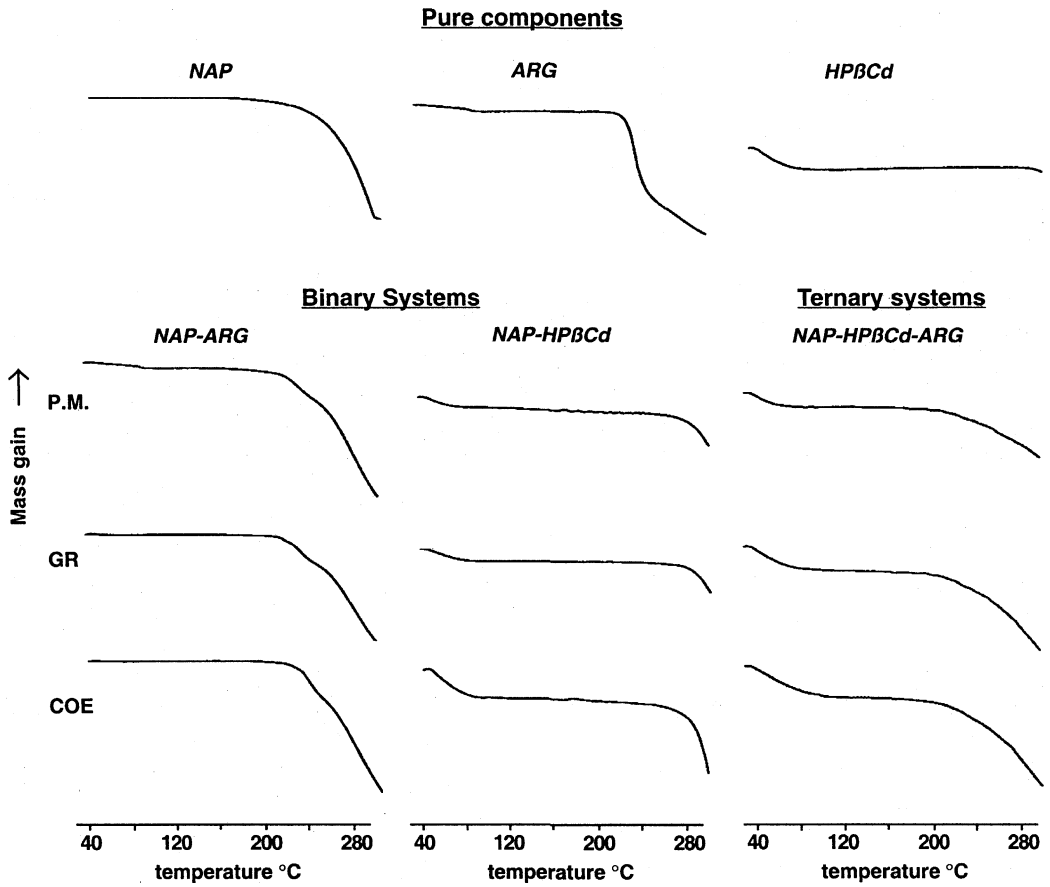

Fig. 4. TGA curves of individual components and binary (NAP-ARG, NAP-HPβCD) and ternary (NAP-ARG-HPβCD) physical mixtures (P.M.), coground (GR) and coevaporated (COE) systems.

effect was recorded also in the TGA curves of coground and coevaporated systems. Instead, no mass losses were observed in any case in correspondence with the drug melting temperature. This confirms that the marked broadening and reduction in intensity or the disappearance of NAP fusion endotherm found, respectively, in DSC analysis of NAP-HPβCD coground and coevaporated products [17] was actually exclusively due to its partial or complete amorphization and/or complexation within the HPβCD matrix [15].

