

## SOLVATES OF INDOMETHACIN

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### Abstract

Indomethacin is known to exhibit polymorphism and solvates, the different forms obtained do not exhibit the same solubility and their bioavailabilities are different. It is of a prime importance to identify the various polymorphic and solvated forms. This study was carried out by: DSC (different scanning calorimetry), TG (thermogravimetric analysis), X-ray diffraction and thermomicroscopy.

Seven solvates, with acetone, benzene, dichloromethane, tetrahydrofurane, propanol, chloroform and diethylether, were isolated and studied. Their formulae have been determined by thermogravimetric analysis and their X-ray patterns on powder are presented, by DSC their behaviour after desolvation is recorded, the temperature and the enthalpy of fusion are measured and by this way the form obtained is deduced.

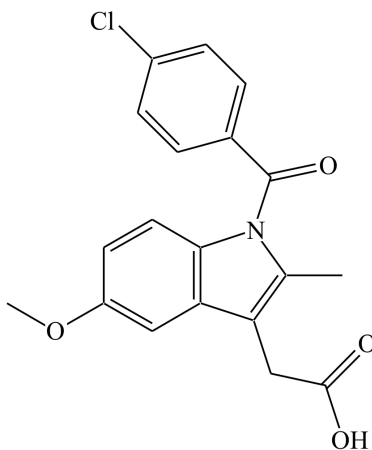
**Keywords:** indomethacin, polymorphism, solvates, TG/FTIR, X-ray

### Introduction

Indomethacin (IMC) formula is  $C_{19}H_{16}ClNO_4$ , 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H indole-3-acetic acid (Fig. 1) with a molecular mass of  $357.81 \text{ g mol}^{-1}$ . Several authors have studied the polymorphism of this compound, and in a recent study we presented the thermodynamic properties of two forms [1] and we explained the consequences of the polymorphism on the dissolution and the importance of the thermodynamic measurements. The various forms are obtained by crystallisation in different solvents, and in some cases solvated compounds are obtained. The existence of solvates with propanol, dimethylether, dichloromethane, benzene, chloroform and acetone was mentioned by [2], with methanol and *t*-butanol by [3]. Methylene chloride solvate of IMC was also obtained when IMC agglomerates were prepared from albumin as protective colloid [4]. But the formulae of the solvates were not determined. The determination of a solvated compound can be carried out by the resolution of the crystallographic structure, this requires a monocrystal. Authors who studied solvates of indomethacin seemed not to succeed to get monocrystals. We explored another way based on thermogravimetric analysis. In this study, we present the solvates, which were

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obtained with acetone, benzene, dichloromethane, tetrahydrofuran, propanol, chloroform and diethylether. Their identification was carried out by X-ray diffraction on powder, and TG coupled with infrared spectroscopy in order to identify the chemical products which evaporate. The formula was deduced from the results of TG.



**Fig. 1** 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid

Measurements of the melting point of the various compounds were obtained by differential scanning calorimetry and enabled us to characterise the form obtained after heating and desolvation.

The aim of this work is to determine the chemical formulae of the solvates and the thermal conditions of desolvation, which is of a prime importance for industrial processes and for knowing if the form obtained is stable or not on a thermodynamic point of view.

## Experimental

### *Differential scanning calorimetry*

DSC 7 (Perkin Elmer): the apparatus was calibrated (temperature and power) with the melting point of indium 5N (NIST–National Institute of Standard and Technology): 156.634°C and tin 5N (Koch-Light) 231.9681°C, for each heating rate. The heat of fusion of indium is 28.44 J g<sup>-1</sup> and the heat of fusion of tin is: 59.22 J g<sup>-1</sup>, these are recommended values by American Society for Materials ASM [5] for the melting point temperatures and Editor Bull. [6] for the heat of fusion of In and Sn.

Pans are in aluminium based alloys and covers with holes are always used in order to keep a constant pressure over the samples. All the experiments were performed under dry nitrogen gas, with a flow of 2·10<sup>-2</sup> L min<sup>-1</sup>.

Thermomicroscopic equipment composed of a Mettler FP5 and an Olympus BH-2 microscope was used for the interpretation of the phenomena observed by DSC.

### *Thermogravimetric analyser*

TG was performed on a Perkin Elmer TGA7 analysis system, on line coupled with a FTIR apparatus. Calibration was performed at different temperatures using Curie magnetic transition for the recommended alloys: Alumel (163°C), Nickel (354°C), calibration (mass) was performed using a standard mass of 100 mg. All the experiments were performed under dry nitrogen, with a flow of  $6 \cdot 10^{-2} \text{ L min}^{-1}$ . Analysis of different compounds was carried out under nitrogen purging using different scanning rates:

- $10^\circ\text{C min}^{-1}$ : this measurement was performed in order to determine the percentage of mass loss with the best precision.
- $60^\circ\text{C min}^{-1}$  for coupled measurements with IR. Because the amounts of product introduced in the TG were very small (between 5 and 10 mg) it was necessary to use the fast heating rate of  $60^\circ\text{C min}^{-1}$  in order to analyse the gases emitted by IR in the shortest time (the signals were too weak at  $10^\circ\text{C min}^{-1}$ ). Gases are transferred from the TG furnace to the heated spectroscopic cell by a line heated at  $200^\circ\text{C}$ . Infrared spectra were collected on a spectrum 2000 Perkin Elmer by averaging 32 scans of resolution of  $2 \text{ cm}^{-1}$ .
- In order to identify the gases emitted, the different solvated forms were analysed by TG coupled with IR and the spectra were compared to those obtained for the pure solvents.

