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Assessment of solid-state interactions of naproxen with amorphous cyclodextrin derivatives by DSC☆

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Abstract

A microcalorimetric method based on differential scanning calorimetry (DSC) of drug-additive binary systems to assess kneading-induced interactions was applied to naproxen (NAP) in combinations with amorphous hydroxypropyl β-cyclodextrin (HPβCd), β-cyclodextrin sulfobutyl ether, sodium salt ($(SBE)_{7m}$-βCd), acetyl β-cyclodextrin (AcβCd) and acetyl γ-cyclodextrin (AcγCd). Modifications of thermal parameters of NAP in DSC curves of physical mixtures indicate heating-induced interactions which resulted in a broadening of the NAP melting endotherm in the combinations with HPβCd, AcβCd and AcγCd. The effect of kneading on the interaction was particularly pronounced for the NAP–HPβCd and NAP–$(SBE)_{7m}$-βCd systems, which show a similar drug-to-carrier interaction ratio (1:2 by weight) as that of the other systems. Drug-to-carrier ratios, calculated considering the amount of NAP which recrystallizes from the melted mixtures equivalent to NAP not bound to the carrier, show a distinctly lower affinity in solid-state of the drug for the anionically charged $(SBE)_{7m}$-βCd with respect to other neutral carriers. The similar affinity of NAP for AcβCd and AcγCd demonstrates that the geometry of the cavity, which is a determinant factor for the inclusion complexation in liquid state, does not influence the interaction process in solid-state.

Keywords: Naproxen; β-Cyclodextrin sulfobutyl ether; Hydroxypropyl β-cyclodextrin; Acetyl-β-cyclodextrin; Acetyl-γ-cyclodextrin; Differential scanning calorimetry; Thermogravimetric analysis

1. Introduction

Solid-state interactions of crystalline drugs with pharmaceutical adjuvants which lead to modification of some physical properties of the drug (e.g. crystallinity or melting point) make differential scanning calorimetry (DSC) a useful tool for investigating the interaction process. Grinding or kneading of drug–cyclodextrin (Cd) combinations may give products which do not show the same DSC melting endotherm as that recorded for the same, untreated combination. In cases where decreases in fusion enthalpy of the pure drug as

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a function of the relative amount of Cd are recorded, the interaction stoichiometry can be often determined [1,2]. In combinations of drugs with amorphous Cds, however, the melting temperature and specific fusion enthalpy can result lower than those of the drug alone even in simple physical mixtures [3–7]. Heating-induced drug–Cd interactions during DSC scans which lead to a loss of drug crystallinity are to be invoked for explaining this phenomenon, which is apparently as more pronounced as higher is the relative amount of Cd present in the mixture. Amorphous βCd derivatives such as hydroxypropyl βCd (HPβCd) and βCd sulfobutyl ether, sodium salt ((SBE)$_{7m}$-βCd) or Captisol are currently available for use in pharmaceutical products [8], and amorphous acetyl βCd (AcβCd) and acetyl γCd (AcγCd) derivatives were recently studied as possible carriers for solid dispersions [9]. We thought worth of interest to investigate from the quantitative point of view the solid-state interaction capacity of such Cds with crystalline drugs. Naproxen (NAP), a poorly water soluble drug ($\approx$ 27 μg ml^{-1} at pH $\approx$ 6 and 25 °C) whose thermal stability and tendency to recrystallize from the melt are known [10], was chosen as a model drug. NAP–Cd physical mixtures and kneading products containing 0.90–0.10 mass fraction of NAP were analyzed by DSC and subjected to thermal cycles (i.e. heating, cooling down and heating a second time) to gain information on the interaction stoichiometry. Comparison of the affinities in solid-state for NAP with HPβCd, (SBE)$_{7m}$-βCd, AcβCd and AcγCd with those in liquid state, expressed in terms of binding constant values of the respective inclusion complexes [9,11], may shed light on the role of molecular parameters (cavity size, nature of substituent, etc.) in the solid-state interaction with NAP.

