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THERMAL BEHAVIOUR AND DISSOLUTION PROPERTIES OF NAPROXEN IN COMBINATIONS WITH CHEMICALLY MODIFIED ß-CYCLODEXTRINS

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ABSTRACT

Binary systems of naproxen with statistically-alkylated ß-cyclodextrins (methyl, hydroxyethyl and hydroxypropyl derivatives) were investigated for both solid phase characterization (differential scanning calorimetry, X-ray powder diffraction) and dissolution properties (dispersed amount and rotating disc methods). Kneading, coevaporation and colyophilization of the 1:1 (mol/mol) naproxen/methyl ß-cyclodextrin combination, as well as colyophilization of analogous combinations of naproxen with hydroxyethyl and hydroxypropyl ß-cyclodextrin, led to amorphous products with higher dissolution rates than the corresponding physical mixtures. A conversion of crystalline to amorphous naproxen was also observed by heating the physical mixtures at about 393 K. The amorphous statistically-

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alkylated ß-cyclodextrins, in particular methyl ß-cyclodextrin, can be employed as amorphizing agents for crystalline naproxen.

INTRODUCTION

The dissolution properties of naproxen (NAP), a non-steroidal anti-inflammatory drug which is practically insoluble in water, in combinations with both natural cyclodextrins (Cds) [1] and polyvinylpyrrolidone (PVP) [2] have been previously investigated. The increase in NAP dissolution rate has mainly been ascribed respectively to complexation with Cds and amorphization induced by amorphous PVP. The amorphization of crystalline drugs in mixtures with various "inert" ingredients such as microcrystalline cellulose [3-5], ß-cyclodextrin (ßCd) [6,7], di-O-methyl ßCd [8], and various Cds [5] has been found in a number of cases to occur with grinding. Since the amorphous state plays a dominant role in the dissolution properties of drugs, it seemed of interest to investigate the performance of some highly water soluble, amorphous alkyl and hydroxyalkyl ßCd derivatives in the improvement of the dissolution features of NAP. Mixed systems of NAP and hydroxypropyl-ßCd, MS 0.9 (HPßCd), hydroxyethyl-ßCd, MS 1.6 (HEßCd), and methyl-ßCd, DS 1.8 (MßCd) were prepared by kneading, coevaporation, colyophilization. The dissolution behaviour in water at 310 K was determined according to the dispersed amount and rotating disc methods. Differential scanning calorimetry (DSC) and X-ray powder diffraction were used to characterize the solid systems and to check the amorphous or crystalline state of NAP in the combinations with Cds.

MATERIAL AND METHODS

Materials - NAP (Sigma) and HPßCd, HEßCd, and MßCd (donated by Wacker-Chemie GmbH, Munich, Germany) of commercial grade were used. Each product was sieved and the relative 75-150 µm granulometric fraction was collected. All other materials and solvents were of analytical reagent grade. Bidistilled water was used throughout the study.

Methods of Preparation - Physical mixtures of NAP and each Cd were prepared in a 1:1 molar ratio by simple blending in an agata mortar at room temperature. Kneaded products were prepared from physical mixtures in a mortar by wetting the powder with the minimum volume of a 1:1 (by volume) mixture of water and ethanol, and grinding thoroughly to obtain a paste which was then dried under vacuum at room temperature up to constant weight. The solid was sieved and the 75-150 μm granulometric sieve fraction collected. Coevaporated products were obtained by dissolving the physical mixtures in the minimum amount of an aqueous ammonia solution (0.0022 g L^{-1}) at room temperature, removing the solvent under vacuum in a rotatory evaporator at 313 K, and drying the residue under vacuum at room temperature up to constant weight. The solid was pulverized with a pestle and mortar and sieved, the 75-150 μm granulometric sieve fraction being collected. Colyophilized products were prepared by freeze-drying the NAP/Cd aqueous ammonia solutions at 223 K and 1.3×10^{-2} mm Hg (Lyovac GT2, Leybold-Heraeus). Neither residual ammonia nor any decomposition products of NAP were detected in either coevaporated or colyophilized samples [1]. The physical and chemical stability of all preparations was tested by performing X-ray, DSC, and dissolution rate tests after 4 months' storage under controlled conditions (room temperature, 75% R.H.).

