*Journal of Pharmaceutical & Biomedical Analysis*
Vol. 8, No. 4, pp. 321–327, 1990
Printed in Great Britain

0731–7085/90 $3.00 + 0.00


# Physico-chemical characterization of a new salt of ibuprofen

M.S. SULEIMAN,* N.M. NAJIB,† M.A. HASSAN and M.E. ABDEL-HAMID

*Faculty of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan*

**Abstract**: A new salt of ibuprofen was prepared by reaction with *t*-butylamine; its formation was confirmed by IR and $^1$H-NMR spectroscopy. The salt was characterized by thermoanalytical, X-ray powder diffraction and solubility studies. The salt was found to be 1.5 times more soluble in water than was ibuprofen, with an enthalpy of solution of $-8.84$ kcal mol$^{-1}$.

**Keywords**: *Ibuprofen-t-butylamine; thermoanalysis; X-ray powder diffraction; solubility studies; IR spectroscopy; $^1$H-NMR spectroscopy.*

## Introduction

Solid state manipulation is one of the techniques that is used to enhance the solubility of drugs that are only slightly soluble in water. This involves crystallization of the drug from different organic solvents to yield new polymorphic, amorphous or solvated forms [1–5], formation of eutectic mixtures [6], preparation of solid dispersions [7–9], incorporation of the drug in glass matrices to form glass dispersions [10], or dispersing the drug on the surface of certain materials to form solid surface dispersions [11]. Physico-chemical characterization of the resulting products has been achieved by melting-point determination, examination under the hot-stage microscope [4, 12], analysis with a thermal analyser [4–6], infrared (IR) spectroscopy [4, 5, 9, 12], X-ray diffraction studies [4–6, 9, 12]; more recently, the use of $^1$H-NMR has been advocated [13].

In a study to enhance the solubility of drugs such as ibuprofen that are poorly soluble in water, solid state manipulation was employed [14]. This was achieved by crystallization of the drug from different organic solvents under different conditions. The unique behaviour exhibited by the product obtained from *t*-butylamine (TBA) prompted further research to elucidate the nature of the product and to study its physico-chemical characteristics.

## Experimental

### *Materials*

Ibuprofen (Sigma Chemical Co., St Louis, MO, USA) was used in the preparation of the salt with TBA (Aldrich Chemical Co., Milwaukee, Wisconsin, USA). Ethyl alcohol (Romil Chemicals Ltd, Leics, England) was used in the preparation of the TBA salt of Ibuprofen. Double-distilled water from an all-glass still was used in the solubility studies.

### *Preparation of ibuprofen-t-butylamine (Ibu–TBA)*

To a solution of Ibu (1.03 g, 5 mmol) in 15 ml of ethanol, TBA (0.37 g, 5 mmol) was added. The mixture was stirred at room temperature overnight. The precipitate formed was filtered and recrystallized from acetone–methanol (10:1, v/v) to give the pure product (1.21 g, 86% yield).

### *Hot stage microscopy*

Samples (1–2 mg) were placed on a microscope slide. A Reichert Thermovar Koffler hot-stage microscope (C. Reichert AG, Austria) equipped with a Kam ES2 camera system was used and the samples were heated continuously from room temperature at a heating rate of 5°C min$^{-1}$. The solid temperatures were those taken at the first signs of

*Present address: United Pharmaceuticals, Amman, Jordan.
†Author to whom correspondence should be addressed.

melting and the liquid temperatures were those taken immediately before the final traces of crystal melted within the field of vision.

*X-ray analysis*

All X-ray diffraction studies were performed on a PW 1729, Philips X-ray diffractometer with monochromatized Cu-$K_\alpha$ ($\lambda$ = 1.54180 Å) radiation. Samples were placed on a glass slide and held in place by Scotch tape. The samples were used without further treatment.

