Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

Interaction of Naproxen with Crystalline and Amorphous Methylated β-Cyclodextrin in the Liquid and Solid State

Paola Mura[a]; Gian Piero Bettinetti[b]; Maria Teresa Faucci[a]; Milena Sorrenti[b]; Alessandra Negri[b]
[a] Dipartimento di Scienze Farmaceutiche, Università di Firenze, FI, Italy [b] Dipartimento di Chimica Farmaceutica, Università di Pavia, PV, Italy

To cite this Article Mura, Paola , Bettinetti, Gian Piero , Faucci, Maria Teresa , Sorrenti, Milena and Negri, Alessandra(2001) 'Interaction of Naproxen with Crystalline and Amorphous Methylated β-Cyclodextrin in the Liquid and Solid State', Supramolecular Chemistry, 12: 4, 379 — 389
To link to this Article: DOI: 10.1080/10610270108027469
URL: http://dx.doi.org/10.1080/10610270108027469

SUPRAMOLECULAR CHEMISTRY, Vol. 12, pp. 379-389
Reprints available directly from the publisher
Photocopying permitted by license only

Interaction of Naproxen with Crystalline and Amorphous Methylated β-Cyclodextrin in the Liquid and Solid State

PAOLA MURA[a*], GIAN PIERO BETTINETTI[b], MARIA TERESA FAUCCI[a], MILENA SORRENTI[b] and ALESSANDRA NEGRI[b]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Firenze, Via G. Capponi 9, 50121 FI, Italy and* [b]*Dipartimento di Chimica Farmaceutica, Università di Pavia, Viale Taramelli 12, 27100 PV, Italy*

(Received June 21, 1999.; In final form May 05, 2000)

Interactions of naproxen (NAP) with amorphous, randomly methylated β-cyclodextrin at a degree of substitution per anhydroglucose unit of 1.8 (RAMEB) and with crystalline heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) were studied in aqueous solution and in the solid state using, respectively, phase-solubility analysis (at 25 °C, 37 °C and 47 °C) and differential scanning calorimetry (DSC) supported by X-ray powder diffractometry. RAMEB and DIMEB displayed similar solubilizing and complexing abilities towards NAP, suggesting analogous inclusion modes of the drug in the host cavity in aqueous solution. Differences were instead observed in interactions in the solid state, where the amorphizing capacity of RAMEB toward NAP (evaluated by DSC) was about twice that of DIMEB at each drug-to-carrier ratio. Assuming that inclusion complexation is also involved in solid-state interactions, molecular modelling accounted for the experimental results in terms of structural features of DIMEB, i.e. the particular inwards orientation of O-6-C-8 groups of three alternate glucoses on the primary hydroxyl side which hampers a deep penetration of NAP in the DIMEB cavity in the solid state. On the contrary, no obstruction of the cavity apparently occurs with RAMEB due its noncrystalline state. The aqueous dissolution rate of NAP from NAP-RAMEB and NAP-DIMEB blends containing 0.59, 0.73, 0.85, and 0.92 mass fraction of carrier linearly increased at decreasing drug-to-carrier ratios. The improvement was 5 to 20 times (from powders) and 50 to 200 times (from discs) the dissolution rate of NAP alone for both carrier. Therefore the choice of the amorphous RAMEB in pharmaceutical formulations can be recommended mainly for economic reasons, though the anhydrous and non-hygroscopic nature of crystalline DIMEB might be of particular advantage in case of moisture sensitive formulations.

Keywords: naproxen, amorphous methyl-β-cyclodextrin, heptakis-(2,6-di-O-methyl)-β-cyclodextrin, molecular modelling, differential scanning calorimetry, X-ray powder diffractometry, dissolution rate

INTRODUCTION

Inclusion complexation with cyclodextrins has been extensively applied to improve the biopharmaceutical and technological properties of a number of drugs (Duchêne, 1987; Fromming, 1994). Previous studies showed that the aqueous dissolution rate of naproxen ((S)-(+)-6-methoxy-a-methyl-2-naphthaleneacetic acid, NAP), a very poorly water soluble (≈ 27 mg·L^{-1} at 25 °C) non-steroidal antiinflammatory drug, can be enhanced by complexation with both native (Bettinetti et al., 1989) and, even more, with

* Corresponding Author.

chemically modified cyclodextrins (Bettinetti et al., 1992 and 1998; Mura et al., 1995; Melani et al., 1995). Of all the examined carriers, randomly methylated amorphous β-cyclodextrin with a substitution degree per anhydroglucose unit (DS) of 1.8 (RAMEB) and crystalline heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) were the most efficient partners for NAP (Bettinetti et al., 1992 and 1998). Different performances of these noncrystalline and crystalline methyl β-cyclodextrin derivatives in improving the pharmaceutical properties of several drugs have been reported (Ou et al., 1994; Szeman et al., 1988; Szeman, 1988; Müller et al., 1988). It seemed, therefore, worthy of interest to more deeply investigate the interactions of NAP with RAMEB and DIMEB in aqueous solution and in the solid state, using, respectively, phase-solubility analysis at various temperatures and differential scanning calorimetry (DSC) supported by X-ray powder diffractometry (XRD). Computer-aided molecular modelling was also carried out to complement the experimental results and possibly to shed light on the interaction mechanism responsible for the solubilizing and amorphizing properties of the carriers. Dissolution rates of NAP from NAP-RAMEB and NAP-DIMEB combinations as both powders and compressed discs at various drug-to-carrier ratios were determined according to the dispersed amount and rotating disc methods. The purpose was to find out possible implications of the solid state (i.e., crystalline or amorphous) of methylated β-cyclodextrins on their functionality as aqueous dissolution rate-enhancing agents for NAP in terms of dissolution efficiency and intrinsic dissolution rate constants.