2. Experimental

2.1. Materials

NAP from Sigma Chemical Company (St. Louis, MO, USA) was recrystallized twice from ethanol. HPβCd with an average degree of substitution per anhydroglucose unit, of 0.65 (which corresponds to $\approx$4.6 hydroxypropyl substituents per macrocycle), and AcβCd and AcγCd with an average degree of substitution per anhydroglucose unit, respectively of 1.1 and 0.95 (both corresponding to $\approx$7.7 acetyl substituents per macrocycle) were kindly provided by Wacker Chemie GmbH (München 70, G). Randomly substituted amorphous (SBE)$_{7m}$-βCd with an average degree of $\approx$ 6.4 sulfobutyl ether substituents per macrocycle, was kindly provided by CyDex, Inc. (Overland Park, KS). Their physicochemical features were: (a) HPβCd (CAVASOL W7 HP): molecular weight 1399; water content by TGA (see below) 3.8 $\pm$ 0.2% (w/w) (three runs), corresponding to $\approx$ 3.1 mol H_2O per HPβCd mol; apparent density 350 kg m^{-3}; aqueous solubility 2300 g l^{-1} at 24 °C; (b) AcβCd (CAVASOL W7 A): average molecular weight 1459; water content by TGA (see below) 2.8 $\pm$ 0.2% (w/w) (three runs), corresponding to $\approx$2.3 mol H_2O per AcβCd mol; apparent density 240 kg m^{-3}; aqueous solubility 2600 g l^{-1} at 25 °C; (c) AcγCd (CAVASOL W8 A): average molecular weight 1616.5; water content by TGA (see below) 3.2 $\pm$ 0.2% (w/w) (three runs), corresponding to $\approx$3 mol H_2O per AcγCd mol; and (d) (SBE)$_{7m}$-βCd (CAPTISOL): average molecular weight 2146; water content by TGA (see below) 8.5 $\pm$ 0.2% (w/w) (three runs), corresponding to $\approx$ 11 mol H_2O per (SBE)$_{7m}$-βCd mol.

All other materials and solvents were of analytical reagent grade.

2.2. Preparation of NAP/Cd binary systems

Physical mixtures of NAP (< 180 μm sieve granulometric fraction) with each Cds (< 180 μm sieve granulometric fraction) ranging from 0.90 to 0.10 NAP mass fraction were prepared by simple homogeneization of the powders by turbula mixing for 10 min. Physical mixtures were wetted in a mortar with the minimum volume (2 ml g^{-1}) of ethanol and thoroughly ground with a pestle to obtain a paste which was then dried at 50 °C in a hot air oven up to constant weight.

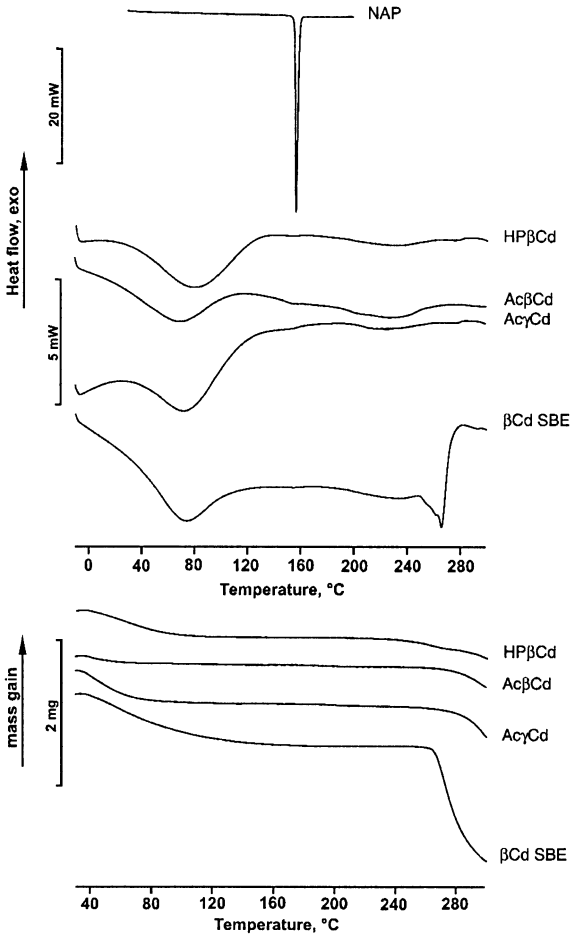

Fig. 1. DSC (upper curves) and TGA (lower curves) of individual components.

