The Optimization of Antisolvent Crystallization in Manganese Sulfate Precipitation

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Abstract

Crystallization is a technique commonly used in industries and analytical chemistry. There are different crystallization methods, one of which is antisolvent crystallization. In antisolvent crystallization, a substance is added to a solution to decrease the solubility of a solute, leading to crystallization. The aim of this study was to optimize precipitation of manganese(II) sulfate using an antisolvent crystallization technique. Ethanol, methanol, isopropanol, and acetone were used as antisolvents. In addition, parameters including amount of antisolvent added, flow rate of antisolvent, and impurities in the solution were examined. Ethanol and acetone were the most effective antisolvents, and cobalt as an impurity had major impacts on crystal shape. Manganese sulfate monohydrate was crystallized, but some pentahydrate were also obtained.

Acknowledgements

Contents

1 Introduction

Crystallization is a technique commonly used in industries and analytical chemistry [1]. The technique is applied when producing pharmaceuticals, photographic chemicals, and polymers [1]. Apart from chemistry, crystallization is also applicable in metallurgy, physiology, and geology [1]. One crystallization technique is antisolvent crystallization, which is extensively used in the pharmaceutical industry when purifying and isolating active pharmaceutical ingredients, also known as APIs [2]. The technique is commonly used in synthetic processes of APIs because of the high yield and the fact that it can be conducted at room temperature [2].

Crystallization can be described as a phase change or a separation method because crystals are precipitated from a solution. Crystals consist of atoms, molecules, or ions that are arranged in infinite regular patterns in space. Normally, crystals appear in a solid-state, but they can also be aqueous. [1]

1.1 Background

A solute is a substance which dissolves in a liquid, and a solvent is the liquid in which the solute dissolves. The word solution usually refers to a solid solute dissolved in a liquid solvent. The maximal amount of solute that can dissolve in a specific amount of a solvent, at a set temperature, is the solubility of the solute, which can be measured in weight percent, wt%. When no more solute can dissolve in a solvent, the solution is considered saturated. In general, the solubility can be raised through an increase in temperature, as shown in Figure 1 [3]. That is not, however, the case for all compounds. [3]
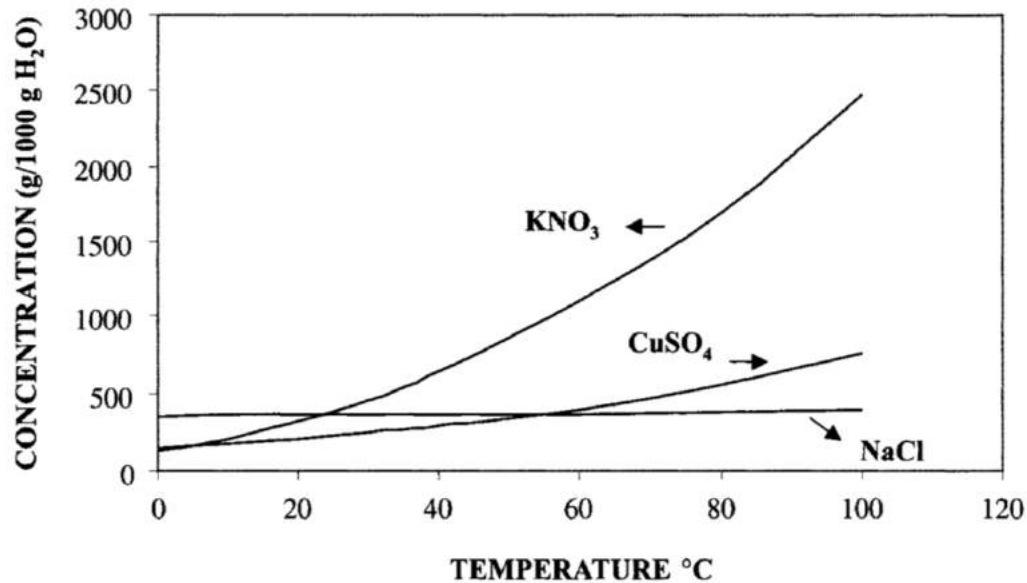
Figure 1: Solubility of some compounds. The concentration is shown as a function of the temperature.

