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Physicochemical Characterization and Dissolution Properties of Nimesulide-Cyclodextrin Binary Systems

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ABSTRACT

The objective of this work is physicochemical characterization of nimesulide-cyclodextrin binary systems both in solution and solid state and to improve the dissolution properties of nimesulide (N) via complexation with α-, β, and γ-cyclodextrins (CDs). Detection of inclusion complexation was done in solution by means of phase solubility analysis, mass spectrometry, and ^{1}H nuclear magnetic resonance (^{1}H-NMR) spectroscopic studies, and in solid state using differential scanning calorimetry (DSC), powder x-ray diffractometry (X-RD), scanning electron microscopy (SEM), and in vitro dissolution studies. Phase solubility, mass spectrometry and ^{1}H-NMR studies in solution revealed 1:1 M complexation of N with all CDs. A true inclusion of N with β-CD at 1:2 M in solid state was confirmed by DSC, powder X-RD and SEM studies. Dissolution properties of N-CD binary systems were superior when compared to pure N.

KEYWORDS: nimesulide, cyclodextrins, physicochemical characterization, dissolution properties

INTRODUCTION

Nimesulide (N), chemically 4'-nitro-2'-phenoxy methane sulfonanilide, is a weakly acidic nonsteroidal anti-inflammatory drug. It differs from other nonsteroidal anti-inflammatory drugs (NSAIDs) in that its chemical structure contains a sulfonanilide moiety as the acidic group rather than a carboxylic group (**Figure 1**). N shows high anti-inflammatory, antipyretic, and analgesic activities in addition to low toxicity, a moderate incidence of gastric side effects, and a high therapeutic index.[1] N is a relatively weak inhibitor of prostaglandin synthesis in vitro and appears to exert its effect through a variety of mechanisms including free radical scavenging, effects on histamine release, the neutrophil myeloperoxidase pathway, bradykinin activity, tumor necrosis factor-a release, cartilage degradation, metalloprotease synthesis, phosphodiesterase type IV inhibition, platelet aggregation, and synthesis of platelet activating factor. It also exhibits a significant selectivity toward cyclooxygenase-2 (COX-2) versus COX-1 inhibition, which may explain the lower incidence of gastric side effects. However, recent findings reported that N has a higher risk of hepatic toxicity when compared to other marketed NSAIDs.[2,3] Like many nonsteroidal anti-inflammatory drugs, N is very sparingly soluble in water (≈ 0.01 mg/mL).[4] The poor aqueous solubility and wettability of N gives rise to difficulties in pharmaceutical formulations for oral or parenteral delivery, which may lead to variable bioavailability. To overcome these drawbacks, increasing the aqueous solubility of N is an important goal. Hence, in this investigation, inclusion complexation of N was tried with α-, β-, and γ-cyclodextrins (CDs) with the aim to improve its pharmaceutical properties (ie, aqueous solubility and dissolution properties).

CDs are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface. CDs are able to form inclusion complexes with poorly water-soluble drugs. These inclusion complexes have been shown to improve the stability, solubility, dissolution rate, and bioavailability of the drug.[5,6] The improvement in hydrophilicity is obtained through the formation of inclusion complexes where the host/guest interaction is dependent on the dimension of the oligosaccharide ring, and/or by means of highly homogeneous assembly between the CD and the drug in the solid state. In most cases these associations provide amenable solution behavior of poorly soluble drugs.

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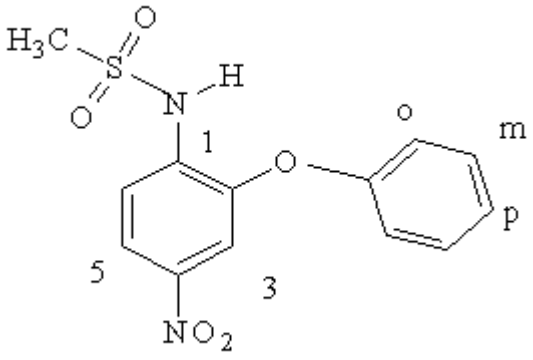

Figure 1. Structure of nimesulide.

MATERIALS AND METHODS

Materials

N was a gift sample from Nicholas Piramal Ind Ltd, Mumbai, India. α-, β-, and γ-CDs were all from Wacker Biochem Corp, Adrian, MI. All other reagents and solvents were of analytical grade.

Preparation of Solid Binary Systems

The following binary systems of N and CDs were prepared at 1:1 and 1:2 molar ratios (1:1 and 1:2 M).

Physical Mixtures

The physical mixtures of N and CDs in 1:1 and 1:2 M were obtained by mixing individual components that had previously been sieved (75-150 µm) together with a spatula.

Kneaded Systems

The physical mixtures of N and CDs in 1:1 and 1:2 M were triturated in a mortar with a small volume of water-methanol (1:1 vol/vol) solution. The thick slurry was kneaded for 45 minutes and then dried at 45°C. The dried mass was pulverized and sieved and a 75-150 µm granulometric sieve fraction was collected.

Coevaporated Systems

The aqueous solution of CD was added to an alcoholic solution of N. The resulting mixture was stirred for 1 hour and evaporated at a temperature of 45°C until dry. The dried mass was pulverized and sieved and a 75-150 µm granulometric sieve fraction was collected.

Detection of Inclusion Complexation in Solution State

Phase Solubility Studies

Excess amounts of N (50 mg) were added to 15 mL of purified water or CD aqueous solutions (0.003-0.048 M concentration range) taken in a series of 25-mL stoppered conical flasks and the mixtures were shaken for 48 hours at room temperature (28°C) on a rotary flask shaker. After 48 hours of shaking to achieve equilibrium, 2-mL aliquots were withdrawn at 12-hour intervals and filtered immediately using a 0.45-µm nylon disc filter. The filtered samples were diluted suitably and assayed for N by measuring absorbance at 397 nm.[4] Shaking was continued until 3 consecutive estimations were the same (96 hours). The solubility experiments were conducted in triplicate (coefficient of variation, CV < 2%). The blanks were performed on the same concentrations of CDs in water so as to cancel any absorbance that may be exhibited by the CD molecules. The apparent stability constants were calculated from the phase solubility diagrams.[7]

Mass Spectrometry Analysis

Electrospray ionization mass spectrometry (ESI-MS) was carried out on a Finnigan LCQ DECA ion-trap mass spectrometer (San Jose, CA) equipped with an electrospray ionization source. N was dissolved in water/methanol/acetic acid (49.5:49.5:1 vol/vol) in the absence and presence of CDs. The final concentrations of N and CDs were 1 mM and 2 mM respectively. Infusion rates were 5 µL/min during sample analysis.