Dissolution Tests - Dissolution rates of NAP from 1:1 (mol/mol) physical mixtures and various NAP/Cd products were determined in water at 310 ± 0.5 K according to the dispersed amount and rotating disc methods, and compared with those of the drug alone. Each test was repeated at least three times. In the dispersed amount procedure, 60 mg of NAP or NAP equivalent (75-150 μm fraction) were directly added to 300 mL of water under the experimental conditions described elsewhere [1,2]. Tablets (1.3 cm in diameter) for rotating disc experiments [9] were prepared by compressing about 300 mg of powder using a laboratory hydraulic press for KBr discs for IR spectroscopy, at a force (about 2 t) giving tablets of surface area 1.33 cm^2 which would not disintegrate within the test interval (5 min). No

lubricant was used. Tablets of the NAP/MßCd (1:1 mol/mol) physical mixture which was kept at 393 K for 20 min, were also prepared. For dissolution testing, a tablet was inserted into a stainless steel holder so that only one face was exposed to the dissolution medium (150 mL). The tablet holder, with the tablet in place, was attached to a metal shaft connected to a stirring motor. The holder was immersed in a 200 mL dissolution vessel, centered and rotated (f = 100 min^{-1}). At appropriate intervals, samples were withdrawn and spectrophotometrycally assayed at 274 nm for NAP content [1].

Differential Scanning Calorimetry - DSC was performed with a Mettler TA3000 apparatus equipped with a DSC 20 cell. Samples were weighed (Mettler M3 microbalance) in Al pans (5-10 mg) pierced with a perforated lid, and scanned at 5 K min^{-1} between 300 and 600 K, using dry nitrogen as a purge gas.

X-ray Diffraction - X-ray powder diffraction patterns were taken with a computer-controlled Philips PW 1800 apparatus over the 2...60° 2 θ range at a scan rate of 1° min^{-1}, using a CuKα radiation which was monochromatized with a graphite crystal.

RESULTS AND DISCUSSION

NAP/MßCd systems in powder form tended to show better dissolution properties in water at 310 K than those with HEßCd and HPßCd (Fig. 1). Assuming that each Cd was totally dissolved, the drug concentration attainable at the equilibrium was 370, 280, and 330 μg mL^{-1} respectively for MßCd, HEßCd and HPßCd [10]. The NAP/MßCd colyophilized product showed the highest initial dissolution rate and the greatest supersaturation state, which was followed by an apparent decline in the amount of drug dissolved (Fig. 1a). A comprehensive picture of the relative increase in initial NAP concentrations in the dissolution medium is given in Fig. 2.