The ternary physical mixture shows DSC thermal effects characteristic of its components, namely a broad endotherm between 70–130 °C due to water loss of HPβCD with a small but sharp dehydration endotherm of the small portion of ARG·$2H_2O$ present (overall mass loss 3.61% by weight by TGA), broad melting of NAP between 130 and 150 °C, and thermal decomposition at $T_{onset} \approx 180$ °C. Heating for 24 h at 90 °C irreversibly dehydrated ARG·$2H_2O$, but no apparent modification of the overall thermal behaviour can be seen. Conversely, no thermal effects attributable to free NAP can be observed in the ternary coground product, where mechanical treatment led to a possible molecular inclusion and/or to the total amorphization of NAP with no alteration of the TGA profile with respect to the ternary physical mixture. DSC curves of the combinations obtained by mixing the third component to the binary coground system are substantially the superposition of those of the individual components, showing water loss of HPβCD and dehydration of ARG·$2H_2O$ followed by decomposition in one case and water loss of HPβCD and crystallization followed by melting with decomposition of the NAP-ARG salt in the other case. Thus, in the DSC scan conditions, the presence of the third component did not induce new interactions (e.g. salification of NAP in NAP-HPβCD coground system due to the presence of free ARG) or interfere in solid-state interactions (e.g. lack of crystallization of NAP-ARG salt in NAP-ARG coground system in the presence of HPβCD).

Thermal behaviour of the ternary coevaporate was very similar to that of the corresponding coground product, implying amorphization and/or inclusion of NAP in the HPβCD cavity. Interestingly, by comparing the ternary system obtained by adding ARG to the NAP-HPβCD coevaporate with that obtained by adding ARG to the NAP-HPβCD coground product, it is evident that totally anhydrous ARG was obtained by coevaporation and not by cogrinding. On the contrary, when cogrinding was carried out on the ternary system, the product did not contain ARG·$2H_2O$ and showed the same thermal behaviour of the ternary coevaporate. Moreover, the ternary system obtained by adding HPβCD to the NAP-ARG coevaporate did not show the exothermal effect due to crystallization of the salt between NAP and ARG present in the corresponding system obtained by adding HPβCD to the NAP-ARG coground product.

In conclusion, solid state studies did not show any significant difference between the ternary systems obtained by cogrinding or coevaporation, indicating that both techniques, when applied to the ternary mixture of the individual components, were effective for preparing homogeneous amorphous systems, as a result of strong interactions between NAP, ARG, and HPβCD. In contrast, the presence of either free drug or free ARG was detected when the third component, HPβCD or ARG, was physically mixed, respectively, with the NAP-ARG or the NAP-HPβCD binary coground or coevaporated systems.

