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Interactions of Nabumetone with Cyclodextrins in Solution and in the Solid State

NEREA GOYENECHEA, MIGUEL SÁNCHEZ*, ITZIAR VÉLAZ, CARMEN MARTÍN, CRISTINA MARTÍNEZ-OHÁRRIZ and ARANTXA ZORNOZA

Departamento de Química y Edafología (Sección Química-Física) Facultad de Ciencias, Universidad de Navarra, 31080 Pamplona, Spain

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Abstract

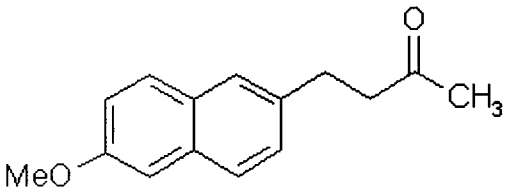
The interactions of nabumetone (NAB) with α-cyclodextrin (α-CD) and γ-cyclodextrin (γ-CD) were studied in aqueous solution by means of phase-solubility analysis. Solid dispersions of NAB with α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), methylβ- (Mβ-CD), hydroxypropylβ-cyclodextrin (HPβ-CD) were prepared by coevaporation and kneading and also by coprecipitation in the case of γ-CD. X-ray diffractometry, thermal analysis and infrared spectroscopy (FTIR) were used to study the possibility of complexation of the drug with the different cyclodextrins. Solid dispersions of nabumetone with γ-CD showed a remarkable improvement in the dissolution rate of nabumetone.

Introduction

Nabumetone ((4,6-methoxy-2-naphthyl)-butan-2-one) (NAB) (Scheme 1) is a non-acidic non-steroidal anti-inflammatory prodrug. This substance is metabolised to an active metabolite (6-methoxy-2-naphthylacetic acid (6-MNA)) which is a relatively selective cyclooxygenase-2 inhibitor and has anti-inflammatory and analgesic properties. NAB is well tolerated in patients with osteoarthritis and rheumatic diseases. This drug is poorly soluble in water.

α-, β- and γ-cyclodextrins are torus-like macrorings built up from six, seven and eight units of glucopyranose, respectively. β-CD is the most rigid cyclodextrin structure and shows a lower solubility in water. Randomly methylated (Mβ-CD) and hydroxypropylated (HPβ-CD) derivatives show higher solubility so their amorphous character.

The apparent stability constants of nabumetone with β-, Mβ- and HPβ-cyclodextrins in solution were calculated by us from spectrofluorimetric measurements in a previous work [1]. In this study, the interactions in solution of nabumetone with α- and γ-CD have been determined by means of phase solubility analysis and the possible complexes of nabumetone with the different cyclodextrins were prepared by coevaporated and kneading methods and also by coprecipitation in the case of γ-CD.



Scheme 1. Chemical structure of nabumetone.

Experimental

Material

Nabumetone (NAB) was obtained from SIGMA, β-CD from LAISA (Levantina Agrícola Industrial, S.A., Barcelona, Spain), Mβ-CD and HPβ-CD from RBI (Research Biochemicals International, Natick, USA) and α- and γ-CD from Wacker Chemie GmbH. All materials and solvents were of analytical reagent grade.

Methods

Solubility studies

Solubility measurements in unbuffered aqueous solution (pH $\approx$ 6) in the absence and in the presence of α-CD (0.12×10^{-2} to 1.5×10^{-2} M) and γ-CD (0.03×10^{-2} to 1.5×10^{-2} M) were carried out by adding to the solutions excess amounts of NAB. The solutions were shaken at 25 °C for 24 h. After equilibrium, the solutions were filtered and the concentrations of NAB were determined spectrophotometrically at 228 nm. The presence of ligands did not interfere in the absorption measurements. The apparent stability constant and

