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ORIGINAL ARTICLE

Comparative study of oxaprozin complexation with natural and chemically-modified cyclodextrins in solution and in the solid state

Francesca Maestrelli · Matteo Cecchi · Marzia Cirri · Gaetano Capasso · Natascia Mennini · Paola Mura

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Abstract The complexing, solubilizing and amorphizing abilities toward oxaprozin (a poorly water-soluble anti-inflammatory agent) of some β-cyclodextrin derivatives (hydroxypropyl-βCd, heptakis-2,6-di-O-methyl-βCd (DIMEB) amorphous randomly substituted methyl-βCd (RAMEB) and semi-crystalline methyl-βCd (CRYSMEB)) were investigated and compared with those of natural (α-, β-, γ-) cyclodextrins. The role of both the cavity size, the amorphous or crystalline state and the presence and type of substituent on the ability of cyclodextrins in establishing effective interactions with the drug has been evaluated. Equimolar drug-cyclodextrin solid systems were prepared by blending, kneading, co-grinding, sealed-heating, coevaporation, and colyophilization. Drug-carrier interactions were studied in both the liquid and solid state by phase-solubility analysis, differential scanning calorimetry, X-ray powder diffractometry, FT-IR spectroscopy and scanning electron microscopy. βCd showed the best performance among the natural Cds, indicating that its cavity was the most suitable for accommodating the drug molecule. The presence of substituents on the rim of the βCd cavity significantly improved its complexing and solubilizing effectiveness towards the drug, and methylated derivatives were better than the hydroxy-propylated ones The amorphous nature of the partner was also important: among the examined methyl-derivatives, RAMEB proved to be the most effective in performing solid state interactions and in improving drug wettability and dissolution properties.

F. Maestrelli · M. Cecchi · M. Cirri · G. Capasso · N. Mennini · P. Mura (✉)
Department of Pharmaceutical Sciences, University of Florence, via U. Schiff 6, Sesto Fiorentino, Florence 50019, Italy
e-mail: paola.mura@unifi.it

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Introduction

Oxaprozin (3-(4,5-diphenyl-1,3-oxazol-2-yl) propionic acid) is a Non-Steroidal Anti-Inflammatory drug, mainly used for the treatment of pain, pyrexia and various inflammatory disorders. Oxaprozin has become one of the leading NSAIDS on the US market, however its low aqueous solubility and poor stability may reduce its therapeutic effectiveness and enhance the appearance of some adverse events such as gastro-duodenal mucosal injury [1]. Cyclodextrins have been successfully used as carriers to improve solubility, dissolution rate, chemical stability and bioavailability of a number of poorly soluble drugs [2–5]. In particular, cyclodextrin complexation of anti-inflammatory drugs allowed obtainment of additional advantages such as masking of taste, lowering of dose, reduction of side effects (particularly gastric irritation) [6–9].

Therefore, in the present work we investigated the possibility of improving the unfavourable chemical–physical properties of oxaprozin by cyclodextrin complexation. With this aim we carefully examined the performance of a series of cyclodextrins, both natural (α-, β-, γ-Cd) and derivative (hydroxypropyl-βCd, heptakis-2,6-di-O-methyl-βCd, amorphous randomly substituted methyl-βCD and semi-crystalline methyl-βCD), in order to evaluate the role of both the cyclodextrin cavity size, their amorphous or crystalline state and the presence and type of substituent on their ability to establish effective interactions with the drug. Moreover, several methods have been proposed for

complex preparation, and the best process must be chosen for each guest to be complexed with each cyclodextrin [10–13]. Therefore, equimolar solid systems of the drug with the selected cyclodextrins were prepared by different techniques (physical mixing, kneading, co-grinding, co-evaporation, sealed-heating and colyophilization), in order to investigate the influence of the preparation method on the physical–chemical properties of the end product and to arrive to a rational and careful selection of the most successful system for improving the oxaprozin dissolution properties. Drug-cyclodextrin interactions in solution and in the solid state were investigated by phase-solubility analysis, Differential Scanning Calorimetry (DSC), Powder X-ray Diffractometry, Fourier Transform Infrared Spectroscopy and Scanning Electron Microscopy. The dissolution rate of the different solid-systems was determined according to the dispersed amount method.

Materials and methods

Materials

Oxaprozin (OXA) was a gift from S.I.M.S. (Incisa Valdarno, Firenze, Italy) and was used as received. Crystalline α-cyclodextrin (αCd), γ-cyclodextrin (γCd) and 2,6 di-O-methyl β-cyclodextrin (DIMEB) were purchased from Sigma Chemical Co. (Saint Louis USA). Amorphous methyl-β-cyclodextrin (RAMEB), with an average molar substitution degree per anhydroglucose unit of 1.8 was a gift from Wacker-Chemie GmbH (München, Germany). Crystalline β-cyclodextrin (βCd), partially crystalline methyl-β-cyclodextrin (CRYSMEB), and amorphous hydroxypropyl-β-cyclodextrin (HPβCd) with an average substitution degree per anhydroglucose unit of 0.65 were kindly donated by Roquette.

