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ORIGINAL ARTICLE

Insight into inclusion complexation of indomethacin nicotinamide cocrystals

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Abstract The objective of this research was to investigate the feasibility of the interaction between indomethacin-nicotinamide cocrystals with β-cyclodextrin and hydroxypropyl-β-cyclodextrin in the solid-state. The study has emphasized on the possibility of inclusion complex formation and its effect on the dissolution performance of the cocrystals. The solid systems in the molar ratio of 1:1 of the host and guest molecules were prepared by co-grinding and co-evaporation methods and compared with their physical mixtures. Furthermore, the molecular behaviors of the cocrystals in all prepared samples were thoroughly characterized by powder X-ray diffraction, differential scanning calorimetry, Fourier-transform infrared spectroscopy, scanning electron microscopy and in vitro dissolution performance. The results of these studies indicated that complexes prepared by the co-evaporation method with hydroxypropyl-β-cyclodextrin have shown complete inclusion of the cocrystals into the cyclodextrin cavity and a partial inclusion with β-cyclodextrin. Moreover, a significant ($p < 0.05$; ANOVA/Tukey) higher in vitro dissolution was achieved in co-evaporate complex prepared with hydroxypropyl-β-cyclodextrin compared to that prepared with β-cyclodextrin, indomethacin-nicotinamide cocrystals and indomethacin itself.

Keywords Cocrystals · β-Cyclodextrins · HP-β-Cyclodextrin · Indomethacin · Inclusion complexation · Nicotinamide

Introduction

In the development and manufacture of pharmaceutical products, improving the physicochemical properties of drugs is often essential but can be challenging. Because these improvements can often be achieved by making new solid forms of the drug without altering its chemical structure. Recent research has focused on identifying polymorphs, hydrates, solvates, salts and, more recently, cocrystals of drugs [1]. Cocrystals are composed of multiple molecular components, including the drug and a benign, non-toxic 'coformer' molecule. The design, formation and understanding of the physicochemical properties of cocrystals have received considerable attention [2–5]. Indeed, pharmaceutical cocrystals are an attractive alternative solid form with the potential to fine tune the physicochemical properties of drugs [6].

Inclusion or host–guest complexes are supramolecular systems where one chemical compound (the *host*) has a cavity, in which molecules of a second compound (the *guest*) are located [7, 8]. The study of non-covalent forces involved in the formation of host–guest complexes is of paramount importance for the design of synthetic inclusion compounds of active pharmaceutical ingredients (APIs).

β-Cyclodextrin (β-CD) is a cyclic oligosaccharide consisting of seven glucose units linked by α (1 → 4) bonds, resulting in a hollow truncated cone shape [9]. In water they have a hydrophilic outer surface and a hydrophobic central cavity able to include a wide variety of lipophilic guest molecules, with suitable polarity and dimensions,

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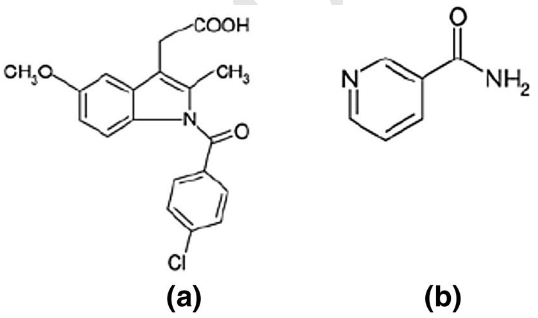
without the formation of any covalent bond [10]. Complexation with β-CD has found extensive applications in pharmaceutical technology to enhance the aqueous solubility, dissolution rate, bioavailability, and stability of poorly water soluble drugs [11, 12]. Unsubstituted β-CD has poor water solubility (16 mg mL^{-1} at 25 °C), whereas random substitution of the hydroxyl groups with alkyl or hydroxyalkyl groups is able to increase solubility. Therefore, several synthetically modified β-CDs were used as multifunctional drug carriers in parenteral formulations, such as hydroxypropyl β-cyclodextrin (HP-β-CD) [13].

Indomethacin (IND) (1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid) (Scheme 1a) is a non-steroidal anti-inflammatory drug [14]. It is known to form cocrystals with a non-toxic coformer, nicotinamide (NIC) (Scheme 1b) [15, 16].

To the best of our knowledge, indomethacin-nicotinamide cocrystals (INDNIC) complexation with different cylcodextrins has not been studied before. There is only an available report in the literature about formulation development of carbamazepine-nicotinamide cocrystals complexed with γ-cyclodextrin using supercritical fluid process [17]. In spite of γ-cyclodextrin is a highly water soluble derivative of cyclodextrins but it is not economic for the pharmaceutical industry. Additionally, the supercritical fluid technology is a complex, expensive and time consuming process. So, the objective of the present work was to study the feasibility of interaction of INDNIC with other types of cyclodextrins e.g., β-CD and HP- β-CD in the solid-state. More economic, simple and fast approaches have been applied to achieve inclusion complex formation which are co-grinding and co-evaporation methods. The study was further aimed to characterize the prepared complexes by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier-transform infrared (FTIR) spectroscopy and scanning electron microscopy (SEM). An in vitro dissolution study was also conducted to show the effect of cocrystals inclusion complexation on the dissolution profile of IND after its complexation with cyclodextrins compared with uncomplexed (free) INDNIC cocrystals and pure IND.