* Author for correspondence. E-mail: misango@unav.es

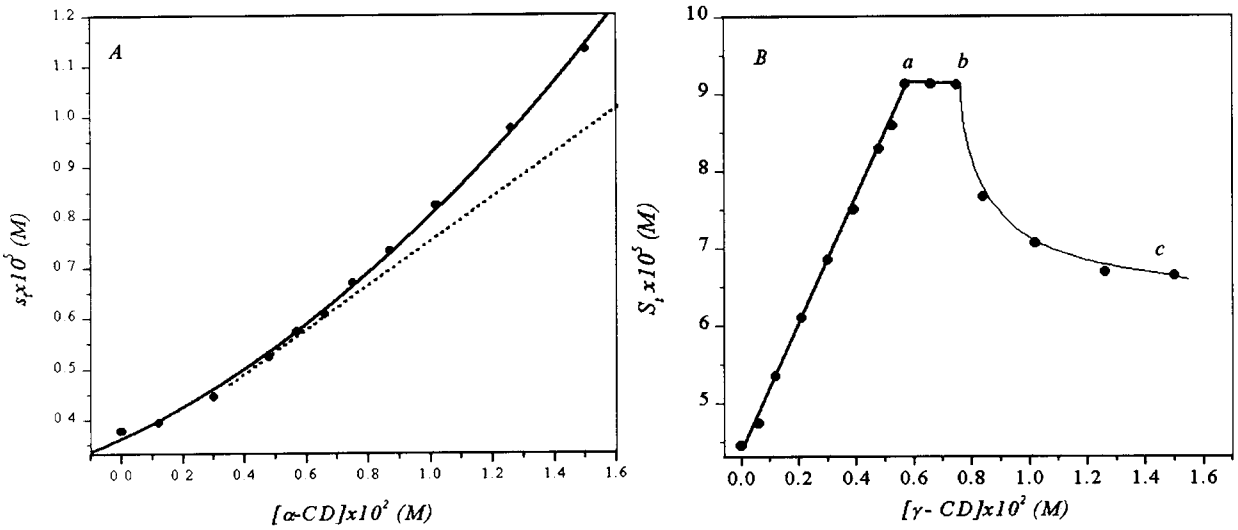


Figure 1. Phase solubility diagrams of nabumetone (NAB) with α-C (A) and γ-CD (B) in aqueous solution at 25 °C.

the stoichiometry were calculated from the phase solubility diagrams [2].

Preparation of solid dispersions

Solid dispersions of the different cyclodextrins and NAB were prepared in 1:1 molar ratio. The kneaded product (KN) was obtained by wetting the cyclodextrin with a minimum volume of a 50% V/V mixture of ethanol and water to obtain a paste with NAB which was subsequently dried at 60 °C. The coevaporated product (CE) were prepared by mixing hydroalcoholic solutions (ethanol/water 50% V/V) of NAB and the different cyclodextrins. The resulting mixture was stirred and the solvent was eliminated under vacuum in a rotatory evaporator at 80 °C and the system was dried at 70 °C. The coprecipitated product (CP) in the case of NAB:γ-CD dispersion was obtained from the point *c* of the Bs type solubility diagram (Figure 1B).

The solid dispersions have been studied by comparison with the corresponding physical mixtures (PM).

Characterisation of solid dispersions

X-ray diffraction. X-ray diffraction patterns were recorded using a Brucker D8 Advance diffractometer, according to the diffraction powder method, with a $CuK_{\alpha 1}$ radiation, 40 kV voltage, 30 mA current, 0.02 increment and 1 sec/step and sweep 2 to 50° 2θ.

Thermal analysis (TGA and DTA). The thermal analysis were performed with a simultaneous SDTA/TGA 851^e Mettler Toledo thermal analyzer. The thermal behaviour was studied by heating about 5 mg of the sample at a scan rate of 10 °C/min in a pierced aluminia crucible under static air atmosphere. The measurements were made in triplicate.

FT-IR. Infrared spectra were obtained with a Nicolet Mod. Avatar 360 infrared spectrophotometer using the KBr pellet technique.

Dissolution studies

Dissolution rates were determined according to the disc method described by Wood *et al.* [3]. For this purpose, the samples were compressed by a hydraulic press for KBr discs for infrared spectroscopy. The dissolution tests were performed according to the USP 25 NF 20 [4] paddle method with a Sotax AT 7 Smart dissolution testing apparatus. Every experiment was conducted under the following conditions: 900 mL of aqueous solution as a dissolution medium maintained at 37 ± 0.1 °C and 100 rpm stirrer. The samples were filtered through Whatman glass microfibre filters and the NAB concentration was spectrophotometrically determined at 228 nm, using an Agilent 8453 spectrophotometer. Dissolution runs for all samples were performed at least six times and the mean values of the dissolved drug were reported.

