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Aspects of the interactions between indomethacin and nicotinamide in solid dispersions

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Abstract

A series of indomethacin/nicotinamide binary system-melts were prepared as models to study some aspects of the potential physico-chemical interactions between indomethacin and nicotinamide. The comparative analysis of the data from FT-IR- and UV spectroscopy, DSC, X-ray diffractometry and equilibrium solubility study showed that formation of complexes of different stoichiometry can take place in the solid state and in solution. The aqueous solubility of the assumed complexes of drug/carrier molar ratio above 1:1 (M/M) did not exceed the solubility of the pure indomethacin (IND) (treated), which was prepared as the model melts. The melts with a low drug content (e.g. 7.5 and 9.1% melts) were found to be in a metastable physical state probably due to the amorphous nature of the indomethacin or its complex. They can be in situ transformed into 1% indomethacin aqueous solution.

Keywords: Indomethacin; Nicotinamide; Binary melts; Interactions; In situ transformation into solution

1. Introduction

Nicotinamide (NA) is known as a potent hydroptropic agent used to increase the aqueous solubility of many drugs (Fawzi et al., 1980; Truelove et al., 1984; Malaviolle et al., 1987; Chen et al., 1994). The hydrotropic effect of the nicotinamide has been claimed to be mainly due to its ability to destroy water structure and/or to form complexes with certain drugs on the basis of π-electron donor–acceptor and hydrogen bonding (Fawzi et al., 1980).

Recently, Hamza et al. (1994) studied the enhanced aqueous solubility of indomethacin (IND) in form of physical mixtures, co-precipitates and melts with nicotinamide as a carrier. The authors reported on the formation of indo-methacin/nicotinamide 1/1 (w/w) or 1/3 (M/M) complex. However, there were no comments about the ob-

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served differences in the dissolution profiles and IR spectra of the samples. The same binary system was earlier described by Eshra et al. (1986) as an eutectic with a m.p. of 107°C. On the basis of the phase diagram constructed by hot stage microscopy (HSM) the authors had also assumed the existence of IND/NA 1/1 and 1/2(M/M) molecular compounds.

The aim of the present work was to show some new aspects of the interactions of indomethacin with nicotinamide in a molten state by means of a comparative analysis of the data from FT-IR- and UV-spectrophotometry, DSC, X-ray difractometry and phase solubility study, as well as to demonstrate that the metastable liquified melts can be in situ transformed into aqueous solutions.

2. Materials and methods

2.1. Materials

Indomethacin (kindly donated by Sopharma, Bulgaria met the requirements of the BP 80), nicotinamide and buffer salts—disodium hydrogen phosphate dihydrate and potassium dihydrogen phosphate (Fluka, Buchs, Switzerland) were used.

2.2. Methods

2.2.1. Preparation of indomethacin/nicotinamide melts and physical mixtures

Binary mixtures of indomethacin and nicotinamide of different composition with indomethacin content varying from 2.5 (w/w) up to 90% (w/w) were heated on an electric hot plate until melted. The liquid melts were immediately cooled under running tap water and then placed in a vacuum dessicator to solidify. After 2 days storage, the solid mass was removed, pulverized and sieved to gather a powder fraction with particle size below 0.2 mm. The reference sample, IND (treated) was similarly prepared from pure indomethacin.

The 7.5 (w/w), 9.1 (w/w) and 60% (w/w) physical mixtures were prepared by simple light mixing in a mortar and used for comparison with some studies.

2.2.2. Equilibrium solubility studies

Amounts of the melts, equivalent to 0.20 g of indomethacin and 0.20 g of the sample IND (treated) for reference, were placed in well closed vials with 20 ml phosphate buffer at pH 7.4. The samples were shaken in a water bath (Vibrotherm L204, Hungary), thermostated at 37 ± 0.1°C until equilibrium was reached. The amounts of indomethacin dissolved were determined spectrophotometrically at 320 nm. The experiments were carried out in triplicate.

2.2.3. FT-IR spectrometry

A FT-IR-8010M spectrometer (Shimadzu, Japan) was used to check the IR spectra of the melts. All preparations were suspensed in nujol.

2.2.4. Differential scanning calorimetry (DSC)

A Perkin Elmer DSC-7 differential scanning calorimeter coupled to a Perkin Elmer TAC-7 Intracooler (Connecticut Corp., CT) was used. A heating rate of 10°C min^{-1} in an atmosphere of nitrogen was employed throughout.

2.2.5. Hot stage microscopy (HSM)

A hot stage microscope (Boetius, Germany) was used.

2.2.6. X-ray studies

X-ray diffraction patterns were obtained on powder samples using a powder diffractometer DRON-1 (Russia) employing Cu K_α radiation ($\lambda = 1.54178$ Å).

