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Characterization of physicochemical properties of naproxen systems with amorphous β-cyclodextrin-epichlorohydrin polymers

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Abstract

Ground mixtures of naproxen with amorphous β-cyclodextrin-epichlorohydrin soluble (βCd-EPS) or insoluble cross-linked (βCd-EPI) polymers were investigated for both solid phase characterization (Differential Scanning Calorimetry, powder X-ray Diffractometry) and dissolution properties (dispersed amount method). The effect of different grinding conditions and of drug-to-carrier ratio was also evaluated. Co-grinding induced a decrease in drug crystallinity to an extent which depended on the grinding time, and was most pronounced for the cross-linked insoluble polymer, particularly in combinations at the lowest drug content. Both cyclodextrin polymers were more effective in improving the naproxen dissolution properties, not only than the parent βCd but also than hydroxyalkyl-derivatives, and their performance was almost comparable to that of methyl-derivatives, previously found as the best carriers for naproxen. Dissolution efficiencies of naproxen from physical mixtures with βCd-EPS, thanks to the high water solubility of this Cd-derivative, were up to three times higher than those from the corresponding products with βCd-EPI. However this difference in their performance became much less evident in co-ground products and tended to progressively diminish with increasing the polymer content in the mixture, according to the better amorphizing power shown by βCd-EPI during the co-grinding process. The 10/90 (w/w) drug–carrier co-ground products exhibited the best dissolution properties, giving dissolution efficiencies about 30 times higher than that of naproxen alone.

Keywords: Naproxen; β-Cyclodextrin-epichlorohydrin polymers; Amorphization; Differential scanning calorimetry; Powder X-ray diffractometry; Dissolution rate

1. Introduction

Naproxen ((*S*)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid, NAP) is a non-steroidal antiinflammatory drug whose very low water solubility (about 27 mg l^{-1} at 25 °C) is enhanced by complexation with both native and particularly

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with chemically modified cyclodextrins (Cds) [1,2]. Randomly methylated amorphous β-Cd and crystalline heptakis-(2,6-di-*O*-methyl)-β-Cd were the most efficient carriers in this respect [3,4]. However, methylated Cd-derivatives show high surface-activity and, as a consequence, are more systematically toxic than parent Cds [5,6]. An interesting alternative approach to Cd modification is the use of Cd polymers, which can simultaneously offer the advantages of the amorphous state and Cd-type complexation without toxic effects [7,8]. Cd polymers can be prepared by reacting Cds with bifunctional agents such as epichloroydrin, obtaining both soluble or insoluble products. The polymeric epichlorohydrin Cds with an average molecular mass up to about 20 000 are highly water-soluble and showed to be useful for increasing solubility, dissolution rate and bioavailability of poorly water-soluble drugs, often more effectively than the parent Cds [9,10]. Cross-linked epichloroydrin-Cd polymers with higher molecular mass are instead insoluble, but show strong swelling and hydrophilic properties and are capable of forming inclusion complexes with a variety of guest molecules [11].

On the other hand, it is known that conversion of poorly water-soluble crystalline drugs into the amorphous state is another possible approach for improving the biopharmaceutical properties of solid dosage forms [12]. Drug amorphization can be obtained producing a molecular dispersion by grinding the drug with suitable pharmaceutical adjuvants (cellulose, chitin or chitosan, Cds, polyvinylpirrolidone, etc.) The extent of amorphization generally depends on both the type and the relative amount of the additive and the grinding time [13–15]. Some of us have previously reported that NAP amorphization can easily be brought about in blends with amorphous methyl- and hydroxalkyl-βCd-derivatives [16–18].

Therefore, it seemed of interest to extend our studies and investigate the performance of two amorphous βCd-epichloroydrin polymers, both soluble or insoluble, in physical and co-ground mixtures with NAP at various drug-to-carrier (w/w) ratios. Differential scanning calorimetry (DSC) supported by powder X-ray diffractometry (XRD) was used to characterize the solid combinations of NAP with both carriers and to shed light on possibile interactions in the solid state, whereas the dissolution properties of all drug–carrier solid products were evaluated according to the dispersed amount method. The results, in terms of both amorphization and solubilization of NAP, are discussed and compared to previous results obtained with alkyl-βCd derivatives in order to gain insight into the role of both carrier properties and drug-to-carrier ratio on the physicochemical properties of the end product.