RESULTS AND DISCUSSION

Host-Guest Interactions in Aqueous Solution

Comparative studies on the solubilizing properties of various β-cyclodextrin derivatives for poorly water soluble drugs showed that the performance of both DIMEB and RAMEB (Ou et al., 1994; Szeman et al., 1988; Müller et al., 1988) is much higher than that of the parent β-cyclodextrin. Phase-solubility analysis showed that NAP aqueous solubility linearly increased as a function of carrier concentration, giving similar A_L-type curves (Higuchi and Connors, 1965) for both carriers (Figure 1). The analogous complexing power and solubilizing efficacy of DIMEB and RAMEB for NAP (Table I) was also displayed for ibuprofen (Ou et al., 1994) and ketoprofen (Szeman et al., 1988), in accordance with the similar complexation mechanism and inclusion mode of these drugs postulated previously (Mura et al., 1998). Thermodynamic parameters obtained from the temperature dependency of the stability constants of NAP-DIMEB and

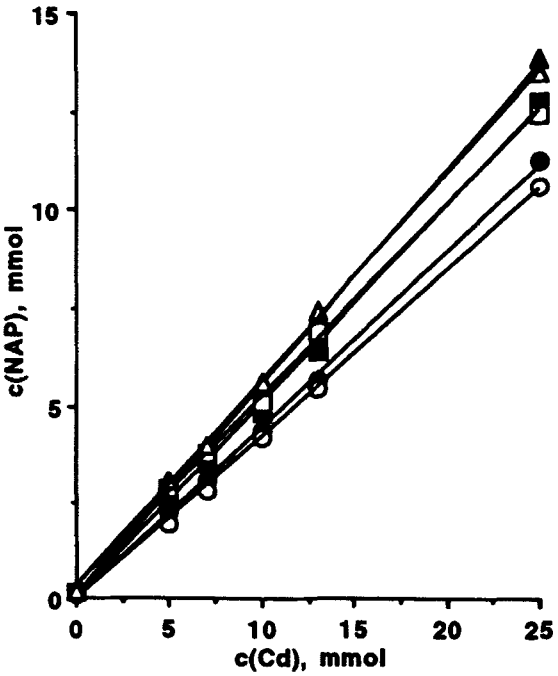

FIGURE 1 Phase-solubility diagrams of naproxen (NAP) with randomly methylated β-cyclodextrin DS 1.8 (RAMEB) (closed symbols) and heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) (open symbols) in aqueous solution at 25°C (•,◦), 37°C (□,■) and 45°C (▲,△)

NAP-RAMEB complexes indicate similar bonding modes of NAP within the cyclodextrin cavity, suggesting that both dipolar or induced dipolar and Van der Waals interactions between host and guest molecules are involved (Table I). A significant contribution of hydrophobic bonding, involving the removal of ordered water molecules surrounding the apolar guest molecule inside the cavity, can also be assumed by the positive entropy changes (Cromwell et al., 1985).

Host-Guest Interactions in Solid State

DSC Analysis

The results of DSC analysis concerning the effect of mechanical grinding on crystallinity changes of NAP in combinations with RAMEB and DIMEB are shown in Figure 2. A sharp endothermal effect (T_{peak} = 156.7±0.3°C, fusion enthalpy 140±6 $J \cdot g^{-1}$) indicated the crystalline anhydrous state of NAP, while the broad endotherms associated with water loss over the 70–130 °C temperature range were characteristic of the carriers. The fusion endotherm of NAP broadened and the peak temperature shifted to lower values (down to 130 °C) in blends with RAMEB and DIMEB, as a consequence of interactions between the components in the respective binary system (Kim et al., 1985). The corresponding decrease in drug fusion enthalpy, which can be directly related to the increase in NAP amorphicity, was clearly more marked in blends with RAMEB than those with DIMEB of the same composition. Actually, at each carrier content, RAMEB was about twice more effective than DIMEB in this respect. The amorphizing effect became more pronounced in ground mixtures, probably as a consequence of a more intimate physical contact between the components brought about by the mechanical treatment (Bettinetti et al., 1996). The extent of drug amorphization increased with the progress of grinding time, and at prefixed grinding times was higher for the combinations at lower drug-to-carrier ratios. It should be noted that in mixtures of NAP with linear maltooligomers, the equimolar ratio was the optimal composition for the strongest amorphizing capacity of the carrier (Bettinetti et al., 1996; Sorrenti et al., 1998). The higher amorphizing capacity of RAMEB (apparent total loss of NAP crystallinity in the mixtures at 0.50 and 0.67 mole fraction of carrier, respectively, ground for 20 min and 10 min,) than DIMEB (50% loss of NAP crystallinity under the same experimental conditions) was evident.