2.2.7. UV spectroscopic studies

The UV spectra (spectrophotometer Cary 1E Varian, USA) were registered of in situ prepared solutions of indomethacin/nicotinamide melts or physical mixtures with a final indomethacin concentration of $3.5 \cdot 10^{-5}$ M.

A series of pH 7.5 buffered solutions of different compositions containing a constant indomethacin concentration of $0.25 \cdot 10^{-4}$ M and nicotinamide in the concentration range $5 \cdot 10^{-4}$ M–$5 \cdot 10^{-3}$ M were also prepared for a more detailed study.

Solutions of nicotinamide with a concentration equivalent to that in the sample for analysis were always used as blanks.

Table 1
Solubility of IND/NA melts in buffer pH 7.4 and at 37°C

IND content in the melts (%)	IND amount dissolved (mg/ml)	IND content in the melts (%)	IND amount dissolved (mg/ml)
7.5	14.1	65.0	4.6
9.1	10.9	75.0	2.9
15.0	8.3	90.0	5.2
20.0	7.5	IND (treated)	5.0
50.0	5.9	IND (non-treated)	1.6
60.0	4.2	—	—

2.2.8. In situ transformation of 7.5% IND and 9.1% IND melts into 1% buffered solutions of indomethacin

The necessary amounts of indomethacin and nicotinamide in weight ratio corresponding to 7.5 or 9.1% IND melts respectively, were mixed and melted together at a temperature around 140°C (oil bath) until a homogeneous yellow liquid was obtained. A 90.0 ml buffer volume at pH 6.8 or 7.4, pre-heated to 50–60°C were added dropwise to the hot liquified melt while stirring (magnetic stirrer). The resulting yellow solution was cooled and then diluted with buffer in a volumetric flask to obtain 1% (w/v) indomethacin solution.

3. Results and discussion

Binary melts of varying ratio of the components were chosen as models for studying the potential physicochemical interactions between indomethacin and nicotinamide. The intimate contact between both partners in the molten state created more favourable conditions for interactions.

All studied indomethacin/nicotinamide melts solidified, immediately after cooling as yellow glassy preparations. The stability of the glassy state of the melts depended on the indomethacin/nicotinamide ratio and increased with the increase of drug weight. These phenomena could be related to the pronounced ability of indomethacin to supercool and to form a metastable glass. This property was earlier described by Allen and Kwan (1969), Borka (1974), Ford and Rubinstein (1978).

As a result of the indomethacin physical transformation its aqueous solubility increased. It was established, e.g. that the the solubility of the sample of the melted and solidified pure indomethacin—IND (treated) was about 3.2 times higher than that of the pure non-treated indomethacin (Table 1). The 90% IND melt behaved similarly. However, the aqueous solubility of the other melts of high drug content (between 90 and 50%) was lower.

The melts of low drug content unlike those discussed above were several times more soluble in water and their solubility depended on the nicotinamide weight.

The results of the phase solubility analysis suggested different kinds of interactions between indomethacin and nicotinamide, which depend on the concentration ratio of both partners. This led to the decision to consider the 50% weight concentration of the drug as a critical one and to classify the melts into two groups.

3.1. Model melts of low indomethacin content

A screening was carried out by means of HSM with a series of melts of increasing indomethacin concentration in the range 2.5–40%. The behaviour of the samples of indomethacin content below and around 5% supported a probable existence of a solid solution. Indomethacin showed similar behaviour in melts with PEG 6000 as described by Ford and Rubinstein (1978).

The 9.1% IND melt as well as the samples of higher drug content showed a crystal transformation around 116°C—the prisms were transformed into needles, which melted in the range 123–

