Chapter 4

Recrystallisation study of ethionamide

4.1 Introduction

In this section the recrystallisation of crystals from different solutions will be discussed, followed by the characterisation of these crystals by means of the various analytical methods as explained in Chapter 2.

4.2 Recrystallisation of ethionamide

A number of general solvents (Table 4.1) were chosen which differed in polarity, from non-polar like chloroform to polar (water).

All solvents were obtained from ACE Chemicals (Johannesburg, SA). Because of toxicological reasons these solvents are not the most desirable substances to use in the preparation of pharmaceutical products. However, the possibility of finding new polymorphs makes it worth the effort of trying nonetheless (Craig, 2007).

Table 4.1: The solvents used in the recrystallisation study

Solvent	Boiling point (°C)	MW (g/mol)
Acetone	56.50	58.10
Acetonitrile	82	41.05
n-Butanol	117.50	74.12
2-Butanol	99	74.12
Chloroform	61.50	119.40
Dichloromethane	39.75	84.93
N,N-Dimethylformamide (DMF)	153	73.09
1,4-Dioxane	101	88.11
Ethanol	78.50	46.10
Ethyl acetate	77.00	88.11
Methanol	64.70	32.00
n-Propanol	97.20	60.10
Iso-propanol	82.50	60.10
Tetrahydrofuran (THF)	66	72.11

4.2.1 Method of recrystallisation from solvents

Recrystallisations were done by a process of slow evaporation from saturated solutions of ethionamide in a variety of organic solvents (see Table 4.1). This was done by placing a predetermined amount of ethionamide in a glass beaker and then adding the solvent in small amounts with a Pasteur pipette while the contents of the beaker are heated to a temperature near the boiling point of the solvent being used and constantly stirring the contents with a heating magnetic stirrer (Velp ® Scientifica - Italy). When all of the ethionamide has dissolved and a saturated concentration is reached the beaker is covered with Parafilm® (Pechiney Plastic Packing, Chicago IL, USA).

When creating crystals by recrystallisation from solvent, it is usually very difficult or even impossible to predict which solvents will result in the formation of useful/valuable crystals. For this reason it should make sense to make use of a multiplicity of solvents to increase the chances of finding useful crystals (Mirmehrabi & Rohani, 2005).

Properties like hydrogen bond acceptor or donor propensity, polarity/dipolarity, dipole moment, dielectric constant, viscosity, surface tension and cohesive energy density (calculated from the heat of vaporisation) are listed by Gu *et al.* (2004) as the 8 appropriate solvent properties to alter for maximisation of diversity in order to make the most out of recrystallisation from solvent methods.

In theory, less stable polymorphs should form before the more stable ones as a result of Ostwald's law of stages (see section 1.3.2.3). When the system develops a solid state from the liquid, it will form a solid state nearest in free energy to that of the liquid state (Carlton, 2003).

In section 1.3.2 the different factors influencing polymorph formation were mentioned and briefly described. The reasons why molecular packing arrangements can differ when recrystallised from different solvents, will be briefly discussed in the following paragraph.

If one considers the conformation of molecules arranged in a solid, there will only be molecules of the particular solid interacting (forming and breaking various bonds, etc.) with each other. In the case of a substance dissolved in a solvent though, one will find these molecules interacting with one another, but also with the solvent molecules. This is true even in highly concentrated solutions, because of the abundance of solvent molecules in the system. The interactions can result in the formation of a range of forms by resulting in differences in conformation, alteration of activation energies for primary nucleation and the interactions are affected by the concentrations of dissolved materials in that it will influence the ratio of solvent-solute and solute-solute interactions (Ymén, 2011).

4.2.2 Crystals obtained from recrystallisation

By means of the crystallisation process, an assortment of crystals were obtained that, when viewed with the naked eye, have a variety of shapes and sizes. It was observed that the size and shape of the crystals formed is dependent on the rate at which the saturated solution was cooled (i.e. simply left at room temperature or placed on a slightly cooler surface for an accelerated rate of cooling).

The crystals formed by placing the glass beaker on a cooler surface after the regular process of creating a super-saturated solution are displayed with an H after the abbreviation used for the crystals formed by the regular method.

With the aforementioned recrystallisation process, crystals were obtained from each of the solvents. It should be noted that some formed almost instantly and others took weeks to months to form (Table 4.2).

Table 4.2: Recrystallisation data

Solvent	Abbreviation	Solubility of the RM	Time to form crystals
Acetone	A	Poor	Slow
Acetonitrile	AN	Poor	Fast
n-Butanol	B1	Poor	Slow
2-Butanol	B2	Poor	Slow
Chloroform	C	Poor	Slow
Dichloromethane	DM	Poor	Slow
Dimethylformamide (DMF)	DMF	High	Slow
1,4-Dioxane	D	Poor	Slow
Ethanol	E	High	Fast
Ethyl acetate	EA	Fair	Slow
Methanol	M	High	Fast
n-Propanol	P1	Fair	Fast
Iso-propanol	P2	Poor	Slow
Tetrahydrofuran (THF)	THF	High	Slow

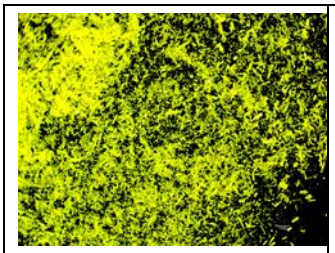
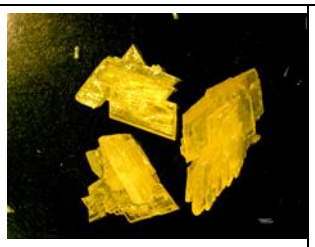
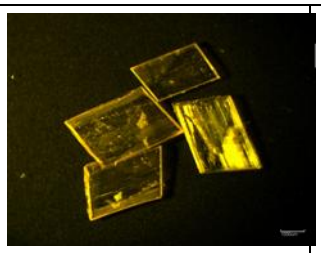
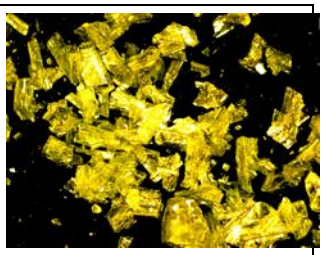
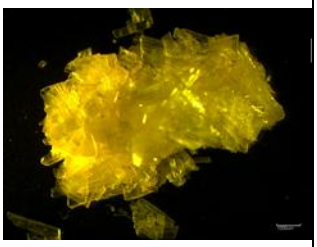
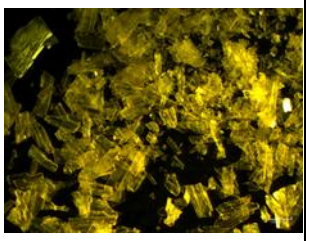
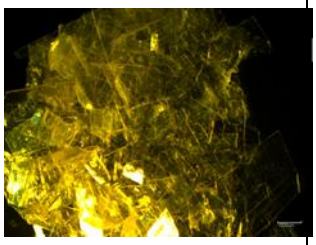
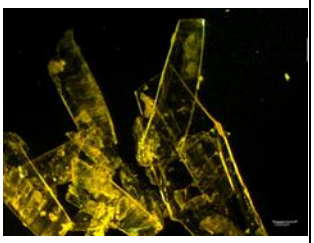
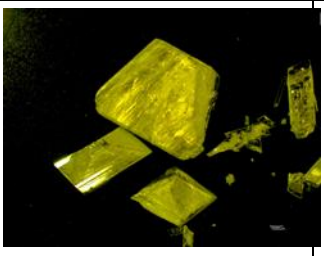
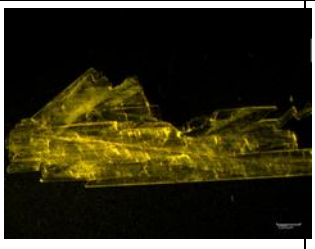
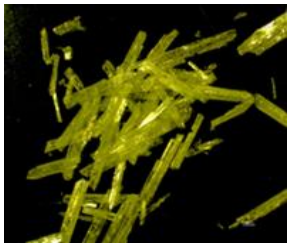
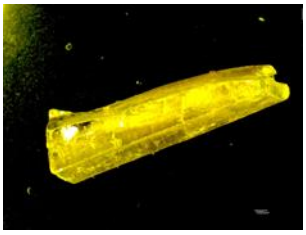
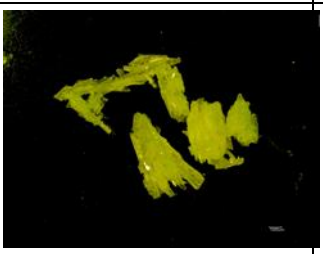
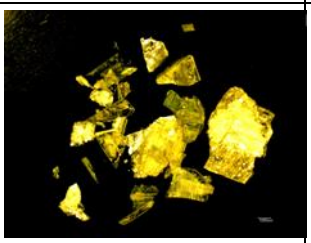
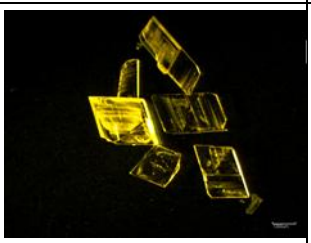
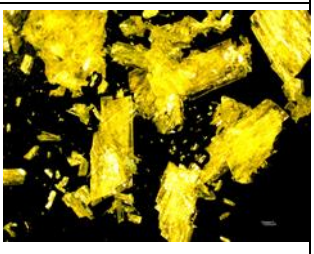
Table 4.2 displays the abbreviations used throughout this section for the crystals formed, the general solubility of the RM in the specific solvent and the general time taken for the crystals to form (the solubilities and time to form are not meant to be accurate or specific, but are merely placed here as guideline indications). In the instances where there is an H following the abbreviation, it indicates that the crystals were obtained by a slightly higher cooling rate by the method mentioned in the previous paragraph.