Structure and Molecular Modelling

Crystalline DIMEB is reported as adopting a round shape, with the cyclodextrin cavity closed at one end by the O-6-C-8 groups of three alternate glucoses (2, 4 and 6) that are oriented towards the molecular axis and stabilized by Van der Waals contacts (Steiner and Saenger, 1995). Moreover, in the crystal packing, the remaining volume of the bowl-shaped cavity is further reduced, being occupied by part of the C-6-O-6-C-8 rim of a neighboring molecule (self-inclusion). This steric hindrance, which hampers solid-state inclusion of a guest molecule which still fits the DIMEB cavity, does not occur in RAMEB where the crystal structure is lacking, so that the cavity of the amorphous carrier is more easily accessible to guest molecules. Molecular modelling confirmed the easier accomodation of NAP within the amorphous carrier cavity in terms of Van der Waals interaction energy values at 0 K, which were −26.8±1.4 $kcal \cdot mol^{-1}$ (average of fifteen different substitution patterns with all primary OH groups methylated and six of the fourteen secondary OH groups per glucose unit randomly methylated) for the NAP-RAMEB complex and −21.2 $kcal \cdot mol^{-1}$ for the NAP-DIMEB complex. Computer-generated structures of the complexes clearly show that a deeper penetration of NAP into the RAMEB than the DIMEB cavity can be reached, leading to formation of a more stable inclusion complex with the amorphous partner (Figure 3). The results accounted for a direct

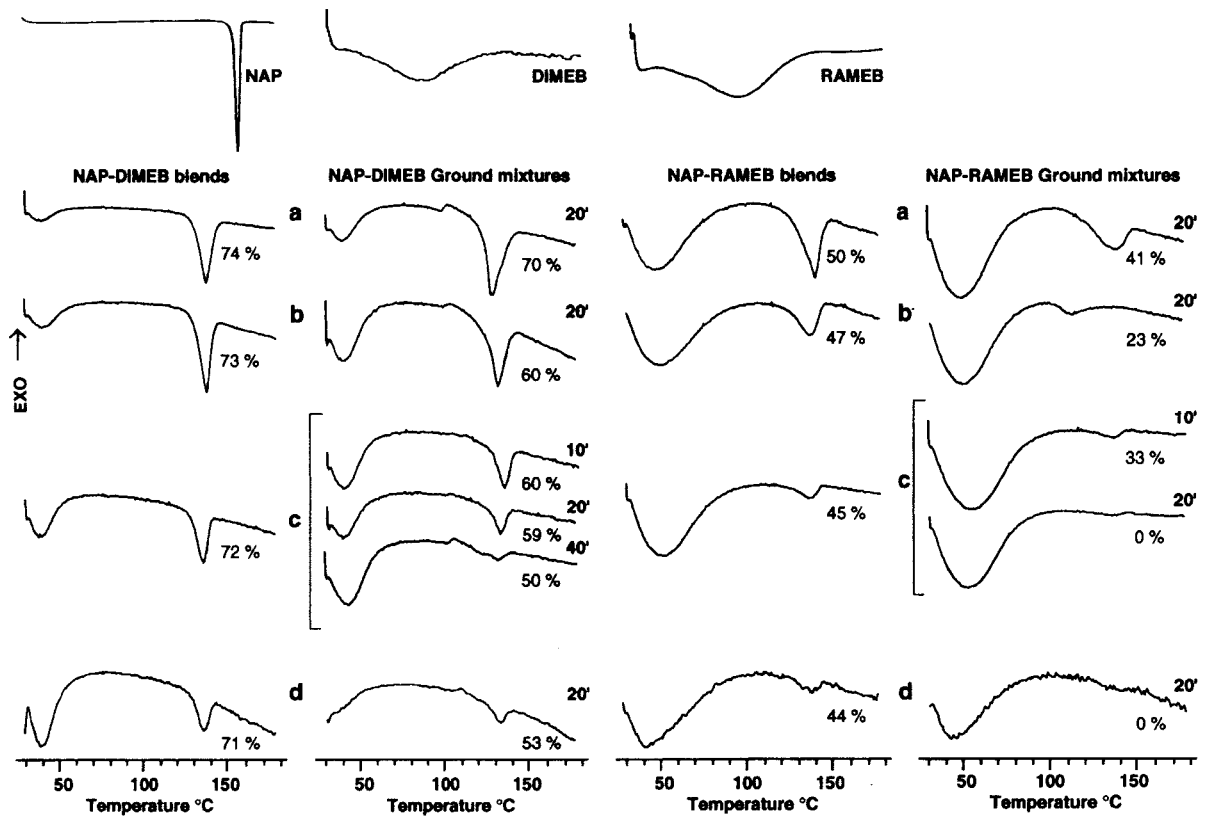

FIGURE 2 DSC curves of naproxen (NAP), randomly methylated β-cyclodextrin DS 1.8 (RAMEB), heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) and NAP-carrier combinations at 0.20 (a), 0.33 (b), 0.50 (c), and 0.67 (d) mole fraction of carrier (grinding time (min) and NAP crystallinity (% NAP mass fraction) on the curves)

implication of inclusion complexation in the solid state interactions of NAP with RAMEB and DIMEB.

XRD Analysis

XRD patterns showed that the diffraction characteristics of the individual components were maintained in drug-carrier blends, where NAP crystallinity appeared almost unchanged (Figure 4). An appreciable loss of NAP crystallinity was instead observed in ground mixtures, probably as a consequence of loosening of crystal forces of NAP which is finely dispersed within RAMEB or DIMEB. The phenomenon became more evident at increasing carrier contents, and was clearly more marked for NAP-RAMEB combinations. The total loss of drug crystallinity in the NAP-RAMEB mixture of equimolar composition ground for 20 min which resulted from DSC analysis (see Figure 2), however, was not evident in the XRD pattern where characteristic peaks of NAP crystals still appeared. Thermal energy supplied during a DSC scan was probably responsible for complete amorphization of NAP, which was brought to a highly dispersed (but not totally amorphous) state by grinding. Complete disappearance of NAP diffraction peaks in the XRD pattern of the ground equimolar mixture previously heated at 130°C for 10 min (Figure 4c') accounted for the supposed physical state of NAP, prone to be brought into an amorphous state by supply of thermal energy.