^{1}H-NMR Spectroscopy

^{1}H nuclear magnetic resonance (1H-NMR) spectroscopic experiments were performed on a Varian 500 MHz Inova NMR (Varian Inc., Palo Alto, CA) with dual full-band channels and z-axis gradients using a Varian Z-axis PFG Inverse detection probe (Varian Inc., Palo Alto, CA). The spectra obtained were measured at 298 K with an operating frequency of 499.742 MHz .The 90° pulse width for 1H was 10.8 µs at a transmitter power of 50. Spatial connectivity between cyclodextrin and drug was established by 1D-ROE or Rotating Frame Overhauser Enhancement Spectroscopy (ROESY) experiments. The solutions of cyclodextrins, N, and solid complexes were prepared by dissolving in 50 mM sodium borate buffer (pH 9.5), which was made up in deuterium oxide, to give a 5-mM solution. Solutions were purged prior to data collection under a stream of argon for 1 hour to reduce the amount of dissolved oxygen.

Table 1. Summary of N-CDs Phase Solubility Studies*

CD	Type of Phase Solubility Diagram	Stability Constant (M^{-1})	Increase of Solubility S_t/S_0
α-	A_L	78	2.21
β-	A_L	167	3.45
γ-	A_L	72	2.06

*N indicates nimesulide; CD, cyclodextrin; S_t, solubility of nimesulide in 15 mM of CD solutions; S_0, solubility of nimesulide in water.

Detection of Inclusion Complexation in Solid State

Differential Scanning Calorimetry

Thermograms of pure materials, their treated components, and all binary systems were recorded on a Seiko, DSC 220C model Differential Scanning Calorimeter (Tokyo, Japan). About 10 mg of samples were sealed in aluminum pans and heated at a rate of 10°C/min from 30-300°C.

Powder X-ray Diffractometry

The powder x-ray diffraction patterns of pure materials, their treated counterparts, and all binary systems were recorded by using an automated Philips X' Pert X- ray diffractometer (Osaka, Japan). The samples were irradiated with monochromatized Cu Ka radiation and analyzed between 2θ angles of 4 and 54°. The voltage, current, and time per step used were 30 Kv, 20 mA, and 0.5 s, respectively.

Scanning Electron Microscopy

The surface morphology of pure materials, their treated counterparts, and all binary systems were examined by scanning electron microscope (Joel, JSM-840A, Tokyo, Japan). The samples were fixed on a brass stub using double-sided tape and then gold coated in vacuum by a sputter coater. The pictures were then taken at an excitation voltage of 20 Kv.

Dissolution Studies

In vitro dissolution studies of pure drug and its treated samples and the binary systems prepared were carried out in 900 mL of alkaline borate buffer of pH 8.4 Indian pharmacopoeia (IP)[8] using USP XXI type 2 Dissolution Rate Test Apparatus by powder dispersed amount method. Samples equivalent to 50 mg of N, a speed of 50 rpm, and a temperature of 37 ± 1°C were used in each test. A 5-mL aliquot was withdrawn at different time intervals, filtered using a 0.45-µm nylon disc filter, and replaced with 5 mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and assayed for N by measuring absorbance at 397 nm. The dissolution experiments were conducted in triplicate.

RESULTS AND DISCUSSION

Phase Solubility Studies

A summary of the findings of the phase solubility studies are given in **Table 1** and shown in **Figure 2**. The solubility of N increased linearly with an increase in the concentration of CDs, giving A_L type solubility diagrams.[7] The increase in solubility in the systems is due to one or more molecular interactions between N and CDs to form distinct species or complexes. The solubilizing efficiency of different CDs is in the order of β-CD > α-CD > γ-CD. The cavity size of the β-CD seems to be optimal for entrapment of the N molecule and consequently provides the greatest solubilization effect. Stability constants (K_S) were calculated from the phase solubility diagrams, K_S was calculated according to the following equation:

$$K_S = \text{slope}/ S_0 (1 - \text{slope}) \quad (1)$$

where S_0 is the intercept.

The stability constant values calculated were 78 M^{-1}, 167 M^{-1}, and 72 M^{-1}, respectively for α-, β-, and γ-CDs. The stability constant value observed for β-CD indicates that N interacts more strongly with this CD.

Mass Spectrometry Analysis

The full scan spectrum of N showed a strong peak at $[M]^+$ 308.2. The full scan spectra of the α-, β-, and γ-N-CD complexes are shown in **Figure 3**. The ions corresponding to N (m/z 308.3), α-CD (m/z 972), β-CD (m/z 1135), and γ-CD (m/z 1297) were seen as strong peaks in full scan spectra of respective N-CD

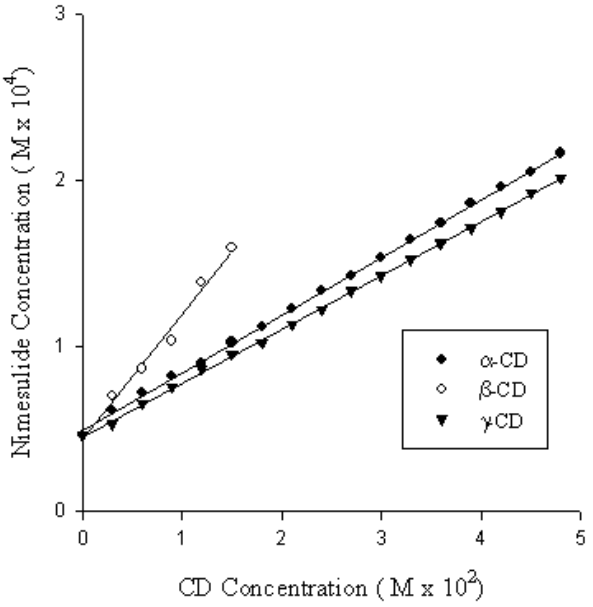

Figure 2. Phase solubility diagram of N-CDs solutions.

solutions. The full scan spectra of N-CD solutions also showed peaks at m/z 1281.4, 1443.2, and 1605.1 ions corresponding to the 1:1 adducts of N with α-, β-, and γ- CDs, respectively. The other ions would represent other fragments, probably of cyclodextrins or dextrins present in the powders. All these results suggest that N interacts with CDs forming inclusion complexes in solution.