The following section is set out to compare the physico-chemical properties of the various crystals that were formed with each other and with that of the raw material.

Most of the results of the methods of characterisation are presented as superimposed/ overlay results and where something of interest was noted further discussion and clarification follows. The results are presented individually for each of the crystals obtained by this method in annexure B of this dissertation. In Figure 4.1 the different recrystallisation products from solvents were displayed.

4.3 Results

4.3.1 Light microscopy (stereomicroscopy)

			
Raw material (RM)	Acetone (A)	Acetone (A-H)	Acetonitrile (AN)
			
Acetonitrile (AN-H)	Acetonitrile (AN-H2)	n-Butanol (B1)	2-Butanol (B2)
			
Chloroform (C)	Chloroform (C)2	Chloroform (C-H)	1,4-Dioxane (D)
			
1,4-Dioxane (D-H)	DM	DM-H	Ethanol (E)

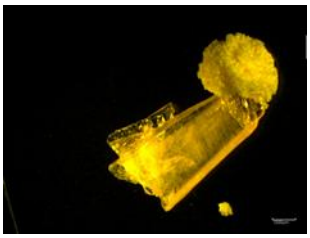
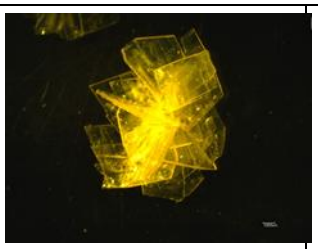
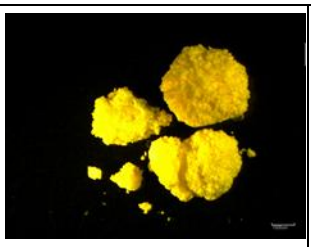
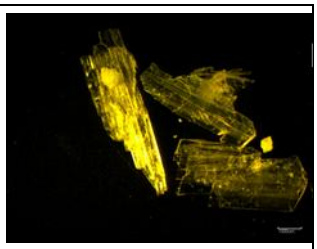
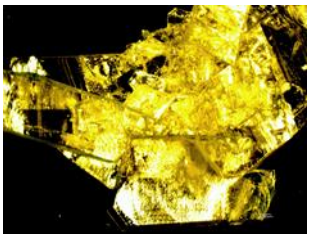
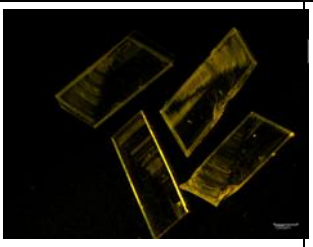
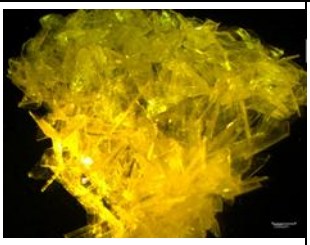
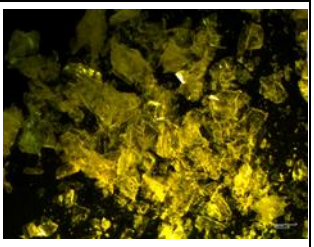
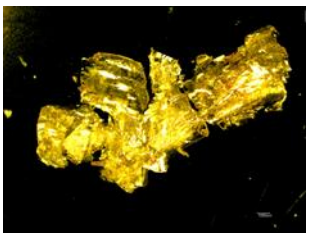
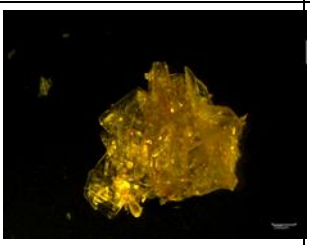
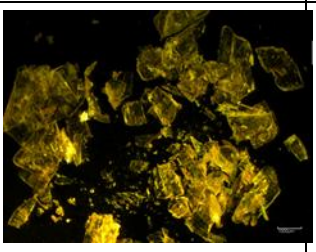
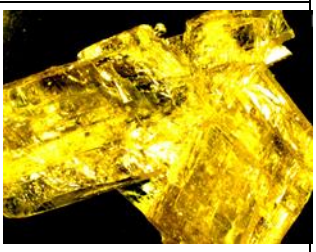
			
EA with spherical shaped crystals	Ethyl acetate (EA)	EA spherical shaped crystals	Ethyl acetate (EA-H)
			
Methanol (M)	n-Propanol (P1)2	n-Propanol (P1)	n-Propanol (P1)
			
Iso-propanol (P2)	Iso-propanol (P2)	Iso-propanol (P2)	THF
			
THF2			

Figure 4.1 Stereomicroscope images of recrystallisation products. (where 2 represents the same method of production that was repeated (i.e. a different batch produced)).

From the images obtained, it is clear that there are visual differences in the various crystals formed from dissolution in different solvents. Another important point to note is that even some of the crystals formed from the same solvents appear to be different when cooled at different rates (indicated with –H after the abbreviations used).

Conclusion

The crystals obtained through recrystallisation from solvents clearly display differences in shapes and sizes, though these visual differences do not tell one much about the properties of these crystals. The different habits of crystals formed can influence dissolution rates by increasing/decreasing the surface area making contact with the medium in which it is to be dissolved, though from these images it appears that the RM already has by far the smallest crystal sizes (the images have similar scale bars for ease of comparison). Further analyses need to be done to tell whether the differences between these different habits are significant regarding the physico-chemical properties.

4.3.2 Differential scanning calorimetry (DSC)

The DSC results appear to be very similar in all the samples analysed. The crystals formed by recrystallisation, displayed a double endotherm, similar to that of the RM (figure 3.3). Although thermal analysis is not always the best analytical instrument to distinguish between different polymorphic forms, it could be an indication of possible differences in the crystal structures like solvates or metastable forms. No desolvation endotherm or recrystallisation exotherms were visible during the analysis. The thermal analysis results, i.e. melting points of all the recrystallisation products seem to be identical to that of the raw material (Figure 4.2).

The DSC traces obtained from the iso-propanol recrystallisation products however differed from that of the RM (Figure 4.3).