The composition of the solvated forms were deduced from the following formula:

$$\Delta m/m_0 = y/(M_A + nM_s)$$
$$y = nM_s$$

where  $\Delta m$  is the mass loss,  $m_0$  is the mass of the solvated product,  $M_A$  is the molecular mass of the non-solvated form,  $M_s$  is the molecular mass of the solvent, and  $n$  is the number of moles of solvent per mole of non-solvated form.

### *X-ray crystallographic analysis on powder*

When using powder, analyses were performed using a Philips 1050 diffractometer and a 1729 Philips X-ray generator. A computer, which controls the program of measurement and analysis, completes this equipment. We used the programs «Gonio» and «Rayon» [7]. The anode used is  $\text{CuK}_\alpha$  ( $\lambda = 1.54051 \text{ \AA}$ ). Measurements were performed at room temperature.

## **Chemical products**

### *Pure indomethacin*

We used indomethacin from Sigma Company, this commercial product is composed of form I (99.5%) and form II (0.5%). This was deduced from DSC by measurement of the enthalpy of fusion [1] which was compared to pure form I and pure form II and confirmed by X-ray cristallography.

For the different experiments, a previous crystallisation was done in various solvents.

By dissolution in distilled water, and evaporation, only the form I was obtained. The same form was obtained with pure methanol.

The measured values for the fusion were:

$$T_{\text{fus}}=159.1\pm 0.5^{\circ}\text{C}$$

$$\Delta_{\text{fus}}H=103.0\pm 1 \text{ J g}^{-1}$$

This form is usually named form I.

Crystallographic structure of form I was solved by Kistenmacher [8] on a single crystal, parameters are:

$$\begin{array}{lll} a=9.295 \text{ \AA} & b=10.969 \text{ \AA} & c=9.742 \text{ \AA} \\ \alpha=69.38^{\circ} & \beta=110.79^{\circ} & \gamma=92.78^{\circ} \end{array}$$

Space group is  $P\bar{1}$  and  $Z=2$

Our crystallographic data are presented in Table 1 for comparison with the selected data of JCPDS.

**Table 1** X-ray pattern results for form I

| Form I         |            | $M.p.=159.1^{\circ}\text{C}$ |            |
|----------------|------------|------------------------------|------------|
| This work      |            | JCPDS                        | 40-1710    |
| $d/\text{\AA}$ | $I/I_0/\%$ | $d/\text{\AA}$               | $I/I_0/\%$ |
| 8.7203         | 19         | 8.701                        | 30         |
| 7.6648         | 65         | 7.609                        | 100        |
| 6.9916         | 17         | 6.916                        | 15         |
| 5.6342         | 5          | 5.619                        | 2          |
| 5.3342         | 74         | 5.315                        | 50         |
| 5.2279         | 33         | 5.203                        | 50         |
| 5.1465         | 37         | 5.111                        | 30         |
| 5.1347         | 38         |                              |            |
| 4.7970         | 16         | 4.773                        | 10         |
| 4.5844         | 35         | 4.587                        | 25         |
| 4.5391         | 46         | 4.513                        | 50         |
| 4.3687         | 14         | 4.357                        | 5          |
| 4.2801         | 8          | 4.254                        | 5          |
| 4.0798         | 100        | 4.068                        | 75         |
| 3.8893         | 20         | 3.887                        | 15         |
| 3.8421         | 21         | 3.832                        | 15         |
| 3.7116         | 19         | 3.696                        | 15         |

**Table 1** Continued

| Form I      |                                     | <i>M.p.</i> =159.1°C |                                     |
|-------------|-------------------------------------|----------------------|-------------------------------------|
| This work   |                                     | JCPDS                | 40-1710                             |
| <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å          | <i>I</i> / <i>I</i> <sub>0</sub> /% |
| 3.4921      | 16                                  | 3.473                | 10                                  |
| 3.3921      | 17                                  | 3.390                | 10                                  |
| 3.3538      | 66                                  |                      |                                     |
| 3.3188      | 23                                  | 3.299                | 10                                  |
| 3.2482      | 15                                  | 3.236                | 10                                  |
| 3.1541      | 15                                  | 3.149                | 10                                  |
| 3.1036      | 13                                  | 3.103                | 5                                   |
| 3.0994      | 13                                  |                      |                                     |
| 3.0491      | 25                                  | 3.037                | 20                                  |
| 2.9430      | 19                                  | 2.935                | 20                                  |
| 2.9084      | 11                                  | 2.905                | 5                                   |
| 2.8363      | 6                                   | 2.827                | 5                                   |
| 2.7456      | 12                                  | 2.739                | 5                                   |
| 2.7196      | 9                                   | 2.710                | 3                                   |
| 2.6719      | 11                                  | 2.656                | 5                                   |
| 2.6311      | 13                                  | 2.620                | 3                                   |
| 2.6274      | 13                                  |                      |                                     |
| 2.5704      | 10                                  |                      |                                     |
| 2.5401      | 6                                   |                      |                                     |
| 2.5108      | 53                                  |                      |                                     |
| 2.4783      | 4                                   |                      |                                     |
| 2.4505      | 5                                   |                      |                                     |
| 2.4021      | 17                                  |                      |                                     |
| 2.3389      | 5                                   |                      |                                     |
| 2.3052      | 7                                   |                      |                                     |
| 2.2783      | 7                                   |                      |                                     |

By dissolution in ethanol (96 GL Rectapur from Merck), followed by an evaporation of the solvent, a mixture of the two forms was obtained. By a second operation of dissolution and crystallisation in the same solvent the pure form II was obtained.