Phase-solubility studies

An excess amount of drug (60 mg) was added to 10 mL of pH 5.5 phosphate buffer solutions containing increasing concentrations of Cd in sealed glass containers preserved from the light and electromagnetically stirred (500 rpm) at constant temperature (25 °C) until equilibrium (3 d). Aliquots were withdrawn, filtered (0.45 μm pore size) and spectrometrically assayed for drug concentration at 285.2 nm (UV/VIS 1600 Shimadzu spectrophotometer, Tokyo, Japan). The presence of Cd did not interfere with the spectrophotometric assay of OXA. In fact it has been verified that the UV absorbance (at the selected λ_{max}) of a 4.0 μg/mL OXA solution did not change in the presence or not of different concentrations of any of the examined Cds. Each test was performed in triplicate (coefficient of variation (C.V.) <3%). The apparent 1:1 binding constants of the different OXA-Cd complexes were calculated from the slope of the straight lines of the phase-solubility diagrams [14].

Preparation of solid systems

Six different methods were used for the preparation of equimolar drug-cyclodextrin solid systems.

Physical mixing

Physical mixtures (PM) were obtained by 15 min tumble mixing equimolar amounts of the respective simple components (75–150 μm sieve granulometric fraction).

Kneading

Kneaded products (KN) were prepared by adding a small volume of ethanol to a known amount of the physical mixture. The resultant mixture was kneaded thoroughly with a pestle to obtain homogeneous slurry and continued until the solvent was completely removed. The sample was kept in an oven at 40 °C for 24 h to remove traces of solvent.

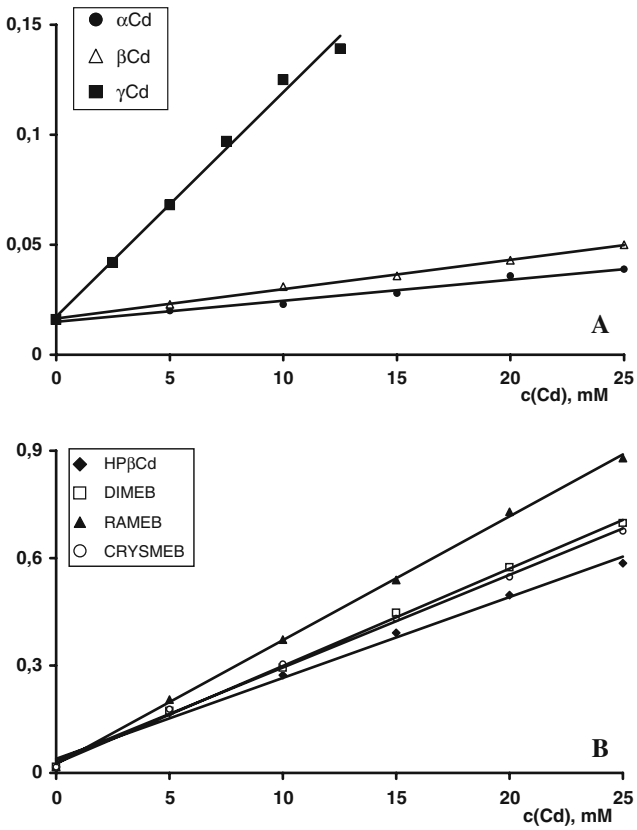

Fig. 1 Phase-solubility studies of oxaprozin (OXA) and natural (**a**) or derivative (**b**) cyclodextrins in pH 5.5 buffered water at 25 °C

Table 1 Apparent stability constants of 1:1 complexes of oxaprozin with the different examined Cds, and related solubilizing efficiency values

Cd type	$K_{1:1}$ M^{-1}	Solubilizing efficiency*
αCd	60	2.25
βCd	350	8.70
γCd	80	2.69
HPβCd	1,445	31.0
DIMEB	1,750	35.9
RAMEB	2,240	45.6
CRYSMEB	1,660	34.2

*ratio between solubility of drug in the presence of 20 mM Cd (or 12.5 mM βCd) and drug alone in pH 5.5 phosphate buffer at 25 °C

Co-grinding

Co-ground products (GR) were prepared by ball-milling physical mixtures in a high-energy vibrational micro-mill (Mixer Mill MM 200 Retsch, GmbH, Düsseldorf, Germany) at a frequency of 24 Hz for 30 min.