2.3. Differential scanning calorimetry (DSC)

Temperature and enthalpy values were measured with a METTLER STAR^{e} system equipped with a DSC821^{e} Module and an Intracooler device for subambient temperature analysis (Julabo FT 900) on 3–5 mg (Mettler M3 Microbalance) samples in aluminium pans with pierced lids under static air. An empty pan was used as reference. The heating rate was 10 K min^{-1} over the 30–200 °C range for NAP and its combinations with Cds and the −10–300 °C range for the individual Cds. Cyclic heat-cooling (30–200–30–200 °C) runs were also performed. Heat of fusion measurements of NAP in drug-carrier combinations were carried out in triplicate.

2.4. Thermogravimetric analysis (TGA)

Mass losses were recorded with a Mettler TA 4000 apparatus equipped with a TG 50 cell at the heating rate of 10 K min^{-1} on 7–10 mg samples in open alumina crucibles in the 30–300 °C temperature range under static air. Measurements were carried out for Cds in triplicate.

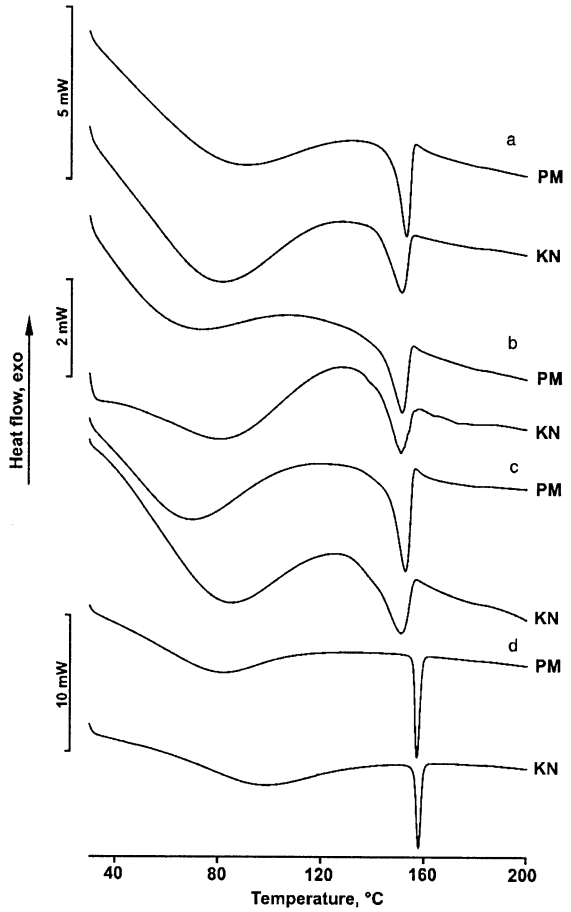

Fig. 2. DSC curves of: (a) NAP–HPβCd; (b) NAP–AcβCd; (c) NAP–AcγCd; and (d) NAP–$(SBE)_{7m}$-βCd systems at the 0.20 NAP mass fraction (PM, physical mixtures; KN, kneading products).

3. Results and discussion

Thermal analysis indicated the crystalline, anhydrous state of NAP [12] ($T_{onset} = 155.8 \pm 0.13$ °C, $T_{peak} = 156.8 \pm 0.17$ °C, enthalpy of melting = 142.5 ± 1.3 J g^{-1} (six runs)) and the amorphous nature of all the Cds tested (Fig. 1). TGA mass losses over the 30–120 °C range of ≈3% (w/w) for HPβCd, AcβCd, AcγCd and of ≈8% (w/w) for $(SBE)_{7m}$-βCd (see Section 2.1) were due to evaporation of loosely bound water, whereas those at higher temperatures to sample decomposition. As can be seen in Fig. 2, broadening of the melting endotherm of NAP was evident in physical mixtures with HPβCd (a), AcβCd (b) and AcγCd (c), but it did not appear particularly modified in the respective kneading products. By plotting the enthalpy values per unit mass of NAP in the NAP–Cd systems, ΔH_{NAP}, as a function of NAP mass fraction in the respective combinations, the trend shown in Fig. 3 was observed. For the systems with AcβCd and AcγCd, a linear decrease in ΔH_{NAP} at decreasing NAP mass fraction with an abrupt change in slope around 0.33 NAP mass fraction can be seen. A similar behaviour was observed for the NAP-HPβCd and NAP–$(SBE)_{7m}$-βCd kneaded products, whereas there was no break point in the line of the respective physical mixtures. This thermal behaviour suggests that during DSC scans, some type of heating-induced interaction takes place between NAP and Cd which apparently results in broadening of the melting endotherm and loss of NAP crystallinity [4,5,13]. No substantial differences were observed for NAP-AcβCd and NAP–AcγCd systems before and after kneading, probably because a complete heating-induced interaction occurs. In the systems with HPβCd and $(SBE)_{7m}$-βCd, instead, thermal