^{1}H-NMR Spectroscopy

The ^{1}H-NMR spectroscopy studies of N with α-, β-, and γ-CDs were carried out to gain insights into the complexation mode(s) of N. The observable changes in chemical shift (Δ δ) upon complexation are relatively modest in magnitude for all cyclodextrins. The greatest changes in chemical shift were generally observed for the upfield shifts of H-3 and H-5, which is characteristic of the formation of an inclusion complex. Unfortunately the chemical shift of the H-5 signal was not always distinguishable from the H-6 resonance. Spatial interactions, arising through dipolar interactions, between proximal protons of the cyclodextrin and guest molecule were determined using 1-dimensional ROE experiments. In these experiments correlations are typically observed between proximal protons that are closer than 4 Å through space. Correlation of the H-3 and H-5 protons of the cyclodextrin to the protons of the guest is strong evidence for the

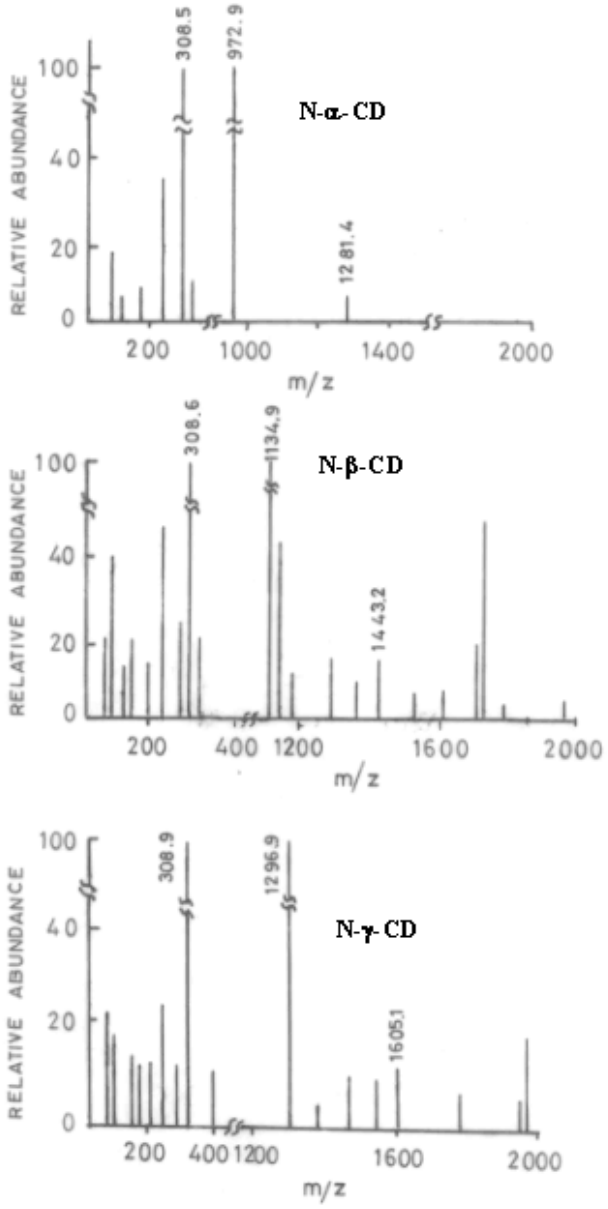

Figure 3. ESI MS spectra of N-CDs solutions.

formation of an inclusion complex. The ^{1}H-NMR data for N, including the complexation-induced shift, Δδ ($\delta_{complex} - \delta_{free}$), in the absence and presence of (α-, (β-, and (γ-CDs is given in **Table 2**. In the presence of α-CD, all protons of N are shielded to some degree, the exceptions being the protons adjacent to the nitro group (H-3 and H-5), which are strongly deshielded. Strong spatial correlations (**Table 3**) were observed between these protons and the H-3/H-5 protons of α-CD indicating deep inclusion of the nitro-substituted ring into the cyclodextrin cavity. Similar spatial correlations were observed between N and β-CD, indicat-

Table 2. ^{1}H Chemical Shift Data for N with and without CDs*

Position	^{1}H, δ (ppm) N	m, J (Hz)	Δδ (ppm) N + α - CD	Δδ (ppm) N + β - CD	Δδ (ppm) N + γ - CD
3	7.663	d, 3.0	0.264	-0.010	-0.242
5	7.933	dd, 9.5, 3.0	0.229	-0.086	-0.402
6	7.341	d, 9.5	0.042	0.058	-0.102
o	6.980	d, 8.0	-0.120	-0.195	-0.108
m	7.351	t, 8.0	-0.069	-0.067	-0.022
p	7.120	t, 8.0	-0.104	-0.105	-0.045
Me	2.880	s	-0.100	-0.148	-0.063

*N indicates nimesulide; CDs, cyclodextrins; $\Delta\delta = (\delta_{complex} - \delta_{free})$.

Table 3. Summary of ROE Intermolecular Interactions (Strong /Weak)

Position	^{1}H, δ (ppm) N	m, J (Hz)	α-CD+N	β-CD+N	γ -CD+N
3	7.663	d, 3.0	H-3/5	H-3, H-5	H-2
5	7.933	dd, 9.0, 3.0	H-3/5	H-3, H-5	H-2, H-3, H-5
6	7.341	d, 9.0	H-3/5	H-3, H-3	H-3
o	6.980	d, 8.5	H-3/5	H-3	----
m	7.351	dd, 7.5,8.5	----	H-3	H-3, H-5
p	7.120	t, 7.5	----	----	----
Me	2.880	s	----	H-3	H-3, H-5

ing a similar mode of inclusion. However, only modest Δδ values were observed for the H-3 and H-5 protons of N. The disparity in Δδ values of the aromatic protons may be attributable to complexation-induced changes in the shielding/deshielding effects (ie, inductive and mesomeric effects) of the substituent groups. Additional ROE interactions between the H-3 proton of β-CD with those of N (H-6, o-H, and the methyl group) indicate that the drug is included more deeply in the cavity than for α-CD. There appears to be a different mode of binding of N to γ-CD. Unlike the α- and β-CD complexes, the nitro-substituted ring is not included in the cavity at all. Only the sulfonamide methyl group and the aromatic protons of the monosubstituted ring of N appear to be included in the cavity with strong ROE correlation of these signals to H-3 and only weakly to H-5. These interactions would indicate shallow inclusion of the drug into the cavity. Interestingly, the H-3 and H-5 protons adjacent to the nitro-group of N exhibit strong spatial correlation to the H-2 protons of the cyclodextrin, which are located on the exterior of the torus. These protons of N (**Table 3**) are also very strongly shielded in the presence of γ-CD only. These large shifts may be due to the influence of the ring substituents upon binding to γ-CD. Thus an alternative mode of binding to γ-CD, rather than by inclusion, must be preferred by N.

