Synthesis of Aspirin

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Abstract:

Aim

The aim of this project was to synthesise aspirin using two methods of heating and to compare the percentage yield and melting points of the product synthesised by the two methods.

Overall findings

The two methods were duplicated giving the following results;
The first method involved heating using hot plate and was found to have a percentage yield of 66.8% and 67.9% and a melting point of 135-136°C and 135-136°C.
The second method involved heating using a microwave and was found to have a percentage yield of 40.1% and 63.4% and a melting point of 120-122°C and 135-136°C.
Both aspirin samples made with method 1 had higher yields than method 2 and both samples made by method 1 had melting point values close to the actual melting point of aspirin (136°C). Only the duplicate of method 2 gave a melting point close to the actual melting point of aspirin.

Introduction

Aspirin ($C_9H_8O_4$) is an ester formed of two substances, Acetylsalicylic (Salicylic) acid and Ethanoic Anhydride, by a condensation reaction. Aspirin is a non-steroidal anti-inflammatory (NSAID) drug which can be used to treat pain, fever, inflammation and heart diseases.

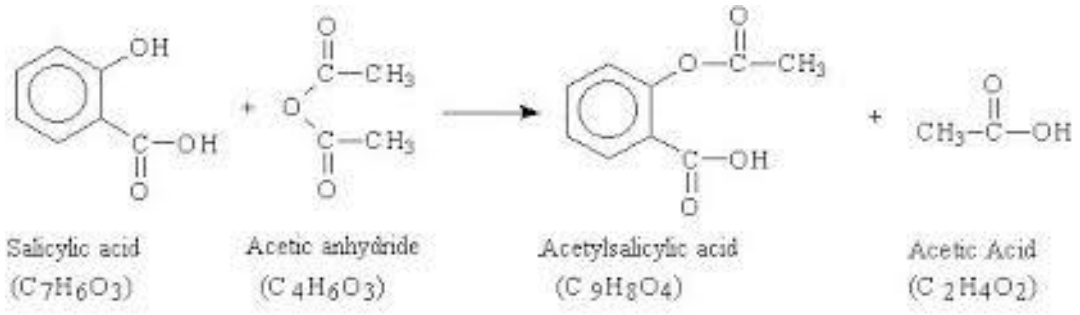


Figure 1: Molecular formula of production of aspirin

Aspirin contains a Benzene ring structure which is a six-carbon ring with a hydrogen attached to each carbon. Benzene used to be thought of as having 3 double and 3 single c-c bonds which would alternate (Kekulé structure). However, there are several flaws with this presumption, as firstly it does not rapidly decolourise bromine which it should if it had c=c double bonds. Secondly, a single c-c bond is 0.154nm and a double c=c is 0.134nm meaning that the hexagon would have an irregular shape. However, we know that all the bonds are the same length and benzene has a perfectly hexagonal shape. Lastly, we also know that all the bonds are the same strength proving it cannot have double and single carbon bonds as they are different strengths. This is what helped scientists discover that the benzene ring actually has partial double bonds that exist from the delocalised electrons spinning around. Each carbon in the benzene ring has three sp^2 hybrid orbitals and forms three sigma bonds with these (Figure 2, Bottom left), and also one p orbital which lie above and below the carbon ring forming a delocalised pi system. The sigma bonds are made when two sp^2 orbitals overlap head on while the pi bond is made from the sideways overlap of two 2p orbitals. This delocalised pi system is formed from all 6 p orbitals overlapping each other (Figure 2, bottom middle) equally thus explaining why there isn't 3 c=c double bonds but a more stable pi system. There are 2 main differences between Sigma bonds and Pi bonds, Sigma bonds are formed by the head on overlap of two atomic orbitals while Pi bonds are formed from the sideways overlap of atomic orbitals. A Sigma bond also consist of an sp^3/s or sp^3/sp^3 orbitals with the orbitals lieing between the 2 nuclei whie a sigma bond has two 2p orbitals

above/below the 2 nuclei. Benzene can only react using electrophilic substitution with a catalyst.