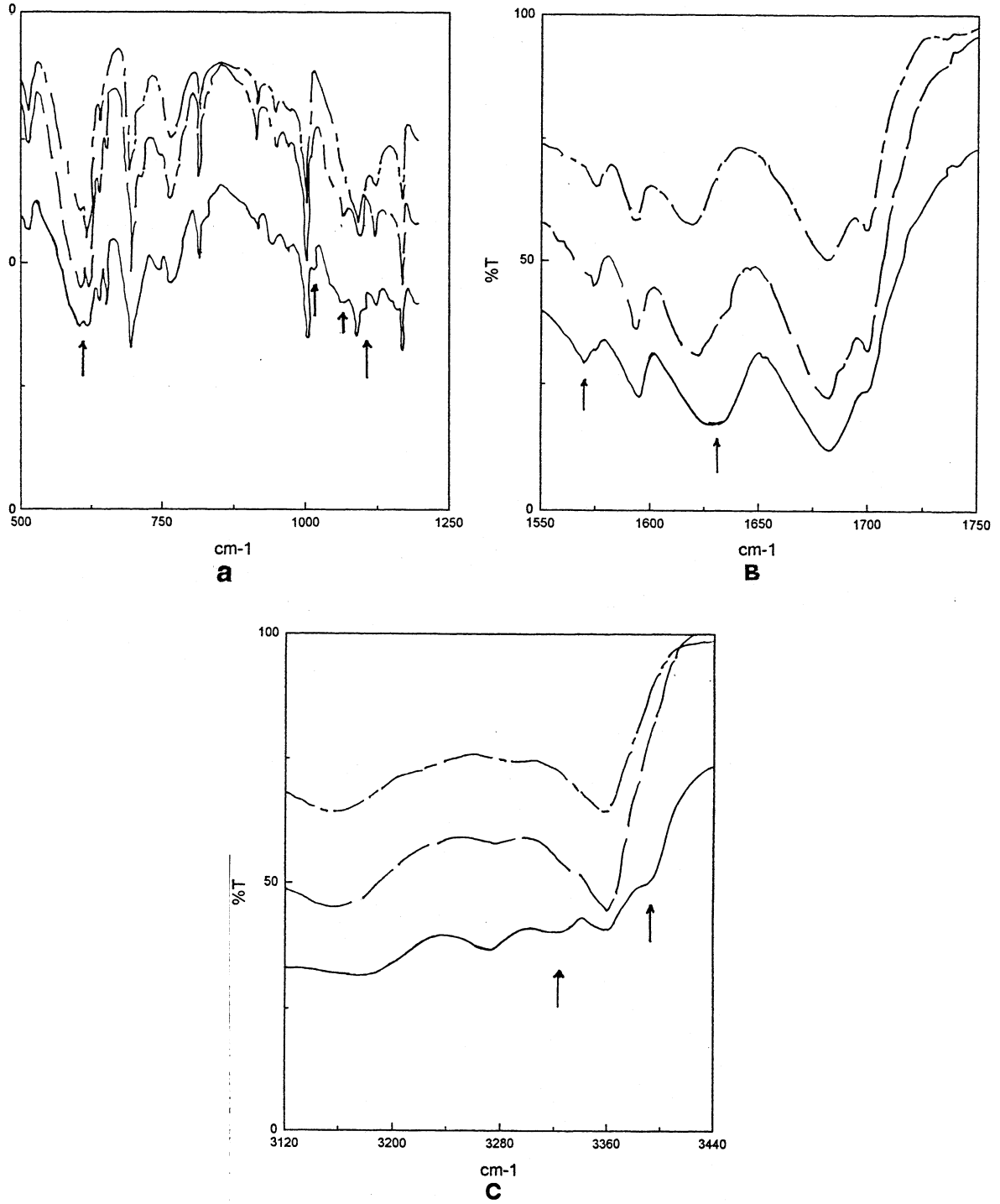

Fig. 1. FT-IR spectra in the regions: (a) 500–1250 cm^{-1}; (b) 1550 cm^{-1}–1750; (c) 3120–3440 cm^{-1}; – · – nicotinamide, – – 7.5% IND melt and —— 9.1% melt.

130°C. The only exception was the 15% IND melt which melted at 124–127°C without crystal transformation.

The 7.5, 9.1 and 15% IND melts were chosen for a more detailed discussion because of their peculiar melting behaviour and high aqueous solubility revealing a tendency for practical application.

The method of the FT-IR spectroscopy, in comparison to the other techniques used, was found to be the most reliable for predicting the possible interactions. The characteristic IR absorption of the melts can be considered in three regions of the spectra: 1550–1750, 3120–3440 (indomethacin has no absorption in this region) and 1250–500 cm^{-1} respectively because they were the most representative. It was established that the 7.5 and 9.1% IND melts behaved differently irrespective of the very low difference (only 1.6%) between the indomethacin content of the both samples. The FT-IR spectrum of the 7.5% melt (Fig. 1) in comparison to that of the 9.1% IND melt was closer to the spectrum of the pure nicotinamide. The most significant differences registered in the spectrum of the 9.1% IND melt were the lack of the nicotinamide band at 1574 cm^{-1}, the shift and the deformation of the maximum at 1620 cm^{-1} as well as the new spectral picture in the ν NH vibrations region. Similar spectral behaviour suggested that the $CONH_2$- group was engaged in stronger interactions.

The DSC traces presented in Figs. 2 and 3 confirmed the spectral results. The 7.5% IND melt revealed an endotherm at 126.9°C and an exotherm at 87.6°C. The endothermic peak at 126.9°C could be ascribed to the nicotinamide melting. It occurred at a temperature about 10° lower than the melting point of the pure nicotinamide. Its endotherm was found to appear at 136°C. Unlike the shift of the nicotinamide endotherm in the trace of the 9.1% IND melt (Fig. 2) was about 5°, irrespective of the higher indomethacin content in the sample. It is very probable that the stronger temperature decrease of the nicotinamide endotherm with the 7.5% IND melt is related to the more pronounced changes in the crystal structure of the carrier. In support of this assumption is the exothermic transition which is usually due to the amorphous solidification of the drug in the carrier and/or to the beginning of a complex formation. Probably, the amorphous drug and assumed complex solidified in the crystalline carrier nicotinamide, a phenomenon described with other solid dispersions (Chiou and Riegelman, 1971).