*Thermoanalytical studies*

A simultaneous thermogravimetric (TG)-derivative thermogravimetric (DIG)-differential scanning calorimetric (DSC) thermal analyzer (STA 785, Stanton Redcroft, London) was used to characterize the thermal behaviour of Ibu and Ibu–TBA. Samples (6 mg) were placed in aluminium pans without lids and heated at 10°C $min^{-1}$ using nitrogen as a purge gas at a flow rate of 50 ml $min^{-1}$. The instrument was calibrated with indium standard before use.

*Thin-layer chromatography (TLC)*

Ibu and Ibu–TBA were examined by TLC. The samples were dissolved in methanol and spotted on silica gel 60 F254 plates (E. Merck, Darmstadt, FRG), which were developed with butanol–water–acetic acid (4:2:1, v/v/v) and were detected by placing the plates in a chamber containing iodine vapour.

*Infrared spectroscopy*

IR spectra were recorded on a Shimadzu IR-435 spectrophotometer equipped with a data recorder DR-7 (Shimadzu Co., Kyoto, Japan) using 2% KBr discs.

*Proton nuclear magnetic resonance*

$^1$H-NMR spectra were recorded on Bruker WP 80 pulse spectrometer, interfaced with a computer system Bruker BNC 28. The spectra of Ibu and Ibu–TBA in $CD_3OD$ were determined under $N_2$ at ambient temperature. Tetramethylsilane was used as an internal reference.

*Solubility studies*

The solubilities of Ibu and Ibu–TBA were determined in water at 30, 40 and 50°C. Excess drug (250 mg) was added to 5 ml of water in screw-capped vials, which were placed in a shaking water-bath (Karl Kolb, Dreieich, FRG) and equilibrated for 24 h. The supernatant was filtered through a 0.45-μm Millipore filter using the Swinney adapter syringe assembly (Philips Export B.V., Eindhoven, Netherlands). The diluted samples were assayed spectrophotometrically for Ibu at 272 nm, using a Shimadzu UV-240 spectrophotometer equipped with a PR-1 graphic printer (Shimadzu Co., Kyoto, Japan). The solubilities were then determined in duplicate by reference to a calibration curve previously prepared. The enthalpy change of solution was obtained by plotting the solubility versus the reciprocal of absolute temperature according to the Van't Hoff equation [2].

## Results and Discussion

Hot-stage microscopic examination revealed that Ibu–TBA was different in crystalline nature (Fig. 1) and melted at 150.9–152.1°C, whereas Ibu melted at 72.1–72.9°C. Moreover, the Ibu–TBA product exhibited a hairy appearance above 95°C (Fig. 2) which was not exhibited by Ibu. This evidence, coupled with the rare occurrence of large differences in the melting point of polymorphic forms of the same drug [12], made it less likely that the product was a polymorphic form of Ibu. The difference in the crystalline nature of the Ibu–TBA product from that of Ibu was further confirmed by X-ray diffraction studies. Examination of Fig. 3 with respect to the number, location, and intensity of the peaks clearly demonstrates that the Ibu–TBA product is different in crystalline nature from that of Ibu. This difference, however, neither confirms salt formation nor precludes the possibility of polymorphic transformation of ibuprofen.

The simultaneous TG–DSC curves of Ibu and Ibu–TBA are shown in Fig. 4. The DSC trace of Ibu shows one sharp endothermic peak at 75.4°C corresponding to the melting point of Ibu and a broad endothermic peak at a higher temperature corresponding to the vaporization of the drug. The TG trace of Ibu does not show any weight loss in the melting region. However, it shows a weight loss above the melting point which is indicative of vaporization. The DSC trace of Ibu–TBA, however, shows two endothermic peaks. The first one is broader and occurs at a higher temperature (150.5°C) than the corresponding peak exhibited by Ibu. The second endothermic peak exhibits the same pattern as that exhibited by Ibu. The