Scheme 1 The chemical structures of **a** IND and **b** NIC

Experimental

Materials

Indomethacin (γ form), nicotinamide, ethyl acetate, methanol were purchased from Sigma-Aldrich (Cairo, Egypt). β-cyclodextrin and HP-β-cyclodextrin were purchased from Fluka Chemie (Switzerland). All chemicals and solvents were of analytical grade and used as received.

Preparation of indomethacin cocrystals

Indomethacin cocrystals were prepared by slurry crystallization [18]. A total of approximately 3.578 g of IND and 1.221 g of NIC in a (1:1 molar ratio) was magnetically stirred in 10 ml of ethyl acetate for 5 days at room temperature. Solids were filtered, dried and analyzed by PXRD, DSC and FTIR.

Preparation of the physical mixtures

Physical mixtures of INDNIC with β-CD and HP-β-CD in (1:1 molar ratio) were prepared by simple blending in a glass mortar for 5 min and stored under vacuum in desiccator over calcium chloride for five consecutive days.

Preparation of the inclusion complexes

Co-grinding method

The ground mixtures of INDNIC with each of β-CD and HP-β-CD in (1:1 molar ratio) were prepared using the vibrational uniball mill (VEB leuchtenbau-KM1, Germany) for 15 min. The ground mixtures were sieved to obtain a particle size range of 125–250 µm, and then stored in a desiccator over calcium chloride for five consecutive days.

Co-evaporation method

Co-evaporates of INDNIC with each of β-CD and HP-β-CD were prepared by solvent evaporation method in the same molar ratio (1:1) as previously reported [19]. Briefly, IND-NIC was dissolved in a sufficient volume of methanol. Both β-CD and HP-β-CD were dissolved at 40 °C in distilled water. INDNIC and respective CD solutions were mixed together with constant stirring and kept at 40 °C for an hour, then gradually cooled to room temperature over a period of 6 h. The solutions were evaporated at 40 °C under vacuum till a constant weight was achieved. The collected powders were sieved to obtain a particle range of 125–250 μm and stored under vacuum in a desiccator over calcium chloride for five consecutive days.

Instrumentation

Powder X-ray diffractometry (PXRD)

The powder X-ray diffraction patterns of the solid samples were recorded using a Philips 1710 powder diffractometer with Cu Kα radiation (1.54056 Å). A Cu target tube operated at a voltage of 40 kV and a current of 40 mA and a single crystal graphite monochromator were employed. A scanning speed of 0.6°/min and a wide angel diffraction of $4° < 2\theta < 60°$ were applied. Standard polycrystalline silicon powder was used to calibrate the instrument.

Differential scanning calorimetry (DSC)

DSC thermograms were obtained by using a Shimadzu DSC-50 (Japan). Samples of about 5 mg were placed in aluminum pans of 50 μL capacity & 0.1 mm thickness, press-sealed with aluminum cover of 0.1 mm thickness. An empty pan sealed in the same way was used as a reference. The thermograms were recorded by heating the samples from 30 to 250 °C at a rate of 10 °C min^{-1}, under nitrogen flow of 40 ml min^{-1}. Indium was used as a standard for calibrating the temperature. Reproducibility was checked by running the samples in triplicate, the standard deviations calculated were found negligible.

Infrared spectroscopy

FT-infrared spectra were collected in triplicate using a Nicolet 6700 FTIR Advanced Gold Spectrometer in the diffuse reflectance mode with potassium bromide as a diluent (1:200), using <10 mg of the solid samples. The spectra were recorded in the range of 400–4000 cm^{-1} at 2 cm^{-1} spectral resolution with the accumulation of 256 spectral scans. The instrument was controlled with OMNIC 8 software. Triplicate spectra were averaged to obtain one spectrum for each sample. All FTIR spectra were exported to the Galactic* SPC format using GRAMS AI (Version 8.0, Thermo Electron Corp. Waltham, MA, USA) with no further processing.

Scanning electron microscopy

Particles were visualized by scanning electron microscopy (SEM; Jeol 5400 LV, Japan).

Particles were mounted on aluminum stubs (pin stubs, 13 mm), layered with a sticky conductive carbon tab and coated in gold (10–15 nm) using an EmiTech K 550X Gold Sputter Coater, 25 mA for 3 min.

In-vitro dissolution

Dissolution experiments were carried out in triplicate with USP apparatus II dissolution using paddle at a rotation speed of 100 rpm. Powdered samples of each preparation equivalent to 25 mg of IND were added to the dissolution medium, 500 mL of phosphate buffer, pH 7.4, kept at 37 ± 0.5 °C. At appropriate time intervals, 5 mL of the solution were withdrawn using cotton plug from the dissolution medium and replaced with an equal volume of the fresh dissolution medium equilibrated at 37 °C. Then aliquots were injected into the HPLC system. The HPLC system, Knauer, D–14163, Germany, consists of HPLC pump, UV- detector, and integration interface box. Chromatographic separation was carried out using Kromasil C-18 column (250 × 4.60 mm, particle size: 20 μm). The detection wavelength, 377 nm, was determined by scanning the maximum absorbance wavelength of IND in the mobile phase (Methanol: distilled water) using an UV–Vis spectrophotometer (Jenway, Model 6305, UK).