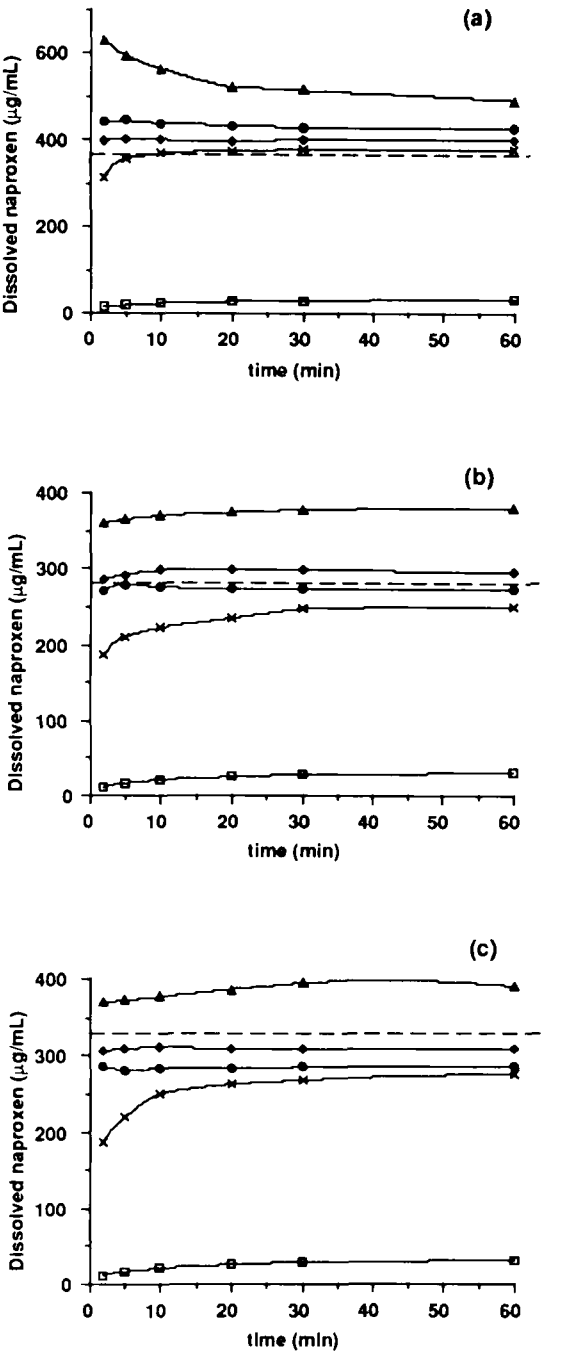

FIGURE 1

Dissolution of naproxen alone and from 1:1 (mol/mol) preparations with (a) methyl ß-cyclodextrin (MßCd); (b) hydroxyethyl ß-cyclodextrin (HEßCd); (c) hydroxypropyl ß-cyclodextrin (HPßCd).

(□) naproxen (NAP) alone; (✖) physical mixture; (◆) coevaporated product; (●) kneaded product; (▲) colyophilized product; (- - - -) NAP concentration attainable at the equilibrium (dispersed amount in water at 310 K, non-sink conditions, coefficient of variation at each time point (n = 3) less than 2%).

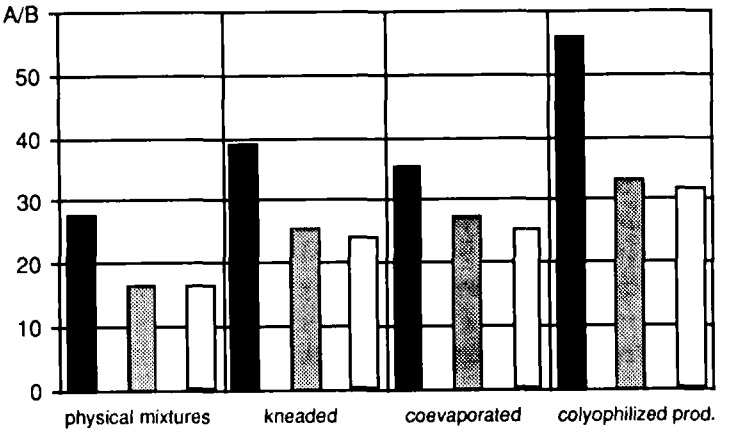

FIGURE 2

Ratio between amount of naproxen (NAP) dissolved from a NAP/cyclodextrin system (A) and amount dissolved from NAP alone (B), at t = 2 min (see Fig. 1). (■) methyl ß-cyclodextrin (MßCd), (□) hydroxyethyl ß-cyclodextrin (HEßCd), (▩) hydroxypropyl ß-cyclodextrin (HPßCd).

The X-ray diffraction patterns of the NAP/HEßCd and NAP/HPßCd systems are shown in Fig. 3. Both Cds and colyophilized products were seen to be amorphous. Diffractional peaks relevant to crystalline NAP were displayed by both kneaded and coevaporated products, and also by physical mixtures. In the previously-described system with MßCd [10], no crystalline NAP was present in the kneaded and coevaporated products. The ability of MßCd to induce the amorphization of NAP may partly explain the increase in the amount of drug dissolved (see Fig. 1). In order to evaluate the influence of differences in the specific surface area, dissolution tests were performed on non-disintegrating tablets at constant surface area. The dissolution profiles of all NAP/Cd preparations showed the same trend as those reported in Fig. 4 for the NAP/MßCd system.