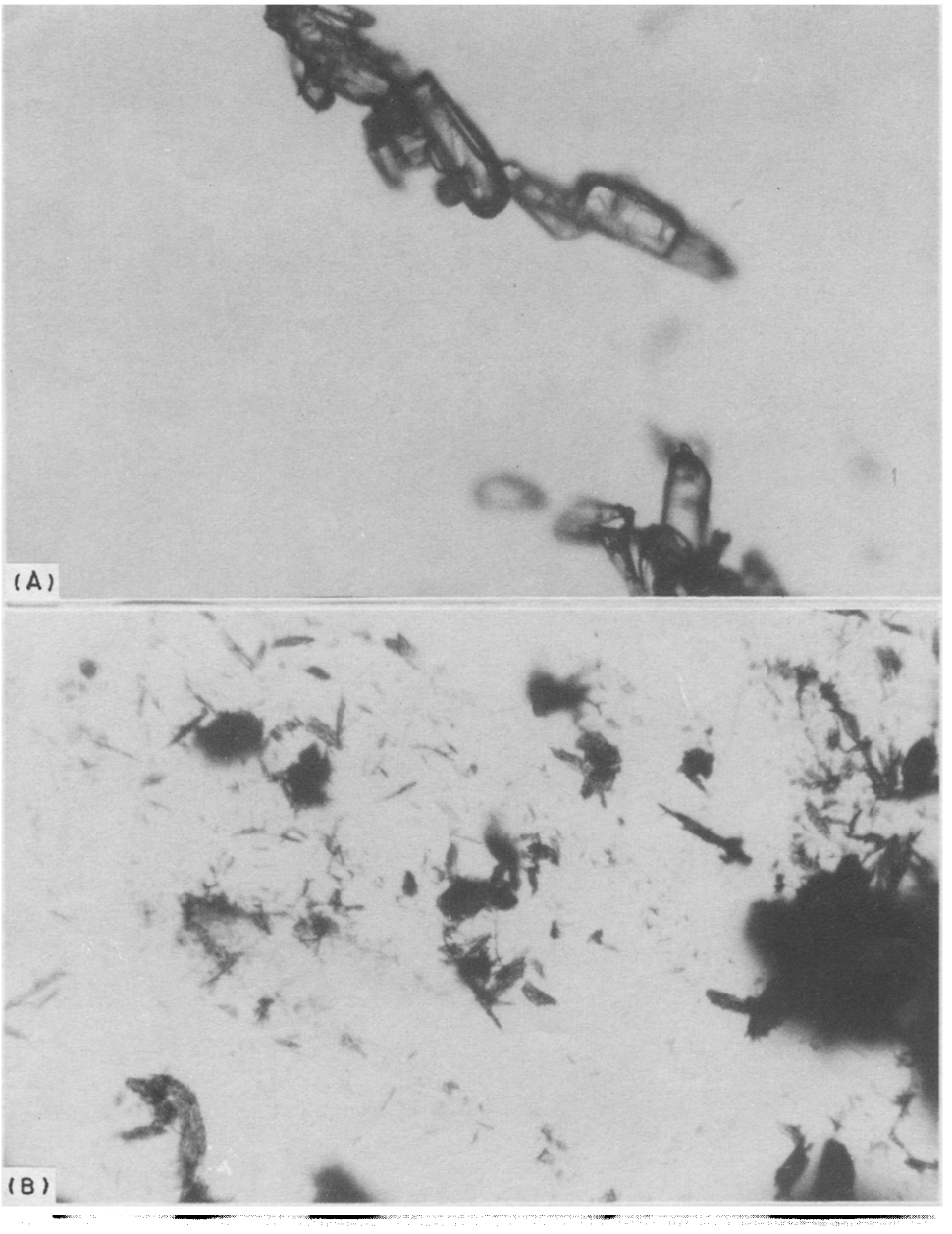



**Figure 1**
Photomicrographs of (A) Ibu and (B) Ibu–TBA.

broadening of the first endothermic peak is due to sublimation of small quantities of Ibu–TBA followed immediately by melting. Evidence for this is the TG curve which shows a slight decrease in weight over the broad part of the peak followed by an increase in weight loss after melting corresponding to vaporization. Examination of the sublimate collected on the cover plate of the hot-stage microscope after heating a sample of Ibu–TBA at about 145°C confirmed this explanation. The above thermal data strongly suggest the occurrence of some type of strong interaction between Ibu and TBA. This was further substantiated by the IR and $^1$H-NMR spectroscopic investigations and by TLC.

