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Inclusion Complexation and Dissolution Properties of Nimesulide and Meloxicam–hydroxypropyl-β-cyclodextrin Binary Systems

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Abstract

The purpose of the work is physicochemical characterization of nimesulide (NI) and meloxicam (ME)–hydroxypropyl-β-cyclodextrin (HP-β-CD) binary systems both in solution and solid states and to improve the pharmaceutical properties of NI and ME via inclusion complexation with HP-β-CD. Binary systems of NI and ME with HP-β-CD have been characterized both in solution and solid state by different physicochemical methods. Three types of drug–HP-β-CD binary systems, namely physical mixtures (PM), kneaded systems (KS) and co evaporated systems (CS) in 1:1 and 1:2 molar ratios (1:1 and 1:2 M) were prepared. Phase solubility and ^{1}H-NMR spectroscopic studies in solution state revealed 1:1 M complexation of NI and ME with HP-β-CD. A partial inclusion of NI with HP-β-CD at both molar ratios of kneaded and co evaporated systems and a true inclusion of ME with HP-β-CD at both molar ratios of co evaporated systems in solid state was confirmed by differential scanning calorimetry (DSC), powder X-ray diffractometry (powder X-RD) and scanning electron microscopy (SEM) studies. Dissolution properties of NI and ME–HP-β-CD binary systems were superior when compared to corresponding pure drugs. The aqueous solubility and dissolution properties of NI and ME can be improved by inclusion complexation with HP-β-CD.

Introduction

Nimesulide (NI) and Meloxicam (ME) are the selective COX-2 inhibitors of non-steroidal anti-inflammatory drugs [1–3]. Nimesulide 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]. ME has good gastrointestinal tolerability and used to treat rheumatoid arthritis, osteoarthritis, and other joint diseases [2, 3]. Like many non-steroidal anti-inflammatory drugs, NI and ME are very sparingly soluble in water. The very poor aqueous solubility and wettability of these drugs 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 NI and ME is an important goal. Hence, in the present investigation inclusion complexation of NI and ME with HP-β-CD was tried with the aim to improve their pharmaceutical properties i.e. solubility in water and dissolution properties.

Cyclodextrins (CDs) are cyclic (α-1,4)-linked oligosaccharides of α-D-glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface[4, 5]. Cyclodextrins 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 drugs [6, 7]. 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 otherwise poorly soluble drugs.

Materials and methods

Materials

Nimesulide, gift sample from Nicholas Piramal Ind. Ltd, India, and meloxicam was supplied by Sun Pharma Ltd,

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Mumbai, India and HP-β-CD was from Wacker Biochem Corp. USA. All other reagents and solvents were of analytical grade.

Preparation of solid binary systems

The following binary systems of NI, ME and HP-β-CD were prepared at 1:1 and 1:2 molar ratios (1:1 and 1:2 M).

Physical mixtures (PM)

The physical mixtures of NI, ME and HP-β-CD in 1:1 and 1:2 M were obtained by mixing, individual components that had previously been sieved (75–150 μm), with the use of spatula.

Kneaded systems (KS)

The physical mixtures of NI, ME and HP-β-CD in 1:1 and 1:2 M were triturated in a mortar with a small volume of water–methanol (1:1 v/v) solution. The thick slurry was kneaded for 45 min and then dried at 45 °C until dryness. The dried mass was pulverized and sieved and a 75–150 μm granulometric sieve fraction was collected.

Co evaporated systems (CS)

The aqueous CD solution was added to alcoholic solution of NI and liquid ammonia solution of ME. The resulting mixture was stirred for 1 h 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 NI and ME (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 h at room temperature (28 °C) on a rotary flask shaker. After 48 h of shaking to achieve equilibrium, 1-ml aliquots were withdrawn at 12-h interval and filtered immediately using a 0.45 μm nylon disc filter. The filtered samples were diluted suitably and assayed for drug contents by measuring absorbance at 397 and 365 nm, respectively for NI and ME. Shaking was continued until the 3 estimations were same (96 h). The solubility experiments were conducted in triplicate (coefficient of variation, CV $<$ 2%). The blanks were performed on the same concentrations of CD 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 [8].