The dissolution rates for the systems containing Cd higher than that obtained with NAP alone are consistent with the formation of soluble

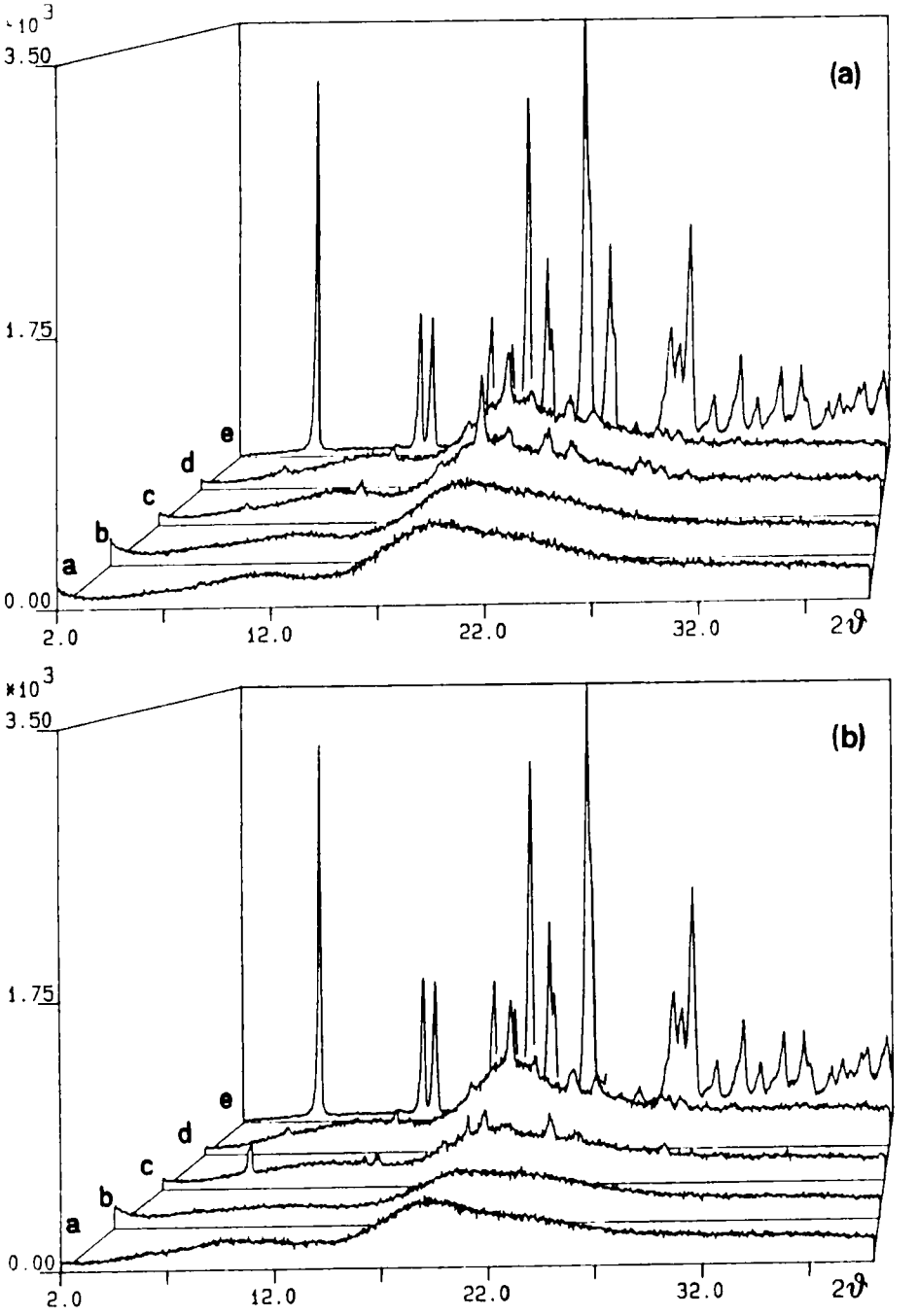

FIGURE 3

X-ray diffraction powder patterns of 1:1 (mol/mol) systems of naproxen (NAP) with (a) hydroxyethyl ß-cyclodextrin (HEßCd) and (b) hydroxypropyl ß-cyclodextrin (HPßCd). *a* HEßCd (a), HPßCd (b); *b* colyophilized products; *c* physical mixtures; *d* kneaded or coevaporated products; *e* NAP.