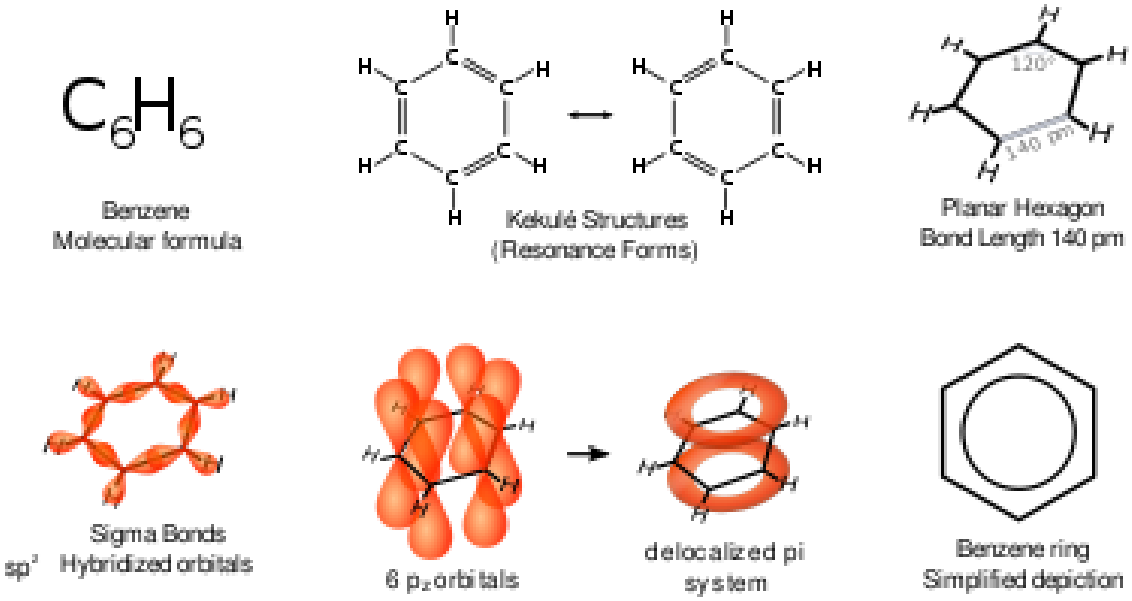


Figure 2: Benzene structure

In Aspirin there is a carboxylic acid and ester functional group each attached to a separate carbon. The carboxylic acid (red) comes from a carbonyl and hydroxyl group joining. While the ester (green) is formed from the esterification of an alcohol and a carboxylic acid. The production of this ester can be reversed by a hydrolysis reaction. (Laney College, 2012)

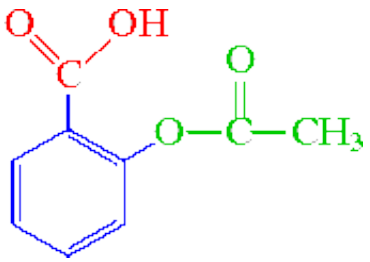


Figure 3: Aspirin structure

The reactant Salicylic acid consists of a benzene ring with a carboxylic acid group and an hydroxide group, however as the OH group is attached to a carbon from a benzene ring making it a phenol group. The structure is acidic as the OH group readily dissociates also making salicylic acid an irritant.

