Journal of Inclusion Phenomena and Macrocyclic Chemistry **44:** 79–85, 2002.

The Cyclodextrins as Modelling Agents of Drug Controlled Release

CATARINA M. FERNANDES and FRANCISCO J.B. VEIGA*
Laboratory of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, 3000 Coimbra, Portugal

(Received: 7 May 2002; in final form: 1 October 2002)

Key words: drug controlled release, hydrophilic CDs, hydrophobic CDs

Abstract

The controlled release of nicardipine (NC) was achieved by hybridizing its hydrophilic and hydrophobic cyclodextrin (CDs) complexes, i.e., those with hydroxypropyl-β-cyclodextrin (HPβCD) and triacetyl-β-cyclodextrin (TAβCD), respectively. ^{1}H-nuclear magnetic resonance (^{1}H-NMR) was performed to examine the interaction between both CDs and NC in solution. The solid complexes of NC : HPβCD and NC : TAβCD were prepared, in a 1 : 1 molar ratio by the spray-drying method. Complexation in the solid state was demonstrated by differential scanning calorimetry (DSC) and powder X-ray diffractometry. In vitro dissolution studies were carried out in simulated gastric (pH 1.2) and intestinal (pH 6.8) fluids, according to the USP basket method. The ^{1}H-NMR studies provided clear evidence of an interaction between the CDs and the aromatic rings of NC. The DSC thermograms of the solid complexes showed no endothermic peak due to NC melting and their diffraction pattern was completely diffuse, which suggested the formation of a novel type solid phase with an amorphous character. The low dissolution rate of NC, a weak basic drug, in alkaline medium was significantly improved by complexation with HPβCD. In contrast, the *in vitro* release of this drug from the NC : TAβCD complexes was markedly retarded in both dissolution media. An optimal formulation was then designed by the combination, in different molar ratios, of these two complexes. The release behavior of these preparations was investigated and it was observed that the retarding effect was dependent on the amount of the NC : TAβCD complex. In addition, the initial release rate became faster as the molar ratio of the NC : HPβCD complex increased.

Introduction

Hydrophilic CDs derivatives such as methylated, hydroxyalkylated and branched CDs are useful to improve the low solubility, dissolution and bioavailability of poorly water-soluble drugs [1–3]. On the other hand, hydrophobic CDs like ethylated and peracylated derivatives have potential as slow/sustained-release carriers of drugs with short biological half-lives [4–6]. Thus, the critical combination of inclusion complexes obtained with these two kinds of CDs derivatives could be a promising drug delivery system, with a prolonged therapeutic effect.

In this study, NC was chosen as a model drug, since it is known that has a short-elimination half-life with significant fluctuations in plasma drug concentrations. NC bioavailability is very limited (15–40%), and like other dihydropyridine derivatives, its standard formulation undergoes rapid absorption and extensive biotransformation in the liver [7].

The interaction between NC and HPβCD or TAβCD was investigated in solution and in solid phase. In addition, the release behavior of these binary systems, as well the corresponding mixtures in different molar ratio, was evaluated in acidic (pH 1.2) and alkaline (pH 6.8) media.

* Author for correspondence. E-mail: fveiga@ci.uc.pt

Experimental

Materials

NC, HPβCD (Kleptose HPB®, MW∼1300, DS 0.63) and TAβCD were purchased from Effechem SRL (Italy), Roquette (France) and Sigma-Aldrich (Germany), respectively.

^{1}H-NMR studies

The NC : HPβCD and NC : TAβCD samples were prepared in D_2O and C_2D_5OD: D_2O (50 : 50) mixture, respectively. The ^{1}H-NMR spectra of the pure components and their respective mixtures were obtained at 298 K on a Varian Unity-500 spectrometer using a 5-mm reverse detection NMR probe. The resonance at 4.8 ppm due to residual solvents (H_2O and HDO) was used as internal reference. Chemical shits were calculated according to: $\Delta\delta = \delta$ (complex) $- \delta$ (free). The stoichiometry of the NC : CDs inclusion complexes was provided using the continuous variation technique (Job's plot) [8]. For each system, solutions with different CD or NC molar ratio were prepared, where the total molar concentration was kept constant, i.e., 5 mM and 2 mM for the NC : HPβCD and NC : TAβCD system, respectively. Samples were left overnight for equilibration before measurement.