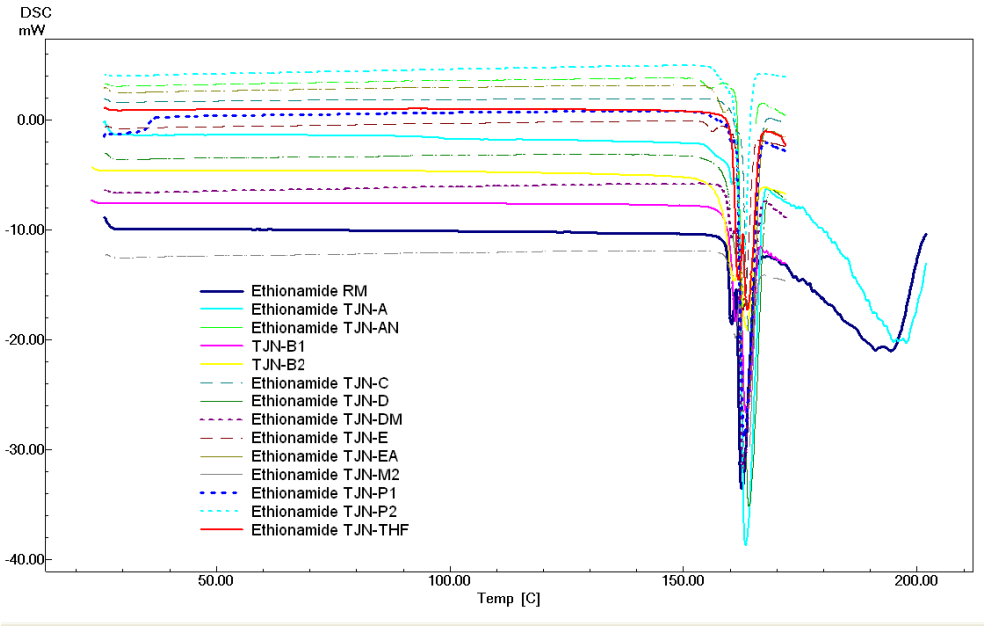


Figure 4.2 A DSC overlay showing similar patterns for the various crystals obtained. (Individual thermograms will be displayed in Annexure B).

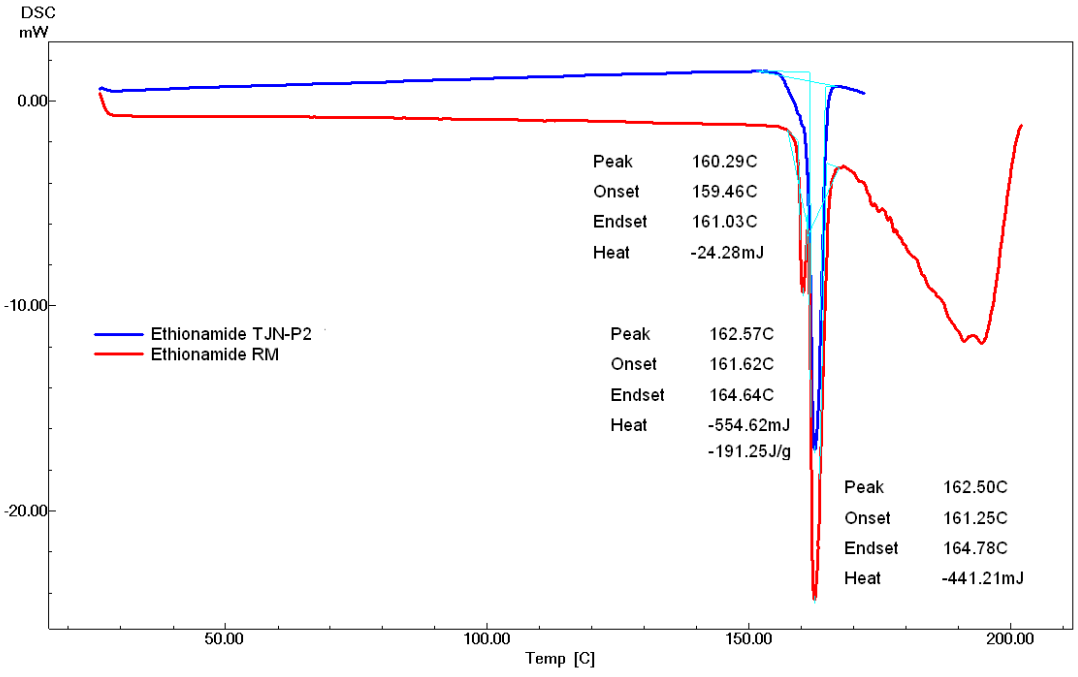


Figure 4.3.1 DSC traces from the recrystallisation product obtained from iso-propanol (P2) (top) and the raw material (bottom) (heating rate of 5°C/min.).

Figure 4.3.1 displays a case that appeared to be different than the other samples analysed. This result shows a single endothermic event and does not match the results seen with the other samples and the raw material. The peak that is assumed to be the melting endotherm can be seen at 162.57°C. This temperature is quite close to the melting endotherm observed in the results of the other samples. There is a visible change in the slope of the endothermic peak. This can be as a result of the two events seen in the other samples occurring almost simultaneously causing an overlap of peaks in the DSC result.

As was mentioned in section 3.2.4 at higher heating rates certain events can be skipped and for this reason a lower heating rate was used.

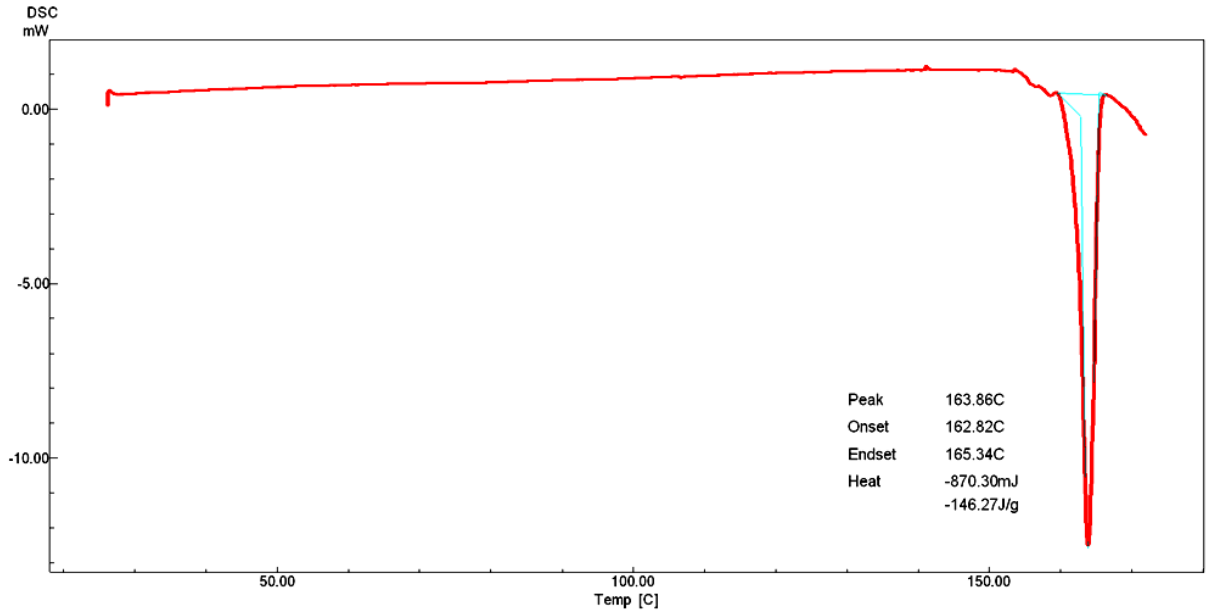


Figure 4.3.2 DSC trace of recrystallisation product from iso-propanol (P2) (heating rate of 2°C/minute).

In this result (Figure 4.3.2) the first endothermic peak, as seen in the other samples, is visible. This shows that the two events were occurring almost simultaneously.