Thin layered chromatography (TLC) was used to investigate if there were any impurities in the samples produced. All the samples and reactants were dissolved in ethanol to act as a mobile phase and then a small drop of each were placed at the bottom of the TLC plate spaced apart in a straight horizontal line. This plate is a thinsheet of glass or plastic which is coated with a thin layer of silica gel. The TLC plate is placed in a glass jar, containing a solvent, so that the solvent is below the drops of samples. The solvent is a 1:1 mixture of Ethyl Acetate and cyclohexane mixture which is used as the solvent to carry the samples up the TLC plate by capillary action, this is brought about due tho the adhesion to the silica gel is stronger than the cohesive forces between the liquid molecules.. After left to rise a UV light was used to show the fluorescent indicator of the samples with dots appearing at different distances. These correlated to different compounds present and a retention factor which is calculated by the distance travelled by the component and distance travelled by solvent. The different compounds travel different distances due to the silica gel being very polar and therefore has varying strengths of bonds between the molecules and the silica gel, resulting in the samples travelling different distances. As the mobile phase rises up the TLC plate it trys to pull the samples upwards while the silica gel trys to hold the samples in place, it is dependant on the samples polarity as to how much distance it travels. It is the intermolecular forces which affect polarity, for example if a molecule can form hydrogen bonds then it is more polar due to the large difference in electronegativity, so therefore will travel a smaller distance than a less polar molecule. The further the dots have traveled, the less polar the molecule. The Ethyl Acetate from the solvent is the ester formed from the esterification of an alcohol and a carboxylic acid (figure 4). The cyclohexane has a molecular formula of C_6H_{12} and has a ring structure which is produced by the hydrogenation of benzene. Hydrogenation is a process where hydrogen (H_2) is reacted with other compounds in the presence of usually a Nickel catalyst. The addition of a hydrogen molecule can also be called electrophilic addition, where the new C-H sigma bonds form simultaneously from two H atoms from a metal catalyst.

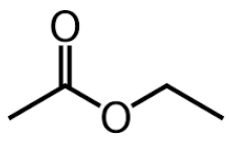


Figure 4: Ethyl Acetate

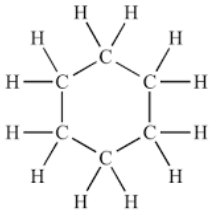


Figure 5: cyclohexan

Aspirin reduces heart attacks by reducing the accumulation of blood platelet cells improving blood flow. Platelets are small blood cells that join together to form a clot to stop bleeding in a wound. Blood clots are very beneficial to stopping bleeding however can often cause heart attacks, Aspirin reduces the production of thromboxane which produces these platelets therefore reducing heart attacks.

The purity of the aspirin produced was measured in two ways, by infrared spectroscopy and by melting points. Infrared spectroscopy is the use of Infrared radiation which has a lower frequency and longer wavelength than visible light. (Radbound University, 2019) The Infrared light interacts with the molecules and this can be analysed by measuring the absorption, emission and reflection of the light. Infrared spectroscopy finds the purity match of substances due to molecules absorbing specific frequencies that are characteristics of their structure. This means that when infrared radiation is passed through the samples, specific frequencies are absorbed and vibrate specific chemical bonds. The different frequencies are recorded and as they are correlating to different bonds or functional groups it can then be matched to a pure aspirin samples frequencies. A graph can then be produced that shows wavenumbers (cm^{-1}) and transmittance (%), the percentage transmittance, ratio of the light energy that passed through sample. The spikes in the % transmitence can be correlated to specific bonds corresponding to the wavenumbers for example the C=O bond in an ester group is found at 1750-1735 cm^{-1} wavenumbers.

Melting points are also a useful way to find purity as each molecule has a specific melting point and the more precise the point the less impurities it will have. Melting a solid breaks the intermolecular forces between molecules, these are the relatively weak forces which attract molecules to each other. Having impurities lowers the melting point due to substances disrupting the repeating patterns of these intermolecular forces weakening the structure therefore taking less energy to break the forces and melt the solid. This means that the more impure a molecule is, the lower the melting point it will have compared with its pure melting point. However having many impurities can also widen the melting point of a molecule due to the weakening of the molecular lattice structure of the solid. This means that not only the melting point, but the range of the melting point is important in finding how pure a sample is. The melting range is the difference in between the temperature where the sample starts to

melt and where it is completely melted. A pure substance has a melting range of 1-2°C while the more impure the sample will have a bigger range.

Procedures

To compare method 1 and method 2 both were duplicated using the same starting products and clean equipment.