The DSC trace of the 9.1% IND melt (Fig. 3) contained a second endotherm at 116°C. This peak was missing in the trace of the corresponding physical mixture but was observed in the trace of the 20% IND melt (Fig. 4). It was very likely this endothermic transition to be identical to that of the complex in the trace of the 50% IND co-evaporate described by Hamza et al. (1994).

The comparative X-ray study (Figs. 5 and 6) of 7.5 and 9.1% IND melts showed that some of the indomethacin peaks observed in the difractograms of the corresponding physical mixtures were missing in the difractograms of the melts. Slight

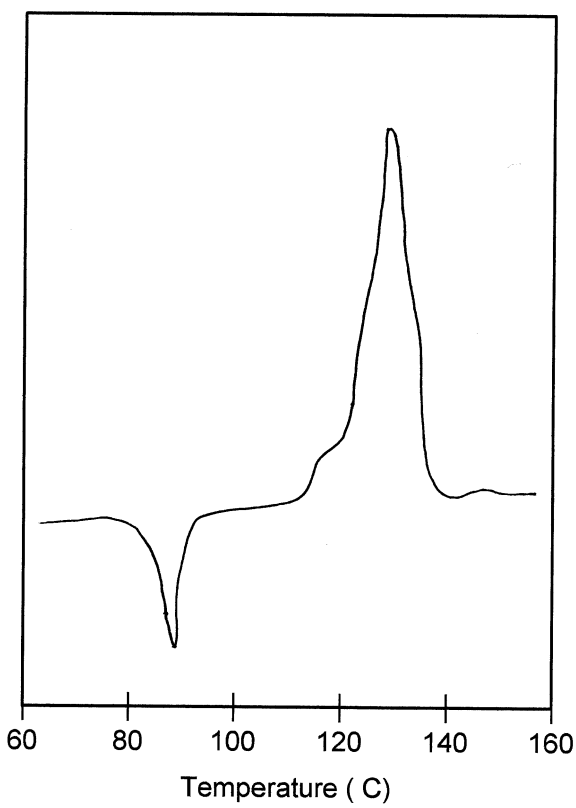

Fig. 2. DSC trace of 7.5% IND melt.

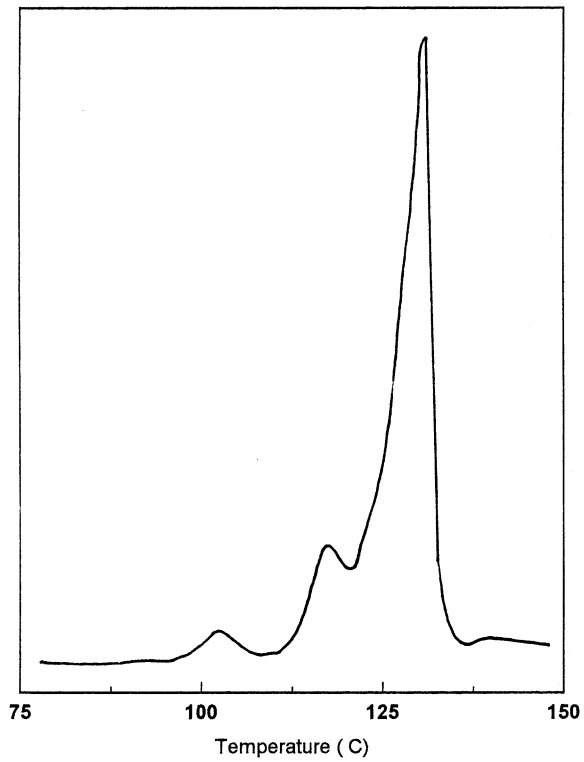

Fig. 3. DSC trace of 9.1% IND melt.

changes of the position or intensity of peaks were also observed.

In conclusion, the FT-IR-spectroscopy, the DSC- and X-ray diffraction studies showed pronounced differences in the behaviour of the 7.5 and 9.1% IND melts, respectively in a solid state. It can be assumed that indomethacin in the 7.5% IND melt was partially amorphous and 'dissolved' in the carrier (Chiou and Riegelman, 1971; Ford and Rubinstein, 1977). The changed physical state of the drug was once again confirmed by the fact that the 7.5% melt possessed the highest aqueous solubility—14.1 mg/ml. The second endotherm in the DSC trace of the 9.1% IND melt as well as the more pronounced spectral changes in the region of the ν NH vibrations could be considered as proofs for complex formation. The solubility of the 9.1% IND melt was about 1.2 times lower than that of the 7.5% melt but about 1.3 times higher in comparison to the solubility of the 15% and 20% IND melts, respectively.