A rotational Overhauser enhancement experiment (ROESY) for detection of intermolecular nuclear Over-

hauser effects (NOEs) between NC and both CDs, was acquired for the 1 : 1 molar ratio at 298 K using the same probe. The ROESY experiments were performed with a mixing time of 500 ms and 100 ms for the NC : HPβCD and NC : TAβCD system, respectively.

Preparation of solid complexes

The NC : HPβCD complex was prepared by spray-drying as previously reported [9]. The NC : TAβCD complex was also prepared by the spray-drying technique. Equimolar quantities of NC and CDs were dissolved in ethanol : water (50 : 50). The resulting mixture was stirred for 24 h at room temperature and the obtained solution was subsequently spray-dried (LabPlant SD-05), under the following conditions: air flow rate – 50 m^3/h; atomising air pressure – 1.0 Bar; inlet temperature – 160 °C, outlet temperature – 85 °C; flow rate of the solution – 400 ml/h. The product was sieved through a 63–160 μm mesh.

Physical mixtures, in 1 : 1 molar ratio, of plain NC and CDs, were also prepared for reference.

Characterization of the solid complexes

DSC studies

DSC measurements were performed on a Shimadzu DSC-50 differential scanning calorimeter. All samples accurately weighed (1 mg of NC or its equivalent) were placed in sealed aluminium pans, before being heated under nitrogen flow (20 ml/min) at a scanning rate of 10 °Cmin^{-1}, from 25 °C to 200 °C (for the NC : HPβCD system) or to 230 °C (for the NC : TAβCD system).

X-ray diffractometry

The powder X-ray diffraction patterns were recorded using a Philips X'Pert, model PW3040/00 diffractometer, with Co as anode material and a graphite monochromator, operated at a voltage of 40 Kv and a current of 35 mA. The samples were analyzed in the 2θ angle range of 5–50° and the process parameters were set as: scan step size of 0.025° (2θ), scan step time of 1.25 s and time of acquisition of 1 h.

Dissolution studies

The dissolution profiles were collected using a Vankel VK7000 apparatus, according to the USP rotating basket method. The dissolution media consisted of 1000 ml of enzyme-free simulated gastric (pH 1.2) and intestinal (pH 6.8) fluids (USPXXIV). Powdered samples (n = 6) containing 30 mg of NC or its equivalent were used. The stirring speed was 100 ± 2 rpm and the temperature was maintained at 37 ± 0.2 °C. At settled time intervals up to 8 hours, the concentration of dissolved drug was automatically determined by UV spectroscopy at 357 nm.

Results and discussion

^{1}H-NMR studies

The drug : CDs interaction in solution was based on the modification of the ^{1}H-RMN spectrum of NC upon complexation. The ^{1}H-NMR spectra reporting the protons of TAβCD, NC, and NC : TAβCD mixture (1 : 1) are presented in Figure 1. Among the different detected signals, those corresponding to the F, O, N and M protons and also the G proton of NC were the most affected ($\Delta\delta$ = 0.016 ppm) by the presence of TAβCD. Similarly, in the NC : HPβCD system (not shown) the F, O, N and M protons and the G proton of NC experienced a pronounced shift variation, i.e., $\Delta\delta$ = 0.020 and 0.025 ppm, respectively.

The stoichiometry for both complexes was established by application of the continuous variation method, which followed the changes in chemical shifts of the G proton, for the NC : HPβCD system, and of the F, O, N and M protons for the NC : TAβCD system (Figure 2). Both plots demonstrated a 1 : 1 stoichiometry, since the maximum was at r_{NC} = 0.5.

From these results, we could propose the coexistence in solution of two different complexes with 1 : 1 stoichiometry, concerning the nitro-phenyl ring and the other phenyl group of the drug. Similar results have been obtained by other authors [10]. This assumption was further confirmed by ROESY experiments (not shown). The ROESY spectra of complexes showed the existence of intermolecular NOEs between several phenyl ring protons (F, O, N, M and G) of NC and the HPβCD protons and also between the drug F, O, N and M protons and the TABCD protons, specially those from the acetyl groups.