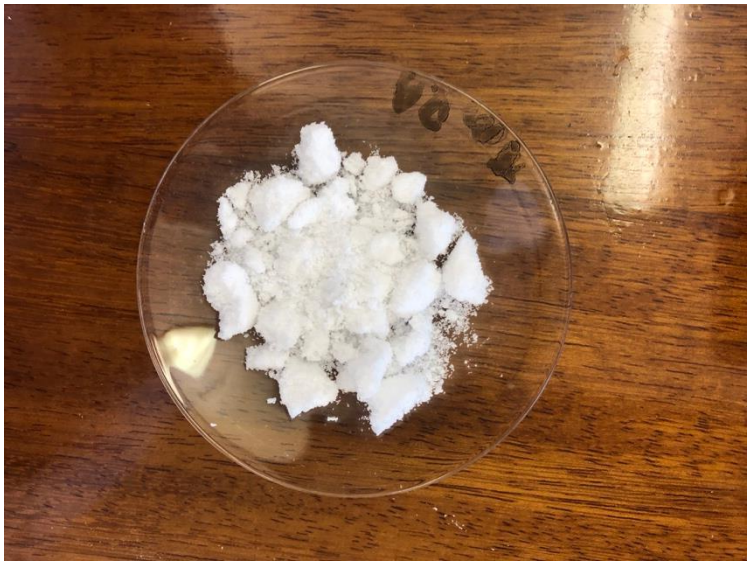
Method 1:

Firstly, a 250cm^3 conical flask was placed on a weighing balance to 2 decimal places and tared then 5.00g of 2-hydroxybenzoic acid was added. The conical flask was then taken into a fume cupboard where, 10cm^3 of ethanoic anhydride measured using a 10cm^3 measuring cylinder was added while the contents were swirled. Roughly 5 drops of 85% phosphoric acid were added with continuous swirling. While still in the fume cupboard, the flask was then placed on a hot plate and heated to roughly 85°C for 10 minutes while constantly mixing. After 10 minutes the mixture was cooled for less than a minute in an ice bath, then poured into approximately 150cm^3 of cold water in a 500 cm^3 beaker, at this point the two clear and colourless liquids turned cloudy and then clear/white crystals started to form. After crystals started to appear the precipitate was filtered off at a water pump and rinsed with cold water. The product was then added to a 100cm^3 conical flask containing 15cm^3 of ethanol measured using a 20cm^3 measuring cylinder and a few anti-bumping granules. The conical flask was then heated gently on a hot plate to around 50°C until all the solid was dissolved. The solution was then poured into a conical flask containing roughly 40cm^3 of water. If at this point an oil started to form it was reheated on a hot plate. Once cooled the crystals (picture 1) that had formed were filtered off at a water pump then transferred to a pre-weighed watch glass and placed in an oven at 100°C measured by a thermometer overnight. The crystals were then weighed to find a percentage yield and analysed for melting point and purity.

Picture 1: Aspirin Crystals

Method 2:

In a fume cupboard, using a 10cm^3 measuring cylinder, 10cm^3 of ethanoic anhydride was added to 5.00g of 2-hydroxybenzoic acid in a 250cm^3 conical flask. The conical flask was first placed on a weighing balance to 2 decimal places and tared. Roughly 5 drops of 85% phosphoric acid were added with continuous swirling. The mixture was put in a microwave for 90 seconds at 600W then stirred and put back in microwave for another 90 seconds. The mixture was allowed to cool then roughly 20cm^3 of water was added. The conical flask was then placed in an ice bath until white crystals formed. The precipitate was filtered off at a water pump and rinsed with cold water. The product was then added to a 100cm^3 conical flask containing 15cm^3 of ethanol measured using a 20cm^3 measuring cylinder and a few anti-bumping granules. The conical flask was then heated gently on a hot plate until all the solid was dissolved. The solution was then poured into a conical flask containing roughly 40cm^3 of water. If at this point an oil started to form it was reheated on a hot plate. Once cooled the crystals that had formed were filtered off at a water pump then transferred to a pre-weighed watch glass and placed in an oven at 100°C measured by a thermometer overnight. The crystals (picture 2) were then weighed to find a percentage yield and analysed for melting point and purity.