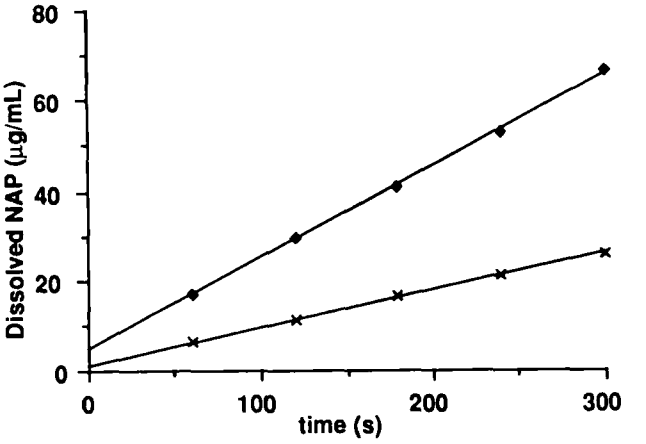

FIGURE 4

Dissolution of naproxen (NAP) from 1:1 (mol/mol) preparations with methyl ß-cyclodextrin (MßCd).
(×) Physical mixture; (◆) kneaded or coevaporated or colyophilized products (rotating disc method in water at 310 K, coefficient of variation at each time point (n = 4) about 8%, rate constants in Table 1).

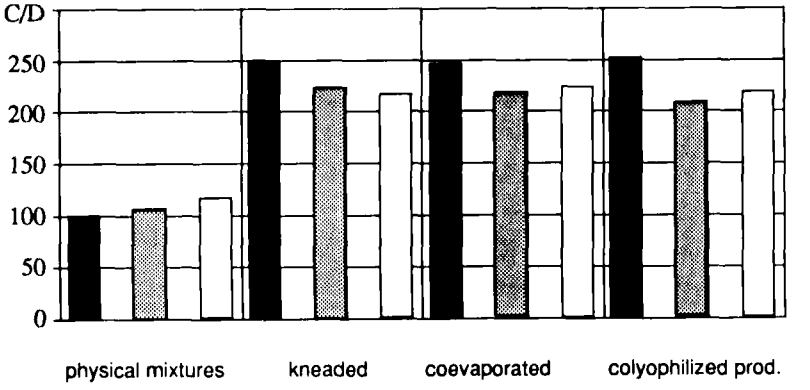

FIGURE 5

Ratio between naproxen (NAP) dissolution rate in the NAP/cyclodextrin system (C) and dissolution rate of NAP alone (D) (see Fig. 4 and Table 1).
(■) methyl ß-cyclodextrin (MßCd), (□) hydroxyethyl ß-cyclodextrin (HEßCd), (✱) hydroxypropyl ß-cyclodextrin (HPßCd).