Characterization of the solid complexes

The complete disappearance of the NC endothermic peak at ca. 174 °C was observed in the NC : HPβCD spray-dried system (Figure 3). Similarly, the NC : TAβCD complex showed no endothermic peaks, due to the melting of both components (Figure 4). These results suggest the formation of an amorphous solid dispersion, the molecular encapsulation of the drug inside the CD cavity, or both [11].

As shown in Figure 5, the diffractograms of the physical mixtures were constituted practically by the simple superposition of each single component, indicating the presence of NC in the crystalline state. In opposite, the spray-dried systems displayed somewhat diffuse diffraction patterns, indicating the amorphous nature of NC. The presence of a new solid phase with lower crystallinity than the drug may be attributed to an interaction between NC and both CDs, where a possible complexation of NC inside the CDs cavity was contemplated [12], corroborating the DSC observations.

Dissolution studies

The dissolutions profiles of NC and NC : CDs binary systems in simulated gastric (pH1.2) and intestinal (pH 6.8) fluids are presented in Figures 6 and 7, respectively. The dissolution characteristics of NC, a weak basic drug, were

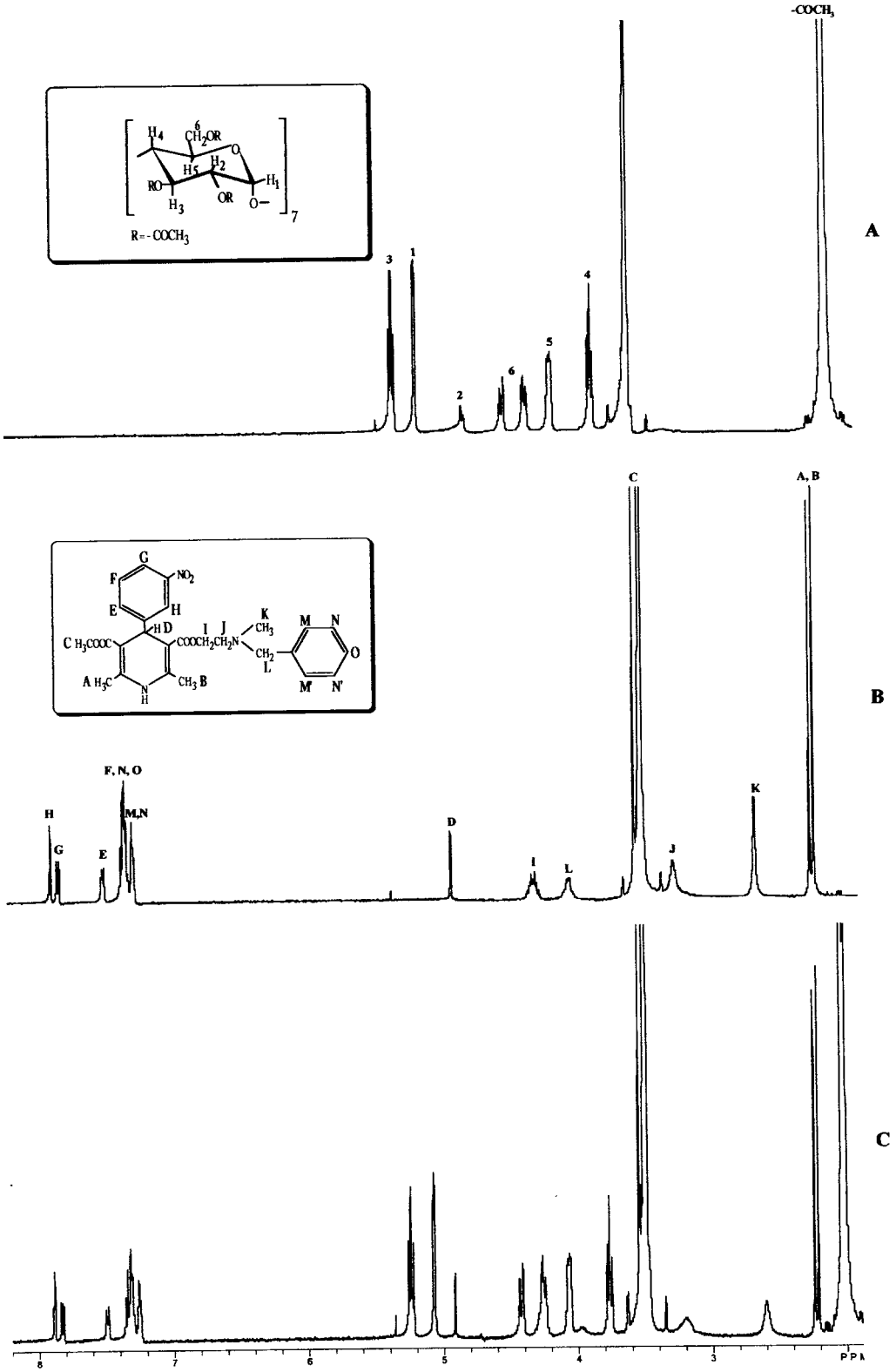

Figure 1. ^{1}H-NMR spectra of TAβCD (A), NC (B) and NC : TAβCD (1 : 1) mixture (C).

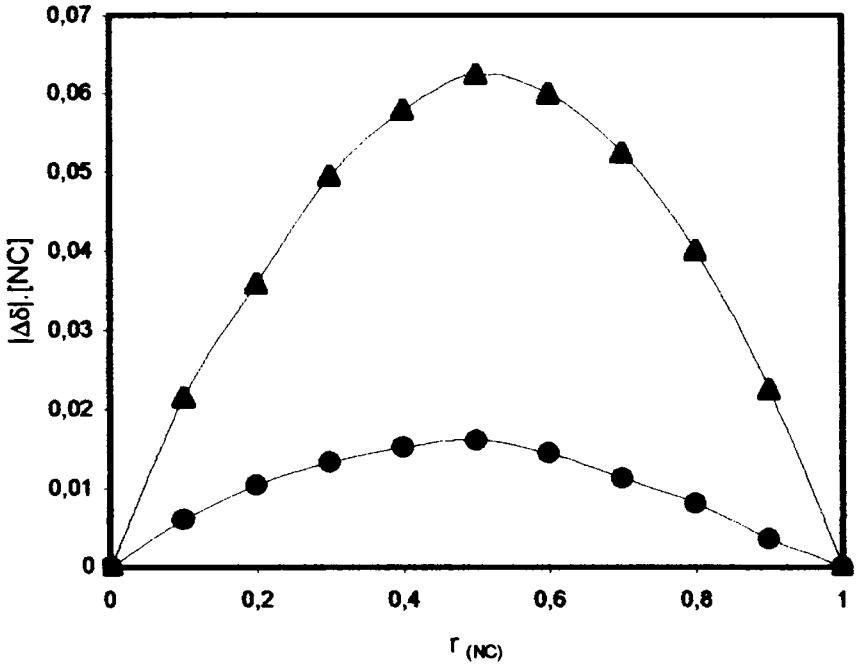

Figure 2. Job's plots corresponding to the chemical shift displacement of the F, O, N, M (●) and the G (▲) protons of drug for the NC : TAβCD and NC : HPβCD system, respectively.

