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**SOLUBILITIES AND CRYSTALLIZATION OF OLANZAPINE USING A MULTI-WELL SETUP:  
EFFECT OF SOLVENT AND COOLING RATE**

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**ABSTRACT**

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In this work, we have studied the cooling crystallization of the two anhydrous phases of Olanzapine in a stagnant medium in the presence of six solvents with different polarities using a multi-well technology. First, we measured solubility from 20 °C to 60 °C. The results showed that the solubility increases with the solvent polarity: Methanol > Ethanol > Acetonitril > Ethyl Acetate > Tetrahydrofuran > Toluene. Second, we evidenced the effect of the solvents and the cooling rates on the crystal habit, crystal phase and crystal size distribution.

**Keywords:** Olanzapine, cristallization; solvents, solubility, cooling rate.

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## 1. INTRODUCTION

Crystallization is a process widely used in many industries including the pharmaceutical industry. The majority of the active pharmaceutical ingredients (APIs) are obtained in solid form by crystallization in solution (presence of solvent). Polymorphism of APIs, the ability of a molecule to exist under at least two distinct crystal structures, is an issue in crystallization because it leads to solid with different physical and physico-chemical properties [1, 2]. Moreover, crystallization is influenced by several physico-chemical parameters such as solute concentrations, temperature, solvents, additives and pH, as well as process parameters such as seeds (shape, size and weight), cooling rate and agitation speed.

Here, we are interested in the crystallization of an API in the presence of six solvents with different polarities based on crystallization by cooling in a stagnant medium using a multi-well setup with video-microscopy [3]. First, we measured the solubility of the API in the different solvents at different temperatures. Second, we studied the influence of these different solvents on the crystallization of the API by highlighting the effect of the cooling rate.

In this work, we studied the crystallization of Olanzapine (OLZ) (Fig.1), its antiepileptic properties place it in the best anticonvulsant sold in the world [4-10]. OLZ belongs to Class II of Biopharmaceuticals Classification System; it dissolves slowly and absorbs rapidly where the dissolution process in the gastrointestinal tract represents the limited step. Consequently, oral and intravenous administrations are privileged galenic form [2, 9, 11].

OLZ is a poorly water soluble API and has more than 25 different phases, polymorphs or solvates [10-13].

**Fig.1** Chemical Structure of Olanzapine.

## 2 Materials and Methods

OLZ was supplied as a crystalline powder, denoted form I and II, by Beker Pharmaceutical Industry (Algeria) and used as received, form II is the stable form of crystalline OLZ as described in the literature [14-16] Methanol, Ethanol, Acetonitrile (ACN), Ethyl Acetate, Tetrahydrofuran (THF), Toluene, all HPLC grade were purchased from Sigma- Aldrich. Their properties are listed in Table 1.

## 2.1 Physical Characterization

### 2.1.1 Optical Microscopy

Crystals were observed by optical microscope (Nikon Eclipse TE2000-U) equipped with lenses X4 or X10, and connected to a CCD camera (Imaging Source DFK41) for real-time image acquisition.

### 2.1.2 Scanning Electron Microscope

Scanning electron microscope (SEM) JEOL 6320F was used; the samples were coated in vacuum with gold. The instrument was used at an acceleration voltage of 3 kV.

### 2.1.3 X-Ray Crystallography

The x-ray powder diffraction INEL was used to identify crystal phases. The samples were placed in capillaries positioned vertically; then, data were collected in the  $2\Theta$  range of  $0-50^\circ$ , with a total time of 10 mn.

### 2.1.4 Multi-Well Setup

The setup used here is home-made [3] (since marketed by ANACRISMAT). This is an inverted microscopy equipped with a multi-well Peltier block to control the temperature of the crystallization vials mounted on an X-Y translation stage, Fig.2. The use of this multi-well setup is well adapted for multiplying the crystallization experiments in the framework of screening of crystallization conditions and phases [3, 17]. Temperature profil (ramp, plateau or jump), displacement of the X-Y motorized stage and sequential image acquisition for each vials are controlled via a Labview interface. This makes it possible to detect events such as nucleation, growth and crystal habit modification in function of the operating conditions [3].

## 2.2 Methods

The solubilities of OLZ in different solvents were determined with the method of successive additions to bracket solubilities with temperature range from 20 to 60 °C (by step of 10°C) as described by Detoisien et al.[3].

OLZ crystallization was performed from the supplied anhydrous forms (form I and form II) in different solvents (Table 1) and was carried out using multi-well setup (Fig.2) with crimped vials of 1 ml for solvent.

Temperature program for crystallization was set as follow: the temperature was first fixed at 60 °C for 60 minutes to ensure complete OLZ solubilization from the saturated solution (checked visually) and second, vials were cooled to 10 °C with a ramp of 1 °C·h<sup>-1</sup>. The same experimental procedure will use for 10 and 20°C·h<sup>-1</sup>. All crystallization experiments were repeated 4 times.

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**Fig. 2** Photo of multi-well with vials of (1) 1mL crimped vial, (2) removable vial support, (3) peltier blocks, (4) optical microscope and (5) X-Y translation stage.

**Table 1** Properties of solvents for crystallization experiments

Solvents	Chemical formula	Range	Boiling point (°C)	Relative Polarity*
Methanol	CH <sub>3</sub> OH	Polar Protic	64.70	0.762
Ethanol	C <sub>2</sub> H <sub>5</sub> OH	Polar Protic	78.37	0.654
ACN	CH <sub>3</sub> CN	Aprotic Polar	82.00	0.46
Ethyl Acetate	C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>	Polar Aprotic	77.10	0.228
THF	C <sub>4</sub> H <sub>8</sub> O	Polar aprotic	66.00	0.207
Toluene	C <sub>6</sub> H <sub>5</sub> -CH <sub>3</sub>	Apolar	110.60	0.099

\* The values for relative polarity are normalized from measurements of solvent shifts of absorption spectra and were extracted from Christian Reichardt [18].

### 3 Results and Discussion

#### 3.1 Characterization of the Raw Materials

First, we performed XRD (Fig. 3) analysis of anhydrous forms of OLZ supplied by Beker Pharmaceutical Industry.

**Fig. 3** XRD for OLZ form I and form II

The diffractogram of the OLZ confirmed the crystallinity of the supplied samples. The main diffraction peaks of the 2 forms are gathered in tab.2.

**Table 2** Main diffraction peaks for form I and form II.

form II		form I	
2 $\theta$	Intensity (%)	2 $\theta$	Intensity (%)
9.06	99.868	8.68	99.757
10.46	14.188	10.48	18.056
12.98	20.982	12.6	13.421
18.62	88.236	14.88	12.043
18.98	27.443	17.1	16.834
19.7	24.316	18.02	15.138
21.3	18.449	18.78	11.142
22	17.593	19	13.354
23.96	15.171	20.24	39.834
24.34	19.828	21.44	81.284
25.78	16.643	21.78	28.695
		22.66	28.813
		24.5	45.789
		25.62	18.904
		30.22	10.57

### 3.2 Solubility of OLZ

The solubilities of OLZ (form I and form II) in the 6 solvents tested in this study were measured by the method of successive additions of OLZ in vials containing 0.8 ml of solvents. OLZ solubility curves are shown in Fig. 4:

**Fig. 4** Solubility of OLZ in different solvents: (a) form I and (b) form II.

The solubility increases with temperature for all six solvents. The comparative study of solubility in different solvents allows highlighting the behavior of OLZ in these solvents. We show a clear difference between the solubilities in the six solvents, and for different temperatures. The solubility of OLZ increases with the solvent polarity (tab.1): Methanol > ETOH > ACN > Ethyl Acetate > THF > Toluene.

For all the solvents tested in the temperature range tested, we observed that the solubility of solid form II is lower than the solid form I. Therefore, we confirm that solid form II is the stable solid form and solid form I is, thus, metastable (solubilities rule).

### 3.3 Influence of the Solvents on the Crystallization Process in a Stagnant Medium

Here, we studied the cooling crystallization of OLZ, starting from form I and form II, in different solvents using the following program: heating up to 60 °C and cooling down to 10 °C with a ramp of 1 °C·h<sup>-1</sup>. Initial concentrations were the solubilities at 60°C in the different solvents determined previously (Fig. 4).

Crystals of the different forms of OLZ supplied and the crystals obtained in the crystallization experiments in the six pure solvents were characterized by optical microscopy in Figs. 5–6, scanning electron microscopy in Figs. 7–8 and XRD in Fig. 9.

**Fig. 5** Optical micrographs of (a) crystals of OLZ form I supplied, (b) crystal of OLZ obtained from form I in Methanol, (c) in Ethanol (d) in ACN and (e) in THF.

**Fig. 6** Optical micrograph of: (a) crystals of OLZ form II supplied, (b) crystal of OLZ obtained from form II in Methanol, (c) in Ethanol, (d) in Ethyl acetate (e) in THF and (f) in Toluene.

**Fig. 7** SEM micrographs of: (a) crystals of OLZ form I supplied, (b) crystal of OLZ obtained from form I in Methanol, (c) in Ethanol and (d) in ACN

**Fig. 8** SEM micrographs of: (a) crystals of OLZ form II supplied, (b) crystal of OLZ obtained from form II in Methanol, (c) in Ethanol, (d) in Ethyl acetate, (e) in THF and (f) in Toluene.

OLZ employed throughout this work appear as regular plates with small size (Fig. 7a) and big size (Fig. 8a) particles, corresponding to form I and form II, respectively. Two anhydrous phases of OLZ crystallize as yellow prismatic crystals (Figs. 5b–5d and Figs. 6b–6e). Unlike from OLZ form I in THF (Fig. 5e) and from OLZ form II in Toluene, yellow needles were obtained (fig. 6f).

**Fig.9** XRD crystal forms of OLZ: a) Methanol, b) Ethanol, c) Ethyl acetate, d) ACN, e) THF, f) Toluene.

Table 3 summarizes the crystallization conditions and the results, nucleation temperature and phases crystallized. Crystals were obtained from OLZ form I in methanol, ethanol, ACN and THF but ethyl acetate and toluene. From OLZ form II, crystals are obtained in all solvents but ACN.

Note that the higher the solubility the higher the nucleation temperature, confirming (the crystallization rule) that the higher the solubility the easier the crystallization.

**Table 3** Crystallization conditions, nucleation temperatures and identified phases.

Starting material	Concentration (kg·l <sup>-1</sup> )	Solvents	Ramp (°C·h <sup>-1</sup> )	T <sub>nucleation</sub> (°C)	Phase
form I	0.074±0.0096*	Methanol	1	48.90±0.01	OLZ methanol solvate [19]
form II	0.051±0.0026	Methanol	1	45.00±0.02	OLZ methanol solvate [19]
form I	0.064±0.0008	Ethanol	1	43.00±0.01	OLZ Ethanol Solvate [15]
form II	0.038±0.0030	Ethanol	1	41.20±0.03	OLZ Ethanol Solvate [15]
form I	0.040±0.0006	ACN	1	36.90±0.01	Form I
form II	0.020±0.0007	ACN	1	—	—
form I	0.028±0.0005	Ethyl acetate	1	—	—
form II	0.018±0.0006	Ethyl acetate	1	21.00±0.04	Form II
form I	0.012±0.0003	THF	1	—	Not enough to characterize
form II	0.009±0.0003	THF	1	11.50±0.01	P1**
form I	0.011±0.0002	Toluene	1	—	—
form II	0.009±0.0007	Toluene	1	12.50±0.05	P2**

\* ± Are the deviations from average values.