Coevaporation

Coevaporated products (COE) were prepared by coevaporation of equimolar drug-Cd ethanol–water (5:5 v/v) solutions in a rotary evaporator (Heidolph Laborota 4000)

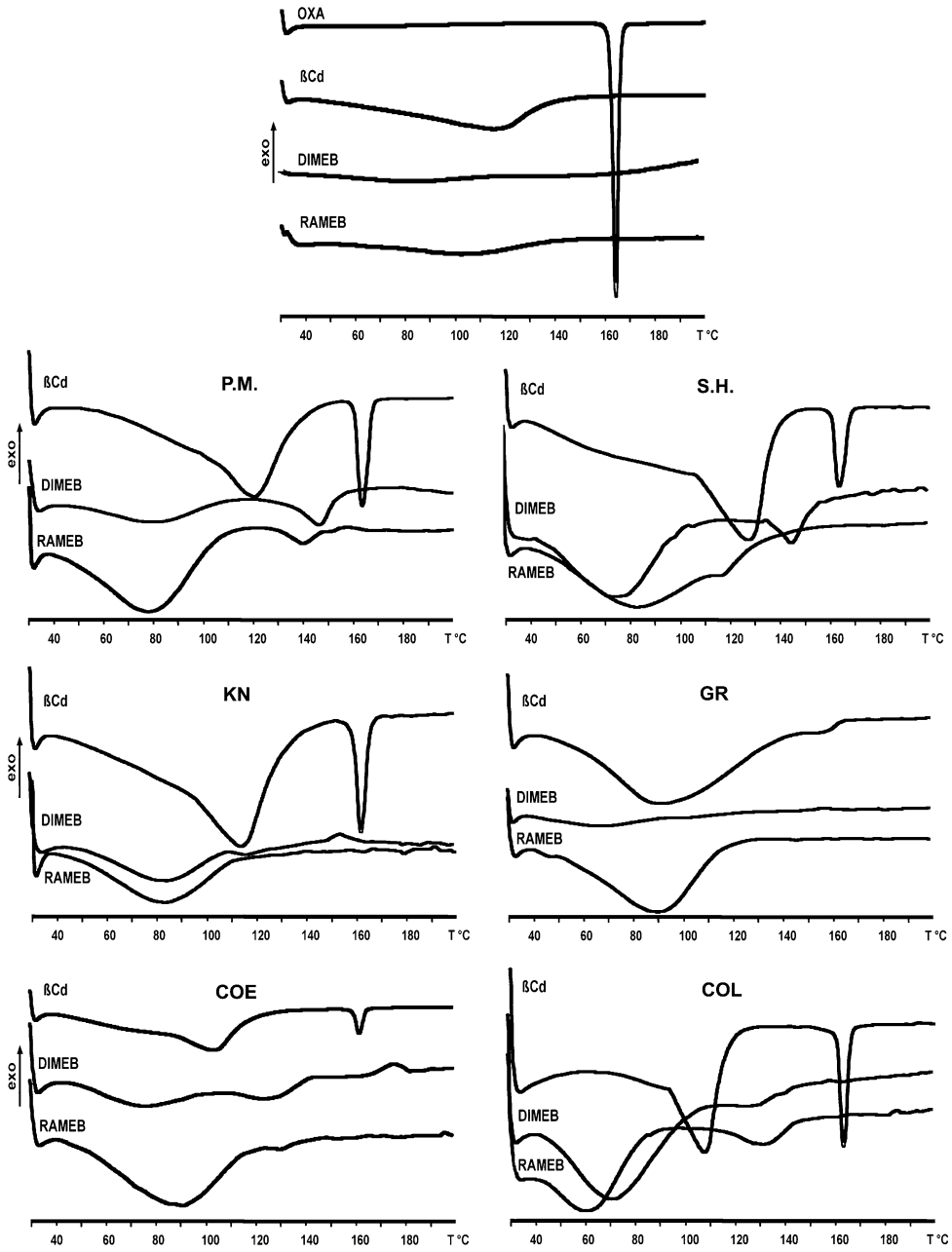

Fig. 2 DSC curves of pure oxaprozin (OXA), βCd, DIMEB and RAMEB and of equimolar drug-Cd physical mixtures (P.M.), sealed-heated (S.H.), kneaded (KN), co-ground (GR), coevaporated (COE) and colyophilized (COL) products

Table 2 Thermal parametres of oxaprozin (OXA), alone and in its equimolar physical mixtures (P.M.), sealed-heated (S.H.), kneaded (KN), coground (GR), coevaporated (COE) and colyophilized (COL) products with the examined Cds

Sample	T_{onset} (°C)	T_{peak} (°C)	ΔH_{fus} (J/g)
OXA	161.3	161.7	121.6
OXA-βCd P.M.	160.2	161.8	124.8
OXA-DIMEB P.M.	133.4	146.1	88.6
OXA-RAMEB P.M.	135.2	140.2	21.6
OXA-βCd S.H.	157.5	160.0	94.2
OXA-DIMEB S.H.	136.4	145.5	55.6
OXA-RAMEB S.H.	112.0	118.0	10.3
OXA-βCd KN	159.6	161.2	120.1
OXA-DIMEB KN	–	–	–
OXA-RAMEB KN	–	–	–
OXA-βCd GR.	140.4	156.4	10.8
OXA-DIMEB GR	–	–	–
OXA-RAMEB GR	–	–	–
OXA-βCd COE	159.7	161.8	40.8
OXA-DIMEB COE	110.6	124.9	12.5
OXA-RAMEB COE	–	–	–
OXA-βCd COL	160.8	162.0	116.1
OXA-DIMEB COL	117.6	133.5	10.3
OXA-RAMEB COL	119.7	130.5	11.6

at 85 °C. The resulting products were then dried in a vacuum desiccator for 48 h to remove traces of solvents.