TABLE I Solubilizing efficiency (S.E), apparent stability constants, and derived thermodynamic parameters for the interaction of naproxen (NAP) with randomly methylated β-cyclodextrin DS 1.8 (RAMEB) and heptakis(2,6-di-O-methyl)-β-cyclodextrin (DIMEB)

Cyclodextrin	*S.E.*[a]	*Apparent stability constant, $K_{1:1}$ (L mol^{-1})*			$\Delta G°_{25°C}$	$\Delta H°$	$\Delta S°_{25°C}$
		25°C	*37°C*	*45°C*	*kJ mol^{-1}*	*kJ mol^{-1}*	*J mol^{-1} K^{-1}*
DIMEB	89	6200	5370	5180	−21.9	−7.3	48.1
RAMEB	94	6778	5720	5550	−21.6	−9.4	41.8

a. At 25 °C in the presence of 0.025 mol L^{-1}Cd.

Dissolution Rate Experiments

Dispersed amount experiments (Figure 5) revealed that the aqueous dissolution rate of NAP from blends of the same composition was improved substantially to the same extent (not statistically significant differences at P>0.1) by RAMEB and DIMEB. The enhanced dissolution rate can be mainly attributed to an increase in solubility and wettability of the drug. The dissolution efficiency (Khan, 1975) was linearly related to the carrier content in the blend and tended to increase in ground combinations, as shown for those at 0.33 carrier mole fraction. The effect could be explained by both the greater surface areas of contact between drug and carrier and the decrease in drug crystallinity. Analogous results were obtained from rotating disc experiments (Figure 6), where for both carriers a parallel increase in NAP dissolution rate was observed at decreasing drug-to-carrier ratios. Intrinsic dissolution rate constants, k_{ID}, calculated from the slope of the dissolution profiles, showed that DIMEB was a slightly more effective enhancer than RAMEB for NAP. A statistically significant difference (P = 0.05) was however found only between discs containing excess of drug with respect to the equimolar composition.

CONCLUSION

Solid-state interactions of NAP with RAMEB and DIMEB resulting in drug amorphization mediated by a highly dispersed physical state of the drug can be related to an inclusion process, which is more favoured for the amorphous than the crystalline carrier. Significant improvements of NAP aqueous dissolution rate (5 to 20 times for powders, 50 to 200 times for discs) can be obtained using blends of the drug with RAMEB or DIMEB at 0.59–0.92 mass fraction of carrier. Such combinations are even more effective than equimolar colyophilized products of NAP with native β-cyclodextrin (Bettinetti et al., 1989). The performance of RAMEB and DIMEB in improving the aqueous NAP dissolution properties being similar, the choice of the amorphous carrier in pharmaceutical formulations can be recommended mainly for economic reasons. The anhydrous and non-hygroscopic nature of crystalline DIMEB, however, might be of particular advantage in case of moisture sensitive formulations (Szeman et al., 1988).

MATERIALS AND METHODS

Materials

NAP from Sigma (St. Louis, MO, USA) was recrystallized twice from 95% ethanol and DIMEB from Cyclolab (Budapest, HU) was used as received. RAMEB (water content 3.2±0.2% as mass fraction) was kindly donated by Wacker Chemie GmbH (München 70, FRG). Blends of NAP (75–250 μm sieve granulometric fraction) with RAMEB or DIMEB at 0.20, 0.33, 0.50, and