\*\* P1 and P2 are phases not yet identified (Fig. 9e– 9f)

### 3.4 Influence of the Cooling Rate on the Crystallization Process in a Stagnant Medium

In order to study the effect of the cooling rate on the crystallization process starting from form II, the stable phase, in a stagnant medium, the nature of the crystal obtained was identified by XRD for the different

cooling rates tested: 1 - 10 and - 20 °C·h<sup>-1</sup> and only for methanol, ethanol THF and Toluene. Results are summarized in Fig. 10– 11 and Table. 4: nucleation temperatures and obtained phases.

**Fig. 10** Influence of cooling rate: a) Methanol with 1 °C·h<sup>-1</sup>, 10 °C·h<sup>-1</sup> and 20 °C·h<sup>-1</sup>, b) Ethanol with 1 °C·h<sup>-1</sup>, 10 °C·h<sup>-1</sup> and 20 °C·h<sup>-1</sup>, c) THF with 1 °C·h<sup>-1</sup>, 10 °C·h<sup>-1</sup> and 20 °C·h<sup>-1</sup> with 1 °C·h<sup>-1</sup>, 10 °C·h<sup>-1</sup> and 20 °C·h<sup>-1</sup>, d) Toluene with 1 °C·h<sup>-1</sup>, 10 °C·h<sup>-1</sup> and 20 °C·h<sup>-1</sup>. P1, P2, P3, P4 and P5 are phases not yet identified (fig. 10c – 10d)

**Table.4** Crystallization conditions, profil of temperature, nucleation temperatures and identified phases.

Starting material	Concentration (kg·l <sup>-1</sup> )	Solvents	Ramp (°C·h <sup>-1</sup> )	T <sub>nucleation</sub> (°C)	Phase
form II	0.051±0.0026*	Methanol	1	45.00±0.02	OLZ methanol solvate
form II	0.051±0.0022	Methanol	10	44.30±0.05	OLZ methanol solvate
form II	0.051±0.0024	Methanol	20	43.70±0.03	OLZ methanol Solvate
form II	0.038±0.0030	Ethanol	1	41.20±0.03	OLZ Ethanol Solvate
form II	0.038±0.0025	Ethanol	10	39.70±0.01	OLZ Ethanol Solvate
form II	0.038±0.0034	Ethanol	20	38.90±0.04	OLZ Ethanol Solvate
form II	0.009±0.0003	THF	1	11.50±0.01	P1**
form II	0.009±0.0001	THF	10	11.50±0.04	P3**
Form II	0.009±0.0002	THF	20	10.90±0.06	P3**
form II	0.009±0.0007	Toluene	1	12.50±0.05	P2**
form II	0.009±0.0006	Toluene	10	13.60±0.04	P4**
form II	0.009±0.0008	Toluene	20	13.90±0.06	P5**

\* ± Are the deviations from average values.

\*\* P1, P2, P3, P4 and P5 are phases not yet identified (fig. 10c – 10d)

**Fig. 11** Optical micrographs of OLZ form II from Methanol obtained with ramp of (a) 1 °C·h<sup>-1</sup>, (b) 10 °C·h<sup>-1</sup>, (c) 20 °C·h<sup>-1</sup>; from Ethanol obtained with ramp of (d) 1 °C·h<sup>-1</sup>, (e) 10 °C·h<sup>-1</sup>, (f) 20 °C·h<sup>-1</sup>; from THF with ramp of (g) 1 °C·h<sup>-1</sup>, (h) 10 °C·h<sup>-1</sup>, (i) 20 °C·h<sup>-1</sup> and from Toluene with ramp of (j) 1 °C·h<sup>-1</sup>, (k) 10 °C·h<sup>-1</sup>, (l) 20 °C·h<sup>-1</sup>.

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2 As a general trend, we observed that the faster the temperature ramp the lower the nucleation temperature  
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4 except for toluene (Table. 4). Moreover, from Fig. 11 which shows the different crystal habits observed  
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6 during the different crystallization experiments, sizes and habits are dependent of the temperature ramp. It is  
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8 noteworthy that the faster the temperature ramp the smaller and the more numerous the crystals. This effect is  
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10 due to different supersaturations during nucleation and growth. Supersaturation, control the crystal number  
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12 via the nucleation frequency and the crystal habit via the crystal growth rates for each face. In addition, for  
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14 methanol and ethanol we obtained the same phase whatever the cooling rate, for toluene, we obtained for a  
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16 slow cooling rate ( $1\text{ }^{\circ}\text{C}\cdot\text{h}^{-1}$ ) a different phase relative to the fast cooling rate ( $10$  and  $20\text{ }^{\circ}\text{C}\cdot\text{h}^{-1}$ ), explaining  
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18 that **the nucleation temperature does not decrease** with increasing temperature ramp (Table. 4). Lastly, for  
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20 THF we obtained different phases for different cooling rates.

#### 21 22 23 **4 Conclusion**

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25 We have studied the cooling crystallization of OLZ in the presence of six solvents with different polarities  
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27 using the multi-well setup developed in CINaM laboratory. First, we measured the solubility of the 2  
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29 polymorphs (form I and form II) of OLZ in the different solvents at different temperatures. The solubility  
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31 increases with the solvent polarity: Methanol > Ethanol > ACN > Ethyl Acetate > THF > Toluene. Second, we  
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33 studied the influence of these different solvents on the cooling crystallization from OLZ form I and II at a  
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35 cooling rate of  $1\text{ }^{\circ}\text{C}\cdot\text{h}^{-1}$ . In the case of methanol and ethanol, we obtained solvates. In ethyl acetate OLZ  
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37 crystallize in form II and in ACN in form I. From OLZ form I, crystals are obtained in all solvents but ethyl  
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39 acetate and toluene. From OLZ form II, crystals are obtained in all solvents but ACN. Lastly, we tested  
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41 different cooling rates ( $1$ ,  $10$  and  $20\text{ }^{\circ}\text{C}\cdot\text{h}^{-1}$ ), starting from OLZ form II. The results showed that the cooling  
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43 rate has no effect on the obtained phase in methanol (OLZ methanol solvate) in ethanol (OLZ ethanol  
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45 solvate). However, for THF and toluene different phases were obtained for different cooling rates.

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47 To conclude, we evidenced the effect of the solvents and the cooling rates on the crystal habit and phase and  
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49 size distribution.