Differential Scanning Calorimetry

The thermogram of N showed a sharp endothermic peak at 151.7°C corresponding to its melting point. The thermal behavior of kneaded nimesulide (KN) and coevaporated nimesulide (CN) is similar to the untreated samples, indicating that their solid-state properties were not substantially affected by the kneading and evaporation processes (**Figure 4**). Differential scanning calorimetry (DSC) thermograms of all CDs (ie, α-, β-, and γ-CDs) showed a broad endothermal effect ranging from 40-150°C due to the dehydration process. The DSC thermogram of β-CD was characterized by a small endothermal peak at about 220°C, which may be attributable to a reverse

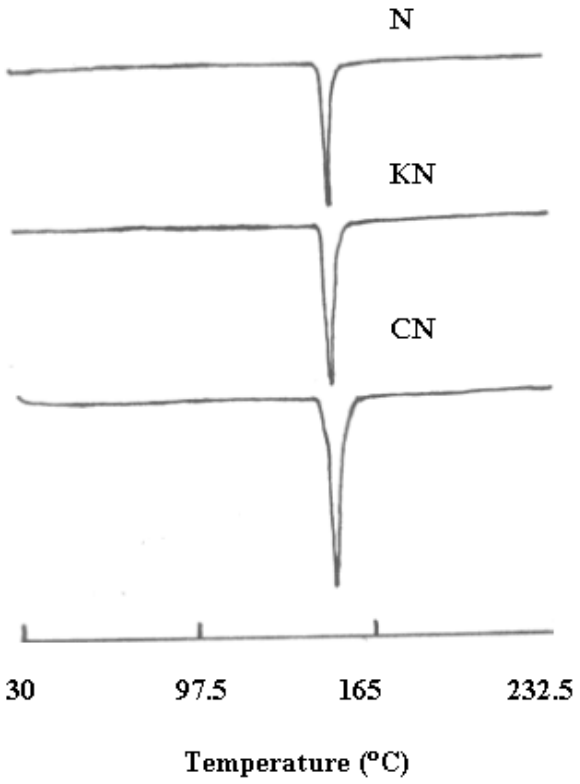

Figure 4. DSC thermograms of N and its treated samples.

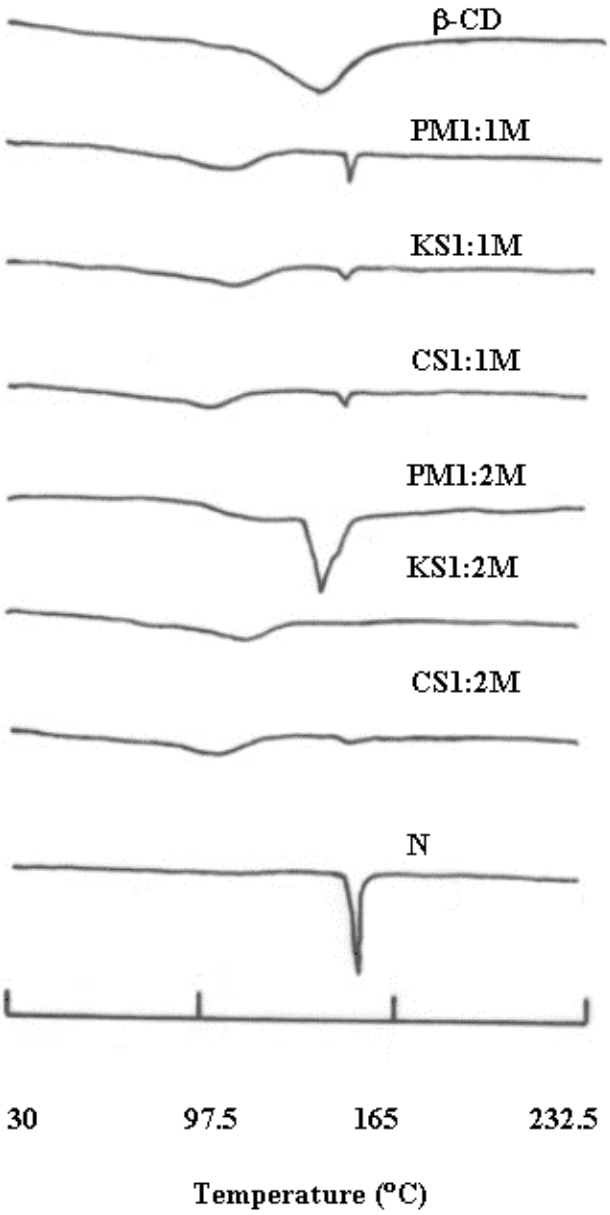

Figure 5. DSC thermograms of N and N-β-CD binary systems.

transformation of β-CD. The fusion endotherm of N maintained its shape in all physical mixtures of N-CDs (1:1 M and 1:2 M) except with the N-β-CD 1:2 M complex (**Figure 3**), where a marked broadening and down shift of the peak temperature of N melting endotherm (140°C) indicating a weaker interaction between N and β-CD.[9] Except with the N-β-CD, 1:2 M kneaded and coevaporated binary systems in all the N-α-, β-, and γ-CDs kneaded and coevaporated binary systems there is a marked reduction in intensity and/or broadening of the N endotherm at around 150°C indicating partial inclusion of N in these CD cavities. In the case of N-β-CD, 1:2 M, kneaded and coevaporated systems of the N endotherm completely disappeared (**Figure 5**). The complete disappearance of the N endothermic peak in these systems indicates the formation of a true inclusion complex.

X-ray Diffractometry Studies

Powder x-ray diffractometry (X-RD) is a useful method for the detection of cyclodextrin complexation in powder or microcrystalline states. The diffraction pattern of the complex is supposed to be clearly distinct from that of the superposition of each of the components if a true inclusion complex is formed. Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary systems with those of a reference. The relationship used for the calculation of crystallinity was relative degree of crystallinity (RDC) = $I_{sam}/I_{ref.}$, where I_{sam} = the peak height of the sample under investigation and I_{ref} = the peak height at the same angle