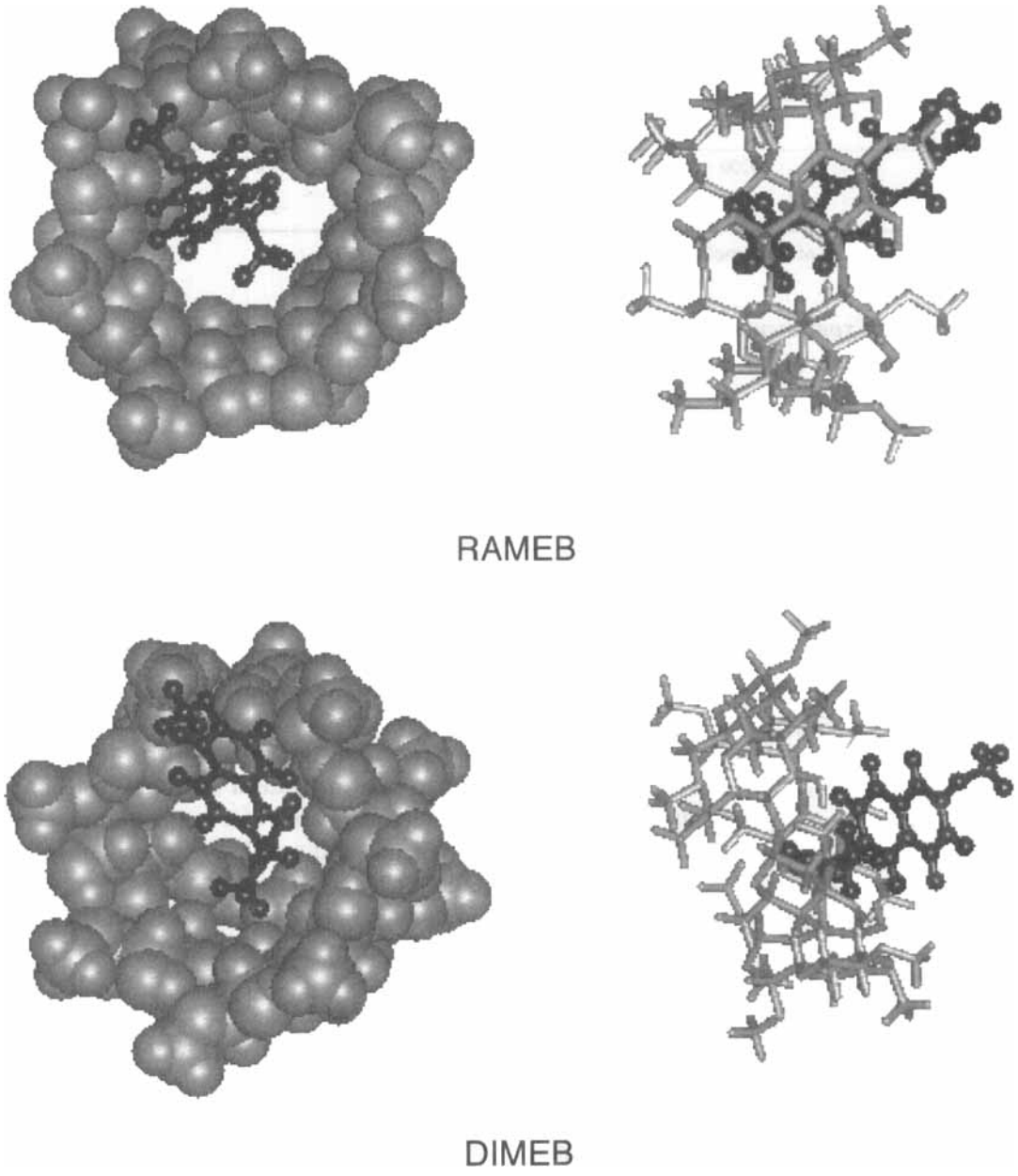

FIGURE 3 Computer-generated inclusion complexes between naproxen (NAP) and methylated β-cyclodextrin at 0 K. Top: NAP inclusion in a model molecule (all primary OH groups and six of the fourteen secondary OH groups per glucose unit methylated) of randomly methylated β-cyclodextrin DS 1.8 (RAMEB); front view (left), side view (right). Bottom: NAP-heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) complex; front view (left), side view (right)

0.67 mole fraction (i.e. 0.59, 0.73, 0.85, and 0.92 mass fraction) of carrier were prepared by turbula mixing for 15 min. Ground mixtures were prepared by manual grinding of the blends in an

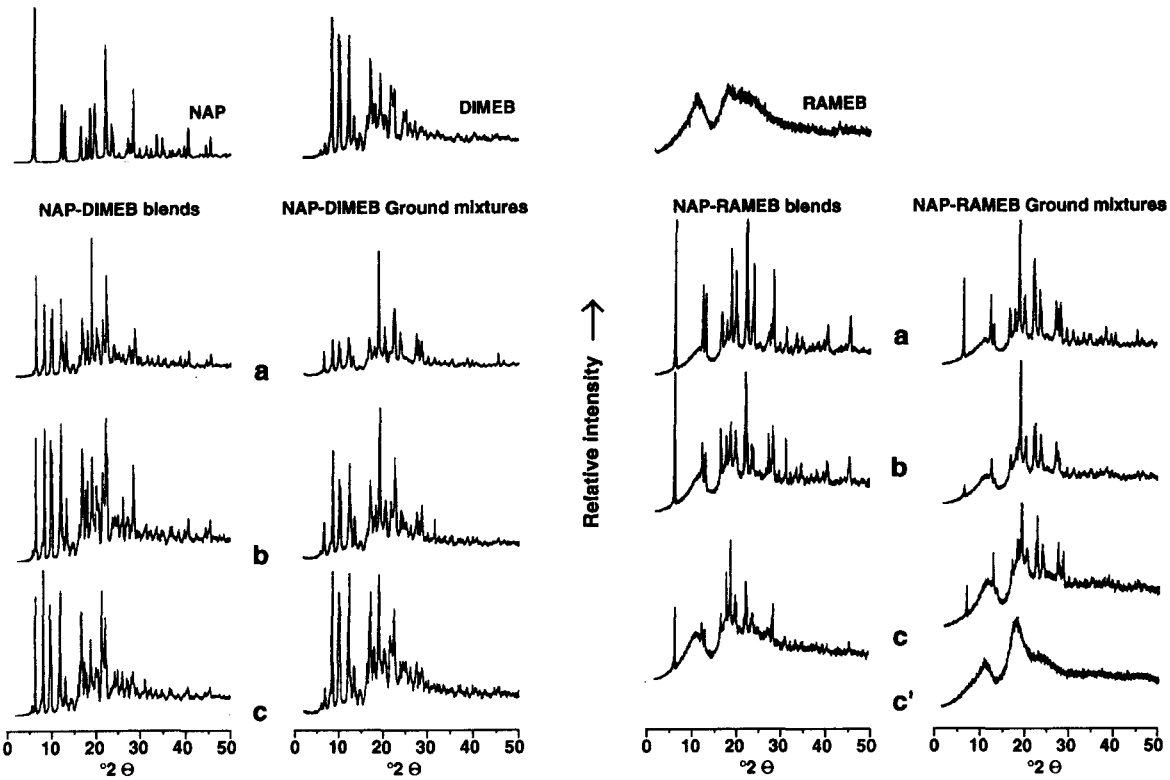

FIGURE 4 Powder X-ray diffraction patterns of naproxen (NAP), randomly methylated β-cyclodextrin DS 1.8 (RAMEB), heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) and NAP-carrier blends and mixtures ground for 20 min at 0.20 (a), 0.33 (b) and 0.50 (c) mole fraction of carrier. Pattern c' refers to the ground mixture kept at 130°C for 10 min

agate mortar with a pestle for prefixed times (10, 20, 30 and 40 min).