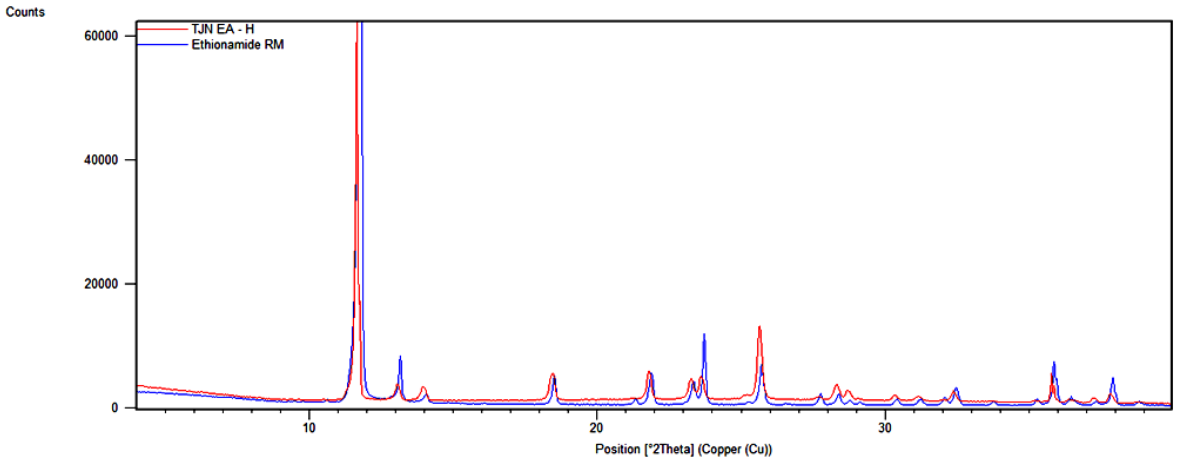
Conclusion

All the samples analysed showed DSC results very similar to that of the RM and from this an assumption can be made that the crystals obtained are merely different habits and do not have different molecular arrangements within the crystal structure. The

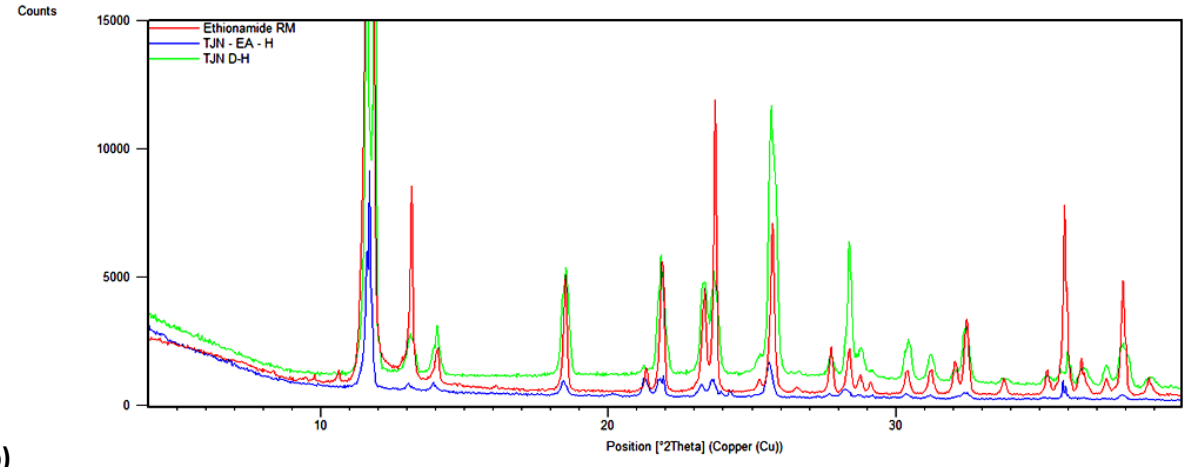
results are, however, not conclusive and require further analyses to verify this assumption. The crystals obtained from recrystallisation from a solution in iso-propanol showed slight variation in DSC results, though to be sure that this variation is of consequence required analyses with other methods to conclude with certainty.

4.3.3 X-ray powder diffraction (XRPD)

No significant differences were observed in the XRPD patterns of the RM when compared to that of the crystals obtained by means of recrystallisation.



a)



b)

Figure 4.4 XRPD of a) ethionamide RM compared to that of EA and b) ethionamide RM compared to EA and D displaying a lower intensity count maximum.

4.3.4 Thermal microscopy (TM)

From the ample amount of images obtained in these experiments, only the images which show significant occurrences were placed in this section. In this experiment the sample was immersed in a drop of oil to make escaping solvents more readily visible.

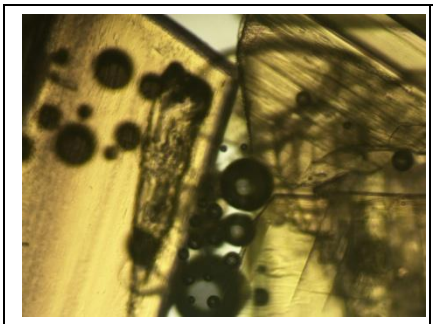
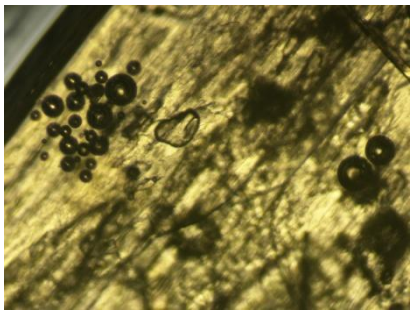
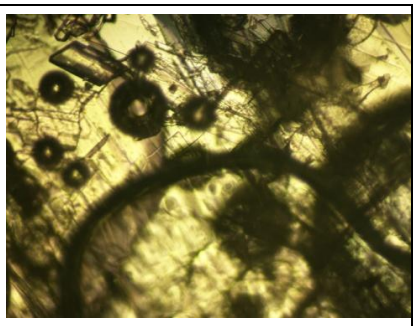
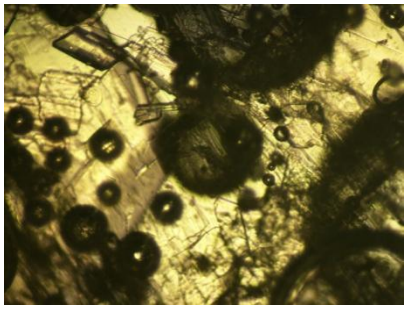
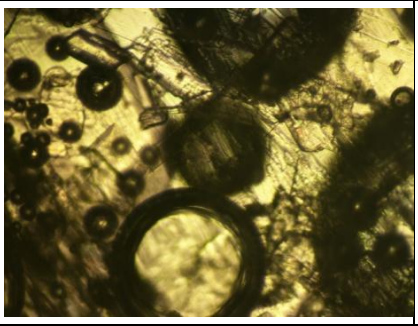
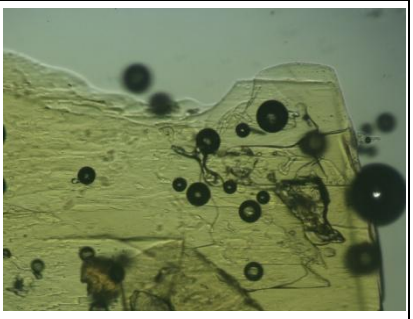
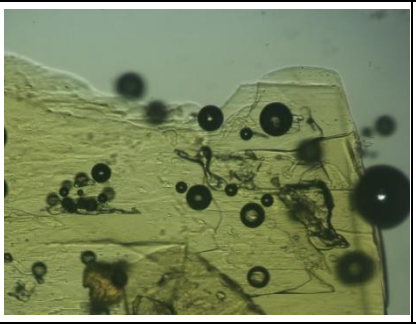
		
(a) Acetone (A) at 145°C	(b) Ethanol (E) at 118°C	(c) Methanol (M) at 104°C
		
(d) Methanol (M) at 125°C	(e) Methanol (M) at 132°C	(f) P2 at 131°C
		
(g) P2 at 132°C (iso-propanol)		

Figure 4.5 TM images of some of the thermal events of significance.