The measured values for the fusion were:

$$T_{\text{fus}}=153.0\pm 0.5^{\circ}\text{C}$$

$$\Delta_{\text{fus}}H=92.05\pm 1 \text{ J g}^{-1}$$

As we can see in each case only one peak appears, and the enthalpy of fusion of form I is higher than that of form II; so form I is stable under 1 bar pressure. By the way form II is metastable, and it is a case of monotropy. With acetonitrile, the same form has been obtained.

This second form was studied by X-ray diffraction, and the difference between the two forms was confirmed.

Crystallographic structure of the form II has been reported by Andronis [9]. This form is monoclinic, space group is  $P2_1$  and  $Z=6$ , parameters are:

$$\begin{array}{lll} a=5.462 \text{ \AA} & b=25.310 \text{ \AA} & c=18.152 \text{ \AA} \\ \alpha=90.00^\circ & \beta=94.38^\circ & \gamma=90.00^\circ \end{array}$$

Results of X-ray diffraction are presented in Table 2 and compared to the JCPDS files.

**Table 2** X-ray pattern results for form II

| Form II     |                                     | <i>M.p.</i> =153.0°C |                                     |
|-------------|-------------------------------------|----------------------|-------------------------------------|
| This work   |                                     | JCPDS                | 39-1883                             |
| <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å          | <i>I</i> / <i>I</i> <sub>0</sub> /% |
| 12.772      | 24                                  | 12.6277              | 31                                  |
| 10.4674     | 72                                  | 10.4023              | 100                                 |
| 8.6227      | 17                                  | 8.58813              | 23                                  |
| 7.7249      | 32                                  | 7.69453              | 29                                  |
| 7.4555      | 70                                  | 7.43677              | 92                                  |
| 6.3747      | 66                                  | 6.37091              | 50                                  |
| 6.2274      | 73                                  | 6.21521              | 66                                  |
| 6.1098      | 82                                  | 6.10861              | 86                                  |
|             |                                     | 5.94551              | 29                                  |
| 5.5106      | 25                                  | 5.50496              | 24                                  |
| 5.2541      | 22                                  | 5.21550              | 16                                  |
| 5.0505      | 38                                  | 5.06760              | 1                                   |
| 4.9170      | 70                                  | 4.92794              | 41                                  |
| 4.8021      | 60                                  |                      |                                     |
| 4.5015      | 62                                  | 4.50636              | 48                                  |
| 4.4041      | 36                                  |                      |                                     |
| 4.2975      | 59                                  | 4.29086              | 30                                  |
| 4.2079      | 30                                  | 4.03112              | 57                                  |
| 4.0277      | 100                                 | 3.91714              | 27                                  |
| 3.9258      | 90                                  | 3.80955              | 9                                   |
| 3.8096      | 60                                  | 3.70023              | 9                                   |

**Table 2** Continued

| Form II     |                                     | <i>M.p.</i> =153.0°C |                                     |
|-------------|-------------------------------------|----------------------|-------------------------------------|
| This work   |                                     | JCPDS                | 39-1883                             |
| <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å          | <i>I</i> / <i>I</i> <sub>0</sub> /% |
| 3.7032      | 43                                  | 3.63328              | 35                                  |
| 3.6259      | 69                                  | 3.56173              | 9                                   |
| 3.5658      | 32                                  |                      |                                     |
| 3.5275      | 55                                  | 3.40126              | 13                                  |
| 3.3619      | 43                                  | 3.27844              | 9                                   |
| 3.2733      | 20                                  |                      |                                     |
| 3.1405      | 58                                  | 3.14259              | 20                                  |
| 3.1137      | 30                                  |                      |                                     |
| 3.0283      | 17                                  |                      |                                     |
| 3.0138      | 17                                  |                      |                                     |
| 2.9848      | 18                                  |                      |                                     |
| 2.8791      | 40                                  | 2.88469              | 22                                  |
| 2.8465      | 37                                  |                      |                                     |
| 2.7940      | 7                                   |                      |                                     |
| 2.7436      | 15                                  |                      |                                     |
| 2.6680      | 25                                  |                      |                                     |
| 2.6129      | 4                                   |                      |                                     |
| 2.5783      | 8                                   |                      |                                     |
| 2.5245      | 5                                   |                      |                                     |

Morphology of the various crystals is described in an article of Slavin [10], and the conditions of crystallisation are presented.

These results are very important because the products obtained with other solvents will be compared to these two forms.

With water, methanol, ethanol and acetonitrile, non-solvated forms were obtained, no mass loss was observed by thermogravimetric analysis, this has been described in [1].

### Solvates of indomethacin

Indomethacin was dissolved in acetone, benzene, dichloromethane, tetrahydrofuran, propanol, chloroform, diethylether, and polar solvents; this dissolution was followed by evaporation of the solvent, the crystals obtained were analysed by X-ray diffraction, TG coupled with infra-red and DSC.