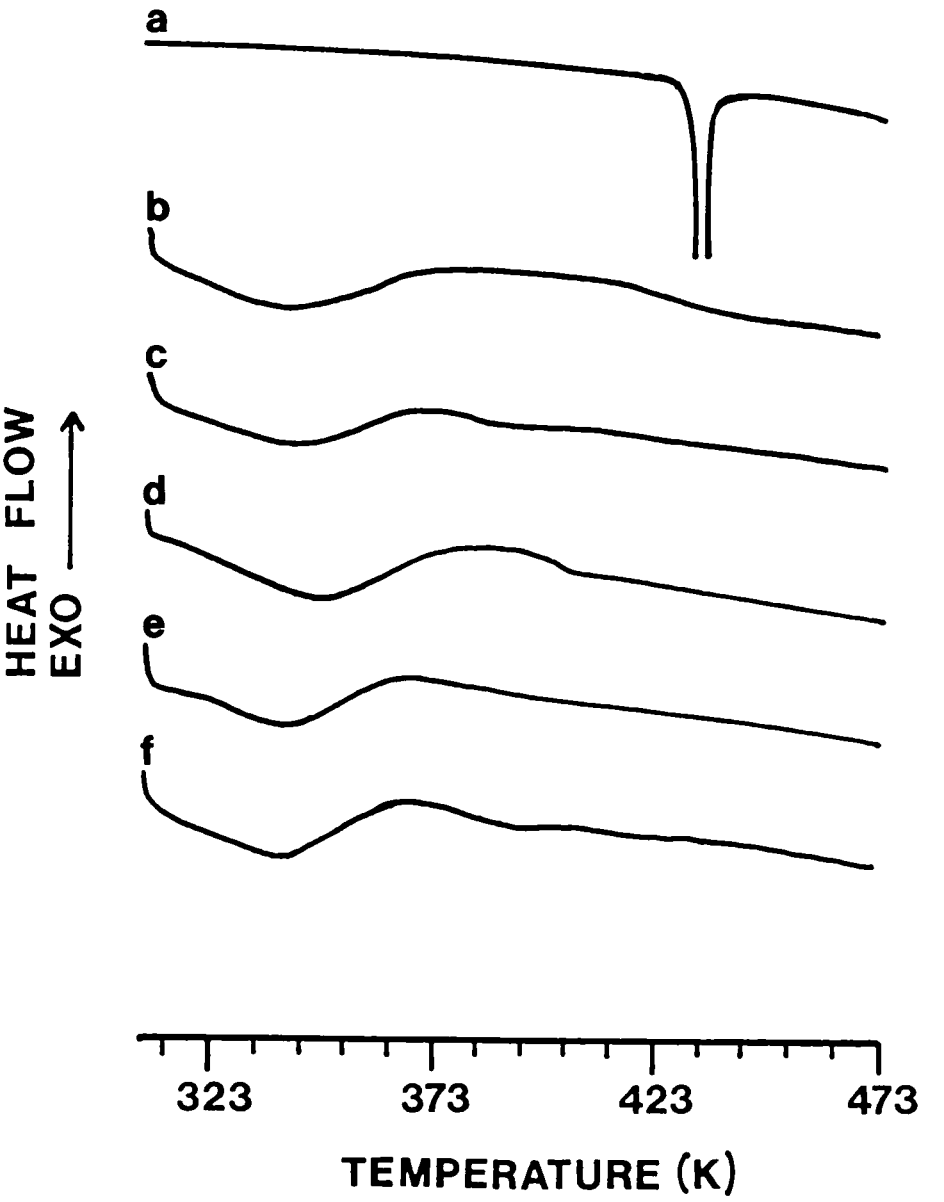

FIGURE 6

DSC curves of naproxen (NAP), methyl ß-cyclodextrin (MßCd), and the respective 1:1 (mol/mol) preparations.
(a) NAP, (b) MßCd, (c) kneaded product, (d) coevaporated product, (e) colyophilized product, (f) physical mixture.