Table 4. Relative Degree of Crystallinity (RDC) Values of N-CD Binary Systems

Sample	RDC			
	KS 1:1M	CS 1:1M	KS 1:2M	CS 1:2M
N-α-CD	0.482	0.690	0.310	0.375
N-β-CD	0.775	0.791	-	-
N-γ-CD	0.333	0.450	0.166	0.168

for the reference with the highest intensity.[10] Pure drug peak at 19.2° 2θ was used for calculating the RDC of kneaded and coevaporated binary systems. The RDC values of corresponding binary systems are given in **Table 4**. A similar diffraction pattern with several intense peaks was achieved for any sample of N, independent of the previous treatment, conclusively displaying its crystalline structure. The CN showed a diffraction pattern similar to that of pure N but with relatively more intense peaks (**Figure 6**). In the case of α- and γ-CD samples, a similar diffraction pattern was observed irrespective of method of treatment. In the case of the β-CD samples, kneaded β-CD showed a diffraction pattern similar to that of pure β-CD, but with a reduction in peak intensities. The evaporated β-CD showed a diffraction pattern similar to that of pure β-CD but with relatively more intense peaks (**Figure 6**). In the cases of diffraction patterns of N-CD 1:2 M physical mixtures, all the principal peaks of N and CDs were present, although with lower intensities than N-CD 1:1 M physical mixtures. This difference in peak intensities in different physical mixtures is due to the presence of different amounts of drug and cyclodextrin. Because of the presence of higher amounts of N in 1:1 M physical mixtures in comparison with 1:2 M counterparts, intensities of N peaks were higher in 1:1 M physical mixtures. The decline in the crystallinity of physical mixtures (as evidenced by peak heights) with respect to pure N was due to their composition because a pure substance was compared with respect to a physical mixture of 2 substances with different diffraction patterns. Except with N-β-CD kneaded systems (KS) and coevaporated systems (CS) 1:2 M, the diffraction patterns of N-α-, γ-CD 1:1 M and 1:2 M and N-β-CD 1:1 M kneaded and coevaporated binary systems the diffractograms are the sum of each component and all the principal peaks of N, α-CD, β-CD, and γ-CD are observed, particularly the peak corresponding to N at 19.2° 2θ, although with lower intensities when com

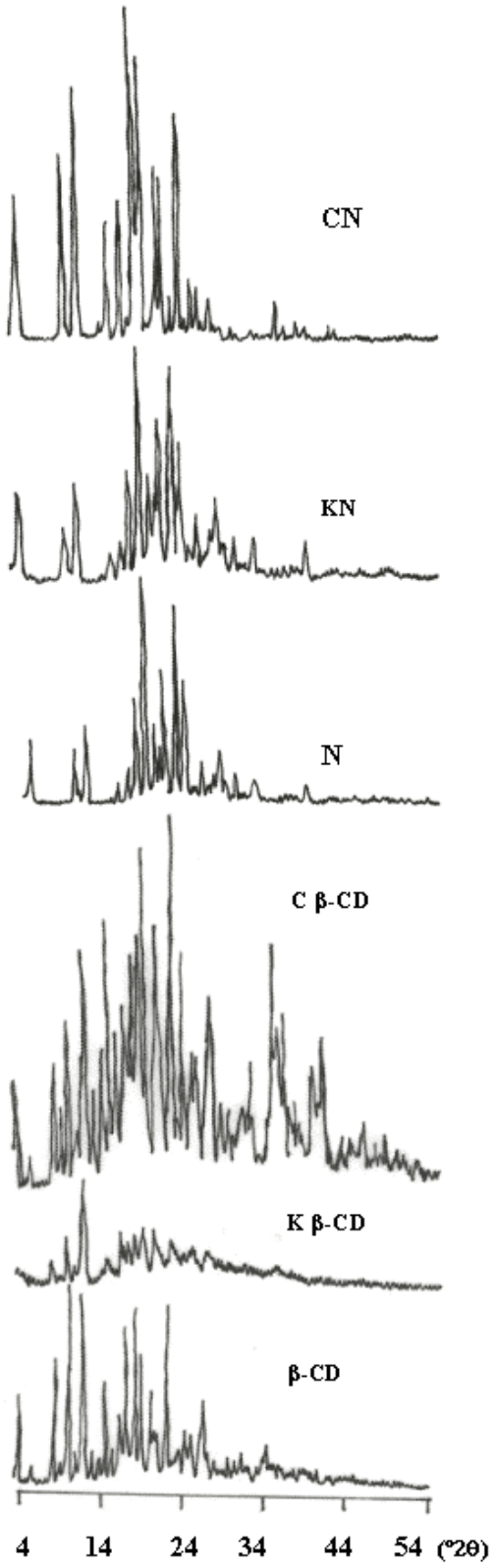

Figure 6. Powder x-ray diffractograms of N, β-CD, and their treated samples.

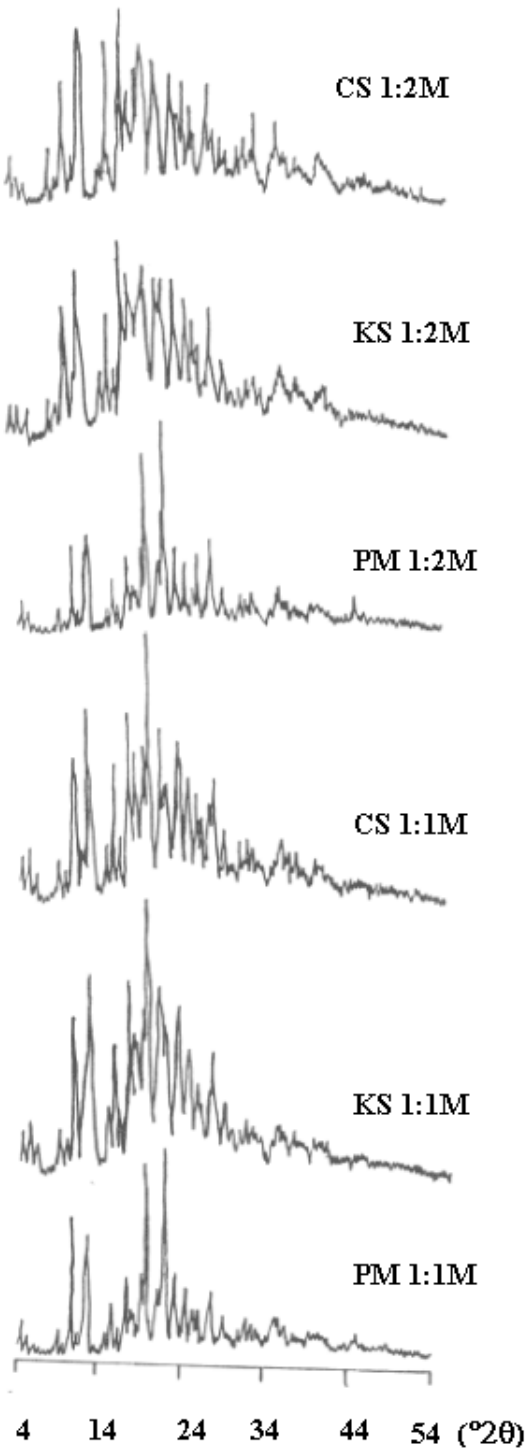

Figure 7. Powder x-ray diffractograms of N-β-CD binary systems.