Results and discussion

Solubility studies

An Ap type [2] equilibrium phase solubility diagram was displayed with α-CD (Figure 1A). The non-linear plot with concave-upward curvature means that at least one complex is present having a stoichiometry > 1 with respect to the ligand. In this case the non-linear fit of the data allows to calculate the apparent constants ($K_{1:1}$ and $K_{1:2}$) for complexes of stoichiometry 1:1 and 1:2 by the following equation (Equation (1))

$$S_t = s_0 + s_0 K_{11}[\alpha\text{-CD}] + s_0 K_{11} K_{12}[\alpha - CD]^2. \quad (1)$$

The values of $K_{1:1}$= 77.3 ± 6.8 M^{-1} and $K_{1:2}$ = 57.7 ± 6.0 M^{-2} obtained for the complexes suggest a weak interaction between NAB and α-CD because naphthalene is too bulky for α-CD cavity [5].

In the system with γ-CD the pattern was of Bs type because of precipitation of an insoluble complex at high

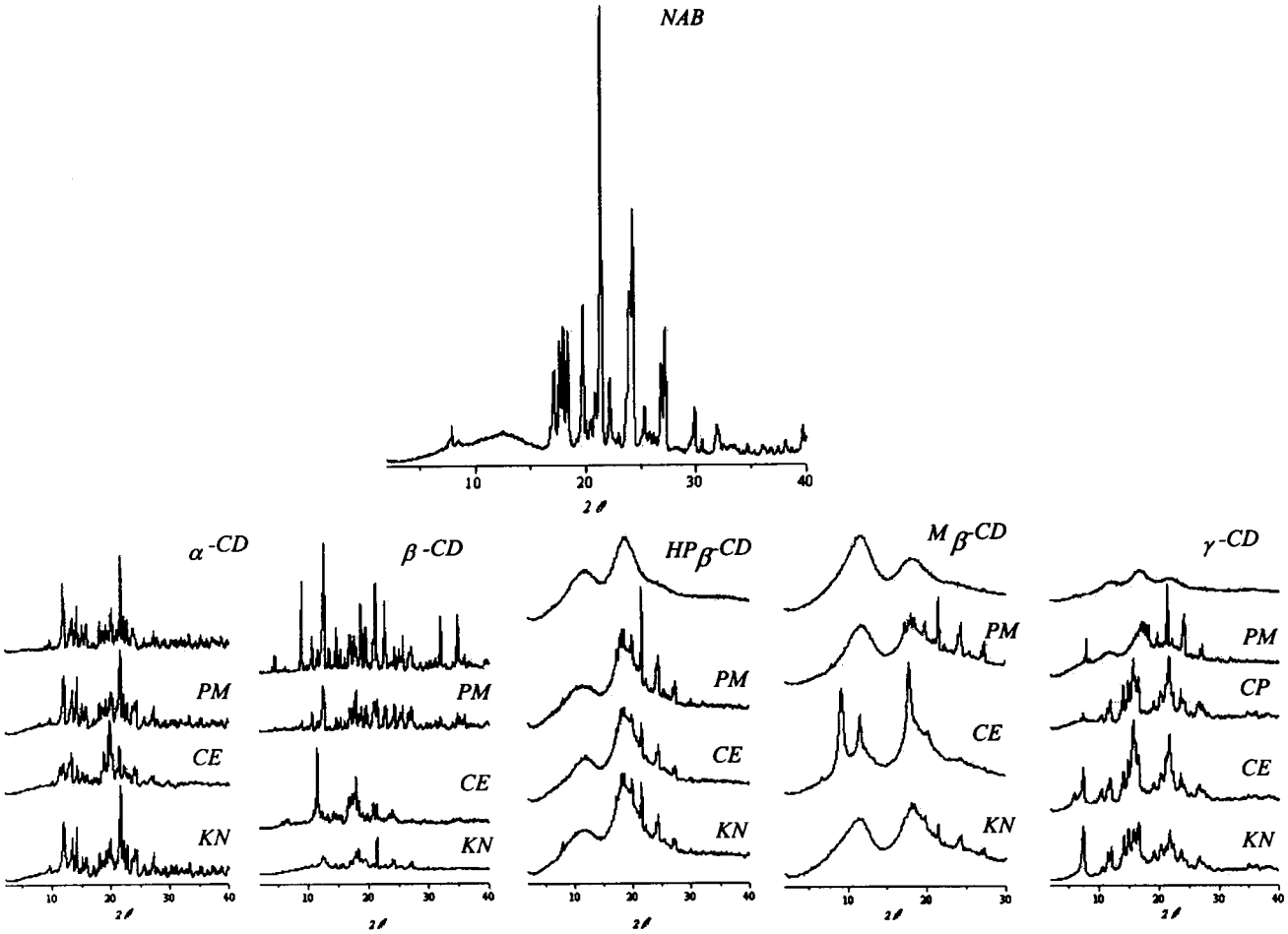


Figure 2. X-ray diffraction patterns of single components and equimolar physical mixtures (PM), coevaporated (CE), kneading products(KN) and coprecipitated (CP) products.

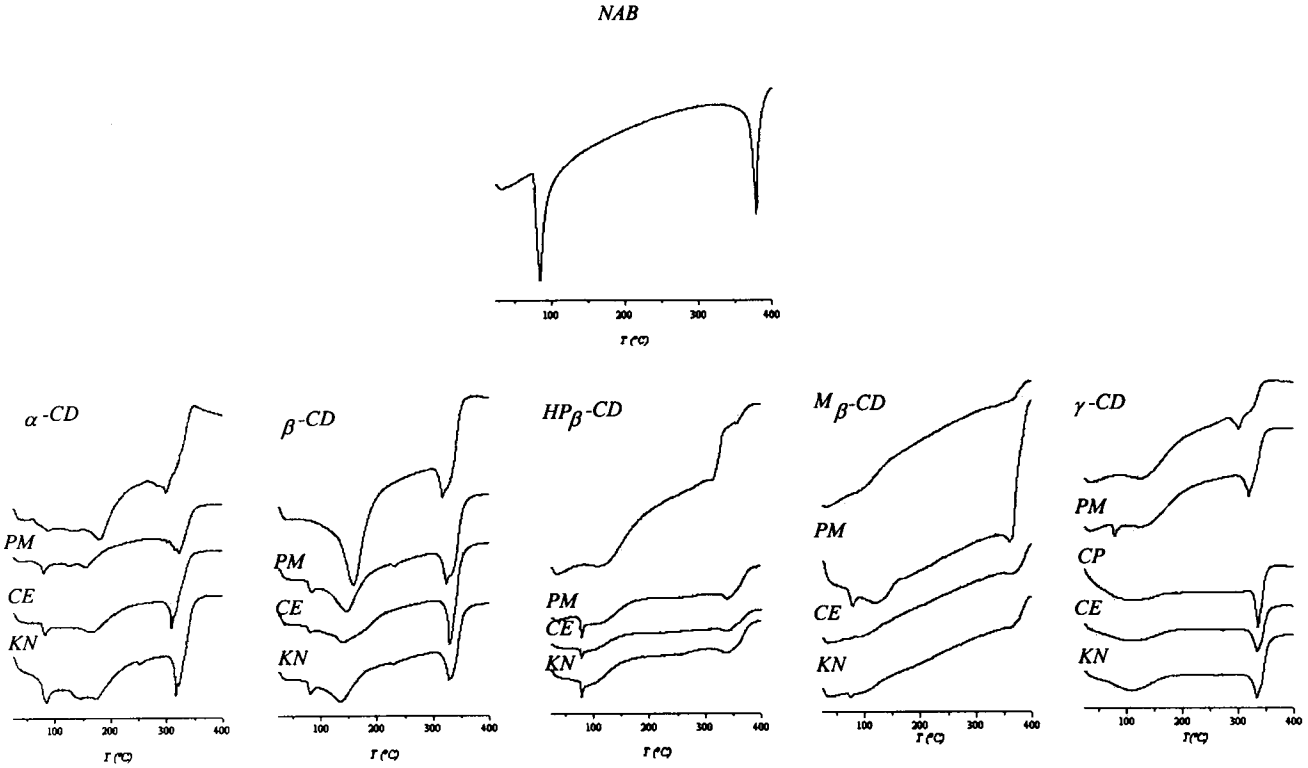


Figure 3. DTA thermograms of nabumetone (NAB), α-CD, β-CD, Mβ-CD, HPβ-CD and γ-C and their respective physical Mixtures (PM), coevaporated (CE), kneaded (KN) and coprecipitated (CP) systems.