The UV spectra of 7.5 and 9.1% IND melts and physical mixtures (Fig. 7) showed that in general, the absorption of the melts was higher than that of the physical mixtures and supported stronger interactions in solution.

A more comprehensive UV study revealed that the indomethacin spectral characteristics changed drastically when the nicotinamide concentration increased. The changes concerned only the indomethacin maximum at 266 nm. Besides, a new well expressed maximum around 244 nm appeared. Its intensity diminished progressively when the nicotinamide concentration increased (Fig. 8B).

Moreover, a similar mechanism of interaction in the solid state and in a solution could be assumed. The UV spectrum of the sample containing 6.8% (1/40 (M/M)) presented in Fig. 8A was a good illustration of this assumption—the spectrum was very close to that of the 7.5% IND melt (Fig. 7).

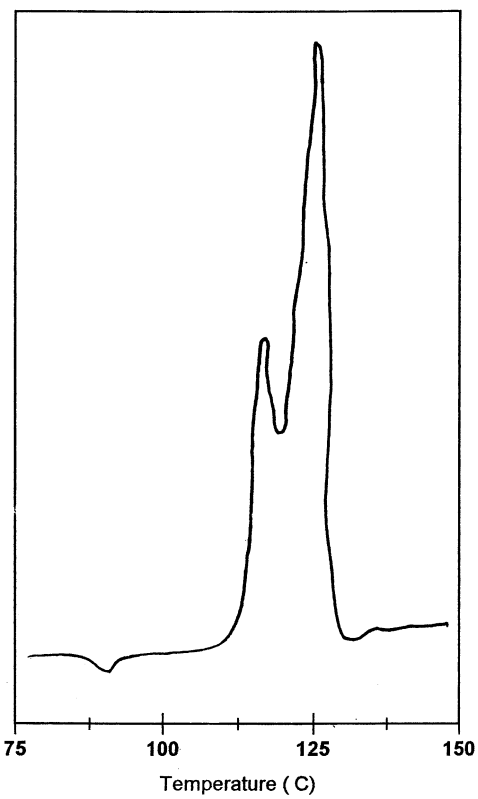

Fig. 4. DSC trace of 20% IND melt.

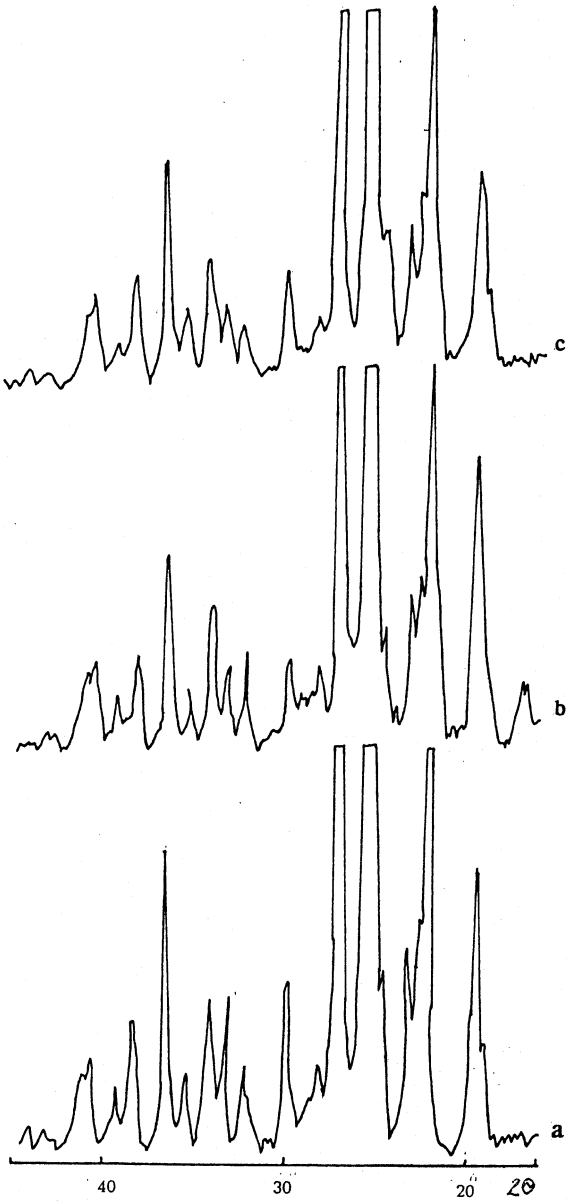

Fig. 5. X-ray diffraction patterns of: (a) nicotinamide, (b) 7.5% IND physical mixture and (c) 7.5% IND melt.