^{1}H-NMR studies

^{1}H-NMR experiments were performed on a Varian 500 MHz Inova NMR with dual full-band channels, and *z*-axis gradients using a Varian *Z*-axis PFG Inverse detection probe. The spectra were obtained at 298 K with an operating frequency of 499.742 MHz (pw90 ^{1}H was 10.8 μs at tpwr of 50). The solutions of HP-β-CD, NI and ME, 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 with argon for one hour, to reduce the amount of dissolved oxygen, prior to data collection.

Detection of inclusion complexation in solid state

Differential scanning calorimetry (DSC)

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

Powder X-ray diffractometry (X-RD)

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. The samples were irradiated with monochromatized Cu Kα radiation and analyzed between 2θ angles of 4 and 54 °. The voltages, current and time per step used were 30 kV, 20 mA and 0.5 s, respectively.

Scanning electron microscopy (SEM)

The surface morphology of pure materials, their treated counterparts and all binary systems was examined by Scanning Electron Microscope (Joel, JSM-840A, 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 drugs and their treated samples and the binary systems prepared were carried out in 900 ml of alkaline borate buffer of pH 8.4 I.P and phosphate buffer of pH 7.4 I.P each for NI and ME using USP XXI type 2 Dissolution Rate Test Apparatus by powder dispersed amount method. Samples equivalent to 50 mg of NI and 15 mg of ME, a speed of 50 rpm and a temperature of 37 $\pm$ 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 drug contents by measuring absorbance at 397 and 365 nm respectively for NI and ME. The dissolution experiments were conducted in triplicate.

Results and discussion

Phase solubility studies

A summary of findings of the phase solubility studies are given in Table 1 and shown in Figure 1. The solubility of NI and ME increased linearly with an increase in the concentration of HP-β-CD, giving A_L type solubility diagrams [8]. The increase in solubility in the systems is due to one or more molecular interactions between drugs and HP-β-CD to form distinct species or complexes. Stability constants (K_S) were calculated from the phase solubility diagram according to the following equation:

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

where S_0 is solubility of drugs in the absence of CD. The stability constant values calculated were 188 ± 3.52 M^{-1} and 170 ± 4.85 M^{-1}, respectively for NI and ME.

^{1}H-NMR studies

The ^{1}H-NMR spectroscopy studies of NI and ME with HP-β-CD were carried out to gain insights into the complexation mode(s). The chemical shift values corresponding to the HP-β-CD protons in absence and presence of NI and ME are given in Table 2. The spatial interactions between proximal protons of the cyclodextrin and guest molecules that arise through dipolar interactions were determined using one-dimensional ROE experiments (1D ROE). In these experiments correlations are typically observed between proximal protons that are closer than 4Å 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 formation of an inclusion complex. The greatest changes in chemical shift were observed for the upfield shifts of H-3 and H-5, which is characteristic of the formation of an inclusion complex. The shift of the H-5 lying on the inner side of the CD cavity at the primary hydroxyl

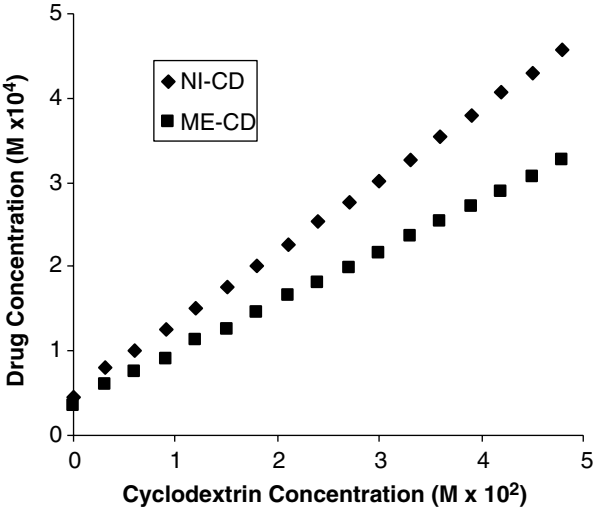

Figure 1. Phase solubility diagram of NI and ME-HP-β-CD solutions. *Key*: Nimesulide (NI); Meloxicam (ME); Hydroxypropyl-β-cyclodextrin (HP-β-CD).