1.1.1 Nucleation

Nucleation is the first step in the formation of a new crystal. The process in which crystals grow, after nucleation, is simply called crystal growth. Nucleation is divided into primary and secondary nucleation. Primary nucleation is further divided into homogeneous and heterogeneous nucleation. Nucleation without the presence of crystals in a solution is called primary nucleation and refers to spontaneous nucleation; that is, in the body of the liquid. The opposite to homogeneous nucleation is heterogeneous nucleation which occurs in the presence of impurities, such as, atmospheric dust. Secondary nucleation occurs with the help of present crystals which may be introduced deliberately via a process called seeding. [1]

1.1.2 Supersaturation

Supersaturation is a state in which the concentration of a solute exceeds the solubility value, and is the driving force of crystallization. Supersaturation is illustrated in Figure 2 [3]. When the solution is cooled from point A to B, the concentration of the solute exceeds

the solubility value represented by the saturation line. Thus, supersaturation has been generated and crystals can be created. The metastable zone is the zone in which the solution is supersaturated but nucleation does not necessarily occur spontaneously. While in the metastable zone, a solution may exist supersaturated for hours or days without nucleating. [3]
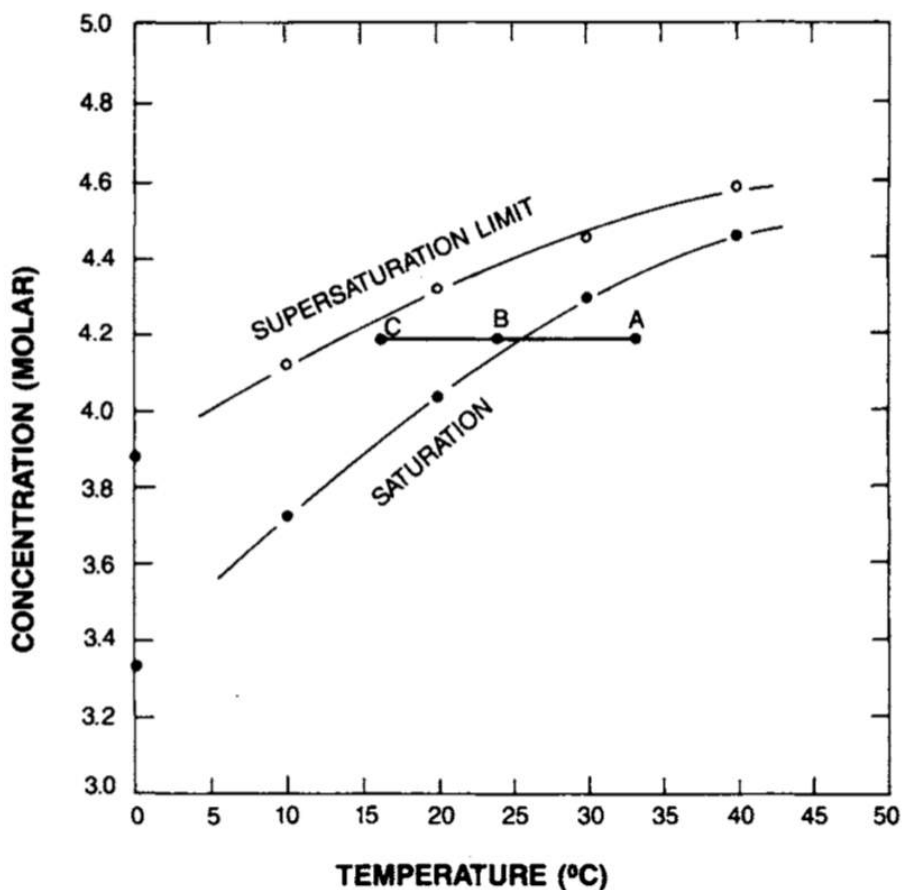
Figure 2: The metastable zone exists between the saturation line and the supersaturation limit. The x-axis represents the temperature and the y-axis represents the concentration. Crystals are formed considerably faster in point C than in point B. If the solution is cooled further, it exits the metastable zone and becomes unstable. In that case, crystals form spontaneously and uncontrollably.

1.1.3   Different Types of Crystallization

Different methods to generate supersaturation include: cooling crystallization, evaporation crystallization, reaction crystallization, and antisolvent crystallization [4].

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Cooling crystallization is a commonly used precipitation technique and generates crystals through cooling the solution. Since the solubility decreases with decreasing temperature, it becomes easier to generate supersaturation. Benefits of cooling crystallization include low risk and low energy requirements, and the operation is also relatively easy to implement. [3, 4]

In cases where the temperature has little effect on the solubility or in cases where the solubility increases with decreasing temperature, other methods have to be considered. Apart from cooling crystallization, another way to generate supersaturation is through evaporation crystallization, which is a suitable technique if the solute has a high vapor pressure. In evaporation crystallization, solvent evaporates at a constant temperature thus increasing the concentration of solute. Consequently, the solution becomes saturated and, after further evaporation, supersaturated. [3]

A third method to generate supersaturation which leads to crystallization is through reaction crystallization. In this method, two solutes are mixed together to form a product with low solubility. [3]