2. Experimental

2.1. Materials

Naproxen (NAP) (Sigma Chemical Co, St Louis, MO) and amorphous highly soluble (average Mw 17 000) and insoluble cross-linked βCd-epichloroydrin polymers (kindly donated by Nihon Shokuhin Kako Company Ltd, Tokyo, Japan, and hereafter shortened to amorphous β-cyclodextrin-epichlorohydrin (βCd-EPS) and βCd-EPI, respectively) were used. All other materials and solvents were of analytical reagent grade.

2.2. Preparation of drug–carrier mixtures

Physical mixtures of NAP (75–250 μm sieve granulometric fraction) with βCd-EPS and βCd-EPI at 50/50, 20/80, 15/85, and 10/90 (w/w) drug-to-carrier ratios were prepared by simple homogenization of the powders by turbula mixing for 10 min. The homogeneity of the blends was checked by DSC measurements (see below) of three samples for each preparation. The physical mixtures were manually ground using an agate mortar with a pestle and the effect of mechanical treatment on drug crystallinity was evaluated by DSC and XRD after grinding times of 0, 10, 20, 30 and 40 min. Grinding was also performed on crystals of pure NAP for control purposes.

2.3. Thermal analysis

Temperature and enthalpy measurements were performed with a Mettler TA4000 apparatus

equipped with a DSC 25 cell (10 K min^{-1}, 30–200 °C) on 5–10 mg samples (Mettler M3 microbalance) in Al pans with perforated lids under static air. The relative degree of crystallinity of NAP in ground samples at a prescribed grinding time (t, min) as percent of the NAP mass fraction in the starting sample, $NAP_{RDC\%(t)}$, was estimated by Eq. (1):

$$NAP_{RDC\%(t)} = \frac{\Delta H_{gr(t)}}{\Delta H_{st}} \times 100 \quad (1)$$

where $\Delta H_{gr(t)}$ and ΔH_{st} are the heats of fusion of NAP measured in the ground samples after t min of mechanical treatment and in the starting pure NAP sample, respectively [19]. Heat of fusion measurements were carried out in duplicate and the relative standard deviation of crystallinity data was $\pm 6\%$.

2.4. X-ray diffraction

X-ray powder diffraction patterns were taken with a computer-controlled Philips PW 1800 apparatus over the 10–50° 2θ range at a scan rate of 1° min^{-1}, using CuKα radiation monochromatized with a graphite crystal.

2.5. Dissolution studies

The dissolution studies of NAP, alone and from various binary systems, were performed in water at 37 ± 0.5 °C according to the dispersed amount method (non-sink conditions). The sample powder (75–150 μm granulometric sieve fraction collected before each experiment) of drug (60 mg) or an equivalent amount of physical or ground mixture with polymeric Cd was added to 75 ml of water in a 150 ml beaker and stirred at 100 rpm with a glass three-blade propeller centrally immersed in the beaker 20 mm from the bottom. At appropriate time intervals, suitable aliquots were withdrawn with a filter-syringe (pore size 0.45 μm) and the NAP concentration was determined with a second derivative spectroscopic method as described previously [1,2]. A correction was calculated for the cumulative dilution caused by replacement of the sample with an equal volume of original medium. Each test was repeated four times (coefficient of variation CV < 1.5%). Dissolution efficiency (DE) was 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 [20].

2.6. Solubility studies

Solubility measurements of NAP were carried out in duplicate by adding 100 mg of drug to 10 ml of water or aqueous solution of βCd-EPS in the 1–7% (w/v) concentration range, in sealed glass containers which were electromagnetically stirred at a constant temperature (25 ± 0.5 °C) until equilibrium was achieved (72 h). An aliquot was withdrawn and spectrophotometrically assayed for drug content as described previously [1,2]. The apparent binding constant of the NAP-βCd-EPS complex was calculated from the slope and intercept of the straight line of the phase–solubility diagram, in terms of Eq. (2) [21]:

$$K_{(1:1)} = \frac{\text{slope}}{\text{intercept}(1 - \text{slope})} \quad (2)$$

2.7. Circular dichroism spectra

Measurements were carried out using a Jasco J-500D recording spectropolarimeter (Tokyo, Japan) at 25 ± 0.5 °C (sensitivity 100 mdeg; step res. 1 nm; response 1 s; scan speed, 100 nm min^{-1}; range, 400–220 nm) on unbuffered (pH ≈ 5) aqueous solutions of NAP (c(NAP) = 0.4 mmol l^{-1}) in the absence and in the presence of βCd or βCd-EPS at a concentration of 4 mmol l^{-1}.