It is very probable the heteroaromatic indomethacin molecule, similarly to other heterocyclic compounds (Fawzi et al., 1980; Truelove et al., 1984) to participate in π-donor–π-acceptor interactions with nicotinamide in a solid state and in solution. The H-bonding can be the other very important mechanism involved in the interactions.

It is noteworthy, that the spectral and thermal behaviour of the 15% IND melt were not comparable with that of the 7.5 and 9.1% IND melts, discussed above.

The IR spectrum of the 15% IND melt depicted in Fig. 9 was more closed to the spectrum of the

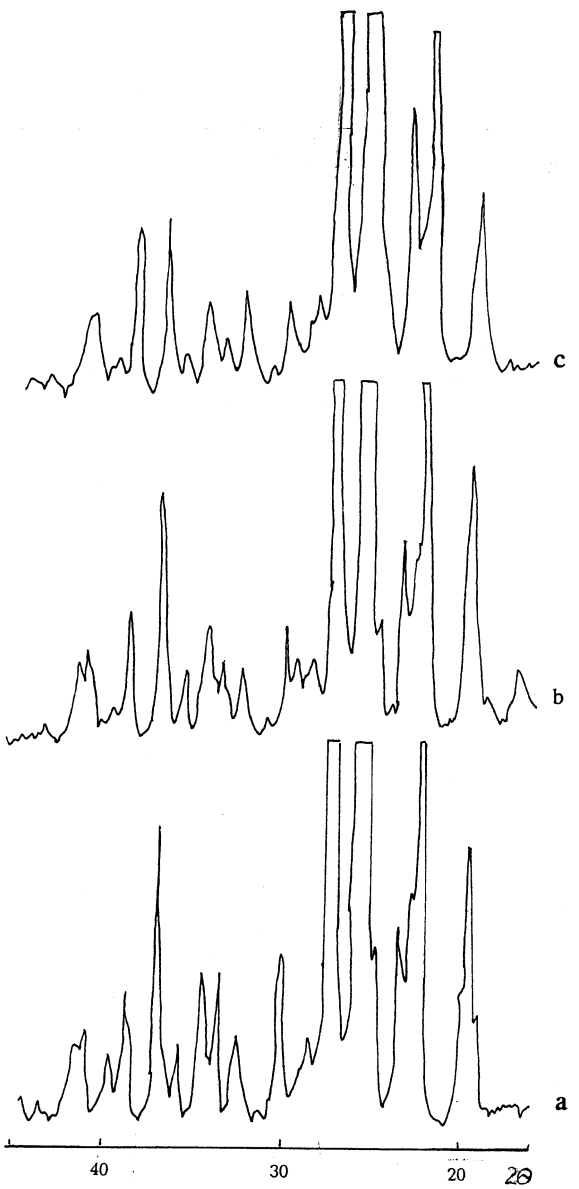

Fig. 6. X-ray diffraction patterns of: (a) nicotinamide, (b) 9.1% IND physical mixture and (c) 9.1% IND melt.

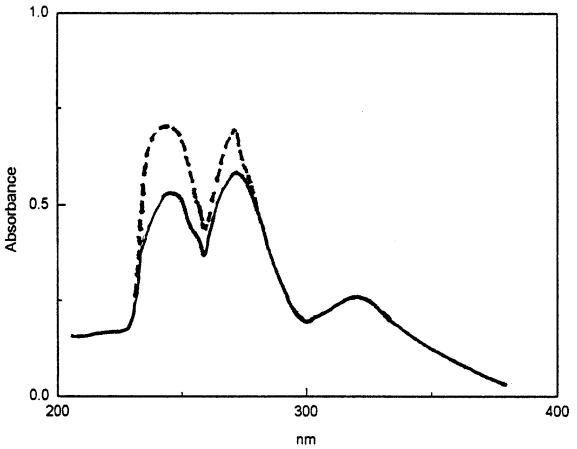

Fig. 7. UV spectra of: ——, 7.5% IND physical mixture and – – –, 7.5% IND melt.

50, 60 and 65% IND melt. The most peculiar spectral characteristics were the new intensive absorption band at 1662 cm^{-1} as well as the new peaks of low intensity in the region of the ν-NH.

The DSC trace of the 15% IND melt supported the peculiar spectral characteristics of the sample revealing only one endothermic peak at 128.8°C.

The melt solubility was about 1.7 times lower in comparison to that of the 7.5% melt, but of the same order as that of the 20% IND melt.

3.2. Melts of high indomethacin content

The indomethacin weight concentration of the studied melts layed in the range from 50 up to 90% and corresponded to indomethacin/nicotinamide molar ratio from 1:3 to 1:0.3 mol. These molar ratios were favourable for complex formation.

