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Phase Characterization of Indomethacin in Adsorbates Onto Hydroxyethylcellulose

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The phase state and solubility of indomethacin in adsorbates onto hydroxyethylcellulose have been studied. The characterization of the adsorbates and their relevant physical mixtures was made by the use of DSC, X-ray diffractometry, FT-IR spectrometry, and solubility analysis. The drug-to-polymer ratio determines either a partial crystallization of the metastable alpha-form onto hydroxyethylcellulose surface or complete inhibition of indomethacin crystallization. Significantly improved drug aqueous solubility was achieved. A stable immobilization of indomethacin molecules onto hydroxyethylcellulose due to drug/polymer interactions can be assumed. The changed indomethacin phase state in the adsorbates remains stable for one-year storage at ambient conditions. These results could be of practical importance.

Keywords indomethacin; hydroxyethylcellulose; adsorbates; phase state; amorphization; improved solubility

INTRODUCTION

There are numerous reports on physical changes of 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, indomethacin (IND) during specific pharmaceutical processing leading to improved drug dissolution (Hancock & Parks, 2000; Yoshioka et al., 1995). Interactions with different excipients resulting in polymorphic transitions, amorphization, particles size reduction, and/or complex formation are also of increased research interest (Taylor & Zografi, 1997; Valizadeh et al., 2004). Our previous studies (Bogdanova & Ford, 1998) demonstrated crystallization of alpha- or beta- polymorphs occurring in the processing of IND adsorbates onto the surface of some hydrophilic polymers. Poly(vinylpyrrolidone) (PVP) is reported to be one of the most studied hydrophilic polymers as potent inhibitor of IND crystallization and complex forming agent (Matsumoto & Zografi, 1999; Taylor & Zografi, 1997; Yoshioka et al., 1995). To our knowledge, however, there are no available data about similar effects of hydroxyethylcellulose (HEC). The only results reported (Bogdanova & Avramova, 2000) on inhibition of IND crystallization occuring by surprise in the processing of IND adsorbate onto the surface of HEC were preliminary and the phenomenon was not explained.

The present study aims to elucidate the character of the physical changes of indomethacin in presence of HEC in the processing of IND/HEC adsorbates and to study the factors contributing to the changes of IND phase state and solubility.

The technical procedure applied to prepare the IND/HEC adsorbates reveal some advantages over the classic solid dispersion technique reviewed by Chiou, Riegelman, 1971. In general, they are: (i) quantitative drug deposition on the surface of the polymer particles, (ii) 96% (v/v) ethanol is a good solvent of IND and an appropriate dispersion medium for the polymer HEC, (iii) the solvent system usually favors crystallization of alpha-IND (the case with adsorbates of HEC concentration below 50%) which in comparison to gamma-polymorph has a higher potential to react and is more soluble in water, (iv) mild process conditions (e.g., dispersing at room temperature and removing of the solvent under vacuum around 50°C). HEC was chosen as a carrier because it is a non-ionic, pH insensitive, water-soluble bioadhesive polymer, with rapid hydration and viscosity development in solution. HEC, moreover, can be used as thickener, protective colloid, stabilizer, suspending excipient in liquid or semi solid dosage forms (Lee et al., 2000)

MATERIALS AND METHODS

Materials

Indomethacin (IND) was kindly donated by Sopharma, Sofia, Bulgaria and hydroxyethylcellulose (HEC), medium viscosity –75 –125 mPa.s. (2% in water, 20°C), potassium

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dihydrogen phosphate (analytical grade), and disodium hydrogen phosphate dihydrate (analytical grade) were purchased from Fluka, Buchs, Switzerland.