3. Results and discussion

3.1. Interaction in the solid state

The thermal behavior of the single components and of their physical and ground mixtures at different drug-to-carrier (w/w) ratios is shown in Figs. 1 and 2. A sharp endothermal effect ($T_{onset} = 153.4 \pm 0.3$ °C, $T_{peak} = 156.7 \pm 0.4$ °C,

fusion enthalpy 140 ± 6 J g^{-1} (4 runs)) was associated with melting of anhydrous crystals of pure NAP, whilst broad endotherms, associated with water loss, over the 70–130 °C temperature range were shown by both amorphous βCd polymers. The temperature of drug melting peak remained almost unchanged in the various physical mixtures, whereas a progressive decrease of drug fusion enthalpy, directly correlated to the decrease of NAP crystallinity was observed with increasing carrier content in the mixture. The drug amorphizing effect became more evident after the mechanical treatment of the blends, due to a more intimate physical contact between the components brought about by the mechanical treatment. The

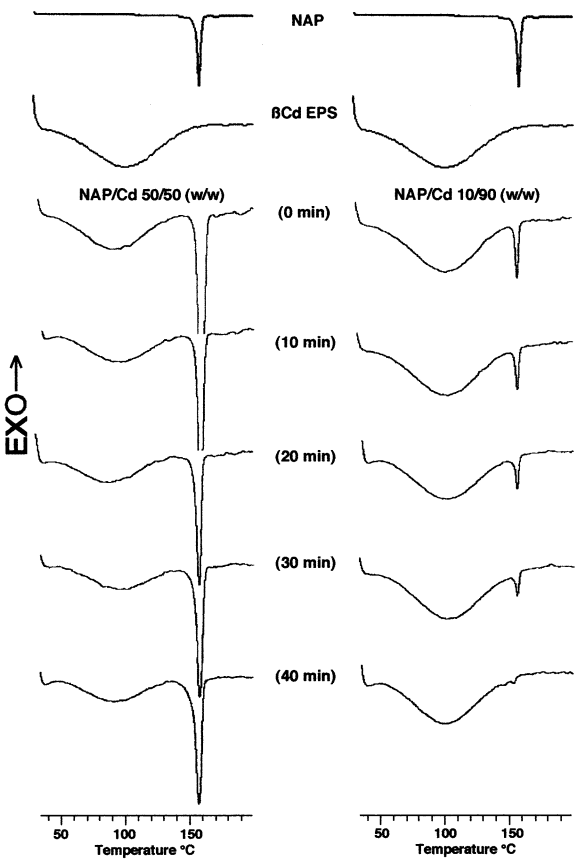

Fig. 1. Differential scanning calorimetry (DSC) curves of single components and physical mixtures (PM) and ground systems (GR) of naproxen (NAP) with highly water-soluble βCd-epichlorohydrin polymer (βCd-EPS) at different drug-to-carrier (w/w) ratios (grinding time (min) on the curves).

