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Integrated Synthesis and Crystallization for the Continuous Manufacturing of Paracetamol

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Abstract

The aim of this thesis was to develop a continuous set-up for the integrated synthesis and crystallization of paracetamol. The synthesis of paracetamol involves the reaction of 4-aminophenol with acetic anhydride in the presence of impurities from the industrial synthesis of paracetamol. The industrial impurities were acetanilide, metacetamol, and 4-nitrophenol. Before building up the continuous process, an HPLC method was developed to investigate the concentrations of 4-aminophenol, paracetamol and impurities. Also, experiments were developed to solve the challenges accompanying the 4-aminophenol decomposition from heat and light. After that, many tests were done in batch to study the influence of impurities on the synthesis of paracetamol with/without impurities with acetic anhydride in different solvents. The chosen solvents were iso-amyl alcohol, 2-propanol, and water. The investigations of the reaction of impurities with acetic anhydride in different solvents (water and iso-amyl alcohol) showed no reaction of the impurities with acetic anhydride in the solvent. However, the influence of different solvents (water, 2-propanol & iso-amyl alcohol) appeared in the yield of synthesis and crystallization of paracetamol. The highest yield was obtained with water (71.07%) > 2-propanol (65.35%) > iso-amyl alcohol (57.62%). The yield did not change a lot after the addition of impurities and still water seems to be the best solvent. Crystallization yields from the investigations of paracetamol synthesis with impurities were water (89.33%) > 2-propanol (48.68%) > iso-amyl alcohol (28.73%). Detailed investigations of the crystallization of the mother liquor showed that the amount of impurities stayed constant with time and the amount of paracetamol decreased with time. Furthermore, for all the mentioned tests the crystal purity was tested using HPLC and only paracetamol peaks were observed. Particle size and shape were investigated using optical microscope where the images showed that paracetamol crystals from water synthesis had the most rounded shape. The continuous set-up was built with optimized parameters from the batch experiment which included using water as a solvent at 40°C for the synthesis and 5°C for crystallization with scaling-up the amounts from the water batch experiment based on the continuous set-up reactor volume. After five main trials, the set-up proved to be successful leading to 21.24% crystallization yield. However, the high solid handling from the tank to the synthesis reactor is still a problem although the process was successful. It was found that the blocking in the pipes from the crystallizer to the filtration part needs further trials and investigations.

Kurzfassung

Das Ziel dieser Arbeit war die Entwicklung eines kontinuierlichen Aufbaus für die integrierte Synthese und Kristallisation von Paracetamol. Die Synthese von Paracetamol beinhaltet die Reaktion von 4-Aminophenol mit Essigsäureanhydrid in Gegenwart von bekannten Verunreinigungen aus der industriellen Synthese von Paracetamol, die in dem Ausgangsmaterial verwendet wurden. Die industriellen Verunreinigungen waren Acetanilid, Metacetamol und 4-Nitrophenol. Vor dem Aufbau des kontinuierlichen Prozesses wurde eine HPLC-Methode zur Untersuchung der Konzentrationen von 4-Aminophenol, Paracetamol und der Verunreinigungen entwickelt. Außerdem wurden Experimente durchgeführt, um die Herausforderungen zu lösen, die mit der Zersetzung von 4-Aminophenol durch Wärme und Licht einhergehen. Danach wurden viele Tests im Batch durchgeführt, um den Einfluss von Verunreinigungen auf die Synthese von Paracetamol mit/ohne Verunreinigungen in verschiedenen Lösungsmitteln zu untersuchen. Die gewählten Lösungsmittel waren Isoamylalkohol, 2-Propanol und Wasser. Die Untersuchungen des Einflusses von Verunreinigungen mit Essigsäureanhydrid in verschiedenen Lösungsmitteln (Wasser und Iso-Amylalkohol) zeigten keine Reaktion der Verunreinigungen mit Essigsäureanhydrid im Lösungsmittel. Der Einfluss verschiedener Lösungsmittel (Wasser, 2-Propanol & Iso-Amylalkohol) zeigte sich allerdings in der Ausbeute nach Synthese und Kristallisation von Paracetamol. Das beste Lösungsmittel war Wasser (71,07%)> 2-Propanol (65,35%)> Isoamylalkohol (57,62%). Die Ausbeute änderte sich jedoch nicht ausschlaggebend nach der Zugabe von Verunreinigungen und Wasser scheint das beste Lösungsmittel. Die Kristallisationsausbeuten aus den Untersuchungen der Paracetamol Synthese mit Verunreinigungen waren Wasser (89,33%) > 2-Propanol (48,68%) > Isoamylalkohol (28,73%). Detaillierte Untersuchungen der Mutterlauge zeigten, dass die Menge an Verunreinigungen mit der Zeit konstant blieb und die Menge an Paracetamol mit der Zeit abnahm. Darüber hinaus wurde für alle erwähnten Tests die Kristallreinheit unter Verwendung von HPLC getestet und es wurden nur Paracetamol Peaks beobachtet. Der Einfluss von Partikelgröße und -form wurde unter Verwendung eines optischen Mikroskops untersucht, wobei die Bilder zeigten, dass Paracetamol Kristalle aus der Wassersynthese die am meisten abgerundete Form aufwiesen. Aus den Chargenexperimenten wurde der kontinuierliche Aufbau mit den optimalen Parametern aufgebaut, die die Verwendung von Wasser als Lösungsmittel für die Synthese und Kristallisation bei 5° C bei 40 ° C mit Maßstabsvergrößerung der Mengen aus dem Batch-Experiment, basierend auf dem kontinuierlichen Setup-Reaktorvolumen, einschlossen. Nach

fünf Hauptversuchen erwies sich das Setup als erfolgreich, mit einer Kristallisationsausbeute von 21,24%. Die Überführung der Suspension mit dem hohem Feststoffgehalt vom Tank zum Synthesereaktor und in weiterer Folge zw. Kristallisator und Filtereinheit ist jedoch immer noch ein Problem, obwohl das Verfahren erfolgreich war.

Acknowledgement

Behind every success, there is a huge support system which makes it withstand. My support system was overseas and everywhere in this big universe. I would like to start by thanking my advisor Ass.Prof. Heidrun Gruber-Wölfler; Heidi, you weren't just a mentor to me, you are a role model for women in science. A devoted worker, mother, and a team leader. Thank you for this opportunity and your patience over the last period of time. I wish you a future full of innovation. I would like to also thank my coSy & Pro team, especially Christoph and Manuel for all their support and help, the visiting scientist during this thesis Vaclav Svoboda from CMAC® Glasgow, Scotland. Now let me please to start thanking the people who were there for me overseas. Of course, I would like to thank every single person in my family and friends but on the top of the list is my mother for always believing in me and handling my absence from home. My dad, for his continuous help and support as a chemical engineer, as well as his financial support to me to achieve my dreams here in Austria. To my sister, Razan, and Brothers Ahmed & Mohammad, you have always looked at me as a genius brain moving around and making sure to mention that to every person you meet. Thanks for being there for me. For my friends who are now spread in every corner in this world. Fatima, I wished that you were with me in Austria as you were with me in Germany but you made sure to cover the absence. Alia, despite the huge time difference between Pullman, US, and Graz, Austria we have made it shorter with our phone calls! To my little family in Graz, thanks a lot for all of you. Carolina, thanking you wouldn't be enough, you were with me in this journey and that definitely makes you my sister from another mother. Snezana, our friendship is the best example for the integration of two different worlds. Also, I would like to thank the Afro-Asiatische institute for accepting me in their team for the last two semesters. Being part of your team helped me meet many great people, like Salem and Karolina, who supported me a lot in the last two semesters. Dear reader, I am sorry for the long thanking page. But for me, coming out from my comfort zone wasn't easy at all and I quote from Stephen Hawking:

"Remember to look up at the stars and not down at your feet. Try to make sense of what you see and wonder about what makes the universe exist. Be curious. And however difficult life may seem, there is always something you can do and succeed at. It matters that you don't just give up."

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Abbreviation

Acetanilide	Actld
4-Aminophenol	4-AP
Active Pharmaceutical Ingredient	API
Acetic anhydride	Ac_2O
Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation	CMAC
Cetyltrimethylammonium bromide	CTAB
Concentration	Conc.
Continuous Stirred Tank Reactor	CSTR
Fourier-Transform Infrared spectroscopy	FTIR
High Performance Liquid Chromatography	HPLC
Methanol 5%: HPLC-water 95%	MeOH:H_2O
Metacetamol and Acetanilide	M+A
Nuclear Magnetic Resonance	NMR
Number	No.
Metacetamol	MCM
4-Nitrophenol	4-NP
Paracetamol	PCM
Total dilution factor	Total D.F
Theoretical concentration	Theo. Conc.
Retention	Ret.

List of symbols

t	Time
T	Temperature
C	Concentration
tr	Retention time
Mw	Molecular weight

Nomenclature

2-propanol	Isopropyl alcohol (IPA)
Iso-amyl alcohol	3-methyl-1-butanol
Paracetamol	Acetaminophen or *N*-(4-hydroxyphenyl) acetamide

I. Introduction

1.1 Background

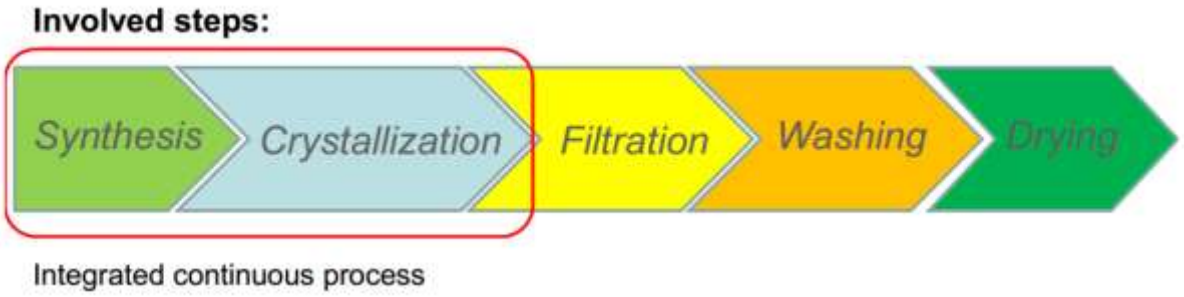
This thesis is a continuation of the work of Ass. Prof. Heidrun Gruber-Woelfler during her stay at CMAC (Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation) Glasgow, Scotland. The project's main goal was the development of a continuous process for the integrated synthesis and crystallization of paracetamol using different solvents, which are: iso-amyl alcohol, 2-propanol and water. Paracetamol was successfully synthesized out of 4-aminophenol and acetic anhydride in batch and continuous flow within 1 minute with 100% conversion using all mentioned solvents. Crystallization of paracetamol was only done out of water in batch and in continuous flow. The continuous process was successfully coupled, but with only 15% overall yield. Thus, in continuation to that work, this thesis was designed [9].

1.2 Paracetamol

Paracetamol (acetaminophen or *N*-(4-hydroxyphenyl) acetamide) is an analgesic and antipyretic painkiller which is used for the treatment of fever. There are more than 20 products available in the pharmacies with some of them being used for the treatment of influenza in different types of formulations. It is considered a safe drug but with dangerous side effects when used in large amounts [8].

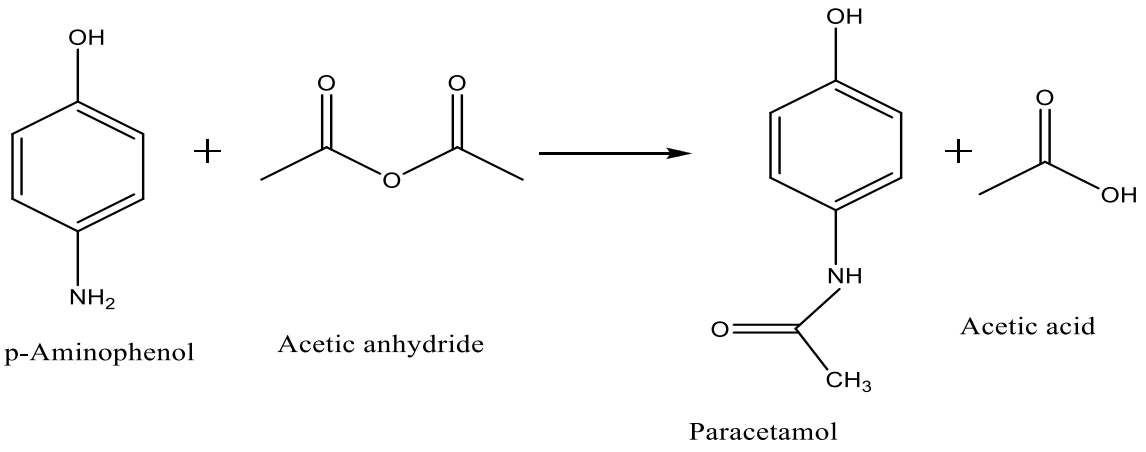
1.3 Main goal and objectives

The main goal of this thesis is the set-up of an integrated synthesis and crystallization process for the continuous manufacturing of paracetamol. The synthesis of paracetamol with different types of solvents with the addition of certain types and quantities of industrial impurities were investigated to determine their effect on the crystal growth. The science behind synthesis and crystallization of paracetamol is known and it has been studied for a long time. To the best of my knowledge it has never been coupled in one process.



Scheme 1.1 Involved steps from the manufacturing steps for paracetamol

The schematic diagram in scheme (1.1) shows the involved steps of the production of paracetamol in the usual batch process. The red block indicates the integration of the synthesis and crystallization processes.



Scheme 1.2 Reaction equation for the last step of paracetamol synthesis

For simplicity, only the last step of the paracetamol synthesis was taken into account as shown in scheme (1.2). The main reaction of 4-aminophenol with acetic anhydride gives paracetamol with acetic acid as a side product. This reaction is carried out in three different solvents; iso-amyl alcohol, 2-propanol and water. Furthermore, the reaction is carried out with and without the addition of impurities.

II. Theoretical Background

In order to build a continuous set-up, a comprehensive understanding is needed and has been studied with the science behind paracetamol as an active pharmaceutical ingredient (API), its solubility, its synthesis from p-aminophenol & the accompanying impurities for the process, as well as the crystallization and continuous manufacturing. This chapter will cover these topics to understand the experimental design in the next chapters. First, an explanation is given about paracetamol as an API from different aspects which is: history, therapeutic significant, clinical treatment and worldwide popular products.

2.1 History of Paracetamol

Paracetamol was discovered by mistake!

In the 1880's Professor Kussmaul from the Department of Internal Medicine University, treated intestinal worms with naphthalene. However, his assistants gave the patients acetanilide instead of naphthalene and that resulted in reducing fever temperature. The assistant immediately registered her invention. Shortly after it was a product on the market for a cheap price but it had many side effects.

From then on, developments have been done which led to a new compound that's less toxic than acetanilide. The new compound was named as "*Phenacetin*". However, long-term usage showed negative effects on the kidney.

The synthesis trials were kept until 1893 when Joseph von Mering invented paracetamol. Nevertheless, he thought it would cause the same side effects as acetanilide. This misleading idea stayed until the 1940's. A small amount of paracetamol was found present in patients dosed with phenacetin. In 1953, Starling-Winthrop Co. marketed paracetamol and it was more preferable than Aspirin®. It was also believed that the antipyretic and analgesic effects of phenacetin are caused by the presence of paracetamol [1, 8].

2.2 Paracetamol (Side-effects)

The main side effects of paracetamol appear on ingestion, relaxation, slight drowsiness, feeling tranquility and euphoria. These effects can also be found with other aniline analgesics, such as acetanilide and phenacetin. Unfortunately, the long-term use of paracetamol may cause it to become habitual for the patient. Paracetamol is also listed as a non-steroidal-analgesic drug without anti-inflammatory effect and subjected to the first-pass metabolism. The main withdrawal symptoms are restlessness and excitement. It's recommended that paracetamol is not taken during a meal or after the meal especially if it's high in carbohydrates [1, 8].

2.3 Clinical Treatment

The main purpose of paracetamol is to treat high fever and mild to moderate pain. Although it has been used for a long time, the mechanism of action isn't completely clear yet. It's considered one of the most popular analgesic products which are produced with a different type of weak opioids. The effective routes of administration are orally (as tablets) or rectally (as suppositories). The amount of API (active pharmaceutical ingredient) in the oral dosage form usually varies between 500-1000 mg for 4-5 hours which is 4 g in total for a daily dose. The side effects of paracetamol are agranulocytosis and other hypersensitivity reactions. It has no low dose effect but can harm the liver and renal when it's over-dosed. This is due to the accumulation of *N-acetylbenzoquinoneimine*, (referred to as NABQI). However, paracetamol is not soluble in aqueous solutions and thus it has no parenteral dosage forms [6].

2.4 Paracetamol Worldwide Popular Products

Paracetamol has many available products worldwide, including: Benuron®, Dafalgan®, Alvedon® & Panadol®. Some products come with codeine combination, like Co-Tylenol® or with Tramadol, like Zaldiar®, Tramcet® or Ultracet®. Also, it has other generic products [6].

However, without solvents and solubility studies paracetamol can't be produced. Thus, the next section will introduce the importance of solubility for APIs especially paracetamol.

2.5 Solubility

Solubility data is very important for the pharmaceutical industry in the selection of the solvent for synthesis and crystallization processes. It provides information for pure solvent or a mixture of solvents for a certain (API crystallization) process [18].

2.6 The Solubility of Paracetamol

Paracetamol has low solubility in non-polar & chlorinated hydrocarbons compounds, such as toluene and carbon tetrachloride. However, it is soluble in alcohols and has a higher solubility in medium polar compounds, such as *N*,*N*-dimethylformamide, dimethyl sulfoxide and diethylamine. Nevertheless, paracetamol has lower solubility in other polar solvents like alcohols. For this thesis, the solubility data of paracetamol in iso-amyl alcohol, 2-propanol and water was the main focus. Previous studies provided data about paracetamol solubility in the chosen solvents at a temperature of 25°C as given in table (2.1) [18].

Table 2.1 Paracetamol solubility in different solvents at 25° C, reference [18]

Solvent	**Solubility of paracetamol g/kg of solvent**
Iso-amyl alcohol	68
2-Propanol	121.15
Water	14.9

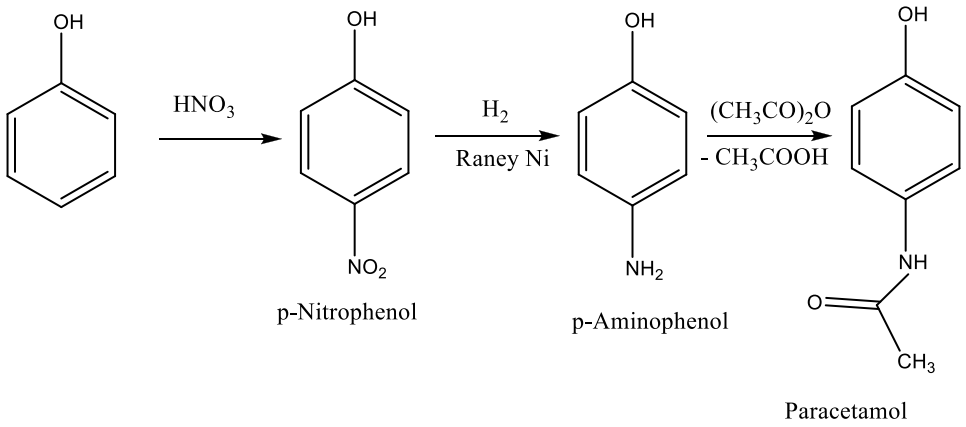
It can be concluded from these studies, that water has lowest paracetamol solubility at room temperature, which is beneficial for crystallization.

The next topic to understand, after the solubility of the API, is the synthesis process. The next section will explain the routes of synthesis for paracetamol used in industry and worldwide.

2.7 Synthesis of Paracetamol

The synthesis of paracetamol on the industrial level is accomplished in four main routes all over the world. The four routes are: 1: Phenol route, 2: p-Nitrochlorophenol route, 3: Nitrobenzene route, 4: Hoechst-Celanese process (p-Hydroxyacetophene hydrazine route). Route numbers (1, 2 (3) have been used for a longer period of time compared to route (4) which gained interest and was used in 1990. A schematic diagram explaining each reaction route is given in the following: [16, 17]

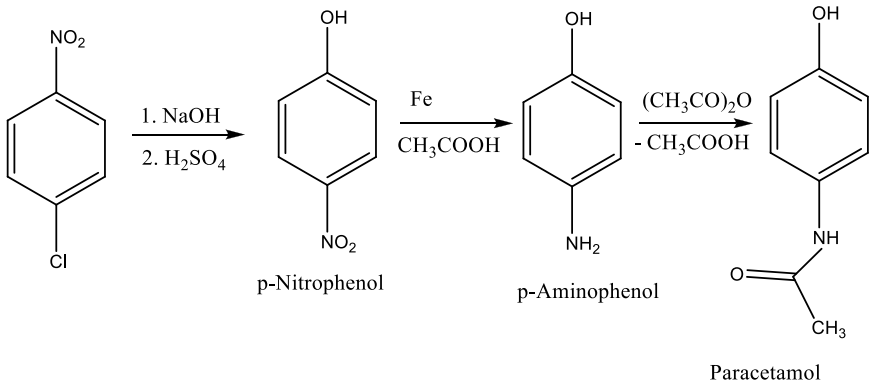
1. Phenol route [17]



Scheme 2.1 Reaction equation to produce paracetamol via the phenol route, reference [17]

Scheme (2.1) represents the reaction equation to produce paracetamol via the phenol route. The reaction is done at under a temperature less than 0°C. The phenol and sodium nitrite solution is cooled to a temperature less than 0°C and then sulphuric acid is slowly added. After that the mass p-nitrosophenol is filtered, washed with water and reduced with sodium sulphide at 50°C. The resulted p-aminophenol is purified using hydrochloric acid with activated carbon. Then the synthesis of paracetamol was done using the obtained p-aminophenol with acetic anhydride [17].

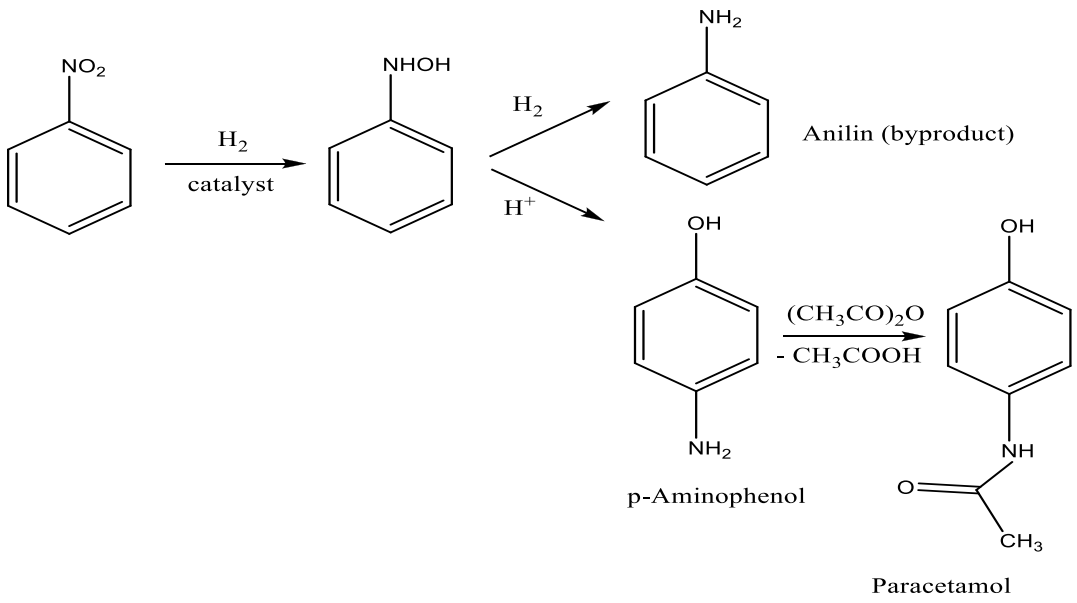
2. p-Nitrochlorobenzene route [17]



Scheme 2.2 Reaction equation to produce paracetamol via the p-nitrochlorobenzene route, reference [17]

Scheme (2.2) shows the reaction equation to produce paracetamol via the p-nitrochlorobenzene route. At a temperature of 160°C and 6 kg/cm³ pressure, the p-nitrochlorobenzene is hydrolyzed with sodium hydroxide. Then at 40°C the sodium salt of p-nitrophenol is reacted with sulphuric acid and then at 100°C with the addition of iron and acetic acid the p-nitrophenol is reduced. Afterwards, the reaction mass is filtered to get rid of iron sludge. The filtrate is cooled to 15°C and filtered again to get p-aminophenol. After the addition of acetic anhydride to p-aminophenol, the synthesis of paracetamol starts [17].

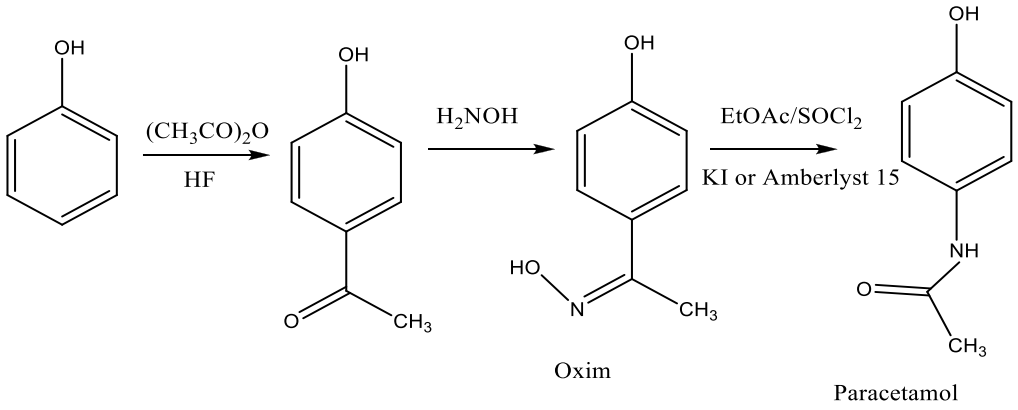
3. Nitrobenzene route [5,17]



Scheme 2.3 Reaction equation to produce paracetamol via nitrobenzene route, reference [5, 17]

Scheme (2.3) explains the reaction equation to produce paracetamol via the nitrobenzene route. Nitrobenzene is treated catalytically in the presence of acid and then the mass is neutralized. The mass is distilled to get aniline and then treated with activated carbon to get pure p-aminophenol. The produced p-aminophenol is reacted with acetic anhydride in order to synthetize paracetamol [5, 17].