Figure 4.5 shows images in which escaping bubbles were visible while the samples were being heated. In the case of P2 (Figure 4.5 f and g) one can clearly see a tear forming in the surface of the crystal and from this tear bubbles are released.

Relating these temperatures to the boiling point temperatures of the various solvents (57°C for acetone, 78°C for ethanol, 65°C for methanol and 82°C for iso-propanol) one will notice that the temperatures where the bubbles were visible, are much higher than the boiling points of these solvents. This phenomenon can be explained by the possibility of the solvents being trapped in the crystal structures within voids, or that the solvents have formed part of the crystal structure or that decomposition of the crystals occurs.

Conclusion

From the results obtained by this method the visible melting points seemed to vary by degrees Celsius in double digits in some cases. The reproducibility of the viewed melting temperatures often proved to be lacking. This places some doubt on the accuracy of the temperatures measured by this method.

The bubbles viewed in Figure 4.5 can lead to the possibility of solvates being formed by this recrystallisation method. This method does, however, not provide conclusive proof of this and further analyses needed to be done to verify whether or not this was case.

4.3.5 Thermogravimetric analysis (TGA)

From the monotony of the results, without any considerable peaks before the temperature at which the raw material sublimes (at temperatures higher than 165°C), it is quite clear that there was no considerable weight loss from any of the crystals obtained through recrystallisation, except for DMF (Figures 4.6 and 4.7).

When looking at the thermal microscopy results of some of these forms when using the oil immersion method, it might seem that some solvent escaped from the samples (Figure 4.5). When comparing the results to those obtained by means of TGA it is made clear that there was no weight loss and these bubbles were most probably just air bubbles escaping.

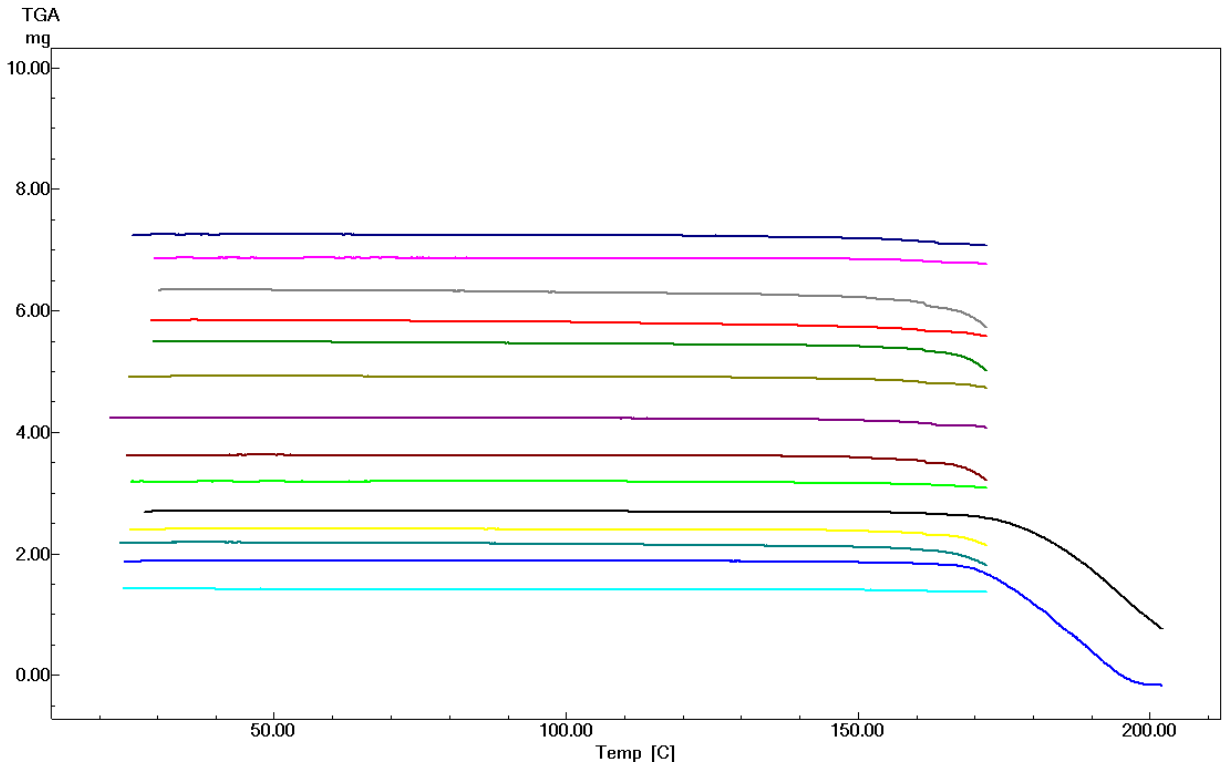


Figure 4.6 TGA results of various crystals obtained.

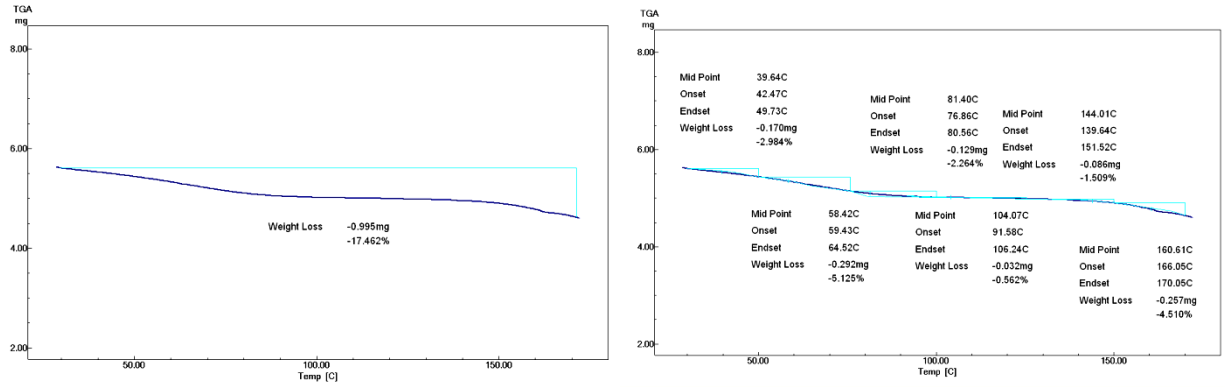


Figure 4.7 TGA of ethionamide DMF crystals showing total weight lost (left) and weight lost at different temperatures (right) (heating rate of 10°C/minute).

This TGA shows a weight loss taking place throughout the entire heating run. This could imply that there is solvent present in the crystal, but does not conclude whether the solvent has formed part of the internal molecular structure or if it is simply trapped in a clathrate or channel (see section 1.3.4).

Conclusion

No significant weight loss was visible and from this one can conclude that the bubbles seen with the TM oil submersion method (Figure 4.5) were merely air bubbles escaping. In the case of DMF one could see significant weight loss and further analyses will verify whether the weight loss was perhaps caused by the solvent being incorporated within the crystal structure or simply accommodated within the crystal structure.

4.3.6 Scanning electron microscopy (SEM)

The SEM images (Figure 4.8) do not show any differences between the surfaces of the formed crystals, except in the case of EA where crystals formed, looking very different from the other forms obtained. From the SEM images one can see the patterns of crystal growth through the various layers formed resulting in different habits.