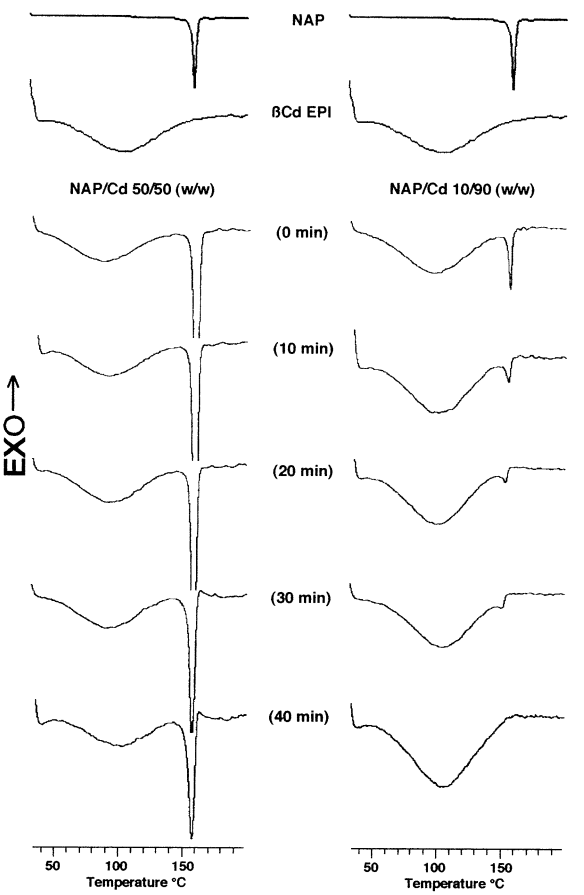

Fig. 2. Differential scanning calorimetry (DSC) curves of single components and physical mixtures (PM) and ground systems (GR) of naproxen (NAP) with insoluble cross-linked βCd-epichlorohydrin polymer (βCd-EPI) at different drug-to-carrier (w/w) ratios (grinding time (min) on the curves).

effect of grinding on drug amorphization increased with the progress of grinding time and was more marked for combinations at higher content of carrier. Quantitative data for NAP crystallinity, extracted from DSC curves in Figs. 1 and 2 and resumed in Table 1, showed that βCd-EPI was more effective than βCd-EPS as concerns the amorphizing properties, particularly in the combinations at lower content of drug. Simple blending with the amorphous carriers caused a reduction of drug crystallinity up to 21 and 14% in 10/90 (w/w) physical mixtures with βCd-EPI and βCd-EPS, respectively. Moreover, for example, 30, 62, and 90% of the NAP mass fraction

Table 1
Effect of grinding on the DSC fusion endotherm of naproxen (NAP) alone or in mixtures with amorphous soluble (βCd-EPS) or insoluble (βCd-EPI) βCd polymers

Sample	NAP/carrier (w/w) ratio	Grinding time (min)	Peak temperature (°C)	NAP crystallinity (%NAP mass fraction)
NAP	100/0	0	156.7	100
		10	156.7	99
		20	156.5	99
		30	156.2	100
		40	156.0	99
NAP/βCd-EPS	50/50	0	156.6	98
		10	156.4	88
		20	156.8	80
		30	156.1	78
		40	155.8	73
	20/80	0	156.3	96
		10	155.9	78
		20	155.7	65
		30	155.7	56
		40	155.2	47
	15/85	0	156.3	92
		10	155.9	68
		20	155.5	50
		30	155.0	32
		40	154.1	16
	10/90	0	156.5	86
		10	155.2	62
		20	154.9	43
		30	154.3	25
		40	152.7	5
NAP/βCd-EPI	50/50	0	156.7	97
		10	156.5	88
		20	155.9	78
		30	155.2	70
		40	154.8	67
	20/80	0	156.8	86
		10	156.4	60
		20	155.8	45
		30	154.9	38
		40	154.6	33
	15/85	0	156.1	83
		10	155.3	52
		20	154.9	34
		30	154.3	21
		40	153.9	10
	10/90	0	155.8	79
		10	154.6	39
		20	153.0	21
		30	151.1	10
		40	–	–

was brought to a non crystalline state after 30 min of grinding in its 50/50, 20/80, and 10/90 (w/w) drug-to-carrier combinations respectively, with the water-insoluble polymeric Cd; on the contrary, the loss of NAP crystallinity in the corresponding NAP-βCd-EPS combinations under the same experimental conditions was only 22, 44 and 75%, respectively. However, with both polymers, almost total disappearance of the drug melting endotherm was obtained after 40 min grinding of 10/90 drug–carrier (w/w) mixtures.