*X-ray diffraction*

After dissolution in acetone the X-ray pattern was different from form I and form II, the result is presented in Table 3.

**Table 3** X-ray pattern results for (IMC)<sub>4</sub>CH<sub>3</sub>COCH<sub>3</sub>

| <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% |
|-------------|-------------------------------------|-------------|-------------------------------------|
| 12.2162     | 24                                  | 4.0532      | 23.08                               |
| 10.6436     | 14                                  | 3.9139      | 27.86                               |
| 8.4020      | 53                                  | 3.6427      | 25.99                               |
| 7.2190      | 100                                 | 3.5511      | 21.21                               |
| 6.1992      | 15                                  | 3.4280      | 34.62                               |
| 5.5865      | 35                                  | 3.3347      | 23.19                               |
| 5.5140      | 34                                  | 3.1492      | 19.58                               |
| 5.4004      | 33                                  | 3.0675      | 31.12                               |
| 4.9787      | 27                                  | 2.9084      | 18.41                               |
| 4.8073      | 25                                  | 2.7588      | 12.47                               |
| 4.3006      | 31                                  | 2.6611      | 15.03                               |
| 4.1698      | 42                                  | 2.4165      | 9.56                                |

This result does not correspond to any file of JCPDS, and the compound can be considered as a novel one.

After dissolution in benzene the spectrum obtained was different from form I and II, the results are presented in Table 4, and they do not correspond to any JCPDS file either.

The crystal obtained after dissolution of non solvated indomethacin in the dichloromethane were observed by X-ray diffraction and the results are presented in Table 5.

After dissolution of non solvated indomethacin in THF and evaporation of the solvent the crystals studied lead to the results presented in the Table 6, it does not correspond to any JCPDS file.

After dissolution of non-solvated indomethacin in propanol and evaporation of the solvent at room temperature, the crystals studied lead to the results presented in Table 7. It does not correspond to any JCPDS file. The same operation was done with chloroform, the results are presented in Table 8, they do not correspond to any JCPDS file either.

After dissolution in diethylether the spectrum obtained is different from the others, but a lot of peaks are the same than those of form II.

By comparison of the different patterns it is possible to conclude that a similitude exists between the solvates with: acetone, tetrahydrofurane, dichloromethane, chloroform and propanol, only some rays are different, they are not at the same position, for the solvate with the diethylether the rays which are not attributed to form II are also similar to the other solvates with also some variations for the two theta values, the solvated form with benzene is different from the other solvates, there is some similitude to the form II but it is doubtless different as we can see on Fig. 2.



**Table 4** X-ray pattern results for (IMC)<sub>4</sub>C<sub>6</sub>H<sub>6</sub>

| <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% |
|-------------|-------------------------------------|-------------|-------------------------------------|
| 11.8560     | 28                                  | 3.6186      | 16                                  |
| 11.2242     | 18                                  | 3.5050      | 60                                  |
| 9.5422      | 14                                  | 3.4202      | 38                                  |
| 8.3861      | 48                                  | 3.2616      | 24                                  |
| 7.4368      | 60                                  | 3.1928      | 24                                  |
| 6.2449      | 16                                  | 3.0465      | 58                                  |
| 5.5276      | 100                                 | 3.0143      | 46                                  |
| 5.1899      | 30                                  | 2.9079      | 14                                  |
| 4.6815      | 26                                  | 2.8159      | 22                                  |
| 4.5739      | 46                                  | 2.7843      | 20                                  |
| 4.1448      | 80                                  | 2.6489      | 12                                  |
| 3.7967      | 44                                  | 2.5931      | 10                                  |
| 3.7463      | 26                                  | 2.4609      | 12                                  |
|             |                                     | 2.2928      | 20                                  |

**Table 5** X-ray pattern results for (IMC)<sub>6,66</sub>CH<sub>2</sub>Cl<sub>2</sub>

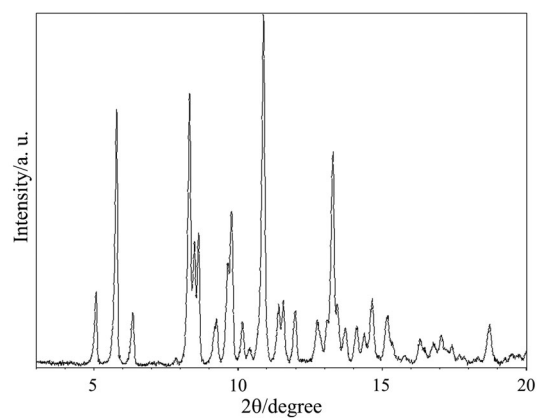
| <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% |
|-------------|-------------------------------------|-------------|-------------------------------------|
| 12.3097     | 20                                  | 3.9586      | 22.12                               |
| 10.6436     | 11                                  | 3.9037      | 23.94                               |
| 8.4299      | 47                                  | 3.8233      | 20.58                               |
| 7.2220      | 97                                  | 3.7896      | 21.44                               |
| 6.4887      | 10                                  | 3.6500      | 23.17                               |
| 6.1755      | 13                                  | 3.5581      | 23.56                               |
| 5.5953      | 32                                  | 3.4358      | 37.98                               |
| 5.3971      | 28                                  | 3.3544      | 21.63                               |
| 4.9940      | 21                                  | 3.2453      | 15.77                               |
| 4.8359      | 32                                  | 3.1552      | 17.79                               |
| 4.6475      | 28                                  | 3.1206      | 17.79                               |
| 4.4981      | 24                                  | 3.0758      | 28.85                               |
| 4.4390      | 25                                  | 2.9232      | 16.15                               |
| 4.3923      | 25                                  | 2.9033      | 16.06                               |
| 4.3465      | 25                                  | 2.8841      | 15.48                               |
| 4.3130      | 27                                  | 2.7415      | 11.92                               |
| 4.1737      | 37                                  | 2.6777      | 13.27                               |
| 4.0440      | 21                                  | 2.6166      | 11.35                               |