Phase-solubility Analysis

Solubility measurements of NAP were carried out by adding 30 mg of drug to 30 mL of water or aqueous solution of DIMEB or RAMEB in the 5 to 25 mmol·L^{-1} concentration range in sealed glass containers equilibrated upon electromagnetical stirring at constant temperature (25±0.5 °C, 37±0.5 °C, 45±0.5 °C) for 3 d. Aliquots were withdrawn, filtered (pore size 0.45 μm) and spectrophotometrically analyzed for drug concentration (Perkin Elmer Spectrophotometer Mod. 552S) with a second derivative spectroscopic method as described elsewhere (Bettinetti et al., 1989). Each experiment was performed in triplicate (coefficient of variation CV < 5%). The apparent 1:1 binding constants ($K_{1:1}$) of the NAP-DIMEB and NAP-RAMEB complexes were calculated from the slope of the straight lines of the phase-solubility diagrams and the aqueous solubility of NAP (Higuchi and Connors, 1965).

Dissolution Studies

Dispersed amount experiments were performed at 37±0.5 °C by adding 60 mg of NAP or NAP equivalent to 75 mL of unbuffered water (pH ≈ 6) in a 100 mL beaker, where a glass three-blade propeller was centrally immersed and rotated at 100 rpm. In rotating disc method, samples of 300 mg were compressed (disc area 1.33 cm^2)

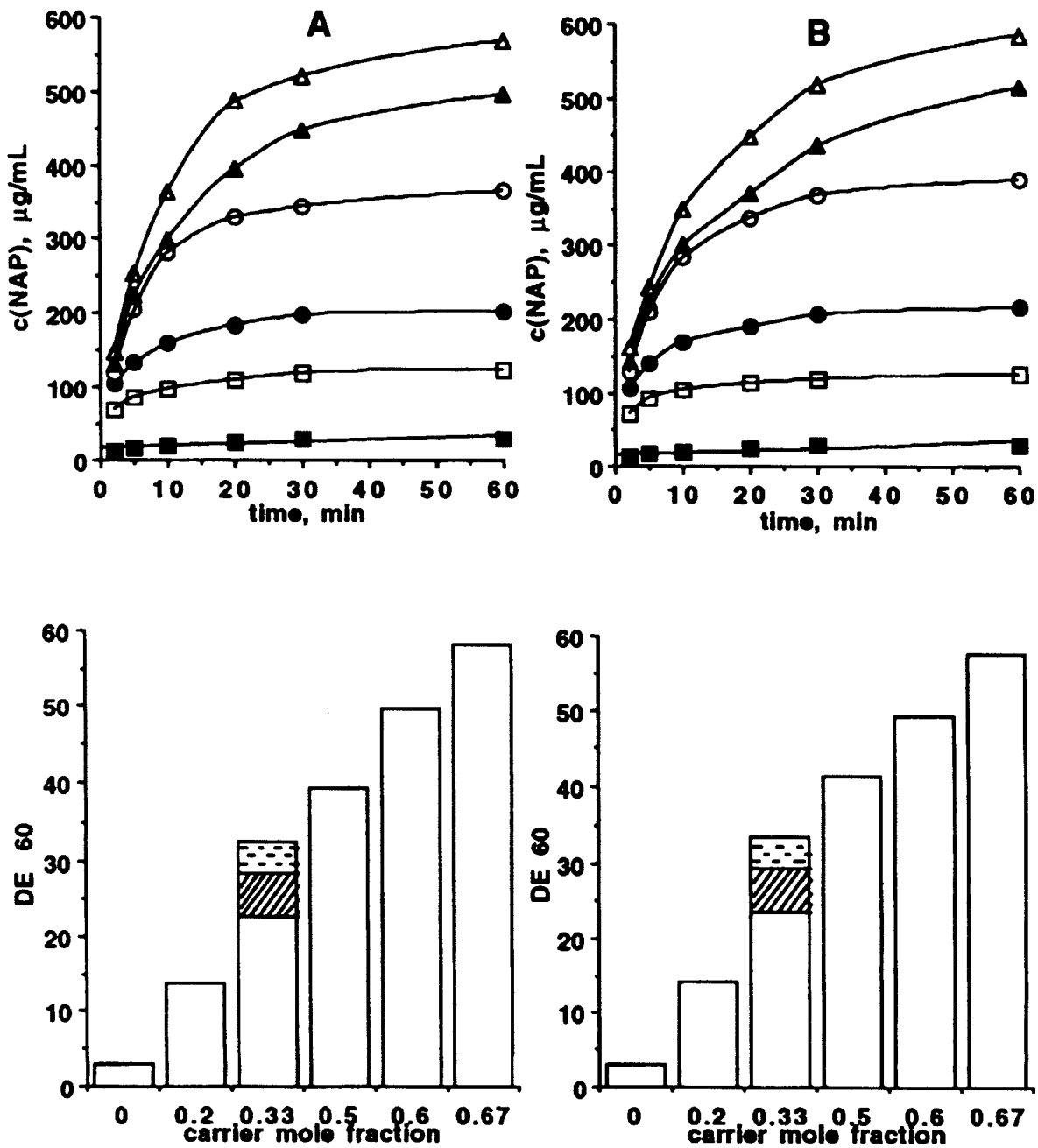

FIGURE 5 Dispersed amount experiments on naproxen (NAP) (■) and its blends with (A) randomly methylated β-cyclodextrin DS 1.8 (RAMEB), (B) heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) at 0.20 (□), 0.33 (•), 0.50 (○), 0.60 (▲) and 0.67 (△) mole fraction of carrier. Top: dissolution curves. Bottom: NAP dissolution efficiency DE_{60} (area under the dissolution curve at t = 60 min (measured using the trapezoidal rule) expressed as % of the area of the rectangle described by 100% dissolution in the same time). The effect of grinding for 10 (//////) and 30 (----) min on DE_{60} of NAP from the mixtures at 0.33 carrier mole fraction is shown