Statistical analysis

All statistical analysis was performed using One-way analysis of variance (ANOVA) with the Tukey's multiple comparisons was employed for comparing the preparations with each other (Minitab®16 Statistical Software). Statistically significant differences were assumed when $p < 0.05$. All values are expressed as their mean ± standard deviation.

Results and discussions

The solid-phase identity and purity of INDNIC cocrystals were verified using PXRD, DSC and FTIR prior to the inclusion complexation. The PXRD pattern and DSC melting curve and FTIR spectrum (Figs. 1a, 3a, 5a, b, respectively) of the INDNIC agreed well with the previously published data [16].

PXRD study

The PXRD patterns of INDNIC, β-CD and their physical, co-ground and co-evaporate mixtures were presented in Fig. 1. Those with HP-β-CD, in turn, were presented in Fig. 2. The diffractograms of both INDNIC cocrystals and β-CD exhibited series of intense peaks, which are

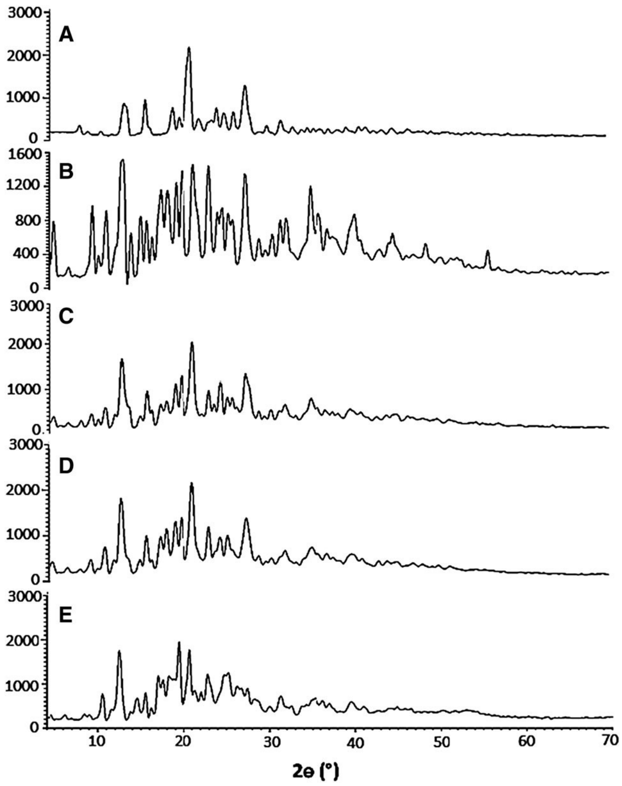


Fig. 1 The PXRD patterns of **a** INDNIC, **b** β-CD, **c** physical mixture, (D) co-ground mixture and (E) co-evaporate product. C, D and E are with β-CD

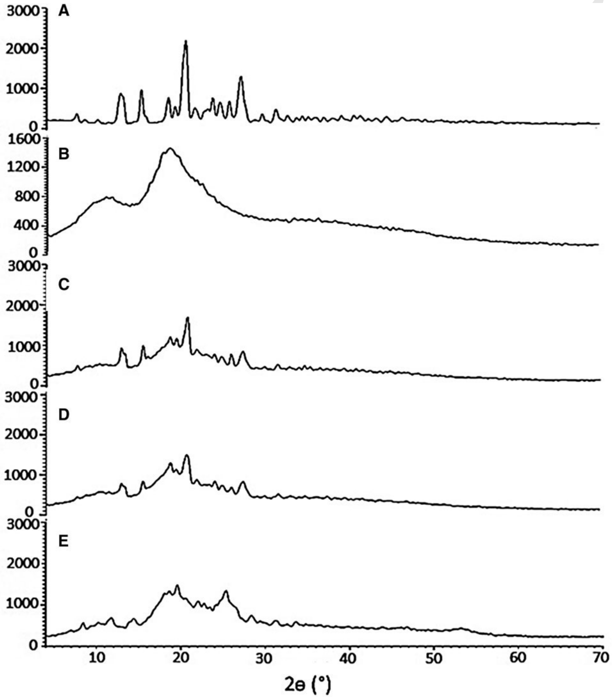


Fig. 2 The PXRD patterns of **a** INDNIC, **b** HP-β-CD, **c** physical mixture, (D) co-ground mixture and (E) co-evaporate product. C, D and E are with HP-β-CD

indicative of their crystallinity. Further, the diffractograms of their physical mixtures, co-ground mixtures still showed the characteristic peaks of both INDNIC and β-CD however, some peaks were reduced in their intensities (Fig. 1; traces C-E). Co-evaporate of INDNIC with β-CD showed further reduction in other crystalline peaks of INDNIC especially the most intense diffraction peaks at (2θ) = 15.35°, 23.89° and 27.22° (Fig. 1; trace D). However, the diffraction peak of INDNIC at (2θ) = 12.94° was disappeared with the recording of a new diffraction peak at (2θ) = 12.51° for their co-evaporate product. This may indicate that some sort of interaction has been occurred in case of the co-evaporate system which has led to formation of compound with lower crystallinity as compared with INDNIC cocrystals.