Preparation of Indomethacin/Hydroxyethylcellulose Adsorbates and Physical Mixtures

Indomethacin/hydroxyethylcellulose adsorbates and physical mixtures were prepared in IND to HEC ratios: 1: 0.5 (w/w) (or 66.7:33.3 wt. %)-; 1:1 (w/w) (or 50:50 wt. %)- and 1:2 (w/w) (33.3:66.7 wt. %). The adsorbates were prepared by dissolving of the required amount of indomethacin in 96% (v/v) ethanol (Eur.Ph.5) using a round bottom flask. The corresponding amounts of HEC were dispersed into the IND solution under continuous stirring (magnetic stirrer). The resulting suspension was stirred additionally for 1 h at room temperature. The solvent was evaporated at 50°C in a Rotavapor R-114 (BÜCHI Labortechnik AG, Flawil, Switzerland). The solid residue was dried overnight in a vacuum desiccator over P_2O_5, pulverized in a mortar with a pestle and passed through a 0.2 mm sieve. The samples in closed vials were kept into the dessicator until use. The IND/HEC physical mixtures were prepared in a mortar with a pestle after blending and co-grinding of both components for 10 min. The samples were passed through a 0.2 mm sieve and stored as described above.

IND content uniformity—amount of IND/HEC adsorbate equivalent to 50 mg IND is dispersed in 50 mL 96% (v/v) ethanol with shaking. The dispersion is filtered and IND concentration determined by UV spectroscopy at 320 nm.

FT-IR Spectrometry

Infrared spectra were obtained using a FT-IR-8010M spectrometer (Shimadzu, Kyoto, Japan). The samples were KBr discs of drug concentration around 1%. The parameters of the spectrum were: resolution, 40 cm^{-1}; accumulation, 40; and detector 1.28 nm s^{-1}.

Thermal Analysis

The differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were performed with a Mettler TA-3000 system. The DSC equipment was calibrated with indium, lead, and zinc. The samples were sealed in aluminium pans with vented covers. The scanning was in the temperature range between 25 and 250°C at heating rate of 10°C min^{-1}. All the experiments were performed under dry nitrogen gas atmosphere.

X-ray Powder Diffraction

X-ray powder diffraction studies were performed on a Siemens Diffractometer with Ni filtered CuK-alpha radiation, 30 kV and 15 mA at a scan rate of 4° min^{-1} over the 2 θ range from 5 to 35.

Apparent Equilibrium Solubility

Samples of IND/HEC drug adsorbates or physical mixtures in amounts equivalent to 0.15 g IND (drug amount in excess) are placed in bottles with glass stoppers and dispersed in 20 mL phosphate buffer pH 6.8. The samples were shaken in a thermostatic water bath at 22 ± 0.1°C until equilibrium. The samples were filtered through 0.45 mm membrane filter and spectrophotometrically assayed in UV at 320 nm (Spectrophotometer Hitachi U-1100, Japan). No drug adsorption onto the filter was established.

The apparent solubility of IND in presence of increasing amount of HEC—0.5, 1.0, and 2.0%, respectively, was determined as described above. All experiments were carried out comparatively with a sample of non-treated IND.

RESULTS AND DISCUSSION

DSC- and X-ray Analysis

The DSC traces of the untreated IND and HEC, IND/HEC 1:0.5 (w/w), (66.6:33.3 wt.%), −1:1(w/w) (50.0:50.0 wt. %) and −1:2 (w/w) (33.3:66.6 wt. %) adsorbates and their relevant physical mixtures are presented in Figures 1, 2, and 3.

The DSC curve of the pure IND (Figures 1, 2, and 3, curves 1), displays only the sharp melting endotherm of the gamma polymorph with maximum at T_m = 161.3 ± 0.5°C and enthalpy ΔH_m = 102 ± 2 J/g. It should be pointed out that no traces of other IND polymorphs have been detected (Legendre & Feutelais, 2004).