Picture 2: Final Aspirin crystals

Melting point method:

A melting-point capillary tube, a very thin glass tube sealed at one end, was filled with a small amount of a sample, this was then placed into the OMEGA melting point measurement device. The sample was heated to 100°C then the temperature was increased slowly by 1°C a minute whilst observing the sample, through the microscope lense, to determine when the sample changes from a solid to liquid. The temperature that the sample first started to change state and when it had completely changed state was recorded.

Infrared spectrometer procedure:

The samples were tested using a Nicolet iS5 Spectrometer with an ID3ATR attachment,this focuses the infrared beam through the samples and onto the crystal. The zinc silica crystal was wiped clean using deionised water and then again with isopropanol and then a background is then taken. A small amount of a sample was added on top of the crystal ensuring it was all covered. The ATR attachment is then placed on over the crystal and screwed on. The information is then collected on a desktop and is compared to a previously known pure aspirn sample.

Figure 6: Nicolet iS5 Spectrometer

Thin layered chromatography (TLC) method:

Firstly, all the samples and reactants were independently dissolved in ethanol which is used as a mobile phase. A horizontal pencil line was drawn 4 centimetetrs above the bottom of the silica TLC plate where a small drop of each mixture was placed using a mircopipet. The TLC plate was placed in a glass jar with a lid containing solvent. The jar was filled so that when the plate was inserted the mixture level was 2 cm below the horizontal pencil line. The plate was then left in the jar until the solvent had almost risen to the top. When it was taken out of the jar a pencil mark was made where the solvent front had risen to. The plate was then put under a UV lamp where the samples appears as a dark spot, these were circled in pencil allowing them to be analysed without the UV light. (Royal Society of Chemistry, 2003). The distances travelled by the solvent front and the spots were measured using a ruler.

Results

Method 1 sample:

Starting mass 2-hydroxybenzoic acid = 5.00g

Mass of watch glass = 78.68g

Mass of watch glass with dried aspirin = 83.03g

Mass of aspirin = 4.35g

Theoretical yield –

2-hydroxybenzoic acid $C_7H_6O_3$ GFM = 138

Aspirin $C_9H_80_4$ GFM = 180

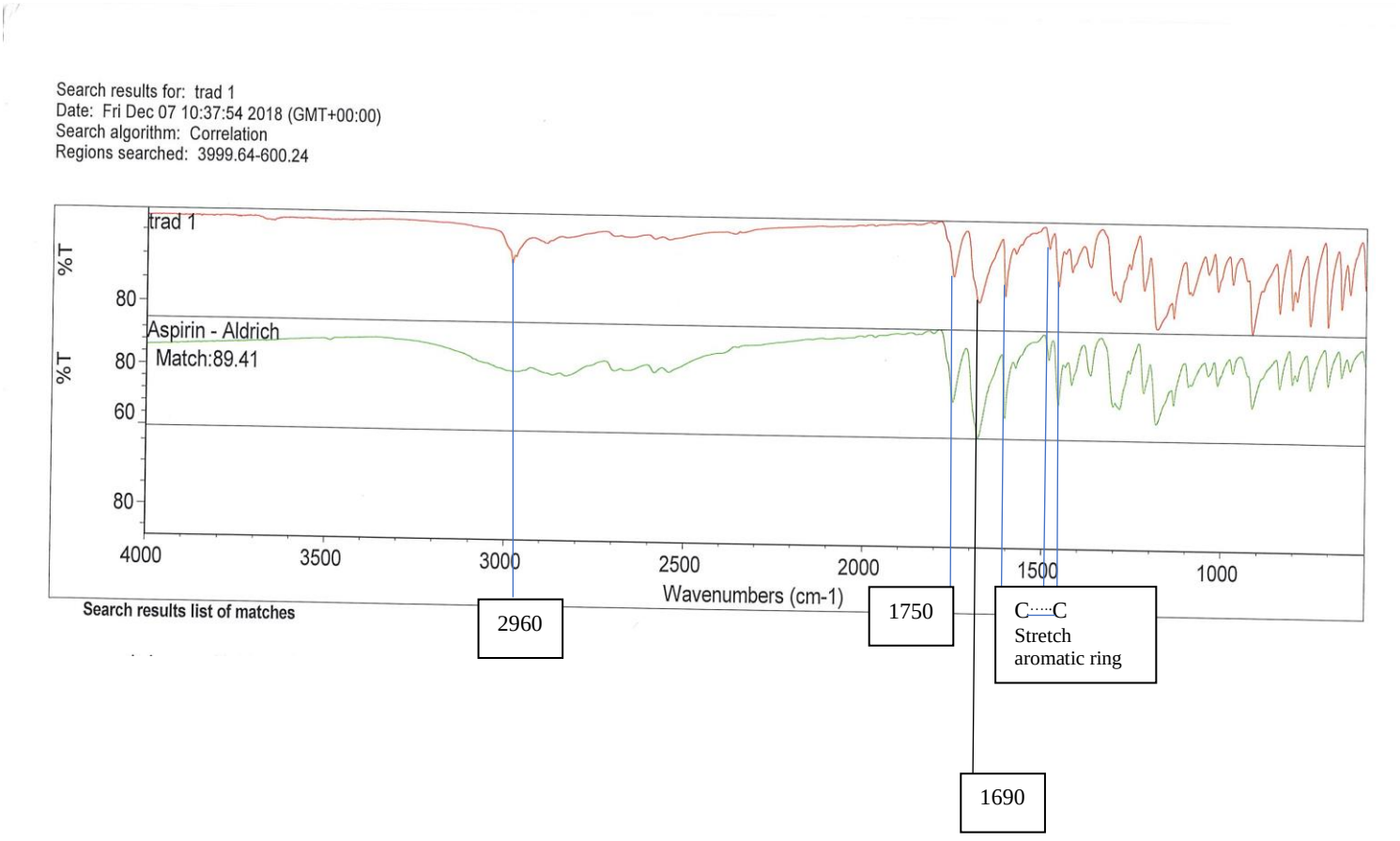
180/138 x 5 = 6.51g

%yield = actual yield/theoretical yield x 100

(4.35)/(6.51) x 100 = 66.8%

Melting point = 135-136°C

Purity match with Aldrich Aspirin = 89.41%



Wavenumber (cm^{-1})	Bond responsible	present in
2960	H bonded OH stretch	Carboxylic acid
1750	C=O stretch	ester
1690	C=O stretch	Aromatic carboxylic acid
1600, 1500, 1450	Partial C=C stretch	Aromatic ring

Method 1 duplicate sample:

Starting mass 2-hydroxybenzoic acid = 5.00g

Mass of watch glass = 78.68g

Mass of watch glass with dried aspirin = 83.10g

Mass of aspirin = 4.42g

Theoretical yield –

2-hydroxybenzoic acid $C_7H_6O_3$ GFM = 138

Aspirin $C_9H_80_4$ GFM = 180

180/138 x 5 = 6.51g

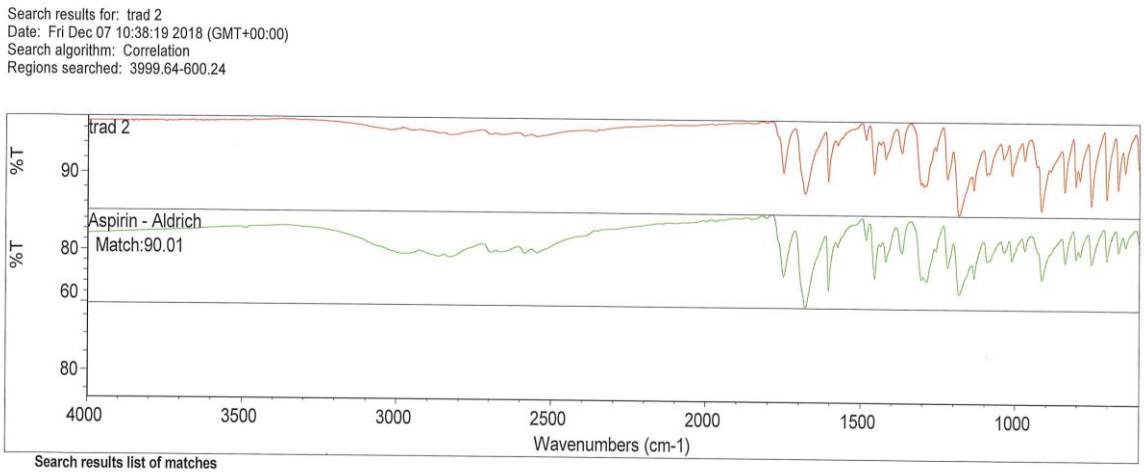
%yield = actual yield/theoretical yield x 100