In case of INDNIC cocrystals with HP-β-CD, in turn, a significant reduction in the diffraction patterns of both the physical and co-ground mixtures of INDNIC/HP-β-CD has been observed (Fig. 2, traces C, D). On the other hand, the co-evaporate mixture of INDNIC and HP-β-CD showed new very small peaks at (2θ) values of 8.44°, 11.80°, 14.44°, 25.36° and 28.36° as compared to their physical and co-ground mixtures (Fig. 2, trace E). The disappearance of the crystalline peaks of INDNIC and recording of other new peaks could indicate the formation of structure with very low crystallinity [20]. On other words, co-evaporate system with HP-β-CD could have the potential to form an inclusion complex with INDNIC fitted inside the HP-β-CD cavity and such complex appeared to be partially amorphous.

The inclusion complexes of INDNIC with either β-CD or HP-β-CD were polycrystalline and of low crystallinity, respectively. Interestingly, Jambhekar et al. [21] concluded that, the inclusion complexes of IND itself with either β-CD or HP-β-CD were polycrystalline and amorphous, respectively.

DSC study

The DSC thermograms of INDNIC cocrystals, β-CD and their physical mixtures, co-ground and co-evaporate solid systems were presented in Fig. 3. Similarly, those with HP-β-CD were presented in Fig. 4.

The peaks corresponding to the evaporation of water vapors from both β-CD and HP-β-CD appeared at 85 and 60 °C; respectively (Figs. 3, 4; trace B) [22, 23].

The physical and co-ground mixtures of INDNIC with β-CD showed a reduced intensity endothermic peaks at 127.73 and 127.21 °C; respectively (Fig. 3; traces C and D) compared to that at 128.50 °C for INDNIC (Fig. 3; trace A). The presence of such endothermic peak in both the physical and co-ground mixtures still reflect the presence of free INDNIC in the prepared solid systems. Also, it was

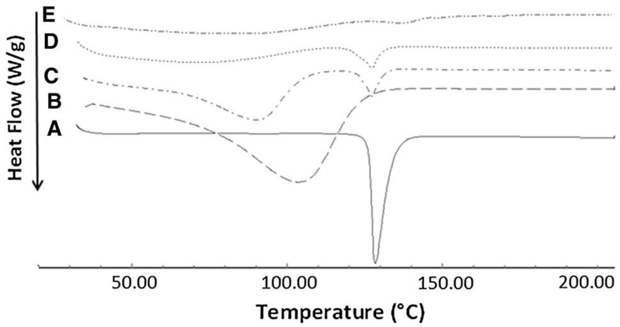


Fig. 3 The DSC thermograms of *A* INDNIC, *B* β-CD, *C* physical mixture, *D* co-ground mixture and *E* co-evaporate product. *C*–*E* are with β-CD

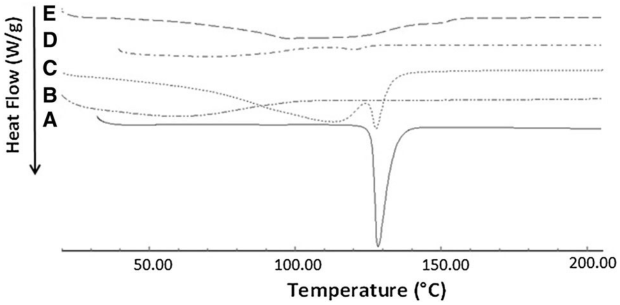


Fig. 4 The DSC thermograms of *A* INDNIC, *B* HP-β-CD, *C* physical mixture, *D* co-ground mixture and *E* co-evaporate product. *C*–*E* are with HP-β-CD

noted that the water evaporation endothermic peak was shifted from 80 to 60 °C in case of the physical mixture with β-CD (Fig. 3, trace C).

Similarly, it was found that the melting endotherm of INDNIC physical and co-ground mixtures with HP-β-CD appeared broader and shifted from 128.50 to 127.50 and 120.26 °C; respectively (Fig. 4, traces C and D). Further, the broadening and reduction of that peak could be attributed to the incomplete complex formation via simple physical and co-ground methods.

However, in case of co-evaporate mixtures with β-CD, a small, highly broad endothermic peak was observed at 135.74 °C concomitantly with broadening of the water evaporation peak (Fig. 3; trace E). This may indicate that some sort of inclusion into the β-CD cavity was occurred and there was still some INDNIC cocrystals cannot fit completely inside the β-CD cavity which is responsible for this small endothermic broad peak [24].

On the other hand, the melting endotherm of co-evaporate with HP-β-CD was completely disappeared which indicated that the new solid compound formed has an amorphous structure (Fig. 4; trace E). These findings come in accordance with the above mentioned PXRD results. Moreover, the complete disappearance of the water evaporation peak of HP-β-CD in case of co-evaporate mixture with INDNIC could indicate that the cocrystal has penetrated into the HP-β-CD cavity and replaced the water molecules.

Solid-state FTIR spectroscopic investigation

FTIR spectroscopy was used to assess the interaction between the cocrystal and the two studied cyclodextrins in the solid state. The chemical interaction between the host and the guest molecules often leads to identifiable changes in the FTIR spectra of complexes. However, some of the changes are very subtle requiring careful interpretation of the spectra.