4. Hoechst-Celanese process (p-Hydroxyacetophene hydrazine route) [6, 12]



Scheme 2.4 Reaction equation to produce paracetamol via Hoechst-Celanese route, reference [6, 12]

Scheme (2.4) shows the reaction equation to produce paracetamol via the Hoechst-Celanese route. The Hoechst-Celanese reaction involves two main steps which is reacting p-hydroxyacetophene with hydroxylamine salt in a base to produce p-hydroxyacetophenone oxime and then it's treated with Beckmann rearrangement catalyst. It's preferred to use thionyl chloride in liquid sulfur dioxide. The obtained p-aminophenol from this route is filtered and dried then with the addition of acetic anhydride the synthesis of paracetamol starts [6, 12].

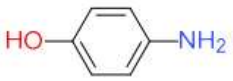
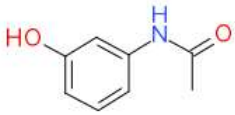
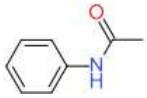
Of course there are other possible synthetic ways but they all follow the same basic principles and for simplicity the very last step will be taken into consideration in this thesis. However, in order to simulate the industrial synthesis the addition of impurities is needed and it will be done in this thesis. Thus, the next section will describe the nature of every compound in the reaction and the effect of the addition of impurities.

2.8 How do the organic impurities appear in paracetamol?

Paracetamol impurities (acetanilide, metacetamol & 4-nitrophenol) are considered process-related. Their presence depends on which synthetic route was chosen, the reagents & solvents used, reaction conditions, process design and final purification. 4-Aminophenol is the primary impurity produced in the pharmaceutical operation of paracetamol whether in the synthesis or due to storage degradation. The amount of 4-aminophenol has to be controlled due to its nephrotoxic and teratogenic effect. The degraded 4-aminophenol products are p-benzoquinone (BQ) and hydroquinone (HQ) [15].

In this work, the additives that have been used are acetanilide, metacetamol & 4-nitrophenol, more information's on these compounds are summarized in table (2.2).

Table 2.2 Known impurities in paracetamol and compounds used in this work

Name	Chemical Structure	Source	Amount	Reference
4-Aminophenol		Unreacted starting material in the last step of the synthetic route		[13]
3-Acetamidophenol (Metacetamol)		Source: 3-nitrophenol (a by-product in first step of phenol route) after hydrogenation and acetylation	4 mol%	[2]
Acetanilide		Product of acetylation of aniline, which is a byproduct in the nitrobenzene route	4 mol%	[2]
4-Nitrophenol		Unreacted starting material of the hydrogenation step of the phenol and nitrophenol route	4 mol%	[13]

2.9 Effect of impurities on the final product

The use of additives to paracetamol in distinctive amounts has shown an impressive control on water content, crystal order & energy, dissolution rate and bioavailability [2].

Metacetamol's main features are that it has an OH-group in the m-position and is a less effective blocker, while acetanilide has no para-group, no steric hindrance, no H- contribution and strongly blocks paracetamol. All in all, metacetamol is considered less effective than acetanilide as a blocker. Table (2.3) summarizes the differences between the two compounds [2]:

Table 2.3 Comparison between the effects of the impurities, reference [2]

Comparison / Compound	Metacetamol	Acetanilide
Uptake level	Higher	Lower
Degree of morphology	Higher	Appreciable
Aspect ratio shift	Higher	Not available

By defining paracetamol as a drug, its solubility, the main synthetic routes and process related impurities, the science behind the first part of the continuous process has been explained and now a small introduction about crystallization and the effect of impurities on it will be given.

2.10 Crystallization

Crystallization is a separation technique that depends on the first-order transition phase between liquid and solid, which can be achieved by using a driving force to push the system away from equilibrium in a multicomponent liquid [10].

Industrial crystallization is the industrial process that's used to investigate the product size, shape, particle size distribution & physical property. One of the major industrial challenges is controlling these properties which is necessary due to their important effect on powder flowability, bioavailability & solubilization.

The importance of crystallization in the pharmaceutical industry is due to the opportunity of investigating the physiochemical properties of API with the ability to purify, improve and tailor its properties. To achieve the desired product quality, the crystallization conditions and the desired solid phase have to be clear. Defining the process condition and solid phase will give an insight into crystal morphology, habit and crystal size distribution (CSD) which all are connected to the quality characteristics of the product. Moreover, defining the process conditions means setting the system parameters from thermodynamics, kinetics, phase diagram and the phase transition kinetics [19].

2.11 Crystal Nucleation

Crystal nucleation is the first step in the crystallization process and happens usually in the supersaturated phase. This step defines the start of the crystalline solid phase and determines the number of crystals, crystal size distribution (CSD) and it might affect the type of crystalline material formed. Crystal formation can occur in two forms, primary and secondary nucleation. Primary nucleation usually occurs from a clear solution. Secondary nucleation can occur from the presence of parent crystals. However, primary nucleation is divided into homogeneous and heterogeneous nucleation. In heterogeneous nucleation, the crystals tend to form at the surface, such as walls and interfaces. Homogeneous nucleation happens from clear solution in the absence of heterogeneous nucleation [10].

2.12 Crystal Growth

Crystal growth or crystal growth rate is the indication for the (residence) time that it takes the crystal to grow to a specific size and shape in the crystallizer. Crystal growth rate depends on many factors which are: prevailing supersaturation in the solution, temperature, pressure, composition of the mother liquor, fluid flow conditions, crystal growth history and the presence of additives or impurities [10]. Precisely taking about the effect of impurities on the paracetamol crystal growth, previous studies have shown a significant change in the crystal properties of paracetamol. A change in the crystal shape was from prismatic to rectangular, triangular & rod-like, depending on the used additive [13].

2.13 How can the impurities affect the crystal growth?

The mechanism of impurities changing the crystal morphology or the crystal growth happens by impurities adsorbing unto the crystal surface, blocking the active sites and changing the surface free energy. The effect of impurities on the crystal growth varies among different types. It can be enhancing the growth, suppressing the growth entirely or producing a selective effect which can influence the levels of crystallographic surface and the crystal habit [2].

It has been observed that the presence of impurities effected crystallization properties and it can be generally summarized as follows:

1. It has an effect on the kinetics of crystal nucleation
2. Growth morphology and dissolution
3. Suppressing nucleation can be affected by the presence of soluble impurities [19].

The presence of acetanilide has shown the following effects on paracetamol crystal [2]:

1. Decreasing the crystallization rate
2. It alters the crystal habit
3. Increases the dissolution rate and surface area
4. Nucleation behavior [2]

After explaining both processes the arising questions are why to switch to continuous manufacturing and what are the advantages of continuous manufacturing.

2.14 Continuous Manufacturing

A manufacturing process which is based on feeding and removing all the materials constantly without any interruption in order to produce a product is called continuous. The operation plan for an optional continuous manufacturing is 24/7 which means 24 h/day, 7 days/week. Continuous manufacturing isn't considered new due to its application in the oil refinery, food, and automotive industry. However, it's considered as a rather new manufacturing method in the pharmaceutical sector. Nevertheless, many unit operations are using continuous manufacturing in the pharmaceutical sector by default, such as roller compaction, tablet compression, extrusion & capsulation.

The advantageous of continuous manufacturing vary in many aspects. It has a positive effect on the environment, patient, and industry. Its main advantage is on the flexibility it provides, increasing of the supply chain, less scale-up problems, less cost and higher social impact by decreasing the environmental problems. The trend towards high-tech jobs will be preferable due to the fact of providing more job opportunities as well [3, 11].

Summary

The aim of this thesis is to set-up an integrated synthesis and crystallization process for the continuous manufacturing of paracetamol and the synthesis of paracetamol with different types of solvents with the addition of certain types and quantities of industrial impurities. In order to achieve the thesis aims, the science behind the process and paracetamol has been discussed in this chapter which is paracetamol effect as a drug, solubility data, routes of synthesis, general background about crystallization, impurities effect and continuous manufacturing.

III. Materials and Methods

This chapter will explain the used materials, equipment and procedure for HPLC-analysis, re-crystallization of 4-aminophenol, the reaction of impurities with acetic anhydride in different solvents, and the synthesis of paracetamol with and without impurities with acetic anhydride in different solvents. The crystal purity experiment and the continuous set-up will be explained in a separate section in the results and discussion chapter.

3.1 Materials

Table (3.1) shows all materials that have been used in the batch and continuous experiments, which will be explained in details in the next section.

Table 3.1 All materials that have been used with the supplier name, CAS number and purity percentage.

Material	Supplier	CAS Number	Purity (%)
Acetanilide	Sigma-Aldrich®	103-84-4	99
Acetic anhydride	Sigma-Aldrich®	108-24-7	99
4-Aminophenol	Sigma-Aldrich®	123-30-8	98
Charcoal	Chemviron Carbon®	64365-11	NA
Cyclo-hexane	Roth®	110-82-7	99.5
CTAB	Sigma-Aldrich ®	57-09-0	99
Iso-amyl alcohol	Roth®	123-51-3	98.5
Metacetamol	Sigma-Aldrich®	621-42-1	97
Methanol for HPLC	Roth®	67-56-1	99.9
4-Nitrophenol	Sigma-Aldrich®	100-02-7	99
Paracetamol	Sigma-Aldrich®	103-90-2	98-102
Phosphoric acid	Sigma-Aldrich®	7664-38-2	85 wt in solution
2-Propanol	Roth®	67-63-0	99.5
Sodium hydrosulfite	Sigma-Aldrich®	7775-14-6	82

Table 3.2 Pipe types, sizes and manufacturer for the continuous set-up

Pipe type	Pipe size (outer/inner diameter)	Manufacturer
Sillicon	4.8 x 2.4 mm	Lactan®
Sillicon	4 x 2 mm	Lactan®
PharMed	4 x 2 mm	Lactan®

Table (3.2) represents the pipe types, sizes and manufactures that were used in the continuous set-up.

Table 3.3 Devices that have been used with the manufacturer's name and device number

Device	Manufacturer	Device model
Water bath	Lauda alpha®	RA 12
Peristaltic pump	Ismatec®	ISM 833C
Peristaltic pump	Fischer scientific®	GP 1100
Hotplate	Heidolph®	MR Hei-Standard
Syringe pump	HLL®	LA 120
Hotplate	IKA®	C-MAG HS 7
HPLC	Agilent Technologies®	1100 series
Optical microscope	Leica®	DM 4000M

Table (3.3) represents the devices that have been used with manufacturer name and device number.

3.2 Methods

This section will explain the procedures that have been used to perform the designed experiments.

1. HPLC-Analysis

The HPLC analysis was developed to detect paracetamol, 4-aminophenol, acetanilide, metacetamol and 4-nitrophenol concentration (throughout the reaction time). The samples were prepared by taking 100 µl sample diluted in 1 ml diluent of methanol 5%: HPLC-water 95% and were analyzed. Using an HPLC Agilent Technologies® model 1100 series. The device was equipped with an online degasser, quaternary pump, auto-sampler, thermostatic column compartment and UV-visible diode array detector. The mobile phase consists of methanol 5%: buffer 95%. The buffer was prepared from 0.05 M KH_2PO_4, pH 6 and 0.01 M CTAB (Cetyltrimethylammonium bromide) [13]. The stationary phase consisted of octadecyl-silylated silica gel Agilent Poroshell 120 EC-C18 reversed column, 2.7 µm particle size.

The sample injection volume was 5 µl at 1 ml/min flowrate. The column temperature was 25°C and the UV-detector's wavelength was 243 nm for 10 minutes run time.

2. HPLC-Analysis (Calibration curve)

1. Around 1.833 mmol of 4-aminophenol were dissolved in 100 ml methanol 5%: HPLC-water 95% solution (Usage of ultrasound is necessary).
2. 1 ml of the stoke solution has been taken and diluted with methanol 5%: HPLC-water 95% in 10 ml volumetric flask. The same procedure was done for 20, 25 and 50 ml volumetric flask with taking 1 ml from the stoke solution and diluted in methanol 5%: HPLC-water 95% solution.
3. Same steps were repeated for 4-nitrophenol, metacetamol, acetanilide and paracetamol.

3. Re-crystallization of 4-aminophenol

1. 412.35 mmol of p-aminophenol were dissolved in 370.55 ml of 6% phosphoric acid at 85°C in a 500 ml round bottom flask.
2. 1.435 mmol of sodium hydrosulfite were added to the solution and heated to 90°C, then 3.6 g of charcoal were added to the hot solution (the amount was calculated based on the available information in example 2, reference [11])
3. The clear hot solution was decanted, filtered and treated with the charcoal using a Buchner funnel under vacuum.
4. The clear solution was left to cool down to room temperature under stirring.
5. To obtain the final white p-aminophenol crystals, the solution was filtered again.
6. The white crystals were collected and left to dry in a desiccator for one night under room temperature. (For this part, the crystallization dish should be covered in order to prevent the decomposing of p-aminophenol with light) [11]

4. The reaction of acetic anhydride with different solvents and impurities

0.966 mmol metacetamol were added to a 50 ml round bottom flask followed by 25 ml water and the mixture was stirred until everything was dissolved (the usage of ultrasound is necessary). When the whole amount was dissolved the first HPLC sample was taken, 100 µl sample was diluted in 1 ml of methanol: water (5:95) solution. Then 0.2 ml of acetic anhydride is added to the solution in the round bottom flask (a sample was taken). The solution was left to heat up to 40°C and a sample was taken every minute. After reaching the desired temperature the solution was kept under stirring for 15 minutes and a sample was taken every minute. For crystallization, the solution was cooled to 5°C for 30 minutes in the thermostat.

Note: The same procedure was done with iso-amyl alcohol instead of water. Also, the same procedure was done for acetanilide (0.954 mmol) and 4-nitrophenol (0.956 mmol).

5. The synthesis of paracetamol with and without impurities

This experiment was done with 4-aminophenol without impurities and with impurities. It has been tried 16 times, with different solvents, different amounts of acetic anhydride and the number of impurities was 4% of 4-aminophenol's used amount. It is heating up the solvent to the desired temperature followed by the addition of 4-aminophenol and acetic anhydride together. An HPLC sample was taken immediately, after dissolving and at the end of the reaction. Samples were taken every minute (or at different time intervals) for further investigations. In the tests with impurities 4 mol% of each impurity were added to 4-aminophenol prior to the experiment.

6. Continuous set-up

The continuous set-up parts, how it was built and the details to the different trials will be explained in details in section (4.10).

IV. Results and discussion

After defining the goals and aims for this thesis, explaining the science behind it and the materials and methods that have been used, this chapter will discuss the results that have been obtained. It will be divided into 10 sections: 1: Solubility data, 2: HPLC-analysis (calibration curves), 3: Challenges with 4-aminophenol, 4: Investigations of impurities behavior, 5: Synthesis of paracetamol without impurities, 6: Synthesis of paracetamol with impurities, 7: Synthesis and crystallization of paracetamol, 8: Crystal purity, 9: Influence of different solvents on particle size and shape, and 10- Continuous set-up.

4.1 Solubility data

This section will present data about paracetamol solubility in different solvents. The main focus will be iso-amyl alcohol (3-methyl-1-butanol), 2-propanol (IPA) and water.

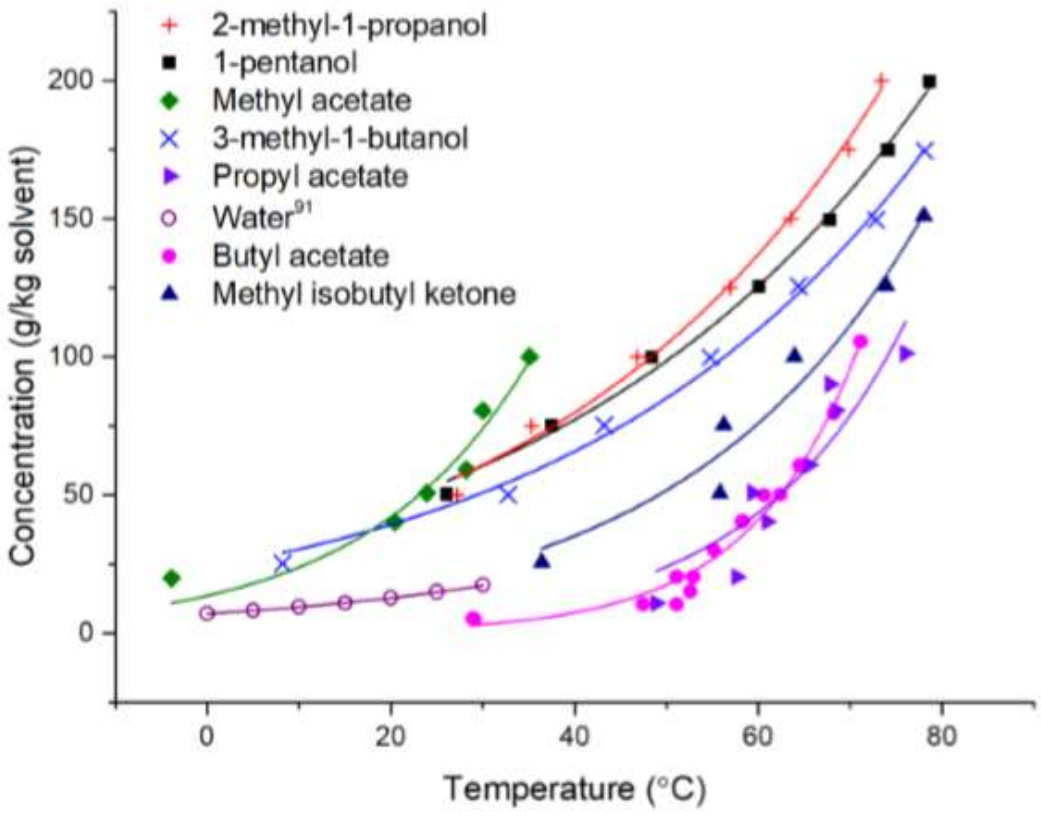


Figure 4.1 Solubility of paracetamol in different solvents along temperature, reference [4]

The solubility experiments for paracetamol in different solvents at elevated temperature were done using Crystalline® in CMAC Glasgow [4], Scotland. The aim for this test was to investigate the solubility profile of paracetamol through elevated temperature in different type of solvents. Figure (4.1), shows the paracetamol solubility in different solvents, the solvents of interest in this figure are water and iso-amyl alcohol (3-methyl-1-butanol), because water and iso-amyl alcohol showed low solubility (good for crystallization) at room temperature and high solubility at an elevated temperature (important for synthesis). For 2-propanol, it showed high solubility at room and at an elevated temperature. Thus, these three solvents were choosen for further investigations. The aim from this data to observe paracetamol concentrations at high temperatures because temperature is an important parameter for increasing solubility. However, the temperature won't exceed 80 °C because 4-aminophenol is sensitive to heat and it will decompose.

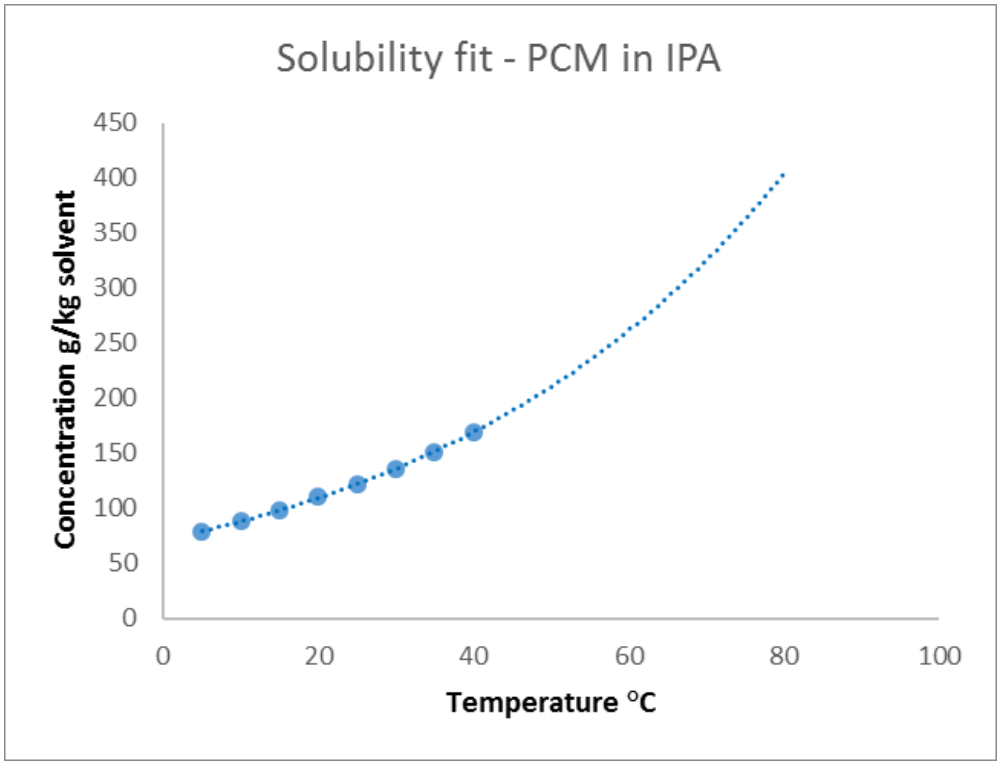


Figure 4.2 Solubility of paracetamol in 2-propanol (IPA) over temperature

For the solubility data for paracetamol in 2-propanol (isopropyl alcohol) in figure (4.2), the experiment was also done with Crystalline® in Glasgow, Scotland, performed by a former visiting scientist to TU Graz Vaclav Svoboda from CMAC Glasgow, Scotland. The solubility data of paracetamol in 2-propanol couldn't be performed at higher temperature than 60 °C due to low boiling point of the solvent.

Conclusion & summary

The aim of the solubility tests were to obtain a solubility profile over elevated temperature. The three solvents of interest in this thesis were water, iso-amyl alcohol and 2-propanol. Based on the solubility tests, which were carried out using Crystalline®, water and iso-amyl alcohol had low solubility at room temperature and higher solubility at elevated temperature. However, 2-propanol had a high solubility at room temperature and at elevated temperatures.

4.2 HPLC-Analysis (calibration curve)

Calibration curves were obtained for 4-aminophenol, paracetamol, and the impurities (4-nitrophenol, metacetamol & acetanilide). The calibration curves were prepared as shown in table (4.1) and described in (Methods and Materials).

Table 4.1 Theoretical & experimental properties for the tested material in HPLC with methanol 5%: HPLC-water 95% mobile phase

Name	Mw (g/mol)	Mass (g)	(g/ml)	Theor. Conc. (mol/l)	Dilution	Ret. time (min)	Peak area (mAU)	Obtained Conc. (mmol/l)
Actld	135.17	0.2212	0.0022	0.0164	Stock	4.164	37834.9	16.4
					1:10	4.285	3966.4	1.60
					1:20	4.290	2042.6	0.80
					1:25	4.292	1645.2	0.60
					1:50	4.300	821.9	0.30
4-NP	139.11	0.2749	0.0027	0.0198	Stock	5.636	11230.8	19.8
					1:10	5.950	1082.4	2.00
					1:20	5.987	554.6	1.00
					1:25	5.995	442.8	0.80
					1:50	6.014	221.5	0.40
MCM	135.11	0.2531	0.0025	0.0187	Stock	1.197	22296.2	19.6
					1:10	1.227	3654.8	2.00
					1:20	1.23	2045.1	1.00
					1:25	1.23	3275.4	0.80
					1:50	1.231	831.7	0.40
4-AP	109.13	0.1066	0.0011	0.0098	Stock	0.751	11944.9	9.8
					1:10	0.997	1049.9	1.0
					1:20	1.017	341.6	0.5
					1:25	0.985	295	0.4
					1:50	0.979	163.8	0.2
PCM	135.11	0.2531	0.0025	0.0187	Stock	1.197	24302.9	18.7
(with methanol:water (5:95) mobile phase)					1:10	1.227	3584	1.90
					1:20	1.230	1788	0.90
					1:25	1.230	1422	0.70
					1:50	1.231	699	0.40

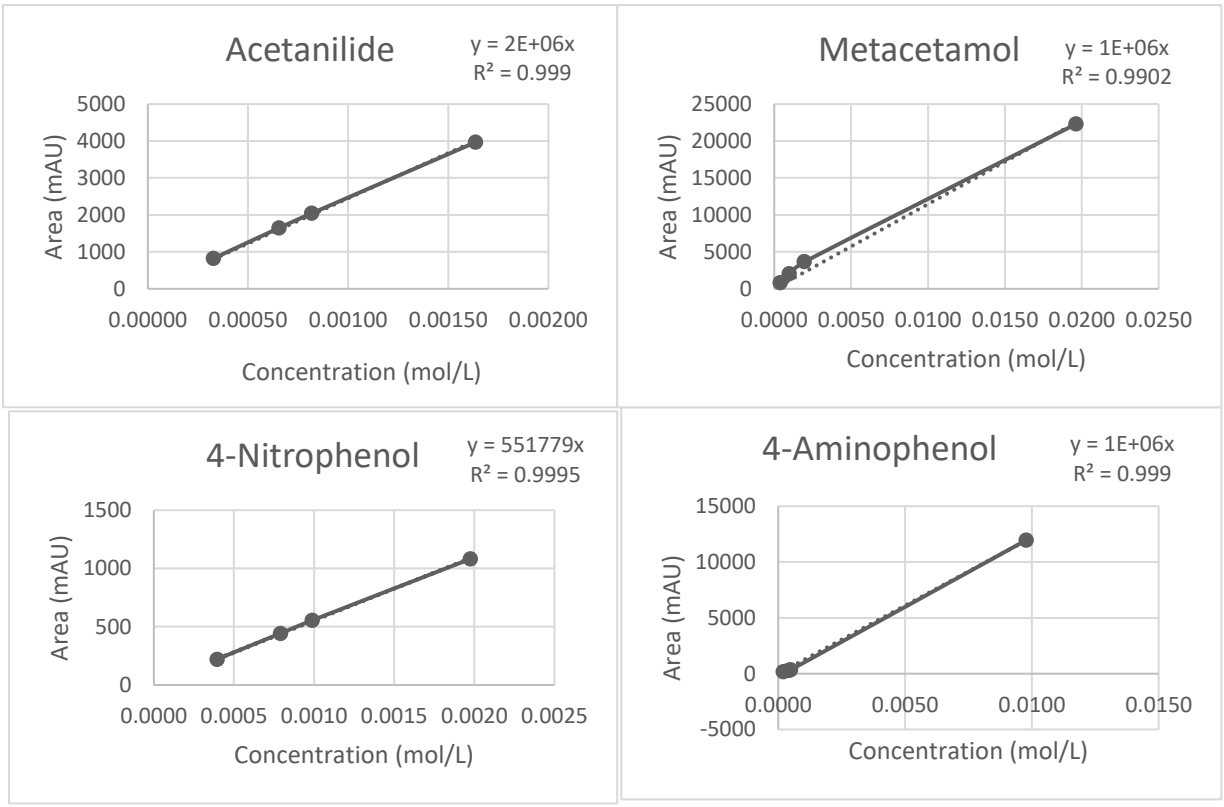


Figure 4.3 Calibration curves for acetanilide, metacetamol, 4-nitrophenol & 4-aminophenol using 5%MeOH/95%H_2O

For every compound, a stock solution was prepared and from this solution, a 1 ml amount was diluted in 10-20-25-50 ml of Methanol: water diluent separately. From every dilution, a 1 ml sample was transferred to HPLC vials in order to be tested. The retention times were almost the same for every dilution from the same material with ascendant concentrations and areas. The area for every solution was plotted to its concentration to get the calibration curve as observed in figure (4.3 & 4.4). Also, the calibration factor for every compound is available in table (4.2).