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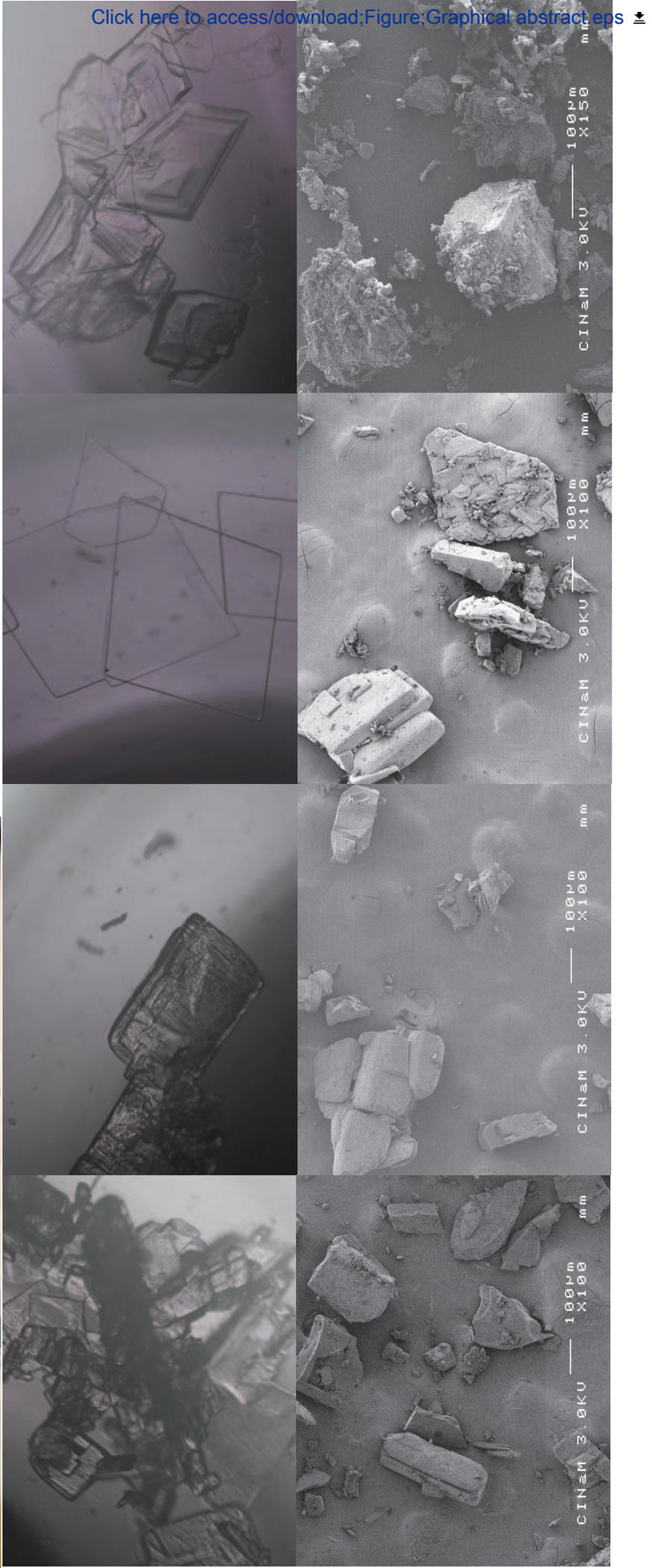
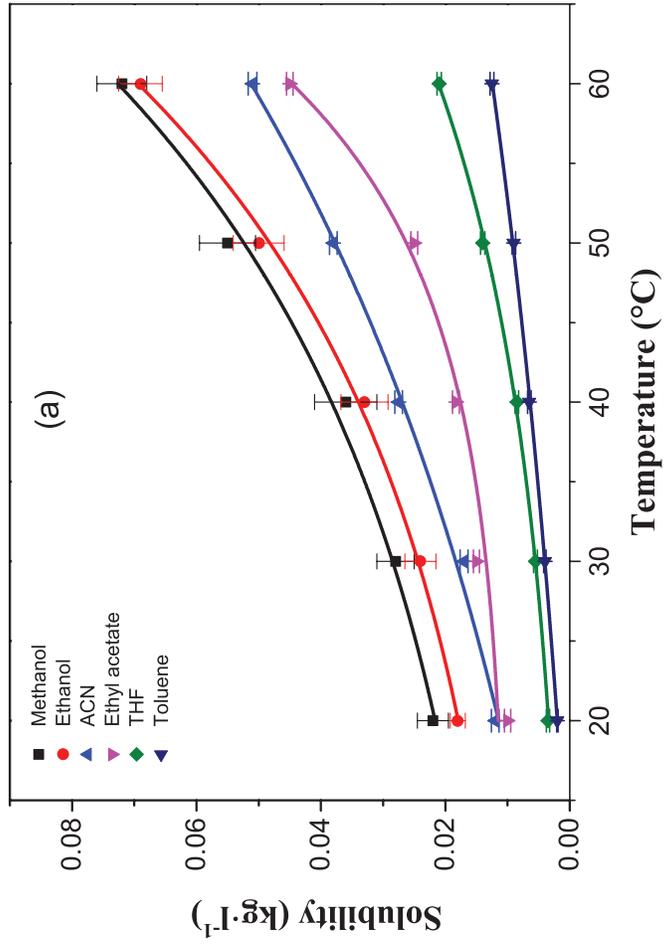
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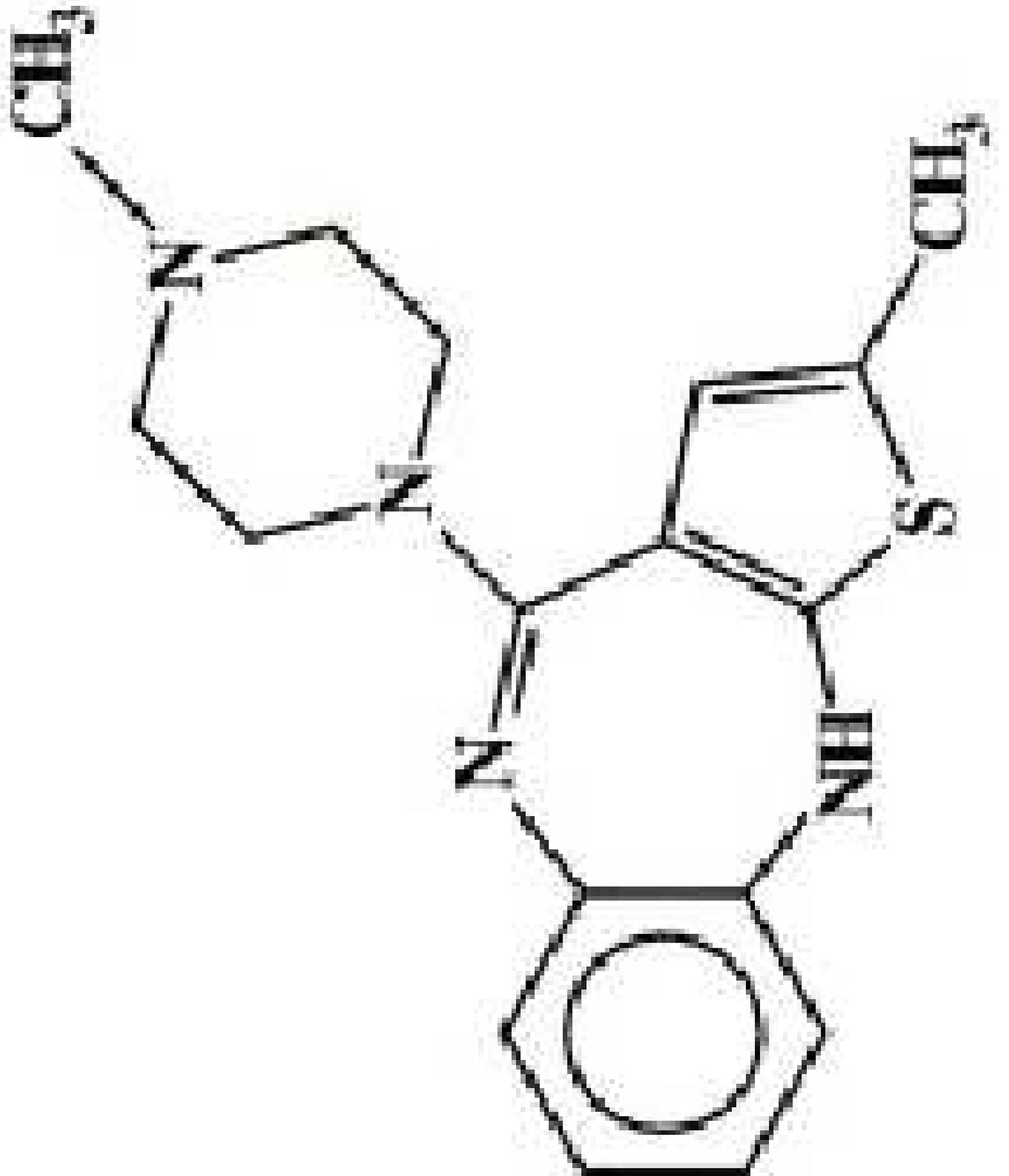
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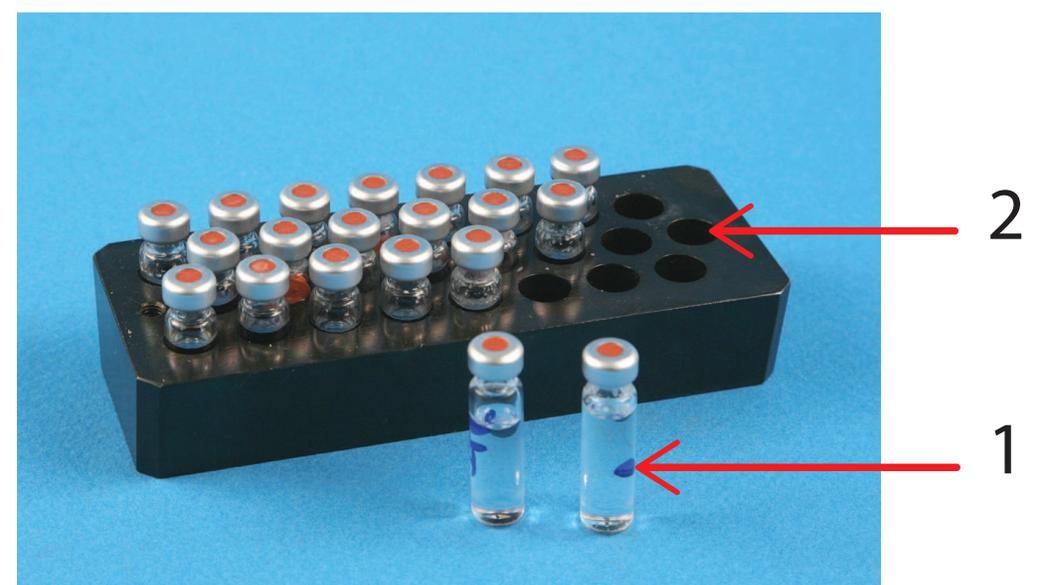
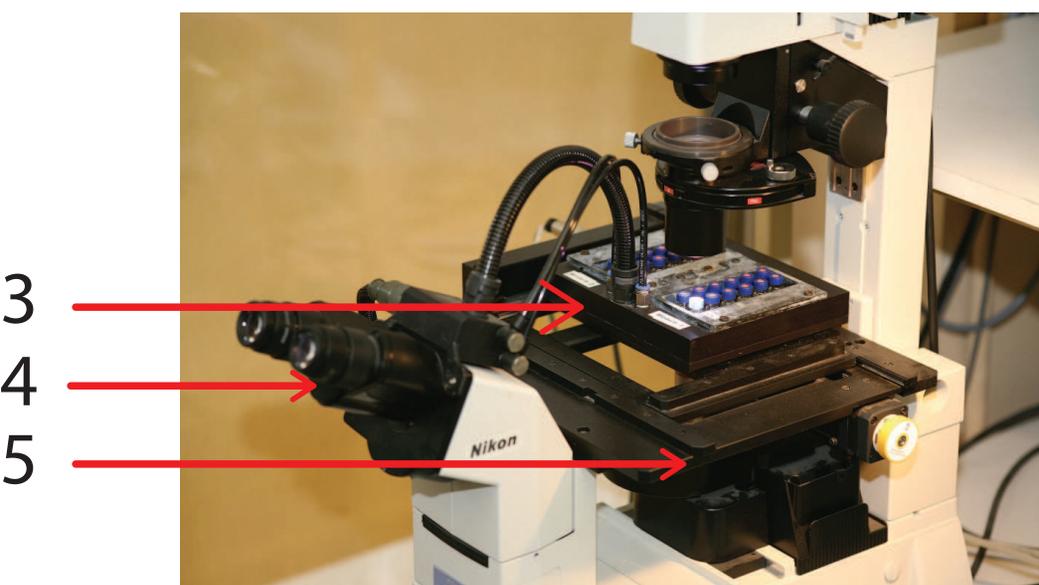
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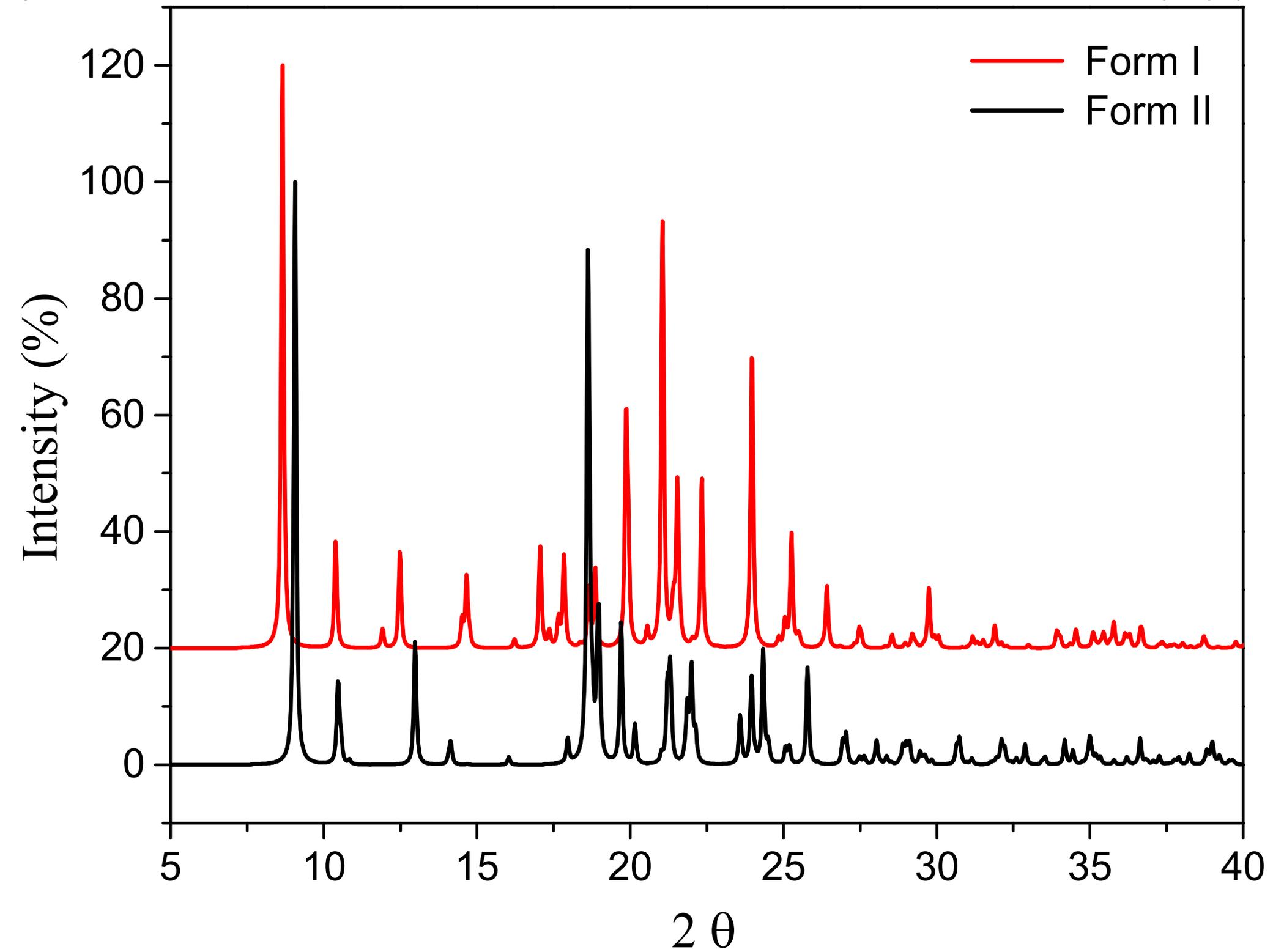
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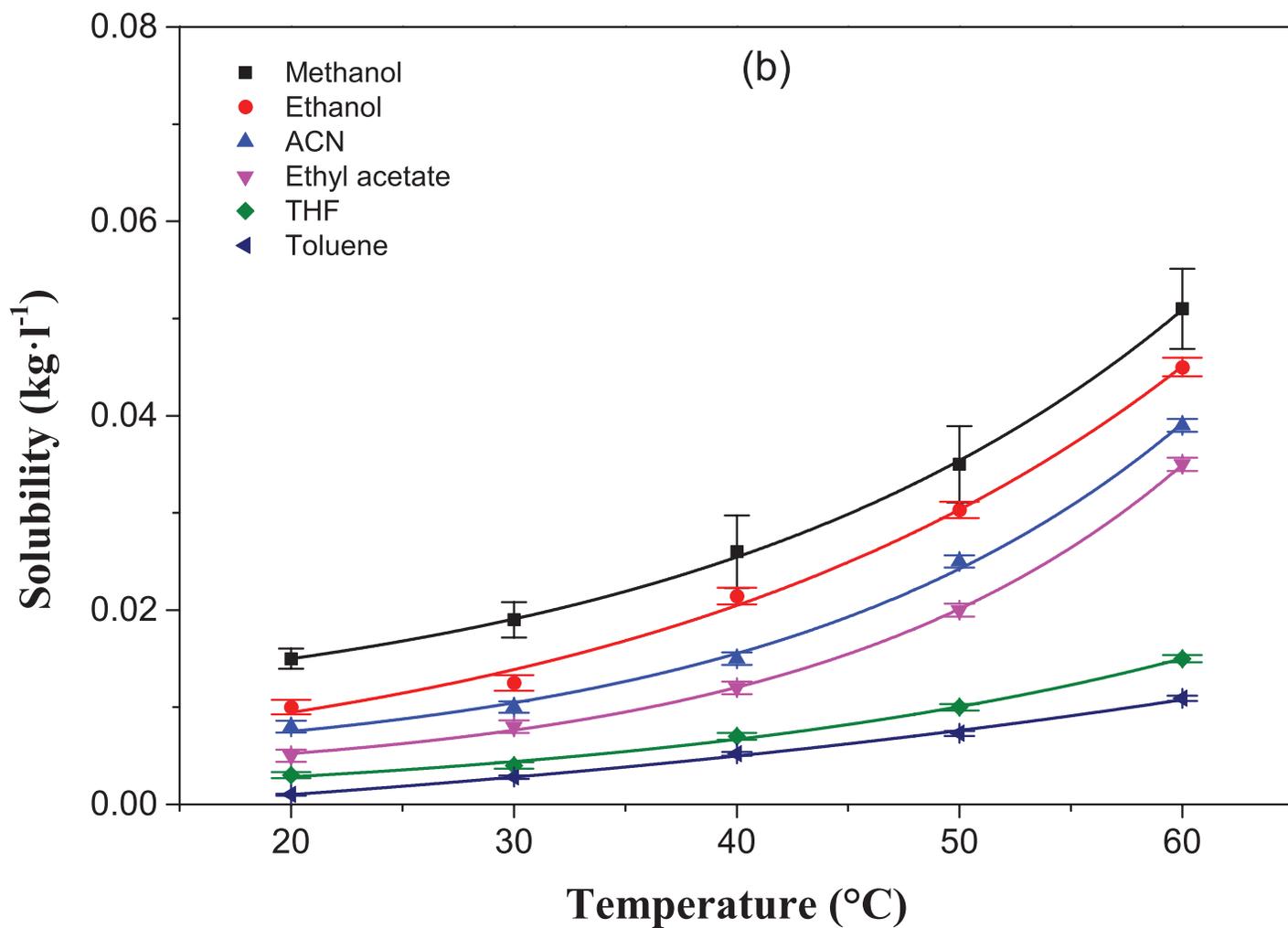
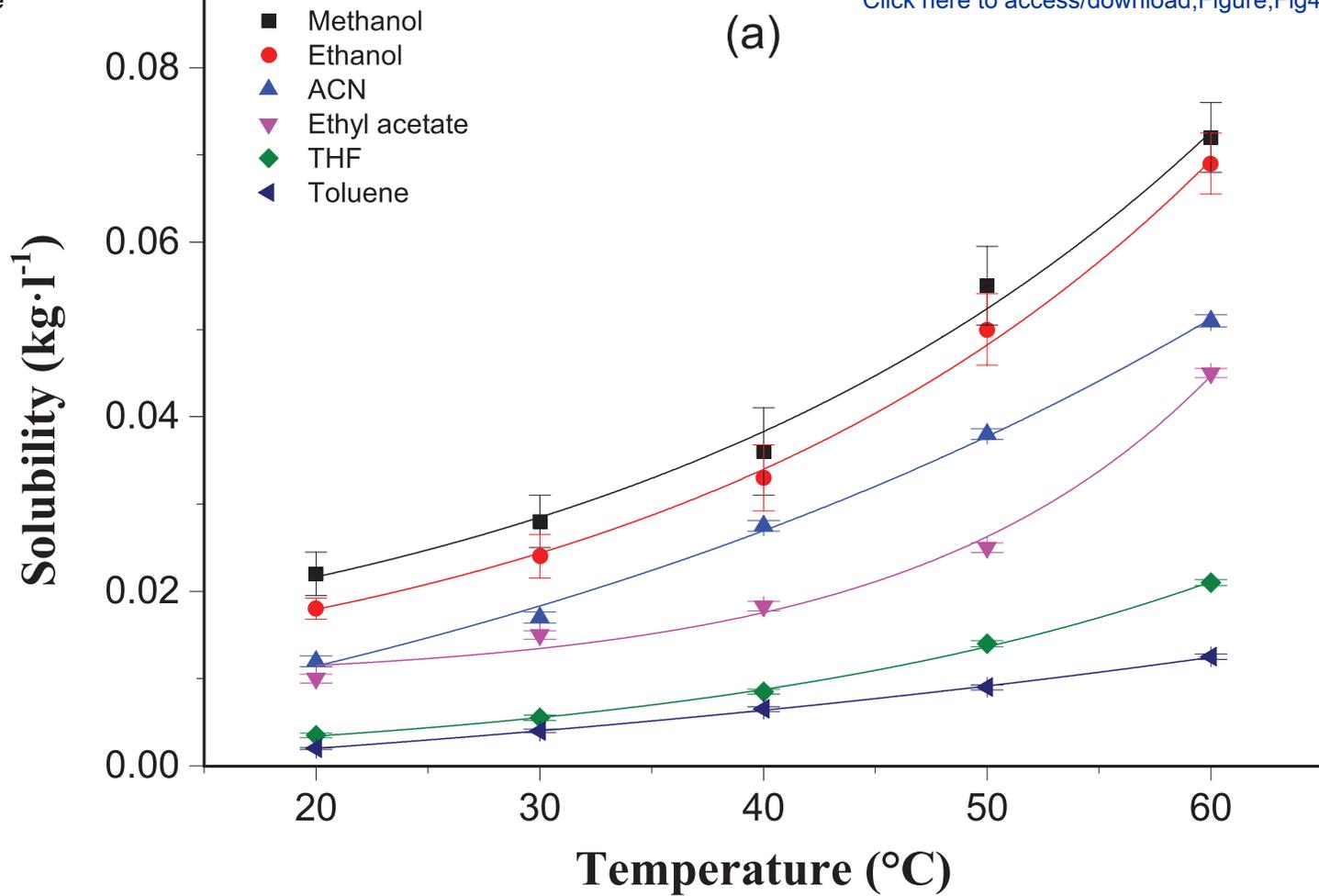
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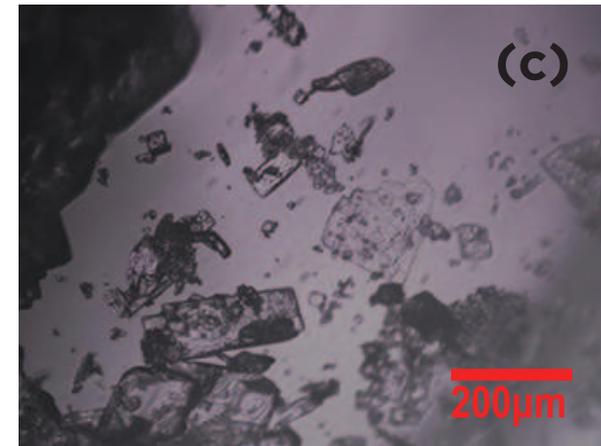
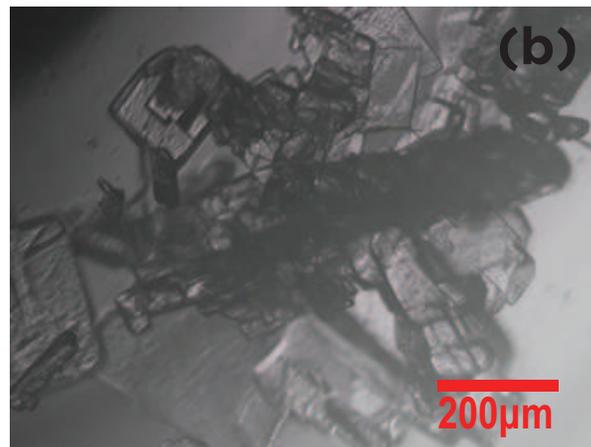
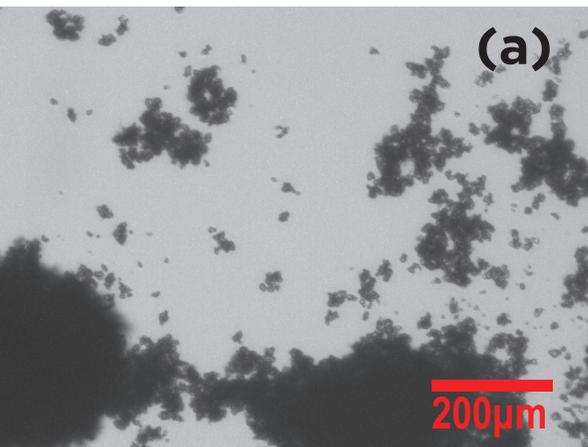