The FTIR spectra of INDNIC, β-CD, HP-β-CD and their respective physical and cog-round mixtures and co-evaporate products exhibited a number of differences in both the fingerprint and high wavenumber regions (Figs. 5, 6). The υ (OH) regions in the FTIR spectra appear as very broad bands in the range of 3400–2500 cm^{-1} which are superimposed on the υ (CH) regions. Both the broad nature and the position of these FTIR bands are characteristic of hydrogen-bonded OH groups [25]. The differences in the shapes of these bands suggest that there may be associated variations in hydrogen bonding.

By close inspection of the FTIR spectra of INDNIC, β-CD and their physical and ground mixtures and their co-evaporate products in the wavenumber range (3400–2500 cm^{-1}), it could be noted that the characteristic sharp υ (OH) bands at 3413 and 3318 cm^{-1} and υ (NH$_2$) bands at 3285 and 3218 cm^{-1} of INDNIC were recorded as broader bands in the FTIR spectra of their physical and ground mixtures with reduced intensities but not in the spectrum of their co-evaporate products except the υ (OH) band at 3413 cm^{-1} (Fig. 5a). That may indicate incomplete inclusion of the cocrystal in the β-CD cavity by physical mixing and co-grinding approaches. The same also may apply to the co-evaporation approach as indicated by the recording of the above weak υ (OH) band at 3413 cm^{-1} in the FTIR spectrum of the co-evaporate product (Fig. 5a, trace E). Based on the above observations, partial inclusion is more efficient by the co-evaporation approach as compared to the two other methods which supports the previous findings from the PXRD and DSC data.

In case of HP-β-CD only the sharp υ (OH) and υ (NH$_2$) bands at 3413 and 3218 cm^{-1}, respectively were recorded as broader bands in the FTIR spectra of their physical and ground mixtures with reduced intensities but not in the spectrum of their co-evaporate products (Fig. 6a). That may indicate more efficient partial inclusion of the cocrystal in the HP-β-CD cavity by physical mixing and co-grinding approaches. However, in case of the co-