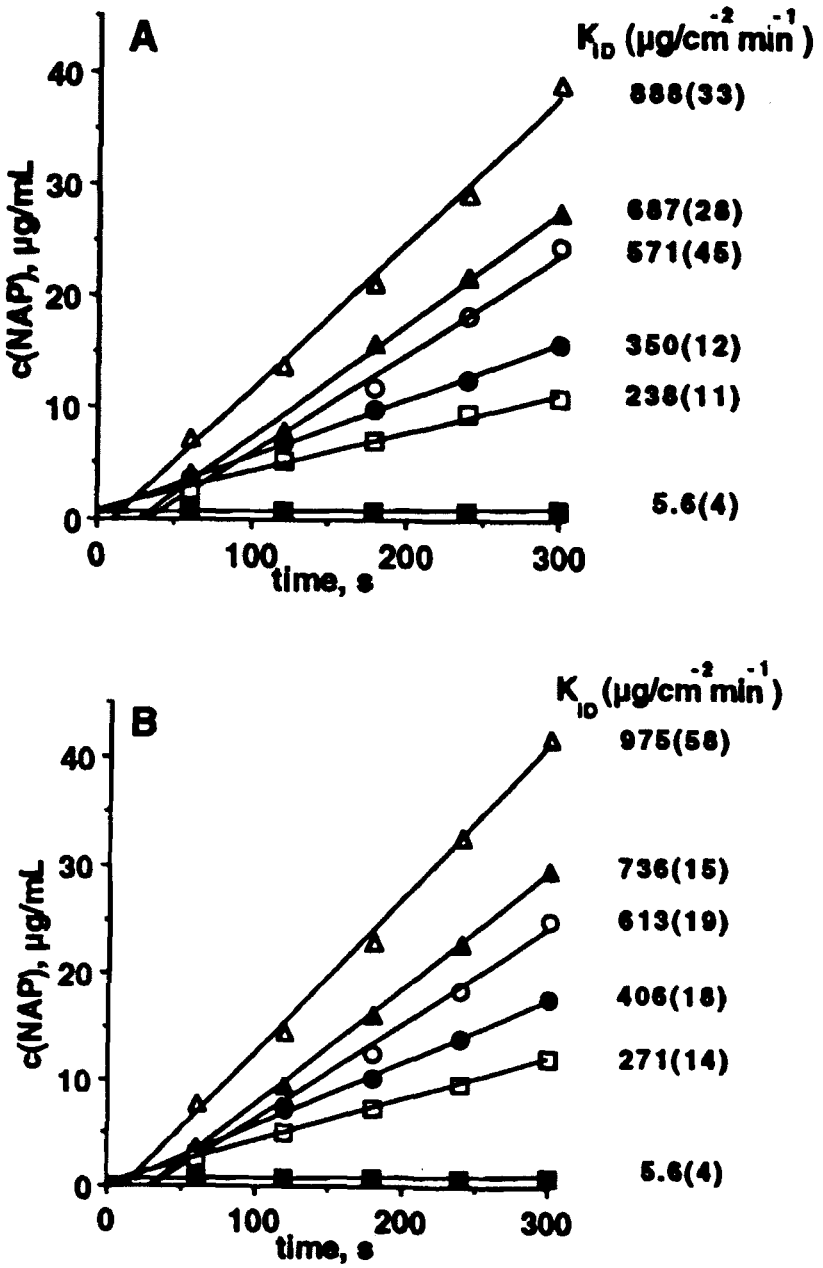

FIGURE 6 Dissolution rate (rotating disc method) of naproxen (NAP) (■) and its blends with (A) randomly methylated β-cyclodextrin DS 1.8 (RAMEB), (B) heptakis-(2,6-di-O-methyl)-β-cyclodextrin (DIMEB) at 0.20 (□), 0.33 (•), 0.50 (○), 0.60 (▲) and 0.67 (△) mole fraction of carrier (intrinsic dissolution rate constants (k_{ID}, mg cm^{-2} min^{-1} with standard deviations in parentheses) on the curves)

and the tablets were inserted into a stainless steel holder, so that only one face was exposed to the dissolution medium; the holder was centrally immersed in a 200 mL beaker containing 150 mL

of unbuffered water at 37±0.5 °C and rotated at 100 rpm. In both methods, at appropriate time intervals suitable aliquots were withdrawn with a filter-syringe (pore size 0.45 μm) and spectrophotometrically assayed for drug content as in Phase-solubility Analysis. A correction was calculated for the cumulative dilution caused by replacement of the sample with equal volume of original medium. Each test was repeated 4 times (coefficient of variation CV < 1.5% for dispersed amount experiments and CV < 8% for rotating disc experiments).

Differential Scanning Calorimetry (DSC)

Temperature and enthalpy values were measured with a METTLER STAR^e system equipped with a DSC821^e Module on 3–5 mg samples in open Al pans, at the heating rate of 10 K·min^{-1} in the 30–180°C temperature range under static air atmosphere. The relative degree of crystallinity of NAP in physical and ground mixtures, expressed as percent of the NAP mass fraction in the starting sample, was estimated by the ratio between the heat of fusion of NAP calculated in the sample and that of pure NAP (Kim et al., 1985).