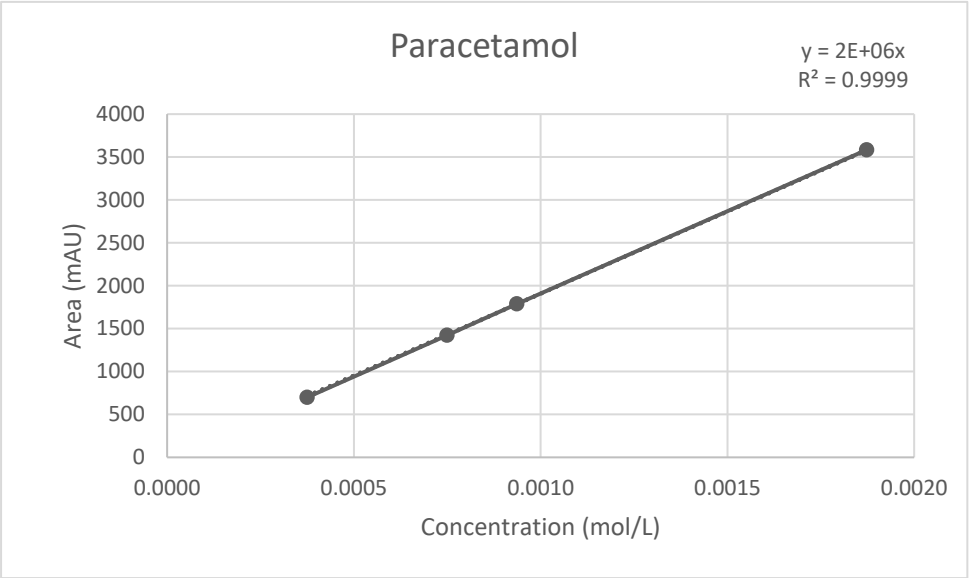


Figure 4.4 Calibration curve for paracetamol using 5%MeOH/95%H_2O

As shown in figure (4.3 & 4.4), the regression for all the compounds was almost 1 and that's shows a good trend for the linear graphs. The calculated equations and calibration factors (table (4.2)) will be used in further calculations to obtain the concentration of the reactant (4-aminophenol), the impurities (acetanilide, metacetamol & 4-nitrophenol) and product (paracetamol).

Table 4.2 Calibration factors obtained from the mobile phase methanol 5%: HPLC-water 95%

Compound	**Calibration factor ((mAU)* L/mol)**
Acetanilide	2000000
Metacetamol	1000000
4-Nitrophenol	551779
4-Aminophenol	1000000
Paracetamol	2000000

Table 4.3 Theoretical & experimental properties for the tested material in HPLC with methanol: buffer mobile phase

Name	Mw (g/mol)	Mass (g)	(g/ml)	Theor. Conc. (mol/l)	Dilution	Ret. time (min)	Peak area (mAU)	Obtained Conc. (mmol/l)
Actld	135.17	0.2212	0.0022	0.0164	Stock	2.838	5593.1	15.7
					1:10	2.92	550.3	1.60
					1:20	2.915	268.2	0.80
					1:25	2.911	238.5	0.60
					1:50	2.91	119.5	0.30
MCM	135.11	0.2531	0.0025	0.0187	Stock	2.757	28064.7	13.9
					1:10	2.908	2625.7	1.40
					1:20	2.916	1460.7	0.70
					1:25	2.915	1126.9	0.60
					1:50	2.92	545.6	0.30
MCM + Actld	135.11 , 135.17	0.1082, 0.1107	0.0007, 0.0008 # of moles	0.015	Stock	2.855	33887.3	15.3
					1:10	2.892	3662.1	1.50
					1:20	2.902	1809.3	0.80
					1:25	2.907	1292.3	0.60
					1:50	2.914	683.9	0.30
4-AP	109.13	0.1066	0.0011	0.0098	Stock	0.74	10595.4	9.80
					1:10	0.75	1276.5	1.00
					1:20	0.75	686.3	0.50
					1:25	0.75	545.3	0.40
					1:50	0.75	334.2	0.20
PCM	135.11	0.2172	0.0022	0.0161	Stock	1.239	23272.3	16.1
(with methanol:KH_2PO_4 buffer 5:95 mobile phase)					1:10	1.247	2948.8	1.60
					1:20	1.251	1534.2	0.80
					1:25	1.253	1197.3	0.60
					1:50	1.254	607.7	0.30

Although calibration curves were obtained, problems with the HPLC column occurred and a new mobile phase was needed to continue the further investigations. This method was modified from the reference [14], where the mobile phase was methanol 60%: buffer 40%, the buffer was prepared from 0.05 M KH_2PO_4, pH 6 and 0.01 M CTAB (Cetyltrimethylammonium bromide). But this composition was modified to 50:50, 25:75, 10:90 and last trial was with 5:95. Last composition was the most successful, it detected the 4-aminophenol and paracetamol without damaging the column or giving overlapped peaks. However, it did not detect 4-nitrophenol and metacetamol & acetanilide were detected in one peak. The new calibration curves concentrations are explained in table (4.3).

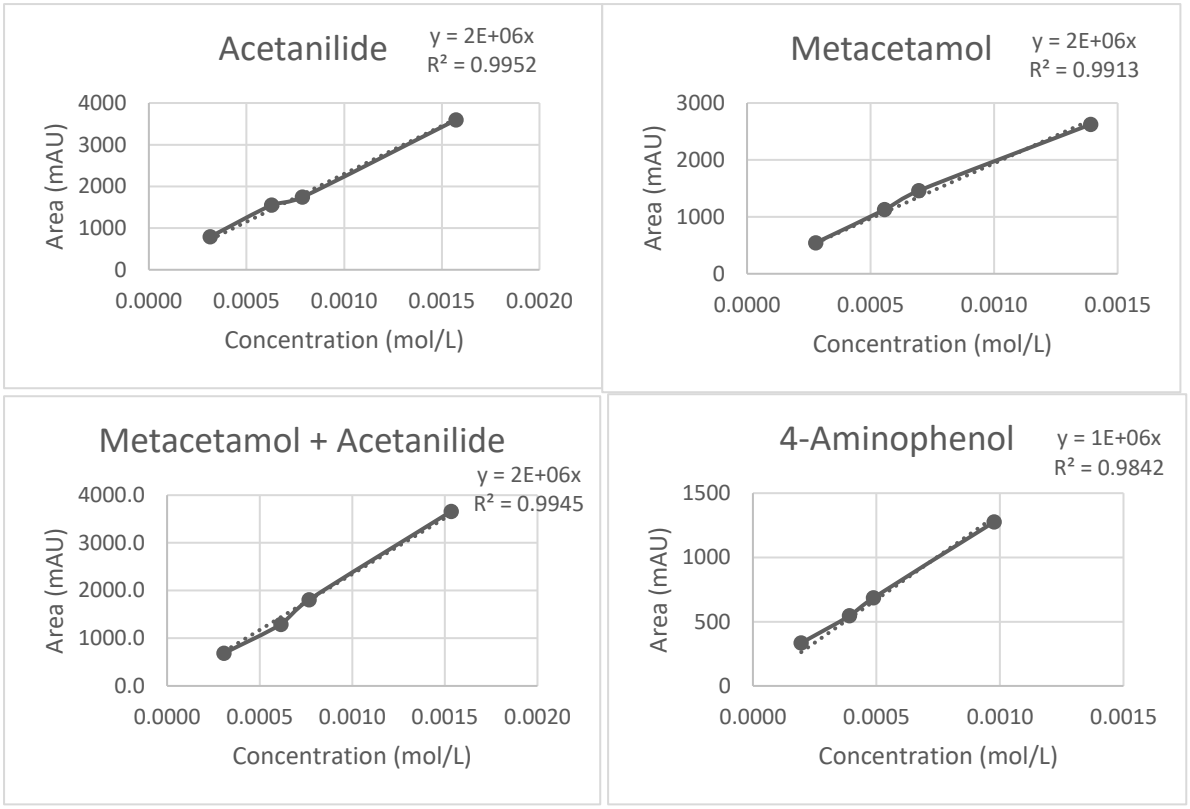


Figure 4.5 New calibration curves for acetanilide, metacetamol, acetanilide and metacetamol & 4-aminophenol using 5% MeOH/95% buffer

The new graphs showed (figure (4.5)) linear trend and a regression of almost 1. The calibration factor values were almost the same as before as shown in table (4.4). The metacetamol and acetanilide calibration curve was obtained by preparing half amount from each compound and diluted in 100 ml diluent of methanol and water for HPLC.

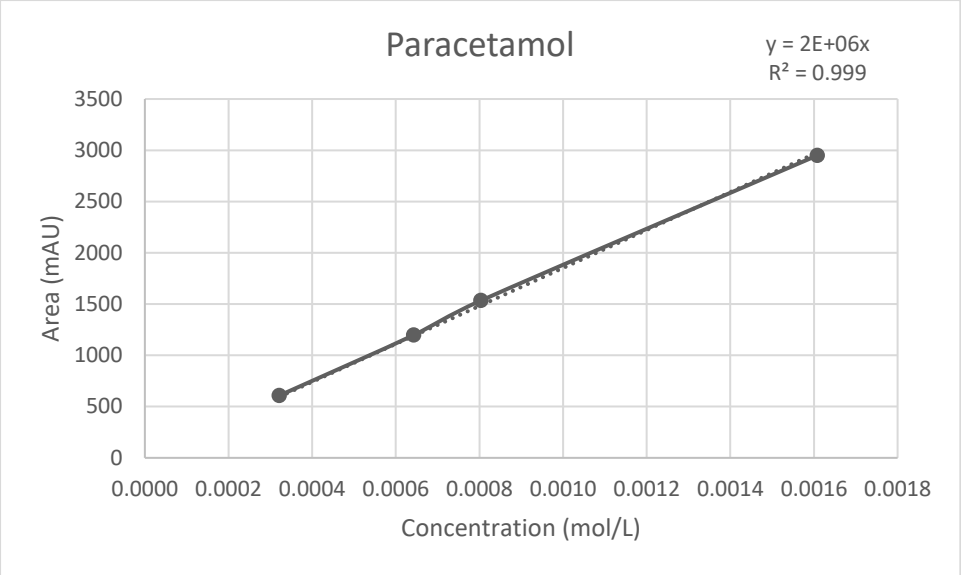


Figure 4.6 New calibration curve for paracetamol using 5% MeOH/95% buffer

Also for paracetamol, the regression was almost 1 as observed in figure (4.6). The calibration factors didn't differ a lot from the old calibration factors as shown in table (4.4) but the HPLC column was safe and thus this method was implemented for further investigations although the 4-nitrophenol calibration curve couldn't be obtained.

Table 4.4 Calibration factors obtained from the mobile phase methanol 5%: buffer 95%

Compound	**Calibration factor ((mAU)* L/mol)**
Acetanilide	2000000
Metacetamol	2000000
Metacetamol + Acetanilide	2000000
4-Aminophenol	1000000
Paracetamol	2000000

Conclusion and summary

The HPLC method using methanol 5%: HPLC-water 95% was successful to obtain all calibration curves but not safe enough for the column. The new method methanol 5%: buffer 95% was safe for the column but did not obtain the calibration curve for 4-nitrophenol. However, it was successful for 4-aminophenol, paracetamol, metacetamol and acetanilide.

4.3 Challenges with 4-aminophenol

Before starting with the synthesis of paracetamol out of 4-aminophenol, solutions for 4-aminophenol challenges had to be found. The challenges are: decomposition by heat and light, high solid handling while pumping and impurities. The solution for high solid handling was milling of 4-aminophenol and obtaining a vibration feed rate instead of having the 4-aminophenol in suspension (for continuous set-up). The decomposition by heat & light and impurities challenges were solved by re-crystallization of 4-aminophenol experiment. Starting with milling 4-aminophenol, a liquid nitrogen was used while milling 4-aminophenol in a mortar and pestle. It was possible to do it with a mortar and pestle for small amounts but not for big amounts above 5 grams. For the vibration feeder, it was impossible to have a steady feeding rate due to the blocking of 4-aminophenol in the funnel opening.

The re-crystallized 4-aminophenol experiment was built based on the US patent (no. 3,703,598 Nov. 21, 1972). The patent presents purification methods for the treatment of crude p-aminophenol and p-aminophenol obtained by reduction of nitrobenzene. Thus, to reduce the amount of 4-nitrophenol, black tars and color bodies. A combination between example 1 & 2 was done to obtain this section experimental procedure [7]. The recrystallization reaction components were done as in the table (4.5). (Procedure is available in chapter 3)

Table 4.5 Batch trials for re-crystallization 4-aminophenol

Batch number	(1)	(2)	(3)
Mass of charcoal (g)	0.3867	0.300	0.324
Mass of 4-AP	4.506	4.506	4.490
Mass of $Na_2S_2O_4$	0.0248	0.0248	0.0247
Volume of phosphoric acid (ml)	37.055	37.055	37.055
Mass of re-crystallized 4-AP (g)	2.616	2.200	3.927
Yield %	58.055	48.823	87.266

After recrystallizing 4-aminophenol, filtering and drying the re-crystallized 4-aminophenol, 5 mg of each crystal batch was diluted with 100 ml (methanol 5%: HPLC-water 95%) diluent then 1 ml was withdrawn and diluted in 20 ml diluent in order to check the purity of 4-aminophenol. The color of crude 4-aminophenol before was pink and the re-crystallized 4-aminophenol was white.

Conclusion

Milling and obtaining a constant vibration feed rate for 4-aminophenol was impossible due to the fast decomposition by light and heat. However, re-crystallization of 4-aminophenol experiments gave interesting results in HPLC. The HPLC gave only peaks for 4-aminophenol and thus the re-crystallized 4-aminophenol was tested for the synthesis of paracetamol.

4.4 Investigations of impurities behavior

The aim from the following reactions was to investigate the reaction of the impurities with acetic anhydride in water & iso-amyl alcohol and to investigate the solubility (crystallization) of the impurities after the reaction. The analysis of samples was performed using the mobile phase (methanol 5%: HPLC-water 95%).

4.4.1 Investigation of the reaction of acetanilide with acetic anhydride in different solvents

The investigation for the reaction of acetanilide with different solvent was done in order to check if acetanilide reacts with acetic anhydride. Also, to investigate if it would stay in solution or it would crystallize after cooling for one night using the fridge with 5°C.

4.4.1.1 Investigation of the reaction of acetanilide with acetic anhydride in water

The first investigation was done for acetanilide with acetic anhydride in water. The suggested amount of acetic anhydride was 2 mmol. The molar ratio of acetic anhydride: acetanilide is 2:1. This small amount was suggested to start the experiments with.

Table 4.6 Acetanilide reaction information with acetic anhydride in water

Material	Water	Acetic Anhydride	Acetanilide
State	Liquid	Liquid	Solid
Mass (g)	25	-	0.128
Volume (ml)	25	0.2	-
Molecular weight (g/mol)	18.02	102.09	135.17
Number of moles (mol)	1.39	0.002	0.001
Density (Total volume) [g/ml]	0.99	0.009	0.005
Concentration (Total volume) [mol/L]	55.07	0.08	0.04
Temperature (°C)	40	-	-
Reaction time (minute)	20	-	-
Color	Clear solution		

As shown in table (4.6), the reaction was performed at 40 °C by heating up the water and then the addition of acetanilide and acetic anhydride. The reaction was left for 20 minutes and a sample was taken every minute. The reaction color was colorless and didn't change with time. The samples didn't show any crystals after cooling for one night in the fridge at 5°C.

Table 4.7 Reaction sampling at different time intervals for acetanilide with acetic anhydride in water reaction

Time (min)	Sample weight (g)	MeOH:H_2O(g)	Dilution factor	Actld peak (mAU), tr= 3.266 (min)	C Actld (mol/L)
0	0.10	1.03	11.82	8463.00	0.05
1	0.10	1.03	11.37	7673.00	0.04
2	0.10	1.03	11.11	8089.90	0.04
3	0.10	1.03	11.49	7925.20	0.05
4	0.10	1.05	11.76	7632.70	0.04
5	0.09	1.02	12.15	7460.10	0.05
6	0.10	1.01	11.30	8038.70	0.05
7	0.09	1.01	11.72	7774.80	0.05
8	0.10	1.01	11.22	8139.00	0.05
9	0.09	1.02	12.12	7385.70	0.04
10	0.04	0.92	22.50	3975.80	0.04
11	0.09	0.97	11.63	7634.60	0.04
12	0.10	0.89	10.31	8904.60	0.05
13	0.09	0.90	10.51	8565.30	0.05
14	0.10	0.99	11.39	8024.50	0.05
15	0.10	0.98	11.22	8064.10	0.05
16	0.09	0.99	11.53	7893.70	0.05
17	0.10	0.99	11.15	8201.60	0.05
18	0.09	0.98	11.43	7975.60	0.05
19	0.09	1.01	11.77	7766.70	0.05

As presented in table (4.7), the first sample was taken at time 0. Immediately after the addition of acetanilide and acetic anhydride. Afterwards, a 100 µl sample was taken every minute. Then diluted with a 1 ml methanol: HPLC water diluent (5:95). Comparing the reaction information about acetanilide concentration in table (4.6 & 4.7) and figure (4.7), the concentration of acetanilide showed a constant values over time, thus apparently no reaction of acetanilide with acetic anhydride occurred.

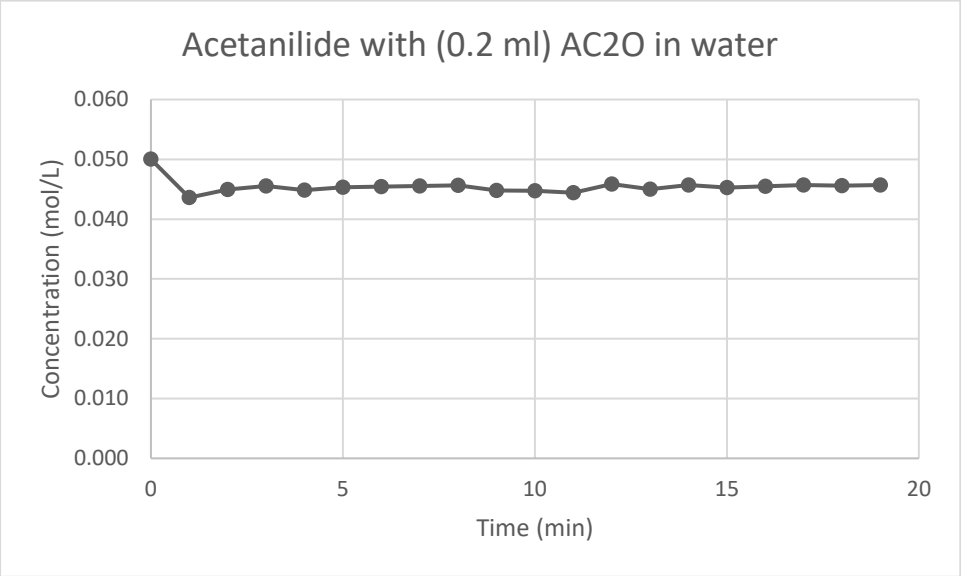


Figure 4.7 Acetanilide concentration during reaction with acetic anhydride in water over time

From figure (4.7) it can be seen the constant concentration over time. Which means there was no reaction over time and thus acetanilide didn't react with acetic anhydride.

4.4.1.2 Investigation of the reaction of acetanilide with acetic anhydride in iso-amyl alcohol

Because of the results from the previous reaction which showed no reaction between acetanilide and acetic anhydride in water, the interest was shifted towards testing the reaction in another solvent which is iso-amyl alcohol. The amount of acetic anhydride increased to 20 mmol which is the same amount that will be used in full synthesis reaction with 4-aminophenol and the impurities.

Table 4.8 Acetanilide reaction information with acetic anhydride in iso-amyl alcohol

Material	Iso-amyl alcohol	Acetic Anhydride	Acetanilide
State	Liquid	Liquid	Solid
Mass (g)	-	-	0.129
Volume (ml)	25	2	-
Molecular weight (g/mol)	88.15	102.09	135.17
Number of moles (mol)	0.23	0.02	0.001
Density (Total volume) [g/ml]	0.75	0.08	0.005
Concentration (Total volume) [mol/L]	8.51	0.78	0.04
Temperature (°C)	80	-	-
Reaction time (minute)	40	-	-
Color	Clear solution		

The amount of solvent and acetanilide is the same as before but the solvent type was changed to iso-amyl alcohol as given in table (4.8). Also, the reaction temperature was 80 °C, performed for 40 minute and there was no color change.

Table 4.9 Reaction sampling at different time intervals for acetanilide with acetic anhydride in iso-amyl alcohol reaction

Time (min)	**Sample weight (g)**	**MeOH:H_2O(g)**	**Dilution factor**	**Actld peak (mAU), tr= 3.148 (min)**	**C Actld (mol/L)**
0	0.07	0.94	14.04	4353.2	0.03
2	0.08	0.94	13.04	4552.7	0.03
12	0.07	0.93	13.92	3916.5	0.03

In this reaction, the results are more constant than in water. Nevertheless, a double peak in the HPLC appeared. Reaction concentration is available in table (4.9).

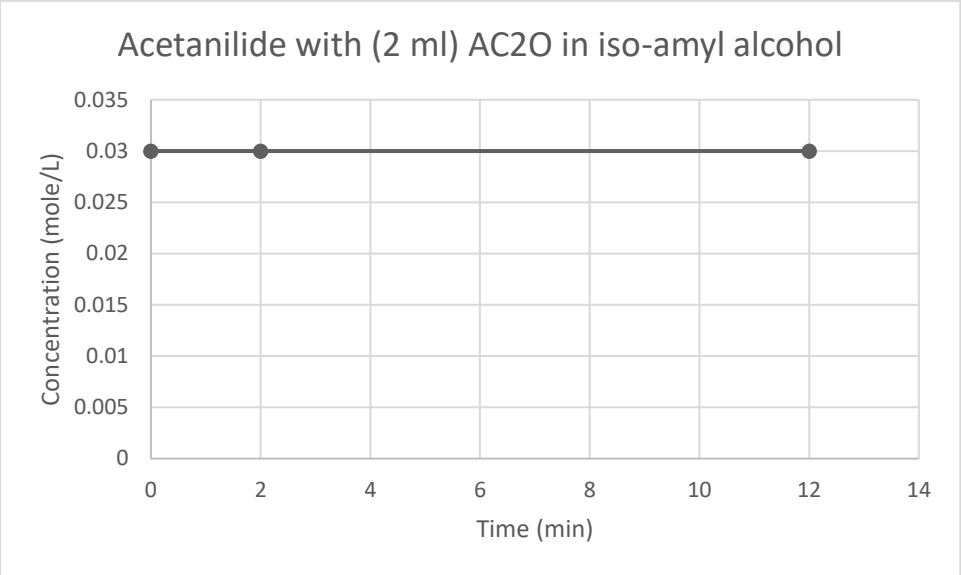


Figure 4.8 Acetanilide concentration during reaction with acetic anhydride in iso-amyl alcohol over time

The chosen times from this reaction showed constant amounts of acetanilide and no reaction with acetic anhydride in iso-amyl alcohol as sown in figure (4.8). The starting amount of acetanilide was the same as the obtained results from HPLC. The acetanilide stayed soluble after the reaction and with cooling there was no presence for crystals.

Conclusion

The reaction of acetanilide with acetic anhydride with water and iso-amyl alcohol didn't show any reaction. Also, the obtained solution that was kept in fridge at 5°C for cooling didn't show any crystal appearance. Thus, this impurity stayed in solution after reaction.

4.4.2 Investigation of the reaction of metacetamol reaction with acetic anhydride in different solvents

Metacetamol was chosen as the second impurity in order to check its reaction with acetic anhydride in different solvents. The expected outcomes are to investigate if there is a reaction between metacetamol and acetic anhydride. Also, to check if it will stay soluble after reaction or it will crystallize after cooling in fridge at 5°C for one night.

4.4.2.1 Investigation of the reaction of metacetamol reaction with acetic anhydride in water

The first investigation for metacetamol was done with a molar ratio 2:1 of acetic anhydride in water. The aim of this experiment was to investigate metacetamol reaction and the crystallization in water after reaction.

Table 4.10 Metacetamol reaction information with acetic anhydride in water

Material	Water	Acetic Anhydride	Metacetamol
State	Liquid	Liquid	Solid
Mass (g)	-	-	0.144
Volume (ml)	25	0.2	-
Molecular weight (g/mol)	18.02	102.09	151.16
Number of moles (mol)	1.39	0.002	0.001
Density (Total volume) [g/ml]	0.99	0.009	0.006
Concentration (Total volume) [mol/L]	55.05	0.08	0.04
Temperature (°C)	40	-	-
Reaction time (min)	22	-	-
Color	Clear solution		

The reaction was carried out at 40 °C for 22 minutes and there was no change in color. The amount of metacetamol from HPLC was double in the amount comparing it with the theoretical concentration, given in table (4.10&4.11). Again that's can be explained due to the inconveniently of the old mobile phase. Although, the difference between the theoretical and experimental amounts, the metacetamol concentration over time showed a constant behavior as presented in figure (4.9). Thus, apparently no reaction of metacetamol with acetic anhydride in water occured.