Sealed-heating

Sealed-heated products (SH) were prepared by heating in a sealed glass containers at 90 °C for 3 h known amounts of drug-Cd physical mixtures, added of 10 μL bidistilled water. Then the samples were removed and kept in a desiccator overnight to remove traces of water.

Colyophilization

Colyophilized products (COL) were prepared by freeze-drying (Lyovac GT2, Leybold-Heraeus) at −50 °C and $1.3 \cdot 10^{-2}$ mmHg 100 mL of equimolar drug-Cd water–ethanol solutions at suitable concentrations on pre-chilled shelves of 20 cm diameter and 18 mm height. Samples were kept in a desiccator, due to their high hygroscopicity.

Each solid product was sieved and the 75–150 μm granulometric sieve fraction used for the following tests.

Differential scanning calorimetry (DSC)

DSC analyses of the individual components or the different OXA-Cd combinations were performed using a Mettler TA4000 Star[e] system equipped with a DSC 25 cell. Weighed samples (5–10 mg, Mettler M3 Microbalance) were scanned in Al pans pierced with a perforated lid at 10 °C/min from 30 to 200 °C temperature range under static air. The instrument was calibrated using Indium as a standard (99.98% purity; melting point 156.61 °C; fusion enthalpy 28.71 J g^{-1}).

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra (Perkin–Elmer Mod. 1600) of the individual components and of the different OXA-Cd solid systems were obtained as Nujol dispersion in the 4,000–600 cm^{-1} region.

X-ray Powder Diffractometry (XRPD)

The X-ray powder diffraction patterns of the individual components or the different OXA-Cd combinations were taken at ambient temperature with a Bruker D8-advance apparatus (θ/θ geometry) using a Cu Kα radiation and a graphite monochromator, at a 40 mV voltage and 55 mA current, over a 5–40° 2θ range at a scan rate of 0.05 s^{-1}.

Scanning Electron Microscopy (SEM)

Surface morphology of pure components and the different drug-Cd equimolar systems obtained by different techniques was examined using a Philips XL-30 Scanning Electron Microscope equipped with an image analysis system. Prior to examination, samples were sputter coated with gold–palladium under argon atmosphere (to render them electrically conductive) using a Fine Coat Ion Sputter (JFC-1100 JEOL).

Dissolution studies

Dissolution rates of OXA, both alone and from the different drug-Cd systems, were determined in pH 5.5 phosphate buffer at 37 ± 0.5 °C according to the dispersed amount method, by adding 30 mg of drug or drug-equivalent to 300 mL of pH 5.5 phosphate buffer, in a 400 mL beaker. A glass three-blade propeller (19 mm diameter) was immersed in the beaker 25 mm from the bottom and rotated (f = 100 min^{-1}). Suitable aliquots were withdrawn with a filter-syringe (pore size 0.45 μm) at the specified times and the drug concentration was spectrometrically assayed (UV/VIS 1601 Shimadzu). The same volume of fresh medium was added to the beaker and the correction for the cumulative dilution was calculated. Each test was repeated three times (coefficient of variation <5%). Dissolution was characterised through the percent of drug dissolved after 10 min, as index of the rate of dissolution, and the Dissolution Efficiency at 60 min, as index of the totality of the process. Dissolution efficiency (D.E.) was