X-ray powder diffraction patterns in the 10–50 2θ range showed that the diffraction peaks of NAP were still detectable and emerged on the diffuse background of the amorphous additive in the respective physical mixtures with each amorphous β-Cd polymeric derivative, showing a progressive NAP crystallinity decrease with increasing the carrier amount in the blend. A more evident loss of NAP crystallinity was observed in ground mixtures, probably as a consequence of loosening of crystal forces of NAP finely dispersed within the amorphous polymeric Cd. The amorphizing phenomenon became gradually more pronounced as a function of both the polymer content and the grinding time, up to obtaining complete disappearance of NAP diffraction peaks after 40 min grinding of the 10/90 (w/w) drug–carrier combination (as is shown for example in Fig. 3 for the series of NAP-βCd-EPS combinations at 50/50 and 10/90 (w/w) drug-to-carrier ratios). These results were in agreement with DSC findings and allowed exclusion of a possible effect of drug amorphization due to the thermal energy supplied during the DSC run, as, on the contrary, we previously found for NAP ground mixtures with randomly methylated β-cyclodextrin (RAMEB) [4].

The results of DSC and powder X-ray diffraction analyses revealed the production of an amorphous state of the drug, as a consequence of drug–carrier solid state interactions induced by grinding, indicative of possible formation of inclusion complexes [22,23] as well as of a mono-molecular dispersion of NAP molecules into the polymeric-βCd matrix [23,24]. However, no definite assumption can be made in this regard. In fact no specific evidence of inclusion complex formation (such as for example the appearence of an exothermic peak due to the formed complex crystallization [22,23]) was observed, and, moreover, disappearance of drug melting peak on DSC curves and amorphous X-ray patterns have been observed also in ground mixtures of drugs with methylcellulose or cellulose microcrystalline [23,24].

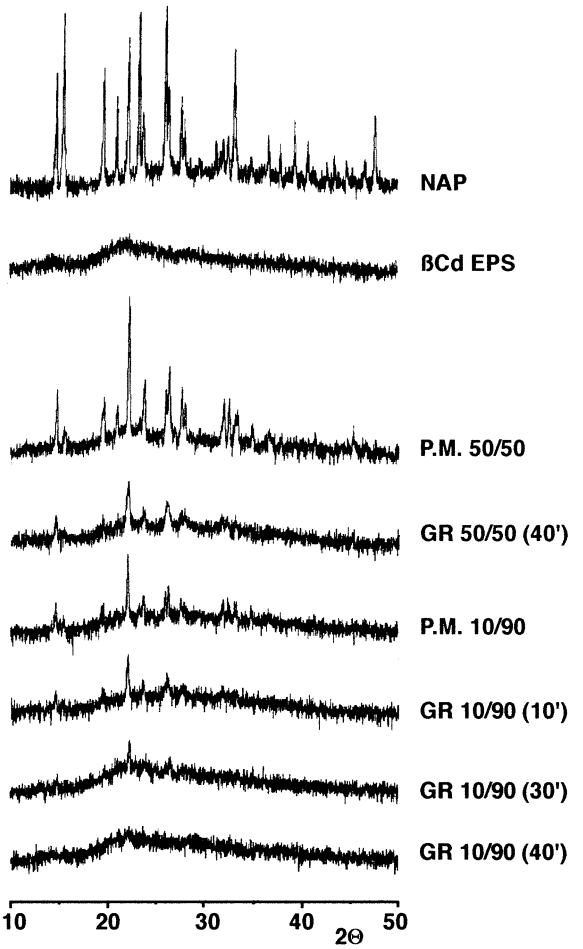

Fig. 3. Powder X-ray diffraction patterns of single components and physical mixtures (PM) and ground systems (GR) of naproxen (NAP) with highly water-soluble β-Cd-epichlorohydrin polymer (βCd-EPS) at different drug-to-carrier (w/w) ratios (grinding time (min) in brackets).