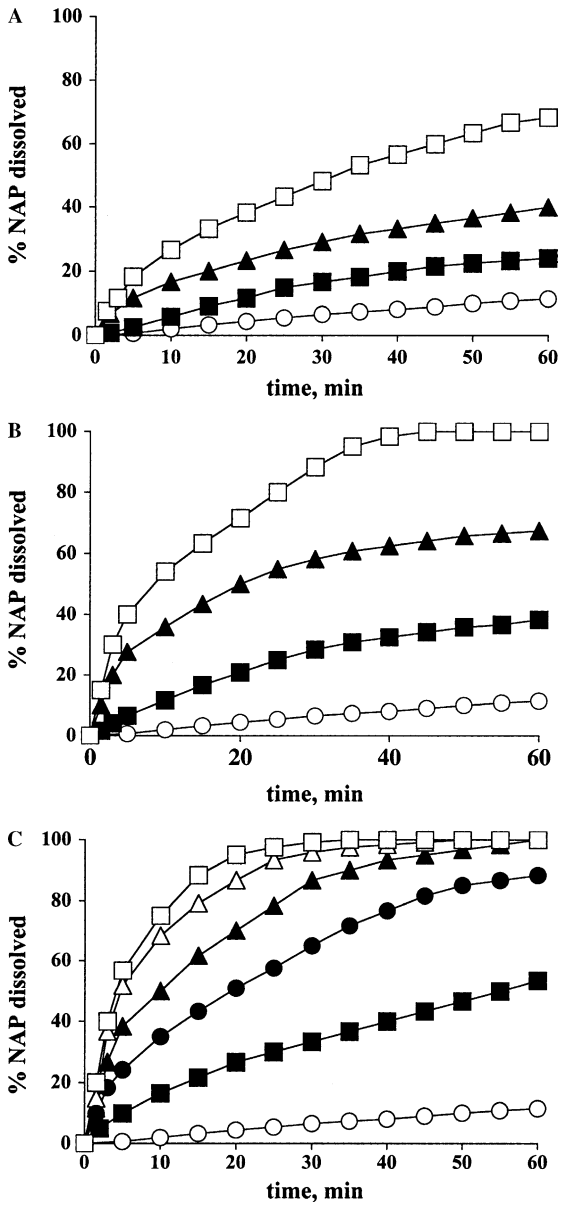

Fig. 5. Dissolution curves of binary and ternary physical mixtures (A), coground mixtures (B) or coevaporate (C) of NAP with ARG and HPβCD. Key. (○) NAP alone; (■) NAP- HPβCD; (▲) NAP-ARG; (□) NAP-ARG-HPβCD; (●) NAP-HPβCD mixed with ARG; (△) NAP-ARG mixed with HPβCD.

Table 1
Percent drug dissolved (PD), dissolution efficiency (DE)[a], and relative dissolution rate (rdr)[b] of naproxen (NAP) from binary and ternary physical mixtures (P.M.), coground (GR) and coevaporated (COE) products with HPβCD and arginine (ARG) (standard deviations in parentheses)

Sample		PD 10′	PD 30′	DE 60′	rdr 5′
NAP		2.02 (±0.05)	6.55 (±0.09)	6.19 (±0.08)	1
NAP-HPβCD >	P.M.	5.80 (±0.09)	16.7 (±0.4)	14.9 (±0.4)	3.8
NAP-ARG	P.M.	16.7 (±0.3)	29.2 (±0.7)	27.4 (±0.6)	17.5
NAP-HPβCD-ARG.	P.M.	26.7 (±0.5)	48.3 (±1.0)	45.5 (±0.9)	27.5
NAP-HPβCD	GR	11.6 (±0.3)	28.0 (±0.7)	25.2 (±0.7)	10.0
NAP-ARG	GR	35.5 (±0.9)	58.0 (±1.3)	53.3 (±1.1)	39.5
NAP-HPβCD-ARG	GR	54.2 (±1.2)	88.3 (±1.8)	80.4 (±1.7)	61.0
NAP-HPβCD	COE	21.7 (±0.5)	36.7 (±1.0)	32.2 (±0.7)	15.0
NAP-ARG	COE	50.0 (±1.4)	84.7 (±2.0)	77.4 (±0.8)	57.5
ARG + NAP-HPβCD	COE	35.0 (±0.8)	65.0 (±1.4)	61.4 (±1.1)	35.5
HPβCD + NAP-ARG	COE	68.3 (±1.3)	97.5 (±2.3)	87.4 (±1.6)	77.5
NAP-HPβCD-ARG	COE	75.0 (±1.5)	99.2 (±2.0)	91.1 (±1.8)	85.0

[a] Calculated from the area under the dissolution curve at 60 min and expressed as % of the area of the rectangle described by 100% dissolution in the same time.
[b] Ratio between amount of drug dissolved from a system and that dissolved from drug alone at 5 min.