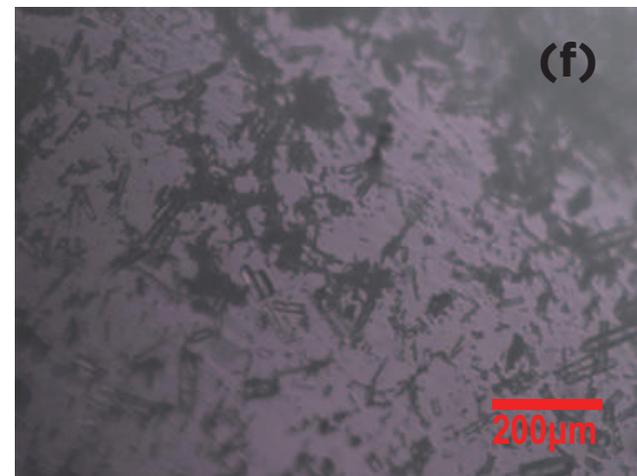
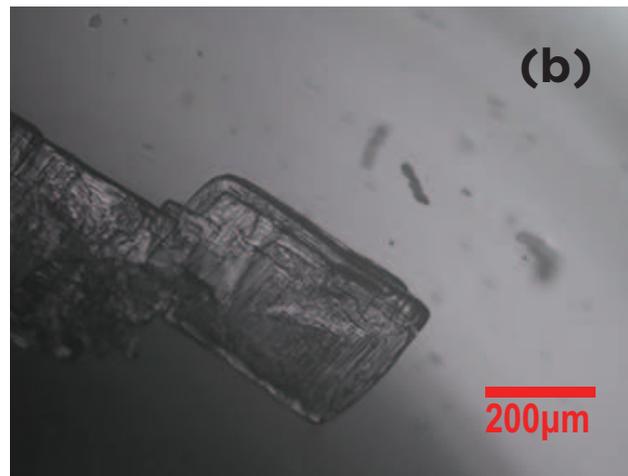
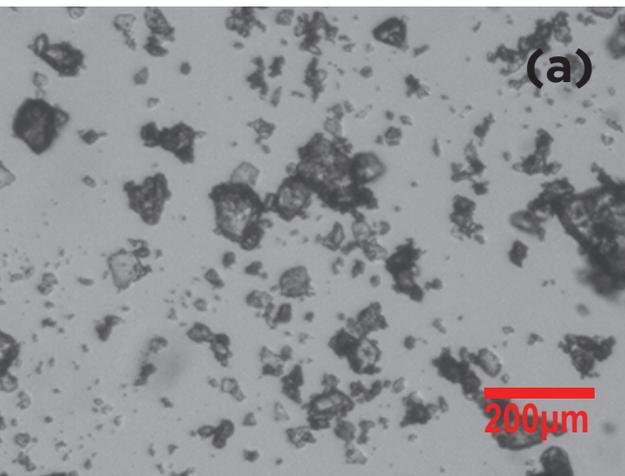