Table 1. Summary of phase solubility studies

Drug	Type of phase solubilty diagram	Stability constant ± SD (M^{-1})	Increase of solubility $*S_t/S_0$
NI	A_L	188 ± 3.52	3.82
ME	A_L	170 ± 4.85	3.47

Key: Nimesulide (NI); Meloxicam (ME); S_t – solubility of NI and ME in 15 mM of CD solutions; S_0 – solubility of NI and ME in water.

Table 2. ^{1}H Chemical shift data for HP-β-CD protons with and without NI and ME

Position	HP-β-CD^{1}H, δ (ppm)	HP-β-CD + NI ^{1}H, δ (ppm)	HP-β-CD + ME ^{1}H, δ (ppm)	Δ δ (ppm)	
				NI	ME
1	4.925	4.915	4.916	−0.010	−0.009
2	3.513	3.500	3.510	−0.013	−0.003
3	3.840	3.686	3.819	−0.154	−0.021
4	3.450	3.437	3.446	−0.013	−0.004
5	3.750 overlap with H6	3.570	3.710 overlap with H6	−0.180	−0.040
6	3.749 overlap with H5	3.737	3.738 overlap with H5	−0.012	−0.011

Key: $\Delta\delta(\delta_{complex} - \delta free)$; Nimesulide (NI); Meloxicam (ME); Hydroxypropyl-β-cyclodextrin (HP-β-CD).

group side was the most prominent followed by H-3 at the secondary hydroxyl group. These results indicate that NI and ME were included in the HP-β-CD cavity from the primary hydroxyl group side. The ^{1}H-NMR data for NI and ME, including the complexation-induced shift,$\Delta\delta(\delta_{complex} - \delta_{free})$, in the absence and presence of HP-β-CD are given in Table 3. In the presence of HP-β-CD all protons of NI are shielded to some degree. However, only modest Δ δ values are observed for the H-3 and H-5 protons of NI. The disparity in Δ δ values of the aromatic protons may be attributable to complexation induced changes in the shielding/deshielding effects, i.e. inductive and mesomeric effects, of the substituent groups. The other protons of NI i.e. H-6, *o*-H, and the methyl group are also shielded, indicating that the drug is included more deeply in the cavity. Therefore, from the chemical shifts obtained, it can be assumed that the NI is deeply included from the primary hydroxyl group side. In the case of ME and HP-β-CD the H-15 and H-18 protons of meloxicam exhibit very strong spatial correlation with both the H-3 and H-5 protons of CD, indicating that the thiazole ring is deeply included into the HP-β-CD cavity (Table 3). The H-5 and H-6 protons of the relatively non-polar ring of the benzothiazine group are also shielded, indicating that ME was also deeply included in the HP-β-CD cavity from the primary hydroxyl group side.

Differential scanning calorimetry

Although the results obtained by the solubility studies strongly indicate the formation of a true complex of NI-HP-β-CD and ME-HP-β-CD, they do not preclude the possibility that the product is simply a physical mixture. Thus the thermal behavior of NI and ME-HP-β-CD binary systems was studied by DSC in order to confirm the formation of a solid inclusion complex. When the guest molecules are incorporated in the CD cavity or in the crystal lattice, their melting, and boiling and sublimation points usually shift to a different temperature or disappear within the temperature range where the CD lattice is decomposed. The thermogram of NI showed a sharp endothermic peak at 151.7 °C corresponding to its melting point. The thermal behavior of kneaded nimesulide (KNI) and evaporated nimesulide (CNI) was much similar to the untreated nimesulide. DSC thermograms of pure, kneaded and evaporated HP-β-CD samples showed a broad endothermal effect ranging from 40–150 °C, due to their dehydration process. The thermograms of ME and KME (kneaded meloxicam) showed a sharp endothermic peak at 257.7 °C corresponding to its melting point. However, the thermogram of CME (evaporated meloxicam) showed a broad endotherm ranging from 113.4–161.7 °C with a peak of 145.3 °C, which may be due to dehydration process, along with the melting endotherm at 251.8 °C. This dehydration peak may be due to the occluded water during the evaporation process, which is present in the liquid ammonia. This was further confirmed from the DSC thermogram of pre heated (0–150 °C) CME sample, where no dehydration peak was found.