The X-ray powder diffraction analysis confirms this observation. The main characteristic peaks of the gamma polymorph

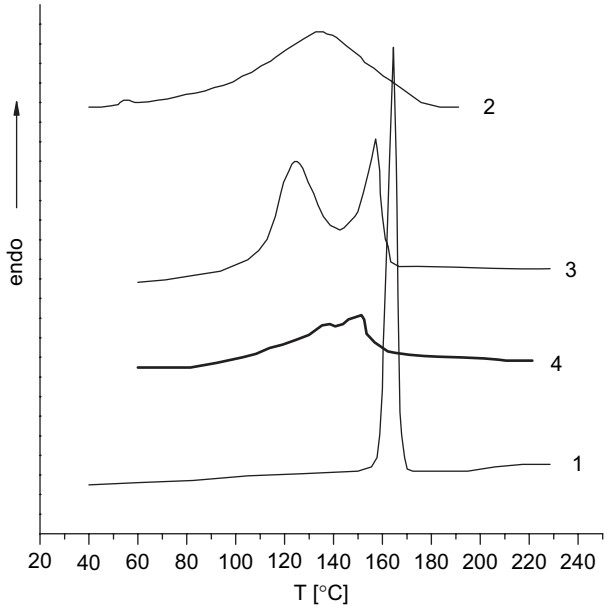

FIGURE 1. DSC traces of: 1. γ-IND 2. HEC; 3. IND/HEC 1:0.5 (w/w) phyical mixture; 4. IND/HEC 1:0.5 (w/w) adsorbate.

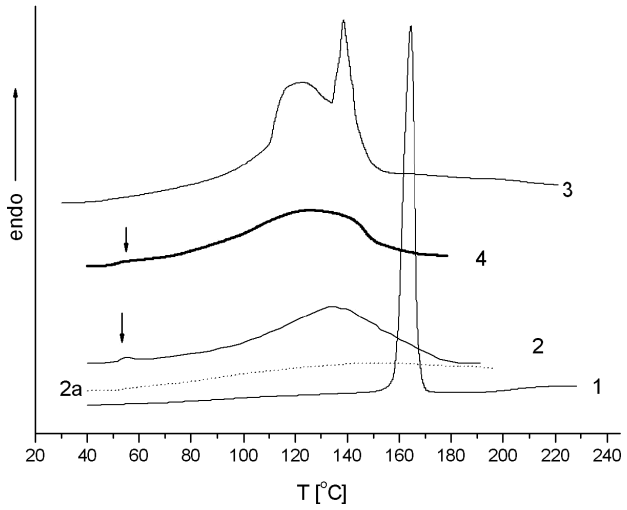

FIGURE 2. DSC traces of: 1. γ-IND; 2. HEC; 2a. HEC (second scan); 3. IND/HEC 1:1 (w/w) physical mixture; 4. IND/HEC 1:1 (w/w) adsorbate.

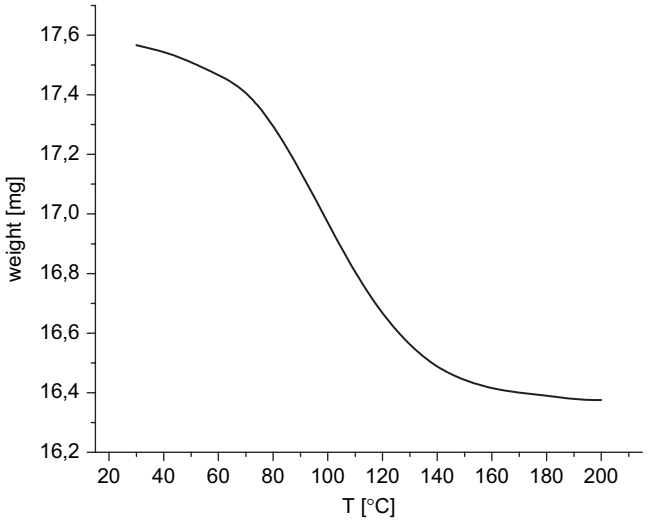

FIGURE 4. Thermogravimetric curve of HEC between 30 and 200°C at heating rate 10°C min^{-1}.