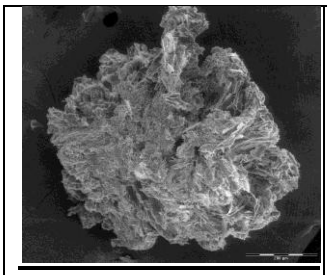
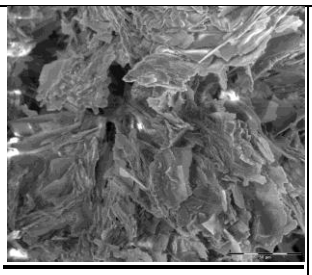
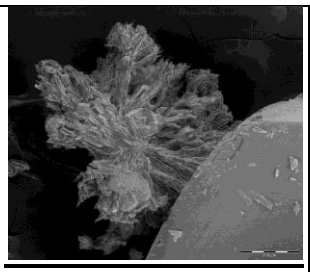
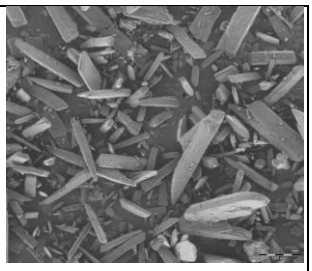
<table>
<tr><td>  </td><td>  </td><td>  </td><td>  </td></tr>
<tr><td>(a) 200 µm scale bar</td><td>(b) 50 µm scale bar</td><td>(c) 200 µm scale bar</td><td>(d) 500 µm scale bar</td></tr>
<tr><td colspan="3">Crystals obtained from recrystallisation from ethyl acetate</td><td>Raw material</td></tr>
</table>

Figure 4.8 SEM of EA (a) showing the spherical shaped crystals formed by recrystallisation from solution (b) magnified view (c) on surface of plate-like crystal.

Conclusion

The SEM results show that when viewing the various forms obtained by the method explained in this section there are no clear differences to be seen at this level of magnification. The EA crystals do, however, show a clear difference between two separate forms that recrystallised from the same solution under the same conditions.

4.3.7 Thin layer chromatography (TLC)

The EA spherical shaped crystals, look very different from all the other crystals obtained, and were analysed for decomposition by means of TLC.

The TLC result showed an additional spot with an RF value of 0.6 along with the regular spot with an RF value of 0.73. This indicates that there was another entity present in these crystals.

Conclusion

The crystals obtained appeared to have possibly undergone some decomposition and in the minute quantities obtained considered not to be a worthwhile direction for the study to be directed in. A DSC was done on the EA spherical crystals as well and showed results that supported the assumption that decomposition had occurred and the EA spherical crystals were set aside for the further duration of this study.

4.3.8 Fourier Transform Infrared (FTIR)

The FTIR spectra (Figure 4.9) showed no differences between the different recrystallisation products obtained. This confirmed the previous assumptions made from the other analyses which indicated no difference in polymorphic form between the raw material and the recrystallisation products obtained. The FTIR should show any solid state difference like the formation of solvates and or other forms.

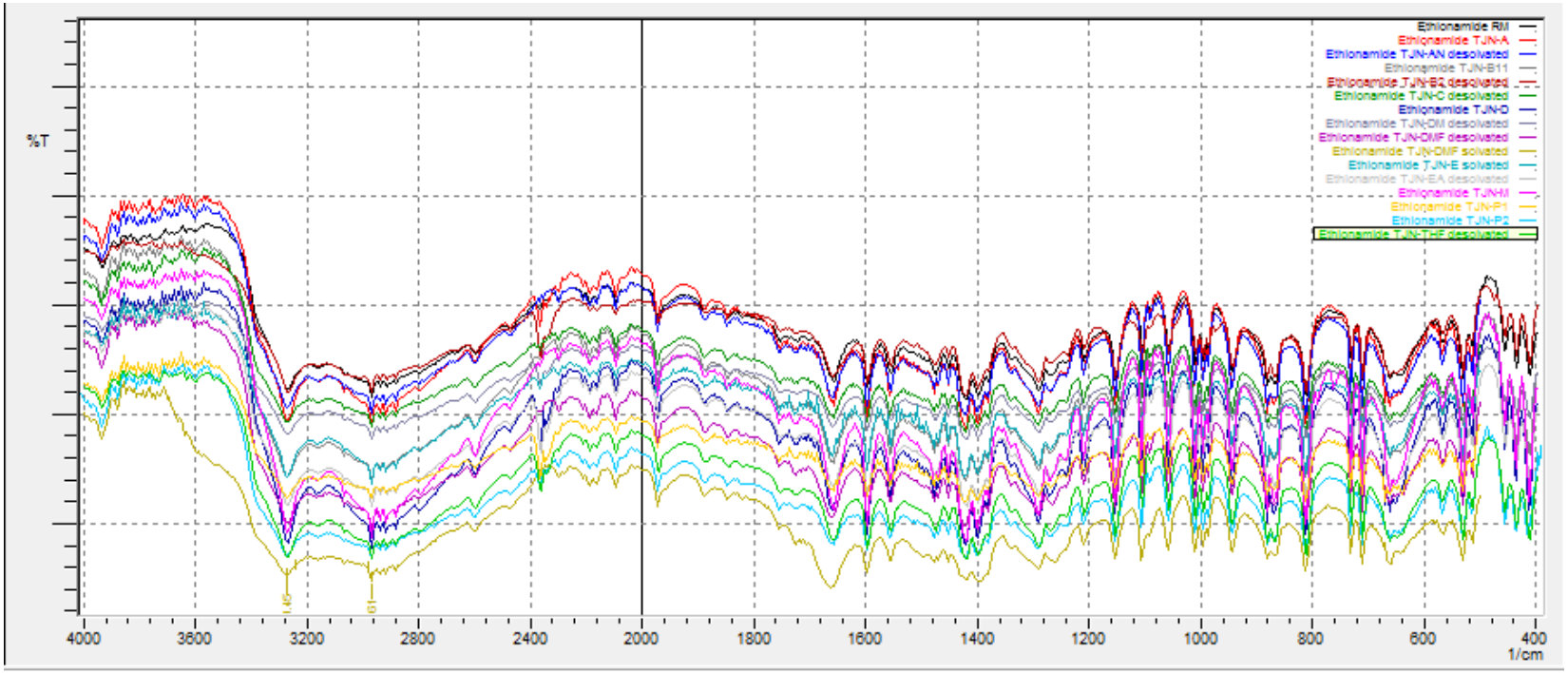


Figure 4.9 FTIR results for ethionamide RM, A, AN, B1, B2, C, D, DM,DMF, E, EA, M, P1, P2 and THF.

Conclusion

The results show that the DMF crystals were not a solvate and the solvent was simply trapped within the crystal structure of the crystals recrystallised from solution in this solvent.

4.3.9 Solubility measurements

The various forms of ethionamide were placed, in amounts exceeding the equilibrium solubility of ethionamide, into 20 ml amber test tubes with screw caps and 10 ml of deionised water was added to each test tube. This is done to get a maximum concentration level so that the maximum amount of each form will dissolve in each test tube to be analysed.

These test tubes were placed in a rack that is attached to a rotating axis that rotates at 54 revolutions per minute for 24 hours while being submerged in a water bath with an ambient temperature of 37°C. All remaining solids were then removed by making use of 0.45 µm Millipore® filters to filter the solutions. The concentration of dissolved API in the solutions was then determined by means of UV spectral analysis with a Shimadzu UV-1800 recording spectrophotometer (Shimadzu, Kyoto, Japan) by making use of Beer's law. Nine test tubes were prepared with each sample in order for the tests to be done in triplets at each time interval (30 minutes, 1 hour and 24 hours).

A standard curve was plotted with the values obtained by preparing different concentrations of ethionamide RM dissolved in water and measuring the absorptivity of these solutions by UV spectral analysis. The UV results and table of values can be seen in annexure A.

For the UV spec. results to be accurate one should use values that correspond with the maximum absorptivity that the spectrometer can measure before reaching a concentration that over saturates the detectors capability. For this reason the solutions from the test tubes had to be diluted for accurate analysis. As the concentrations of dissolved test materials were higher at 24h than at 30 minutes and 60 minutes the solutions were diluted to a greater extent for the analysis at 24h than at 30 and 60 minutes.