(4.42)/(6.51) x 100 = 67.9%

Percentage yield = 67.9%

Melting point = 135 - 136°C

Purity match with Aldrich Aspirin = 90.01%



Method 2 sample:

Starting mass 2-hydroxybenzoic acid = 5.00g

Mass of watch glass = 78.68g

Mass of watch glass with dried aspirin = 81.29g

Mass of aspirin = 2.61g

Theoretical yield –

2-hydroxybenzoic acid $C_7H_6O_3$ GFM = 138

Aspirin $C_9H_80_4$ GFM = 180

180/138 x 5 = 6.51g

%yield = actual yield/theoretical yield x 100

(2.61)/(6.51) x 100 = 40.1%

Percentage yield = 40.1%

Melting point = 120-122°C

Method 2 duplicate sample:

Starting mass 2-hydroxybenzoic acid = 5.00g

Mass of watch glass = 78.68g

Mass of watch glass with dried aspirin = 82.81g

Mass of aspirin = 4.13g

Theoretical yield –

2-hydroxybenzoic acid $C_7H_6O_3$ GFM = 138

Aspirin $C_9H_80_4$ GFM = 180

180/138 x 5 = 6.51g

%yield = actual yield/theoretical yield x 100

(4.13)/(6.51) x 100 = 63.4%

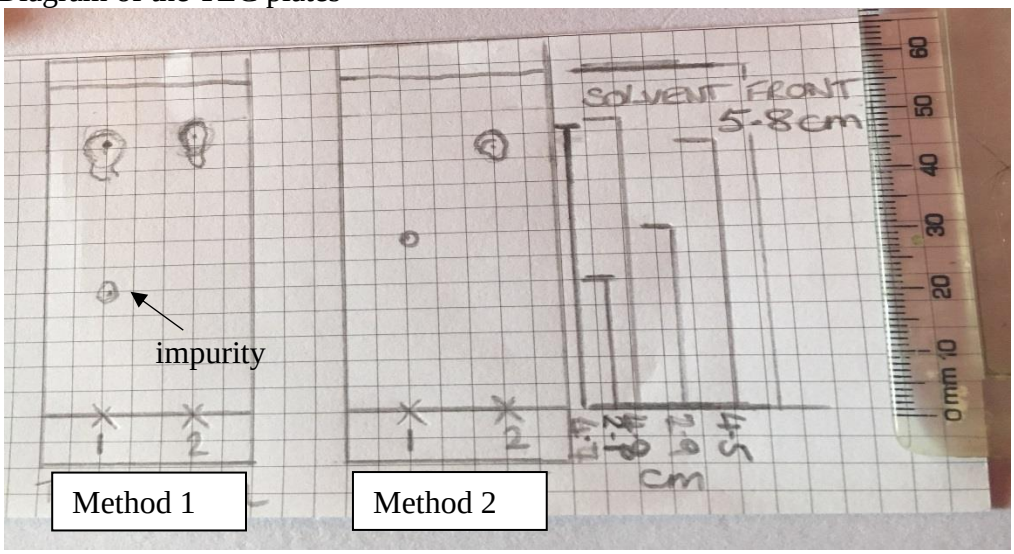
Percentage yield = 63.4%

Melting point = 135-136°C

Purity match with Aldrich Aspirin = 91.34%

TLC analysis

Solvent used - 1:1 mixture of Ethyl Acetate and cyclohexane
Diagram of the TLC plates