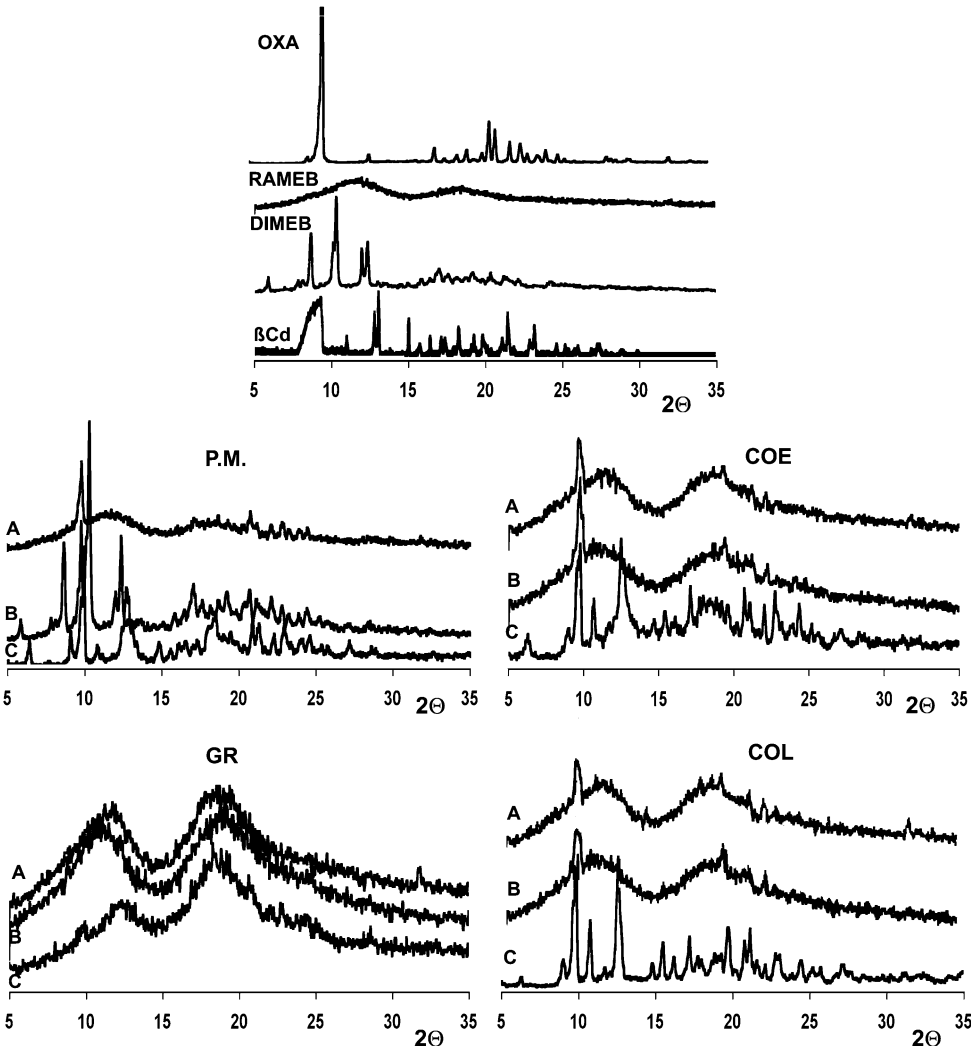

Fig. 3 X-ray diffraction patterns of pure oxaprozin (OXA), ßCd, DIMEB and RAMEB and of equimolar drug-Cd physical mixtures (P.M.), coevaporated (COE), co-ground (GR), and colyophilized (COL) products

calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [15].

Results and discussion

Phase-solubility studies

The solubility of OXA increased linearly with increasing cyclodextrin concentration, giving in all cases A_L-type phase-solubility diagrams, indicative of the formation of soluble complexes of probable 1:1 mol:mol stoichiometry [14] (Fig. 1a, b). The apparent 1:1 stability constants, calculated from the straight lines of the diagrams, and the relative solubilizing efficiency values are collected in Table 1. Among the natural Cds, βCd was clearly the most effective partner, indicating that its cavity has the most suitable dimensions to accommodate the OXA molecule. However, the stability constants of the complexes with all the examined βCd-derivatives were distinctly higher than that of the parent βCd. Analogous results have previously been obtained with other NSAIDs derivative of propionic acid such as naproxen [16], ketoprofen [17] and flurbiprofen [18]. The better performance of these derivatives has been attributed to the presence of hydroxypropyl and even more of methyl substituents that expanded the hydrophobic region of the macromolecule, by capping the edge of the cavity, and increased substrate binding via a hydrophobic effect. The stability constant values of the complexes with OXA were in the order RAMEB > DIMEB $\approx$ CRYSMEB $\geq$ HPβCd >>βCd >>γCd $\approx$ αCd. The same rank order was observed also as for their solubilizing efficiency towards OXA (Table 1).

Based on these results, βCd, among the natural Cds, and RAMEB and DIMEB, among its derivatives, were selected for further studies as the best potential carriers for OXA. Solid drug-Cd binary systems with selected Cds were then prepared at 1:1 molar ratio (as indicated by phase-solubility