To obtain utilizable results the solutions from the test tubes at 30 minutes and 60 minutes were diluted from 1 ml to 16 ml with water. The solutions from the test tubes at 24h were diluted from 1 ml to 21 ml.

The kinetics of solubility or the rate of dissolution is dependent on the particulate features of the material such as the particle size and crystal habits and that the intrinsic solubility is dependent on the molecular and supramolecular properties, the reason why these solubility tests are run for 24 hours should become clear.

The reason for this is that the differences in the rate of solubility caused by the various sizes and habits of crystals formed should be taken out of the picture so that the focus lies solely on the intrinsic solubility of the crystals formed. This is because the focus of this experiment is to determine whether or not the differences in molecular packing had an influence on the intrinsic solubility of the material analysed.

The concentrations measured at 30 minutes and 60 minutes were to compare the variation in the kinetics of solubility of the various habits and sizes obtained through the recrystallisation methods in section 3.3.

Solubility measurements can be used to rank polymorphs by order of stability as the most stable polymorph will have the lowest solubility as a result of having the lowest free energy (Kawakami & Ida, 2005).

The reason why the solubility experiments were only conducted at a single temperature (37°C) is because this is essentially the temperature at which one would want it to have greater dissolution ability as this is the temperature at which it will have to dissolve in the human body. This experiment was carried out on all the crystals of which a high enough mass was obtained, with which to do the experiment. The mass of crystals needed for this experiment is quite large if one takes the small yields of the methods employed into consideration.

From the results in Figure 4.10, it is clear that at 30 minutes the concentrations of most of the test samples were very similar. In comparison to the RM only A, DMF, AN, AN-H and P2 had achieved higher concentrations. The concentration difference was small in all test samples (the maximum lower solubility value differed with ±14% and the

maximum higher solubility value with ±16%) except in P2 and DMF. The difference in concentration between P2 and the RM appeared to be noteworthy, showing an increased solubility of ±27%, though the standard deviation was high (±8.4 mg/100 ml) when considering the difference in values of concentration. DMF showed a significant difference in concentration values when compared to that of the RM (±73% higher). When looking at the absorbance results of DMF in Figure 4.11 one will notice that the peak value is diffuse and does not show a single peak value. This is because at the higher concentration the absorptivity is less accurately measured by this apparatus. For this reason the other charts (Figures 4.12 and 4.13) do not show the values for DMF as the absorbance was too high and gave unusable readings. The problem could have been averted by simply diluting the solutions further and adjusting the calculations. Though in this case the unusable results were discarded, because it was already determined that the DMF sample was not a solvate, but merely accommodating the solvent within its crystal structure. This would be the probable cause of the higher solubility, but will make the sample useless in terms of pharmaceutical applicability.

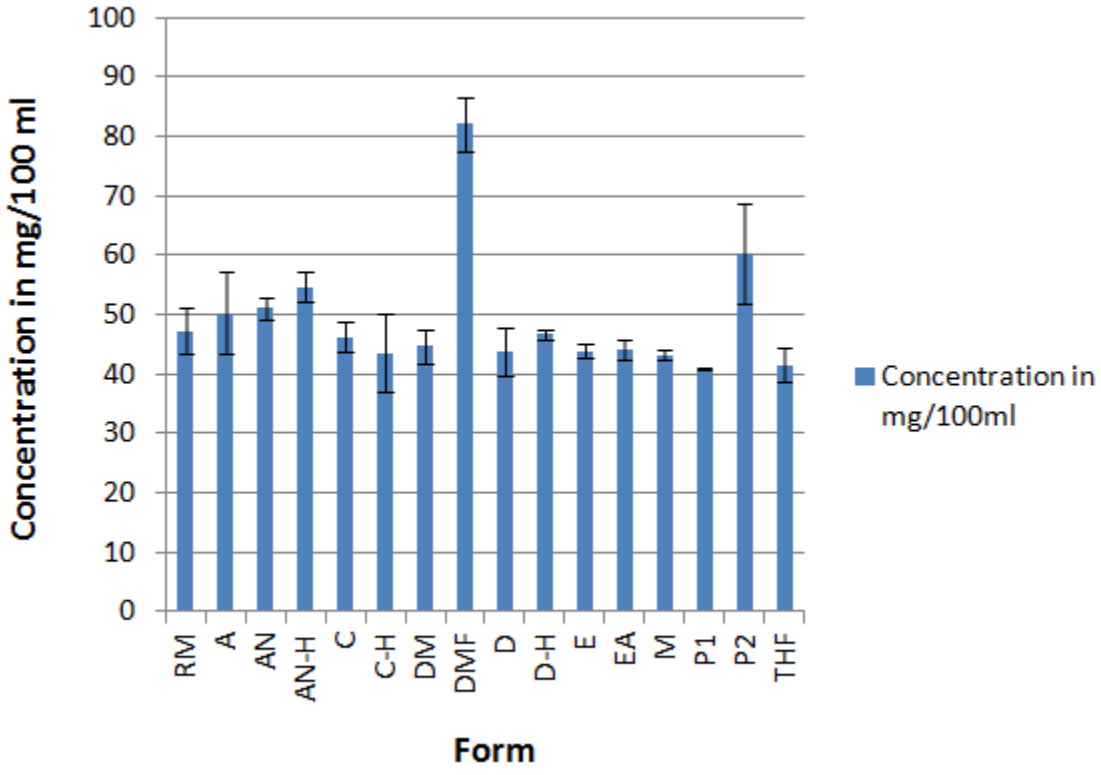


Figure 4.10 Chart displaying the concentrations obtained after 30 minutes.

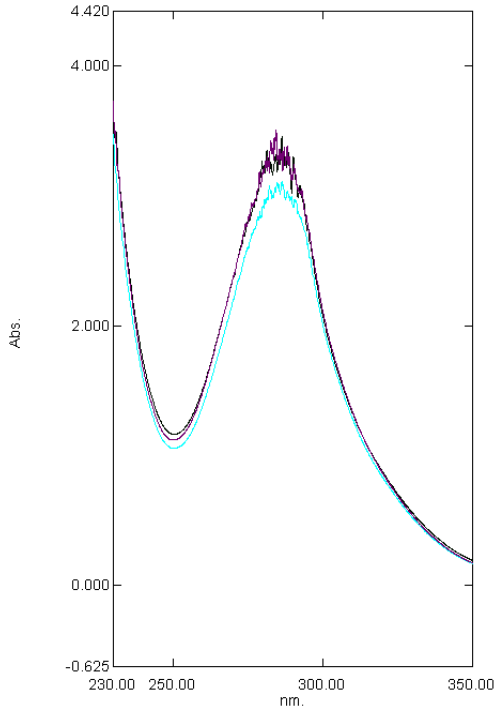


Figure 4.11 UV absorbance results after 30 minutes for DMF showing diffuse peaks.