The fusion endotherm of NI and ME maintained its shape in physical mixtures of NI-HP-β-CD and ME-HP-β-CD at both 1:1 and 1:2 M (Figure 2a, b). In the cases of NI-HP-β-CD kneaded and co evaporated binary systems there is a marked reduction in intensity and/or broadening of NI endotherm at around 150 °C, indicating partial inclusion of NI within HP-β-CD cavity (Figure 2a). Except with ME-HP-β-CD 1:1 and 1:2 M co evaporated systems, the thermal curves of the ME-HP-β-CD kneaded binary systems invariably showed the typical meloxicam endotherm, which progressively reduced in its peak intensity and shifted to lower temperatures. This marked reduction in intensity and/or broadening and shift to a lower temperature of the ME endotherm in kneaded systems indicates a partial inclusion of ME in the HP-β-CD cavity. In the case of the ME-HP-β-CD 1:1 and 1:2 M co evaporated systems the ME endotherm is completely disappeared indicating the formation of a true inclusion complex (Figure 2a).

X-RD studies

Powder X-ray diffractometry is a useful method for the detection of cyclodextrin complexation in powder or microcrystalline states. The diffraction pattern of the drug–cyclodextrin complex is supposed to be the clearly distinct from that of the superposition of each

Table 3. ^{1}H Chemical shift data for NI and ME with and without HP-β-CD

Position		NI^{1}H δ (ppm)	ME^{1}Hδ (ppm)	NI + HP-β-CD ^{1}H, δ (ppm)	ME + HP-β-CD ^{1}H, δ (ppm)	Δ δ (ppm)	
NI	ME					NI	ME
3	3	7.663	7.735	7.613	7.712	−0.050	−0.023
5	4	7.933	7.663	7.847	7.827	−0.076	−0.020
6	5	7.341	7.753	7.399	7.374	−0.042	−0.025
o	6	6.980	7.953	6.785	7.935	−0.165	−0.018
m	10 Me	7.351	2.770	7.284	2.754	−0.047	−0.016
p	15	7.120	6.992	7.015	6.956	−0.095	−0.036
Me	18 Me	2.880	2.278	2.732	2.247	−0.132	−0.031

Key: $\Delta\delta(\delta_{complex\ -\ \delta free})$; Nimesulide (NI); Meloxicam (ME); Hydroxypropyl-β-cyclodextrin (HP-β-CD).