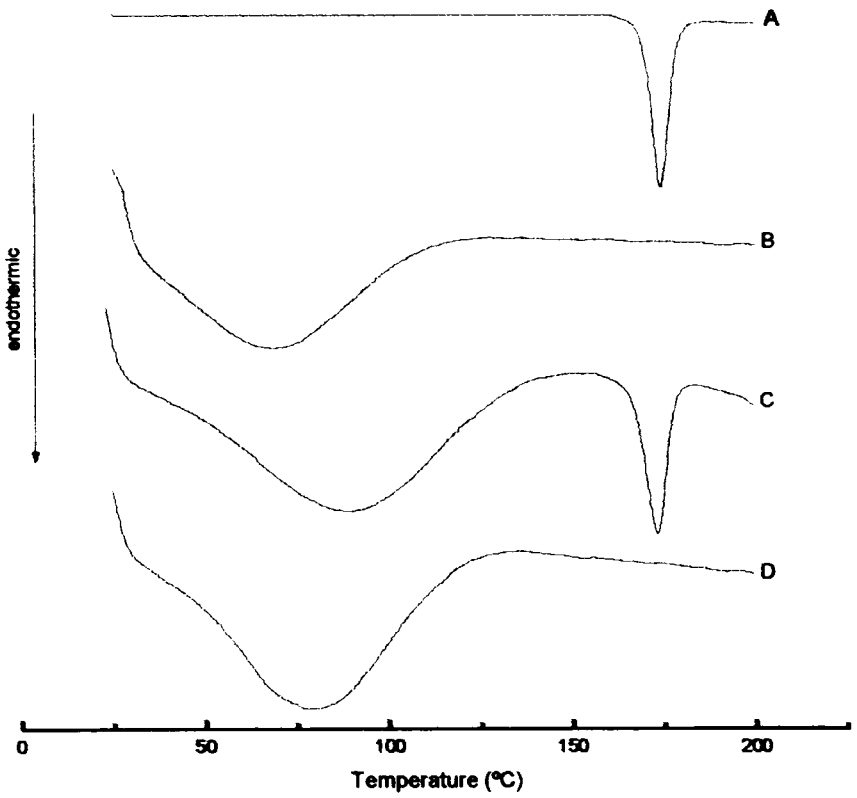

Figure 3. DSC thermograms of NC (A), HPβCD (B), NC : HPβCD physical mixture (C) and NC : HPβCD (D) spray-dried system.

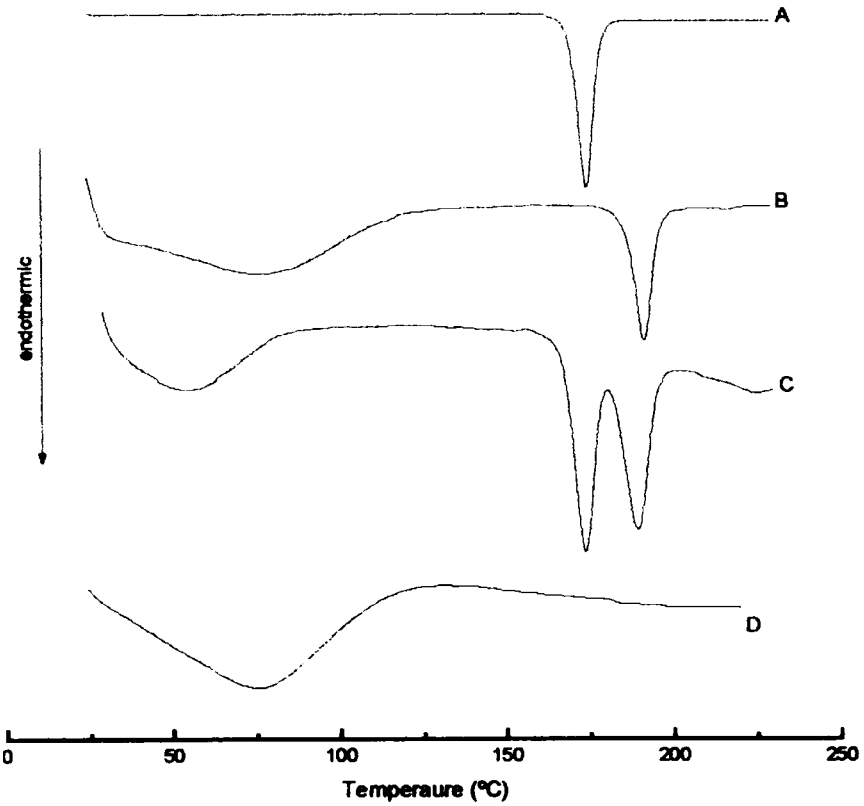

Figure 4. DSC thermograms of NC (A), TAβCD (B), NC : TAβCD physical mixture (C) and NC : TAβCD (D) spray-dried system.