The IR spectra of Ibu–TBA were measured in the region 600–4000 $cm^{-1}$ (Fig. 5). Ibu exhibits a broad band at about 2500–3000 $cm^{-1}$ due to carboxylic O–H stretching vibration which is involved in intermolecular hydrogen bonding. At this frequency, Ibu–TBA shows separate and well-defined bands at 2920, 2620 and 2200 $cm^{-1}$ due to $^+NH_3$ bend-

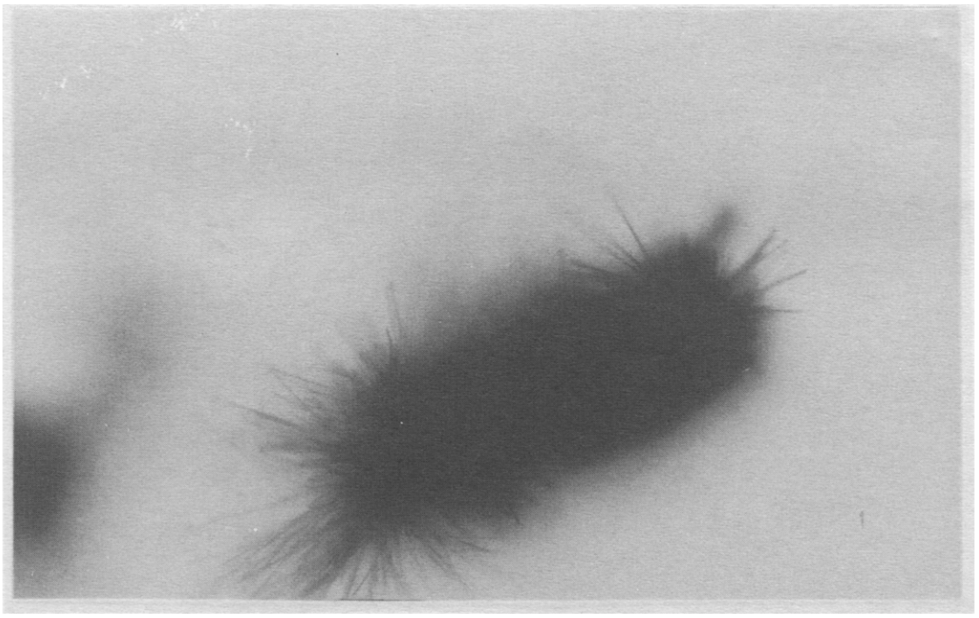


**Figure 2**
Photomicrographs of Ibu–TBA at 106°C.

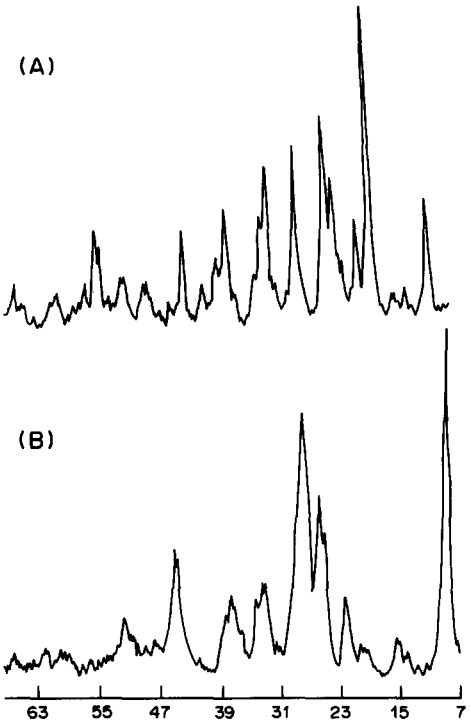



**Figure 3**
X-ray diffractograms of (A) Ibu and (B) Ibu–TBA.

ing vibration. In the carbonyl frequency region, Ibu displays a strong band at 1720 $cm^{-1}$ due to CO stretching. The band appeared at a higher frequency due to intermolecular hydrogen bonding in the carboxylic group. The location of the CO band in Ibu–TBA is dramatically shifted to lower frequency