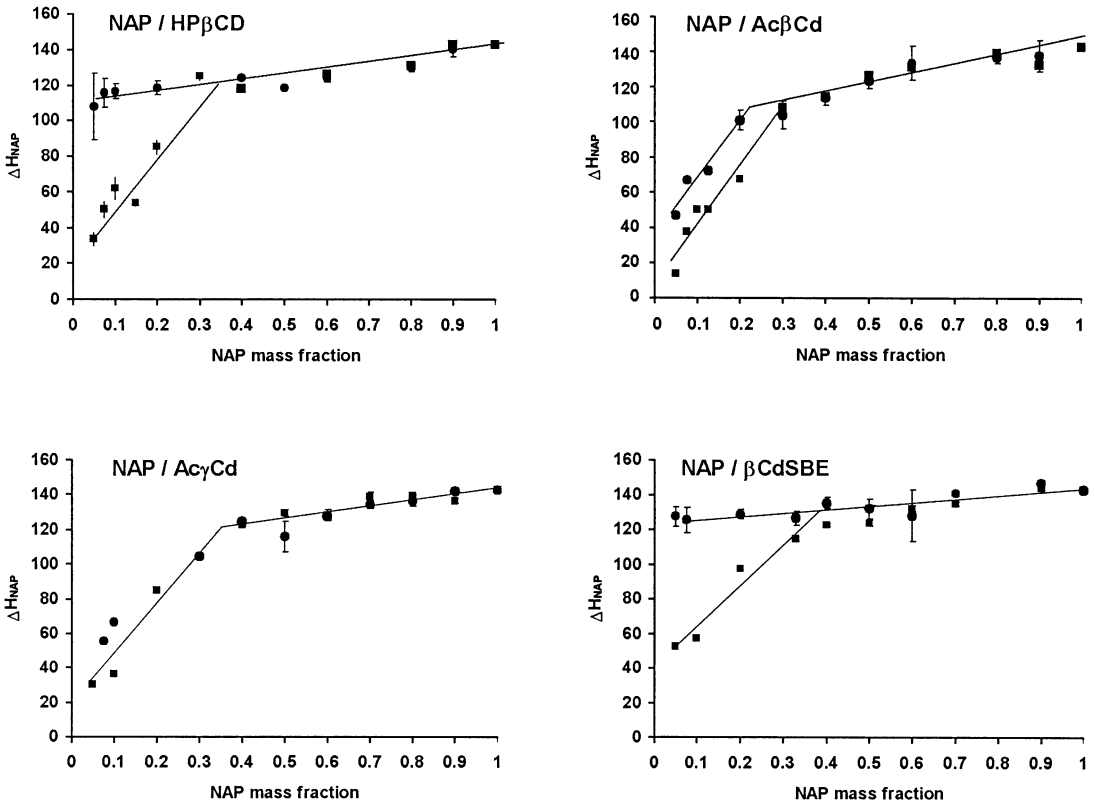

Fig. 3. Enthalpy per unit mass of NAP (ΔH_{NAP}) vs NAP mass fraction interaction plots for the NAP–HPβCd, NAP–AcβCd, NAP–AcγCd and NAP–$(SBE)_{7m}$-βCd systems (●, physical mixtures; ■, kneading products).