The crystallization technique used in this work was antisolvent crystallization. This method has not been researched as much as the other crystallization techniques. A substance called the antisolvent is added to a solution thus reducing the solubility of the solute [5]. The antisolvent should be miscible with the solvent, it should be able to form a homogeneous solution with the solvent, but the solute should be insoluble in the antisolvent [1]. A solvent has a dielectric constant, often denoted ε, which is a measure of the solvent's capacity to reduce electric fields around ions [6, 7]. Solvents with high dielectric constants dissolve salts and ions better. Consequently, if the antisolvent has a lower dielectric constant than the solvent it is mixed with, the solubility of the solute will

decrease, and supersaturation can be generated [6]. Benefits of antisolvent crystallization include the facts that it can be conducted at room temperature, and that it requires less energy than evaporation crystallization if the separation of solvent and antisolvent is done correctly [5, 8].

1.2   Aim of Work

The primary aim of this work was to optimize antisolvent crystallization by precipitation of manganese sulfate. The secondary aim was to provide more data of manganese sulfate in antisolvent crystallizatoin systems. Different parameters, including choice of antisolvent, amount of antisolvent added, and antisolvent flow rate and the effects they have on crystals were investigated. Antisolvents studied included ethanol, isopropanol, acetone, and methanol. Isopropanol had the lowest dielectric constant, followed by acetone, ethanol, and methanol [9, 10]. Moreover, cobalt as an impurity was studied to determine if the shape of crystals would be affected.

2   Method

All manganese sulfate used were manganese(II) sulfate monohydrate, $MnSO_4 \cdot H_2O$. The salt was dissolved in 500 grams of 3 M sulfuric acid, H_2SO_4, because of the low vapor pressure. No prior data of the solubility of manganese sulfate in sulfuric acid was found. Consequently, a preliminary experiment with the purpose of investigating the solubility of manganese sulfate in sulfuric acid was conducted by slowly adding manganese sulfate to 20 grams of sulfuric acid under constant stirring, until saturation. Approximately 4.5 grams of manganese sulfate were dissolved in 20 grams of sulfuric acid.

2.1   Preparations

The solubility data from the preliminary experiment was used to prepare a larger volume of saturated solution of manganese sulfate in sulfuric acid. Therefore, 450 grams of sulfuric

acid were measured, and manganese sulfate was slowly added under constant stirring. When approximately 100 grams of manganese sulfate had been added, the time required for manganese sulfate to dissolve increased noticeably as it took more than half an hour for one to two grams to dissolve. However, due to time constraints, approximately ten grams of manganese sulfate were added. If not all salt dissolved, sulfuric acid would slowly be added to the solution until all manganese sulfate had been dissolved. In total, 109.3 grams of manganese sulfate were added to 500.9 grams of sulfuric acid.

2.2   Examining Different Antisolvents

The first stage of the experiment included examinations of different antisolvents. Ethanol, methanol, isopropanol and acetone, all organic antisolvents, were studied and compared. In this case, the efficiency of an antisolvent was determined by their O/A ratio, the organic to aqueous volumetric ratio, in which nucleation occurred [11].

A volume of 20 ml of manganese sulfate in sulfuric acid was measured and transferred to a cup containing a magnetic stirrer. A burette was used to add antisolvent at intervals of 2 ml. After every addition, the solution was inspected for nucleation. Nucleation occurred when 30 ml of ethanol had been added, at an O/A ratio of 1.5. The same process was repeated for isopropanol. However, when 18 ml of isopropanol had been added, the isopropanol was no longer miscible in the solvent. Phase separation therefore took place before nucleation, and isoproanol was excluded from the experiment. Acetone was also used as an antisolvent, and crystals were seen after 24 ml of acetone had been added; that is, at an O/A ratio of 1.2. Lastly, methanol was investigated as an antisolvent. However, there was no nucleation after 40 ml of methanol had been added. An attempt to seed the solution with manganese sulfate was made, but nucleation did still not occur. Consequently, methanol was also excluded from the experiment.