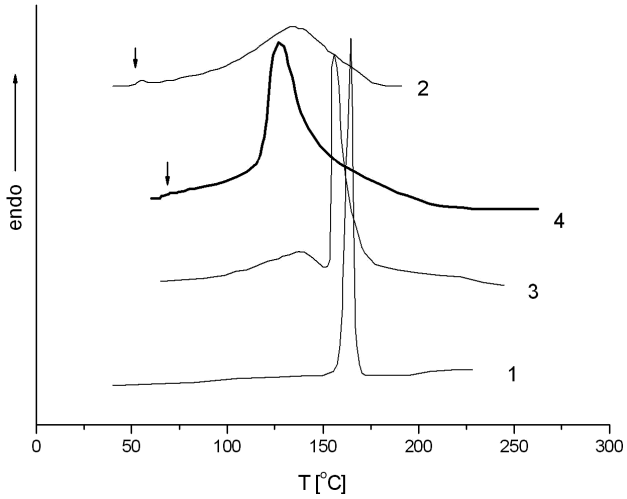

FIGURE 3. DSC traces of: 1. γ-IND; 2. HEC; 3. IND/HEC 1:2 (w/w) physical mixture; 4. IND/HEC 1:2 (w/w) adsorbate.

at 2θ : 11.6, 16,8, 19.6, 21.8, and 26.6 (Otsuka et al., 2003) can be clearly distinguished in the diffraction profile of the studied untreated IND (Figure 5, curve 1).

After the first run the IND sample was cooled into DSC and second scanning was carried out. Neither endo- nor exotherms were observed, a fact confirming the IND vitrification after melt cooling (Andronis & Zografi, 2000; Tong & Zografi, 1999).

As seen from Figures 1, 2, and 3, curves 2, the pure HEC reveals an endotherm in a very wide temperature interval with a maximum at 135°C. The enthalpy of the endotherm is ΔH = 145 J/g and is evaluated by peak integration between 65 and 186°C. It is worth noting that the effect disappears at the second run of the sample (Figure 2, curve 2a). Thus, it can be assumed that the observed broad endothermal effect is caused by two processes: (i) evaporation of adsorbed water at lower temperatures and (ii) reaction of dehydration between the vicinal polymer hydroxyls occuring at higher temperatures. The weight loss of HEC sample registered by TGA measurement confirms these suggestions (Figure 4). Similar assumptions were reported by Avramova & Fakirov, 1990 for native cellulose.

The presented DSC trace of pure HEC indicates a completely amorphous structure. The latter was additionally confirmed by X-ray powder diffraction analysis (Figure 5, curve 5).

The DSC study reveals marked differences in the thermal behaviour of the physical mixtures and the corresponding adsorbates with all drug concentrations (Figures 1, 2, and 3, curves 3, 4).

The thermograms of all studied IND/HEC physical mixtures (curves 3 of the Figures 1, 2, and 3) display the characteristic endotherms of HEC and gamma-IND. The observed shift of the IND melting peak to lower temperatures could be mainly related to the presence of HEC. The shape and the position of the peaks are influenced by the components ratio and assume interactions to a certain extent during co-grinding.

The X-ray diffraction analysis, similarly to DSC, excludes a phase transformation. In the diffractogramm of the IND/HEC1/2 (w/w) physical mixture (Figure 5, curve 3) presented as an illustration, the gamma-IND main crystalline peaks at 2θ : 11.6, 16,8, 19.6, 21.8, and 26.6, can be clearly distinguished.

The thermal behaviour of IND/HEC adsorbates (curves 4, Figures 1, 2, and 3) proves that: (i) IND undergoes physical change during the adsorbate processing, (ii) the type of the change depends namely on the HEC concentration, and (iii) the HEC concentration of 50 wt. % is critical for IND crystallinity loss.

The DSC thermogram of IND/HEC 1:0.5 (w/w) adsorbate shows a double endothermal effect (Figure 1, curve 4). In