3.2. Dissolution rate experiments

Fig. 4 shows the dissolution profiles of the ground samples of NAP with both βCd-EPS and βCd-EPI at different drug-to-carrier (w/w) ratios,

compared with those of the corresponding physical mixtures and drug alone. Dissolution data, expressed as drug dissolved percentage at 10 min, DE over 60 min, time necessary to dissolve 50% drug, and relative dissolution rate are presented in Table 2. It must be underlined that the dissolution behavior of NAP ground alone was found to be not significantly different from that of the intact drug. DSC analysis (see data in Table 1) indicated that grinding of NAP alone did not provide an extensive amorphous state of the pure drug; on the contrary, it could cause aggregation and agglomeration of hydrophobic drug particles to some extent [25]. The increase in drug dissolution rate observed for physical mixtures may be mainly attributable to the hydrophilic effect of the carriers, which can reduce the interfacial tension between the poorly-soluble drug and the dissolution medium, thus leading to a higher dissolution rate. As expected, the NAP dissolution rate increased with increasing the amount of polymer in the mixture, but this effect was clearly more marked for βCd-EPS: at each drug-to-carrier (w/w) ratio, the DE of NAP from physical mixtures with such a carrier was from 2 to 3 times higher than from the physical mixtures with βCd-EPI of the same composition. The greater effectiveness of βCd-EPS can be reasonably attributable to its high water solubility. In fact, it can be assumed that in the early phase of the dissolution process, the highly soluble polymer, dissolving more rapidly than the drug, can act on the hydrodynamic layer surrounding the drug particles, resulting in an 'in situ' inclusion process which gives rise to a rapid increase of the amount of dissolved drug, as described by other authors [25,26]. Ground products were clearly more effective than the corresponding blends in enhancing NAP dissolution. The faster dissolution rates of the ground mixtures could be explained by both the greater surface areas of contact between drug and carrier and the decrease in NAP crystallinity as a consequence of specific drug–carrier interactions induced by grinding, as demonstrated by DSC and X-ray diffraction analyses. The different performance of the two polymers shown from their physical mixtures with NAP became much less evident in co-ground products and tended to progressively diminish with increasing the polymer content in the mixture. This effect could be explained on the basis of the stronger amorphizing power of βCd-EPI toward the drug during the co-grinding process (as shown by DSC and X-ray diffraction findings). From a comparison with previous results, it appeared that 10/90 (w/w) ground products of NAP

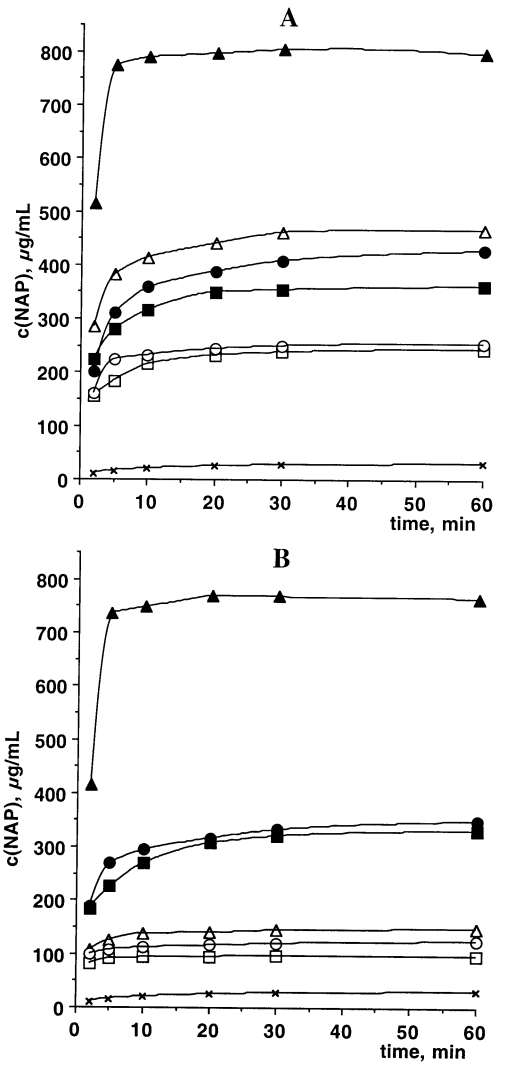

Fig. 4. Dissolution curves of naproxen (NAP) alone (×) and from its physical mixtures (open symbols) and ground products (closed symbols), with water-soluble βCd-epichlorohydrin polymer (βCd-EPS) (A), or insoluble βCd-epichlorohydrin polymer (βCd-EPI) (B). (Dispersed amount method, mean of four experiments, CV < 1.5%, error bars omitted for the sake of clarity). *Key:* drug-to-carrier (w/w) ratios: 20/80 (■, □); 15/85 (●, ○); 10/90 (▲, △).