2.3   Collection of Solid and Solution Samples

For the second stage of the experiment, only ethanol and acetone were studied, both at O/A ratios of 1.5 and 2.0. Each experiment was conducted twice. The purpose was to collect solid and solution samples. A solution of 20 ml was measured and antisolvent was added without controlling the flow rate. Solution samples were collected using syringes with syringe filters to avoid obtainment of crystals. All solution samples were tightly fixed with lids to avoid evaporation. The remains were poured in a Buchner funnel connected to a vacuum adapter with a clamp, as shown in Figure 3. Solvent was poured in the funnel, through the filtration paper and vacuum adapter, and ended up in the vacuum flask. The filtration paper and the obtained crystals were put in a container without lid so that any liquid left would evaporate. All experiments were conducted under room temperature. Manganese sulfate transforms from pentahydrate to monohydrate at 23.9 °C [12]. Therefore, either the pentahydrate or monohydrate form could have been obtained. The masses of the obtained crystals were measured using a scale.
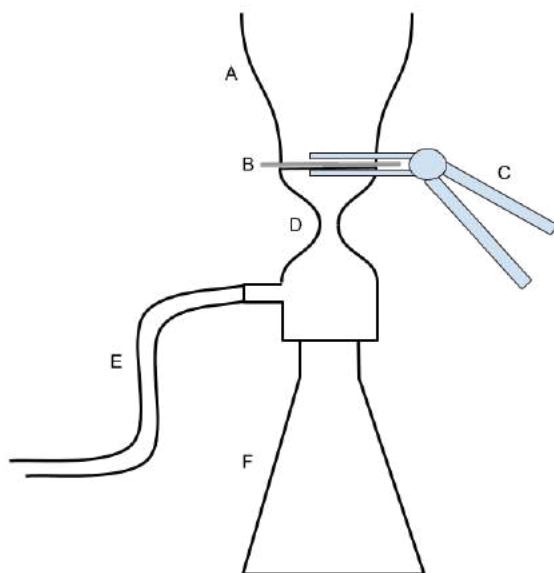

Figure 3: Equipment used to take solid samples. A. Buchner funnel. B. Filtration paper. C. Clamp. D. Vacuum adapter. E. Vacuum tube. F. Vacuum flask.

2.4   Controlling the Flow Rate

Stage three of the experiment included the analysis of flow rate and crystal shape. A solution of 20 ml was measured and transferred to a cup, and an O/A ratio of 1.5 was used. A magnetic stirrer was continuously used while a syringe pump slowly added antisolvent, in this case acetone as it was the most effective antisolvent, at a constant speed of 0.6 ml per minute. Solid and solution samples were collected after all acetone had been added.

2.5   Adding an Impurity

The aim of stage four of the experiment was to investigate if an impurity would affect the shape of the manganese sulfate crystals. Cobalt(II) sulfate heptahydrate was used as an impurity because it was soluble in sulfuric acid. A new solution was prepared by slowly dissolving cobalt sulfate into 40 grams of manganese sulfate solution under constant stirring. In total, 2.2 grams were added. A new solution of 20 ml with cobalt sulfate was measured and 30 ml of acetone was added as antisolvent. Crystals formed, and solid and solution samples were collected.

2.6   Analyzing Solid and Solution Samples

The last stage of the experiment included the analysis of solid and solution samples. In total, there were 10 solid samples and 10 solution samples: 16 samples were from stage two, 2 samples from stage three, and 2 samples from stage four. Solid samples were examined under a microscope, and mixed with small droplets of oil to mitigate cluster formations.

The solution samples were analyzed using Inductively Coupled Plasma - Optical Emission Spectrometry, ICP-OES. Most solution samples were diluted by 100, some by 1000, with 5 %v/v of 69 %v/v nitric acid, HNO_3. Each diluted sample was analyzed using ICP-OES, which presented the concentration of manganese in ppm. As the concentration of manganese was given in ppm, a proportional calculation was done to calculate the

concentration of manganese sulfate in ppm: $c_{MnSO_4} = c_{Mn} \cdot \frac{M_{MnSO_4}}{M_{Mn}}$. The concentration was converted to wt% by dividing the concentration by 10,000: $c_{wt\%} = \frac{c_{ppm}}{10,000}$. With the concentration of manganese sulfate in wt%, the recovery was calculated using Equation (1) where P is the recovery in %, W_1 the initial mass of the solution, W_2 the final mass of the solution, C_1 the initial concentration and C_2 the final concentration of manganese sulfate [13]. The equation was slightly modified from its source as the concentration was given in wt%. Additionally, Equation (2) was used to calculate the yield, Y, in wt%, using the molar mass, M, of the hydrate and anhydrous salt [14]. The mass was then calculated by dividing the yield by 100.