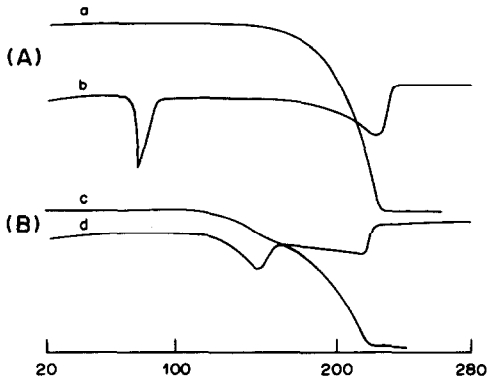



**Figure 4**
Thermal curves of (A) Ibu and (B) Ibu–TBA. a+c: TG curves. b+d: DSC curves.

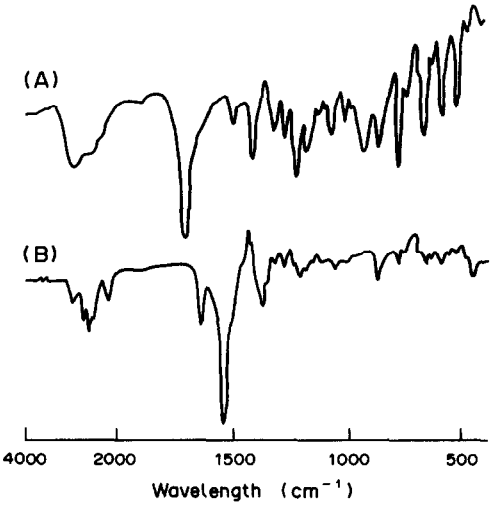



**Figure 5**
IR spectra of (A) Ibu and (B) Ibu–TBA.

(1550 $cm^{-1}$) due to the disappearance of intermolecular hydrogen bonding.

The $^1$H-NMR spectra of Ibu and Ibu–TBA are shown in Fig. 6. The $^1$H-chemical shift for the protons and the number of the different kinds of protons are provided in Table 1. As shown in the table an up-field chemical shift of the protons nuclei in Ibu–TBA in comparison to Ibu was observed for the CH—$CH_3$ group. The peak at $\delta$ = 4.93 ppm is for the —OH proton of the solvent and exchanged carboxylic proton. The appearance of a *t*-butyl group signal at $\delta$ = 1.37 ppm with the correct integration of the different protons indicates the formation of Ibu–TBA salt.

TLC studies gave additional evidence of salt formation. The $R_f$ value for Ibu–TBA was 0.41, compared with 0.90 for Ibu using butanol–water–acetic acid (4:2:1, v/v/v) as the mobile phase. The $R_f$ value of Ibu using methanol–dichloromethane (0.5:9.5, v/v) as the mobile phase was 0.4, whereas the spot corresponding to Ibu–TBA remained at the origin.

The IR and $^1$H-NMR spectroscopic studies indicates a proton transfer from the weak acid,