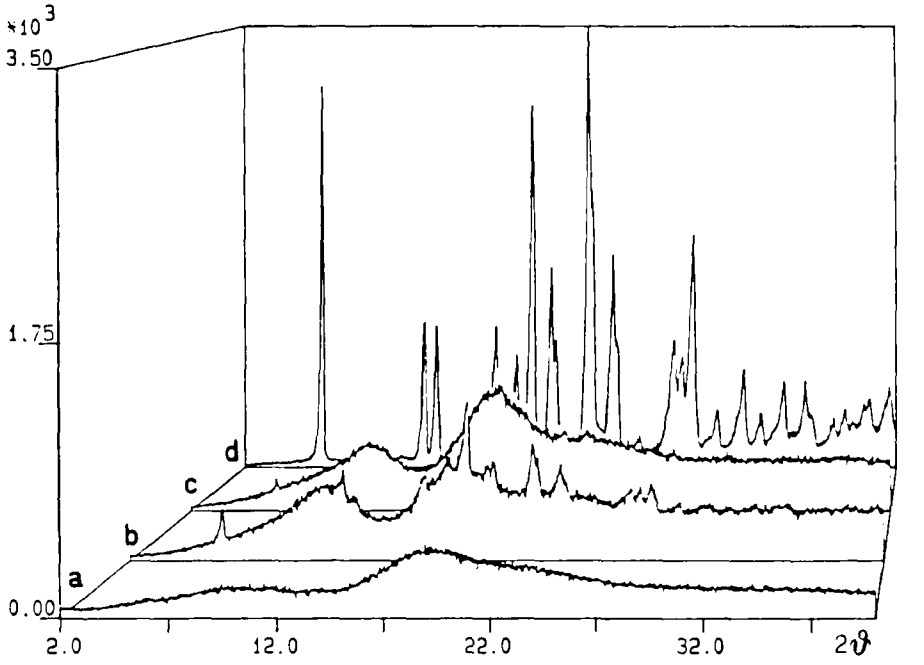

FIGURE 7

X-ray diffraction powder patterns of (a) methyl ß-cyclodextrin (MßCd), (d) naproxen (NAP), and the respective 1:1 (mol/mol) physical mixture (b) at room temperature, (c) kept at 393 K for 20 min.

complexes in the dissolution medium [10,11]. The ratio between the rate constant calculated by the linear portion of the dissolution profile of a given NAP/Cd preparation and the analogous value of the drug alone gives the relative increase in NAP dissolution rate (Fig. 5). It is evident that NAP/Cd kneaded, coevaporated and colyophilized products in the form of compressed discs give substantially similar dissolution rates. Thus, the dissimilar dissolution profiles of the same products in powder form (see Fig. 1) can be ascribed to differences in the particle size and hence specific surface area and/or wetting of the samples.

The DSC curves of NAP [12], MßCd, and their 1:1 (mol/mol) preparations in the 308...473 K temperature range are shown in Fig. 6. The NAP

TABLE 1

Dissolution Rates of Naproxen (NAP) and its 1:1 (mol/mol) Systems with Methyl ß-Cyclodextrin (MßCd) (Rotating Disc Method)

Sample	k(μg cm^{-2} s^{-1})[a]
NAP	0.093(3)
Physical Mixture	9.3(4)[b] 13(1)[c]
Kneaded or Coevaporated or Colyophilized Product	23(2)

a) Dissolution rate, standard deviation in parentheses (4 runs)
b) Discs obtained from mixtures at room temperature
c) Discs obtained from mixtures kept at 393 K for 20 min

fusion peak appeared neither in the DSC curves of kneaded, coevaporated and colyophilized products, which were all amorphous [10], nor in the physical mixtures, despite the presence of crystalline drug in the original sample. X-ray analysis of the 1:1 (mol/mol) physical mixture before and after heating at 393 K showed that crystalline NAP became amorphous with the supply of thermal energy (Fig. 7). In order to seek the influence of this phase transition on the dissolution behaviour, the NAP dissolution rate was measured on discs obtained by compaction of physical mixtures which were previously kept at 393 K for 20 min. The results are given in Table 1, together with data relevant to other NAP/MßCd preparations. An increase of 40% in the NAP dissolution rate expresses the contribution of the amorphous state of the drug in the equimolar physical mixture with MßCd.

The DSC curves of the systems of NAP with HEßCd and HPßCd in the 308...473 K temperature range are shown in Fig. 8. The thermal