$$P = \frac{W_1 C_1 - W_2 C_2}{W_1 C_1} \cdot 100 \tag{1}$$

$$Y = (W_1 C_1 - W_2 C_2) \cdot \frac{M_{Hydrate}}{M_{Anhydrous}} \tag{2}$$

3 Results

The obtained crystals were observed under a microscope. Figure 4a and 4b show the effect of different antisolvents at an O/A ratio of 1.5. Figure 5a and 5b show the crystals after crystallization at an O/A ratio of 2.0. Figure 6a shows crystals when acetone was added uncontrollably, and Figure 6b shows the effect of a controlled flow rate. Figure 7a and 7b compare crystals that have cobalt as an impurity with crystals without cobalt.
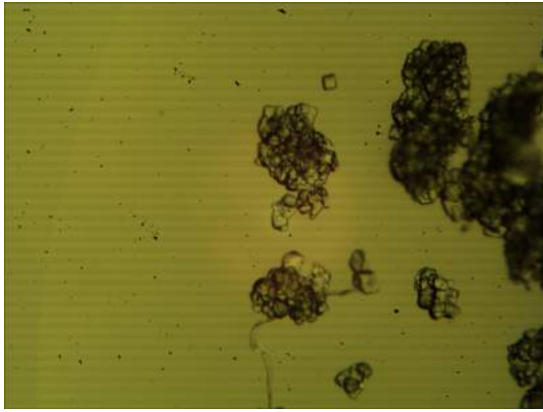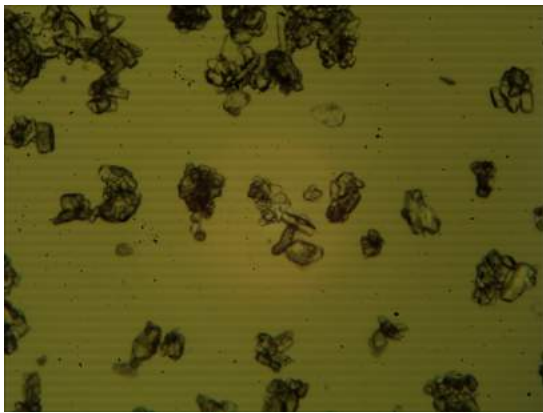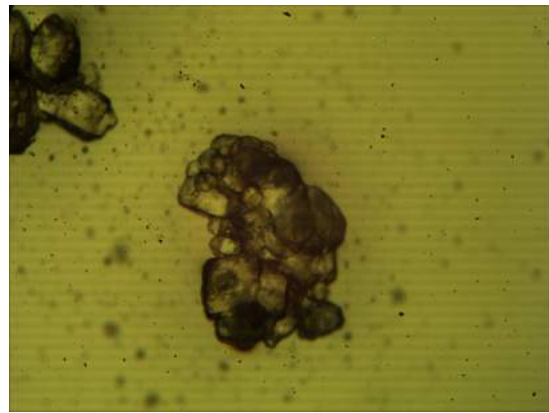
(a) Ethanol as antisolvent. O/A=1.5.
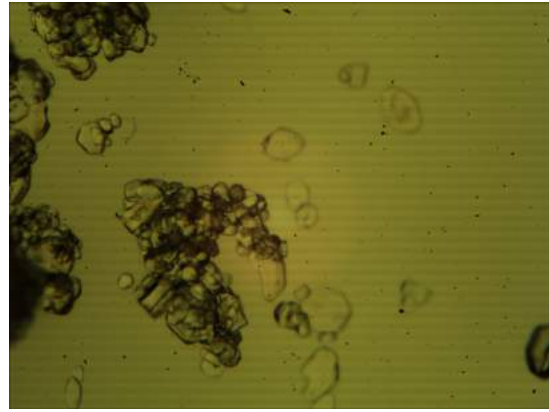
(b) Acetone as antisolvent. O/A=1.5.

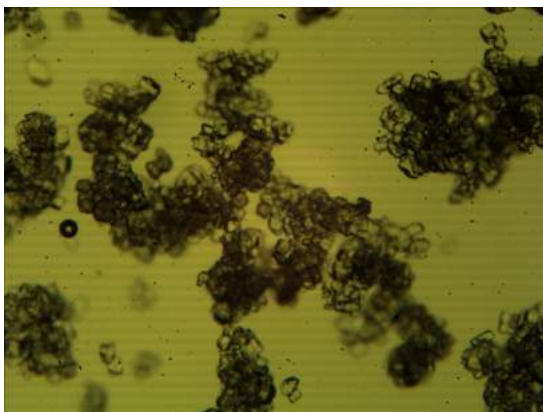Figure 4: Comparison of ethanol and acetone as antisolvents at an O/A ratio of 1.5.
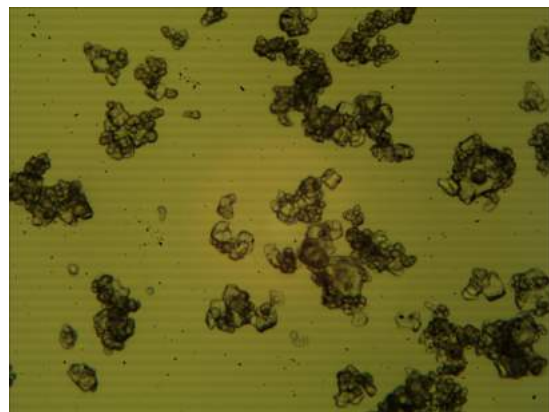

(a) Ethanol as antisolvent. O/A=2.0.