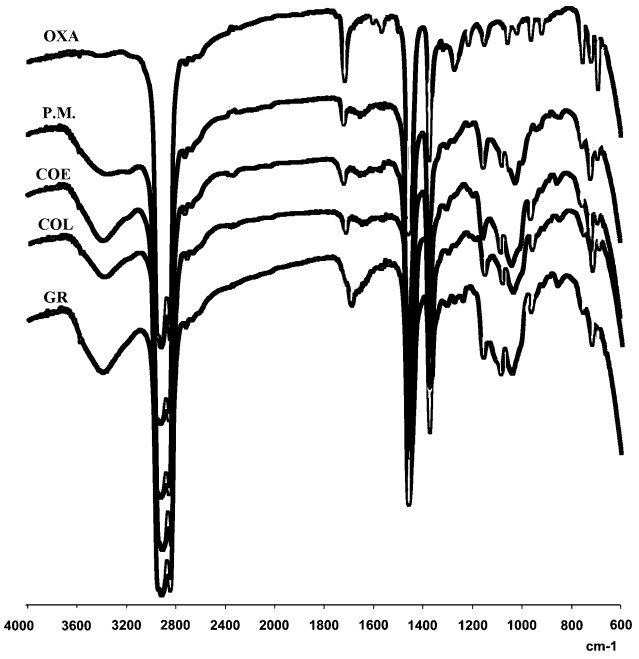

Fig. 4 FT-IR spectra of pure oxaprozin (OXA), βCd, and RAMEB and of equimolar drug-Cd physical mixtures (P.M.), coevaporated (COE), colyophilized (COL), and co-ground (GR) products

studies) by using different techniques (physical mixing, kneading, coevaporation, co-grinding, sealed-heating, and freeze-drying), in order to select the most suitable one for the preparation of solid inclusion complexes [10–12]. The solid-state properties of the obtained products were then examined by DSC, FT-IR, XRPD and SEM analyses.

Solid-state studies

The DSC curves of pure components and of the various drug-Cd equimolar systems obtained with the different techniques are shown in Fig. 2, whereas the relevant thermal parameters are collected in Table 2. The DSC curve of OXA was typical of a crystalline anhydrous substance, with a sharp fusion endotherm peaked at 161.3 °C. Liberation of crystal water from βCd (14.5% as mass fraction) was observed as an intense endothermic effect peaked at about 119 °C. Broader endotherms were instead associated with water losses from βCd-derivatives, respectively of 5.7% and 16% as mass fraction for DIMEB and RAMEB, respectively. The thermal profile of the drug maintained its shape in its P. M. with βCd, while a marked broadening with a concomitant shift to lower temperatures was evident in its blend with DIMEB and even more with RAMEB. The characteristic drug melting peak appeared practically unchanged in all the examined binary systems with ßCd, except in COE products, where it appeared to be strongly reduced in intensity, and in GR products, where it almost totally disappeared. This modification of the DSC melting peak can taken as a proof of interactions between the components and/or of consequent progressive drug amorphization. As previously observed with other NSAIDs [17, 19, 20], hydrophilic βCd-derivatives were more effective than natural βCd in establishing solid-state interactions with the drug. In fact, OXA fusion endotherm was markedly broadened and reduced in intensity in all the systems with DIMEB and RAMEB, up to its complete disappearance in KN and GR products. Moreover, it was confirmed that also the crystalline or amorphous state of the carrier plays a role in inducing drug amorphization, mediated by a highly dispersed physical state of the drug within the carrier matrix [21]. In particular the amorphous derivative, i.e. RAMEB, demonstrated the highest amorphizing power toward the drug with all the preparation techniques used, as can be observed by comparing the corresponding ΔH_{fus} values of OXA in the different systems (Table 2).

On the other hand, as for the influence of the preparation method, co-grinding technique appeared as the most powerful in inducing drug-Cd interactions as well as drug amorphization with all the examined Cds. This was a rather unexpected result, since colyophilization technique often showed to be more efficacious in this regard than simple co-grinding [22–24]. However, the suitability of Cd co-grinding technique to obtain and stabilize drugs in the amorphous form has been well demonstrated [25–27].

X-ray diffraction patterns (Fig. 3) substantially confirmed the results of DSC analysis. In fact, only the co-grinding technique allowed total or almost total sample amorphization of products with derivatives and natural βCd, respectively. On the contrary, typical drug crystallinity peaks were present in both COE and COL systems with βCd and some slight residual drug crystallinity, as revealed by the characteristic peak of OXA at 9° 2 Θ, was still detectable in the corresponding systems with RAMEB and DIMEB.

FTIR analysis further evidenced the greatest effectiveness of the co-grinding technique in producing effective drug-carrier solid-state interactions. In fact, no important variations with respect to the corresponding physical mixture were observed in the patterns of the products obtained with the different techniques, except the co-ground systems, where a broadening of the characteristic acid carbonyl stretching band of OXA accompanied by a significant shift from 1,718 to 1,700 cm^{-1} was observed, as is shown in Fig. 4 for the series of OXA-RAMEB binary systems. This effect can be attributed to the breakdown of the intermolecular hydrogen bonds and formation of a monomeric dispersion of drug as a consequence of the interaction with the Cd [17].