**Table 6** X-Ray Pattern results for (IMC)<sub>2</sub>C<sub>4</sub>H<sub>8</sub>O

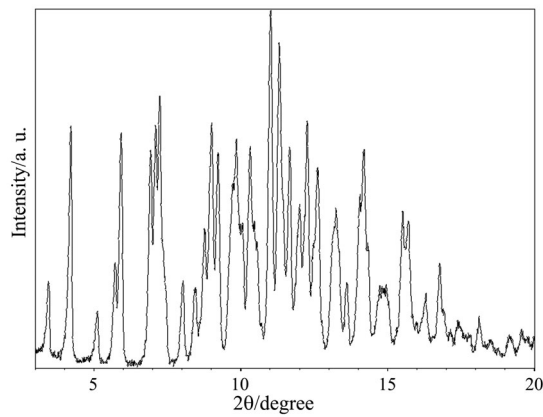
| <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% |
|-------------|-------------------------------------|-------------|-------------------------------------|
| 14.5479     | 13                                  | 3.9656      | 60                                  |
| 12.9687     | 6                                   | 3.8969      | 34                                  |
| 11.9199     | 14                                  | 3.6273      | 34                                  |
| 10.6436     | 14                                  | 3.4541      | 65                                  |
| 8.2765      | 44                                  | 3.3507      | 20                                  |
| 7.1092      | 49                                  | 3.2418      | 21                                  |
| 5.9764      | 6                                   | 3.0619      | 47                                  |
| 5.4700      | 100                                 | 2.9577      | 31                                  |
| 5.3809      | 85                                  | 2.7987      | 10                                  |
| 4.9566      | 66                                  | 2.7717      | 10                                  |
| 4.7511      | 32                                  | 2.6557      | 22                                  |
| 4.5414      | 18                                  | 2.5362      | 9                                   |
| 4.4467      | 28                                  | 2.4959      | 6                                   |
| 4.2628      | 48                                  | 2.3671      | 5                                   |
| 4.1238      | 94                                  | 2.2750      | 5                                   |

**Table 7** X-Ray Pattern results for (IMC)<sub>3</sub>C<sub>2</sub>H<sub>5</sub>CH<sub>2</sub>OH

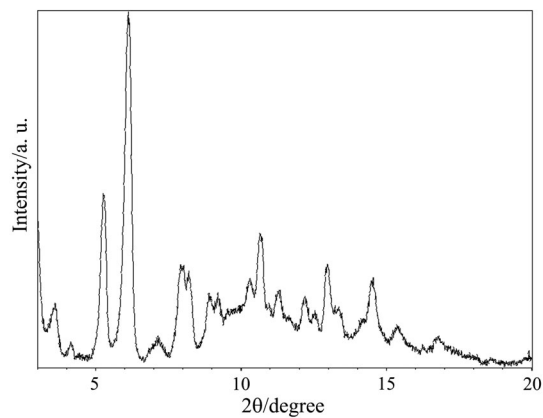
| <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% | <i>d</i> /Å | <i>I</i> / <i>I</i> <sub>0</sub> /% |
|-------------|-------------------------------------|-------------|-------------------------------------|-------------|-------------------------------------|-------------|-------------------------------------|
| 14.7175     | 28                                  | 4.8333      | 29                                  | 3.3997      | 27                                  | 2.36611     | 16                                  |
| 12.0827     | 16                                  | 4.7385      | 25                                  | 3.3669      | 26                                  | 2.6338      | 17                                  |
| 10.7601     | 15                                  | 4.6987      | 27                                  | 3.3273      | 20                                  | 2.6248      | 17                                  |
| 8.3309      | 47                                  | 4.5391      | 27                                  | 3.2686      | 14                                  | 2.5916      | 11                                  |
| 8.0219      | 10                                  | 4.4139      | 24                                  | 3.2349      | 15                                  | 2.5537      | 13                                  |
| 7.5959      | 13                                  | 4.2955      | 41                                  | 3.1917      | 21                                  | 2.5279      | 12                                  |
| 7.1608      | 59                                  | 4.1543      | 100                                 | 3.0878      | 41                                  | 2.4913      | 10                                  |
| 6.1499      | 10                                  | 4.0440      | 20                                  | 3.0753      | 40                                  | 2.4780      | 10                                  |
| 6.0413      | 9                                   | 3.9902      | 26                                  | 3.0034      | 17                                  | 2.4570      | 9                                   |
| 5.7899      | 10                                  | 3.8372      | 38                                  | 2.9492      | 24                                  | 2.4262      | 9                                   |
| 5.5311      | 59                                  | 3.7261      | 18                                  | 2.9153      | 17                                  | 2.4130      | 9                                   |
| 5.3776      | 60                                  | 3.6419      | 29                                  | 2.8474      | 13                                  | 2.3293      | 9                                   |
| 5.2448      | 13                                  | 3.5785      | 16                                  | 2.8124      | 17                                  | 2.3081      | 10                                  |
| 5.1659      | 12                                  | 3.5365      | 17                                  | 2.7642      | 12                                  | 2.2635      | 10                                  |
| 4.9676      | 47                                  | 3.5063      | 21                                  | 2.7281      | 12                                  |             |                                     |
| 4.8888      | 31                                  | 3.4515      | 64                                  | 2.6719      | 16                                  |             |                                     |