(b) Acetone as antisolvent. O/A=2.0.

Figure 5: Comparison of ethanol and acetone as antisolvents at an O/A ratio of 2.0.
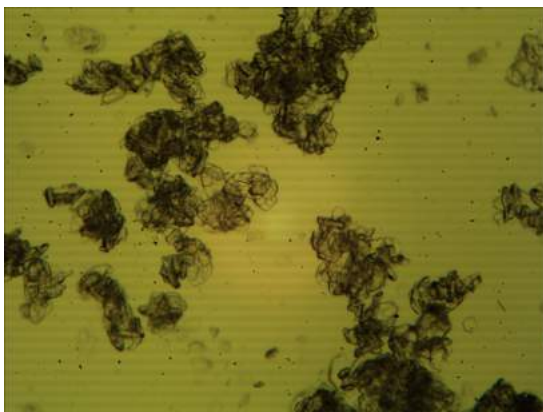

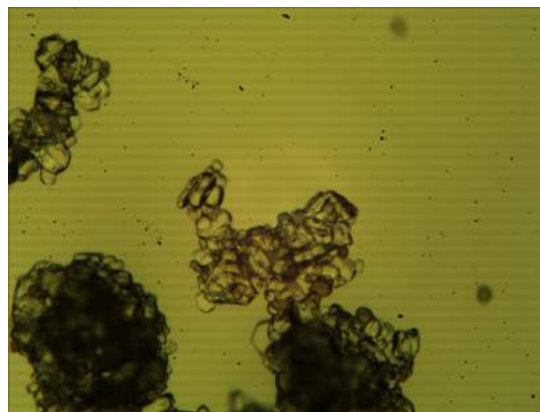(a) Acetone as antisolvent. O/A=1.5.
Uncontrolled flow rate.

(b) Acetone as antisolvent. O/A=1.5.
Controlled flow rate.

Figure 6: Comparison of uncontrolled and controlled flow rate.

(a) Cobalt as impurity. O/A=1.5. Acetone as antisolvent.

(b) No impurities present. O/A=1.5. Acetone as antisolvent.

Figure 7: Comparison of crystals that have an impurity and crystals without impurity.

3.1 Concentration and Recovery

Figure 8 and Figure 9 are based on data from ICP-OES which analyzes the concentration of selected elements under different wavelengths. The concentration of manganese was analyzed, and is shown at different O/A ratios in Figure 8. The initial concentration varies depending on the calculation method. However, the average initial concentration obtained from ICP-OES was used when calculating recovery. All dots in the figure represent values from ICP-OES, except the red dot which represents the concentration calculated by dividing the mass of solute by the mass of the solution. There are two dots for each antisolvent at each O/A ratio. Figure 9 shows the recovery of manganese sulfate.
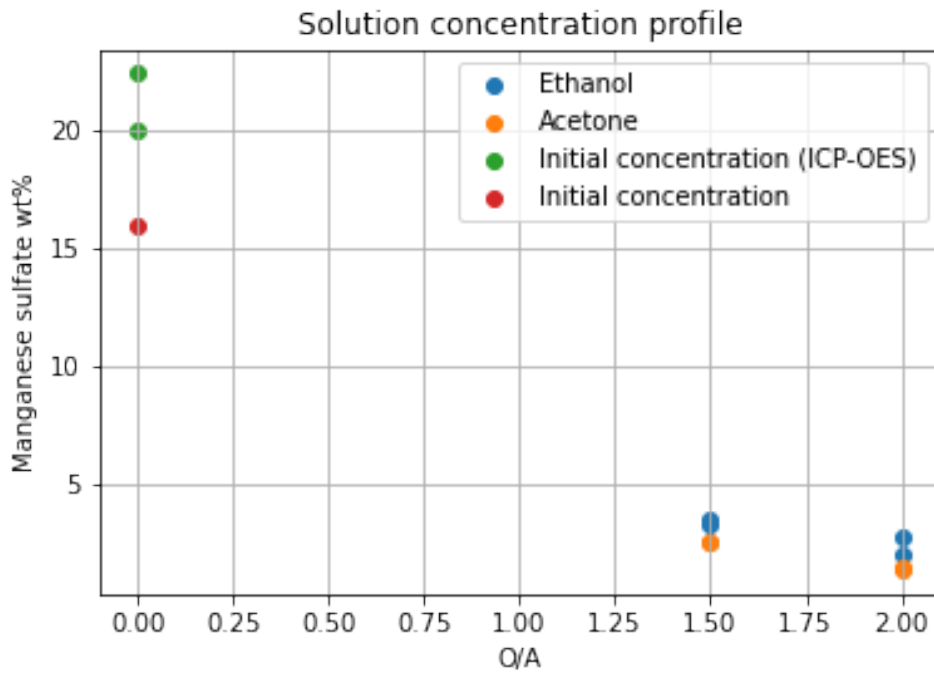
Figure 8: Concentration of manganese sulfate as a function of O/A ratio.
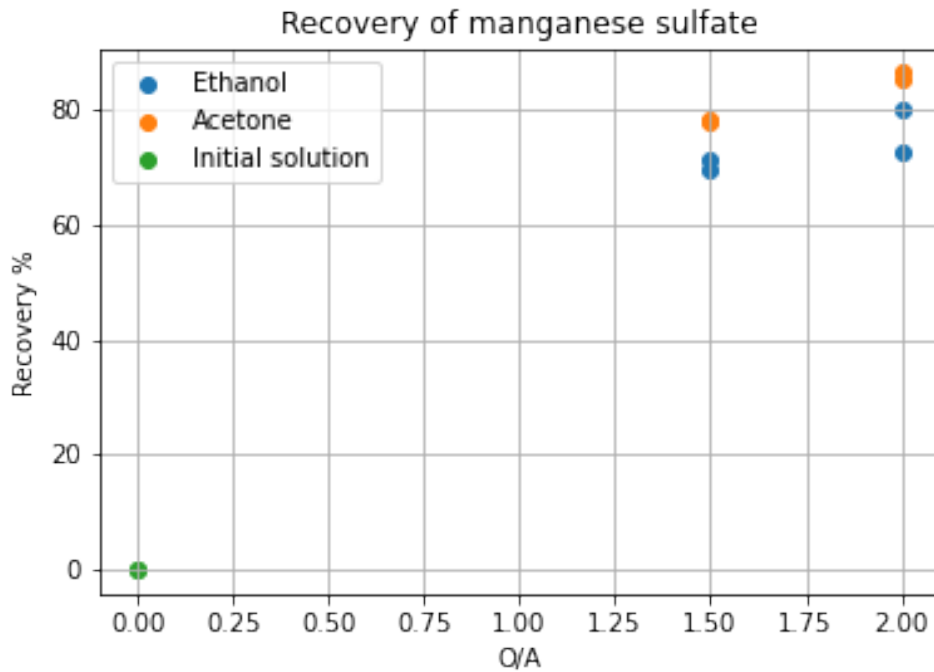