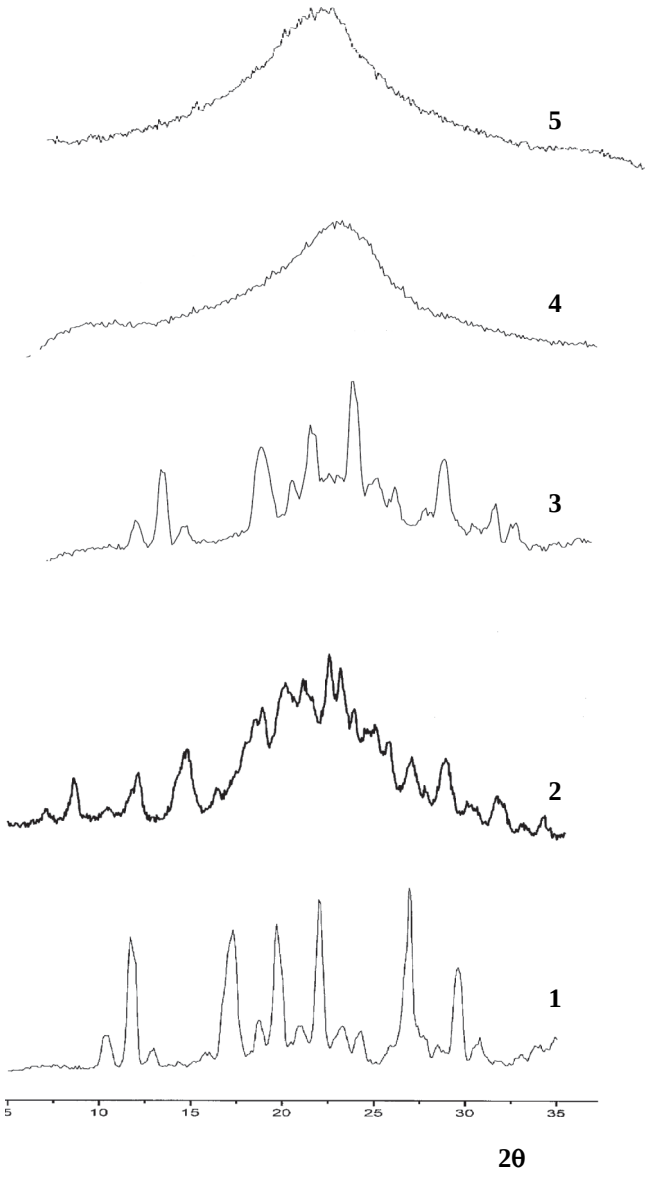

FIGURE 5. Powder X-ray diffractograms of: 1. γ-IND; 2. IND/HEC 1:0.5 (w/w) adsorbate; 3. IND/HEC 1:2 (w/w) physical mixture; 4. IND/HEC 1:2 (w/w) adsorbate; 5. HEC.

contrast to the endotherms in the DSC trace of the relevant physical mixture (Figure 1, curve 3) both peaks are not separated and not well expressed. In addition to the HEC endotherm, another overlapping peak appears with a maximum at 150.5°C which could be related to the melting of the metastable alpha-IND. The peak shape indicates a significant lowering of the degree of IND crystallinity.

The observed marked changes in the thermal behaviour of the 1:0.5 adsorbate compared to that of the physical mixture can be related to IND/HEC specific interactions. They are: (i) IND crystallizes partially as alpha polymorph; (ii) the assumed dehydration process of HEC at heating is suppressed because IND molecules are oriented and attracted to HEC hydroxyl groups, and (iii) the effect of suppression is much better expressed if compared to that of 1:1 (w/w) adsorbate (curves 4, Figures 1 and 2). The normalized ΔH-value of the IND/HEC 1:0.5 (w/w) adsorbate (containing an excess of IND) is approximately 5-times lower than the ΔH of 1:1 (w/w) adsorbate (containing 50.0 wt. % HEC).

The X-ray diffraction profile of the IND/HEC 1/0.5 (w/w) adsorbate shown in Figure 5, curve 2 confirms the DSC results. It reveals that the main diffraction peaks are at 2θ—8.4, 14.4, 18.5, and 22.0°, which correspond to those reported for alpha-IND (Otsuka et al., 2003).

The DSC results indicate that both IND/HEC 1:1 and 1:2 adsorbates are amorphous. Only broad endothermic effects around 125°C are observed, there is no peak which can be attributed to IND melting (Figures 2 and 3, curves 4). The second run traces of IND/HEC 1:1- and 1:2 (w/w) adsorbates display no thermal effects and are similar to that of pure HEC (Figure 2, curve 2a). The amorphous structure is definitively supported by the X-ray analysis (Figure 5, curve 4).