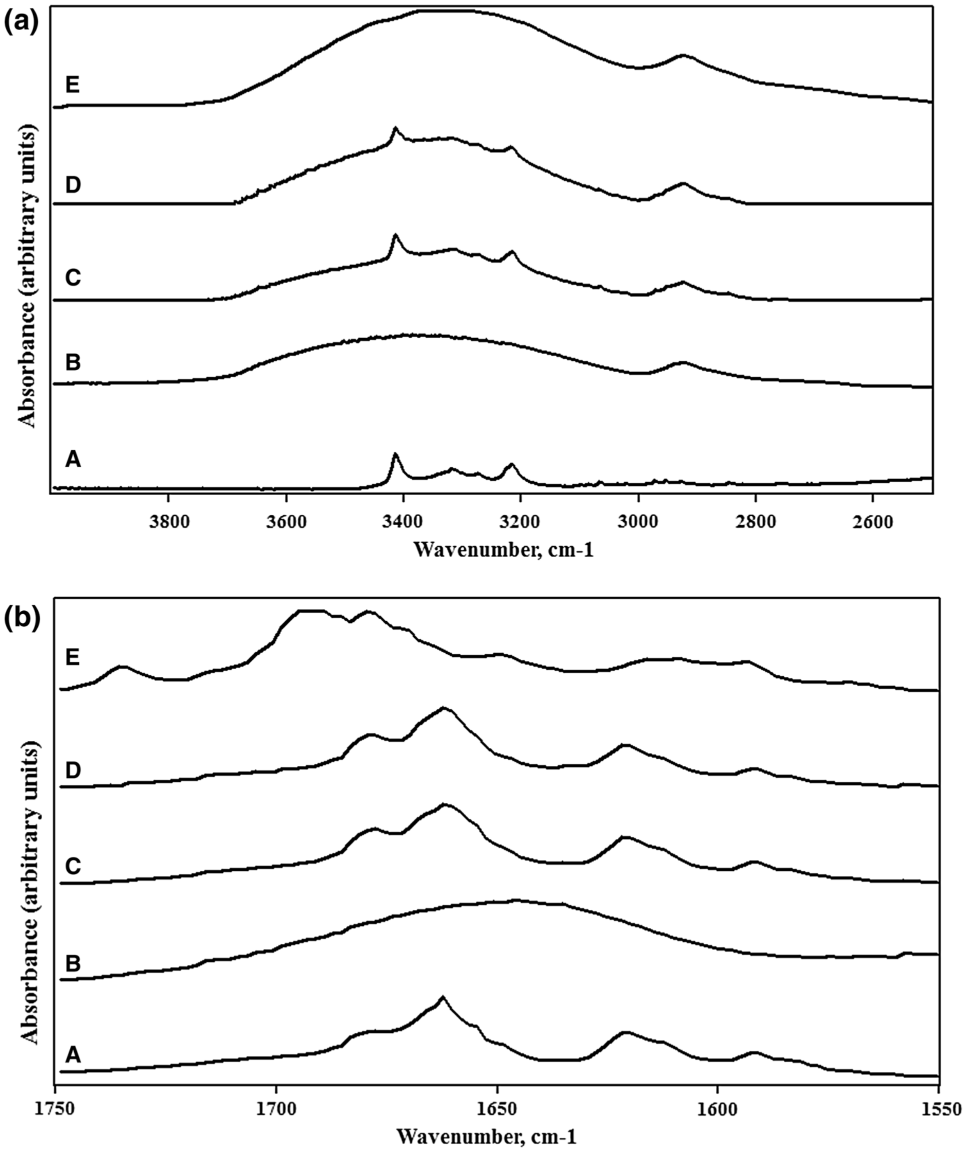


Fig. 5 **a** The FTIR spectra in the wavenumber range (2500–4000 cm^{-1}) of *A* INDNIC, *B* β-CD, *C* physical mixture, *D* co-ground mixture and *E* co-evaporate product. *C*–*E* are with β-CD. **b** The FTIR spectra in the wavenumber range (1550–1750 cm^{-1}) of *A* INDNIC, *B* β-CD, *C* physical mixture, *D* co-ground mixture and *E* co-evaporate product. *C*–*E* are with β-CD

evaporation approach, the inclusion complexation appears to be complete (*cf.* that with β-CD).

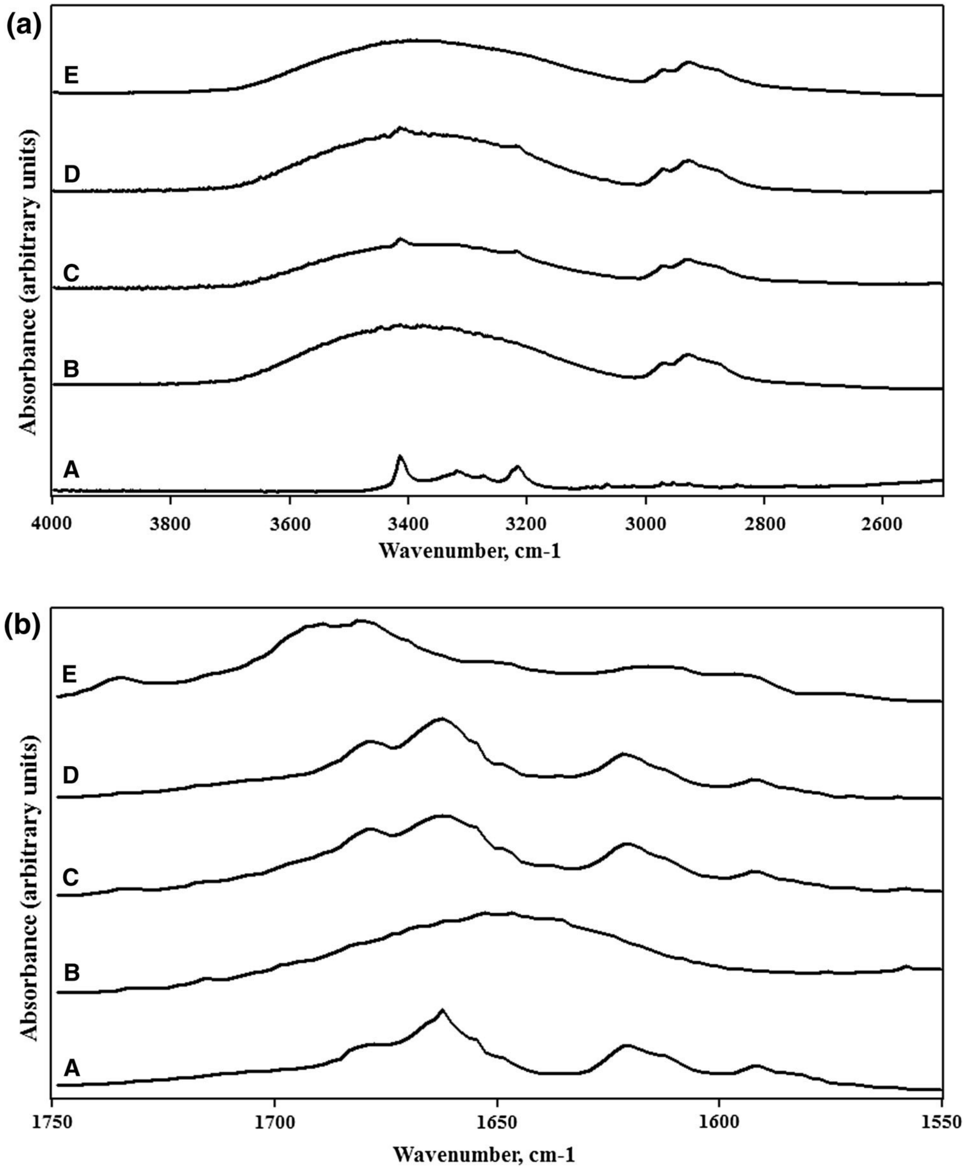
By careful inspection of the FTIR spectra of INDNIC, β-CD, and their physical and ground mixtures and their co-evaporate products in the wavenumber range (1550–1750 cm^{-1}) region, in turn, rather interesting findings were apparent (Fig. 5b).The characteristic υ(C=O) bands of INDNIC at 1661 and 1680 cm^{-1} were recorded in the FTIR spectra of their physical and ground mixtures. However in the FTIR spectrum of their co-evaporate product they were shifted to 1680 and 1691 cm^{-1}, respectively with the recording of a new υ(C=O) band at 1735 cm^{-1}. These significant shifts together with the recording of a new υ(C=O) band suggest the formation of new hydrogen bonding between the cocrystal and the OH groups in the interior cavity of β-CD during their more efficient partial inclusion. The same was also noted with HP-β-CD (Fig. 6b). These shifts together with the recording of a new υ(C=O) band at 1735 cm^{-1} further confirm the complete inclusion of the cocrystal with the HP-β-CD using the co-evaporation approach. These findings further confirm the above PXRD and DSC observations.