Figure 9: Recovery of manganese sulfate as a function of O/A ratio.

3.2 Mass of Obtained Crystals

The yield can be calculated using Equation (2). Thus, the mass can also be obtained.

Calculations were made under the assumption that all obtained crystals were manganese

sulfate monohydrate. These calculated values can be compared to the measured values of manganese sulfate.

Table 1: Calculated mass versus weighted mass. FR is flow rate and Co is cobalt.

Experiment	Calculated mass (g)	Measured mass (g)
Experiment 1	4.6	3.9
Experiment 2	4.6	4.5
Experiment 3	4.8	5.2
Experiment 4	5.3	5.5
Experiment 5	5.1	5.4
Experiment 6	5.1	5.2
Experiment 7	5.6	6.7
Experiment 8	5.7	6.2
Experiment 9 FR	4.3	4.3
Experiment 10 Co	5.6	6.9

4   Discussion

The effectiveness of an antisolvent can be measured in different ways. In this paper, it was measured by observing the amount of antisolvent required for nucleation. However, the effectiveness of an antisolvent may also be measured by observing the effect it has on crystal shape and size. Crystallization is frequently used in the pharmaceutical industry where the shape and size of crystals may be of importance.

Acetone was the most effective antisolvent, of the ones studied, as it had the lowest O/A ratio for nucleation. As shown in Table 1, acetone also crystallized the largest amount of manganese sulfate. Neither methanol nor isopropanol were effective antisolvents. Even though isopropanol had the lowest dielectric constant, it was not miscible with sulfuric acid in all proportions. Acetone, which had the second lowest dielectric constant, was instead the most effective antisolvent. Methanol had the highest dielectric constant of the ones studied and was also the least effective antisolvent. The properties of manganese sulfate also determined the efficiency of the antisolvent.

4.1 Shape of Crystals

Comparing Figure 4a and 4b where acetone and ethanol were used as antisolvents, there were no major differences in crystal shape. There were no major differences in crystal shape resulting from the O/A ratio, when comparing Figure 4a and 4b to Figure 5a and 5b. The obtained crystals had a cubic or spherical shape, and were arranged in a regular pattern. Some crystals, as shown in Figure 5a, had a more sharp and oblong shape. All crystals were clustered if not purposely scattered. Figure 6a and 6b show that the flow rate did not have a major impact on crystal shape in this experiment. Cobalt as an impurity significantly affected the shape of the crystals, as shown in Figure 7a. Compared to the other pictures, the crystals in Figure 7a are disorganized and clustered. The reason might be that cobalt influenced manganese sulfate during nucleation so that manganese sulfate crystallized into a different shape, although there is also a possibility that cobalt crystallized together with manganese sulfate. In that case, cobalt crystals are also seen in Figure 7a.