Measurement	Distance travelled (cm)	Rf calculation	Rf value
Solvent front	5.8	-	-
Method 1 sample (1)	4.7	4.7/5.8	0.81
Method 1 (1) impurity	2.1	2.1/5.8	0.36
Method 1 duplicate sample (2)	4.8	4.8/5.8	0.83
Method 2 sample (1)	2.8	2.8/5.8	0.48
Method 2 sample (2)	4.5	4.5/5.8	0.78

Conclusion

The two methods were duplicated giving the following results;
Method 1 was found to have a percentage yield of 66.8% and 67.9% and a melting point of 135-136°C and 135-136°C.
Method 2 was found to have a percentage yield of 40.1% and 63.4% and a melting point of 120-122°C and 135-136°C.
For both duplicates of method 1 and the method 2 duplicate the melting points show that aspirin was made. The literature value of the melting point of aspirin is 136°C. The IR spectra showed a good match to pure aspirin spectra.

Evaluation

Upon evaluating there was found to be faults with the experiments, specifically with Method 2 sample 1. During the heating of the mixture in the microwave a pungent smell was produced highlighting that the mixture was being heated for too long or at a too powerful setting. As a result of this when the mixture was added to a conical flask containing water, stage 8, an oil formed. The mixture was heated twice to dissolve the oil however it reformed after being cooled. To remove the oil more ethanol had to be added and the mixture reheated. Upon analysis of the method 2 sample 1 it was found that the melting point was significantly lower than expected therefore it is anticipated that the 40.1% yield may not be accurate as may contain many impurities. To reduce this source of error the mixture could be heated for the same time but on a lower power setting.

In the first TLC there was an impurity found in method 1 sample 1. It was noted that it was close in value to the first sample from method 2. If there was more time then another TLC could have been setup of the method 1 sample 1 and the first sample of method 2 along 2-hydroxybenzoic acid and ethanoic anhydride to see if the impurity was some of the reactants that had not reacted fully. There was no impurity in the second TLC meaning that there may have also been a contamination or error with the first TLC.

At two stages in each experiment the precipitate was filtered off at a water pump. This may have lead to some loss of precipitate as not completely all of the product was transferred from the water pump filter to the conical flask or watch glass it was intended for. This may of lead

to a decrease in the percentage yield as it will decrease the total final mass of product. In hindsight leaving the filter paper to dry then scraping the product off would have limited the loss of mass. This would only reduce the overall yield by a small amount and so does not account for the yields obtained. The reaction may not have gone to completion and so not all of the salicylic acid reacted to become aspirin.

The yield of the final product could have been increased by scratching the sides of the conical flask to encourage crystalisation. This would allowed the crystals to form quicker and therefore minimise the time that they were left in the lab where possible contamination may have occurred.

The repeats of the experiments were done the day after the initial experiment with each experiment overlapping the previous. This was done to minimise the time that solutions or products were left out. Any solutions were left in a dark cupboard and wrapped in cling film to reduce any evaporation and any solid/powders were left in a desiccator. This is a sealable glass jar that encloses items in a dry environment preventing the items absorbing moisture.

The results for the method 2 duplicate sample had the highest infrared purity match of 91.34% this shows that the method 2 produced a purer aspirin product however as the method 2 produced inconcordant results for melting point and % yield that the method 1 must be the best one as those results were much closer to each other.

The Infrared graphs of the samples all showed nearly identical spikes at $1450cm^{-1}$, $1500cm^{-1}$, $1600cm^{-1}$, $1690cm^{-1}$ and $1750cm^{-1}$. The $1450cm^{-1}$,$1500cm^{1}$, $1600cm^{-1}$ spikes are due to the partial c=c bond of the benzene ring, the $1690cm^{-1}$ spike correlating to a carboxyl acid c=o stretch and the $1750cm^{-1}$ spike from the c=o stretch of the ester group. These peaks are the three main functional groups found in aspirin. These peaks found in the synthesised aspirin are also found in the pure aspirin signifying that the samples produced all have a strong match to aspirin.

References

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