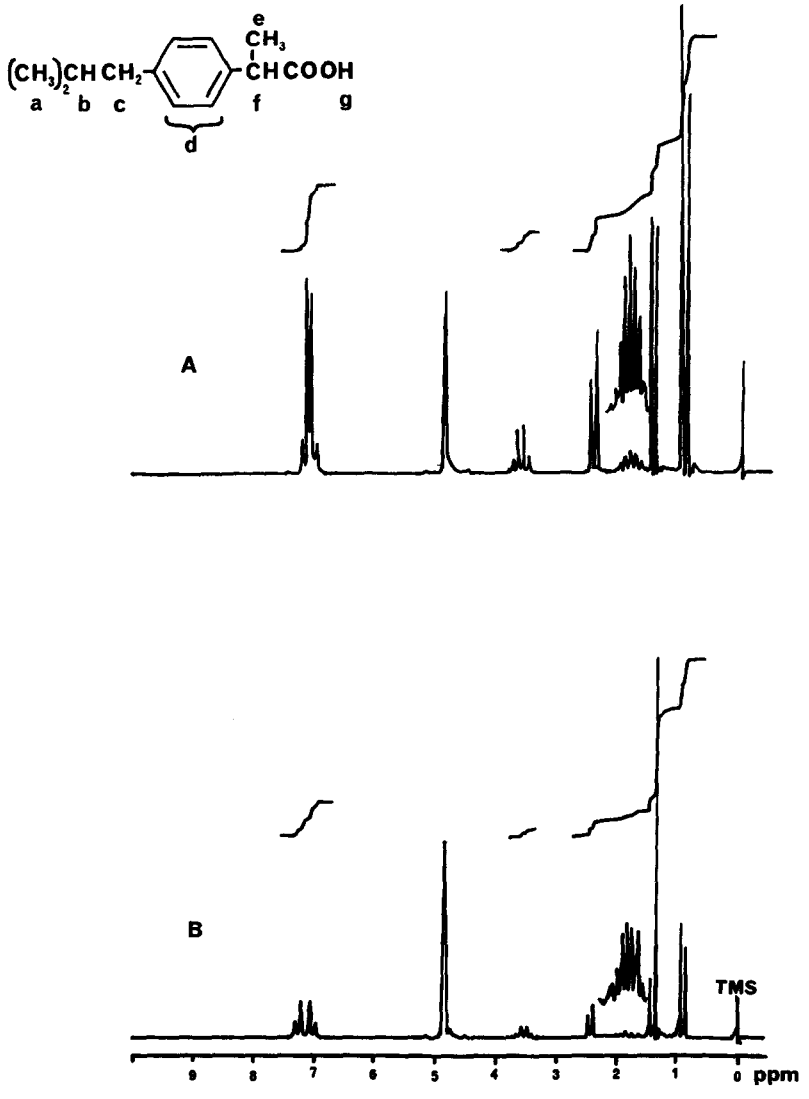
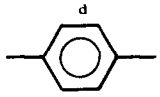


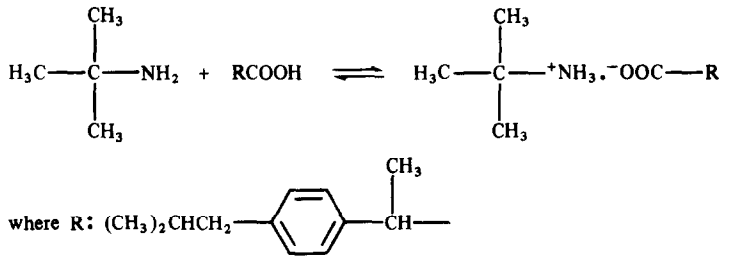

**Figure 6**
$^1$H-NMR spectra of (A) Ibu and (B) Ibu–TBA.

**Table 1**
$^1$H-NMR chemical shift for Ibu and Ibu–TBA

| Proton nucleus* | δ (ppm) Ibu | Ibu–TBA |
|---|---|---|
| $(\overset{a}{CH_3})_2$ — CH | 0.9 (6H, doublet) | 0.9 (6H, doublet) |
| $(CH_3)_2$ — $\overset{b}{CH}$ | 1.48 (1H, multiplet) | 1.42 (1H, multiplet) |
| —CH— $\overset{c}{CH_2}$— | 1.87 (2H, doublet) | 1.87 (2H, doublet) |
| $\overset{e}{CH_3}$ \| —CH— | 2.5 (3H, doublet) | 2.47 (3H, doublet) |
| $CH_3$ \| —$\overset{f}{CH}$— | 3.73 (1H, quartet) | 3.6 (1H, quartet) |
|  | 7.23 (4H, doublet–doublet) | 7.23 (4H, doublet–doublet) |
| —$C(CH_3)_3$ (TBA) | — | 1.37 (9H, singlet) |

*Refer to Fig. 6.