Another important observation made is that small endothermic effects between 45 and 68°C appear only in the DSC scans of the pure HEC and the adsorbates containing an excess of HEC (Figures 2 and 3, curves 2 and 4). We suggest that this small increase of the specific heat capacity, c_p, is due to relaxation by intramolecular motions of small kinetic units such as the short grafted oxyethylene chains in the HEC macromolecule (Figure 6). To our knowledge, such effect is not mentioned for HEC in the literature. In our opinion, it should be related to a sub-glass transition phenomenon. Unlike, the adsorbate containing an excess of IND, does not display a sub-glass transition. This fact could be explained with a suppression of the mobility of grafted oxyethylene chains carrying adsorbed IND molecules.

As it concerns the glass transition (T_g), it is caused by motions of the main chain segments of HEC. Their motion should be expected at much higher temperature since the HEC macro-chain is inherently rigid and the segmental length is large. Besides, the assumed process of dehydration should lead to cross-linking and further increase of the rigidity. All these effects probably mask the T_g of HEC.

To gain a better understanding of the mechanism of the IND/HEC interactions we converted the weight fractions to mole fractions using the molecular mass of the HEC monomer unit. IND/HEC 1:0.5 (w/w) ratio corresponds to 3:1 (mol/mol)-; 1:1 (w/w) to 1.5:1 (mol/mol)- and 1:2 (w/w)–to 0.7:1 (mol/mol) ratio, respectively.

As it was discussed above, both DSC and X-ray data show a strong dependence of IND phase state on drug/polymer ratio. With drug concentration corresponding to at least three IND molecules per one HEC monomer (3:1 mol/mol) a metastable IND alpha form appears. The decrease of IND below three molecules per one HEC monomer hinders a crystal phase formation. The 1.5:1- and 0.7:1 (mol/mol) IND/HEC adsorbates are amorphous (Figure 5).

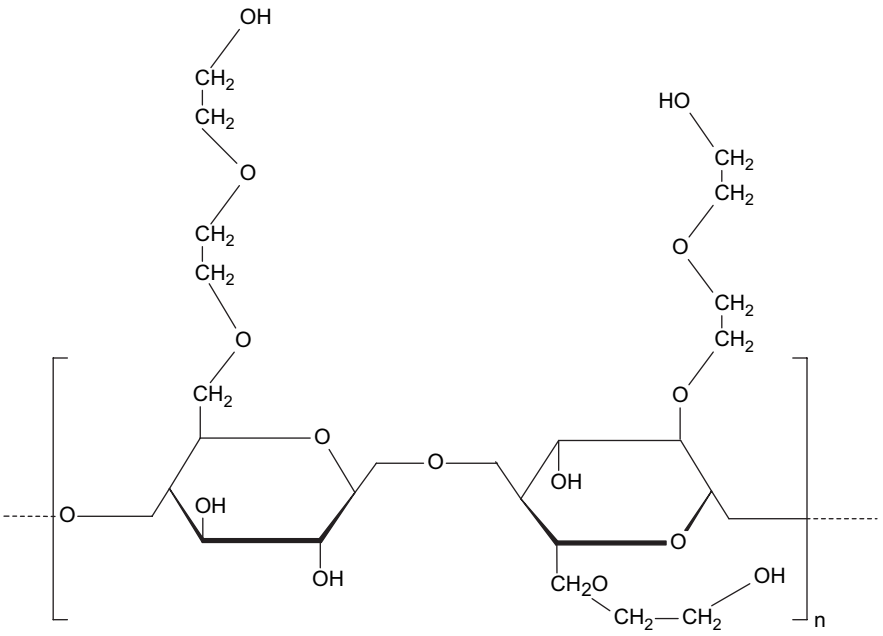

FIGURE 6. Idealized structure of HEC (Natrvosol®. Hydroxyethylcellulose. Physical and Chemical properties. Aqualon. A Division of Hercules Inc., 1998).