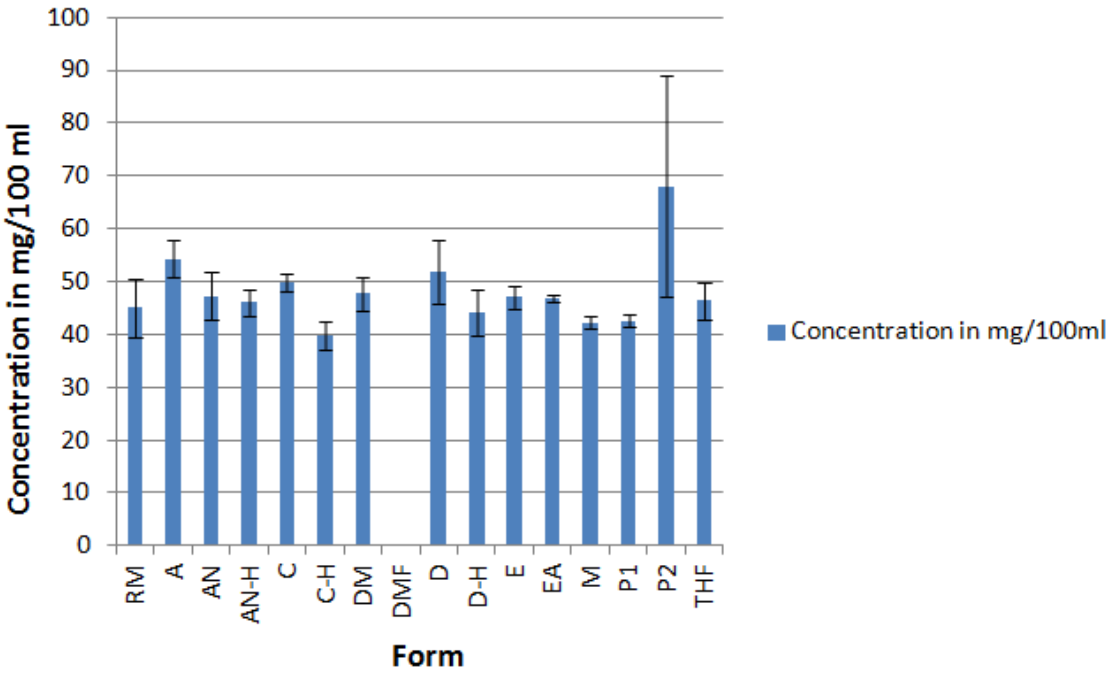


Figure 4.12 Chart displaying the concentrations obtained after 60 minutes.

At 60 minutes the resulting concentrations of the different crystals did not increase a great deal when compared to the values at 30 minutes. This is most probably because the rate of dissolution has decreased for the reason that the concentration of dissolved material present has caused the concentration to become closer to the saturated/equilibrium value. In some cases the concentrations were even found to be lower. This can be explained by taking into consideration that the crystals formed by the same methods, representing the samples used, had various crystal sizes. This, to an extent, leads to the altered kinetics of solubility even for the same material. The differences between the concentrations of the samples were close in this instance as well (ranging from 39-54 mg/100 ml), again with the exception of P2. The concentration of P2 has even increased when compared to the value it showed at 30 minutes (60 mg/100 ml at 30 minutes and 68 mg/100 ml at 60 minutes). The results show an improvement in solubility of P2 compared to the RM of ±51% in this instance, though the standard deviation was so large (±21 mg/100 ml) in this instance that the value has hardly any significance.

At this point it is important to note that a maximum level of saturation has probably not yet been reached in the test tubes after 60 minutes of this experiment. The aim thus far as mentioned earlier was only to see whether the various crystal habits (see section 1.4.1.1) show variation in kinetics of solubility. The next step in this experiment was to see whether there was variation in the intrinsic solubility of the prepared crystals when compared to the RM.

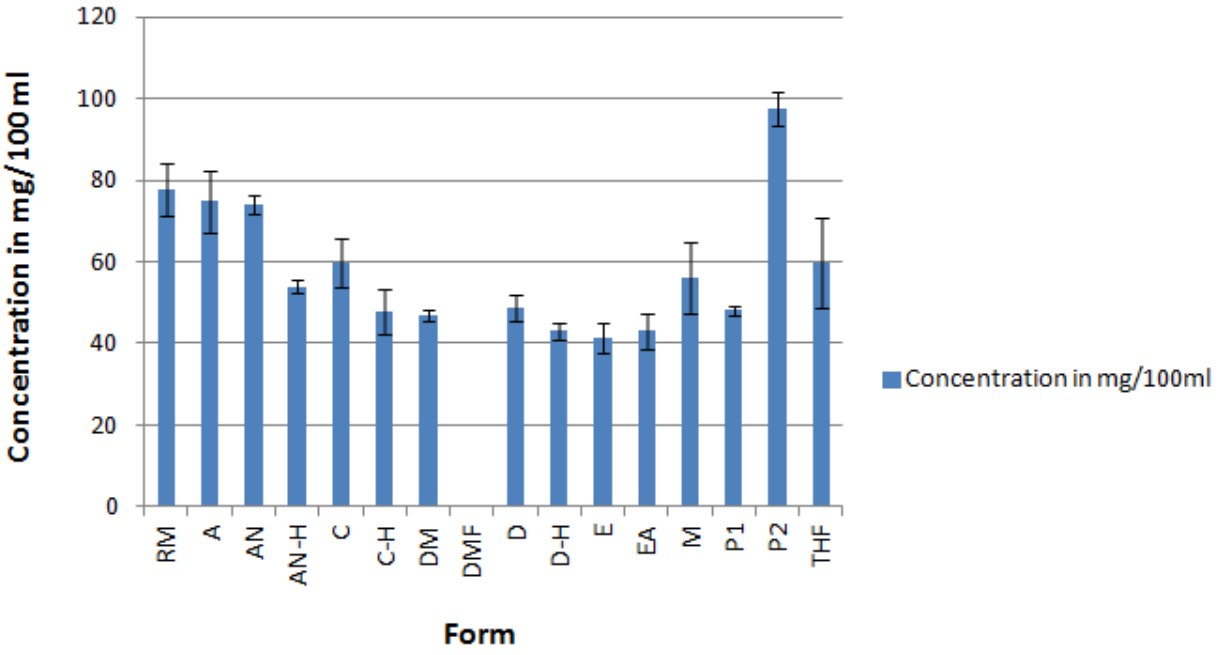


Figure 4.13 Chart displaying the concentrations obtained after 24 hours.

After 24 hours the resulting concentrations displayed greater variation between the various products than those observed after 30 minutes and 60 minutes, ranging from ±41 to ±78 mg/100 ml (when leaving out P2 as was done in the former instances). Though in this case all the other materials showed a lower concentration, relating to a lower solubility than the RM, again with the exception of P2. The results show an improvement in solubility of ±26% when comparing P2 with the RM and in this instance the standard deviation was much smaller (±4 mg/100 ml). The results show that the maximum saturated/equilibrium concentrations obtainable by these materials under these conditions possibly differ, because the idea behind this method was that equilibrium should be reached after 24 hours. The time for maximum saturation/ equilibrium to be reached was, however, not determined prior to this experiment and uncertainty exists whether equilibrium was reached on this occasion.

If equilibrium was reached at this time, however, the higher and lower concentrations of the various sample solutions would be very difficult to explain as the results obtained with DSC, FTIR, TM and TGA indicate that the various crystals obtained are merely different habits of the same molecular packing arrangements/coordinations.

Conclusion

From these results it would appear that P2 had a greater solubility than the RM at all three intervals at which the samples were analysed. The standard deviations seen for P2 at 30 and at 60 minutes make the values less significant though. At 24 hours there was a visible difference in the concentrations of P2 and the RM, though the margin was not very large in this instance and the significance of this result does not appear to be major. DMF on the other hand showed a major difference in concentration to that of the RM. The values obtained were too high to measure accurately with the method that was being used though. From these results it would appear that only DMF showed potential in being a more soluble option than the RM, though would not be pharmaceutically applicable in any way.

Experimental precision was limited by the mass of crystals available for experimentation and the consequential restricted amount of analyses that were possible. Repetition of this experiment with adjustments to obtain more precise values was thus made impossible. The results are of value though and the reason why this experiment was done was not to obtain precise values, but simply to see whether or not more soluble forms were created. This objective was accomplished and the knowledge gained can be used to lead one in ideas for conducting the next experiments.

4.4 Conclusion

The preparation method explained in this section yielded a large number of crystals that when viewed with the naked eye appear to be significantly different. A variety of different analytical methods were used to characterise these crystals in order to obtain enough information to characterise accurately the crystals without having to rely on too many assumptions. From the sum of data obtained by these methods it is possible to conclude that the crystals do possess different habits, though the molecular packing of the crystals do not differ and these crystals are of the same polymorphic form.

A single crystal produced (DMF) turned out to be a clathrate, though the nature of the solvent renders this product useless i.t.o. any pharmaceutical applicability. This method did not produce any solvates or polymorphs, though with the large amount of variables

that one can manipulate when using this method, it does not suggest by any means that forming solvates or polymorphs of this material by this method is impossible.