Ibu, to the strong base, TBA. This interaction can be represented according to the following equilibrium:




The equilibrium solubility of Ibu and Ibu–TBA as a function of temperature is shown in Fig. 7. It is evident that the solubility of Ibu–TBA is higher than that of Ibu. However the enthalpy of solution ($\Delta H_s$) for Ibu–TBA and Ibu as determined from the slopes of the two straight lines were −8.84 and −7.54 kcal $mol^{-1}$, respectively. Thus, the difference in solubility between Ibu–TBA and Ibu cannot be explained on the basis of $\Delta H_s$. The difference can rather be explained on the basis of the higher entropy change associated with the solvation of Ibu–TBA resulting in a lower free energy change as compared with Ibu.

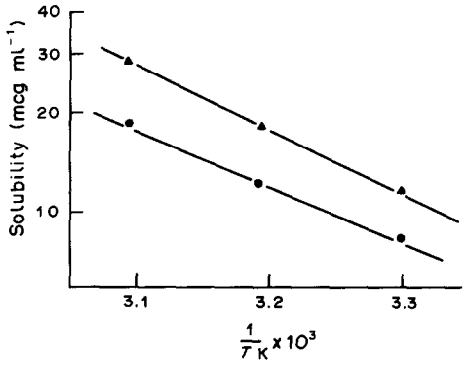



**Figure 7**
Van't Hoff plot of the equilibrium solubility against the reciprocal of absolute temperature. ●, Ibu; ▲, Ibu–TBA.

## Conclusion

Ibu–TBA salt was formed by reacting Ibu and TBA using ethanol as a solvent. Evidence for the salt formation was obtained using a number of techniques such as thermal analysis, X-ray diffraction, TLC, IR and NMR spectroscopy. Solubility studies indicated that the Ibu–TBA salt was 1.5 times more soluble in water than was Ibu free base.

## References

[1] W.I. Higuchi, P.K. Lau, T. Higuchi and J.W. Shell, *J. Pharm. Sci.* **52**, 150–153 (1963).
[2] W.I. Higuchi, P.D. Bernardo and S.C. Mehta, *J. Pharm. Sci.* **65**, 200–207 (1967).
[3] L. Maury, J. Rambaud, B. Pauvert, Y. Lasserre, G. Berg and M. Audran, *J. Pharm. Sci.* **74**, 422–426 (1985).
[4] S.A. Botha, J.K. Guillory and A.P. Lotter, *J. Pharm. Biomed. Anal.* **4**, 573–587 (1986).
[5] M.S. Suleiman and N.M. Najib, *Int. J. Pharm.* **50**, 103–109 (1989).
[6] W.L. Chiou and S. Niazi, *J. Pharm. Sci.* **62**, 498–501 (1973).
[7] N.M. Najib and M.S. Suleiman, *Int. J. Pharm.* **51**, 225–232 (1989).
[8] W.L. Chiou and S. Riegelman, *J. Pharm. Sci.* **60**, 1281–1302 (1971).
[9] A.P. Simonelli, S.C. Mehta and W.I. Higuchi, *J. Pharm. Sci.* **65**, 355–361 (1976).
[10] L.V. Allen, V.A. Yanchiak and D.D. Maness, *J. Pharm. Sci.* **66**, 494–497 (1977).
[11] D.C. Monkhouse and J.L. Lach, *J. Pharm. Sci.* **61**, 1430–1435 (1972).
[12] J.A. Biles, *J. Pharm. Sci.* **52**, 1066–1070 (1963).
[13] M.A. El-Hinnawi and N.M. Najib, *Int. J. Pharmaceut.* **37**, 175–177 (1987).
[14] M.S. Suleiman and N.M. Najib, in preparation.

[*Received 12 December 1989*]