It can be suggested that with lower drug concentrations the crystallization is impeded because of the larger distance between the adsorbed drug molecules and the rigidity of the carrier. We assume also that the amorphous state of adsorbates can be considered as an indirect proof that IND molecules are immobilized onto HEC surface by specific drug/carrier interactions.

It should be pointed out that the DSC of aged IND/HEC 1:2 (w/w) adsorbate revealed that the achieved amorphous structure of IND remains unchanged after one year storage at ambient conditions (25 ± 2°C and 60 ± 5%). The established physical stability could be of serious practical importance having in mind the improved aqueous solubility of the IND/HEC 1:2 adsorbate which will be discussed latter in the text.

FT-IR Study

FT-IR spectra (Figures 7 and 8) provide additional evidences in support of interactions taking place in the process of IND/HEC adsorbates development.

Examination of the IR spectra reveals that:

i. 1750 –1500 cm^{-1} region of the spectra of IND/HEC 1:1- and 1:2 (w/w) adsorbates reminds that of the spectrum of untreated HEC (Figure 7, curve 2). In contrast, the corresponding physical mixtures show in the same region the bands of the gamma-IND at 1716, 1690, and 1587 cm^{-1} (Figure 7, curve 1),

ii. the weak stretching vibrations at 2624 and 2727 cm^{-1}, respectively, in the spectrum of the non-treated gamma-IND related to the cyclic dimerized hydroxyl groups of gamma-IND (Bogdanova et al., 2005), can be seen only in the spectra of the physical mixtures. In the spectra of the adsorbates regardless of the drug/polymer ratio these peaks

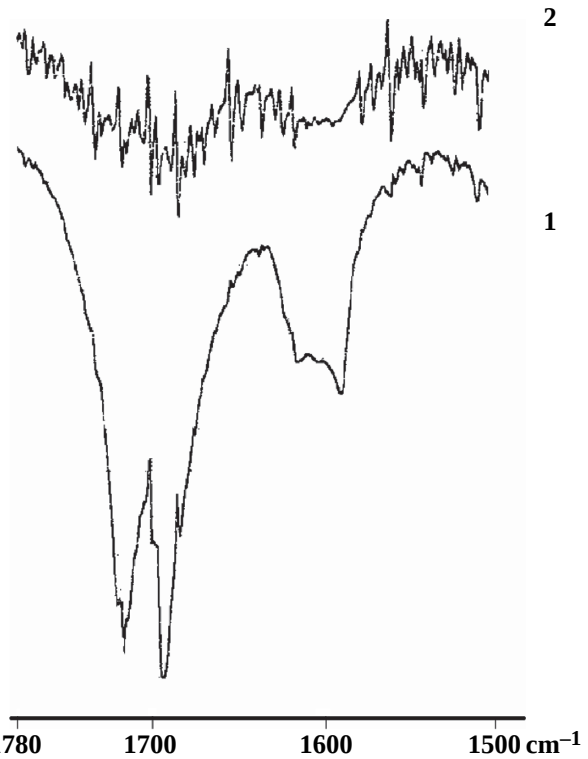

FIGURE 7. FT-IR spectra in the 1780–1500 cm^{-1} region: 1. IND/HEC 1:2 (w/w) physical mixture; 2. IND/HEC 1:2 (w/w) adsorbate.