X-ray Powder Diffractometry (XRD)

XRD patterns were taken with a computer-controlled Philips PW 1800/10 apparatus equipped with specific PC-APD software. Wavelengths: $CuK_{\alpha,1}$= 1.54060 Å, $CuK_{\alpha,2}$= 1.54439 Å. Scan range: 2–50 °2Θ. Scan speed: 0.02 °2Θ·s^{-1}.

Molecular Modelling

Analysis and modelling of the NAP-DIMEB and NAP-RAMEB complexes were carried out using the INSIGHT II 95.0 program (Biosym/MSI). NAP molecule was made as described previously (Mura et al., 1995) through the proper Builder Module of the INSIGHT II programme. The molecular structure of β-cyclodextrin was obtained from crystallographic parameters provided by the Cambridge Structural Data Base System (Cambridge crystallographic data Centre; Lindner and Saenger, 1982). DIMEB molecule was built-up on the basis of crystal structure data (Steiner and Saenger, 1995), by applying suitable constrains to the carbon atoms to stabilize the intramolecular O-3-H---O-2 hydrogen bonds between neighboring glucose units, and to comply with the inward orientation of O-6-C-8 groups of 2, 4 and 6 glucoses. RAMEB molecule was built-up by randomly adding to the base β-cyclodextrin molecule 13 methyl groups according to the average substition degree DS (1.8 per anhydroglucose unit, i.e. 12.6 methyl groups per macrocycle). Several patterns of substituent distribution were examined by varying the relative position of methyl groups on glucoses according to the preferential distribution found for statistically partially methylated β-cyclodextrin (Yamamoto et al., 1988). NAP was fitted into the cavity of methylated β-cyclodextrin in an axial orientation, with the carboxyl group directed towards the widest rim of the cavity (Bettinetti et al., 1991). Each structure was subjected to a simulated annealing process, from 900 to 0 K, performing iterations up to a minimum constant value of conformational energy.

Acknowledgements

This work was supported by a grant from MURST (Rome).

References

Bettinetti, G.P.; Mura, P.; Liguori, A.; Bramanti, G; Giordano, F.; *Farmaco* 1989, 44, 195.

Bettinetti, G. P.; Melani, F.; Mura, P.; Monnanni, R; Giordano, F.; *J. Pharm. Sci.* 1991, 80, 1162.

Bettinetti, G.P.; Gazzaniga, A.; Mura, P.; Giordano, F.; Setti, M.; *Drug Dev. Ind. Pharm.* 1992, 18, 39.

Bettinetti, G.P.; Mura, P.; Melani, F.; Rillosi, M.; Giordano, F.; *J. Incl. Phenom.* 1996, 25, 327.

Bettinetti, G. P.; Sorrenti, M.; Negri, A.; Mura, P.; Faucci, M. T.; *Proc. 9th Int. Symp. Cyclodextrins*, Kluwer Academic Publishers, 1999, pp 371-374.

Biosym/MSI, 9865 Scranton Road, S. Diego, CA 92121–2777.

Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, England.

Cromwell, W.C.; Bystrom, K.; Eftink, M.R.; *J. Phys. Chem.* 1985, 89, 326.

Duchêne, D.; in *Cyclodextrins and their industrial uses*, Ed. De Santé, Paris, 1987.

Fromming, K. H.; Szejtli J.; in *Cyclodextrins in* Pharmacy, Davies, J.E.D. (Ed.), Kluwer Academic Publishers, Dordrecht-Boston-London, 1994.

Higuchi, T.; Connors, K.A.; *Adv. Anal. Chem Instr.* 1965, 4, 117.

Khan, K.A.; *J. Pharm. Pharmacol.*, 1975, 27, 48.

Kim, K. H.; Frank, M. J.; and Henderson, N. L.; *J. Pharm. Sci.* 1985, 74, 283.

Lindner, K.; Saenger, W.; *Carbohydr. Res.* 1982, 99, 103.

Melani, F.; Bettinetti, G.P.; Mura, P; Manderioli, A.; *J. Incl. Phenom.* 1995, 22, 131.

Müller, B.; Brauns, U.; Backensfeld, T.; *Proc. 4th Int. Symp. Cyclodextrins*, Huber, O. and Szejtli, J. (Eds.), Kluwer Academic Publishers, 1988, pp. 369–382.

Mura, P.; Bettinetti, G.P.; Melani, F.; Manderioli, A.; *Eur. J. Pharm. Sci.* 1995, 3, 347.

Mura, P.; Bettinetti, G.P.; Manderioli, A.; Faucci, M.T.; Bramanti, G.; Sorrenti, M.; *Int. J. Pharm.* 1998, 166, 189.

Ou, D.; Ueda, H.; Nagase, H.; Endo, T.; Nagai, T.; *Drug Dev. Ind. Pharm.* 1994, 20, 2005.

Sorrenti, M.; Negri, A.; Bettinetti, G. P; *J. Therm. Anal.* 1998, 51, 993.

Steiner, T.; Saenger, W.; *Carbohydr. Res.* 1995, 275, 73.

Szeman, J.; Szente, L.; Szabò, T.; Szejtli, J.; *Proc. 4th Int. Symp. Cyclodextrins*, Huber, O. and Szejtli, J., Eds., Kluwer Academic Publishers, 1988, p 393.

Yamamoto, K.; Tsuchiyama, Y.; Sato, M.; Yagi, Y.; Ishikura, T.; Jpn. Kokai Tokkyo koho, Nos. Jp. 63, 41, 505 88, 41505 (1988).