Table 4.11 Reaction sampling at different time intervals for metacetamol with acetic anhydride in water

Time (min)	Sample weight (g)	MeOH:H_2O(g)	Dilution factor	MCM peak (mAU), tr= 8.42 (min)	C MCM (mol/L)
0	0.10	1.01	11.05	7145.1	0.08
1	0.10	1.01	11.40	6830.3	0.08
2	0.10	1.04	11.17	6955.8	0.08
3	0.10	1.01	11.28	7022.9	0.08
4	0.10	1.01	11.11	7086.6	0.08
5	0.10	1.01	11.27	6951.5	0.08
6	0.10	1.02	11.42	6807.4	0.08
7	0.19	1.02	6.28	12477.8	0.08
8	0.10	1.02	11.54	6922.9	0.08
9	0.10	1.02	11.37	7011.6	0.08
10	0.10	0.94	10.56	6880.7	0.07
11	0.09	1.01	11.91	6555.4	0.08
12	0.10	1.02	11.39	6875.2	0.08
14	0.09	1.02	12.26	6417.5	0.08
15	0.10	1.01	11.36	6926.9	0.08
16	0.10	1.01	11.30	7006.6	0.08
19	0.09	1.04	12.23	6857.2	0.08
20	0.09	1.03	11.86	6932.4	0.08

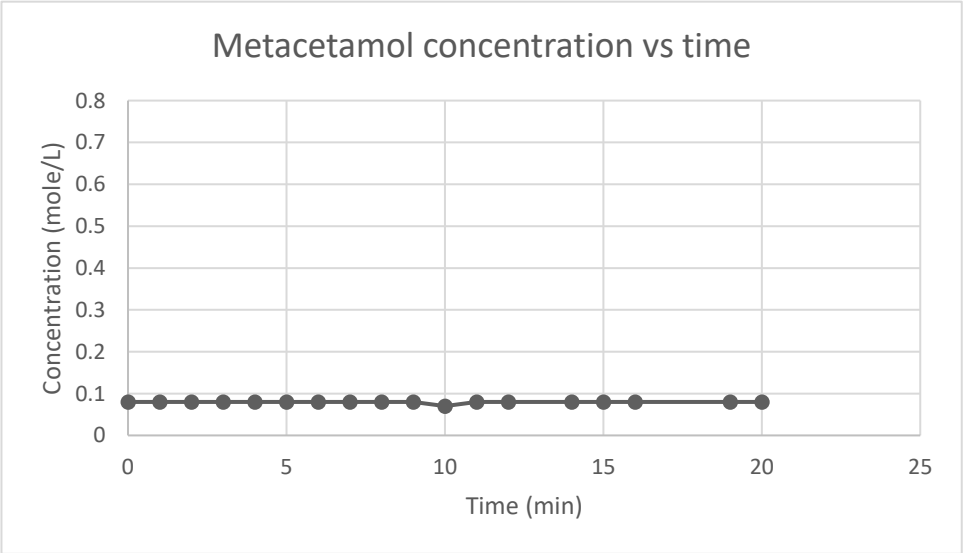


Figure 4.9 Reaction of metacetamol with acetic anhydride in water over time

4.4.2.2 Investigation of metacetamol reaction with acetic anhydride in iso-amyl alcohol

In this experiment, the amount of acetic anhydride was increased with a molar ratio 20:1. The solvent was changed to iso-amyl alcohol with the same amounts of water.

Table 4.12 Metacetamol reaction information with acetic anhydride in iso-amyl alcohol

Material	Isoamyl alcohol	Acetic Anhydride	Metacetamol
State	Liquid	Liquid	Solid
Mass (g)	-	-	0.146
Volume (ml)	25	2	-
Molecular weight (g/mol)	88.15	102.09	151.16
Number of moles (mol)	0.23	0.02	0.001
Density (Total volume) [g/ml]	0.75	0.08	0.005
Concentration (Total volume) [mol/L]	8.51	0.78	0.04
Temperature (°C)	80	-	-
Reaction time (min)	30	-	-
Color	Clear solution		

The reaction was carried out at 80 °C, stayed for 30 minutes and there was no change in color as shown in table (4.12). The amounts of metacetamol were almost constant with time. Some points showed fluctuation in amounts due to human error while sampling using the pipette (sample at time 16 min) as presented in table (4.13). However, most of the sample concentration showed constant values as shown in figure (4.10). Therefore, apparently there was no reaction between metacetamol and acetic anhydride in iso-amyl alcohol and even after cooling there was no presence for crystal formation.

Table 4.13 Reaction sampling at different time intervals for metacetamol with acetic anhydride in iso-amyl alcohol reaction

t (min)	Sample weight (g)	MeOH:H_2O(g)	Dilution factor	MCM Peak (mAU), tr= 2.636	C MCM (mol/L)
0	0.07	1.03	15.25	1462.2	0.02
2	0.11	1.01	9.86	2230.9	0.02
4	0.14	1.03	8.44	3527.2	0.03
6	0.07	1.05	16.69	1945.2	0.03
8	0.07	1.05	16.63	1701.2	0.03
10	0.07	1.03	15.74	2172.7	0.03
11	0.07	1.04	16.82	1382.0	0.02
12	0.07	1.05	15.82	1266.9	0.02
13	0.07	1.03	15.16	1422.7	0.02
14	0.08	1.01	14.32	1567.7	0.02
15	0.07	1.05	16.47	1450.8	0.02
17	0.07	1.08	16.85	1423.0	0.02
18	0.14	1.04	8.25	2096.2	0.02
19	0.07	1.05	15.85	1376.0	0.02
20	0.06	1.04	18.97	1334.8	0.03
21	0.07	1.04	16.58	1417.4	0.02
22	0.08	0.96	13.73	2186.2	0.03
23	0.08	1.04	13.73	1176.3	0.02
24	0.08	1.05	14.50	1299.3	0.02
25	0.06	1.04	19.16	1837.1	0.04

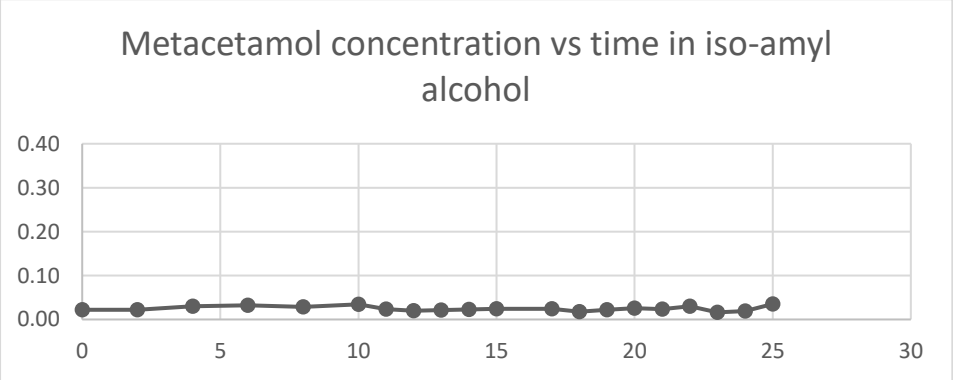


Figure 4.10 Metacetamol concentration with acetic anhydride in iso-amyl alcohol over time

Conclusion

The reaction of metacetamol with acetic anhydride in water and iso-amyl alcohol didn't show any reaction and the obtained solution didn't crystallize after cooling in the fridge. Thus, the metacetamol is proved not to react and to stay soluble after cooling to 5°C for 24 h.

4.4.3 Investigation of 4-nitrophenol reaction with acetic anhydride in different solvents

4-Nitrophenol is the third impurity and it will be tested if it reacts with acetic anhydride in different solvents (water and iso-amyl alcohol). Also, to investigate if it will crystallize after cooling or stay soluble in solution.

4.4.3.1 Investigation of 4-nitrophenol reaction with acetic anhydride in water

The first investigation for 4-nitrophenol was done with a molar ratio of 2:1 acetic anhydride in water. The aim was investigate if 4-nitrophenol would react with acetic anhydride in water.

Table 4.14 4-Nitrophenol reaction information with acetic anhydride in water

Material	Water	Acetic Anhydride	4-Nitrophenol
State	Liquid	Liquid	Solid
Mass (g)	-	-	0.132
Volume (ml)	25	0.2	-
Molecular weight (g/mol)	18.02	102.09	139.11
Number of moles (mol)	1.39	0.002	0.001
Density (Total volume) [g/ml]	0.99	0.009	0.005
Concentration (Total volume) [mol/L]	55.07	0.08	0.04
Temperature (°C)	40	-	-
Reaction time (min)	18	-	-
Color	Light yellow		

The reaction was carried out at 40 °C, lasted for 18 minutes and the color started light yellow and didn't change with time. The concentration of 4-nitrophenol was almost constant and within the initial concentration .However, the HPLC gave two peaks. The first peak, at tr= 8.412 from the time (0-7 min) and the second peak at tr= 8.223 from the time (8-17 min). The retention time between the two peaks didn't show a huge difference and the sum between the two concentration gave the same concentration from the peak tr= 8.42 as shown in table (4.15). All the results show constant concentration compared to the starting material concentration presented in table (4.14). The constant concentration over time is presented in figure (4.11).

Table 4.15 Reaction sampling at different time intervals for 4-nitrophenol with acetic anhydride in water reaction

Time (min)	Sample weight (g)	MeOH: H_2O(g)	Dilution factor	4-NP Peak (mAU), tr= 8.42 (min)	4-NP Peak (mAU), tr= 8.412 (min)	4-NP Peak (mAU), tr= 8.223 (min)	4-NP Conc., tr (8.420-8.412) (min)	4-NP Conc., tr (8.420-8.223) (min)
0	0.09	1.02	12.35	1796.8	-	-	0.040	0.040
1	0.09	1.05	12.70	1679.4	-	-	0.039	0.039
2	0.10	1.04	11.94	1734.1	-	-	0.038	0.038
3	0.09	1.04	12.33	1679	-	-	0.038	0.038
4	0.09	1.06	12.73	1685.4	-	-	0.039	0.039
5	0.09	1.04	12.41	1680.2	-	-	0.038	0.038
6	0.09	1.04	12.50	1683.8	-	-	0.038	0.038
7	0.09	1.04	12.50	1737.9	-	-	0.039	0.039
8	0.09	1.06	12.94	-	1164	438.1	-	0.038
9	0.09	1.05	12.44	-	1201	470	-	0.038
10	0.08	1.04	13.68	-	1013.9	467.5	-	0.037
11	0.09	1.05	13.00	-	1120.7	464.6	-	0.037
12	0.10	1.05	11.77	-	1230.9	511.9	-	0.037
13	0.10	1.05	12.01	-	1211.7	519.2	-	0.038
14	0.08	1.04	14.38	-	989.7	455.5	-	0.038
15	0.09	1.06	12.82	-	1110.8	509.5	-	0.038
16	0.09	1.04	12.16	-	1126.6	527.9	-	0.036
17	0.06	1.04	19.05	-	729.5	389.7	-	0.039

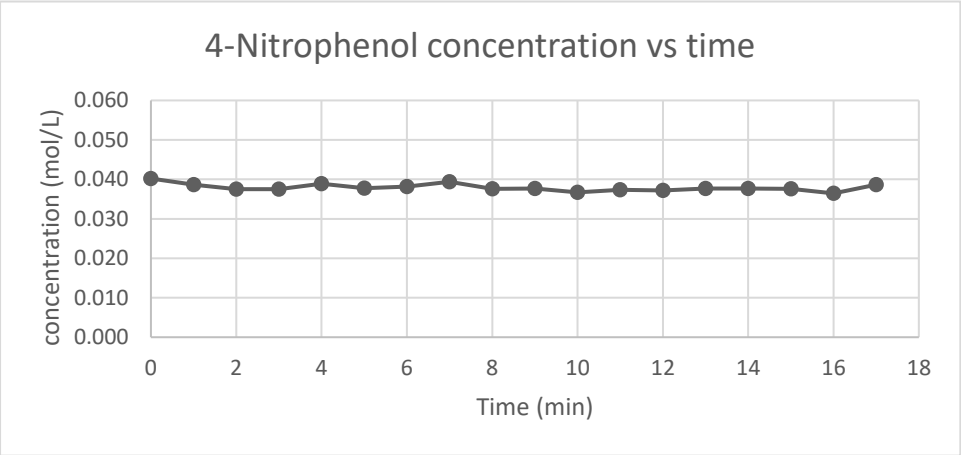


Figure 4.11 Reaction of 4-nitrophenol with acetic anhydride in water over time

4.4.3.2 Investigation of 4-nitrophenol reaction with acetic anhydride in iso-amyl alcohol

The second experiment was with a molar ratio 20:1 acetic anhydride in the same amount of iso-amyl alcohol and 4-nitrophenol.

Table 4.16 4-Nitrophenol reaction information with acetic anhydride in iso-amyl alcohol

Material	Isoamyl alcohol	Acetic Anhydride	4-Nitrophenol
State	Liquid	Liquid	Solid
Mass (g)	-	-	0.132
Volume (ml)	25	2	-
Molecular weight (g/mol)	88.15	102.09	139.11
Number of moles (mol)	0.23	0.02	0.001
Density (Total volume) [g/ml]	0.750	0.080	0.005
Concentration (Total volume) [mol/L]	8.51	0.78	0.04
Temperature (°C)	80	-	-
Reaction time (min)	22	-	-
Color	Light yellow		

Table 4.17 Reaction sampling at different time intervals for 4-nitrophenol with acetic anhydride in iso-amyl alcohol

Time (min)	**Sample weight (g)**	**MeOH:H_2O(g)**	**Dilution factor**	**4-NP peak (mAU), tr= 7.35**	**4-NP Conc. (mol/L)**
0	0.07	1.00	16.03	219.0	0.006
2	0.07	1.01	14.47	278.0	0.007
7	0.07	1.00	15.25	278.9	0.008
22	0.08	1.01	14.07	237.0	0.006

As shown in table (4.16), the reaction was carried out at 80 ℃ for 22 minute and the color was light yellow and didn't change with time. The concentration of 4-nitrophenol over time is shown in table (4.17) and figure (4.12). The obtained concentrations from HPLC showed higher concentration from the expected concentration and that's cannot be reliable and it might be due to the instability of HPLC.

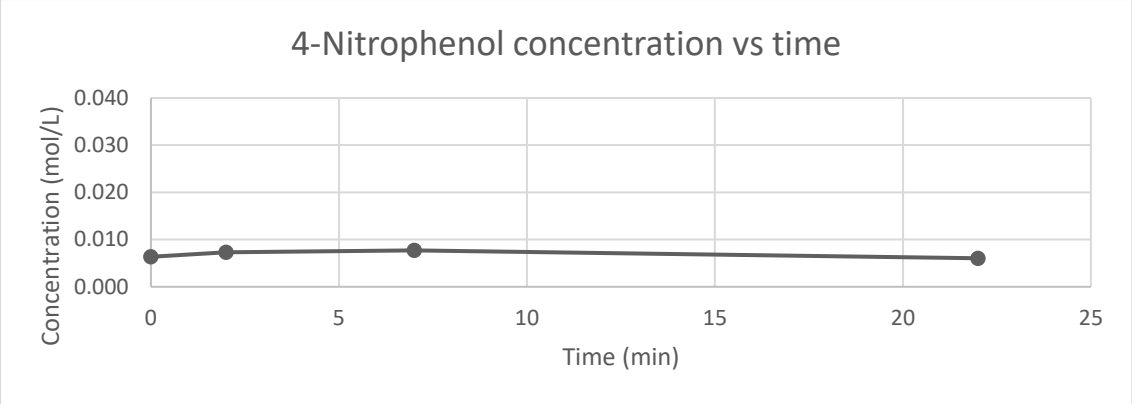


Figure 4.12 4-Nitrophenol concentration with 2 ml acetic anhydride in water over time

Conclusion

The reaction of 4-nitrophenol with acetic anhydride in water and iso-amyl alcohol didn't show any reaction and stayed in solution after cooling over night at 5 ℃.

Summary

The investigations of impurities reaction (acetanilide, metacetamol and 4-nitrophenol) with acetic anhydride in different solvents (water and iso-amyl alcohol) didn't show any reaction with different amounts of acetic anhydride in different solvents. Also, all the impurities stayed soluble after cooling in the fridge at 5 ℃.

4.5 Paracetamol synthesis without impurities

After investigating the behavior of impurities reaction with acetic anhydride in different solvents (water and iso-amyl), it was concluded that the impurities do not react and stay in solution after cooling. However, the reaction behavior between 4-aminophenol and acetic anhydride in different solvents with or without impurities needed to be tested. So, firstly the reaction behavior of 4-aminophenol without impurities with acetic anhydride in different solvents (water, iso-amyl alcohol & 2-propanol) was studied and will be described in this section. All new samples were tested using the new mobile phase methanol 5%: buffer 95% solution. The synthesis yield was calculated based on the product final concentration (from HPLC) over the expected concentration of the product (starting material concentration). The dilution was done twice due to deficiencies that were faced in the previous test. So, the dilution factor is the total of two dilutions.

4.5.1 Paracetamol synthesis without impurities in iso-amyl alcohol

Synthesis of paracetamol without impurities with acetic anhydride in iso-amyl alcohol was investigated in order to check the reaction behavior in iso-amyl alcohol as a solvent and how much yield can be achieved.

Table 4.18 Paracetamol synthesis reaction information in iso-amyl alcohol with acetic anhydride

Material	Iso-amyl alcohol	Acetic anhydride	4-Aminophenol
State	Liquid	Liquid	Solid
Mass (g)	20.250	3.564	2.951
Volume (ml)	25	3.3	-
Molecular weight (g/mol)	88.148	102.09	109.13
Number of moles (mol)	0.230	0.035	0.027
Density (Total volume)[g/ml]	0.716	0.126	0.104
Concentration (Total volume) [mole/L]	8.118	1.234	0.956
Density (solvent volume)[g/ml]	0.810	0.143	0.118
Concentration (solvent volume) [mol/L]	9.189	1.396	1.082
Mole equivalence	8.495	1.291	1.000
Temperature (°C)	80	-	-
Reaction time (min)	20	-	-
Color	Light brown/ Light yellow		
Synthesis yield (%)	80.22		

Table 4.19 Reaction sampling at different time intervals for the synthesis of paracetamol in iso-amyl alcohol

Time (min)	**Sample weight (g)**	**MeOH:H_2O(g)**	**Total D.F**	**PCM peak (mAU), tr= 1.19 (min)**	**PCM Conc. (mol/L)**
20	0.1003	1.016	147.510	11769.7	0.868

As given in table (4.18), the reaction was carried out at 80 °C for 20 minutes, the color changed from light brown to light yellow after the addition of acetic anhydride. From HPLC results as shown in table (4.19), it can be seen the concentration of paracetamol at time 20 minutes. The synthesis yield was only 80.22%. The reason for not having 100% yield, might be due to the inconveniently of the mobile phase or side reactions.

4.5.2 Paracetamol synthesis without impurities in 2-Propanol

The next chosen solvent is 2-propanol in which 4-aminophenol has a higher solubility in as shown in solubility data section. Therefore, different amounts of 4-aminophenol were used as well as acetic anhydride.

Table 4.20 Paracetamol synthesis reaction information in 2-propanol with acetic anhydride

Material	2-Propanol	Acetic anhydride	4-Aminophenol
State	Liquid	Liquid	Solid
Mass (g)	19.65	5.022	4.600
Volume (ml)	25	4.65	-
Molecular weight (g/mol)	60.1	102.09	109.13
Number of moles (mol)	0.327	0.049	0.042
Density (Total volume)[g/ml]	0.663	0.169	0.155
Concentration (Total volume) [mole/L]	0.011	0.002	1.422
Density (solvent volume)[g/ml]	0.786	0.201	0.184
Concentration (solvent volume) [mol/L]	13.078	1.968	1.686
Mole equivalence	7.757	1.167	1.000
Temperature (°C)	60	-	-
Reaction time (min)	20	-	-
Color	Light brown / light yellow		
Synthesis yield (%)	63.22		

Table 4.21 Reaction sampling at different time intervals for the synthesis of paracetamol in 2-propanol

Time (min)	**Sample weight (g)**	**MeOH:H_2O(g)**	**Total D.F**	**PCM peak (mAU), tr= 1.19 (min)**	**PCM Conc. (mol/L)**
20	0.120	0.989	128.643	16570.1	1.066

The reaction was carried out at 60 °C, for 20 minutes with color change from light brown to light yellow as presented in table (4.20). Table (4.21) shows the main aim of this reaction which was to investigate whether the 4-aminophenol will dissolve completely or not. Thus, only one sample was withdrawn after the 4-aminophenol was completely dissolved and at the end of the reaction. Also, the synthesis yield was 63.22%.

4.5.3 Paracetamol synthesis without impurities in water

In this experiment the used solvent is water, the reactants are acetic anhydride and 4-aminophenol without any impurities addition.

Table 4.22 Paracetamol synthesis reaction information in water with acetic anhydride

Material	Water	Acetic anhydride	4-Aminophenol
State	Liquid	Liquid	Solid
Mass (g)	-	-	1.80
Volume (ml)	25	1.80	-
Molecular weight (g/mol)	18.015	102.09	109.13
Number of moles (mol)	1.388	0.019	0.016
Density (Total volume)[g/ml]	0.933	0.073	0.067
Concentration (Total volume) [mole/L]	51.781	0.711	0.615
Density (solvent volume)[g/ml]	1.000	0.078	0.072
Concentration (solvent volume) [mol/L]	55.509	0.762	0.660
Mole equivalence	84.135	1.154	1.000
Temperature (°C)	80	-	-
Reaction time (min)	20		
Color	Light brown / light yellow		
Synthesis yield (%)	70.15		

Table 4.23 Reaction sampling at different time intervals for paracetamol with acetic anhydride in water

Time (min)	**Sample weight (g)**	**MeOH:H_2O(g)**	**Total D.F**	**PCM peak (mAU), tr= 1.19 (min)**	**PCM Conc. (mol/L)**
0	0.1847	1.6182	167.456	4196.4	0.351
2	0.1643	1.4169	153.540	6036.0	0.463

The reaction was carried out at 80 °C, for 20 minutes with color change from light brown to light yellow as observed in table (4.22). The synthesis yield was 70.15% and only 2 samples were taken in the beginning of the reaction to investigate how long it takes 4-aminophenol to convert to paracetamol and it was 2 minutes as seen in table (4.23).

Conclusion & Summary

The aim from synthesis of paracetamol without impurities with acetic anhydride in different solvents to observe the full conversion of 4-aminophenol to paracetamol and the crystallization yield. Comparison between the synthesis yield from the previous reactions isn't fair due to the difference between reaction times, the synthesis yield was calculated for iso-amyl alcohol (80.22%) after the reaction was done at 20 minutes, water (70.15%) was calculated after 2 minutes and 2-propanol (63.22%) after 20 minutes. 2-Propanol showed probably the lowest yield due to the higher temperature used in water and iso-amyl alcohol reaction. Based on the solubility data, the higher temperature the higher the solubility gets. Also, 2-propanol low boiling point was the prohibiting factor to increase its reaction temperature to 80 °C. For iso-amyl alcohol synthesis yield being higher than water, that can be explained due to the higher solubility of paracetamol in alcohols.

4.6 Paracetamol synthesis with impurities

After the investigations of impurities and 4-aminophenol synthesis separately, the next step was to investigate the synthesis of paracetamol with 4-aminophenol in the presence of impurities.

4.6.1 Paracetamol synthesis with impurities in iso-amyl alcohol

The amount of iso-amyl alcohol was the same as the synthesis reaction without impurities. Also, the reaction temperature was 80 °C. However, the amount of 4-aminophenol and acetic anhydride has been changed. For impurities, 4 mol% [2] was taken and mixed with the 4-aminophenol.

Table 4.24 Paracetamol synthesis reaction information with impurities in iso-amyl alcohol with acetic anhydride

Material	Iso-amyl alcohol	Ac_2O	4-AP	4-NP	MCM	Actld
State	Liquid	Liquid	Solid	Solid	Solid	Solid
Mass (g)	20.250	3.078	2.530	0.129	0.140	0.125
Volume (ml)	25.000	2.850	-	-	-	-
Molecular weight (g/mol)	88.148	102.09	109.13	139.11	151.16	136.17
Number of moles (mol)	0.230	0.030	0.023	0.001	0.001	0.001
Density (Total volume)[g/ml]	0.727	0.111	0.091	0.005	0.005	0.004
Concentration (Total volume) [mole/L]	8.249	1.083	0.832	0.033	0.033	0.033
Density (solvent volume)[g/ml]	0.810	0.123	0.101	0.005	0.006	0.005
Concentration (solvent volume) [mol/L]	9.189	1.206	0.927	0.037	0.037	0.037
Mole equivalence	9.909	1.300	1.000	0.040	0.040	0.040
Temperature (°C)	80					
Reaction time (min)	24					
Color	Brown/yellow					
Synthesis yield (%)	83.28					

Table 4.25 Reaction sampling at different time intervals for synthesis of paracetamol and impurities in iso-amyl alcohol

No.	Time (min)	Sample weight (g)	MeOH: H_2O(g)	Total D.F	PCM peak (mAU), tr= 1.19 (min)	PCM conc. (mol/L)	M+A peak (mAU), tr= 3.1 (min)	M+A conc. (mol/L)
B	0	0.008	1.031	125.921	0.00	0.00	1272.5	0.053
0	2	0.008	1.027	125.509	7210.7	0.453	1154.3	0.048
4	8	0.010	1.026	106.753	9812.1	0.524	981.2	0.035
8	10	0.010	1.030	104.000	12459.4	0.648	1234.4	0.043
12	14	0.009	1.039	116.489	12941.2	0.754	1276.0	0.050
14	16	0.009	1.028	116.483	13263.6	0.772	1315.1	0.051

The reaction took 24 minutes with a change in color from brown to yellow as given in table (4.24). For paracetamol, the obtained concentration is reasonable with constant increase during the reaction. However, the 4-nitrophenol peak wasn't deductible with the new mobile phase and using the old mobile phase with any presence for 4-aminophenol would harm the HPLC column. So, the investigation for its concentration won't be available. However, the new mobile phase gave an overlapped peak at the retention time (2.9-3.1) which is the same retention time for both metacetamol and acetanilide in the calibration curve. Thus, the obtained concentrations from the HPLC at retention time (2.9-3.1) minute will represent both impurities concentration. The amount of obtained concentration is reasonable compared to the starting concentration and it's within the range as given in table (4.25).