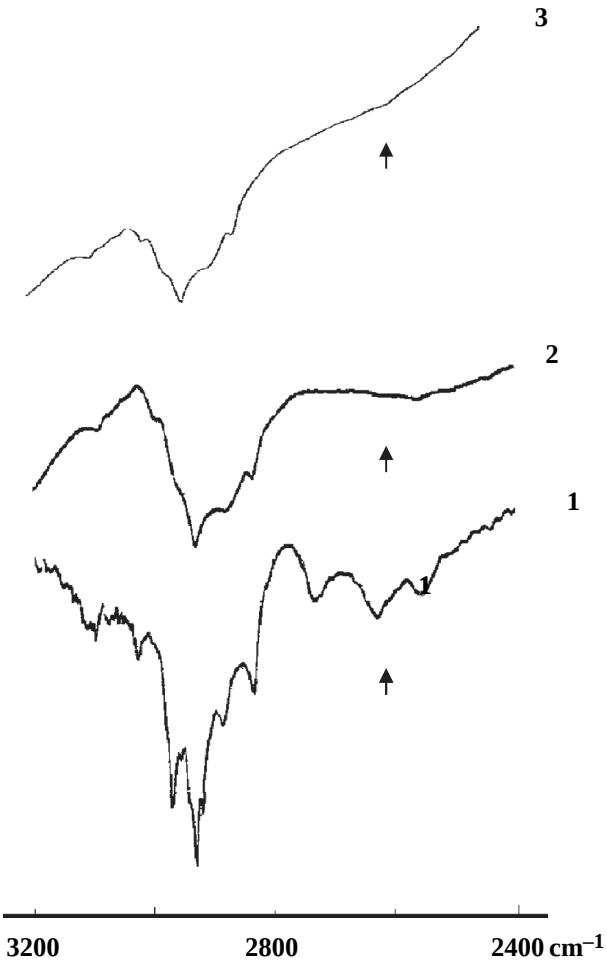

FIGURE 8. FT-IR spectra in the region 3200–2400 cm^{-1}: 1. IND/HEC 1:2 (w/w) physical mixture; 2. IND/HEC1:2 (w/w) adsorbate; 3. IND/HEC 1:0.5 (w/w) adsorbate.

disappear (Figure 8). This observation is in a good agreement with the DSC and X-ray results confirming the existence of alpha-IND in 1/0.5 (w/w) adsorbate.

iii. the fingerprint region between 1450–800 cm^{-1} of the spectra of the IND/HEC adsorbates relative to that of the spectra of the corresponding physical mixtures and non-treated IND reveal some differences.

In general, IR results are in agreement with the above-discussed assumption for chemosorption of IND onto HEC carrier. Unfortunately, HEC absorbs in the 1750 –1500 cm^{-1} region masking the stretching vibrations of the IND carboxyl carbonyl. Thus, no information supporting H-bonds formation could be obtained. However, H-bonds are expected to play a significant role in the interactions between IND and HEC.

Solubility Studies

The apparent equilibrium solubility data are presented in Table 1 and show the improved apparent solubility of indomethacin adsorbed onto the surface of the hydrophilic HEC. For example, the amorphous indomethacin/hydroxyethylcellulose 1:2 (w/w) adsorbate possesses the highest solubility, which is about 14.5 times higher than that of the pure non-treated drug. The increase found with the corresponding 1:0.5 (w/w) adsorbate containing alpha-IND was 6.5 times, probably because the sample was partially crystalline.

TABLE 1
Apparent Solubility of Indomethacin/hydroxyethylcellulose Adsorbates in Phosphate Buffer pH 6.8 at 22 ± 0.5°C

Model Preparations	Amount of IND Dissolved(g/100 mL)
Pure gamma-IND	0.03 ± 0.01
IND/HEC 1/0.5 (w/w) adsorbate	0.21 ± 0.01
IND/HEC 1/2 (w/w) adsorbate	0.47 ± 0.02
Pure IND in presence of HEC:	
0.5%	0.032 ± 0.002
1.0%	0.030 ± 0.002
2.0%	0.031 ± 0.002

It can be assumed that the changed IND phase state in the IND/HEC adsorbate has the main contribution to the increased indomethacin aqueous solubility. In support of such concerns is the fact that the apparent solubility of the untreated IND does not change in presence of increasing concentrations of hydroxyethylcellulose (Table 1).

CONCLUSION

Changes in the phase state of IND during processing of IND adsorbates onto the hydrophilic HEC carrier have been established.

The drug-to-polymer ratio determines either a partial crystallization of the metastable alpha-form onto HEC surface or complete inhibition of IND crystallization.

The registered changes of IND phase state in the IND/HEC adsorbates provoke a significantly improved drug aqueous solubility. The achieved physical structure of IND in the adsorbates remains stable for one-year storage at room temperature. These results could be of practical importance.

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