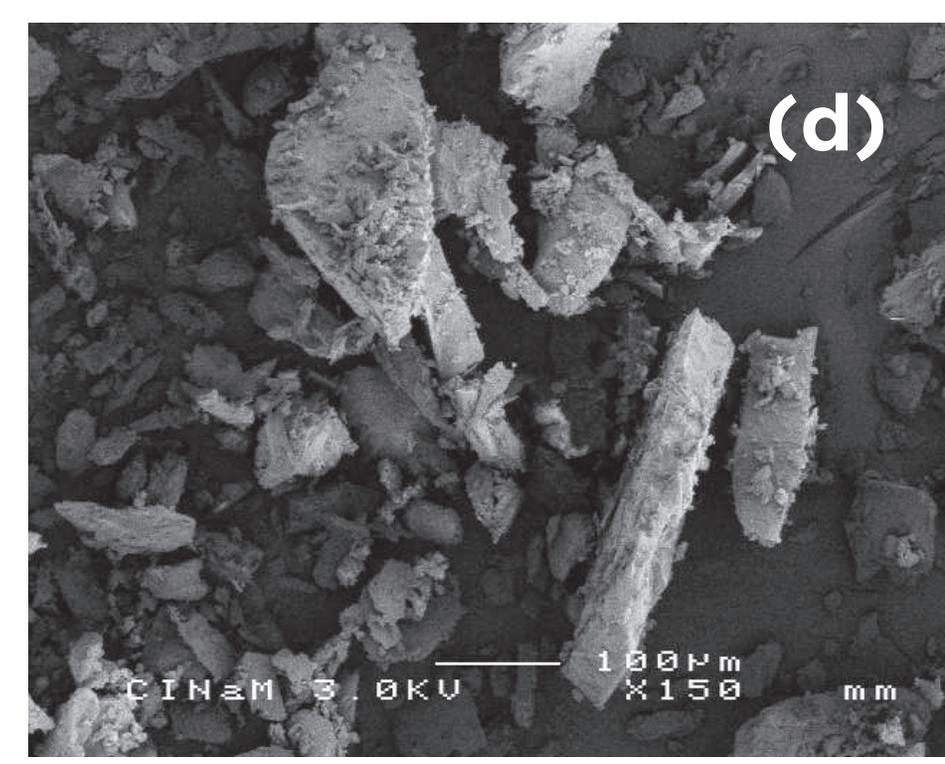
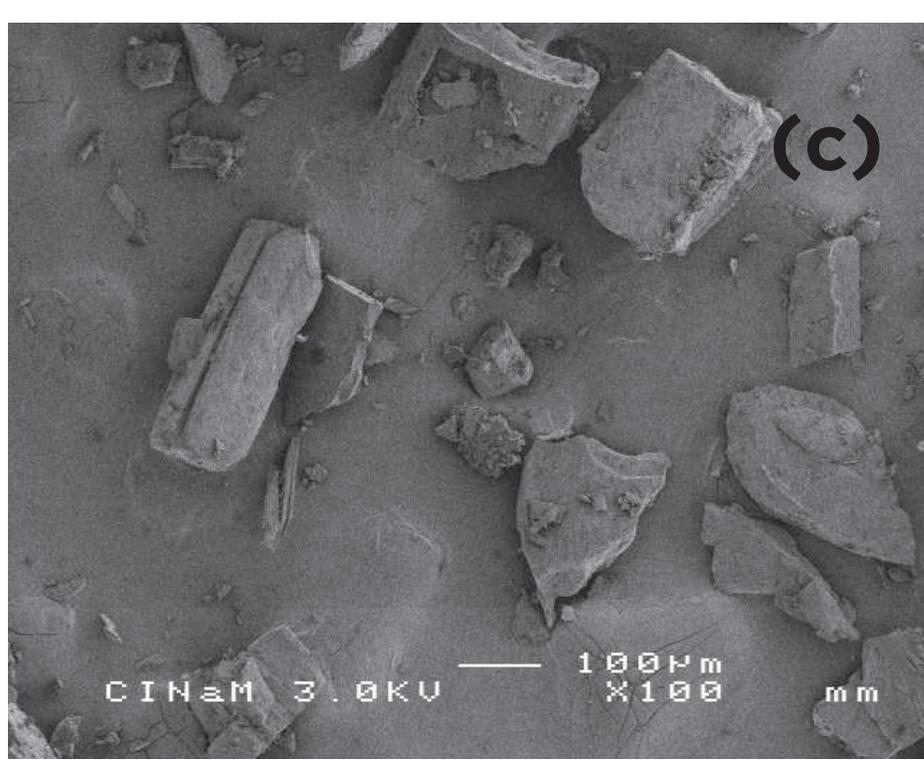
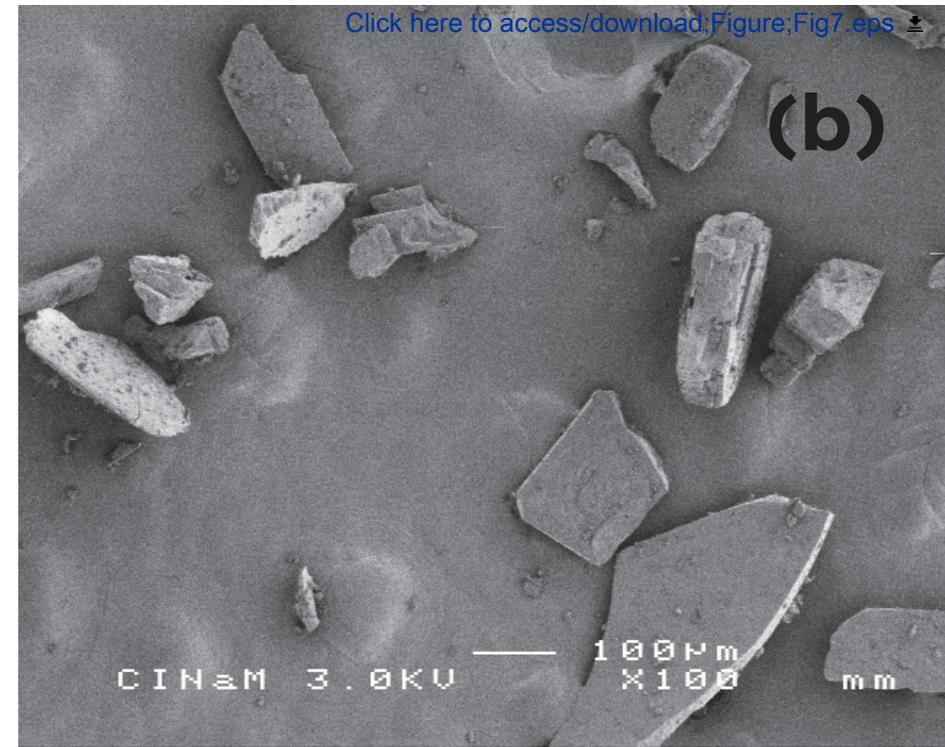
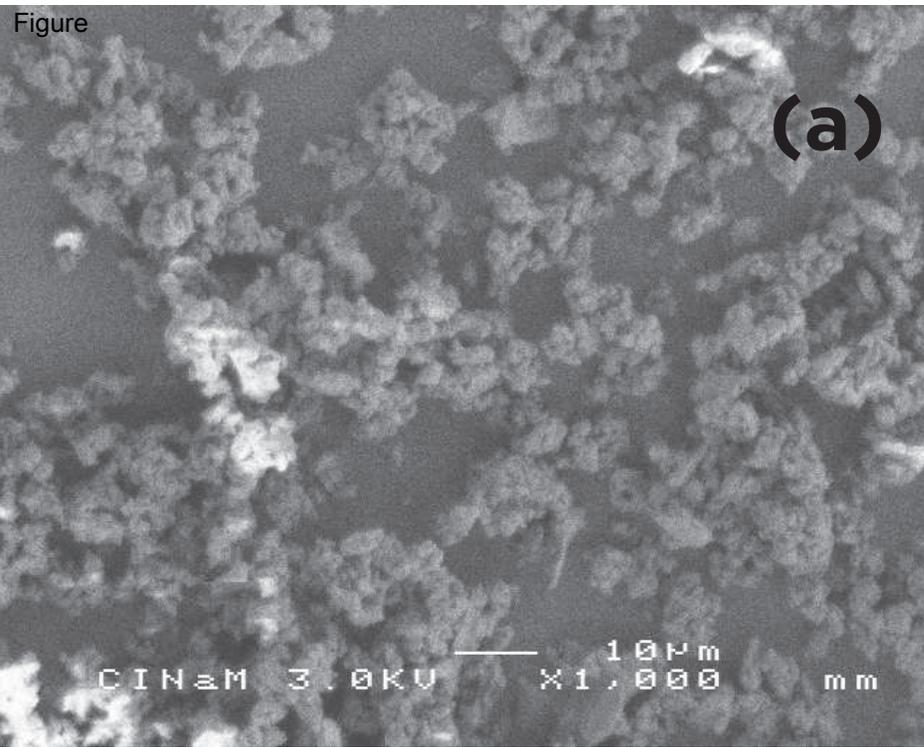