concentrations of the carrier (Figure 1B). Calculation of the stoichiometry was made from the plateau data (Equation (2))

$$\text{molar ratio} = \frac{[\text{NAB}]_t - [\text{NAB}]_a}{[\gamma - \text{CD}]_b - [\gamma - \text{C}]_a}, \qquad (2)$$

where $[\text{NAB}]_t$ is the total concentration of NAB in the solution and $[\text{NAB}]_a$, $[\gamma\text{-CD}]_a$ and $[\gamma\text{-CD}]_b$ the concentrations of NAB and γ-CD in points a and b respectively. The calculated value was 1:1. The apparent 1:1 stability constant, calculated from the straight portion of the diagram (Figure 1B), was $K_{1:1} = 219 \pm 1\ M^{-1}$ (Equation (3))

$$S_t = s_0 + \frac{K_{11} s_0 [\gamma\text{-CD}]_t}{1 + K_{11} s_0}. \qquad (3)$$

The low stability constant given by the NAB:γ-CD complex suggests weak interactions which would result in premature release of the drug from the γ-CD cavity [6].

Characterisation of solid dispersion

X-ray diffraction

The diffraction patterns of the physical mixture and kneaded product of NAB with α-CD correspond to a superimposition of both components (Figure 2). The coevaporated pattern profile is different to that of the physical mixture, but this fact can be attributed to a change in α-CD crystallinity obtained when the solvent is evaporated.

The diffraction pattern of NAB:β-CD coevaporated system shows some significant differences with respect to physical mixture and kneaded product (Figure 2). The appearance of a new reflection at 11.5°2θ and the decrease of intensity of other peaks suggest changes of crystallinity due to a partial inclusion of NAB in β-CD cavity.

The X-ray diffractograms of NAB:HPβ-CD showed peaks corresponding to the drug and the carrier, indicating that NAB retained its crystalline nature in these systems (Figure 2).

The NAB:Mβ-CD dispersion prepared by kneading presents a similar diffraction pattern as the physical mixture. The coevaporated product showed new peaks with high intensity at 9.13; 11.5 and 17.7°2θ indicating the formation of a crystalline complex (Figure 2).

The NAB:γ-CD coevaporated and coprecipitated products showed similar diffraction patterns which differ significantly with that of the physical mixture (Figure 2). The presence of new peaks with high intensity at 7.5; 11.9; 14.1; 14.9; 15.8; 16.6; 21.7 and 23.6°2θ in the coprecipitated and coevaporated products and with reduced intensity in the kneaded dispersion, suggests the formation of a new solid phase with high crystallinity.

Thermal analysis

The DTA of NAB showed two sharp endotherms (Figure 3), the first corresponding to the melting point, centered at 83–84 °C and the second associated to the descomposition process at 377–378 °C with a total loss of mass (>99%) detected by TGA. The melting endotherm and also the superimposition of descomposition endotherms corresponding to NAB and CD were observed in NAB:α-CD and NAB:HPβ-CD systems (Figure 3). A complete disappearance of the melting endotherm of NAB was seen in the coevaporated with Mβ- and γ-CD and also in the coprecipitated and kneaded dispersions with γ-CD (Figure 3). The results are consistent with complex formation. The melting endotherm of NAB is reduced in the dispersion prepared by coevaporation method with β-CD, suggesting the possibility of a partial inclusion of NAB in β-CD cavity.

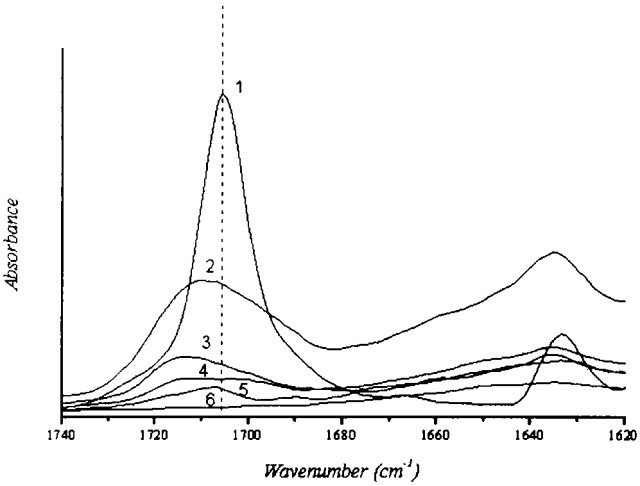


Figure 4. FTIR spectra of single components and equimolar physical mixtures (PM) and coevaporated (CE), kneaded (KN) and coprecipitated products with γ-CD (1: NAB, 6: γ-CD, 5: PH, 2: CE, 4: KN, 3: CP).