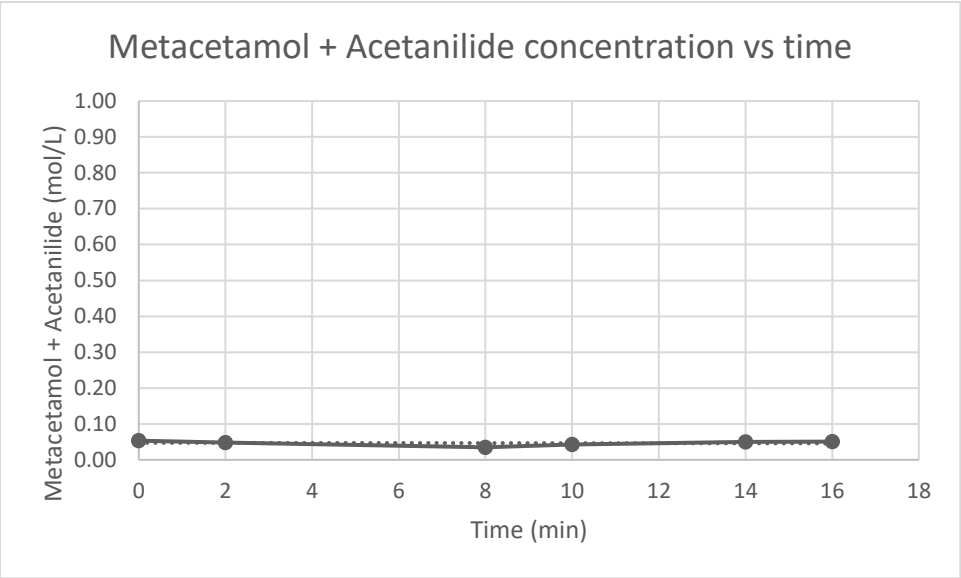


Figure 4.13 Metacetamol + acetanilide concentration over time

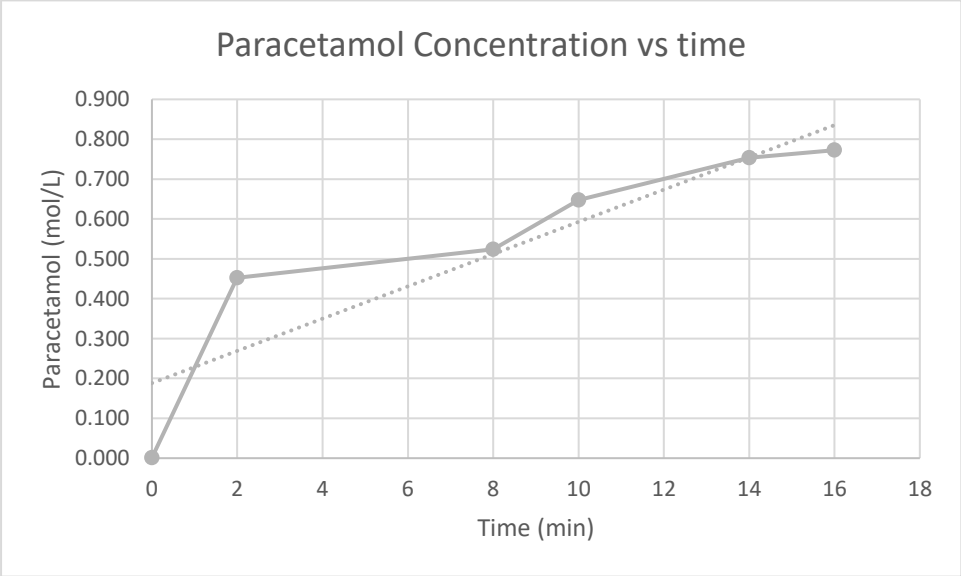


Figure 4.14 paracetamol concentration over time

Figure (4.13) shows constant concentration of metacetamol and acetanilide over time. For paracetamol, figure (4.14) shows constant increase of the amounts over time. The synthesis yield was 83.2% which is higher than the synthetic reaction of paracetamol without impurities and that's might be due to the addition of impurities or due to longer reaction time.

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4.6.2 Paracetamol synthesis with impurities in water

The second part of the paracetamol synthesis with impurities was in water as a solvent in different amount of acetic anhydride and 4-aminophenol.

Part (1):

Table 4.26 Paracetamol synthesis reaction information with impurities in water with acetic anhydride

Material	Water	Ac_2O	4-AP	4-NP	MCM	Actld
State	Liquid	Liquid	Solid	Solid	Solid	Solid
Mass (g)	25.000	2.16	1.82	0.092	0.099	0.086
Volume (ml)	25.000	2.00	-	-	-	-
Molecular weight (g/mol)	18.015	102.09	109.13	139.11	151.16	135.17
Number of moles (mol)	1.39	0.02	0.02	0.0007	0.0007	0.0006
Density (Total volume)[g/ml]	0.93	0.08	0.07	0.0034	0.0037	0.0032
Concentration (Total volume) [mole/L]	51.40	0.78	0.62	0.02	0.02	0.02
Density (solvent volume)[g/ml]	0.93	0.09	0.07	0.0037	0.0040	0.0035
Concentration (solvent volume) [mol/L]	55.51	0.85	0.67	0.026	0.026	0.026
Mole equivalence	83.34	1.27	1.000	0.04	0.04	0.04
Temperature (°C)	80					
Reaction time (min)	20					
Color	Brown/yellow					
Synthesis yield (%)	83.6					

The reaction was carried out at 80 °C for 20 minutes. The reaction color changed from brown to yellow and the synthesis yield was 83.6% which is almost equivalent to the synthesis yield of iso-amyl alcohol in the previous section 83.28 %. Available information is given in table (4.26).

Table 4.27 Reaction sampling at different time intervals for paracetamol and impurities with acetic anhydride in water

No.	Time (min)	sample weight (g)	MeOH: H_2O(g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	PCM conc. (mol/L)	M+A peak (mAU), tr= 3.1 (min)	M+A conc. (mol/L)
5	12	0.104	1.012	120.87	9137.0	0.55	746.8	0.045
6	15	0.104	1.003	121.04	9321.5	0.56	761.4	0.046

Table (4.27) presents the concentration of paracetamol, metacetamol and acetanilide over time. The chosen samples to be tested in HPLC didn't show good increasing values for paracetamol or constant for metacetamol and acetanilide. The reason of this instability, is the HPLC. Thus, there was not enough data to fit in a figure for this reaction.

Part (2):

The next reaction was performed using the recrystallized p-aminophenol with the same reaction amounts for the synthesis of paracetamol with acetic anhydride and impurities in water. The aim of this reaction was to investigate the recrystallized p-aminophenol behavior in reaction. Table (4.28) shows the reaction amounts for the re-crystallized 4-aminophenol and impurities with acetic anhydride in water, temperature was 40 °C, the paracetamol crystals color was white. The reaction took 18 minutes.

Table 4.28 Paracetamol synthesis reaction information using re-crystallized 4-aminophenol

Material	Water	Ac_2O	4-AP	4-NP	MCM	Actld
State	Liquid	Liquid	Solid	Solid	Solid	Solid
Mass (g)	25.000	2.16	1.805	0.095	0.103	0.085
Volume (ml)	25.000	2.00	-	-	-	-
Molecular weight (g/mol)	18.015	102.09	109.13	139.11	151.16	136.17
Number of moles (mol)	1.388	0.02	0.017	0.0007	0.0007	0.00063
Density (Total volume)[g/ml]	0.93	0.08	0.07	0.0035	0.0038	0.0031
Concentration (Total volume) [mole/L]	51.40	0.784	0.61	0.025	0.025	0.023
Density (solvent volume)[g/ml]	1.00	0.09	0.07	0.0038	0.0041	0.0034
Concentration (solvent volume) [mol/L]	55.51	0.85	0.66	0.027	0.027	0.025
Mole equivalence	83.90	1.28	1.00	0.041	0.041	0.038
Temperature (°C)	40					
Reaction time (minute)	18					
Crystal color	White					

Table 4.29 Sampling at different time intervals for the synthesis of paracetamol with acetic anhydride in water using re-crystallized 4-aminophenol

No.	Time (min)	Sample weight (g)	MeOH :H_2O (g)	Total D.F	PCM Peak (mAU), tr= 1.2 (min)	PCM conc. (mol/ L)	M+A Peak (mAU), tr= 3.2 (min)	M+A conc. (mol/ L)	4-AP Peak (mAU), tr= 0.74 (min)	4-AP conc. , (mol/L)
1	0	0.101	0.996	116.33	3643.9	0.21	574.3	0.022	59.4	0.007
2	1	0.093	0.995	121.60	4049.1	0.25	665.7	0.027	61.3	0.007
3	2	0.095	0.994	123.69	3643.2	0.23	598.5	0.025	57.3	0.007
4	3	0.096	0.980	119.26	3729.7	0.22	622.7	0.025	59	0.007
5	4	0.096	0.986	120.94	4343.9	0.26	712.6	0.029	58.1	0.007
6	5	0.087	0.985	132.58	3697.1	0.25	609.1	0.027	61.5	0.008
7	6	0.096	0.996	122.74	3499	0.21	574.6	0.024	61.4	0.008
8	7	0.094	0.992	124.20	4141.2	0.26	676	0.028	62.5	0.008
9	8	0.089	0.999	129.95	3808.1	0.25	619.7	0.027	62.1	0.008
10	10	0.092	0.998	125.94	3796.3	0.24	620.4	0.026	72.2	0.009
11	12	0.087	0.999	129.32	3702.3	0.24	607.2	0.026	60.4	0.008
12	14	0.089	0.998	125.80	3981.5	0.25	652.8	0.027	63.9	0.008
13	16	0.088	0.992	128.50	4127.7	0.27	675.2	0.029	63.7	0.008
14	18	0.075	0.995	151.80	3080.3	0.23	502.6	0.025	57.8	0.009

Paracetamol concentration through the reaction showed an almost constant concentration over time. Metacetamol and acetanilide concentration (M+A conc.) over time can be considered constant this can be observed in table (4.29). However, a peak for 4-aminophenol (4-AP conc.) appeared in every single sample which means the full conversion of the re-crystallized 4-aminophenol was not achieved. The time (0) in table (4.29) points out to the time when the re-crystallized 4-aminophenol was added with acetic anhydride to the water medium. This shows immediate synthesis for paracetamol. This sample can't be considered a blank.

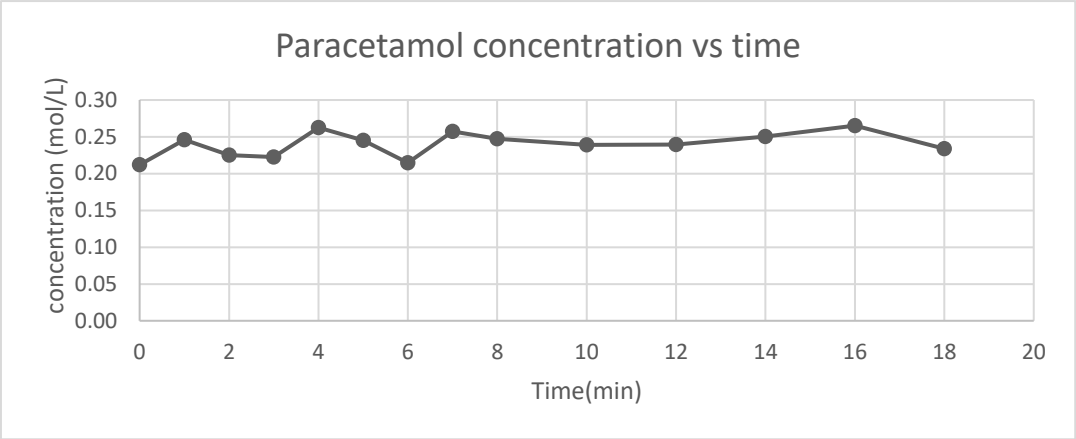


Figure 4.15 Paracetamol concentrations in water over time using recrystallized 4-aminophenol

Figure (4.15) shows paracetamol concentrations over time synthetized in water using the re-crystallized 4-aminophenol with impurities and acetic anhydride. The concentration got constant over time.

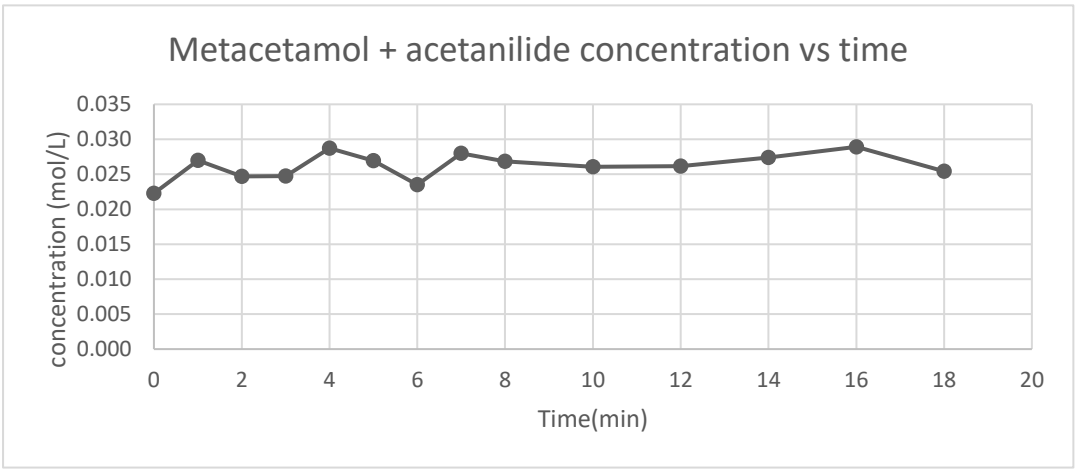


Figure 4.16 Metacetamol + acetanilide concentrations in water over time using recrystallized 4-aminophenol

Figure (4.16) shows the metacetamol and acetanilide concentrations over time in the reaction of re-crystallized 4-aminophenol with impurities and acetic anhydride in water. The concentrations were almost constant over the time.

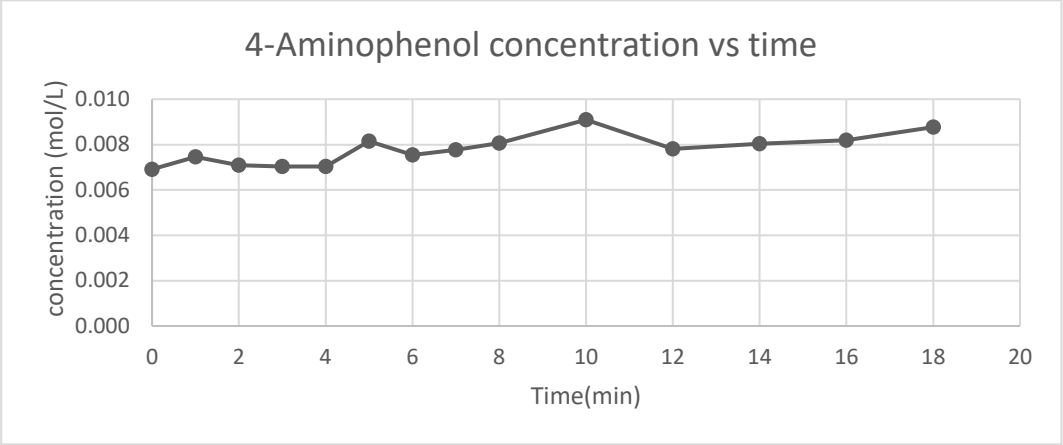


Figure 4.17 4-Aminophenol concentrations in water over time using recrystallized 4-aminophenol

As presented in figure (4.17), an increasing amount of 4-aminophenol appeared in every sample. Which indicates there was no full conversion of the re-crystallized 4-aminophenol. Furthermore, investigations are needed to observe the nature of the synthetized material then repeating the investigation in synthesis for the production of paracetamol. The produced material needed further investigations with other analytical devises such as: FTIR.

Conclusion

Re-crystallization of 4-aminophenol experiments gave interesting results in synthesis but the appearance of 4-aminophenol through the run was enough to stop using the re-crystallized material. Thus, discovering the material nature with HPLC wasn't enough and further analytical techniques are needed such as: FTIR or any other analytical method, such as NMR.

4.6.3 Paracetamol synthesis with impurities in 2-propanol

In the third part of paracetamol synthesis with impurities, the chosen solvent was 2-propanol. The amount of it, is the same as the previous reactions. For 4-aminophenol and acetic anhydride, the amounts is higher based on the solubility data in section (4.1).

Table 4.30 Paracetamol synthesis reaction information with impurities in 2-propanol with acetic anhydride

Material	2-Propanol (IPA)	Ac_2O	4-AP	4-NP	MCM	Actld
State	Liquid	Liquid	Solid	Solid	Solid	Solid
Mass (g)	19.65	5.044	4.097	0.2042	0.2304	0.2045
Volume (ml)	25.000	4.67	-	-	-	-
Molecular weight (g/mol)	60.10	102.09	109.13	139.11	151.16	136.17
Number of moles (mol)	0.327	0.049	0.038	0.001	0.002	0.002
Density (Total volume)[g/ml]	0.662	0.170	0.138	0.007	0.008	0.007
Concentration (Total volume) [mole/L]	11.020	1.665	1.265	0.049	0.051	0.051
Density (solvent volume)[g/ml]	0.786	0.202	0.164	0.008	0.009	0.008
Concentration (solvent volume) [mol/L]	13.078	1.976	1.502	0.059	0.061	0.061
Mole equivalence	8.7100	1.316	1.000	0.0391	0.0406	0.0403
Temperature (°C)	60					
Reaction time (min)	18					
Color	Brown/yellow					
Synthesis yield (%)	89.21					

The reaction was carried out at 60 °C, for 18 minutes with color change from brown to yellow and the synthesis yield was 89.21% as given in table (4.30).

Table 4.31 Results of samples taken at different time intervals for the synthesis of paracetamol and impurities with acetic anhydride in 2-propanol

No.	Time (min)	Sample weight (g)	MeOH: H_2O(g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	PCM conc. (mol/L)	M+A peak (mAU), tr= 3.2 (min)	M+A conc. (mol/ L)
1	0	0.0959	0.9808	128.91	16124.8	1.04	1513.5	0.10
2	3	0.1027	0.9761	150.33	17762.9	1.34	1708.2	0.13

The 4-aminophenol showed full dissociation in 2-propanol with good result in paracetamol as shown in table (4.31). However, the results are not enough to draw a figure.

Conclusion & summary

The aim from the investigations of the synthesis of paracetamol with impurities and acetic anhydride in different solvent is to observe the effect of impurities into the reaction. The impurities didn't show any reaction but an effect to the synthesis yield. That's can be explained by the addition of impurities. The comparison between the yields and solvents are described in table (4.32).

Table 4.32 Synthesis yield comparison among different solvents

Solvent	Synthesis yield without impurities %	Reaction time (min)	Synthesis yield with impurities %	Reaction time (min)
Iso-amyl alcohol	80.22	20	83.28	16
Water	70.15	2	83.6	15
2-propanol	63.22	20	89.21	3

The synthesis yield with impurities increased in all solvents. The main reason is the addition of impurities. However, in this section the highest synthesis yield was 2-propanol > water > iso-amyl alcohol. The explanation for this is 2-propanol has high solubility in high temperature (as discussed in reference [4] solubility data) even though the water and iso-amyl alcohol had higher reaction temperature. Also, the synthesis yield for water and iso-amyl alcohol is too close and incomparable.

4.7 Synthesis and crystallization of paracetamol

In this section, the previous three reactions were repeated and a sample was taken every 10 minutes during 30 minutes cooling from 80/60°C to 5°C and during 60 minutes in the ice bath at 5°C. The expected outcomes from these tests are to have an increasing amount of impurities during cooling and decreasing amount of paracetamol in solution because of selective crystallization of paracetamol. Also, to find out how long the crystallization time should be. The samples were taken using a syringe with a 0.5 µm filter in order to make sure no crystals were in the sample. The synthesis yield was calculated based on the product final concentration (from HPLC) over the expected concentration of the product (starting material concentration). The crystallization yield was calculated based on the actual crystal obtained over the expected amount of product. The dilution was done twice due to deficiencies that was faced in the previous test. So, the dilution factor is the total of two dilutions.

4.7.1 Investigations of paracetamol crystallization in water

The first investigation was done with water in the same reaction conditions as in the synthesis. Reaction temperature was 80 °C, took 20 minutes and the color changed from yellow to white during the crystallization.

Table 4.33 Paracetamol synthesis and crystallization in water

Material	Water	Ac_2O	4-AP	4-NP	MCM	Actld
State	Liquid	Liquid	Solid	Solid	Solid	Solid
Mass (g)	25.000	2.16	1.808	0.095	0.0998	0.084
Volume (ml)	25.000	2.00	-	-	-	-
Molecular weight (g/mol)	18.015	102.09	109.13	139.11	151.16	135.17
Number of moles (mol)	1.39	0.02	0.02	0.0007	0.0007	0.0006
Density (Total volume)[g/ml]	0.93	0.08	0.07	0.0035	0.0037	0.0031
Concentration (Total volume) [mole/L]	51.40	0.78	0.61	0.025	0.024	0.023
Density (solvent volume)[g/ml]	1.00	0.09	0.07	0.0038	0.0040	0.0034
Concentration (solvent volume) [mol/L]	55.51	0.85	0.66	0.027	0.026	0.025
Mole equivalence	83.76	1.28	1.000	0.041	0.04	0.037
Temperature (°C)	80					
Reaction time (min)	20					
Color	Yellow/white					
Synthesis yield (%)	96.96					
Crystallization yield (%)	87.73					

The synthesis yield was 96.96% which is the highest among all reactions. The crystallization yield was 87.73 % as given in table (4.33). The reason of the high yield might be there is no side reaction occurring.

Table 4.34 Sampling at different time intervals for paracetamol crystallization in water

No.	Time (min)	T (°C)	Sample weight (g)	MeOH: H_2O(g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	PCM conc. (mol/L)	M+A peak (mAU), tr= 3.2 (min)	M+A conc. (mol/ L)
1	10	47	0.13	1.01	72.54	17683.2	0.64	639.7	0.02
2	20	37	0.10	1.01	90.48	10022.8	0.45	871.6	0.04
3	30	27	0.10	1.01	54.33	15232.2	0.41	1880.9	0.05
4	40	17	0.10	1.01	59.74	6805.0	0.20	1392	0.04
5	50	10	0.11	1.02	50.45	3148.6	0.08	773.6	0.02
6	60	5	0.10	1.01	81.12	3064.7	0.12	795.0	0.03
7	70	5	0.09	1.01	71.00	3257.1	0.12	975.7	0.03
8	80	5	0.10	1.01	139.36	1961.3	0.14	605.6	0.04
9	90	5	0.10	1.01	76.33	2839.5	0.11	920.1	0.04
10	100	5	0.10	1.01	65.59	3211.8	0.11	1038.6	0.03
11	110	5	0.12	1.01	106.61	2385.8	0.13	806.0	0.04
12	120	5	0.10	1.02	138.86	3581.8	0.25	1235.4	0.09

The concentration of metacetamol and acetanilide should start increasing because from previous experiments it stayed in solution and did not crystallize with time then after a certain time should show constant behavior. As shown in table (4.34) and figure (4.18) the amount of metacetamol & acetanilide started at 20 mmol/L concentration and increased to 40 mmol/L and maintained almost a constant concentration.

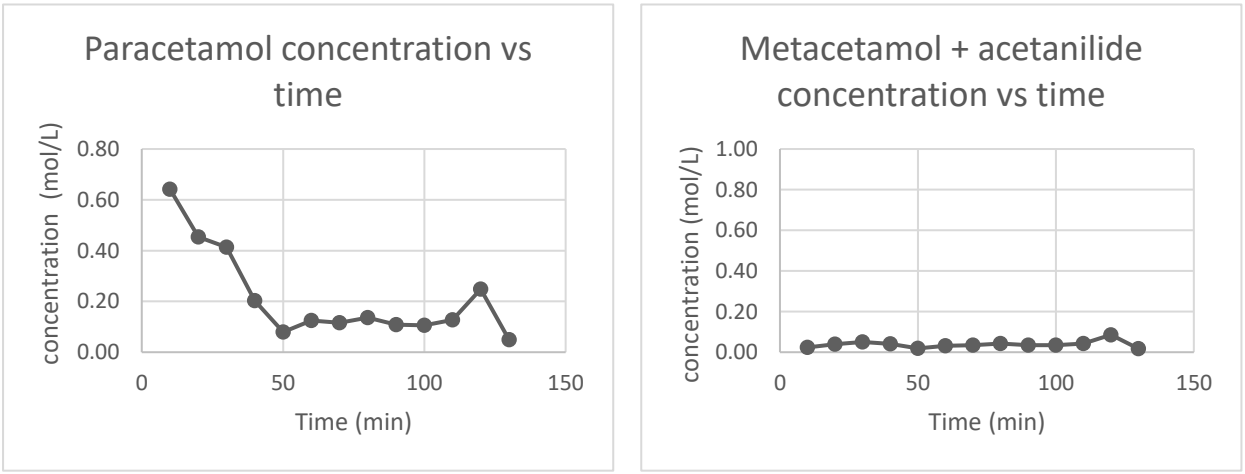


Figure 4.18 Paracetamol & metacetamol+ acetanilide concentrations in water over time during crystallization

For paracetamol, the concentrations decreased and then showed a constant concentration which is the solubility of paracetamol in water at 5°C. In figure (4.18), paracetamol concentration was decreasing over time. Thus 50 minutes seems to be enough for crystallization from 47°C to 5°C.

4.7.2 Investigations of paracetamol crystallization in 2-propanol

Same reaction conditions as in the synthesis were repeated in order to obtain the paracetamol crystallization data in 2-propanol.

Table 4.35 Paracetamol synthesis and crystallization in 2-propanol

Material	2-Propanol (IPA)	Ac_2O	4-AP	4-NP	MCM	Actld
State	Liquid	Liquid	Solid	Solid	Solid	Solid
Mass (g)	19.65	5.044	4.17	0.1967	0.2304	0.2028
Volume (ml)	25.000	4.67	-	-	-	-
Molecular weight (g/mol)	60.10	102.09	109.13	139.11	151.16	136.17
Number of moles (mol)	0.33	0.049	0.038	0.001	0.001	0.002
Density (Total volume)[g/ml]	0.662	0.170	0.141	0.007	0.007	0.007
Concentration (Total volume) [mole/L]	11.020	1.665	1.288	0.048	0.049	0.051
Density (solvent volume)[g/ml]	0.786	0.202	0.167	0.008	0.009	0.008
Concentration (solvent volume) [mol/L]	13.078	1.976	1.528	0.059	0.058	0.061
Mole equivalence	8.558	1.293	1.000	0.037	0.038	0.039
Temperature (°C)	60					
Reaction time (min)	12					
Color	Pink/white					
Synthesis yield (%)	86.39					
Crystallization yield (%)	63.61					

The reaction was carried out at 60 °C for 12 minutes, the synthesis yield was 86.39%, the crystallization yield was 63.61% and the crystal color changed from pink to white during crystallization as given in table (4.35).

Table 4.36 Sampling at different time intervals for paracetamol crystallization in 2-propanol

No.	T (min)	T (°C)	Sample weight (g)	MeOH: H_2O(g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	C PCM (mol/L)	M+A peak (mAU), tr= 3.2 (min)	C M+A (mol/L)
1	10	47	0.0952	1.011	157.62	16757.9	1.32	1462.4	0.12
2	20	35	0.1036	1.001	139.88	18495.4	1.29	1642.7	0.11
3	30	28	0.1018	1.003	72.72	28233.0	1.03	3642.9	0.13
4	40	19	0.0954	0.979	90.19	25894.0	1.17	3810.7	0.17
5	50	10	0.1017	1.006	50.15	26543.3	0.67	3426.6	0.09
6	60	5	0.1025	1.008	86.79	9921.1	0.43	574.7	0.02
7	70	5	0.1044	1.004	108.77	11021.3	0.60	1285.8	0.07
8	80	5	0.0996	1.004	66.95	21287.5	0.71	2992.6	0.10
9	90	5	0.0956	1.000	109.27	14916.7	0.82	1915.8	0.10
10	100	5	0.1031	1.012	114.14	18981.4	1.08	2577.4	0.15
11	110	5	0.1012	1.008	71.55	21339.4	0.76	3146.2	0.11
12	120	5	0.1019	1.006	68.12	21008.1	0.72	3242.9	0.11

The amount of paracetamol was decreasing over time. However, metacetamol and acetanilide were almost constant over time. Data presented in table (4.36) and figure (4.19).