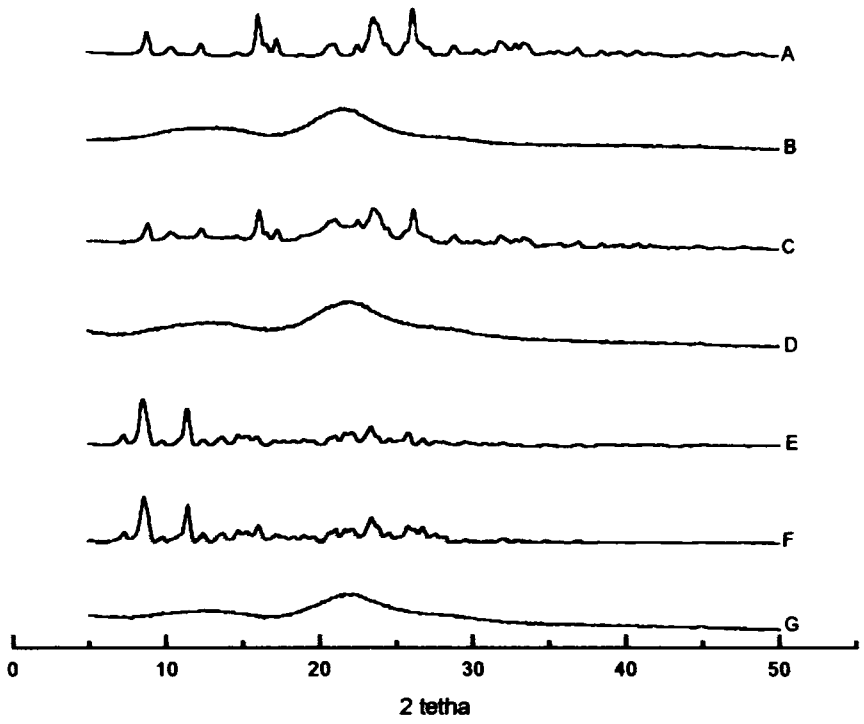

Figure 5. X-ray diffractograms of NC (A), HPβCD (B), NC : HPβCD physical mixture (C) and NC : HPβCD spray-dried system (D), TAβCD (E), NC : TAβCD physical mixture (F) and NC : TAβCD spray-dried system (G).

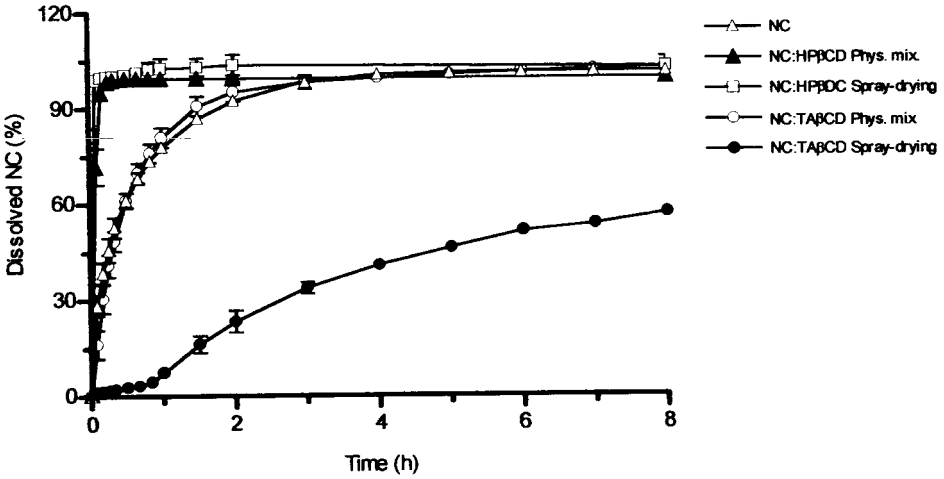

Figure 6. Dissolution profiles of NC and NC : HPβCD and NC : TAβCD systems at pH 1.2.