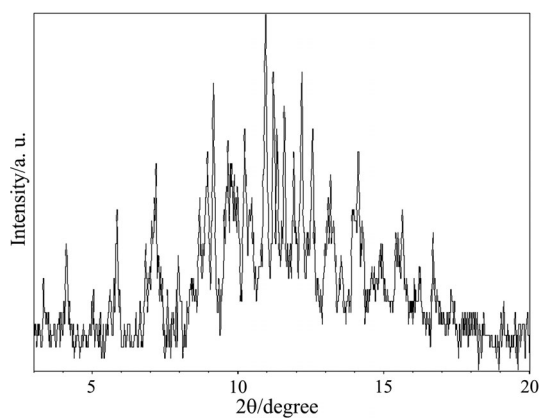
**Fig. 2a** X-ray pattern for form I



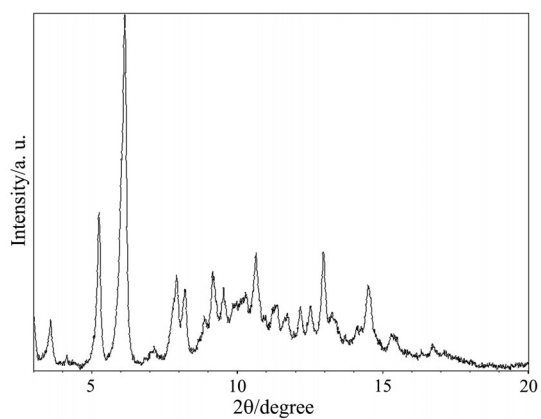
**Fig. 2b** X-ray pattern for form II



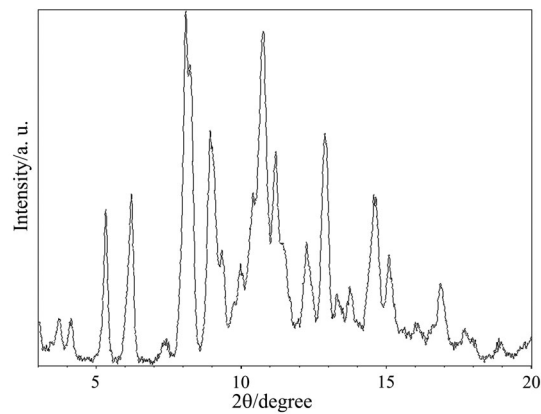
**Fig. 2c** X-ray pattern for  $(\text{IMC})_4\text{CH}_3\text{COCH}_3$



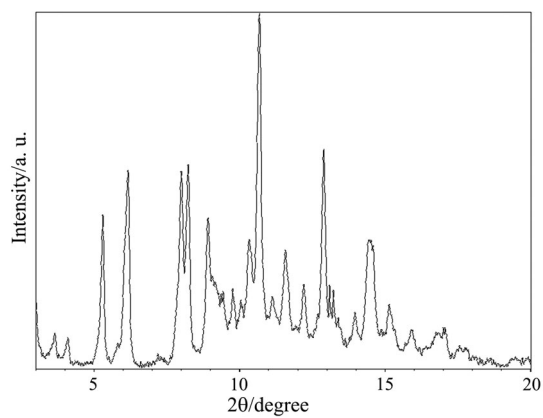
**Fig. 2d** X-ray pattern for (IMC)<sub>4</sub>C<sub>6</sub>H<sub>6</sub>



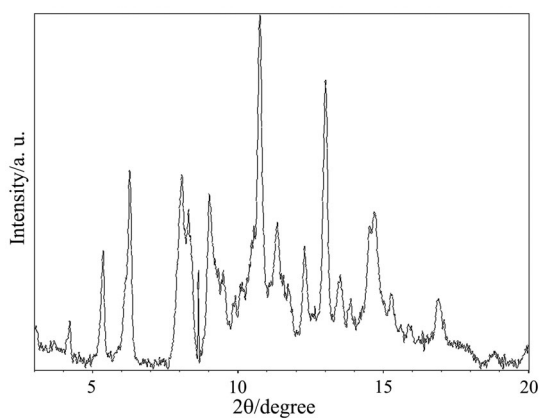
**Fig. 2e** X-ray pattern for (IMC)<sub>6,66</sub>CH<sub>2</sub>Cl<sub>2</sub>



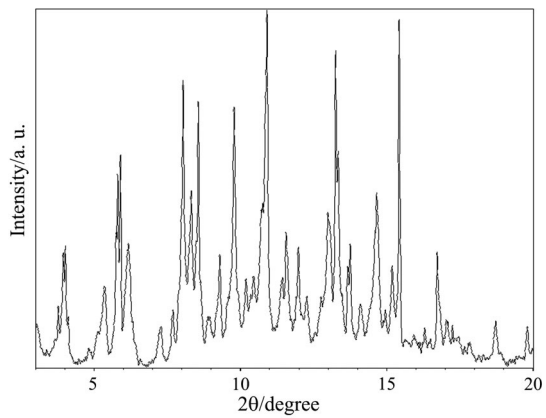
**Fig. 2f** X-ray pattern for (IMC)<sub>2</sub>C<sub>4</sub>H<sub>8</sub>O