3.2. Dissolution rate studies

The results of the dissolution experiments performed according to the continuous flow through method are presented in Fig. 5, and summarized in Table 1 in terms of percent dissolved (PD) after 10 and 30 min, dissolution efficiency (DE) at 60 min and relative dissolution rate (rdr) at 5 min. Statistical analysis of all dissolution parameters showed that for all the examined systems the rank order in terms of both dissolution efficiency, percent dissolved and relative dissolution rate was always: coevaporated > coground > blend systems ($P < 0.001$). Coground products, despite their fully amorphous state, showed significantly worse dissolution parameters ($P < 0.001$) than the coevaporated ones. Possible particle aggregation, which is generally associated with grinding of solids [21], is probably responsible for this phenomenon. NAP-ARG binary systems showed better performance than the corresponding NAP-HPβCD systems, indicating that salt formation was more effective than simple binary complexation in improving the drug dissolution properties.

All ternary systems, indeed, showed significantly better drug dissolution parameters than the corresponding binary systems ($P < 0.001$). This effect was likely due to the peculiar synergistic improvement of drug solubility obtained when ARG is used in combination with HPβCD, as demonstrated in previous studies on the effect of the simultaneous presence of HPβCD and a series of aminoacids on NAP aqueous solubility [17]. This synergistic effect cannot be simply attributed to a favourable pH variation of the dissolution medium due to the presence of the basic aminoacid. In fact, solubility studies previously performed in pH 7 phosphate buffer solution showed that the solubility of the NAP-ARG-HPβCD system was about 2.6 times higher than that of NAP-HPβCD and about 2 times higher than that of NAP-ARG systems [17]. As a further confirmation of the synergistic effect, the ternary system solubility at pH 7 was higher than the theoretical one calculated by adding the solubility in the presence of Cd or aminoacid, separately, at the same pH.

Ternary coevaporate was the best system and it was significantly more effective ($P < 0.001$), in terms of percent dissolved at 10 min, dissolution efficiency at 60 min and relative dissolution rate at 5 min, not only than the ternary product obtained by physical mixing of ARG with the NAP-HPβCD coevaporate, but also than that obtained by physical mixing of HPβCD with the NAP-ARG coevaporate.

Therefore it is reasonable to hypothesize a specific role of ARG in the formation of a ternary complex in the solid state, with improved cyclodextrin solubilizing power toward NAP, as a result of the potential ability of the basic aminoacid to simultaneously interact with both the cyclodextrin (via hydrogen bonding) and the drug (via electrostatic interactions and salt formation) [22,23]. On the other hand, the marked increase in solubility of the highly hydrophobic drug when the multicomponent complex is dissolved in water can be explained by a mutual interaction among the components. In fact the drug, in the presence of the basic aminoacid which acts as a counter-ion, may give rise to an amphyphilic structure characterized by a strongly hydrophobic portion and a hydrophilic polar head. In the presence of HPβCD, the hydrophobic portion of this amphyphilic structure (i.e. the drug molecule) can interact with the hydrophobic CD cavity, whereas, at the same time, the hydrophilic portion can act as a surfactant toward the cyclodextrin complex, lowering the aqueous surface tension, and thus favouring its wettability and dissolution [24]. Such hypothesis of a specific role of ARG in the molecular assembly of a ternary complex in solution is further supported by the 3.6 times increase (from 100 to 360 M^{-1}) in the apparent stability constant of the NAP-HPβCD complex in the presence of ARG as found by

phase-solubility studies performed in pH 7 buffered solutions [25].

4. Conclusion

Complexation with HPβCD and simultaneous salt formation with ARG was successfully applied for improving the solubility and dissolution properties of NAP.

All ternary systems always showed better dissolution performances than the corresponding drug-aminoacid or drug-CD systems. The positive effect of ternary complexation was particularly evident in the first phase of the dissolution process, with percent of drug dissolved at 10 min about 1.5 and 3.5 times higher than that dissolved, respectively, from the corresponding NAP-ARG or NAP-HPβCD systems.

Despite solid state studies did not evidence significant differences between ternary coground mixture and coevaporate, this last exhibited significantly ($P < 0.001$) better drug dissolution properties. Therefore, ternary coevaporate appears as the most valuable product for developing fast release NAP formulations which could be particularly useful in the treatment of all clinical conditions requiring quick pain relief.

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