pared to corresponding physical mixtures and pure N. These observations were in accordance with the results of the DSC studies indicating that no true inclusion complexation occurred in solid state in the cases of N-α-CD, γ-CD 1:1 M and 1:2 M, and N-β-CD 1:1 M kneaded and coevaporated binary systems. These results imply that no alteration was produced in the crystal structure of N, but crystallinity was modified because peak position (angle of diffraction) is an indication of crystal structure and peak heights are the measures of sample crystallinity (crystallite size) in a diffractogram. From the RDC values (**Table 4**), it is observed that when pure N was considered as a reference sample, a decrement in crystallinity was observed with all of the N-α-CD, γ-CD 1:1 M and 1:2 M, and N-β-CD 1:1 M kneaded and coevaporated binary systems. The decrement in crystallinity is in the order of KS > CS at both molar ratios. In the cases of N-β-CD KS and CS 1:2M, the diffraction patterns were quite different from that of the corresponding 1:2 M physical mixture (PM) diffraction pattern, with the existence of the newer peak at 17° 2θ , indicating the formation of solid inclusion complexes (**Figure 7**). These observations were in accordance with the results of the DSC studies, where the characteristic endothermic peak of N at 150.7°C disappeared, indicating the formation of true solid inclusion complexes.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) is used to study the microscopic aspects of the raw materials (ie, CDs and drug substances) and the products obtained by different methods of preparation like kneading and coevaporation. Even if there is a clear difference in crystallization state of the raw materials and the products, this study is inadequate to affirm inclusion complexation, but nevertheless helps to assess the existence of a single component in the preparations obtained. The commercial N particles are in the form of tabular-shaped crystals with smooth surfaces. The kneaded sample displayed a similar appearance to the commercial sample, but the size of the particles was reduced with the adherence of smaller particles onto the surfaces of the larger particles. Whereas the evaporated particles were well-developed tabular crystals where smaller particles were adhered to surfaces of larger ones (**Figure 8**). The commercial α-CD particles were prismatic with well-developed faces. The kneaded and evaporated particles were irregular in shape. All the β-CD particles, kneaded (K β-CD) and evaporated (C β-CD), were irregular in shape (**Figure 8**). The micrographs of commercial β-CD showed the adherence of smaller particles onto the surfaces of larger particles. The commercial γ-CD particles were tabular in shape with slightly diffused

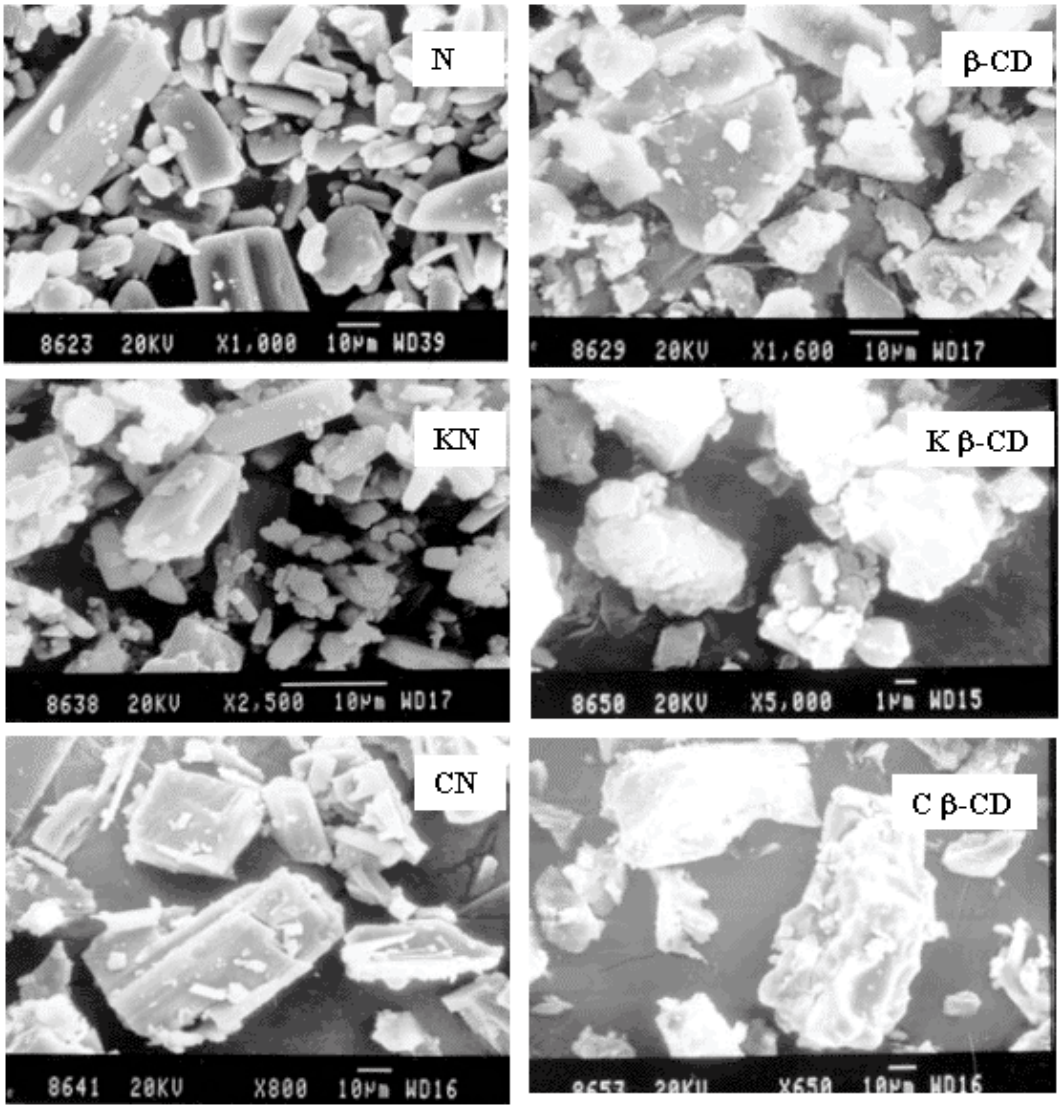

Figure 8. SEM photographs of pure N, β-CD, and their corresponding treated samples.

outlines, whereas the kneaded and evaporated particles were irregular in shape. All of the commercial CDs (α-, β-, γ-) showed cracks on the surfaces. All the physical mixtures (N-α-, β-, and γ- CDs) were characterized by the presence of particles of both the components (ie, N and CDs) without any modification in shape or size. In contrast all the SEMs of kneaded and coevaporated systems of N-CDs 1:2 M showed the effect of kneading and coevaporation techniques where the samples were homogeneous. In particular, with the kneaded systems it was impossible to differentiate crystals of both components indicating the better interaction of drug particles with CDs. The particles were all irregular in shape. Although the SEM technique is inadequate to conclude genuine complex formation, the obtained micrographs support the idea of the consecution of a new single component. Thus, the case of N-β-CD 1:2 M kneaded and coevaporated binary systems (**Figure 9**), along with the results of DSC and X-RD studies, confirm the inclusion process.