**Fig. 2g** X-ray pattern for  $(\text{IMC})_3\text{C}_2\text{H}_5\text{CH}_2\text{OH}$



**Fig. 2h** X-ray pattern for  $(\text{IMC})_4\text{CHCl}_3$



**Fig. 2i** X-ray pattern for solvate of IMC –  $\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$

No solvates appeared after dissolution in water, methanol, ethanol and acetonitrile, whose evaporation leads to the following forms:

| Solvent                          | IMC form I or II |
|----------------------------------|------------------|
| H <sub>2</sub> O                 | I                |
| CH <sub>3</sub> OH               | I                |
| C <sub>2</sub> H <sub>5</sub> OH | II               |
| CH <sub>3</sub> CN               | II               |

It is worthy to notice that Borka [2] got different results: he obtained both form I and II with acetonitrile; the conditions of evaporation are not described by [2], so in this case it is not possible to compare the experiments; form II was obtained with water and ethanol, and with methanol form II and an other form that he named IV with a melting temperature of 134°C was obtained, but no X-ray diffraction analysis was presented. The difference between these results is not in fact conflicting, it means that all the details are important in a crystallisation by solvent evaporation and it is very easy to obtain a mixture of two polymorphic forms, or of solvated and non solvated forms.

#### *TG analysis*

This coupled method was performed in order to know whether the X-ray recordings correspond to another polymorphic form or a solvate. The result obtained after dissolution in acetone, showed that no loss of mass was observed before 60°C, it means that this is a solvate, because if acetone were only adsorbed on the surface of indomethacine crystals, the mass loss would start at lower temperature. The mass loss between 60 and 140°C corresponds to 3.97%. The gas was analysed using the FTIR on-line coupling. The spectra collected during this step showed specific vibration bands corresponding to the ketone group. In addition, this gas emitted was compared with pure acetone solvent evaporated in the TG furnace in the same conditions; the spectral results are similar. By calculation we found that the mass loss corresponds to 0.25 mole of acetone per mole of IMC. So the formula of the solvate is:  $(C_{19}H_{16}ClNO_4)_4CH_3COCH_3$ .

After dissolution in benzene, the TG analysis did not lead to any mass loss before 60°C. However between 70 and 170°C, the mass loss measured is 5.50%: this corresponds to  $n=0.27$ . The IR analysis of the emitted gas compared with the spectrum of pure benzene showed that it is benzene. The formula of the solvate is  $(C_{19}H_{16}ClNO_4)_4C_6H_6$ .

The mass loss corresponding to 3.39%, measured by TG, started at 40 up to 145°C, for the crystal dissolved in dichloromethane. This percentage gave a value of  $n$  equals to 0.15. In this case it is ambiguous to deduce the formula  $(C_{19}H_{16}ClNO_4)_{6.66}CH_2Cl_2$ . In addition, the IR analysis of the gas emitted leads to the spectrum corresponding to  $CH_2Cl_2$ .

**Table 8** X-ray pattern results for  $(\text{IMC})_4\text{CHCl}_3$ 

| $d/\text{Å}$ | $I/I_0$ /% | $d/\text{Å}$ | $I/I_0$ /% | $d/\text{Å}$ | $I/I_0$ /% |
|--------------|------------|--------------|------------|--------------|------------|
| 12.3873      | 17         | 4.7562       | 35         | 3.0701       | 47         |
| 11.9521      | 18         | 4.6669       | 34         | 3.0364       | 50         |
| 10.4427      | 22         | 4.4756       | 28         | 2.9265       | 29         |
| 10.0628      | 14         | 4.3751       | 32         | 2.8643       | 21         |
| 9.7632       | 14         | 4.2347       | 43         | 2.8176       | 22         |
| 8.2457       | 40         | 4.2030       | 46         | 2.7584       | 19         |
| 7.0360       | 60         | 4.1276       | 100        | 2.7370       | 19         |
| 6.4863       | 13         | 3.9139       | 47         | 2.7112       | 19         |
| 6.3656       | 12         | 3.8421       | 33         | 2.6859       | 20         |
| 6.1755       | 13         | 3.7904       | 31         | 2.6527       | 28         |
| 5.9326       | 13         | 3.66172      | 41         | 2.6203       | 23         |
| 5.4801       | 59         | 3.5172       | 25         | 2.3834       | 15         |
| 5.3358       | 50         | 3.4202       | 83         | 2.3451       | 14         |
| 5.1244       | 29         | 3.2959       | 34         |              |            |
| 4.9103       | 54         | 3.2109       | 28         |              |            |

The loss of mass obtained by TG started at 70 up to 170°C for the crystal after dissolution in tetrahydrofuran, corresponding to 8.76%, we can deduce that  $n=0.48$ . The IR analysis of the gas emitted corresponds to  $\text{C}_4\text{H}_8\text{O}$ . The formula of the solvate is:  $(\text{C}_{19}\text{H}_{16}\text{ClNO}_4)_2\text{C}_4\text{H}_8\text{O}$ .