SEM analysis

The SEM images of INDNIC, HP-β-CD and their co-evaporate and co-ground products, β-CD and its co-evaporate product with INDNIC were presented in Fig. 7 (traces A, B, C D, E and F, respectively).

Striking differences in the morphology of the particles were observed upon careful inspection of the SEM images. INDNIC particles were appeared as rectangular crystals

Fig. 6 **a** The FTIR spectra in the wavenumber range (2500–4000 cm^{-1}) of *A* INDNIC, *B* HP-β-CD, *C* physical mixture, *D* ground mixture and *E* co-evaporate product. *C*–*E* are with HP-β-CD. **b** The FTIR spectra in the wavenumber range (1550–1750 cm^{-1}) of *A* INDNIC, *B* HP-β-CD, *C* physical mixture, *D* ground mixture and *E* co-evaporate product. *C*–*E* are with HP-β-CD

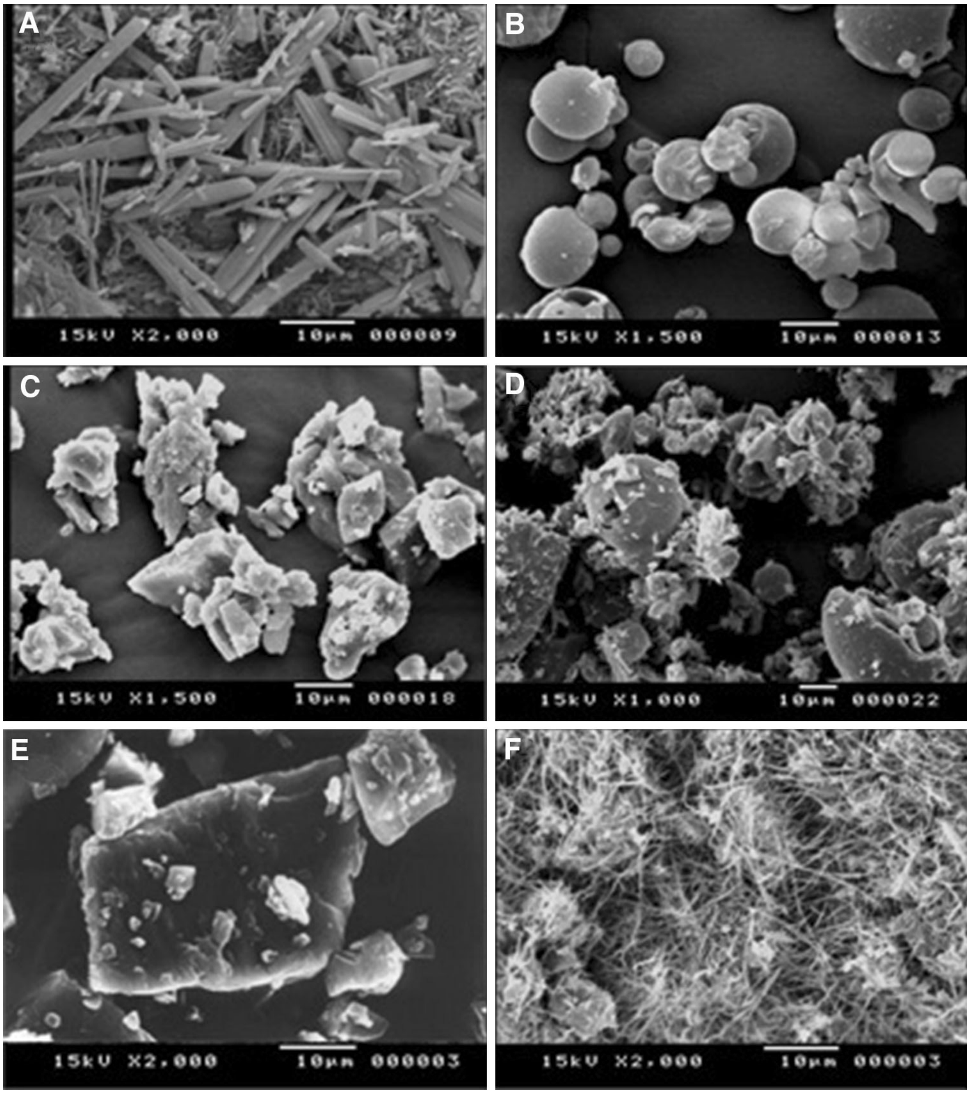


while HP-β-CD was presented as aggregated spherical particles (Fig. 7, traces A and B). By comparing the morphology of the co-evaporate and co-ground products of INDNIC with HP-β-CD, it could be noted that, the co-evaporate product appears as large irregular aggregates of thick lumps which differ in morphology than both INDNIC and HP-β-CD (Fig. 7, trace C), which could indicate the loss of the crystalline shape of INDNIC and formation of another complex structure with a new morphology. The co-ground product, in turn, shows the loss of the spherical appearance of HP-β-CD particles with the appearance of the cocrystals (Fig. 7, trace D). The loss of the spherical characters could be possibly attributed to the grinding process. These observations are in agreement with our above findings from PXRD, DSC and FTIR studies which further confirm the complete inclusion of the cocrystal with the HP-β-CD using the co-evaporation approach.