Dissolution Studies

When an assumed drug-CD binary system is dispersed in a dissolution medium, a very rapid dissolution is often observed. Rapid dissolution is the characteristic behavior of inclusion complexes. The most often used dissolution rate tests are the rotating disk method and the dispersed amount method. In the present investigation, the dispersed amount method is

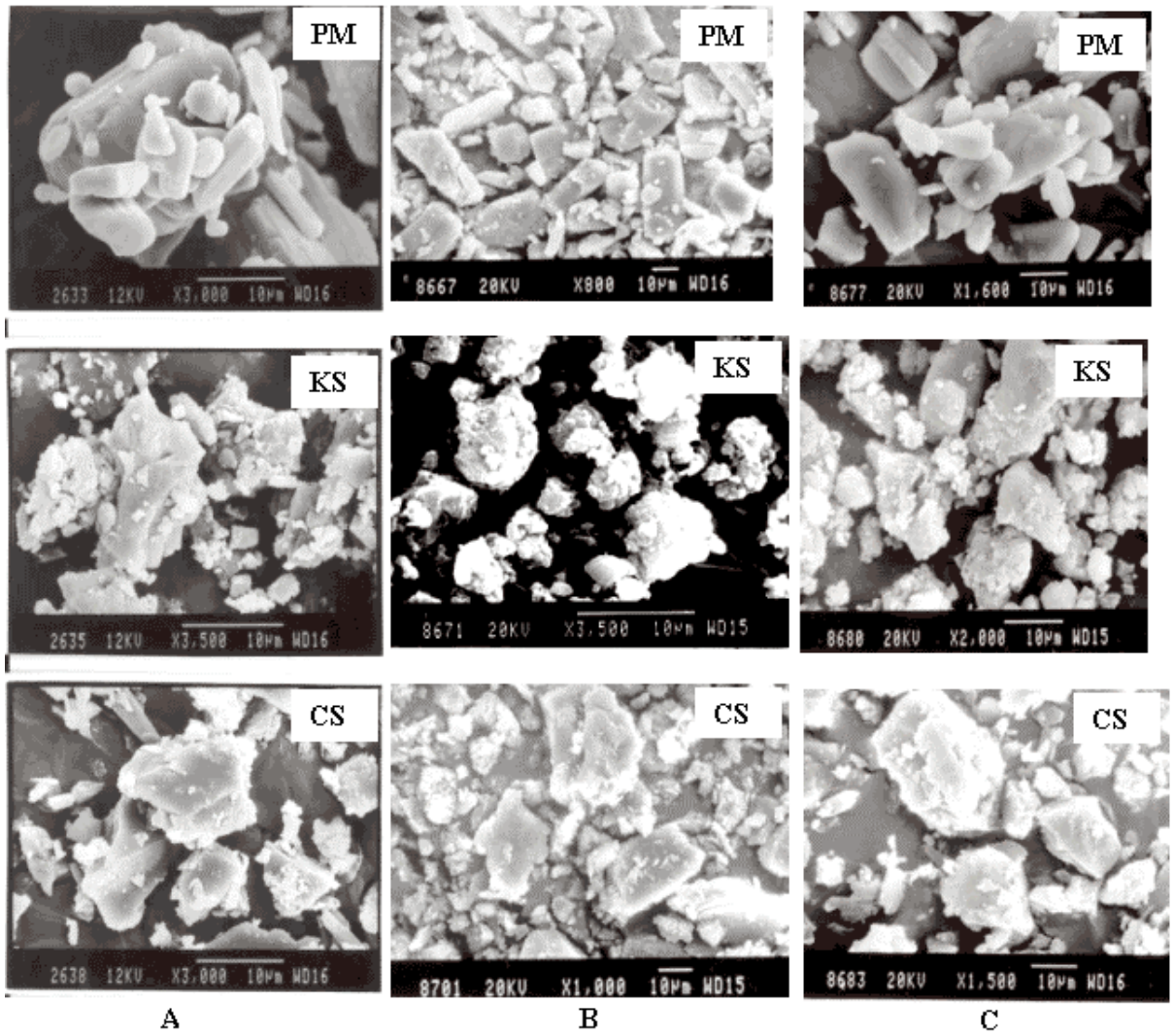

Figure 9. SEM photographs of N-α-CD (A), N-β-CD (B), and N-γ-CD (C) 1:2 M binary systems.

used to investigate the various dissolution parameters of N and N-CD binary systems. The results in terms of dissolution efficiency[11] at 10 minutes (DE_{10} %) and percent of active ingredient dissolved at 30 minutes (DP_{30}) are presented in **Table 5** and the dissolution profiles are shown in **Figure 10**. One-way ANOVA was used to test the statistical significance of differences between pure and treated samples. Significance of differences in the means was tested using Fishers LSD at 95% confidence. The DP_{30} and DE_{10} values of KN are significantly higher ($P < .05$) when compared to pure N and CN. Overall, the rank order of DE_{10} and DP_{30} values of physical mixtures of N with different CDs at both 1:1 M and 1:2 M ratios is γ-CD > α-CD > β-CD. The increase in dissolution rate and efficiency values recorded for the physical mixtures may be explained on the basis of the solubility of the drug in aqueous CD solutions. Since the CDs dissolve more rapidly in the dissolution medium than the pure drug, it can be assumed that, in early stages of the dissolution process, the CD molecules will operate locally on the hydrodynamic layer surrounding the particles of the drug. This action results in an in situ inclusion process, which produces a rapid increase of the amount of the dissolved drug.[12] Overall, the rank order of the DE_{10} and DP_{30} values of kneaded and coevaporated binary systems with different CDs are in the order of γ-CD > α-CD > β-CD. The DE_{10} and DP_{30} values of N-CDs kneaded systems were higher than those of coevaporated systems. The superior dissolution properties observed with kneaded systems over coevaporated systems may be due to the better interaction of N with CDs during the kneading process. The differences observed among the solubilizing effi-

Table 5. Mean ± SD Values of DP_{30} and DE_{10} for N and N-CD Binary Systems (n = 3)*