Table 2
DE, percent drug dissolved at 10 min (DP), time to dissolve 50% drug ($t_{50\%}$) and relative dissolution rate (RDR) of naproxen (NAP) from physical mixtures (PM) and ground products (GR) with amorphous soluble (βCd-EPS) or insoluble (βCd-EPI) βCd polymers

Sample	NAP/carrier (w/w) ratio	DE[a]	DP	$t_{50\%(min)}$	RDR[b]
NAP-βCd-EPS PM	20/80	28.2	26.9	>60	12
NAP-βCd-EPS GR	20/80	41.8	39.5	>60	18
NAP-βCd-EPS PM	15/85	29.8	29.1	>60	14
NAP-βCd-EPS GR	15/85	47.6	44.7	30	19
NAP-βCd-EPS PM	10/90	54.1	51.7	10	24
NAP-βCd-EPS GR	10/90	96.4	98.6	<2	49
NAP-βCd-EPI PM	20/80	11.6	11.6	>60	6
NAP-βCd-EPI GR	20/80	37.2	33.7	>60	14
NAP-βCd-EPI PM	15/85	14.4	15.0	>60	7
NAP-βCd-EPI GR	15/85	39.2	36.7	>60	17
NAP-βCd-EPI PM	10/90	17.3	17.2	>60	8
NAP-βCd-EPI GR	10/90	91.9	93.4	<2	46

NAP alone: DE = 3.1; DP = 2.5.

[a] Calculated from area under the dissolution curve at $t = 60$ min, 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 NAP-Cd system and that dissolved from NAP alone at 5 min.

with both soluble or insoluble βCd-polymers were more effective in improving the drug dissolution properties not only than combinations with the parent βCd [1], but also than those with hydroxyethyl- and hydroxypropyl-β-cyclodextrin [2,18] and their performance was almost comparable to that of co-ground products with methyl-β-derivatives, previously found as the best carriers for NAP [3,4].

3.3. Host–guest interaction in aqueous solution

The formation of an inclusion compound between the soluble polymer βCd-EPS and NAP in aqueous solution can be assumed by the A_L-type phase–solubility diagram, i.e. by the linear relationship between dissolved drug concentration and amount of solubilizing agent (Fig. 5). It was not possible to perform analogous phase–solubility studies in the case of the insoluble βCd-EPI polymer. The 'strength' of complexation of βCd-EPS with NAP in terms of binding constant at 25 °C ($K_{1:1} = 2800\ l\,mol^{-1}$ calculated taking the βCd repeating unit as its molecular weight) was higher than for βCd ($K_{1:1} = 1700\ l\,mol^{-1}$ [1]) and of the same order as that with hydroxypropyl- and hydroxyethyl-derivatives ($K_{1:1} = 2300$ and $2600\ l\,mol^{-1}$, respectively [2]) but lesser than with the methyl-β-derivatives which remain the best complexing partners for NAP ($K_{1:1} = 6200$ and $6780\ l\,mol^{-1}$ for DIMEB and RAMEB, respectively [3,4]). The relative increase of NAP solubility at 25 °C in the presence of 50 mmol l^{-1} of

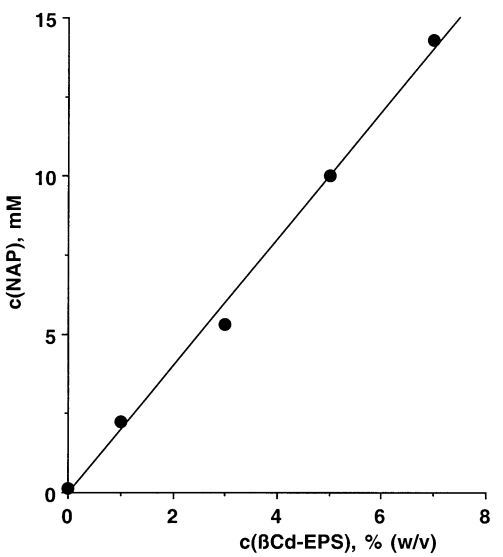

Fig. 5. Phase–solubility diagram of naproxen (NAP) with highly water-soluble βCd-epichlorohydrin polymer (βCd-EPS) in water at 25 °C.