energy uptake is not high enough to carry out interaction in the mixtures at ≤ 0.33 NAP mass fraction and a contribution of mechanical energy is necessary. From a purely phenomenological point of view, it could be thought that a sort of saturation of the NAP/Cd interaction capability is reached when the NAP content in the mixture is about 33% (w/w). To gain further insight on NAP-amorphous Cd affinity in solid-state, thermal cycles were performed on both physical and kneaded mixtures by heating to 200 °C, cooling down to 30 °C, and heating a second time to 200 °C (Fig. 4). Solidification and remelting of NAP, whose thermal stability and tendency to recrystallize from the melt are known [10], occur in preparations containig ≥ 0.40 mass fraction of NAP for NAP–HPβCd, NAP–AcβCd and NAP–AcγCd systems, and even at very lower drug mass fractions for the NAP–$(SBE)_{7m}$-βCd system (see Fig. 4d′). If one assumes that the recrystallized NAP corresponds to the amount of drug which is not bound to Cd, i.e. to the amount of free NAP in the mixture after interaction, an analogous equation to that reported in Ref. [1] can be derived (see Section 3.1 paragraph). Fig. 5 reports the theoretical curves calculated using this equation along with the experimental DSC data. Drug-to-carrier ratios of 1:1 (w/w) for NAP–HPβCd, 2:3 (w/w) for both NAP–AcβCd and NAP–AcγCd, and 1:10 (w/w) for NAP–$(SBE)_{7m}$-βCd comelted systems revealed that the neutral HPβCd (as well as neutral AcβCd and AcγCd) were a better 'solvent' for NAP than the anionically charged $(SBE)_{7m}$-βCd, i.e. a lower affinity for NAP with $(SBE)_{7m}$-βCd with respect to HPβCd in solid-state. In a comparative study on the inclusion complexation in aqueous solution the binding constant for NAP with $(SBE)_{7m}$-βCd ($(3.6 \pm 0.9) \times 10^3$ l mol^{-1}) was more than twice that with HPβCd ($(1.7 \pm 0.8) \times 10^3$ l mol^{-1}) [11], i.e. the affinity for NAP with $(SBE)_{7m}$-βCd was stronger than that with HPβCd. In an anologous investigation on NAP with AcβCd and AcγCd, the affinity in liquid state for NAP with AcβCd ($K_{1:1,25\ °C} = 4.5(4) \times 10^3$ l mol^{-1}) was about six times stronger than that with AcγCd ($K_{1:1,25\ °C} = 0.80(7) \times 10^3$ l mol^{-1}) [9], in spite of the similar affinity for NAP with the same partners displayed in solid-state.

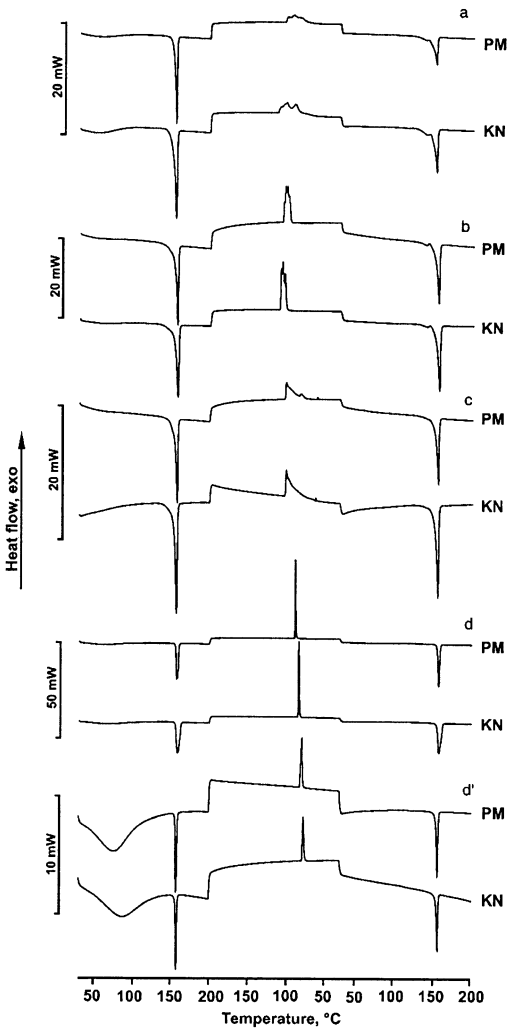

Fig. 4. Cyclic heat-cooling DSC runs for: (a) NAP–HPβCd; (b) NAP–AcβCd; (c) NAP–AcγCd; (d) NAP–$(SBE)_{7m}$-βCd systems at the 0.80 NAP mass fraction and (d′) NAP–$(SBE)_{7m}$-βCd systems at the 0.20 NAP mass fraction (PM, physical mixtures; KN, kneading products).