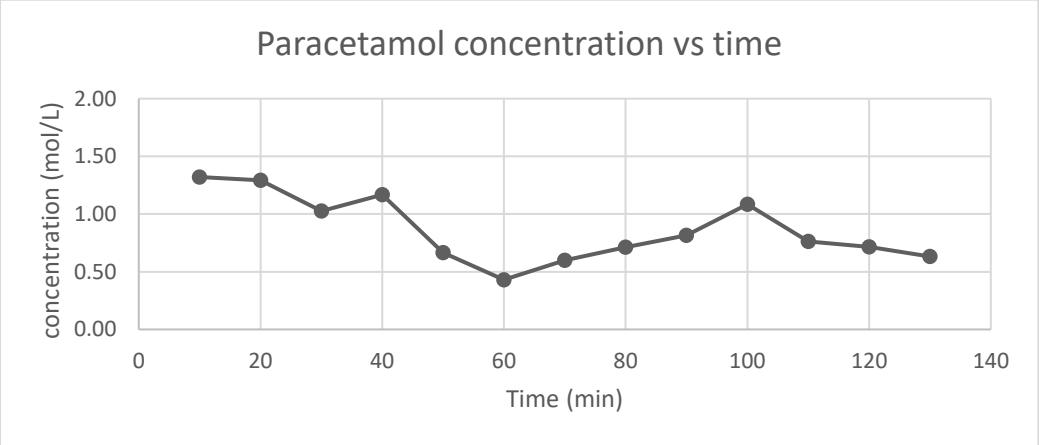


Figure 4.19 Paracetamol concentrations in 2-propanol over time during crystallization

As shown in figure (4.19), the amount of paracetamol was decreasing until the minute 60, indicating that the crystallization time in 2-propanol seems 60 minutes. However, a sudden increase happened then the concentration dropped and decreased again. The reason for that is unclear. A re-disolution of paracetamol seems to be unlikely.

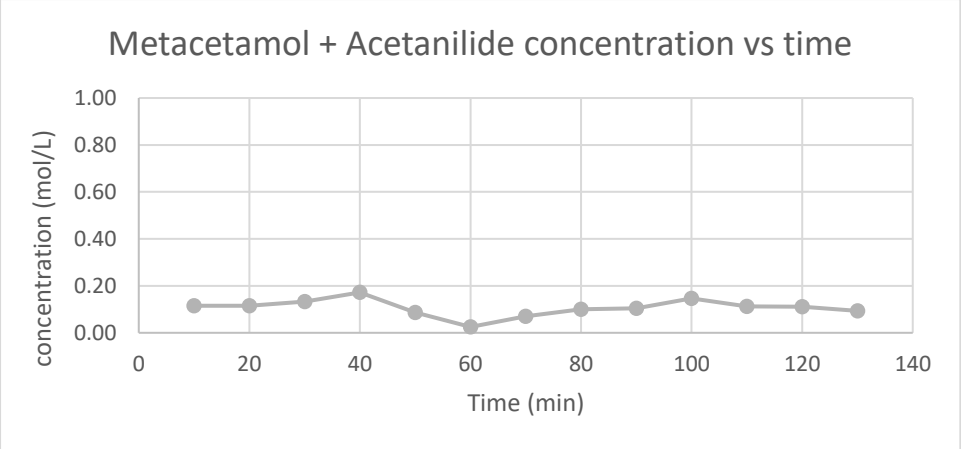


Figure 4.20 Metacetamol + acetanilide concentrations in 2-propanol over time during crystallization

Figure (4.20) shows that for the first 30 minute, the amounts of metacetamol and acetanilide were constant. Then it showed fluctuation and then constant concentration. That might be due to problems while taking samples.

4.7.3 Investigations of crystallization kinetics in iso-amyl alcohol

The amounts and reaction conditions were repeated for the synthesis of paracetamol in iso-amyl alcohol.

Table 4.37 Paracetamol synthesis and crystallization in iso-amyl alcohol

Material	Iso-amyl alcohol	Ac_2O	4-AP	4-NP	MCM	Actld
State	Liquid	Liquid	Solid	Solid	Solid	Solid
Mass (g)	20.250	3.11	2.65	0.129	0.140	0.135
Volume (ml)	25.000	2.88	-	-	-	-
Molecular weight (g/mol)	88.148	102.09	109.13	139.11	151.16	136.17
Number of moles (mol)	0.230	0.030	0.024	0.001	0.001	0.001
Density (Total volume)[g/ml]	0.727	0.111	0.095	0.005	0.005	0.005
Concentration (Total volume) [mole/L]	8.249	1.083	0.87	0.033	0.033	0.04
Density (solvent volume)[g/ml]	0.810	0.123	0.106	0.005	0.005	0.0054
Concentration (solvent volume) [mol/L]	9.189	1.22	0.97	0.037	0.036	0.04
Mole equivalence	9.47	1.300	1.000	0.040	0.040	0.040
Temperature (°C)	80					
Reaction time (min)	23					
Color	Yellow/white					
Synthesis yield (%)	65.97					
Crystallization yield (%)	31.22					

As shown in table (4.37), the reaction was carried out at 80 °C for 23 minutes with change in color from yellow to white, the synthesis yield was 65.97% and the crystallization yield was 31.22%. The low values of synthesis yield might be due to side reactions. For crystallization yield, although the solubility data showed lower solubility of paracetamol in iso-amyl alcohol at lower temperature, still there is a high concentration of paracetamol in iso-amyl alcohol at low temperature. Comparing the concentrations with water, water showed a better solvent for crystallization.

Table 4.38 Sampling at different time intervals for paracetamol crystallization in iso-amyl alcohol

No.	t (min)	T (°C)	Sample weight (g)	MeOH: H_2O(g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	C PCM (mol/ L)	M+A peak (mAU), tr= 3.2 (min)	C M+A (mol/L)
1	10	47	0.0958	1.00	101.38	12710	0.64	763.7	0.04
2	20	43	0.0957	1.00	125.01	10550.6	0.66	658.7	0.04
4	40	18	0.0903	1.00	117.31	10866.8	0.64	684.5	0.04
5	50	5	0.0841	0.99	148.29	9150.2	0.68	621.4	0.05
6	60	5	0.0913	0.99	100.95	10547.4	0.53	629.9	0.03
9	90	5	0.0868	0.95	142.12	9542.6	0.68	706.4	0.05
10	100	5	0.0940	0.93	105.81	11859.3	0.63	906.5	0.05
11	110	5	0.0901	1.01	138.47	7746.8	0.54	602.7	0.04
12	120	5	0.0930	1.01	110.23	10533.8	0.58	807.6	0.04

In order to have a nice trend for the concentration of paracetamol over time, the samples at time (30, 70 & 80 min) were deleted. Because sample at time (10 min) had human error and samples at time (70 & 80 min) had unstable peak from HPLC. The used data in figure (4.21 & 4.22) are presented in table (4.38).

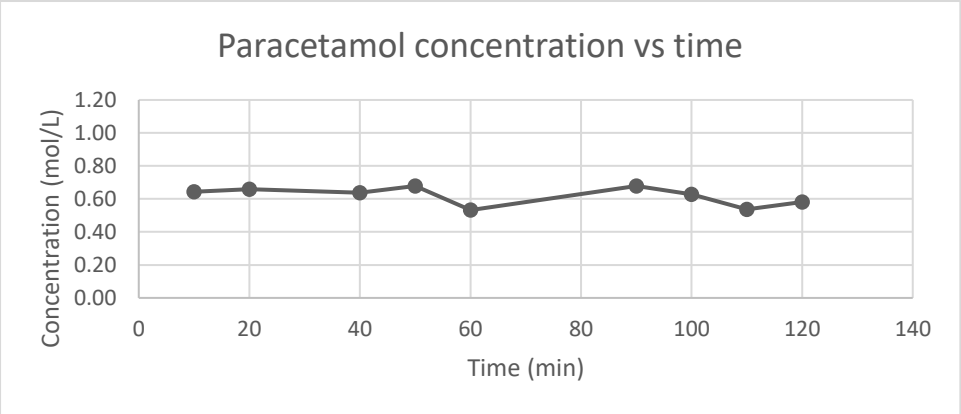


Figure 4.21 Paracetamol concentrations in iso-amyl alcohol over time during crystallization

Figure (4.21) shows paracetamol concentration over time in iso-amyl alcohol while crystallization. The paracetamol concentration over time did not show decreasing but constant concentration over time. It showed constant trend from the first sample. This might indicate to the solubility of paracetamol in iso-amyl alcohol is not low like in water and a certain concentration will be soluble after time, although as soon as the temperature reaches 5°C, at time (50 min), crystals where formed.

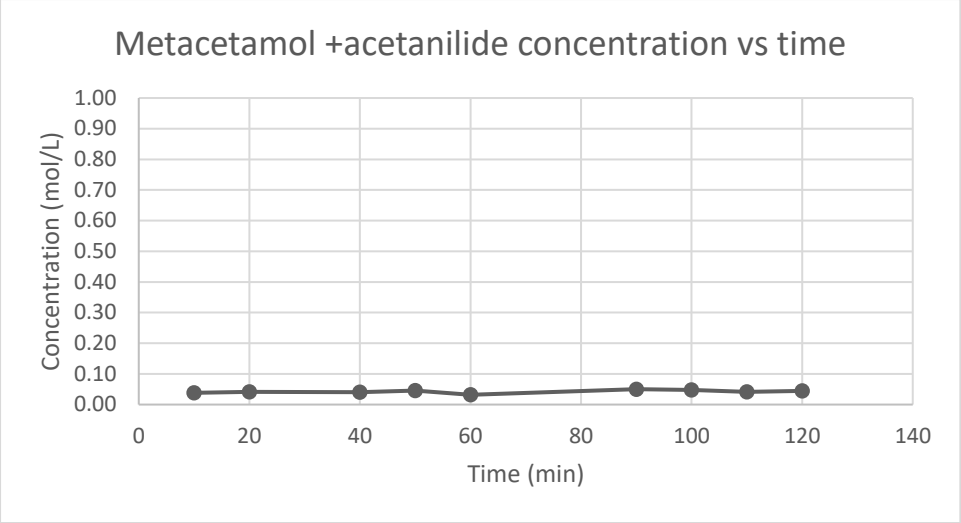


Figure 4.22 Metacetamol + acetanilide concentration in iso-amyl alcohol over time during crystallization

For the metacetamol & acetanilide concentration, it doesn't show constant behavior. However, taking a deep look into the data and taking samples at time (10, 20, 40, 50, 60, 90, 100,110 & 120 min), figure (4.22) showed a constant behavior which is the main goal from the test.

Conclusion & summary

The aim from repeating the synthesis and crystallization of paracetamol with impurities and acetic anhydride in different solvents is to investigate the crystallization of paracetamol over time. Paracetamol was crystallized in all solvents however the highest synthesis & crystallization yield was for water > 2-propanol > iso-amyl alcohol and that's due to the low solubility of paracetamol in water at 5°C more than 2-propanol and iso-amyl alcohol. The table below (4.39), shows a comparison between the synthesis and crystallization yield of paracetamol in the three solvents (water, iso-amyl alcohol & 2-propanol). For the synthesis, it might differ from the previous experiment due to HPLC instability or human error while sampling.

Table 4.39 Synthesis and crystallization yield comparison among different solvents

Solvent	Synthesis yield (%)	Crystallization yield (%)
Water	96.96	87.73
2-propanol	86.27	63.61
Iso-amyl alcohol	65.97	31.22

4.8 Crystal purity

After the investigations of synthesis, crystallization and obtaining a stable method for analyses (HPLC), it was interesting to check the obtained crystal. Crystal purity test means; the obtained crystals from the reaction were diluted again and tested with HPLC to figure out the presence of impurities and the percentage of purity for the paracetamol. This test was done in three different ways, due to the instability of HPLC. First, it was prepared by diluting 10 mg of the crystals in 100 ml methanol: HPLC-water diluent (5:95). Secondly, by diluting 0.5 mg of the crystals in 2 ml methanol: HPLC-water diluent (5:95). Thirdly, by diluting 10 mg of crystals in 100 mg methanol: HPLC-water diluent, then taking 1 ml and diluting it again with 1 ml of the same diluent in HPLC vial then filtrating it with 0.2 µm filter. The crystallization was carried out by cooling for 30 minutes from 80/60°C to 5°C and during 60 minutes in the ice bath at 5°C. Filtration was done using Buchner funnel under vacuum and then drying overnight.

First procedure

The first test was performed on the crystals produced from the synthetic reaction of paracetamol and impurities with acetic anhydride in iso-amyl alcohol. The synthesis yield was 83.28% and the crystallization yield was 24.21% which is principally low and that might be due to the insufficient technique of filtration. The color of crystals is yellow as mentioned in table (4.40) and that means there is a presence for some impurities. However, in the HPLC only paracetamol peak appeared. Nevertheless, the available HPLC method wasn't able to detect 4-nitrophenol. (Experiments from section 4.6)

Table 4.40 Crystal purity test information for the paracetamol synthesis with impurities & acetic anhydride in iso-amyl alcohol

Reaction information	Isoamyl alcohol, with impurities
Amount	10 mg crystal, 100 ml water/methanol
Synthesis yield (%)	83.28
Crystallization yield (%)	24.21
Dilution factor (-)	0.0001
Area (mPa)	125.8
Crystal color	Light yellow
Mass of sample (g)	0.01
Mass of diluent (g)	98.865

Table 4.41 Crystal purity test information for the paracetamol synthesis with impurities & acetic anhydride in water

Reaction information	Water, with impurities
Amount	10 mg crystal, 100 ml water/methanol
Synthesis yield (%)	83.60
Crystallization yield (%)	89.33
Dilution factor (-)	0.0001
Area (mPa)	151.7
Crystal color	Dark yellow
Mass of sample (g)	0.01
Mass of diluent (g)	98.865

Same procedures were used for the synthetic reaction of paracetamol and impurities with acetic anhydride in water. As shown in table (4.41) the synthesis yield was 83.60% and the crystallization yield was 89.33%, the higher percentage for crystallization is due to the filtration technique and water content. For the 4-nitrophenol, it wasn't deductible with HPLC from the beginning of the tests and in this stage as well. However, the color of the crystals was yellow and that might indicate the presence of 4-nitrophenol. Metacetamol and acetanilide, didn't appear in the chromatogram.

Table 4.42 Crystal purity test information for the paracetamol synthesis with acetic anhydride in 2-propanol

Reaction information	2-propanol, with impurities
Amount	10 mg crystal, 100 ml water/methanol
Synthesis yield (%)	89.21
Crystallization yield (%)	48.68
Dilution factor (-)	0.0001
Area (mPa)	228.5
Crystal color	white
Mass of sample (g)	0.01
Mass of diluent (g)	98.865

Table (4.42) shows the synthetic reaction of paracetamol with impurities & acetic anhydride in 2-propanol. The HPLC showed only paracetamol peak and no impurities presence. However, the synthesis yield was 89.21% and the crystallization yield was 48.68%. The crystallization yield is low due to the high solubility of paracetamol in 2-propanol.

Second procedure:

In this part, the reason behind not diluting is the absence of impurities and there was no risk on the HPLC column. As mentioned before, it was simple preparations which consist of dissolving 0.5 mg of the crystals in 2 ml of the diluent methanol: HPLC-water (5:95) in HPLC vial then diluted and filtered with a 0.2 µm higher again. (Experiments from section 4.5)

Table 4.43 Crystal purity test information for the paracetamol synthesis without impurities with acetic anhydride in water

Reaction information	Water, without impurities
Amount	0.5 mg crystal, 2 ml water/methanol
Synthesis yield (%)	70.15
Crystallization yield (%)	71.07
Total dilution factor (-)	24882.878
Area (mPa)	663.6
Crystal color	Light pink
Mass of sample (g)	0.187
Mass of diluent (g)	1.438

The synthetic reaction of paracetamol without impurities with acetic anhydride in water gave light pink crystals after crystallization and only paracetamol peak appeared in the HPLC. The synthesis yield was 70.15% and the crystallization yield was 71.07% as given in table (4.43). The higher percentage of crystallization is due to the filtration technique and inefficient drying.

Table 4.44 Crystal purity test information for the paracetamol synthesis without impurities with acetic anhydride in 2-propanol

Reaction information	2-propanol, without impurities
Amount	0.5 mg crystal, 2 ml water/methanol
Synthesis yield (%)	63.22
Crystallization yield (%)	65.40
Total dilution factor (-)	17246.521
Area (mPa)	1520.4
Crystal color	White
Mass of sample (g)	0.13
Mass of diluent (g)	0.989

The synthetic reaction of paracetamol without impurities with acetic anhydride in 2-propanol gave white crystals and only paracetamol peak in the HPLC. The synthesis yield was 63.22% and the crystallization yield was 65.40 %, crystallization yield is higher than synthesis due to the filtration technique and water content. Information are given in table (4.44).

Table 4.45 Crystal purity test information for the paracetamol synthesis without impurities with acetic anhydride in iso-amyl alcohol

Reaction information	Iso-amyl alcohol, without impurities
Amount	0.5 mg crystal, 2 ml water/methanol
Synthesis yield (%)	80.22
Crystallization yield (%)	57.60
Total dilution factor (-)	18413.432
Area (mPa)	186.8
Crystal color	White
Mass of sample (g)	0.1
Mass of diluent (g)	1.01

The synthetic reaction of paracetamol without impurities with acetic anhydride in iso-amyl alcohol gave white crystals. The synthesis yield was 80.22% and the crystallization yield was 57.60 %, it's considered to be low compared to the other solvents results. Results described in table (4.45).

Third procedure:

The third procedure of crystal purity investigations was done by diluting 10 mg of crystals in 100 ml diluent then diluting 100 µl in 1 ml of diluent then filtration. (Experiments from section 4.7)

Table 4.46 Crystal purity test information for the paracetamol synthesis with impurities & acetic anhydride in water with impurities

Reaction information	Water, with impurities
Amount	10 mg crystal, 100 ml water/methanol
Synthesis yield (%)	96.96
Crystallization yield (%)	87.73
Total dilution factor (-)	74510.76
Area (mPa)	143.8
Crystal color	Yellow
Mass of sample (g)	0.15
Mass of diluent (g)	1.00

The given information's in table (4.46) represent synthetic reaction of paracetamol with impurities and acetic anhydride in water (investigation of paracetamol crystallization). The synthesis yield was 96.96% and the crystallization yield was 87.73%, the difference between the two yields is due to an error while filtration and drying. The crystal color was yellow and the HPLC showed only peaks for paracetamol. However, the yellow color of the crystals might indicate a presence for the impurity 4-nitrophenol.

Table 4.47 Crystal purity test information for the paracetamol synthesis with impurities & acetic anhydride in 2-propanol

Reaction information	2-propanol, with impurities
Amount	10 mg crystal, 100 ml water/methanol
Synthesis yield (%)	86.27
Crystallization yield (%)	63.61
Total dilution factor (-)	70876.86
Area (mPa)	1524.0
Crystal color	Light pink
Mass of sample (g)	0.162
Mass of diluent (g)	1.002

The synthetic reaction of paracetamol with impurities and acetic anhydride in 2-propanol (investigation of paracetamol crystallization in 2-propanol) showed light pink crystals with only paracetamol peaks in the HPLC. The synthesis yield was 86.27% and the crystallization yield was 63.61% as given in table (4.47). Synthesis yield is higher than crystallization due to the high solubility of paracetamol in 2-propanol.

Table 4.48 Crystal purity test information for the paracetamol synthesis with impurities & acetic anhydride in iso-amyl alcohol

Reaction information	Iso-amyl alcohol, with impurities
Amount	10 mg crystal, 100 ml water/methanol
Synthesis yield (%)	65.97
Crystallization yield (%)	31.22
Total dilution factor (-)	90085.69
Area (mPa)	151.5
Crystal color	Light yellow
Mass of sample (g)	0.124
Mass of diluent (g)	1.01

The synthetic reaction of paracetamol with impurities and acetic anhydride in iso-amyl alcohol (investigation of paracetamol crystallization in iso-amyl alcohol) showed light yellow crystals with only paracetamol peaks in the HPLC. The synthesis yield was 65.97% and the crystallization yield was 31.22%, for both yields it's considered low. For synthesis, it can be explained for the side reaction occurrence. For crystallization, due to the high solubility of paracetamol in iso-amyl alcohol at 5°C. However, the yellow color can indicate to an impurity presence. Information is given in table (4.48).

Conclusion & summary

The crystal purity test showed no presence for metacetamol and acetanilide and only paracetamol peak in the HPLC. However, HPLC can't detect 4-nitrophenol and it might be present in some samples. Also, 100% conversion of 4-aminophenol was achieved because there was no peak for it in the HPLC. But the synthesis yield was always less than 100%. That's due to many factors, HPLC instability or a possible side reaction occurring. Also for crystallization, it was never 100% yield, and that's due to filtration technique and high solubility of paracetamol at 5°C for iso-amyl alcohol and 2-propanol. Table (4.49), shows a comparison between synthesis and crystallization yield of paracetamol with/without impurities.

Table 4.49 Comparison between synthesis and crystallization yield among different synthetic reactions and solvents

Solvent	Water	Iso-amyl alcohol	2-propanol
Synthesis yield without impurities (%)	70.15	80.22	63.22
Crystallization yield without impurities (%)	71.07	57.60	65.40
Synthesis yield with impurities (%)	83.60	83.28	89.21
Crystallization yield with impurities (%)	89.33	24.21	48.68
Synthesis yield (investigations of crystallization) (%)	96.96	65.97	86.27
Crystallization yield (investigations of crystallization) (%)	87.73	31.32	63.61

From the synthesis reaction of paracetamol without impurities, the highest synthesis yield was iso-amyl alcohol > water > 2-propanol, this order can be explained due to the higher temperature used for water and iso-amyl alcohol. Iso-amyl alcohol had higher solubility than water because its alcohol. For crystallization the highest yield water > 2-propanol > iso-amyl alcohol. It can be explained due to the low solubility of paracetamol in water > 2-propanol > iso-amyl alcohol. Comparing the synthesis yield from the reaction of paracetamol with impurities, 2-propanol > water > iso-amyl alcohol, that's agree with the solubility studies which states that paracetamol is more soluble in alcohol. For crystallization, water > 2-propanol > iso-amyl alcohol, due to low solubility of paracetamol in water at 5°C. For the crystallization investigations yields, synthesis highest yield was water > 2-propanol > iso-amyl alcohol in these trials it might be instability of HPLC outcomes. For crystallization, again the best solvent was water > 2-propanol > iso-amyl alcohol.

4.9 Influence of different solvents on particle size and shape

After the investigations for the synthesis and crystallization of paracetamol, it was interesting to have a look at the particle size and shape using the optical microscope**.** Unfortunately, the size was difficult to obtain due to agglomeration of particles.

Figure 4.23 Crystals from the synthesis with impurities in iso-amyl alcohol

Figure (4.23) shows the particle size and shape for the crystals obtained from the synthetic reaction in iso-amyl alcohol. The crystals have a rod-like shape.

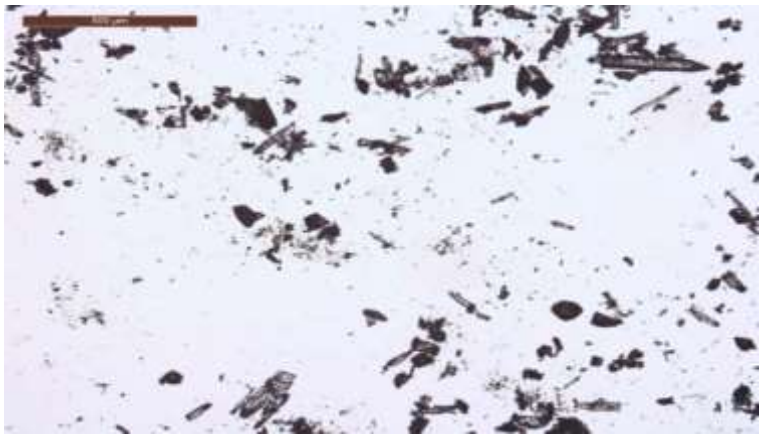


Figure 4.24 Crystals from the synthesis with impurities in water

However, crystals in figure (4.24) show more round particle. These crystals were obtained from the synthetic reaction in water.

Figure 4.25 Crystals from the synthesis with impurities in 2-propanol

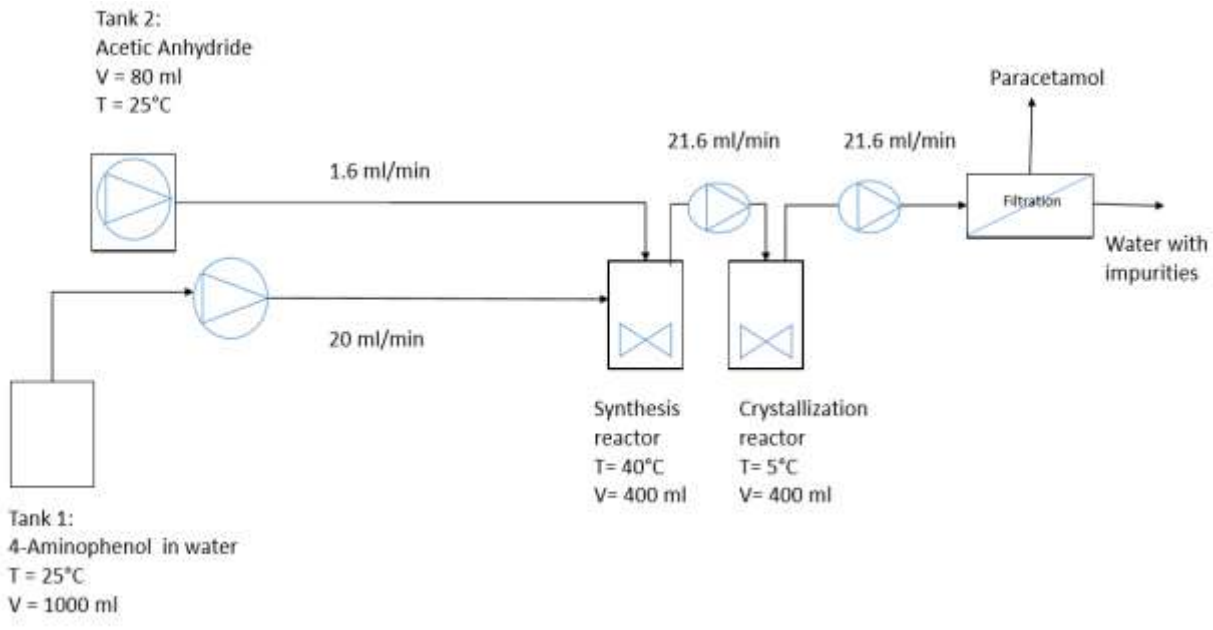
Also, the crystals obtained from 2-propanol (shown in figure (4.25)) had a prismatic to round particle shape.

Conclusion

Based on the microscopic images, the most round shaped particles were obtained from water > 2-propanol > iso-amyl alcohol. Having round shape particles is important for further processes.