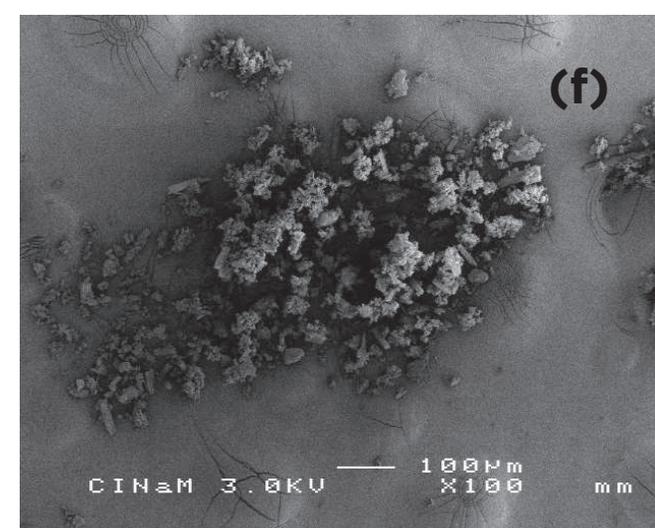
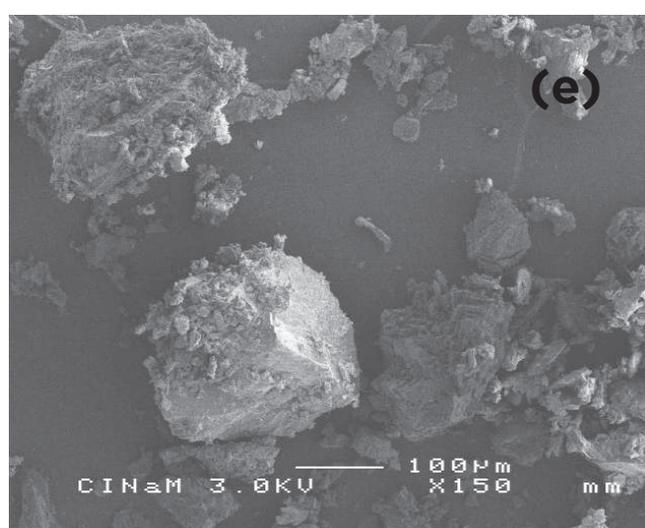
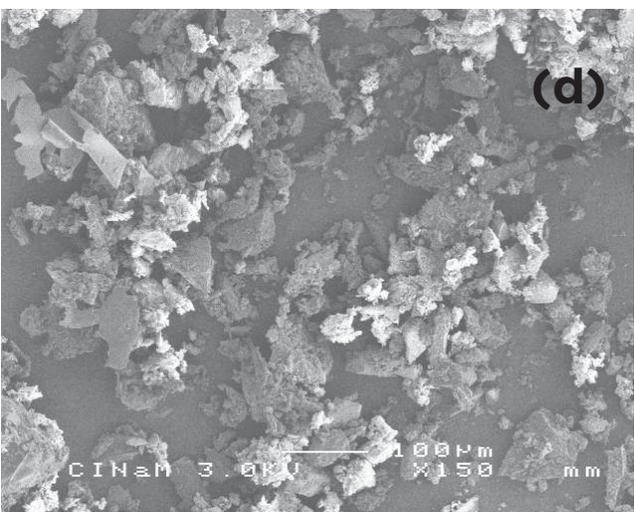
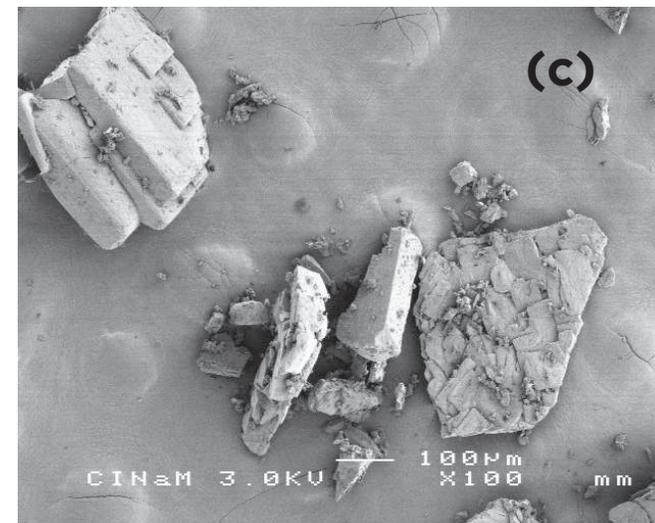
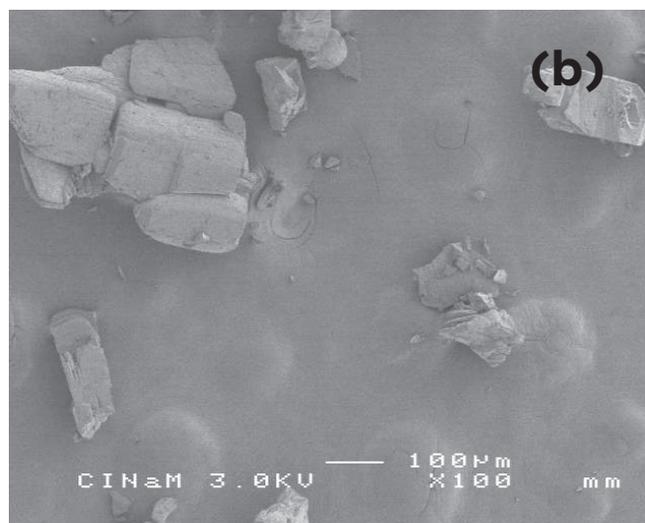
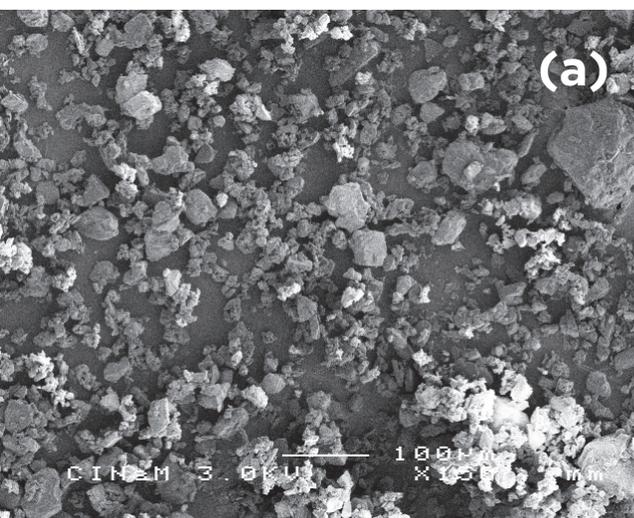




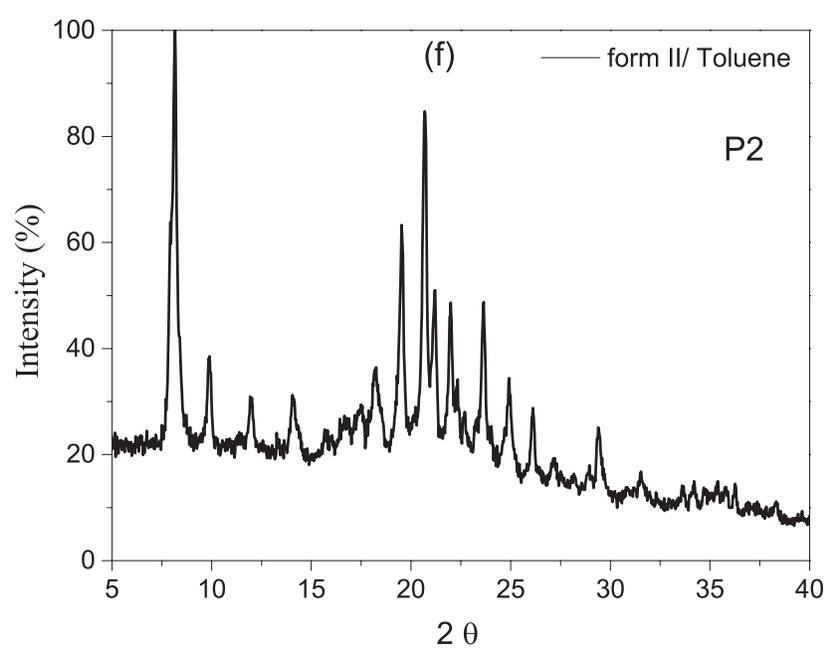
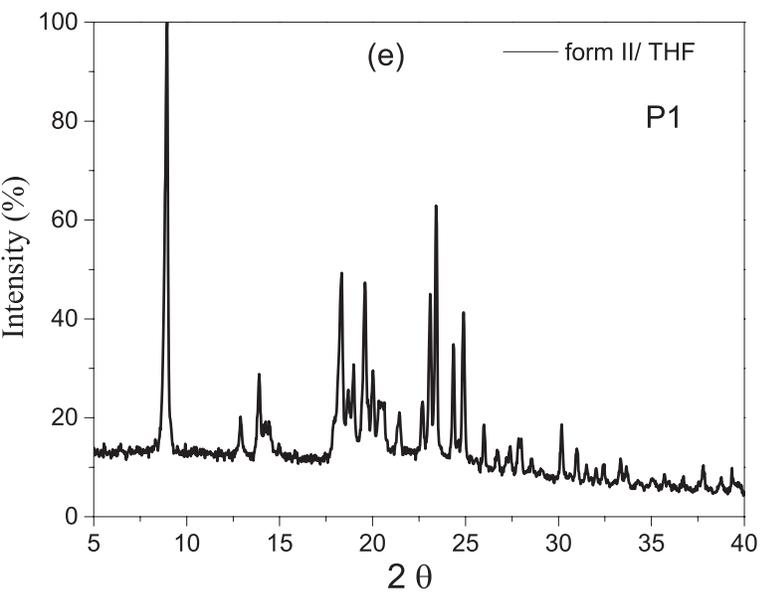
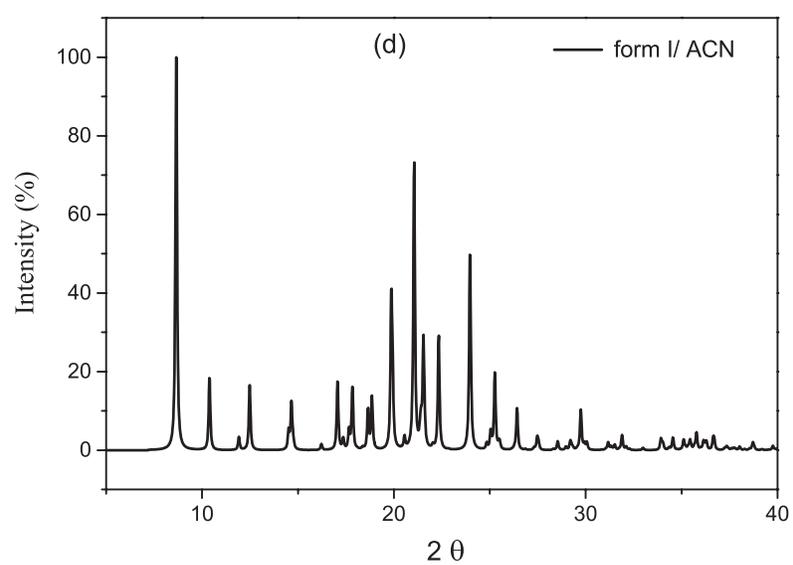
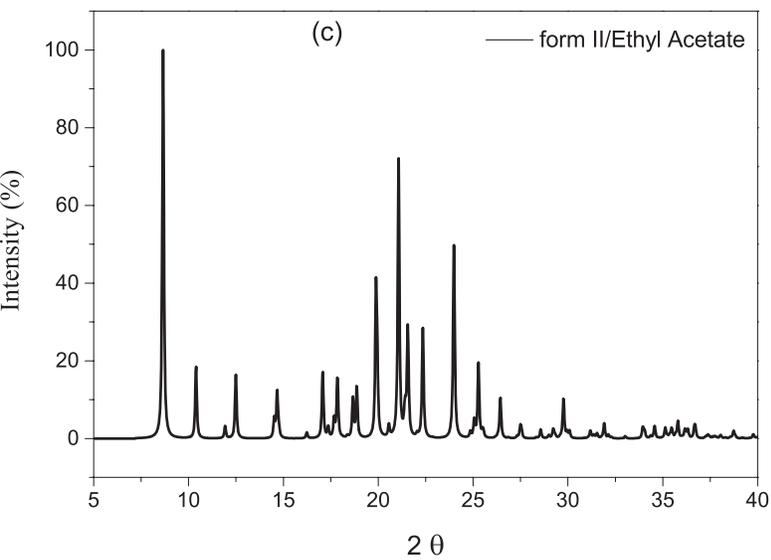
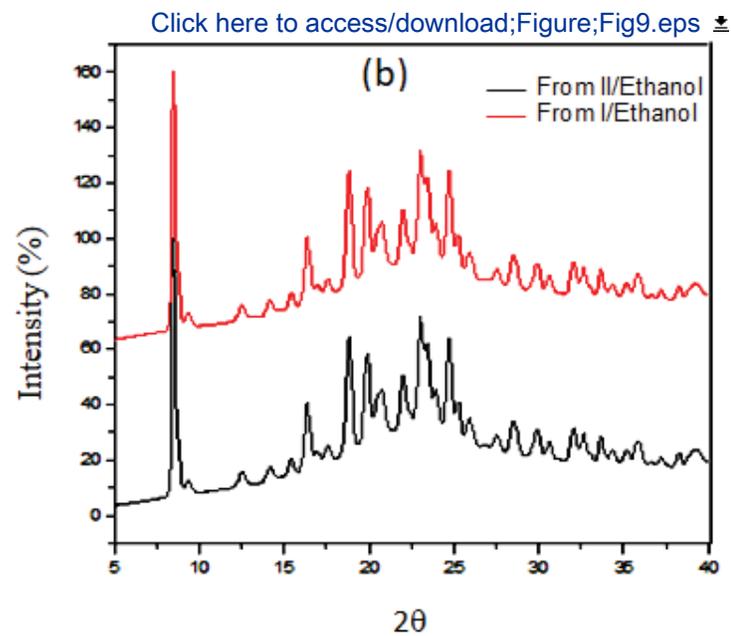
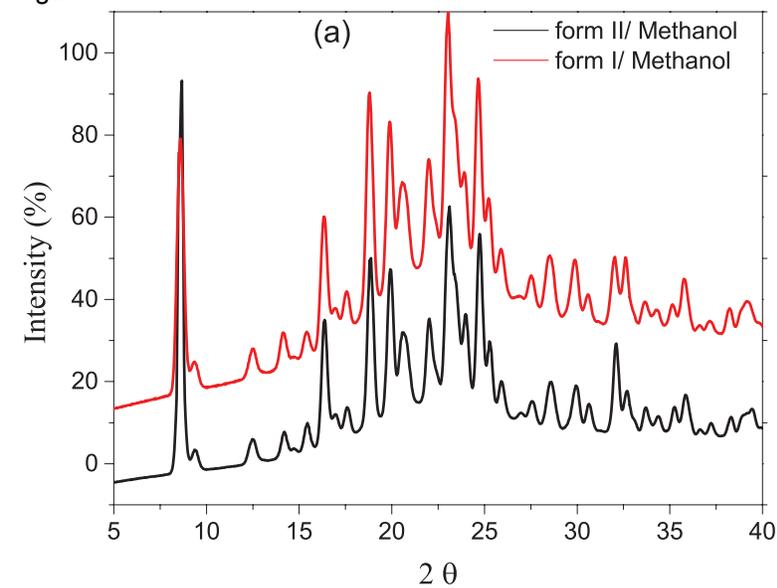