After dissolution in propanol, the TG analysis of IMC (start: 75 – end: 140°C) leads to the 5.70% loss of mass, corresponding to the  $n$  value equal to 0.35. The IR analysis of the gas emitted corresponded to propanol. In view of this results we propose the following formula for the solvate:  $(\text{C}_{19}\text{H}_{16}\text{ClNO}_4)_3\text{C}_3\text{H}_8\text{O}$ .

In chloroform, the loss of mass of 7.34%, obtained by TG analysis, corresponding to 0.24 mole of solvent per mole of IMC. In view of these results we propose the following formula for the solvate  $(\text{C}_{19}\text{H}_{16}\text{ClNO}_4)_3\text{CHCl}_3$ . It is mainly form II that appears after evaporation of the solvent.

The result obtained for TG analysis of the crystal after dissolution in diethyl ether showed that the loss of mass obtained from TG analysis is around 1% and started at 80°C. This temperature is too high to be attributed to the desorption of the solvent (this would occur at 30°C). The very small value of the mass loss does not allow proposing a reasonable formula for the solvate. We conclude that there is a mixing between pure IMC, probably form II according to the X-ray pattern results, and the solvated form IMC diethylether, but this last one being in very low proportion.

#### DSC analysis

By DSC the endothermic phenomenon of desolvation was generally observed between 60 and 101°C. For IMC dissolved in acetone, a small exothermic pheno-

menon was observed at 110°C, it means that after the desolvation the products was crystallised. Two endothermic peaks appeared one at 152.9°C with an enthalpy of 81.8 J mol<sup>-1</sup>, corresponding to the melting temperature of form II: it is possible to evaluate the proportion of this form at 89%; another peak of a smaller intensity was observed at 159°C with an enthalpy of 0.59 J g<sup>-1</sup>, corresponding to the stable form I (0.5%), as anyone can see the sum is not of 100%, so probably 10.5% is amorphous.

In dichloromethane, the DSC results showed that the desolvation occurs between 80 and 110°C, then an exothermic peak corresponding to a recrystallisation occurs between 110 and 140°C, then two endothermic peaks are observed, the first one at 149°C with an enthalpy of 50.46 J g<sup>-1</sup> and another one at 159°C which corresponds to the form I. It seems that the desolvated solid is a mixture of a metastable phase and the stable form I, the metastable phase could be the form III mentioned by [2], without succeeding in isolating it.

An endothermic peak between 70 and 125°C was observed for IMC dissolved in tetrahydrofuran and analysed by DSC. This peak corresponds to the desolvation. A very small endothermic peak was then observed around 159°C (form I), it means that a very small amount of the product is crystallised after the desolvation and it may be considered as amorphous. But in another run performed using the same conditions the desolvation was the same but the recrystallisation was more important and an endothermic peak at 153.2°C with an enthalpy of 92.7 J g<sup>-1</sup> corresponding to 90% of form II was observed; we deduced that 10% was amorphous. It is necessary to be very careful about the interpretation of these observations: the only conclusion is that the free energies of activation of the reactions leading to the forms I and II must be very close.

A large endothermic peak appearing between 80 and 105°C, followed by a double exothermic peak was obtained for IMC in propanol. Then two endothermic peaks appeared at 152.0 and 158.7°C corresponding to the non-solvated forms I and II with respective enthalpies of fusion of 48.08 and 29.97 J g<sup>-1</sup>. This corresponds to 46% of form I and 32.6% of form II. For this case the separation of the two peaks is not easy and an overlap is observed. DSC after TG shows also two peaks of fusion at 150.1 and 158.2°C, as here also an overlap is present, a precise evaluation of the proportion is hazardous.

**Table 9** Summary of the results

| Solvent  | Mass loss/% | Formula   | Form I | Form II |
|--|-------------|---|--------|---------|
| CH <sub>3</sub> COCH <sub>3</sub>                | 3.97        | (IMC) <sub>4</sub> CH <sub>3</sub> COCH <sub>3</sub>                | *      | ***     |
| C <sub>6</sub> H <sub>6</sub>                    | 5.50        | (IMC) <sub>4</sub> C <sub>6</sub> H <sub>6</sub>                    | **     | **      |
| CH <sub>2</sub> Cl <sub>2</sub>                  | 3.39        | (IMC) <sub>6,66</sub> CH <sub>2</sub> Cl <sub>2</sub>               | ***    | *       |
| C <sub>4</sub> H <sub>8</sub> O(THF)             | 8.76        | (IMC) <sub>2</sub> C <sub>4</sub> H <sub>8</sub> O                  |        | ****    |
| C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> OH | 5.80        | (IMC) <sub>3</sub> C <sub>2</sub> H <sub>5</sub> CH <sub>2</sub> OH | **     | **      |
| CHCl <sub>3</sub>                                | 7.34        | (IMC) <sub>4</sub> CHCl <sub>3</sub>                                | *      | ***     |
| (C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O  | 1.7–2       | Not determinable  | *      | ***     |



## Conclusions

Seven solvated forms of indomethacin were isolated and their X-ray patterns given for the first time. The formula of six of them was determined, with the diethylether the products obtained were a mixture of form II and a solvated form. TG coupled IR has been particularly efficient to prove the real existence of the solvated forms. The results are summarised in the Table 9. Both forms I and II appear after evaporation of the solvent, except in the case of tetrahydrofurane where only form II appears, and ether for which nearly only form I crystallises after desolvation.

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