3.1. Background

Let w_D and w_C be the grams, respectively of drug (NAP) and carrier (Cd) in the physical mixture where excess NAP with respect to the NAP-to-Cd (by weight) interaction ratio R is present. After the components have interacted, the grams of free NAP in the mixture, w_D^{free}, will be given by

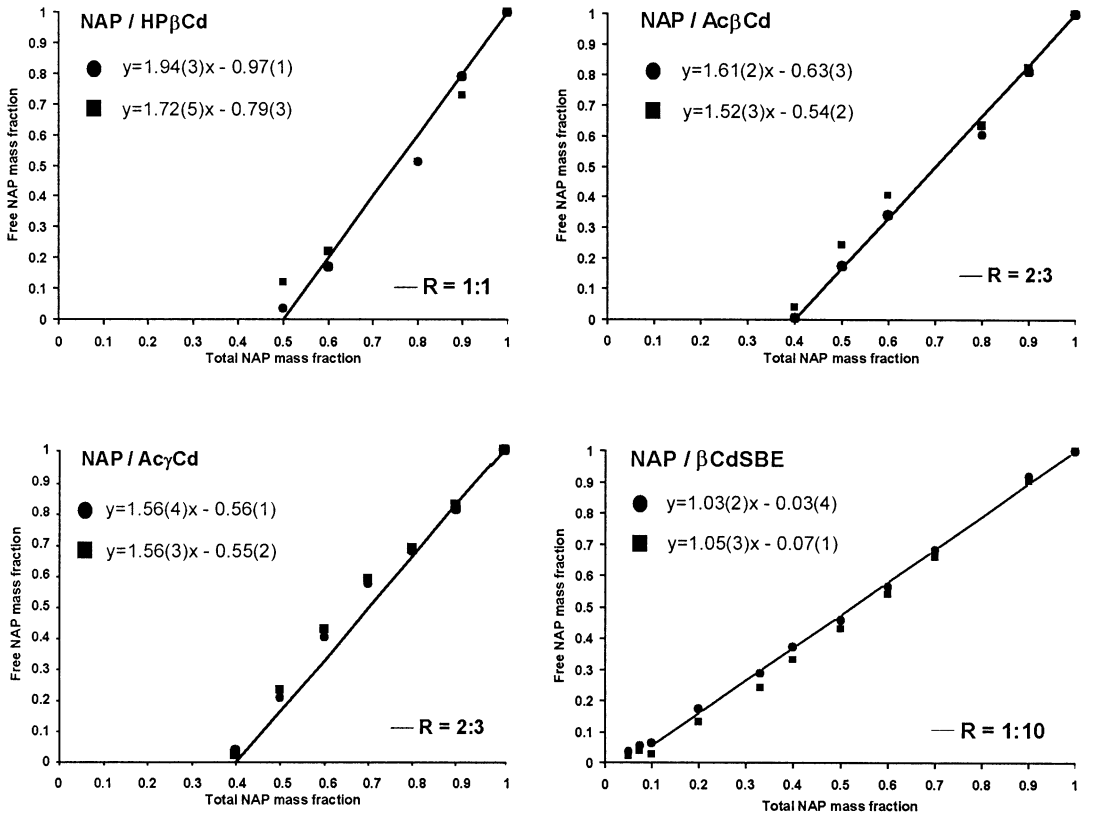

Fig. 5. Free NAP mass fraction vs total NAP mass fraction interaction plots for the NAP–HPβCd, NAP–AcβCd, NAP–AcγCd and NAP–$(SBE)_{7m}$-βCd comelted systems. Theoretical lines calculated from Eq. (5) (see Section 3.1) for the indicated NAP-to-Cd (by weight) interaction ratio R are drawn. Least-squares linear regression equations for comelted physical mixtures (●) and kneading products (■) are reported (standard uncertainties in brackets).

$$w_D^{free} = w_D - w_C R, \tag{1}$$

where

$$w_C R = w_D^{bound}, \tag{2}$$

are the grams of NAP which has interacted with Cd. Because all Cd interacted, no free Cd will be present ($w_C^{free} = 0$) and the grams of interacted Cd will correspond to those present in the physical mixture, i.e.