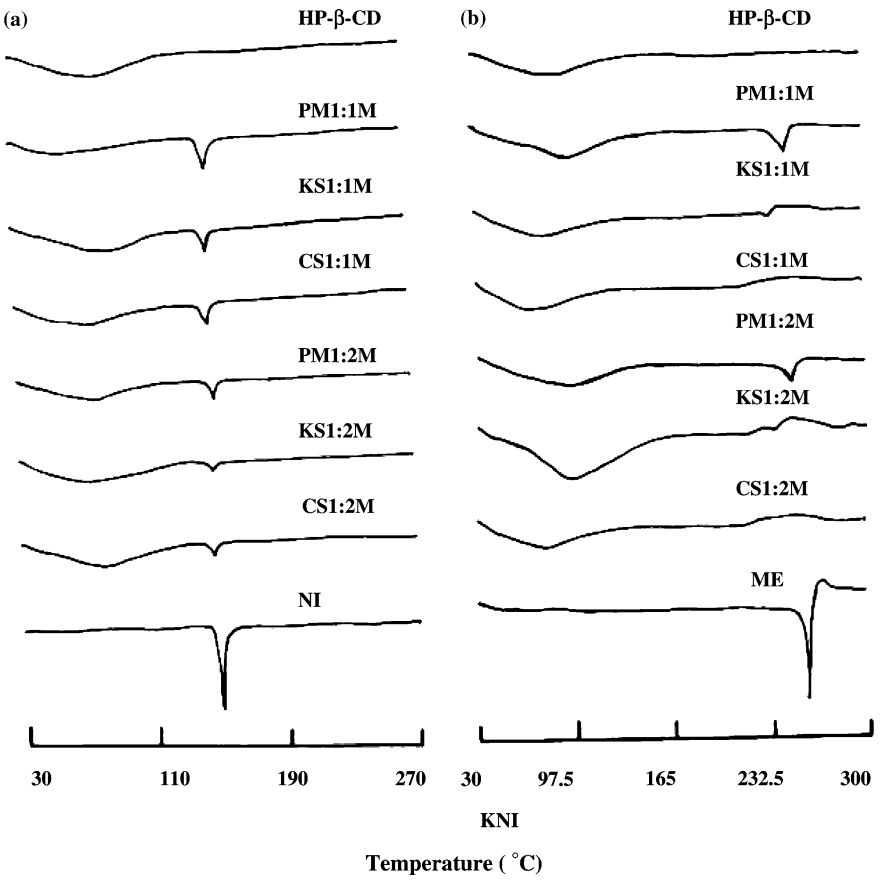

Figure 2. DSC thermograms of NI-HP-β-CD (a) and ME-HP-β-CD (b) binary systems. *Key:* Hydroxypropyl-β-cyclodextrin (HP-β-CD); Nimesulide (NI); Meloxicam (ME); Physical mixture (PM); Kneaded systems (KS); Co evaporated systems (CS); 1:1 M (1:1 Molar ratio) 1:2 M (1:2 Molar ratio).

of the component if a true inclusion complex is formed. A similar diffraction pattern with several intense peaks was achieved for any sample of NI, independently of the previous treatment, conclusively displaying its crystalline structure. The CNI showed a diffraction pattern similar to that of pure NI but with relatively more intense peaks. In the case of HP-β-CD samples a similar diffraction pattern was observed irrespective of method of treatment and absence of any peak is indicative of its amorphous nature. A similar diffraction pattern with several intense peaks was achieved for any sample of ME, independently of the previous treatment, conclusively displaying its crystalline structure. However, the CME showed a diffraction pattern similar to that of pure ME but with relatively less intense peaks.

In the cases of diffraction patterns of NI and ME-HP-β-CD 1:2 M physical mixtures all the principal peaks of NI, ME and HP-β-CD were present, although with low intensities than 1:1 M physical mixtures. This difference in peak intensities in different physical mixtures is due to the presence of different amounts of drugs and cyclodextrin. Because of the presence of higher amounts of NI and ME in 1:1 M physical mixtures in comparison with 1:2 M counter parts, intensities of NI and ME 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 NI and ME was due to their composition because a pure substance was compared with respect to physical mixture of two substances with different diffraction patterns. The diffraction patterns of NI-HP-β-CD kneaded and co evaporated binary systems at both molar ratios are the sum of each component and all the principal peaks of NI, HP-β-CD are observed, particularly the peak corresponding to NI at 19.2° 2θ, although with lower intensities when compared to corresponding physical mixtures and pure NI. 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 kneaded and co evaporated binary systems at both molar ratios. These results imply that no alteration was produced in the crystal structure of NI, 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. The peak heights of kneaded systems were low when compared to co evaporated systems.

Except with ME-HP-β-CD 1:1 and 1:2 M co evaporated systems the diffraction patterns of ME-HP-β-CD 1:1 and 1:2 M kneaded binary systems are the sum of each component and all the principal peaks of ME and HP-β-CD are observed, particularly the peak corre-

sponding to ME at 25.7° 2θ, although with lower intensities when compared to corresponding physical mixtures and pure ME indicating no true inclusion complexation of ME with these binary systems. In the case of ME-HP-β-CD 1:1 and 1:2 M co evaporated systems, the diffractogram showed a diffuse pattern without any peaks and is completely different to that of corresponding physical mixture, indicating the formation of solid inclusion complex. These observations were in accordance with the results of the DSC studies.

SEM studies

SEM is used to study the microscopic aspects of the raw materials i.e. CDs and drug substances and the products obtained by different methods of preparation like kneading and co evaporation etc. 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 NI particles are in the form of tabular shaped crystals with smooth surfaces. The kneaded sample (KNI) displayed similar appearance as the commercial sample but size of particles was reduced with the adherence of smaller particles on to the surfaces of larger particles. The evaporated particles (CNI) were well-developed tabular crystals, where smaller particles are adhered to surfaces of larger ones. The commercial ME particles are in the form of prismatic crystals with a relatively well-defined outline. The smaller particles are adhered to surfaces of larger ones. The kneaded sample (KME) displayed similar appearance as the commercial sample without changing the shape and size of the particles, whereas the evaporated particles (CME) were well-developed rectangular crystals, where smaller particles are adhered to surfaces of larger ones. The commercial HP-β-CD sample consists of very small particles generally having round shape, smooth faces and big holes covered by smaller particles, whereas the kneaded and evaporated particles are irregular in shape.