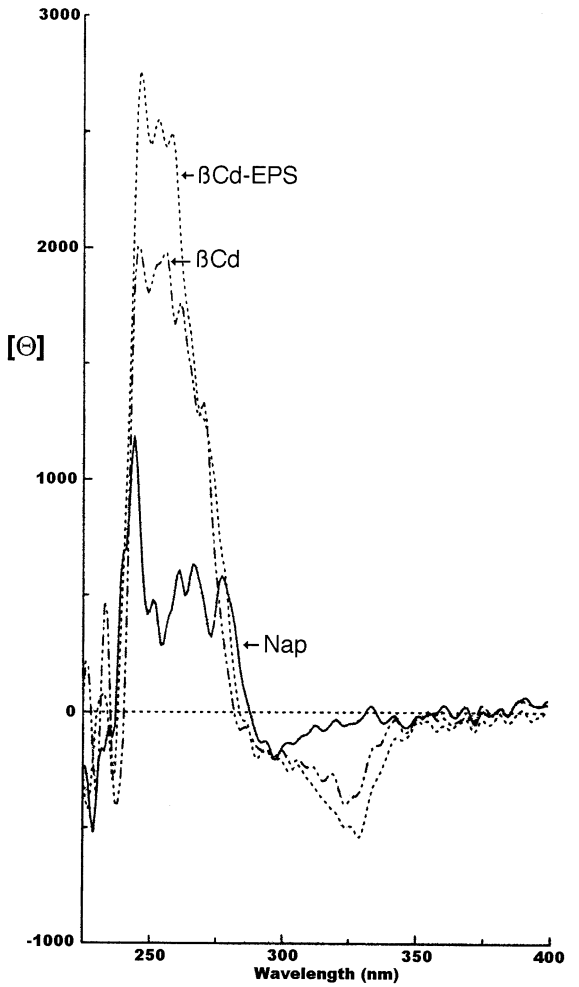

Fig. 6. Circular dichroism spectra of naproxen (NAP) (c(NAP) = 0.4 mmol l^{-1}) in aqueous solutions, in the absence (continuous line) and in the presence (dotted lines) of βCd or soluble βCd-epichlorohydrin polymer (βCd-EPS) (c(Cd) = 4 mmol l^{-1}).

βCd-EPS was about 120 times, clearly better than the increase of about 18 times obtained in saturated βCd concentration [1], about 20% higher than that found in the presence of 50 mmol l^{-1} of hydroxypropyl-βCd [2], and similar to that obtained in ternary systems of NAP with the hydroxypropyl-derivative and PVP [27]. However, it was about 50% less than that observed in the presence of the methyl-derivatives [4].

Fig. 6 shows the NAP circular dichroism spectra in the absence and presence of βCd or βCd-EPS. All positive peaks of NAP in the range between 280 and 240 nm, as well as its negative band between 330 and 290 nm, showed a strong increase in intensity and a shift in the presence of βCd and even more so with βCd-EPS. Spectroscopic studies showed that host–guest interactions were qualitatively the same in the presence of both carriers, suggesting a similar orientation and/or arrangement of the guest drug molecule within the host cavity. The more intense spectral modifications observed in the presence of the polymeric carrier can be considered the effect of a stronger interaction of βCd-EPS with NAP, in confirmation of the results of phase–solubility studies.

4. Conclusion

Both the examined βCd polymeric carriers, i.e. the soluble and the insoluble one, emerged as effective carriers for improving NAP amorphization and enhancing its dissolution properties. On the whole, their performance can be considered comparable, even though βCd-EPI showed a greater amorphizing power, whereas βCd-EPS revealed better solubilizing properties, particularly in simple blends with the drug. The best results were obtained from co-ground products at 10/90 (w/w) drug-to-carrier ratio, where the total NAP amorphization was achieved and whose dissolution efficiencies were more than 30 times higher than that of the pure drug. Therefore polymeric β-Cds can be considered a preferential partner for NAP, also taking into account their absence of toxicity, even when chronically administered, due to their high molecular weight which prevents oral absorption [10,28].

Acknowledgements

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