4.2 ICP-OES

When manganese sulfate crystallizes, it precipitates and thus the concentration in the solution decreases. At an O/A ratio of 1.5, the concentration of manganese sulfate in the solution is less than 5 wt% for both antisolvents. The concentration is slightly lower when acetone is used because it is a more effective antisolvent. At an O/A ratio of 2.0, the recovery of manganese sulfate is approximately 80 %. The recovery is higher for acetone as acetone is a better antisolvent.

4.3 Comparing Crystal Masses

As can be seen in Table 1, the mass calculated with Equation (2) is less than the measured mass, in the majority of the experiments. This might be because of the fact that the calculations were done assuming that only manganese sulfate monohydrate was obtained.

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Manganese sulfate transforms from pentahydrate to monohydrate at 23.9 °C. Because the experiments were conducted at room temperature, it is also a possibility that manganese sulfate pentahydrate crystallized. If only the molar mass of manganese sulfate pentahydrate is used in Equation (2), the calculated and measured masses will differ more than it does in Table 1. Consequently, it is likely that manganese sulfate monohydrate was obtained in larger amounts than manganese sulfate pentahydrate. However, there is also a possibility that all water did not evaporate. In that case, the measured mass is greater than the actual mass of manganese sulfate.

4.4 Future Research

In order to optimize antisolvent crystallizaition, a proper antisolvent has to be used. Thus, for future studies, other antisolvents, such as butanol, can be examined. Different impurities that are soluble in the solvent can also be added in order to further investigate the effect they have on crystals in antisolvent crystallization. A better microscope can also be used to analyze crystal shape. Furthermore, it may also be interesting to analyze crystal size. Further studies regarding which hydrate that can be obtained should also be carried out. A possible method is to heat the crystals to an anhydrous state and measure the amount of evaporated water.

4.5 Conclusion

The primary aim of the work was to optimize antisolvent crystallization by precipitation of manganese sulfate, and it has been done by varying different parameters. Acetone and ethanol were the most effective antisolvents for crystallization of manganese sulfate in sulfuric acid. Antisolvent flow rate did not affect the shape of manganese sulfate, in this specific experiment. Cobalt as an impurity had a major impact on the shape of the manganese sulfate crystals. Furthermore, the dielectric constant was shown to have little to no correlation to the effectiveness of an antisolvent. A greater understanding of

antisolvent crystallization has thus been obtained from this work.

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A   Measured Experimental Values

The experimental values used for the calculations can be found in Table 2, Table 3, and Table 4. Table 2 and 3 show volumes and weights of solutions and antisolvents, and O/A ratios. Gross weight and net weight only apply to solid samples, and can be found in Table 4.

Table 2: Results from all experiments, where FR is flow rate and Co is cobalt.

Experiment	Antisolvent	Solution (ml)	Soltution (g)
Experiment 1	Ethanol	20	27.4
Experiment 2	Ethanol	20	27.8
Experiment 3	Acetone	20	27.8
Experiment 4	Acetone	20	27.6
Experiment 5	Ethanol	20	27.8
Experiment 6	Ethanol	20	27.8
Experiment 7	Acetone	20	27.7
Experiment 8	Acetone	20	27.6
Experiment 9 FR	Acetone	20	27.6
Experiment 10 Co	Acetone	20	28.0

Table 3: Continuation of Table 2

Experiment	Antisolvent (ml)	Antisolvent (g)	O/A
Experiment 1	30	23.0	1.5
Experiment 2	30	23.5	1.5
Experiment 3	30	23.6	1.5
Experiment 4	30	23.7	1.5
Experiment 5	40	31.4	2.0
Experiment 6	40	31.2	2.0
Experiment 7	40	31.4	2.0
Experiment 8	40	31.2	2.0
Experiment 9 FR	30	23.6	1.5
Experiment 10 Co	30	23.6	1.5

Table 4: Continuation of Table 2 and 3. The tare weight was 6.7 grams for all solid samples.

Experiment	Gross weight (g)	Net weight (g)
Experiment 1	10.6	3.9
Experiment 2	11.1	4.4
Experiment 3	11.8	5.1
Experiment 4	12.1	5.4
Experiment 5	12.1	5.4
Experiment 6	11.9	5.2
Experiment 7	13.3	6.6
Experiment 8	12.9	6.2
Experiment 9 FR	11.0	4.3
Experiment 10 Co	13.6	6.9