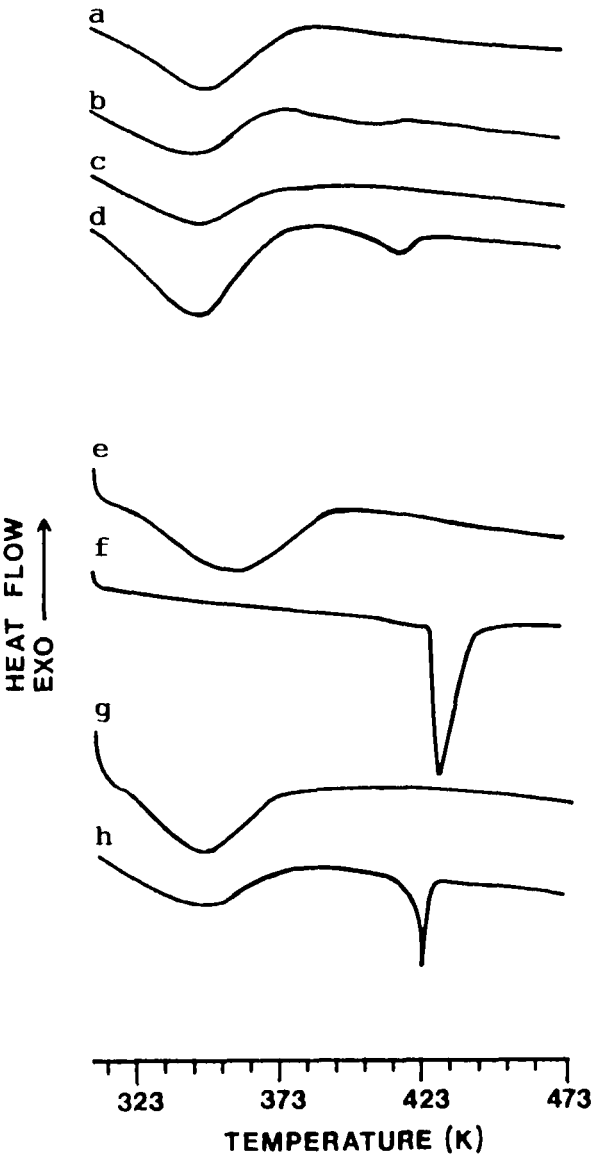

FIGURE 8

DSC curves of naproxen (NAP)/hydroxyethyl ß-cyclodextrin (HEßCd) and NAP/hydroxypropyl ß-cyclodextrin (HPßCd) 1:1 (mol/mol) systems.
(a) HEßCd, (b) NAP/HEßCd kneaded product, (c) NAP/HEßCd colyophilized product, (d) NAP/HEßCd physical mixture; (e) HPßCd, (f) NAP/HPßCd kneaded product, (g) NAP/HPßCd colyophilized product, (h) NAP/HPßCd physical mixture.

behaviour of NAP with HEßCd is analogous to that in the system with MßCd (see Fig. 7). The crystalline drug in both the physical mixture and the kneaded product (see Fig. 3) was easily amorphized by the supply of thermal energy during the DSC run. In the NAP/HPßCd system, instead, the drug maintains its crystallinity under the same experimental conditions. The NAP/Cd solid state interaction can be interpreted by assuming that in the physical mixture prepared by blending NAP and MßCd in a 1:1 (mol/mol) ratio at room temperature, microcrystalline drug remains embedded in the amorphous Cd matrix. By heating the sample, the drug molecules can either be dispersed onto the surface or included into the Cd's cavity. Differences in this behaviour of NAP with MßCd, HEßCd and HPßCd in terms of decreasing ability to amorphize can thus also be explained by structural parameters, taking into account the influence of substituents of the ßCd derivative. No decomposition and no tendency to recrystallize was shown by the drug upon storage under controlled conditions (room temperature, 75% R.H.).

CONCLUSIONS

Of the ßCd derivatives tested, MßCd showed the highest complexing ability with NAP in aqueous solution [13] and proved to be very active also in performing solid state interaction, *i.e.* amorphization of the crystalline drug. This particular behaviour, which resembles that of some adsorbents in pharmaceutical use [14], can be exploited in the design of solid dosage forms in order to obtain definite advantages in terms of bioavailability. On the other hand, the limited physical stability of the amorphous phases represents a major problem in drug formulation. Whether or not the ease of amorphization shown by MßCd as compared to HEßCd and HPßCd might be directly related to a sort of "stabilization" of the metastable phase is a question which certainly merits further attention.

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