The most surprising fact established was that the FT-IR spectra of 50, 60 and 65% IND melts were almost identical and very close to the spectrum of the 15% IND melt discussed above (Fig. 9).

The FT-IR spectra of the melts of indomethacin content above 65% gave no information because of the broad absorption bands, indicating that the samples were partially amorphous.

The X-ray difractogram of the 60% IND melt (Fig. 10) unlike the corresponding physical mixture was almost amorphous with some peaks characteristic for the nicotinamide which were slightly shifted.

The DSC analysis also revealed a very complicated picture.

However, the DSC traces and the X-ray difractograms of the samples of high indomethacin content clearly demonstrated the indomethacin ability to supercool and to bear polymorphic transitions (Ford and Rubinstein, 1978). The thermogram of the 90% IND melt depicted in Fig. 11 can be considered as an example of similar transformations. A typical T_g at ≈ 47°C was followed by the exotherm of the amorphous indomethacin around 95°C which recrystallized into higher melting point modifications, can be seen.

The X-ray difractogram of the 90% IND melt (Fig. 10) demonstrated that the sample was fully amorphous.

The solubility studies unlike to the other techniques gave more information and supported complex formation. It was established that the 75% and especially the 60% IND melts were sparingly soluble in water. (These concentrations expressed in moles corresponded to indomethacin/nicotinamide 1:1 and 1:2 M/M, respective ratio.) The solubility of the 1/1 (M/M) complex for example, was 1.7 times lower than the solubility of the sample IND (treat). This fact was underlined by Eshra et al. (1986) and Hamza et al. (1994), too.

3.3. In situ transformation of liquified melts into 1% IND aqueous solutions

A technological approach for in situ preparation of a physically stable 1% IND aqueous solution was proposed. The technique consisted in dissolving of the hot liquified melt in a warmed buffer at appropriate pH value.

The principal prerequisite for successful transformation of a given binary system melt in aqueous solution was to contain the drug in a metastable state caused by physico-chemical interactions. The study showed that the indomethacin/nicotinamide melts of indomethacin concentration

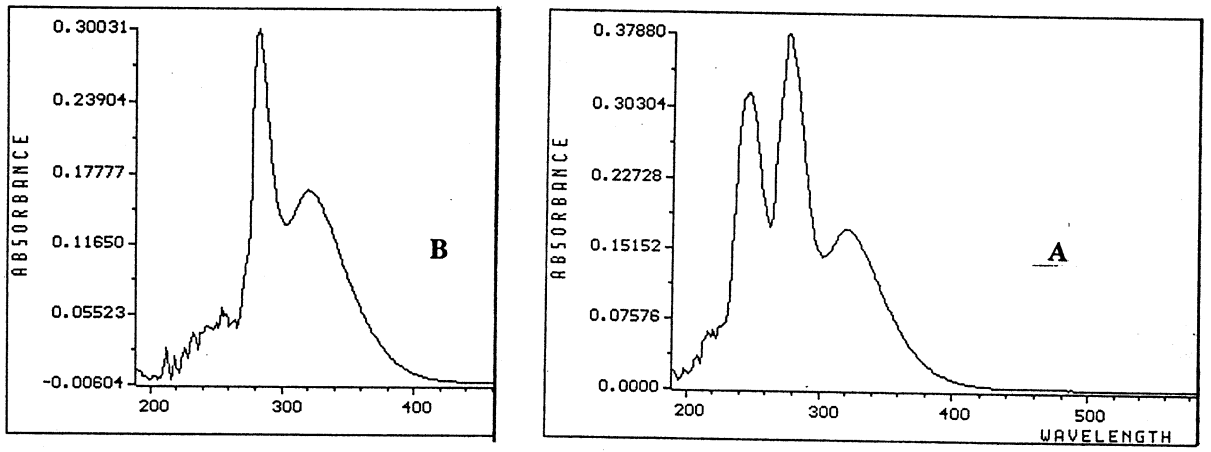

Fig. 8. UV spectra of $0.25 \cdot 10^{-4}$ M indomethacin in presence of nicotinamide: (A) $0.1 \cdot 10^{-2}$ M and (B) $0.5 \cdot 10^{-2}$ M.

in the range from 2.5 up to 9.1% possessed the highest aqueous solubility mainly because of the solid solubility and amorphous nature of the drug and/or of the assumed complex. This approach can not be applied with the melts of higher drug content because the assumed complexes of the