4.10 Continuous set-up

The aim for building the continuous set-up was to couple the synthesis part with the crystallization part based on the collected parameters and information from the previous explained batch investigations. The used HPLC method was methanol 5%: buffer 95% solution because it didn't harm the column although it wasn't applicable to obtain the 4-nitrophenol peak. From the batch experiments, the investigations of impurities behavior showed no reaction with acetic anhydride in any solvent and all of them were soluble in solution after crystallization. The investigations of 4-aminophenol with and without impurities showed that the highest crystallization yield was obtained using water as a solvent with 20 mmol acetic anhydride. Higher temperatures didn't show any improvement to the reaction. Thus, the starting points for the continuous set-up were: the reaction at 40°C, the experiment from the investigation of paracetamol synthesis with impurities in acetic anhydride with water will be scaled-up to the continuous set-up reactor volume with synthesis time 20 minute pumping with 1.6 ml/min flowrate for acetic anhydride pump, 20 ml/min for the solid suspension pump. For crystallization, the time will be 20 minute with 21.6 ml/min flowrate.



Scheme 4.1 Schematic diagram for the continuous process for integrated synthesis and crystallization of paracetamol

As shown in scheme (4.1), tank (1) had water, 4-aminophenol and impurities at 25°C pumped with a peristaltic pump (GP 1000) to the synthesis reactor (CSTR Vmax=400 ml) using silicon pipe with 4.8x2.4 mm (outer/inner diameter) with 20ml/min flow rate. The synthesis reactor was covered by a GL 18 and heated up with water bath to 40°C. For the acetic anhydride, it was pumped using a syringe pump (represented in the scheme as tank (2)) to the synthesis reactor with 1.6 ml/min flow rate. From the synthesis reactor to the crystallization reactor (CSTR Vmax= 400ml) a peristaltic pump Ismatec type was used with silicon type 4x2 mm (outer/inner diameter) with 21.6ml/min flow rate. The crystallizer was covered with GL 18 cover and cooled with water bath 5°C. Using another peristaltic pump Ismatec type with silicon type 4x2 mm (outer/inner diameter) the crystallized paracetamol was pumped into a Buchner funnel for filtration with 21.6 ml/min flow rate. More details about the manufacturers of equipment's and material are mentioned in chapter 3.

Table 4.50 Materials and amounts that are used in the continuous set-up for 1 residence time

Entity	**Amounts in batch scale**	**Amounts for Vr=400 ml**	**scale up factor**
water	25 ml	400 ml	16
Ac_2O	2 ml	32 ml	
4-AP	1.808 g	28.928 g	
4-NP	0.0953 g	1.5248 g	
Acetanilide	0.0839 g	1.3424 g	
Metacetamol	0.0998 g	1.5968 g	

Table (4.50) shows the batch experiment used amounts and the scaled- up that was used in the synthesis reactor. The scale-up factor was calculated by dividing by the full CSTR reactor volume (Vmax = 400 ml) over the batch volume. These number were used in the trials (1 and 2).

Table 4.51 Materials and amounts that are used in the continuous set-up for 2.5 residence time

Entity	**Amounts batch scale**	**Amounts in Vr=1000 ml**	**scale up factor**
water	25 ml	1000 ml	40
Ac_2O	2 ml	80 ml	
4-AP	1.808 g	72.32 g	
4-NP	0.0953 g	3.812 g	
Acetanilide	0.0839 g	3.356 g	
Metacetamol	0.0998 g	3.992 g	

Table (4.51) shows the batch experiment used amounts and the scaled- up that was used in the tank (1). The scale-up factor was calculated by dividing by a 2.5 full CSTR reactor volume (Vmax= 400ml) over the batch volume (25 ml) to have a continuous operations for 2 residence time and a half. These numbers were used in all trials and the batch amounts of 4-aminophenol and impurities were scaled-up by factor 40, scaled-up values are given in table (4.52).

Table 4.52 Paracetamol synthesis reaction information using the continuous set-up

Material	Water	Ac_2O	4-AP	4-NP	MCM	Acetld
State	Liquid	Liquid	Solid	Solid	Solid	Solid
Mass (g)	1000	-	72.3	3.812	3.9918	3.356
Volume (ml)	1000	80	-			
Molecular weight (g/mol)	18.015	102.09	109.13	139.11	151.16	135.17
Number of moles (mol)	55.51	0.85	0.66	0.03	0.03	0.02
Density (Total volume)[g/ml]	0.9259	0.0800	0.0723	0.0038	0.0040	0.0034
Concentration (Total volume) [mole/L]	51.3975	0.7836	0.6137	0.0254	0.0245	0.0230
Mole equivalence	65.59	1.42	1.00	0.03	0.03	0.03

The tank flow rate was calculated by dividing the full CSTR volume (Vmax= 400 ml) over the batch time (20 min). The acetic anhydride was calculated by dividing the water pump flow rate over the ratio between the water batch amounts to the acetic anhydride batch amount (25:2). Residence time is calculated by dividing the full tank volume over the water pump flow rate. Vales are given in table (4.53).

Table 4.53 Used flow rates in the set-up

Water pump flow rate=	400/20	20 ml/min
Ac2O pump flow rate=	20/12.5	1.6 ml/min
Residence time =	400/20	20 min

Five trials with different parameters for the continuous set-up were carried out. Every trial had a problem which was solved for the next trial. The biggest challenge was the high solid handling amount that has been pumped from tank (1) as seen in scheme (4.1). Also, a blocking in the pipes towards the synthesis reactor occurred. Furthermore, the pipes from the synthesis reactor to the crystallization reactor had blocking in one trial. From the crystallization reactor to the filtration part in some trials didn't show any blocking and in some trials it did.

Trial (1):

The first trial was done by preparing 1 liter of solvent (water) with impurities and crude 4-aminophenol in the tank (1) as given in table (4.51). The reactor volume was used to its maximum capacity of 400 ml with impurities, amounts for this reactor are available in table (4.50). The principle was to have 1 liter of water with impurities at 25°C in tank (1), acetic anhydride in the tank (2) at 25°C and, impurities with 400 ml water heated up with water bath at 40°C. The crystallization reactor was empty adjusted with a water bath at 5°C. Two peristaltic pumps Ismatec® type were used, one to pump from tank (1) to the synthesis reactor and another one from the synthesis reactor to the crystallization reactor. A syringe pump was used for pumping acetic anhydride to the synthesis reactor with a Y-shaped connector. The experiment was designed for 2.5 residence times which means 2 full reactor volumes and a half will be used. The peristaltic pump flow rate was 20 ml/minute and 1.6 ml/minute for syringe pump. During the process, the pipes didn't withstand that long and a blocking occurred in the pipes going out from tank (1) and most of the solid components were precipitating in the bottom of tank (1) even with the usage of stirrer bar.

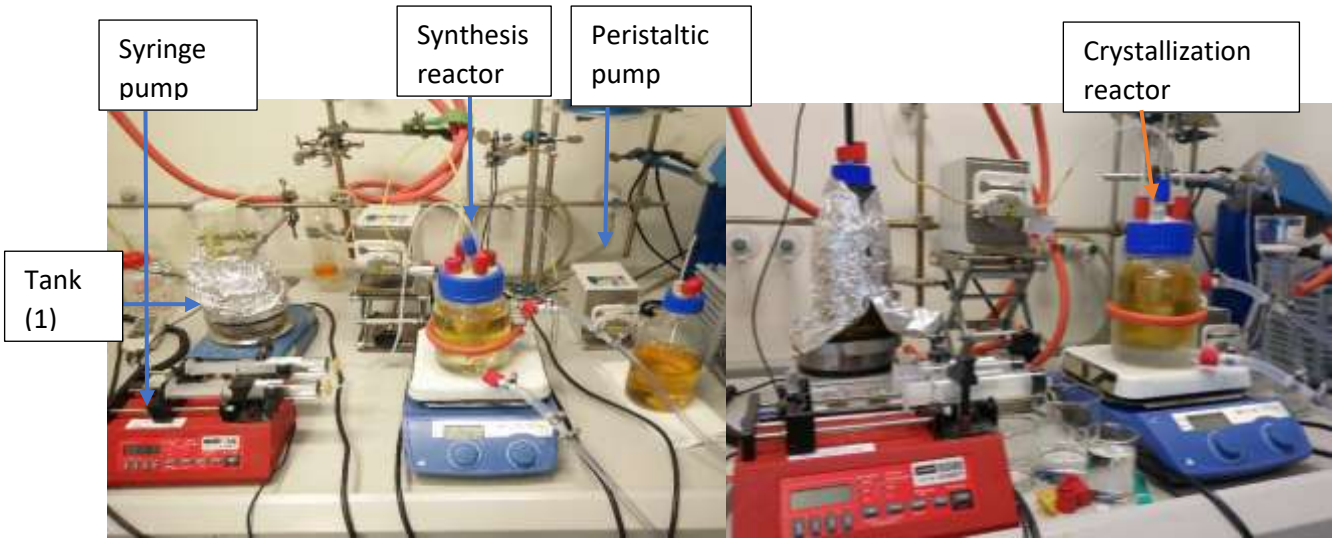


Figure 4.26 Trial (1) step-wise set-up for the synthesis and crystallization of paracetamol

Figure (4.26) shows the step-wise set-up for the synthesis and crystallization of paracetamol. The picture on the left represents the synthesis set-up which was built first and the product from it was stored in the fridge overnight for the next day. The picture on the right represents the crystallization set-up which was built next day from the synthesis set-up. The product was heated up to 40°C in order to simulate the synthesis temperature. The crystallization reactor was cooled to 5°C.

Trial (2):

This trial was done step-wise by starting with the synthesis part then with the crystallization part to make sure if the available pipes can withstand through the process. The starting amounts for the tank (1) given in table (4.51) and the starting amounts for the synthesis reactor given in table (4.50).

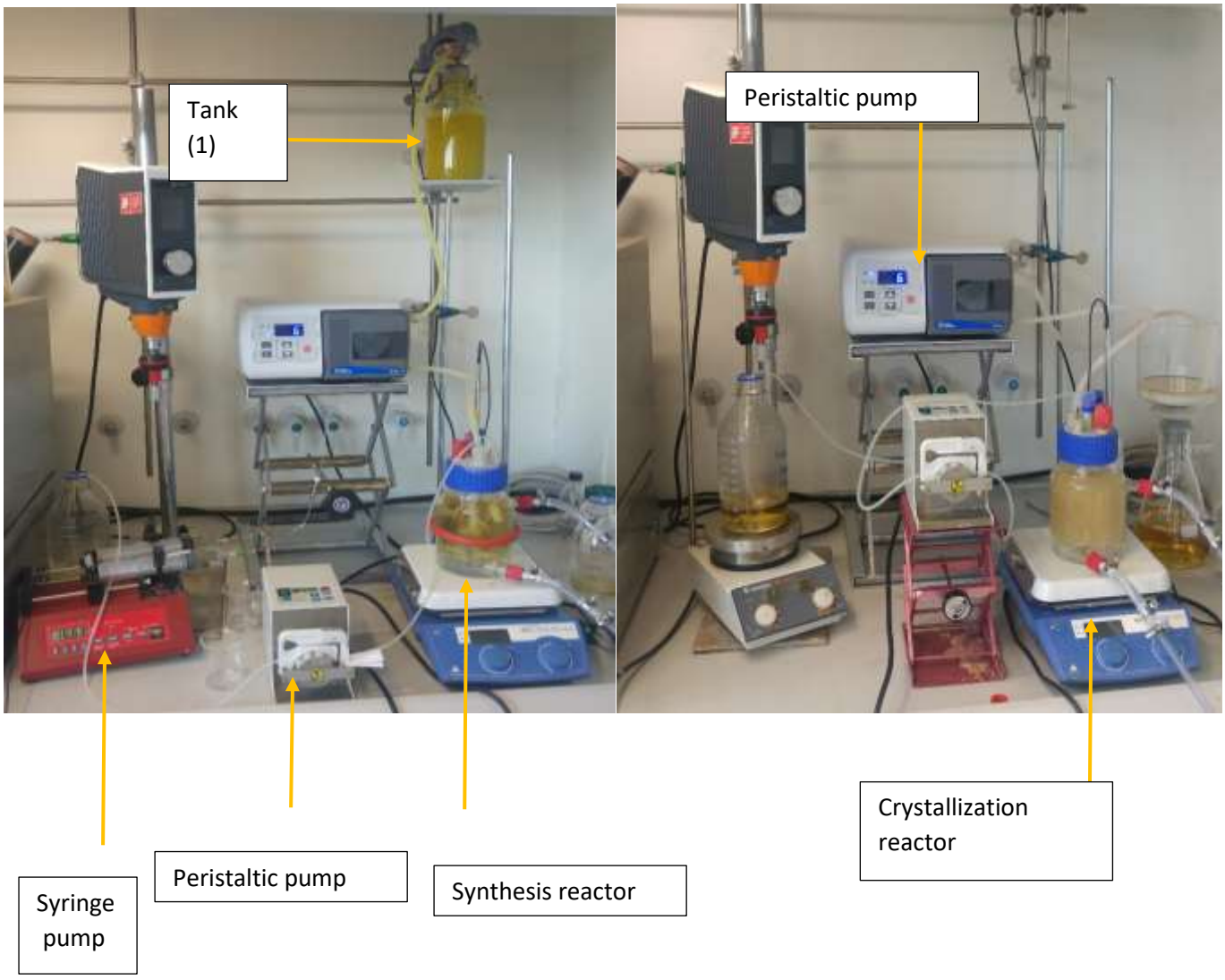


Figure 4.27 Step-wise set-up for the synthesis and crystallization of paracetamol trial (2)

Figure (4.27) shows the set-up for the step-wise synthesis and crystallization of paracetamol in trial (2). The reaction was performed at 40°C for the synthesis and 5°C for crystallization.

Table 4.54 Sampling at different time intervals for the synthesis of paracetamol using continuous set-up

No.	t (min)	T (°C)	Sample weight (g)	MeOH: H_2O (g)	Total D.F	Area PCM (mAU), tr= 1.2 (min)	PCM conc. (mol/L)	Area M+A, tr= 3.2 (min)	M+A conc. (mol/L)
1	ST	25	0.1	1.0	103.7	12.9	0.00	1192.9	0.06
2	SR	40	0.1	1.0	244.7	0	0.00	1685.2	0.21
3	5	40	0.1	1.0	86.0	437.6	0.02	1856.2	0.08
4	10	40	0.1	1.0	60.0	1153.8	0.03	2134.6	0.06
5	15	40	0.1	1.0	115.0	1744	0.10	815.2	0.05
6	20	40	0.1	1.0	47.6	6960.2	0.17	2678.6	0.06
7	25	40	0.1	1.0	47.3	7606.9	0.18	2286.2	0.05
8	30	40	0.1	1.0	84.7	4884.6	0.21	1423.8	0.06
9	35	40	0.1	1.0	82.7	4208.3	0.17	1237.3	0.05
10	40	40	0.1	1.0	86.7	4004	0.17	1207.7	0.05
11	45	40	0.1	1.0	50.2	6271.8	0.16	1726.1	0.04
12	50	40	0.1	1.0	67.8	5630.7	0.19	1711.9	0.06
13	SRf	40	0.1	1.0	88.5	4120.6	0.18	1116.7	0.05

For the synthesis part, thirteen samples were withdrawn during the reaction by detaching the peristaltic pump tube from the GL 18 cover. The cover was tighten with para film in order to detach it easily. Each sample was taken after five minutes. In table (4.54), ST is the sample taken from tank (1), SR is the sample taken from the synthesis reactor at time 0 and SRf is the sample taken from the reactor after the end of the experiment.

Table 4.55 Sampling at different time intervals for the crystallization of paracetamol using continuous set-up

No.	t (min)	T (°C)	Sample weight (g)	MeOH:H_2O (g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	C PCM (mol/L)	Area M+A, tr= 3.2 (min)	C M+A (mol/L)
1	CR	5	0.1	1.0	112.4	4347.5	0.24	474.7	0.03
2	5	5	0.1	1.0	90.3	3824.6	0.17	1007.4	0.05
3	10	5	0.2	1.0	70.8	4455	0.16	1315.9	0.05
4	15	5	0.1	1.0	88.9	3340.6	0.15	928.3	0.04
5	20	5	0.1	1.0	65.1	1492.4	0.05	452.7	0.01
6	25	5	0.1	1.0	61.5	3261.2	0.10	774.7	0.02
7	30	5	0.1	1.0	118.6	3833.1	0.23	778.9	0.05
8	35	5	0.1	1.0	120.3	898.4	0.05	6.9	0.00
9	40	5	0.1	1.0	82.2	3500.1	0.14	1108	0.05
10	45	5	0.1	1.0	94.4	3235.7	0.15	795.8	0.04
11	50	5	0.1	1.0	122.9	2518.7	0.15	834.3	0.05
12	R(ML)	5	0.1	1.0	94.2	3083	0.15	1086.2	0.05
13	T(ML)	25	0.1	1.0	78.2	4596.8	0.18	1444.8	0.06

The crystallization part was done after one day from the synthesis. The reactor was full with water and impurities at 5°C and the tank was heated to 40°C and pumped to the reactor with 21.6 ml/min and out with the same flowrate to the filtration part. A sample was taken every five minutes by detaching the peristaltic pump pipe. In table (4.55), CR represents crystallizer reactor sample, R(ML) the sample was taken after filtrating the residual crystals from the crystallizer mother liquor and T(ML) is the filtrate mother liquor from the final tank. The crystallization yield was 21.38%.

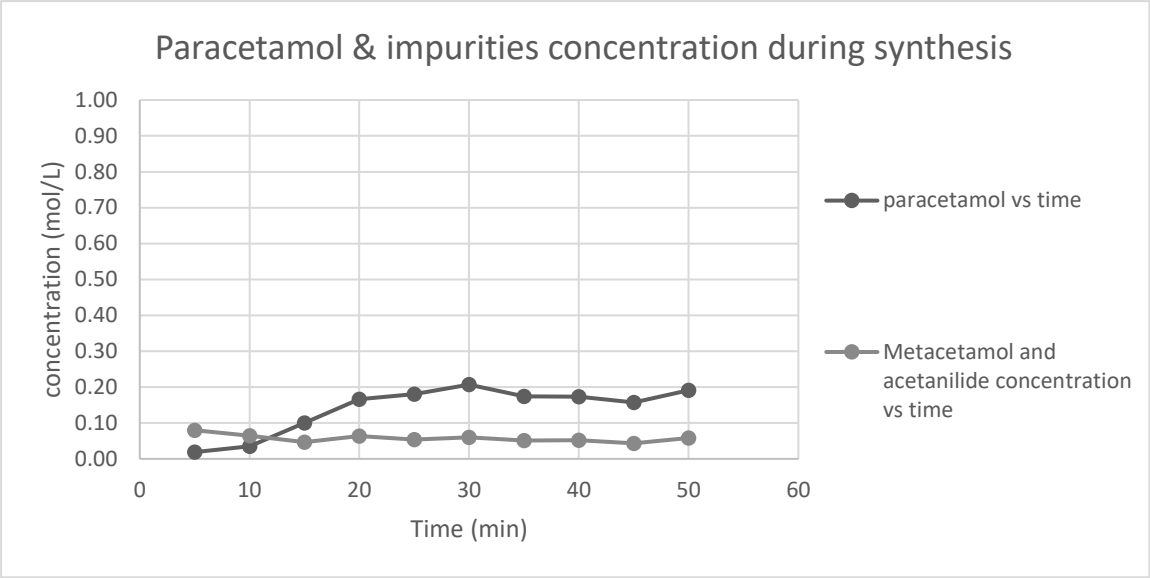


Figure 4.28 Trial (2) synthesis part concentration values over time

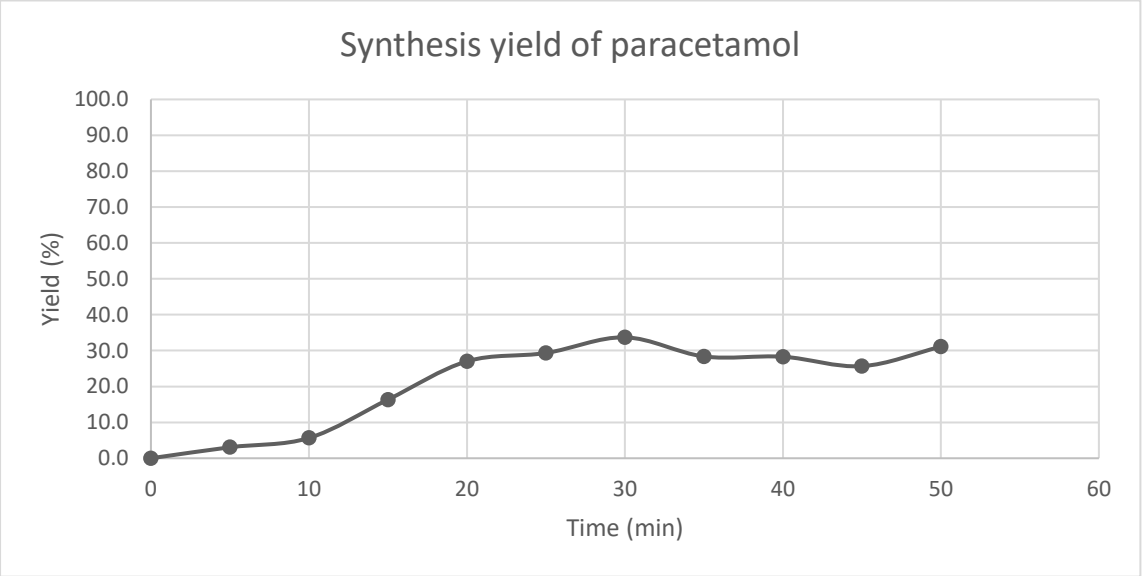


Figure 4.29 Synthesis yield of paracetamol trial (2) over time

Figure (4.28) shows paracetamol concentration over time for trial (2). The concentrations were increasing and then had a constant trend. Also, looking at the synthesis yield (27%) over time in figure (4.29), it showed a good trend. For metacetamol and acetanilide, they had an almost constant amount over time.

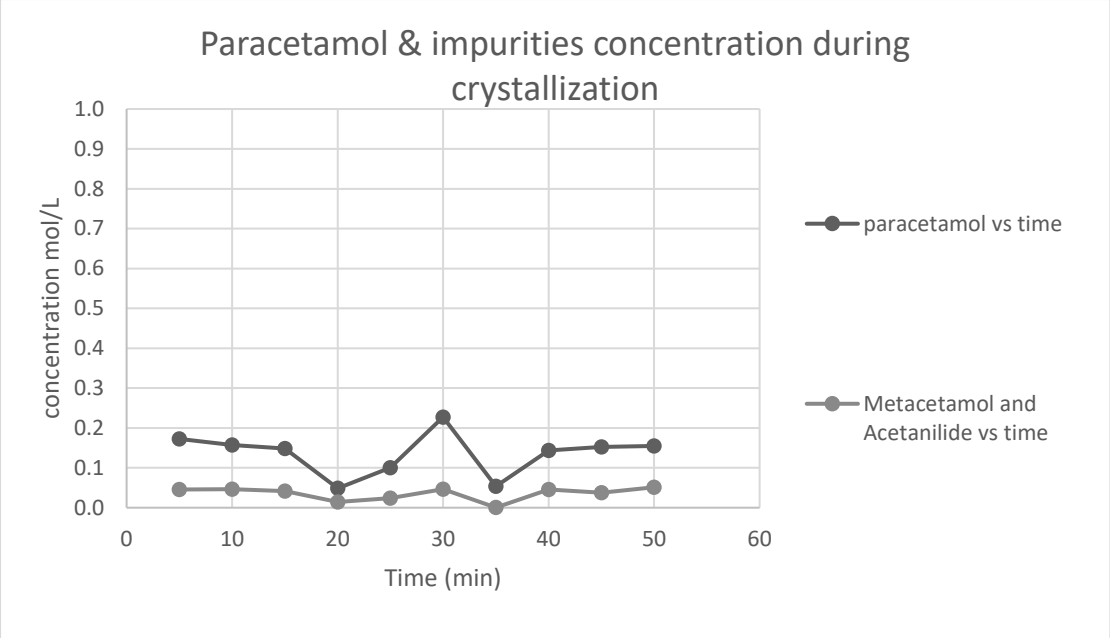


Figure 4.30 Trial (2) crystallization part concentration values over time

For the crystallization part, it was not constant like the synthesis. The paracetamol amount should be decreasing then constant over time but it had some fluctuation. However, metacetamol and acetanilide showed constant concentration over time as seen in figure (4.30).

Trial (3):

Due to the instability with the HPLC results in trial (2), it was advantageous to do this trial without impurities and not to add water to the reactor. So, the pumped material was directly pumped to the empty reactor immediately. However, a smaller tube was added to the pipe pumping out from the tank to the synthesis reactor to improve the solid handling. But it didn't help and there was no crystal appearing with time. So, this trial is considered a failure.

Trial (4):

The added tube to the tank was removed. The idea from this trial was to do the synthesis for 20 minutes which provides full reactor volume and there will be no disturbance from the pipe to the stirrer blade and won't stop during the process. Then the material is pumped out to the crystallizer after 20 minute. The pumping out from the crystallizer was done immediately. However, few crystals appeared during pumping. The tank amounts as given in table (4.51) and the temperature in the synthesis reactor at 40°C and 5°C for crystallization without impurities.

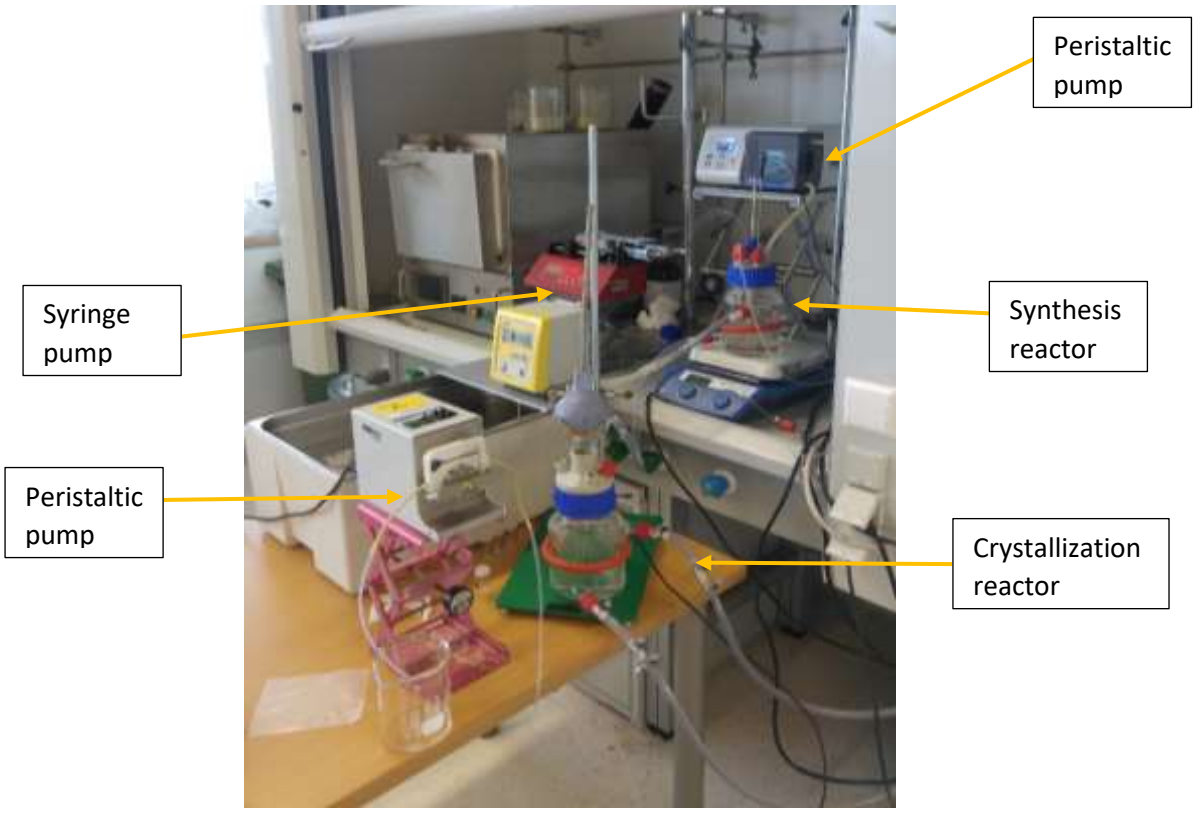


Figure 4.31 Synthesis and crystallization continuous set-up for paracetamol trial (4)

Figure (4.31) shows the continuous set-up for the synthesis and crystallization of paracetamol with impurities in trial (4).