Selected micrographs obtained from SEM analysis are shown in Fig. 5. OXA particles appeared under scanning

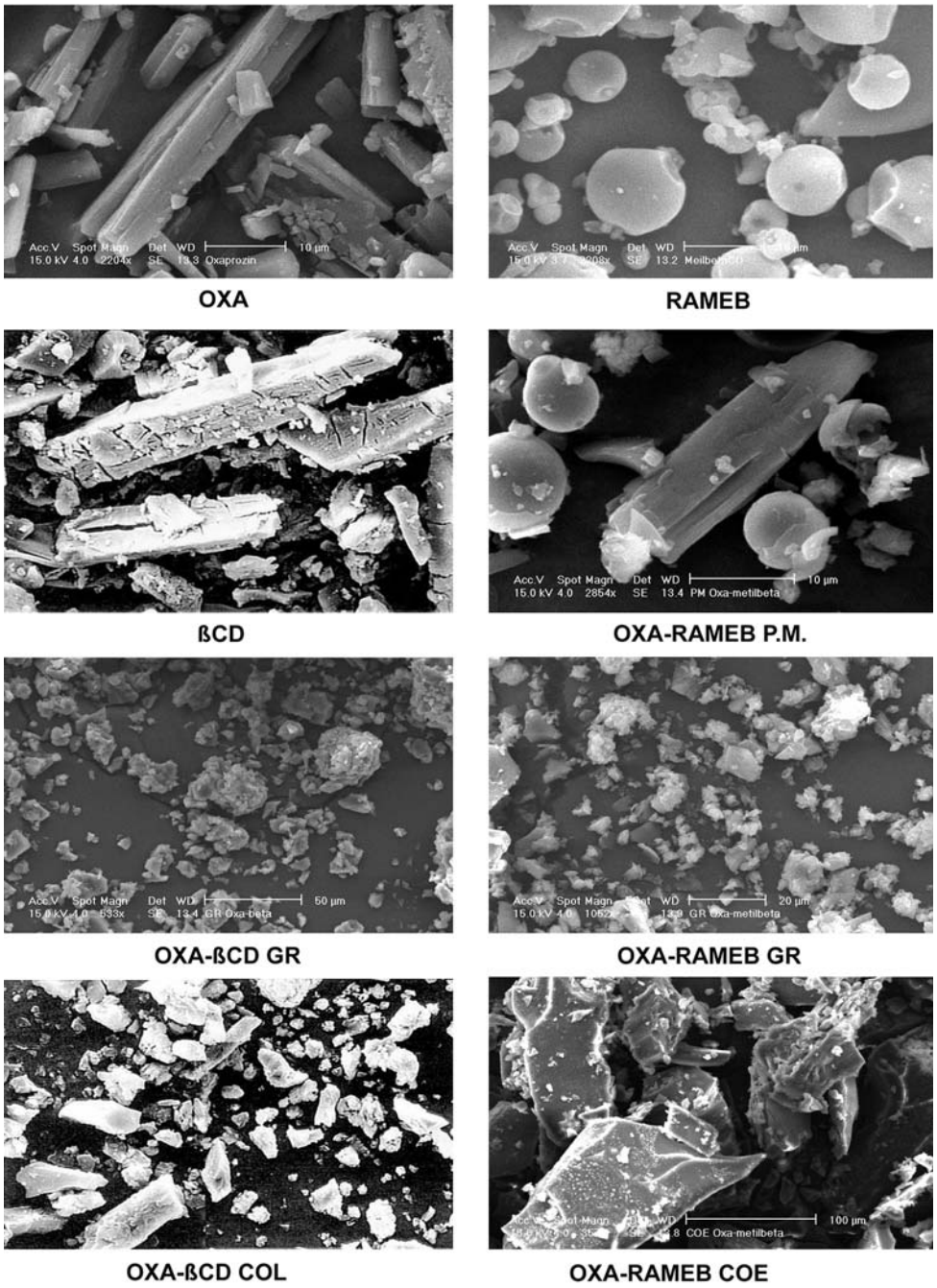

Fig. 5 SEM micrographs of of equimolar drug-Cd physical mixtures (P.M.), co-ground (GR), coevaporated (COE) and colyophilized (COL) products

electron microscopy as polyhedric crystals with smooth surfaces, partially agglomerated in bundles. βCd and DIMEB consisted of large crystalline particles of rather irregular shape and size, whereas RAMEB appeared as amorphous spherical particles. In keeping with the DSC and X-ray analyses findings, the characteristic drug crystals, mixed with Cd particles, were clearly evident in all physical mixtures. Distinctive drug crystals, dispersed or adhered to the surface of the carrier, were well detectable in all the products with βCd, except the GR one. In fact, in this case, the original morphology of both drug and βCd disappeared, and only amorphous pieces of irregular size were present, making it no longer possible to differentiate the two components. A similar aspect was found for GR products with DIMEB and RAMEB, while some residual drug crystals were still noticed in the corresponding COE and COL systems.