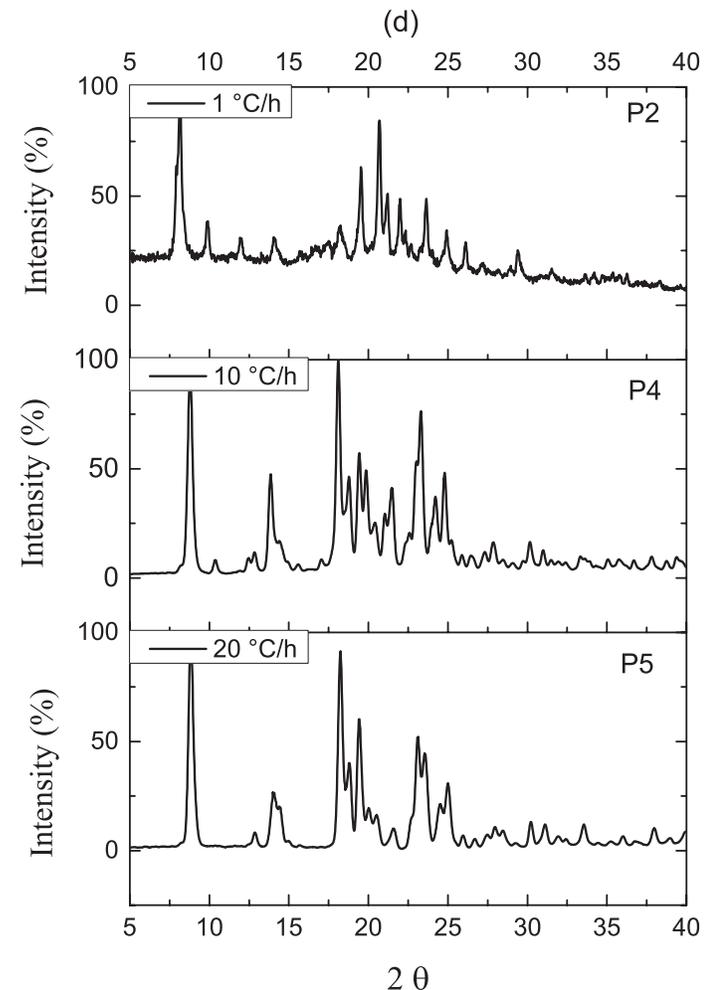
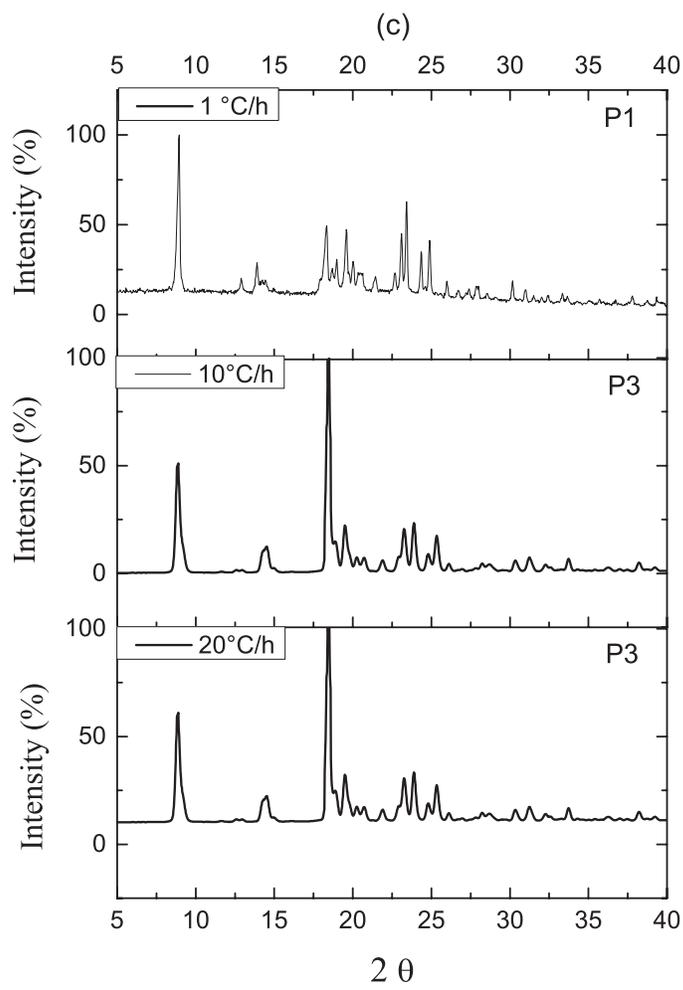
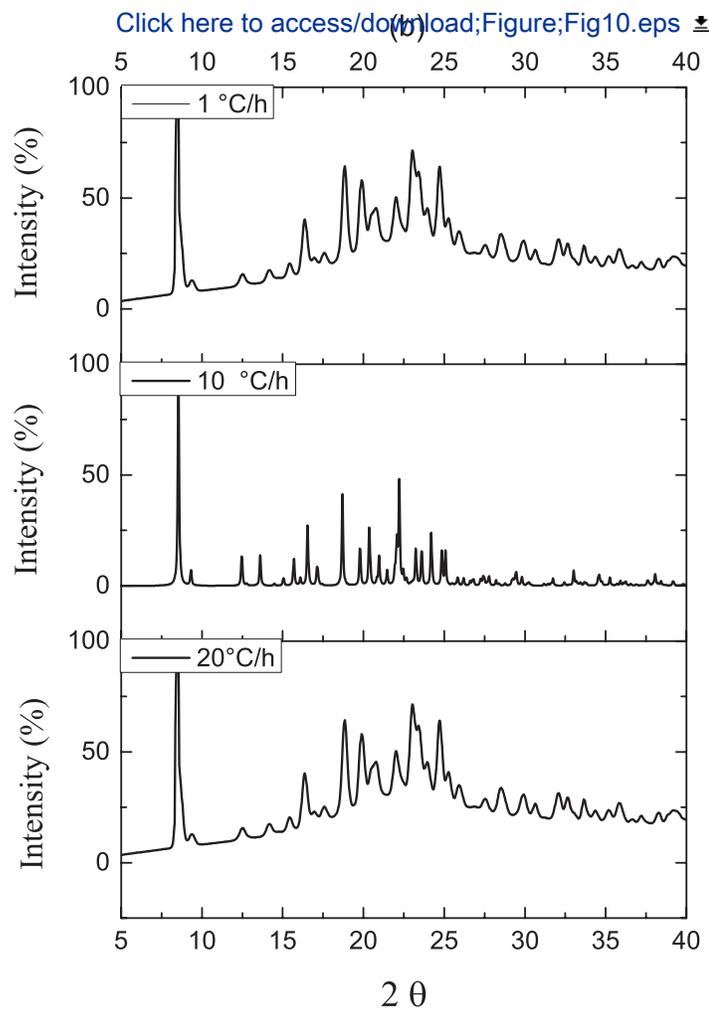
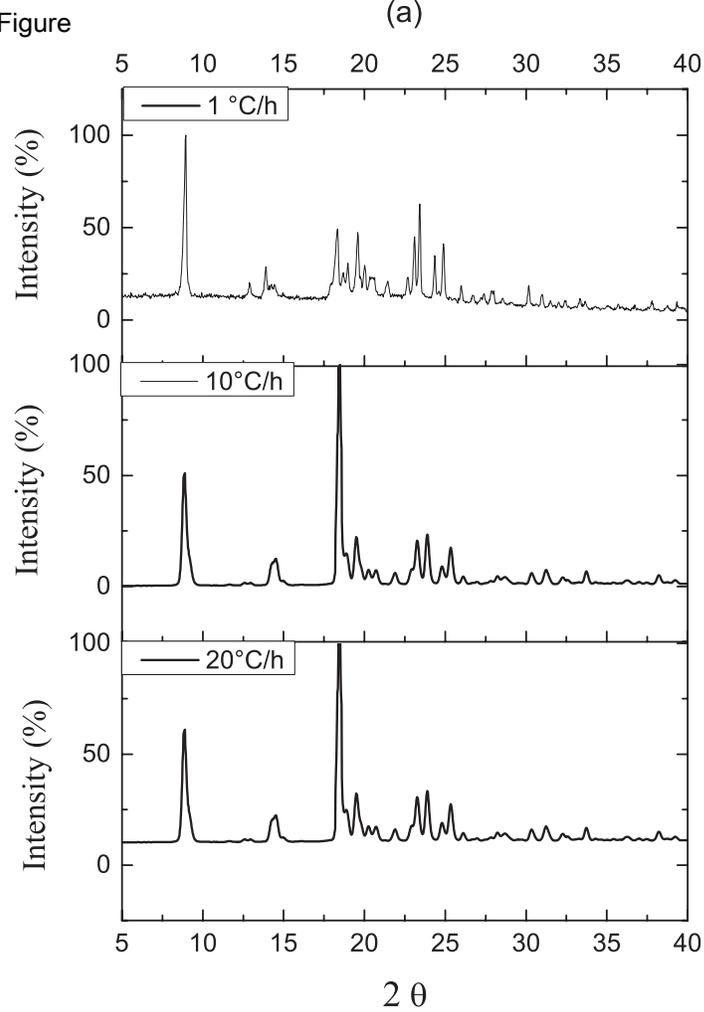