Table 4.56 Trial (4) sampling at different time intervals for the synthesis of paracetamol

No.	t (min)	T (°C)	Sample weight (g)	MeOH: H_2O (g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	C PCM , (mol/L)
1	ST	25	0.1	1.0	121.5	0	0.00
2	5	40	0.1	1.0	94.3	2117.5	0.10
3	10	40	0.1	1.0	72.0	2857.4	0.10
4	15	40	0.1	1.0	89.7	3771.2	0.17
5	20	40	0.1	1.0	157.1	1856.03	0.15
6	25	40	0.1	1.0	74.9	3060	0.11
7	30	40	0.1	1.0	89.6	5317	0.24
8	35	40	0.1	1.0	78.7	4371.4	0.17
9	40	40	0.1	1.0	97.7	5280.9	0.26
10	45	40	0.1	1.0	97.4	4174.2	0.20
11	50	40	0.1	1.0	95.2	2923.2	0.14

11 samples were taken (by detaching the pipe from GL 18) at different time intervals as shown in table (4.56). Some of the paracetamol areas showed a stable increase but mostly didn't show a nice trend.

Table 4.57 Trial (4) Sampling at different time intervals for the crystallization of paracetamol

No.	t (min)	T (°C)	Sample weight(g)	MeOH: H_2O (g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	C PCM (mol/L)
1	5	5	0.1	1.0	106.0	3075.4	0.16
2	10	5	0.1	1.0	101.8	2041.8	0.10
3	15	5	0.1	1.0	82.8	3663.6	0.15
4	20	5	0.1	1.0	95.5	2440.6	0.12
5	25	5	0.1	1.0	103.5	1093.6	0.06
6	30	5	0.1	1.0	112.7	2677.7	0.15
7	35	5	0.1	1.0	209.3	3892.4	0.41
8	40	5	0.1	1.0	113.5	2382.1	0.14
9	45	5	0.1	1.0	91.4	1655	0.08
10	50	5	0.1	1.0	102.6	2488.3	0.13
11	F(ML)	25	0.1	1.0	114.3	2715.7	0.16

As shown in table (4.57) samples were taken every 5 minutes but there were few crystals appearing. And after drying the obtained crystal the yield was 6.41% which relatively low percentage compared to the obtained crystal yield (21.38%) from the step-wise set-up. F(ML) the sample taken from the filtration mother liquor. The sample showed an amount of paracetamol although it shouldn't have any presence of it. Based on solubility data in section (4.1), paracetamol has low solubility in water at 5°C. This presence of paracetamol might be due to inefficient filtration technique.

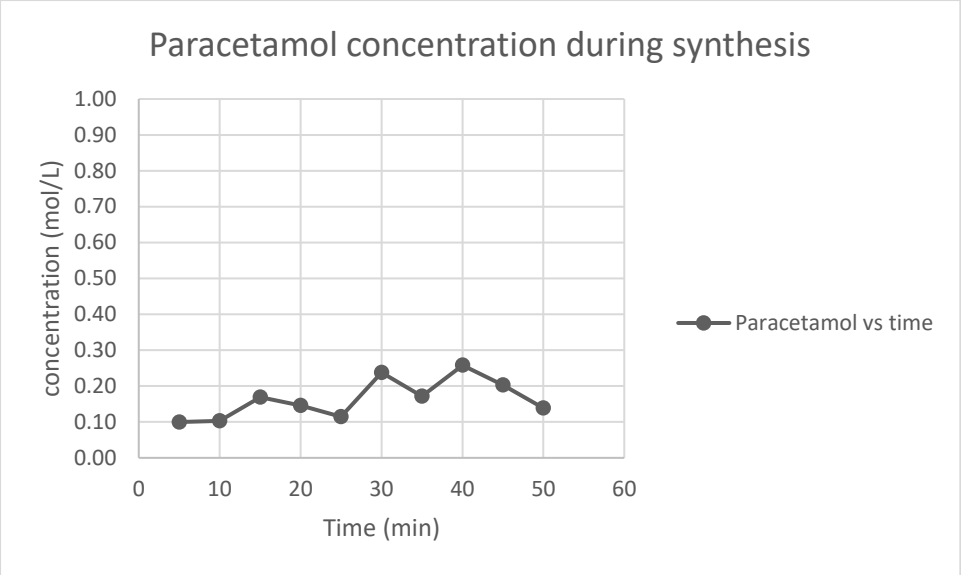


Figure 4.32 Trial (4) synthesis part concentration values over time

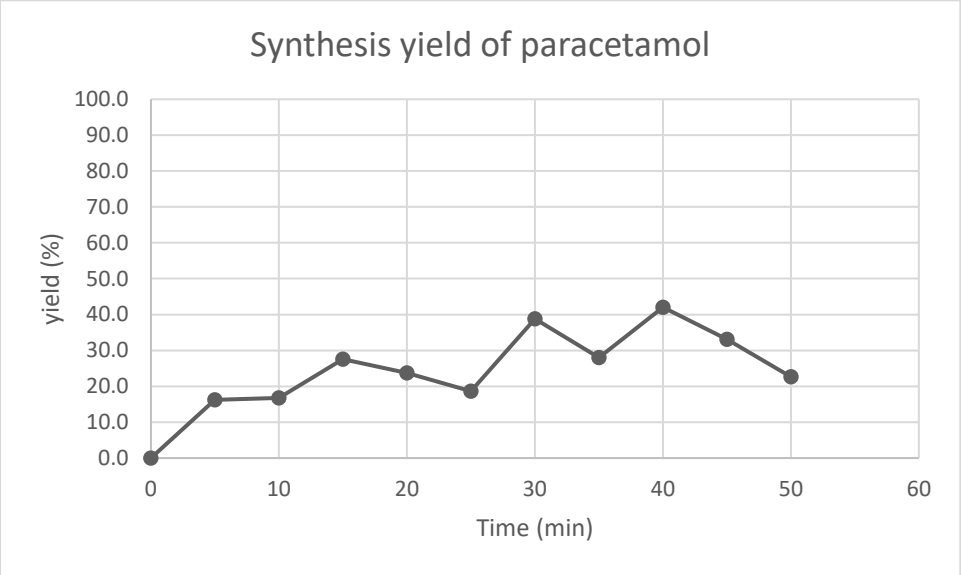


Figure 4.33 Synthesis yield of paracetamol trial (4)

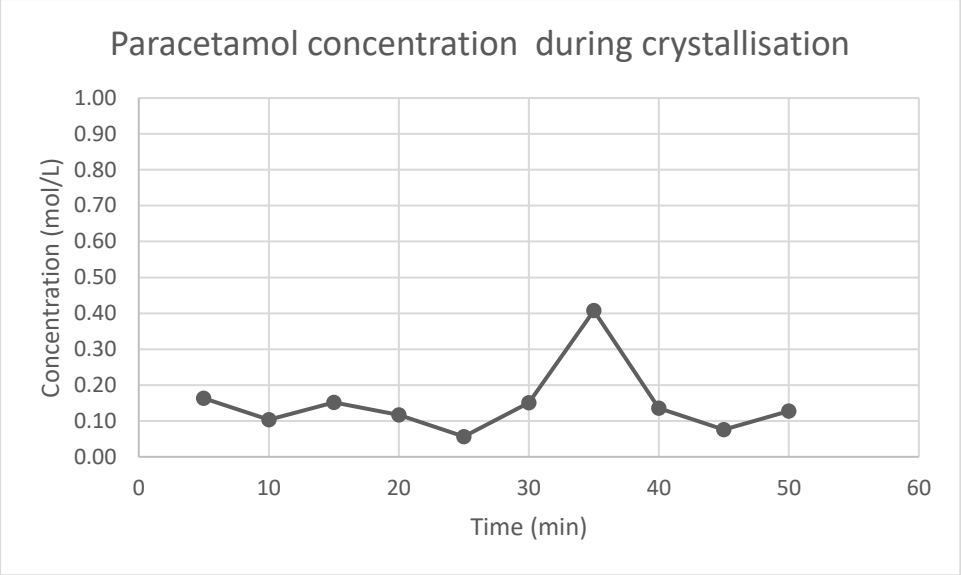


Figure 4.34 Trial (4) crystallization part concentration values over time

Figure (4.32) shows, that the paracetamol concentration over time was not stable. Also, in figure (4.33) the paracetamol synthesis yield over time was not stable. Figure (4.34) shows the paracetamol concentration over time in crystallization. The concentrations were not constant.

Trial (5):

This trial procedure was done by running the synthesis reactor for 20 minute (to obtain full reactor volume and a complete residence time at 20 minute) then pumping the material to the crystallizer for 20 minutes, in both cases when the reactor reached the full volume, pumping to the next unit operation started. That's in order to prevent pipes from interrupting the stirring and to give the crystals more time in the crystallizer to crystallize. Same residence time, flow rates, temperature and material amounts were used as given in table (4.46 & 4.47) but without using impurities.

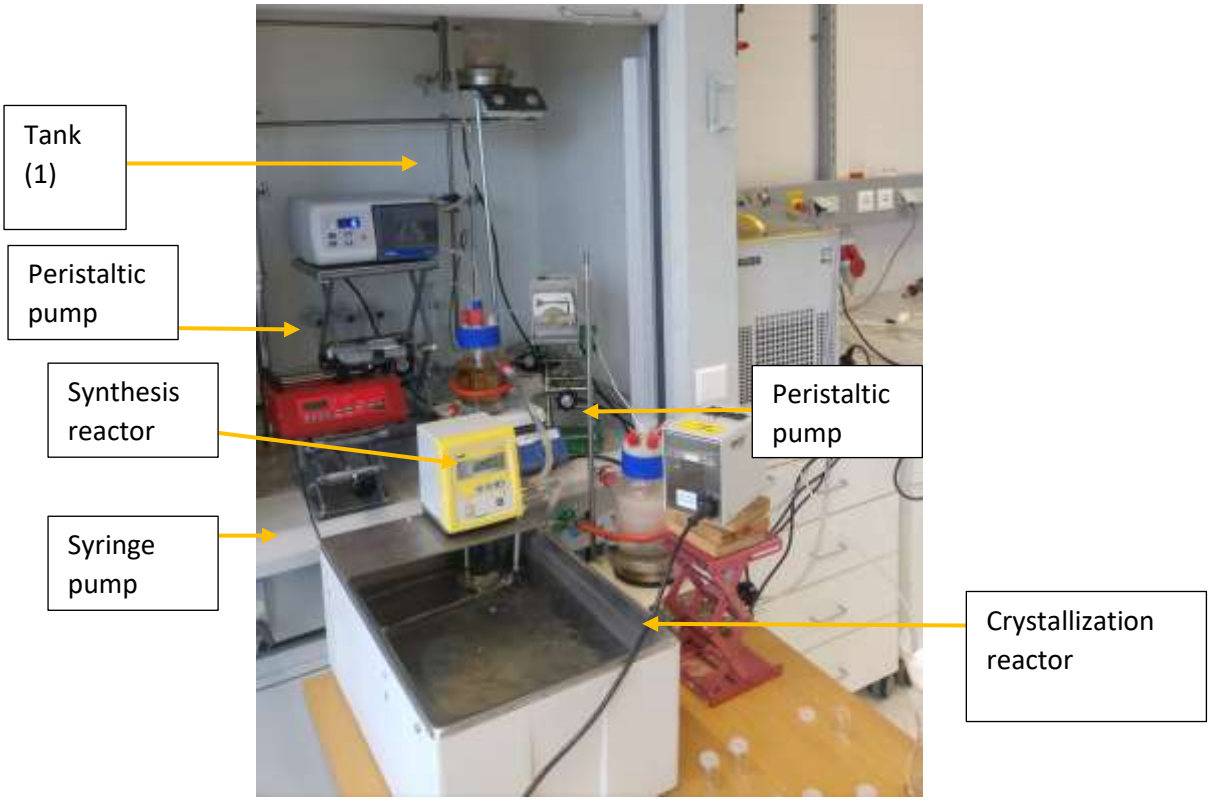


Figure 4.35 Synthesis and crystallization continuous set-up for paracetamol trial (5)

Figure (4.35) shows the continuous synthesis and crystallization of paracetamol in continuous set-up for trial (5). In this set-up, more crystals were formed and no crystal growth on the walls of crystallizer or the bottom occurred and thus primary nucleation occurred but a blocking in the pipes from crystallizer to the filtration part occurred and the process was stopped twice for solving the problem.

Table 4.58 Trial (5) Sampling at different time intervals for the synthesis of paracetamol

No.	t (min)	T (°C)	Sample weight (g)	MeOH :H_2O (g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	C PCM (mol/L)
1	ST	25	0.1	1.0	104.2	0	0.0
2	5	40	0.1	1.0	116.8	2665.8	0.1
3	10	40	0.1	1.0	87.4	1515.1	0.1
4	15	40	0.1	1.0	171.9	1219.8	0.1
5	20	40	0.1	1.0	77.4	3374.9	0.3
6	25	40	0.1	1.0	199.9	2617.5	0.1
7	30	40	0.1	1.0	121.2	3554.1	0.4
8	35	40	0.1	1.0	189.4	1585	0.1
9	40	40	0.1	1.0	136.1	3115.4	0.3
10	45	40	0.1	1.0	70.4	2866.4	0.2
11	50	40	0.1	1.0	124.1	2546.3	0.1

Samples were taken every 5 minutes, areas obtained from HPLC show more stable values than the previous trial (4). In table (4.58) ST, represents the sample taken from the tank before synthesis.

Table 4.59 Trial (5) Sampling at different time intervals for the crystallization of paracetamol

No.	t(min)	T (°C)	Sample weight (g)	MeOH :H_2O (g)	Total D.F	PCM peak (mAU), tr= 1.2 (min)	C PCM (mol/L)
1	5	5	0.1	1.0	130.6	2352.2	0.1
2	10	5	0.1	1.0	226.3	2697.8	0.1
3	15	5	0.1	1.0	110.0	2031.6	0.1
4	20	5	0.1	1.0	116.3	4109.7	0.2
5	25	5	0.1	1.0	155.9	2799.7	0.1
6	30	5	0.1	1.0	70.2	0.0	0.0
7	35	5	0.1	1.0	164.4	1754.8	0.1
8	40	5	0.1	1.0	71.9	3561.5	0.2
9	45	5	0.1	1.0	95.7	2379.6	0.1
10	50	5	0.1	1.0	213.0	1197.0	0.1

For the crystallization part, as given in table (4.59), samples were taken every 5 minutes. Sample (6), wasn't deductible with HPLC. Samples from the filtration mother liquor was taken and showed a certain amount of paracetamol. Testing the crystal purity using HPLC showed only appearance of paracetamol peak. The crystallization yield was 21.24% which is closer to the discontinuous process crystallization yield 21.38 %.

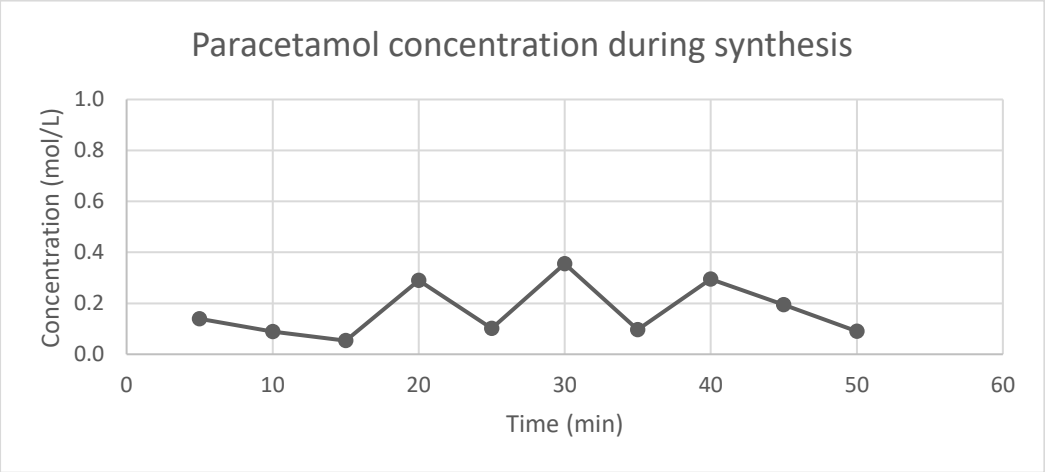


Figure 4.36 Trial (5) synthesis part concentration values over time

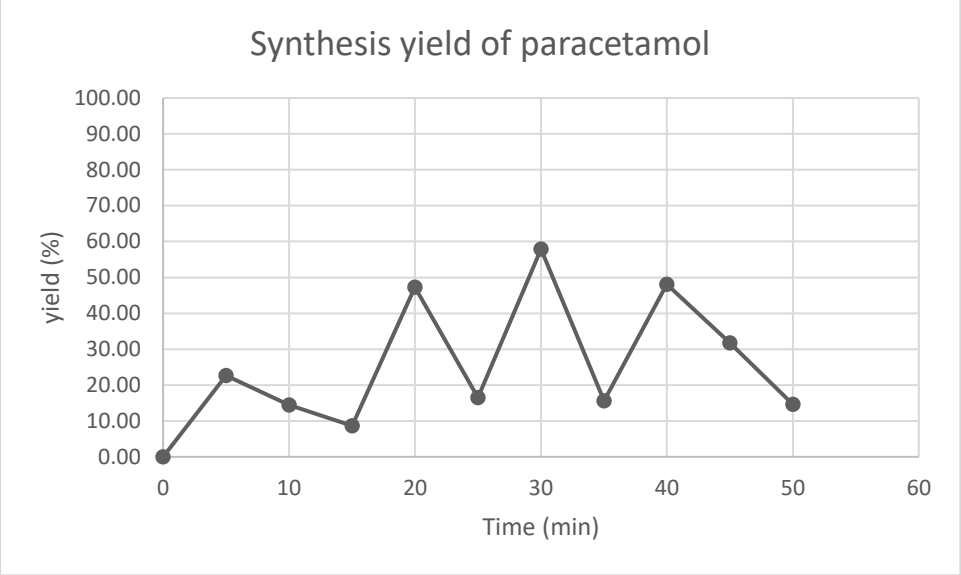


Figure 4.37 Synthesis yield of paracetamol trial (5)

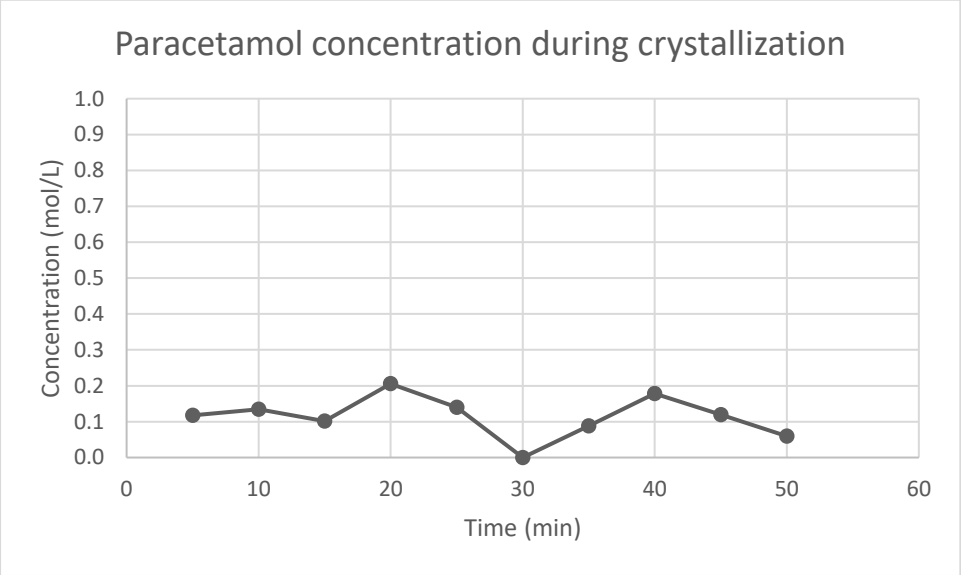


Figure 4.38 Crystallization part concentration values over time trial (5)

Figure (4.36) presents the paracetamol concentration during the synthesis process over time. The concentration shows fluctuation and steady state might not have been reached. Figure (4.37) presents the synthesis yield in trial (5), also, it shows unstable increase for paracetamol. Figure (4.38), presents the crystallization concentration over time, it's a bit better than synthesis but still it's not constant.

Conclusion & summary

The aim for building the continuous set-up was coupling the synthesis and crystallization processes for the manufacturing of paracetamol. After determining the parameters from batch experiment , which is synthesis process at 40 °C, crystallization process at 5 °C, using water as a solvent and the water batch-experiment amount for scaling-up to the continuous process. First trial had problems with pumping from the tank to the synthesis reactor. A new pump was used from the tank to synthesis reactor and the trial was set step-wise in order to test the efficiently of the new pump. The trial worked out and it gave 21.38% crystallization yield. However, the yield is considered very low and a small pipe was adjusted to the bigger pipe in the peristaltic pump from the tank to the synthesis reactor. This trial was a failure and the adjusted pipe didn't help and it was removed in the next trial. So, the next trial had no smaller pipe and was set continuously but the procedure differed from before. In this trial the synthesis reactor was left to synthetize for a full residence time which is 20 minute, then pumping occurred to the crystallizer and from crystallizer to the filtration part. This trial gave 6.41% crystallization yield. In the last trial the procedure was also changed in order to give the crystallizer more time to crystallize. So, the trial was set by operation the synthesis reactor for 20 minutes then pumping to the crystallizer without pumping out from it for 20 minutes. Then after reaching volume in crystallization reactor pumping to filtration part start. This procedure was successful in obtaining crystallization yield of 21.24%. However, it didn't show a constant paracetamol concentration and a blocking occurred in the pipes between crystallizer and filtration part.

V. Conclusion and Outlook

This section will be divided into 8 main parts, which is: 1: HPLC analyses, 2: Challenges with 4-aminophenol, 3: Investigations of impurities reaction with acetic anhydride in water and iso-amyl alcohol, 4: Investigation of paracetamol synthesis with acetic anhydride in different solvents (iso-amyl alcohol, 2-propanol and water), 5: Investigations of paracetamol synthesis with impurities & acetic anhydride in different solvents (iso-amyl alcohol, 2-propanol and water), 6: Crystal purity, 7: Influence of different solvents on particle size and shape & 8: Continuous set-up.

The HPLC mobile phase of methanol 5%: HPLC-water 95% was changed due to the problems with 4-aminophenol. The new mobile phase methanol 5%: buffer 95% was convenient with the HPLC column and the 4-aminophenol presence did not harm it. However, it was not efficient to investigate the peak of 4-nitrophenol and to separate metacetamol and acetanilide.

The aim from milling 4-aminophenol before starting the synthesis was to unify the particle size distribution in the suspension for the up-coming batch and continuous set-up experiments. However, the decomposition of 4-aminophenol with heat and light was not controllable. Thus, the experiment for re-crystallizing 4-aminophenol was developed but the new material needed further investigations with FTIR or other analytical method and more batch experiments to discover the nature of whether it is 4-aminophenol or not.

The impurities did not show any reaction with acetic anhydride in water or iso-amyl alcohol and it had a constant concentration through the reaction. Even after cooling the resulted solution in the fridge at 5°C, there was no presence of crystals.

For the paracetamol synthesis without impurities, the best solvent concerning crystallization yield was water (71.07%) > 2-propanol (65.35%) > iso-amyl alcohol (57.62%).

The addition of impurities to the synthesis reaction has increased the percentage yield of paracetamol synthesis in water. However, the highest crystallization yield was water (89.33) > 2-propanol (48.68) > iso-amyl alcohol (28.73) due to the impure crystal.

In both parts, the conversion of 4-aminophenol was 100% (there was no presence of it in the HPLC). But the yield didn't reach 100% due to many factors: filtration technique, losses during sampling and the possibility for a side reaction.

It can be concluded from the crystal purity that the 4-aminophenol got 100% conversion into paracetamol. No presence for metacetamol and acetanilide could be detected in pure crystals but in solution (reaction mother liquor) which is the main goal. However, due to the deficiencies that were faced with the HPLC, it was hard to detect 4-nitrophenol. It is recommended to use the methanol 5%: HPLC-water95% mobile phase for further investigation only to detect the presence of 4-nitrophenol.

The obtained microscope images showed rod-like particles for paracetamol crystals synthesized from iso-amyl alcohol, prismatic to round shape particles synthesized from 2-propanol and the most round shape being obtained from the synthesized reaction in water. Though paracetamol particles synthesized in water did not show a spherical shape. Moreover, the microscopic image is not 100% reliable due to the hygroscopicity of the particles and it was difficult to obtain better images for the current crystals.

Out of the findings of the batch experiments, a continuous set-up was created with the following parameters: water as a solvent, reaction temperature 40°C and the amounts of acetic anhydride, 4- aminophenol & impurities (acetanilide, metacetamol and 4-nitrophenol) scaled-up from batch experiment to the continuous reactor volume.

The most stable trial was number five due to the new procedure where it gave better crystals, and the nearest yield to discontinuous trial. However, the problem of pumping high amounts of solid from tank (1) needs more improvement. For the synthesis reactor, it showed stable pumping out. The crystallizer in this trial was in the best shape between all trials. It had no crystals growing on the walls nor on the bottom which indicated the primary nucleation of the particles but still was not reliable due to the blocking in the pipes. It is recommended to use a similar peristaltic pump to the tank between the crystallizer and the filtration part. Additionally, to use a better technique for filtration rather than Buchner funnel.

VI. References

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