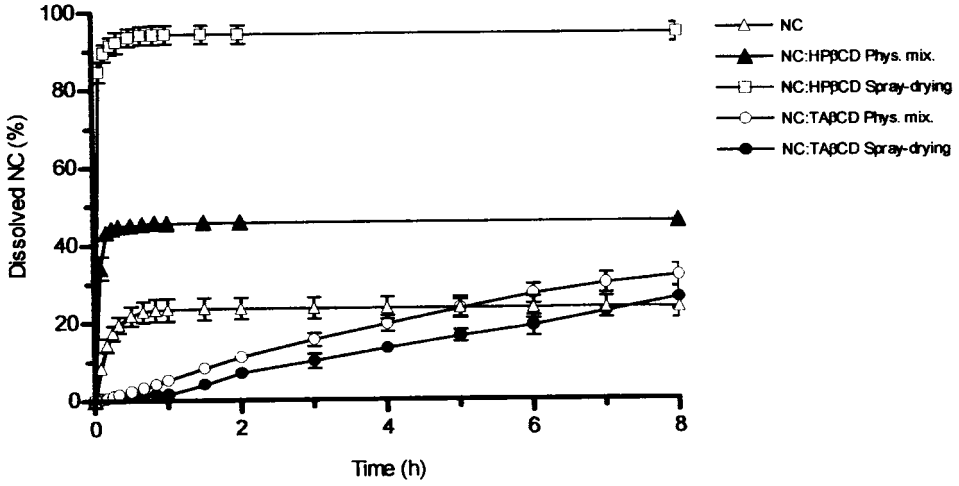

Figure 7. Dissolution profiles of NC and NC : HPβCD and NC : TAβCD systems at pH 6.8.

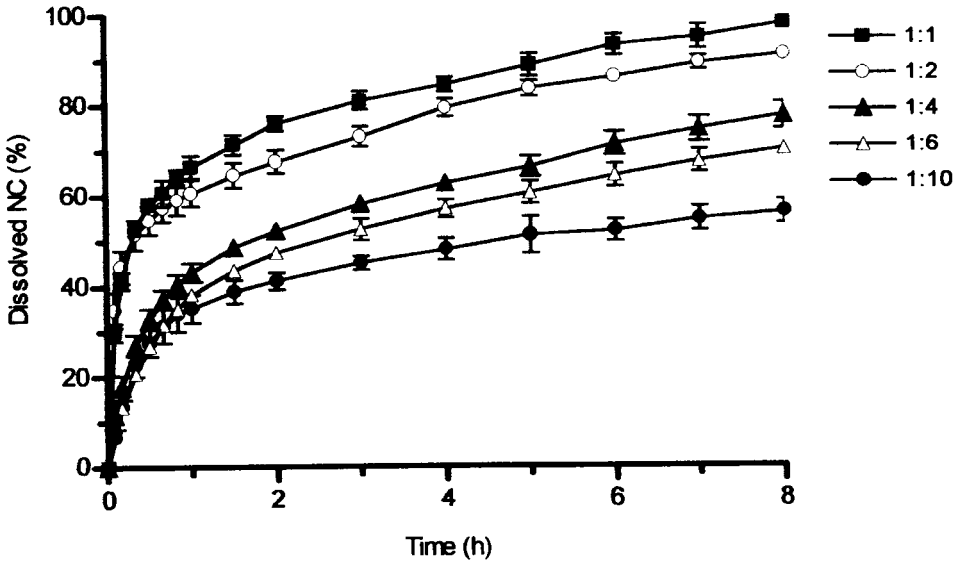

Figure 8. Dissolution profiles of (NC : HPβCD complex): (NC : TAβCD complex) in different molar ratios at pH 1.2.