To further confirm our findings, the morphology of β-CD particles and their co-evaporate product with INDNIC were also compared. Interestingly, the cocrystals were appeared as a huge network of aggregated filaments on the surface of β-CD particles (Fig. 7, trace E). Such morphology may indicate the incomplete inclusion of the cocrystals using the co-evaporation approach.

The variations in the particles morphology among the above products despite similar processing conditions could be explained by considerable differences in the crystallization kinetics or crystal lattices.

Fig. 7 The SEM images of **a** INDNIC, **b** HP-β-CD, **c** co-evaporate product of INDNIC with HP-β-CD, **d** co-ground product of INDNIC with HP-β-CD, **e** β-CD and **f** co-evaporate product of INDNIC with β-CD



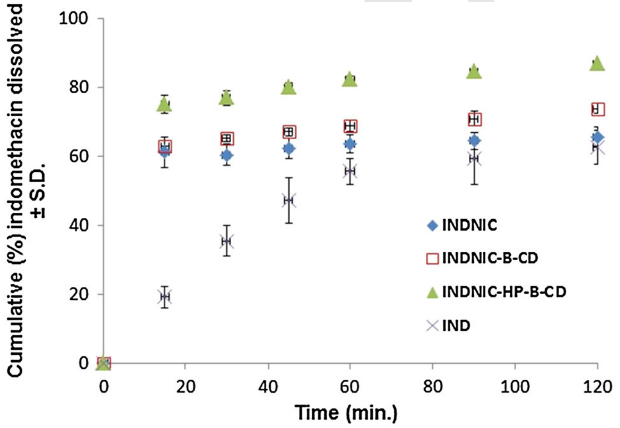


Fig. 8 The dissolution profiles of IND, INDNIC and the co-evaporate mixtures of INDNIC with β-CD and HP-β-CD

In vitro dissolution study

Figure 8 shows the dissolution profiles of IND, INDNIC and co-evaporate mixtures of INDNIC with β-CD and HP-β-CD in pH 6.8. It was found that the percentages of IND powder dissolved after 15 and 120 min were 19.32 % ± 6.5 and 62.55 % ± 4.9; respectively. INDNIC cocrystals and co-evaporate mixtures of INDNIC with β-CD and HP-β-CD showed a significantly ($p < 0.05$; ANOVA/Tukey) higher increase in the dissolution rate of IND 61.20 % ± 4.5, 62.96 % ± 1.8 and 75.16 % ± 2.7 after 15 min; respectively compared with untreated IND powder, 19.32 % ± 6.5, after the same time interval. Further, the co-evaporate mixture of INDNIC with HP-β-CD gives a significantly ($p < 0.05$; ANOVA/Tukey) higher increase in the dissolution rate of IND 75.16 % ± 2.7 and 86.76 % ± 0.7 after 15 and 120 min; respectively compared to INDNIC cocrystals which showed 61.20 % ± 4.5 and 65.77 % ± 2.8 IND percentage released after the same time. INDNIC cocrystals significantly increased the dissolution rate of IND compared with the untreated IND powder possibly as previously reported with indomethacin-saccharin cocrystals [18]. Furthermore, the effect of HP-β-CD on the dissolution rate of certain drugs was higher than that of β-CD due to its higher water solubility and the bigger capacity of its cavity [19, 26, 27]. It is worth to note that, the co-evaporate mixture with HP-β-CD produces a significant ($p < 0.05$; ANOVA/Tukey) rapid dissolution after 15 and 120 min as compared to that with β-CD co-evaporate system. That may be attributed to local solubilisation action operating in the micro-environment or the hydrodynamic layer surrounding the cocrystals particles in the early stages of the dissolution process. Additionally, HP-β-CD dissolves in a short time compared with β-CD thus improves the wettability of the cocrystals and hence their dissolution [23]. Also, one could not neglect that, the formation of the complete inclusion complex with a new partially amorphous structure which could enhance the dissolution process compared to the co-evaporate system with β-CD and this is in agreement with PXRD, DSC and FTIR studies.

Conclusions

Partial and complete inclusion complexes of INDNIC cocrystals with β-CD and HP-β-CD were prepared successfully by the co-evaporation method in a molar ratio of 1:1 of the guest to host molecules. This was confirmed by various analytical techniques. The co-evaporate mixture of INDNIC with HP-β-CD showed new morphological structure as observed from SEM Study. The prepared inclusion complexes enhanced the dissolution rate of IND significantly as compared with the untreated IND and INDNIC cocrystals. Furthermore, the highest improvement in IND in vitro dissolution was observed in the inclusion complex prepared with HP-β-CD.

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