$$w_C^{bound} = w_C. \tag{3}$$

The mass fraction of NAP which remains in the free state in the mixture after interaction, ω_D^{free}, is given by

$$\omega_D^{free} = \frac{w_D^{free}}{w_D^{free} + w_D^{bound} + w_C^{free} + w_C^{bound}} = \frac{w_D - w_C R}{w_D + w_C} = \omega_D - \omega_C R, \tag{4}$$

which, being $\omega_D + \omega_C = 1$, can be rearranged to

$$\omega_D^{free} = (1 + R)\omega_D - R. \tag{5}$$

From Eq. (5), which bears a physical meaning provided that $w_D/w_C \geq R$ and $\omega_D^{free} \geq 0$, by plotting ω_D vs ω_D^{free} a straight line with $(1+R)$ slope and $-R$ intercept is obtained. This line intersects the X-axis in correspondence with the mass fraction of NAP which has interacted with Cd.

4. Conclusion

The nature of the substituent of the amorphous βCd derivatives tested influences their interactions with NAP in both liquid and solid-state. Anionically charged $(SBE)_{7m}$-βCd, which has been reported also as a useful freeze-drying pharmaceutical excipient [14], is less prone to solid-state interaction than other neutral carriers in physical mixtures by heating or kneading. The geometry of the Cd cavity, which is a determinant factor for the inclusion complexation in liquid state of NAP with AcβCd and AcγCd, seems not to influence the interaction process in solid-state. Dispersion of NAP crystals onto the Cd surface rather than inclusion into the Cd cavity in physical mixtures by heating or kneading can be therefore considered responsible for weakening of some O–H···O type hydrogen bonds involved in molecular packing of NAP and formation of crystallites with lower melting point and heat of fusion than intact NAP crystals.

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References

[1] F. Giordano, G. Bruni, G.P. Bettinetti, J. Thermal Anal. 38 (1992) 2683–2691.
[2] F. Giordano, G.P. Bettinetti, M. Rillosi, A. Gazzaniga, Boll. Chim. Farm. 132 (1993) 75–77.
[3] G.P. Bettinetti, A. Gazzaniga, P. Mura, F. Giordano, M. Setti, Drug Dev. Ind. Pharm. 18 (1992) 39–53.
[4] P. Mura, G.P. Bettinetti, F. Melani, A. Manderioli, Eur. J. Pharm. Sci. 3 (1995) 347–355.
[5] F. Melani, G.P. Bettinetti, P. Mura, A. Manderioli, J. Inclusion Phenom. Mol. Recognit. Chem. 22 (1995) 131–143.
[6] P. Mura, G.P. Bettinetti, A. Manderioli, M.T. Faucci, G. Bramanti, M. Sorrenti, Int. J. Pharm. 166 (1998) 189–203.
[7] P. Mura, G.P. Bettinetti, M.T. Faucci, M. Sorrenti, A. Negri, Supramol. Chem. 12 (2001) 379–389.
[8] D.O. Thompson, Crit. Rev. Therap. Drug Carrier Syst. 14 (1997) 1–104.
[9] G.P. Bettinetti, S. Rossi, F. Ferrari, M. Sorrenti, P. Carraro, Proceedings of the 10th International Cyclodextrin Symposium, Wacker Biochem. Corp., Adrian, Mich., 2001, pp. 365–370.
[10] G.P. Bettinetti, P. Mura, F. Giordano, M. Setti, Thermochim. Acta 199 (1991) 165–171.
[11] K. Okimoto, R.A. Rajewski, K. Uekama, J.A. Jona, V.J. Stella, Pharm. Res. 13 (1996) 256–264.
[12] G.P. Bettinetti, M. Sorrenti, A. Negri, P. Mura, M.T. Faucci, M. Setti, in: J.J. Torres Labandeira, J.L. Vila-Jato (Eds.), Proceedings of the 9th International Symposium on Cyclodextrins, Kluwer Academic, The Netherlands, 1999, pp. 367–370.
[13] K.H. Kim, M.J. Frank, N.L. Henderson, J. Pharm. Sci. 74 (1985) 283–289.
[14] D.Q. Ma, R.A. Rajewski, V.J. Stella, S.T.P. Pharma Sci. 9 (1999) 261–266.