Dissolution studies

The most significant dissolution parameters obtained from the different OXA-Cd systems examined are collected in Table 3, while the drug dissolution profiles from selected binary products are shown in Figs. 6 and 7. As for the influence of the preparation technique (Fig. 6), dissolution tests revealed that co-grinding was clearly the most effective one in improving the drug dissolution behaviour, followed by colyophilization, and then by coevaporation

Table 3 Percent dissoved at 10 min (P.D.10) and Dissolution Efficiency (D.E.60) at 60 min of oxaprozin (OXA), alone and from its equimolar physical mixtures (P.M.), sealed-heated (S.H.), kneaded (KN), coground (GR), coevaporated (COE) and colyophilized (COL) products with the examined Cds

Sample	P.D.10	D.E.60
OXA	6.5	6.9
OXA-βCd P.M.	9.8	10.3
OXA-DIMEB P.M.	11.3	12.6
OXA-RAMEB P.M.	12.4	13.0
OXA-βCd S.H.	10.2	10.8
OXA-DIMEB S.H.	11.6	12.9
OXA-RAMEB S.H.	12.7	13.3
OXA-βCd KN	12.4	13.1
OXA-DIMEB KN	13.5	14.0
OXA-RAMEB KN	14.1	14.7
OXA-βCd GR.	16.4	18.4
OXA-DIMEB GR	28.6	29.7
OXA-RAMEB GR	46.6	46.9
OXA-βCd COE	13.0	13.7
OXA-DIMEB COE	16.3	17.0
OXA-RAMEB COE	17.3	18.1
OXA-βCd COL	14.1	14.8
OXA-DIMEB COL	17.4	18.7
OXA-RAMEB COL	18.1	19.7

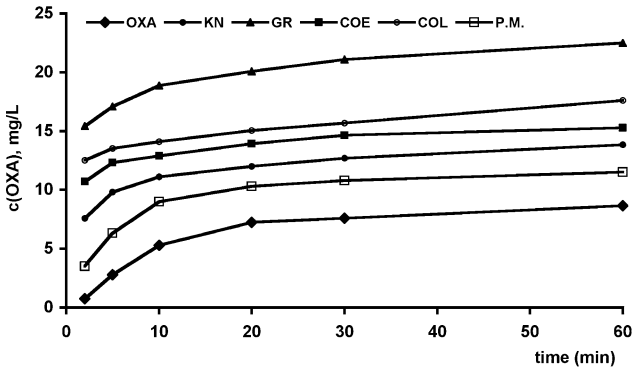

Fig. 6 Dissolution curves of oxaprozin (OXA) alone and from equimolar physical mixtures (P.M.), kneaded (KN), co-ground (GR), coevaporated (COE) and colyophilized (COL) products with βCd

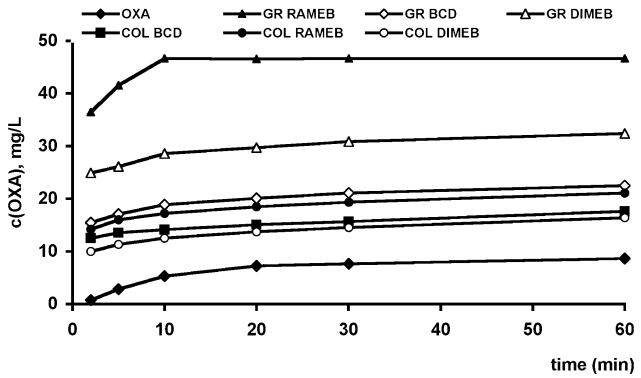

Fig. 7 Dissolution curves of oxaprozin (OXA) alone and from equimolar co-ground (GR) and colyophilized (COL) products with βCd, DIMEB and RAMEB

while sealed-heating (curve not shown) was the worst one, giving results not significantly different from the simple physical mixture. These results were in full agreement with those of solid-state studies. In fact, the best dissolution profiles shown by co-ground products can be attributed to the higher amorphization degree and stronger drug-Cd solid-state interactions obtained with the co-grinding technique, as revealed from DSC, X-ray diffractometry and FT-IR analyses.

On the other hand, a comparison of the performance of the three different carriers (Fig. 7) evidenced the same trend observed in previous phase solubility studies. In particular, RAMEB confirmed to be the best partner for OXA, exhibiting the highest complexing and solubilizing power, and giving rise to the product with the best dissolution profile. Moreover, over-saturation levels were not achieved with respect to the drug solubility values obtained in phase-solubility studies, and therefore high stability of the obtained solutions is expected.

Conclusions

Cyclodextrin complexation was successful in improving OXA dissolution properties. βCd showed the best performance among the natural Cds, indicating that its cavity was the most suitable for accommodating the drug molecule. The presence of substituents on the rim of the βCd cavity significantly improved its complexing and solubilizing effectiveness towards the drug, and methylated derivatives were better than the hydroxy-propylated ones. Moreover, also the amorphous nature of the partner was important. In fact, among the examined methyl-derivatives, RAMEB proved to be the most effective in performing solid-state interactions and in improving drug wettability and dissolution properties. Therefore the choice in pharmaceutical formulations of the amorphous RAMEB rather than the

crystalline DIMEB can be recommended, also taking into account economic considerations. However, the anhydrous and non-hygroscopic nature of crystalline DIMEB could be particularly advantageous in case of moisture-sensitive formulations [21].

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