The physical mixtures were characterized by the presence of particles of both the components i.e. NI, ME and HP-β-CD without any modification in shape or size (Figure 3a & b). In contrast, all the micrographs of kneaded and co evaporated systems showed the effect of kneading and co evaporation techniques, where the samples were homogeneous, and it was impossible to differentiate crystals of both components indicating the better interaction of NI and ME particles with HP-β-

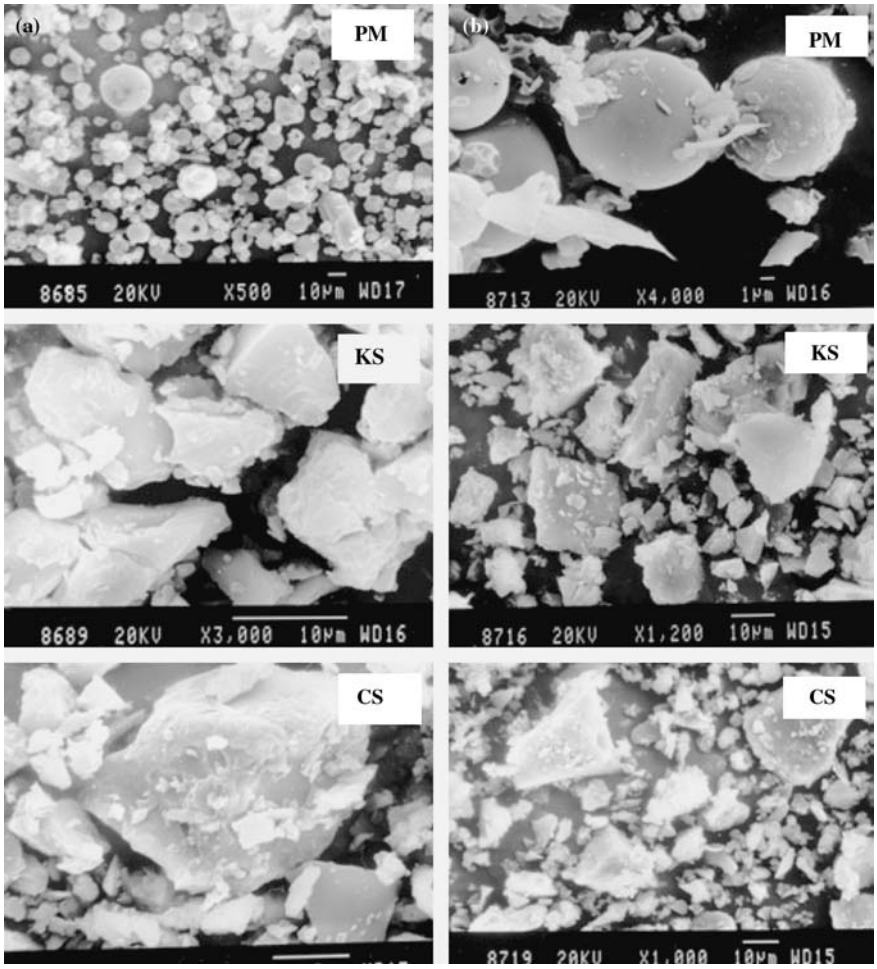

Figure 3. SEM photographs of NI-HP-β-CD (a) and ME- HP-β-CD (b) 1:2 M binary systems. *Key*: Nimesulide (NI); Meloxicam (ME); Physical Mixture (PM); Kneaded Systems (KS); Co evaporated Systems (CS); 1:2 M (1:2 Molar ratio).