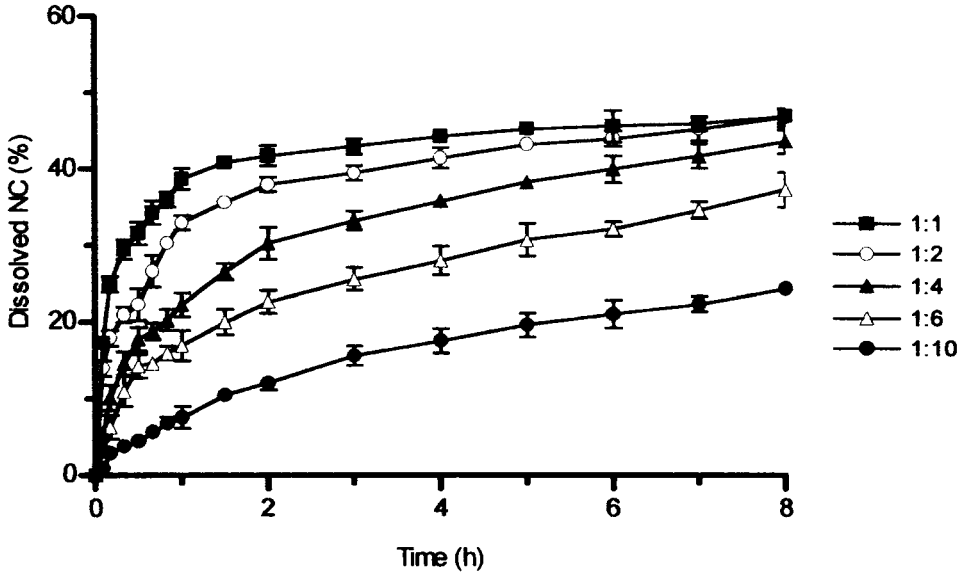

Figure 9. Dissolution profiles of (NC : HPβCD complex): (NC : TAβCD complex) in different molar ratios at pH 6.8.

significantly improved by complexation with HPβCD, specially in alkaline medium. In contrast, the drug release rate from the NC : TAβCD spray-dried complex was markedly retarded in both media.

An optimisation of the release profile of NC was further attempted by changing the mixing ratio of each complex in the formulation. The release profiles of NC from formulations consisting of mixtures of NC : HPβCD and NC : TAβCD complexes in various molar ratios, at pH 1.2 and pH 6.8 are presented in Figures 8 and 9, respectively.

The drug release from the different formulations occurred in two stages: faster release in the initial stage (up to 1 hour) and slower release in the second stage. It is evident that TAβCD retarded the drug release rate, being this retarding effect dependent on the amount of hydrophobic complex in the formulation. On the other hand, the initial release rate of the drug increased with increasing amount of the hydrophilic complex. Among the various combinations, we selected the 1 : 4 formulation to further in vivo studies in rabbits.

From the above reported data it was mainly concluded that the drug release could be arbitrarily controlled by the combination of hydrophilic and hydrophobic complexes in an appropriate molar ratio.

References

1. J. Moyano, J. Gines, M. Arias, and A. Rabasco: *Pharm. Acta Helv.* **69**, 81 (1994).
2. S. Badawy, A. Marshall, M. Ghorab, and M. Adeyeye: *Drug Dev. Ind. Pharm.* **22**, 959 (1996).
3. C. Ventura, G. Puglisi, M. Zappalà, and G. Mazzone: *Int. J. Pharm.* **160**, 163 (1998).
4. F. Hirayama, M. Yamasaka, T. Horikawa, and K. Uekama: *Chem. Pharm. Bull.* **43**, 130 (1995).
5. V. Lemesle-Lamache, D. Wouessidjewe, M. Chéron, and D. Duchêne: *Int. J. Pharm.* **141**, 117 (1996).
6. Y. Ikeda, K. Kimura, F. Hirayama, H. Arima, and K. Uekama: *J. Control. Release* **66**, 271 (2000).
7. E. Sorkin and S. Clissold: *Drugs* **33**, 296 (1987).
8. P. Job: *Ann. Chim.* **9**, 113 (1925).
9. C.M. Fernandes, M.T. Vieira, and F.J.B. Veiga: *Eur. J. Pharm. Sci.* **15**, 79 (2002).
10. C.A. Ventura, S. Tirendi, G. Puglisi, E. Bousquet, and L. Panza: *Int. J. Pharm.* **149**, 1 (1997).
11. S. Lin and Y. Kao: *Int. J. Pharm.* **56**, 249 (1989).
12. J. Moyano, J. Ginés, M. Arias, and A. Rabasco: *Int. J. Pharm.* **114**, 95 (1995).