Sample	DP_{30}	DE_{10} (%)
N	34.26 ± 1.01	2.99 ± 0.32
KN	36.44± 0.65	4.33±0.03
CN	18.22± 0.14	1.87±0.06
N-α-CD PM 1:1 M	51.98 ± 0.13	11.88 ± 0.04
N-α-CD KS 1:1 M	96.36 ± 0.39	59.14 ± 0.33
N-α-CD CS 1:1 M	89.22 ± 0.05	45.0 ± 0.25
N-α-CD PM 1:2 M	70.16 ± 0.21	23.70 ± 0.40
N-α-CD KS 1:2 M	100.10* ± 0.01	70.35 ± 0.12
N-α-CD CS 1:2 M	100.01 ± 0.02	63.64 ± 0.10
N-β-CD PM 1:1 M	45.86 ± 0.76	9.93 ± 0.10
N-β-CD KS 1:1 M	95.13 ± 0.13	56.35 ± 0.01
N-β-CD CS 1:1 M	87.17 ± 0.05	41.79 ± 0.48
N-β-CD PM 1:2 M	62.46 ± 0.31	19.68 ± 0.05
N-β-CD KS 1:2 M	100.01 ± 0.01	68.85 ± 0.04
N-β-CD CS 1:2 M	99.98 ± 0.05	62.23 ± 0.20
N-γ-CD PM 1:1 M	61.81 ± 0.26	14.86 ± 0.10
N-γ-CD KS 1:1 M	100.00 ± 0.03	67.35 ± 0.07
N-γ-CD CS 1:1 M	94.24 ± 0.06	60.49 ± 0.07
N-γ-CD PM 1:2 M	78.41 ± 0.33	26.73 ± 0.11
N-γ-CD KS 1:2 M	100.02*± 0.02	73.72 ± 0.11
N-γ-CD CS 1:2 M	100.10 ± 0.05	70.80 ± 0.07

*Complete drug dissolution achieved within 15 minutes. DP indicates percent of active ingredient dissolved at 30 minutes; DE, dissolution efficiency at 10 minutes; N, nimesulide; CD, cyclodextrin; KN, kneaded nimesulide; CN, coevaporated nimesulide; PM, physical mixture; KS, kneaded systems; CS, coevaporated systems.

ciency and stability constant values did not reflect the similar differences in improving the dissolution rate and efficiency values of the binary systems. Various authors suggested that dissolution rates from drug-CD binary systems are also dependent on other factors, such as diffusion and dissociation of the complex in the dissolution medium[13,14] and decrease in crystallinity and enhanced wettability of the drugs by the inclusion complexation.[15] In the present investigation, mainly crystallinity of the drug along with other factors played an important role in increasing dissolution

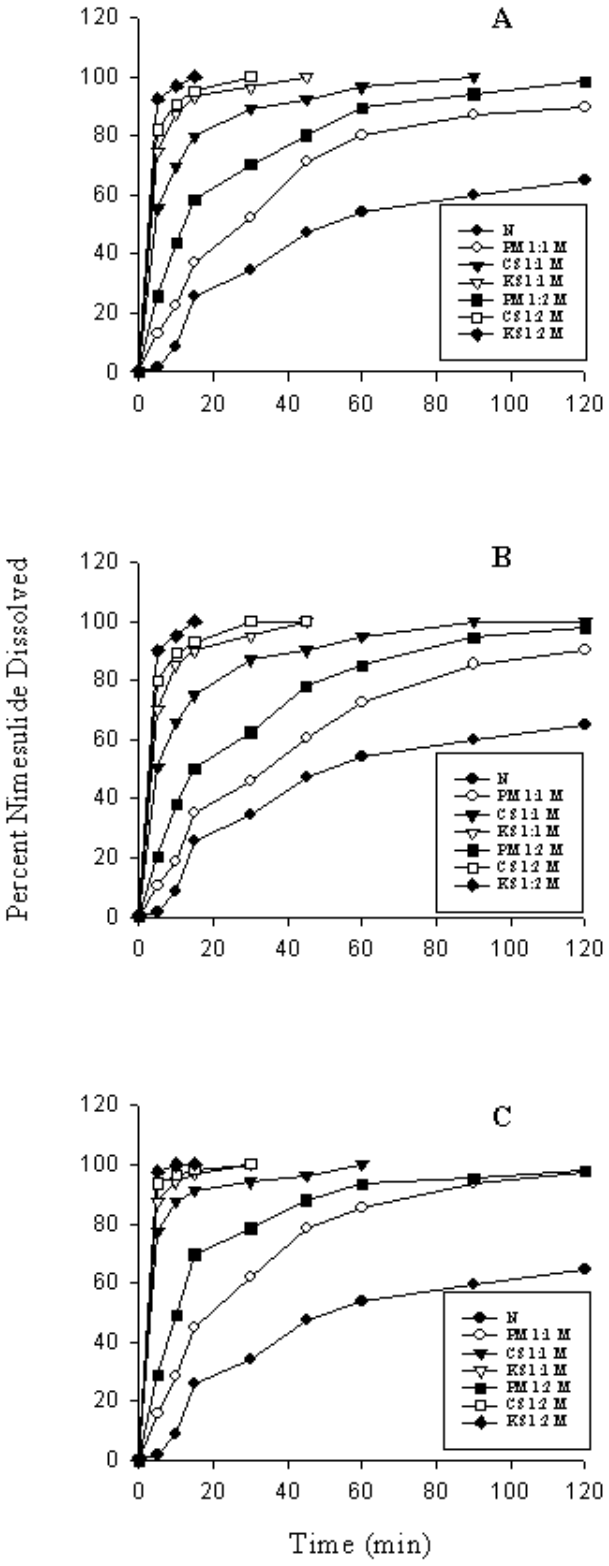

Figure 10. Dissolution profiles of N and N-α-CD (A), N-β-CD (B), and N-γ-CD (C) binary systems.

rate and efficiency values of N-CDs kneaded and coevaporated binary systems as evidenced by RDC values obtained from powder X-RD studies (**Table 4**). In the cases of N-β-CD 1:2 M kneaded and coevaporated binary systems, the dissolution rate and efficiency values were not as anticipated, even though a true inclusion of the N occurs in β-CD cavity. This may be attributable to the formation crystalline inclusion complexes as evidenced by existence of several crystalline peaks in their X-RD patterns.

CONCLUSION

Physicochemical characterization of N-cyclodextrin binary systems in solution state by phase solubility, mass spectrometry, and ^{1}H-NMR studies revealed 1:1 M complexation of N with all CDs. A true inclusion of N with β-CD at 1:2 M in the solid state was confirmed by DSC, powder X-RD, and SEM studies. Dissolution properties of N-CDs binary systems were superior when compared to pure N. Overall, kneaded systems showed superior dissolution properties when compared to coevaporated systems and physical mixtures.

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