FTIR

FTIR was suitable for detection of the interaction with γ-CD (Figure 4). The characteristic ketonic carbonyl stretching band of the pure drug (1705 cm^{-1}) appeared unchanged in the physical mixture and broaded and shifted to a higher frequency (1710 cm^{-1}) in coevaporated, coprecipitated and kneaded products. This effect could be attributed to the breakdown of the intermolecular hydrogen bonds of the crystals [7] associated to the inclusion of the drug monomer into the hydrophobic cavity of the carrier [8].

Dissolution studies

Dissolution profiles of NAB:γ-CD coevaporated (CE) and physical mixture (PM) products in distilled water are showed in Figure 5. Due to the low solubility of NAB, it exhibited a slow rate of dissolution with only 3% released in two hours. The dissolution rate of the physical mixture was considerably greater than that of the pure drug (about 40% of NAB dissolved in 120 min) probably due to the improvement in drug wettability. The CE showed better dissolution properties. After 10 min drug released was approximately 80%. This remarkable improvement in drug dissolution could be attributable to an increase in solubility and wettability of NAB in the solid dispersion due to the complexation.

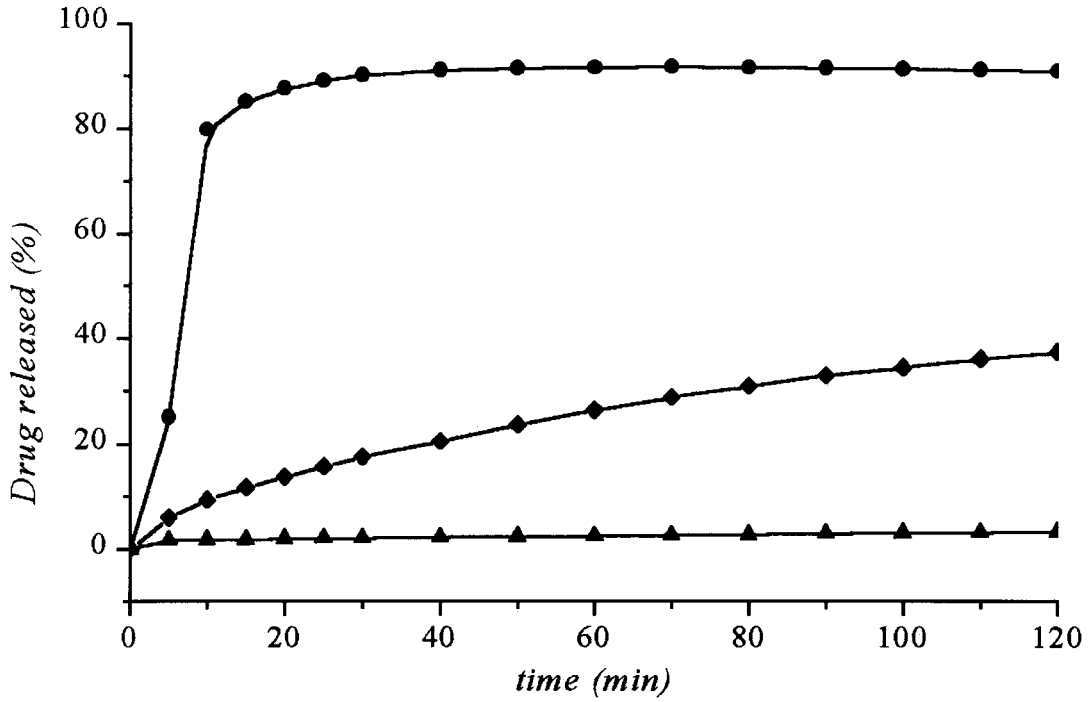


Figure 5. Dissolution profile of coevaporated product (●) and physical mixture (♦) of NAB (▲) with γ-CD in water.

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