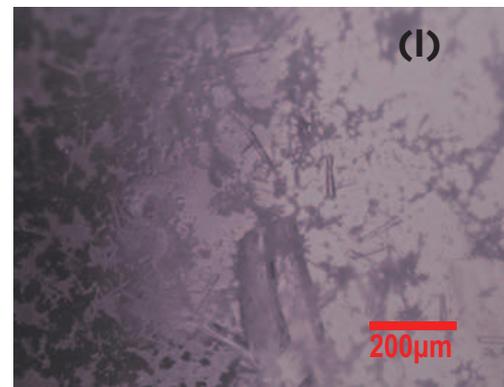
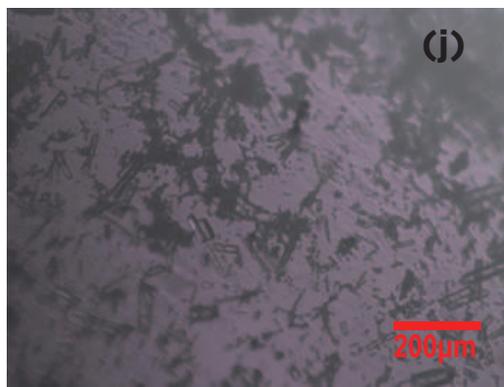
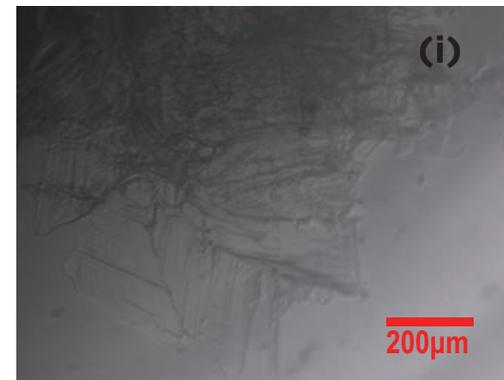
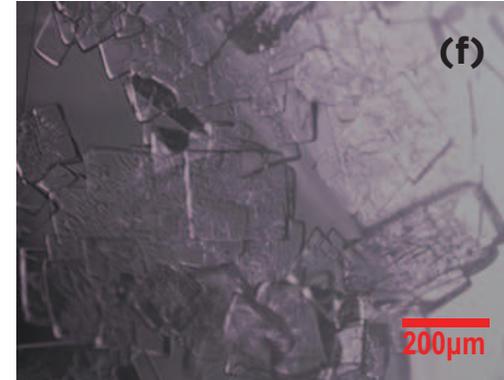
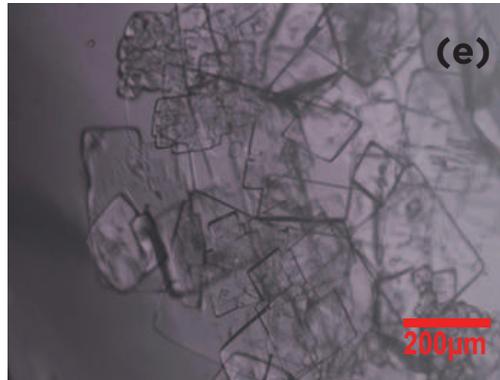
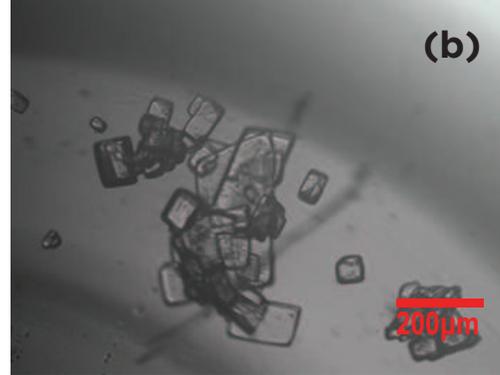
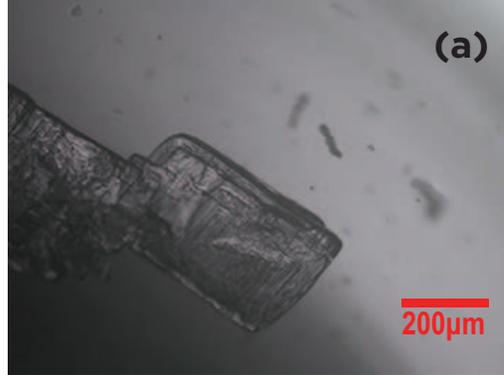


Figure



Figure





**SOLUBILITIES AND CRYSTALLIZATION OF OLANZAPINE USING A MULTI-WELL SETUP:  
EFFECT OF SOLVENT AND COOLING RATE**

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**Table 1** Properties of solvents for crystallization experiments

Solvents	Chemical formula	Range	Boiling point (°C)	Relative Polarity*
Methanol	CH <sub>3</sub> OH	Polar Protic	64.70	0.762
Ethanol	C <sub>2</sub> H <sub>5</sub> OH	Polar Protic	78.37	0.654
ACN	CH <sub>3</sub> CN	Aprotic Polar	82.00	0.46
Ethyl Acetate	C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>	Polar Aprotic	77.10	0.228
THF	C <sub>4</sub> H <sub>8</sub> O	Polar aprotic	66.00	0.207
Toluene	C <sub>6</sub> H <sub>5</sub> -CH <sub>3</sub>	Apolar	110.60	0.099

\* The values for relative polarity are normalized from measurements of solvent shifts of absorption spectra and were extracted from Christian Reichardt [18].

**Table 2** Main diffraction peaks for form I and form II.

form II		form I	
2 $\theta$	Intensity (%)	2 $\theta$	Intensity (%)
9.06	99.868	8.68	99.757
10.46	14.188	10.48	18.056
12.98	20.982	12.6	13.421
18.62	88.236	14.88	12.043
18.98	27.443	17.1	16.834
19.7	24.316	18.02	15.138
21.3	18.449	18.78	11.142
22	17.593	19	13.354
23.96	15.171	20.24	39.834
24.34	19.828	21.44	81.284
25.78	16.643	21.78	28.695
		22.66	28.813
		24.5	45.789
		25.62	18.904
		30.22	10.57

**Table 3** Crystallization conditions, nucleation temperatures and identified phases.

Starting material	Concentration (kg·l <sup>-1</sup> )	Solvents	Ramp (°C·h <sup>-1</sup> )	T <sub>nucleation</sub> (°C)	Phase
form I	0.074±0.0096*	Methanol	1	48.90±0.01	OLZ methanol solvate [19]
form II	0.051±0.0026	Methanol	1	45.00±0.02	OLZ methanol solvate [19]
form I	0.064±0.0008	Ethanol	1	43.00±0.01	OLZ Ethanol Solvate [15]
form II	0.038±0.0030	Ethanol	1	41.20±0.03	OLZ Ethanol Solvate [15]
form I	0.040±0.0006	ACN	1	36.90±0.01	Form I
form II	0.020±0.0007	ACN	1	—	—
form I	0.028±0.0005	Ethyl acetate	1	—	—
form II	0.018±0.0006	Ethyl acetate	1	21.00±0.04	Form II
form I	0.012±0.0003	THF	1	—	Not enough to characterize
form II	0.009±0.0003	THF	1	11.50±0.01	P1**
form I	0.011±0.0002	Toluene	1	—	—
form II	0.009±0.0007	Toluene	1	12.50±0.05	P2**

\* ± Are the deviations from average values.

\*\* P1 and P2 are phases not yet identified (Fig. 9e– 9f)

**Table.4** Crystallization conditions, profil of temperature, nucleation temperatures and identified phases.

<b>Starting material</b>	<b>Concentration (kg·l<sup>-1</sup>)</b>	<b>Solvents</b>	<b>Ramp (°C·h<sup>-1</sup>)</b>	<b>T<sub>nucleation</sub> (°C)</b>	<b>Phase</b>
form II	0.051±0.0026*	Methanol	1	45.00±0.02	OLZ methanol solvate
form II	0.051±0.0022	Methanol	10	44.30±0.05	OLZ methanol solvate
form II	0.051±0.0024	Methanol	20	43.70±0.03	OLZ methanol Solvate
form II	0.038±0.0030	Ethanol	1	41.20±0.03	OLZ Ethanol Solvate
form II	0.038±0.0025	Ethanol	10	39.70±0.01	OLZ Ethanol Solvate
form II	0.038±0.0034	Ethanol	20	38.90±0.04	OLZ Ethanol Solvate
form II	0.009±0.0003	THF	1	11.50±0.01	P1**
form II	0.009±0.0001	THF	10	11.50±0.04	P3**
Form II	0.009±0.0002	THF	20	10.90±0.06	P3**
form II	0.009±0.0007	Toluene	1	12.50±0.05	P2**
form II	0.009±0.0006	Toluene	10	13.60±0.04	P4**
form II	0.009±0.0008	Toluene	20	13.90±0.06	P5**

\* ± Are the deviations from average values.

\*\* P1, P2, P3, P4 and P5 are phases not yet identified (fig. 10c – 10d)