CD (Figure 3a & b). 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 in the case of ME-HP-β-CD 1:1 and 1:2 M co evaporated binary systems along with the results of DSC and X-RD studies one can 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 the drug–CD binary systems. The most often used dissolution rate tests are the rotating disk method and dispersed amount method. In the present investigation dispersed amount method is used to investigate the various dissolution parameters of NI and ME NI and ME–HP-β-CD binary systems. The dissolution profiles of NI and NI-HP-β-CD, ME and ME–HP-β-CD binary systems were shown in Figure 4a and b. The results in terms of dissolution efficiency [9] at 10 min (DE_{10}%) and the percent of active ingredient dissolved at 30 min (DP_{30}) are presented in Tables 4 and 5. DE is defined as the area under the dissolution curve up to the time, t expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution Efficiency (DE)} = \left(\frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \right) 100$$

The dissolution efficiency can have a range of values depending on the time interval chosen. In any case constant time intervals should be chosen for comparison. In the present investigation DE_{10} values were calculated from the dissolution data of each product and used for comparison.

One-way ANOVA was used to test the statistical significance of differences between pure and treated samples of NI and ME. Significance of differences in the means was tested using Fishers LSD at 95% confidence.

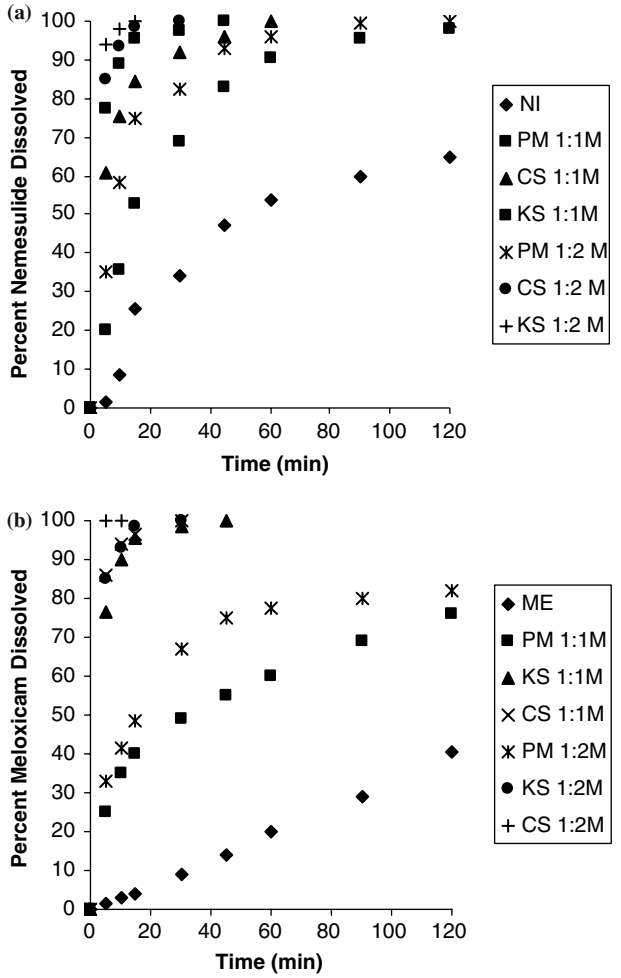

Figure 4. Dissolution profiles of NI-HP-β-CD (a) and ME-HP-β-CD (b) binary systems. *Key*: Nimesulide (NI); Meloxicam (ME); Physical Mixture (PM); Kneaded Systems (KS); Co evaporated Systems (CS); 1:1 M (1:1 Molar ratio) 1:2 M (1:2 Molar ratio).

Table 4. Mean ± SD values of DP_{30} and DE_{10} for NI and NI-HP-β-CD binary systems (n = 3)

Sample	DP_{30}	DE_{10} (%)
NI	34.26 ± 1.01	2.99 ± 0.32
KNI	36.44 ± 0.65	4.33 ± 0.03
CNI	18.22 ± 0.14	1.87 ± 0.06
NI-HP-β-CD PM 1:1 M	68.78 ± 0.53	19.02 ± 015
NI-HP-β-CD KS 1:1 M	91.75 ± 0.80	49.17 ± 0.03
NI-HP-β-CD CS 1:1 M	97.38 ± 0.14	61.07 ± 0.05
NI-HP-β-CD PM 1:2 M	82.42 ± 0.30	32.19 ± 0.17
NI-HP-β-CD KS 1:2 M	100.1 ± 0.01	65.89 ± 0.03
NI-HP-β-CD CS 1:2 M	100.02 ± 0.01	71.56 ± 0.01

Key: Nimesulide (NI); Kneaded Nimesulide (KN); Evaporated Nimesulide (CN); Physical Mixture (PM); Kneaded systems (KS); Co evaporated systems (CS) 1:1 M (1:1 molar ratio); 1:2 M (1:2 molar ratio); Hydroxypropyl-β-cyclodextrin (HP-β-CD).