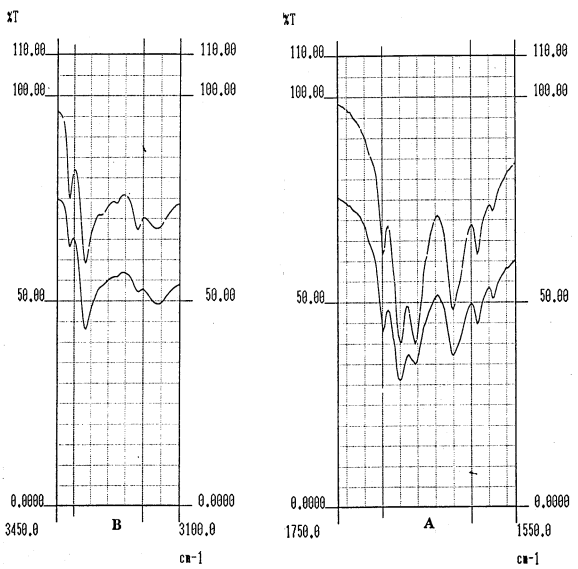

Fig. 9. FT-IR spectra in the region: (A) 1550–1750 cm^{-1} and (B) 3120–3450 cm^{-1}; – –, 50% IND melt and ——, 15% IND melt.

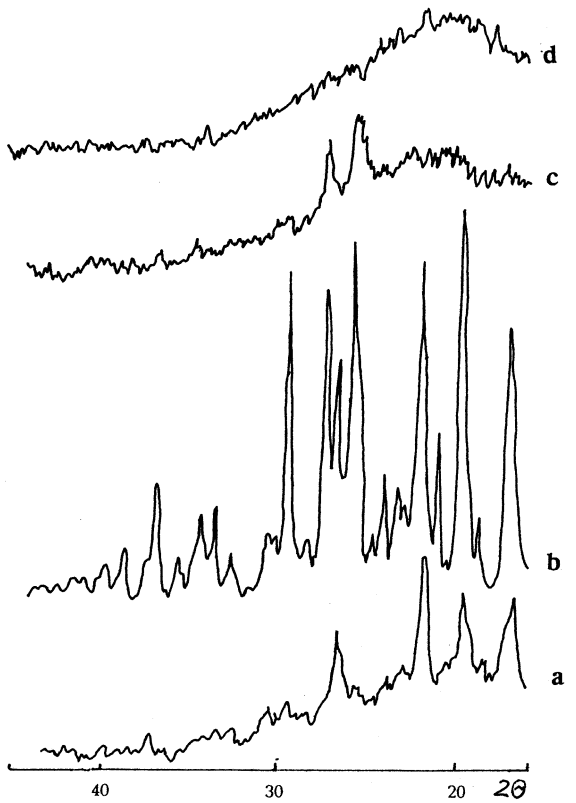

Fig. 10. X-ray diffraction patterns of melts with drug content above 50%. (a) IND (treated), (b) 60% IND physical mixture, (c) 60% IND melt and (d) 90% IND melt.

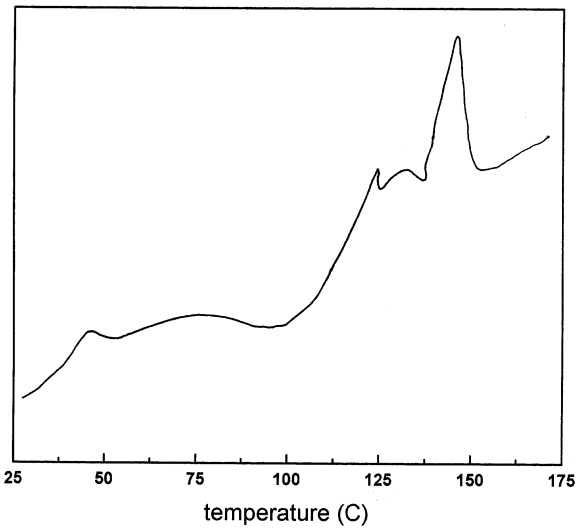

Fig. 11. DSC of 90% IND melt.

indomethacin had significantly lower aqueous solubility than the pure drug.

The main advantages of the proposed technique were that this approach eliminated the isolation of the solid dispersion, the problems related to their stability in a solid state caused by 'ageing' and worsening of the drug aqueous solubility. The method showed a good reproducibility and displayed some possibilities to formulate liquid dosage forms—oral liquida, ophthalmica or parenteralia.

4. Conclusions

Formation of complexes of different stoichiometry between indomethacin and nicotinamide can take place in a molten state or in solution. H-bonding and π-electron donor–acceptor links are probably the main contributions to the interaction mechanism. The aqueous solubility of the assumed complexes of drug/carrier molar ratio above 1/1 (M/M) did not exceed the aqueous solubility of the sample IND (treated). The binary melts of low drug content (e.g. 7.5 and 9.1% IND melts) were found to be in a metastable physical state due to the amorphous nature of the drug or the drug complex so that they can be in situ transformed into 1% indomethacin aqueous solution.

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