Table 5. Mean ± SD values of DP_{30} and DE_{10} for ME and ME-HP-β-CD binary systems (n = 3)

Sample	DP_{30}	DE_{10} (%)
ME	9.18 ± 0.14	1.60 ± 0.14
KME	12.46 ± 0.03	2.90 ± 0.22
CME	60.30 ± 1.32	18.14 ± 0.33
ME-HP-β-CD PM 1:1 M	48.96 ± 0.17	21.35 ± 0.43
ME-HP-β-CD KS 1:1 M	98.44 ± 0.18	60.86 ± 0.48
ME-HP-β-CD CS 1:1 M	100.06 ± 0.06	66.42 ± 0.20
ME-HP-β-CD PM 1:2 M	67.00 ± 0.64	26.82 ± 0.20
ME-HP-β-CD KS 1:2 M	100.07 ± 0.07	69.83 ± 0.10
ME-HP-β-CD CS 1:2 M	100.06 ± 0.04	74.99 ± 0.01

Key: Meloxicam (ME); Kneaded Meloxicam (KME); Evaporated Meloxicam (CME); Physical Mixture (PM); Kneaded systems (KS); Co evaporated systems (CS); 1:1 M (1:1 molar ratio); 1:2 M (1:2 molar ratio); Hydroxypropyl-β-cyclodextrin (HP-β-CD).

The DP_{30} and DE_{10} values of KNI are significantly higher ($p < 0.05$) when compared to pure NI and CNI, whereas in the case of CME the values are significantly higher ($p < 0.05$) when compared to pure ME and KME.

The DE_{10} and DP_{30} values of the 1:2 M NI and ME–HP-β-CD binary systems are superior to those of 1:1 M binary systems (Tables 4 and 5). The increase in dissolution rate and efficiency values that were recorded for the physical mixtures when compared to pure drugs may be explained on the basis of the solubility of the drugs in aqueous CD solutions. Since the CDs dissolve more rapidly in the dissolution medium than the pure drug, it can be assumed that, in the early stages of the dissolution process, the CD molecules will operate locally on the hydrodynamic layer surrounding the particles of the drug, this action resulting in an *in situ* inclusion process, which produces a rapid increase of the amount of the dissolved drug [10].

The DE_{10} and DP_{30} values of NI-HP-β-CD kneaded systems were higher than those of co evaporated systems at both molar ratios. This may be due to the less crystallinity of the NI-HP-β-CD kneaded systems than those of the co evaporated systems at both molar ratios as evidenced by their characteristic peak heights in X-ray diffractograms. Overall, the improvement in dissolution properties of NI-HP-β-CD are in the order of KS > CS > PM at both molar ratios.

The DE_{10} and DP_{30} values of ME-HP-β-CD co evaporated systems are higher than those of kneaded systems at both molar ratios. This improvement in dissolution properties is due to the true inclusion complexation of ME with HP-β-CD in co evaporated systems. Overall, the improvement in dissolution properties of ME–HP-β-CD binary systems are in the order of CS > KS > PM at both molar ratios. Thus the dissolution properties of NI and ME can be improved by inclusion complexation with HP-β-CD.

Conclusions

Physicochemical characterization of NI and ME–HP-β-CD binary systems in solution state by phase solubility and ^{1}H-NMR spectroscopy studies revealed 1:1 M complexation. A true inclusion of ME with HP-β-CD at 1:1 and 1:2 M of co evaporated systems in solid state was confirmed by DSC, powder X-RD and SEM studies. Dissolution properties of NI and ME-HP-β-CD binary systems were superior when compared to pure NI and ME. Thus the aqueous solubility and dissolution properties of NI and ME can be improved by complexation with HP-β-CD.

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