

Experiment 6

Synthesis Of Aspirin (Acetylsalicylic Acid)

Purpose:

The purpose of this experiment is to synthesize the common pain killer aspirin via an esterification reaction between Salicylic Acid and Acetic Anhydride in the presence of concentrated sulfuric acid acting as a catalyst.

Background:

Aspirin is one the best known and most widely used medicines in modern society. Aspirin has a long past. In the 5th century B.C. Hippocrates first used a bitter powder obtained from ground willow bark to ease aches and pains and to reduce fever. American Indians chewed on willow bark to obtain these same results. In 1829, the pharmacist Leroux showed that the substance in the willow bark that made people feel better is **salicin**, the pharmacological ancestor of a family of drugs called salicylates. Salicin can be converted by the body after it is eaten to another chemical, **salicylic acid**.

The problem with salicylic acid is that it causes irritation to the mucous membranes of the mouth and esophagus; and can severely upset the user's stomach. The large doses, 6 - 8 grams, of sodium salicylate that were used at that time to treat arthritis could not be tolerated by many patients. In the late 19th century, a German named Hoffmann set about to find a drug to ease his father's arthritis without causing the severe stomach irritation that was associated with sodium salicylate, the standard anti-arthritis drug of the time.

Hoffman viewed the acidity of the salicylic acid from the salicylates as the source of the irritation in the stomach, and started looking for a less acidic formulation. His search lead him to synthesize **acetylsalicylic acid**, a compound that shared the therapeutic properties of other salicylates and might cause less stomach irritations. He did this by putting the compound through a couple of chemical reactions that replaced hydrogen from a phenolic hydroxyl group (OH) group with an **acetyl** group converting it to **acetylsalicylic acid**.

The new compound reduced fever, relieved moderate pain and at higher doses alleviated rheumatic and arthritic conditions. Hoffman was confident that his new compound would be more effective than the salicylates then in use.

His superiors did not share his enthusiasm. They doubted that acetylsalicylic acid would ever become a valuable commercially successful drug because in large doses salicylates commonly produced shortness of breath and an alarmingly rapid heart rate. It was taken for granted that

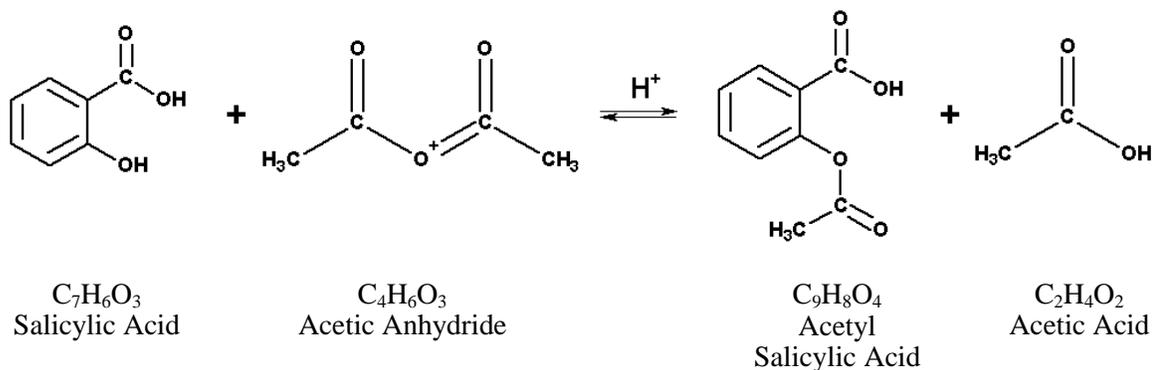
acetylsalicylic acid would weaken the heart and that physicians would be reluctant to prescribe it.

In 1899, Heinrich Dreser, a top chemist with Friedrich Bayer and Co., gave acetylsalicylic acid the now familiar name **aspirin**, but in 1897 Bayer didn't think aspirin had much of a future. Little did they know what the future held for aspirin.

Today, Americans consume an estimated 80 billion aspirins a year and the physicians' desk reference lists more than 50 over the counter drugs which contain aspirin as the principle active ingredient.

The Experiment:

In this experiment, aspirin will be synthesized utilizing a reaction very similar to the way it is manufactured industrially. Salicylic acid acting as an alcohol is reacted with acetic anhydride acting as the acid in an esterification reaction to produce an ester, acetylsalicylic acid (aspirin). Concentrated sulfuric acid is used as a catalyst.



Limiting Reagent and % Yield:

Synthesizing a compound in the laboratory usually requires the student to compare the experimental yield of product with the amount that is theoretically possible based on the amounts of materials used.

The first step in this process is to determine the molar ratio of the reactants actually used relative to the stoichiometric molar ratio as defined in the balanced equation of the reaction. In most laboratory courses one of the reagents has an insufficient number of moles to react with the other reagent. This reagent is referred to the “limiting Reagent,” while the other reagent is considered “in excess.” Thus, the limiting reagent is totally consumed in the reaction and it dictates, on a molar equivalent basis, the theoretical amount of product that can be expected from the reaction.

The % yield of the experiment is then determined from the ratio of the amount of product actually obtained to this theoretical amount (mass or moles can be used for the calculation).

$$\% \text{ Yield} = \frac{\text{Actual Yield}}{\text{Theoretical Yield}} \times 100$$

Example:

Determine the theoretical and % experimental yield for an experiment in which 4.210 grams of solid salicylic acid is reacted with 15.0 ml of liquid acetic anhydride.

1. Determine moles of reactants

- a. Salicylic acid (Mol Wgt – 138.12 g/mol)

$$\text{Moles salicylic acid used} = 4.210 \text{ g} \times \frac{1 \text{ mol}}{138.12 \text{ g}} = 0.0305 \text{ mol}$$

- b. Acetic Anhydride (Den – 1.08 g/ml; Mol Wgt – 102.09 g/mol)

$$\text{Moles acetic anhydride used} = 15.0 \text{ ml} \times \frac{1.08 \text{ g}}{1 \text{ ml}} \times \frac{1 \text{ mol}}{102.09 \text{ g}} = 0.159 \text{ mol}$$

2. Compute actual molar ratio of reactants

$$\text{Actual Molar Ratio} = \frac{0.0305 \text{ mol salicylic acid}}{0.159 \text{ mol acetic anhydride}} = 0.192$$

3. Since the stoichiometric molar ratio of salicylic acid to acetic anhydride is 1:1 and the actual molar ratio is 0.191 (< 1), there is insufficient salicylic acid to react with the acetic anhydride. Thus, salicylic acid is limiting and a maximum of 0.0305 moles (5.50 g) of acetylsalicylic acid can be produced in the reaction (theoretical yield), based on a 1:1 molar ratio of salicylic acid to acetylsalicylic acid in the balance equation.

$$0.0305 \text{ mols salicylic acid} \times \frac{1 \text{ mol aspirin}}{1 \text{ mol salicylic acid}} \times \frac{180.17 \text{ g aspirin}}{1 \text{ mol aspirin}} = 5.50 \text{ g aspirin}$$

4. Assume the experiment yielded 3.92 g of product; thus the % yield would be:

$$\% \text{ Yield} = \frac{3.92 \text{ g}}{5.50 \text{ g}} \times 100 = 71.3 \%$$

Laboratory Techniques:

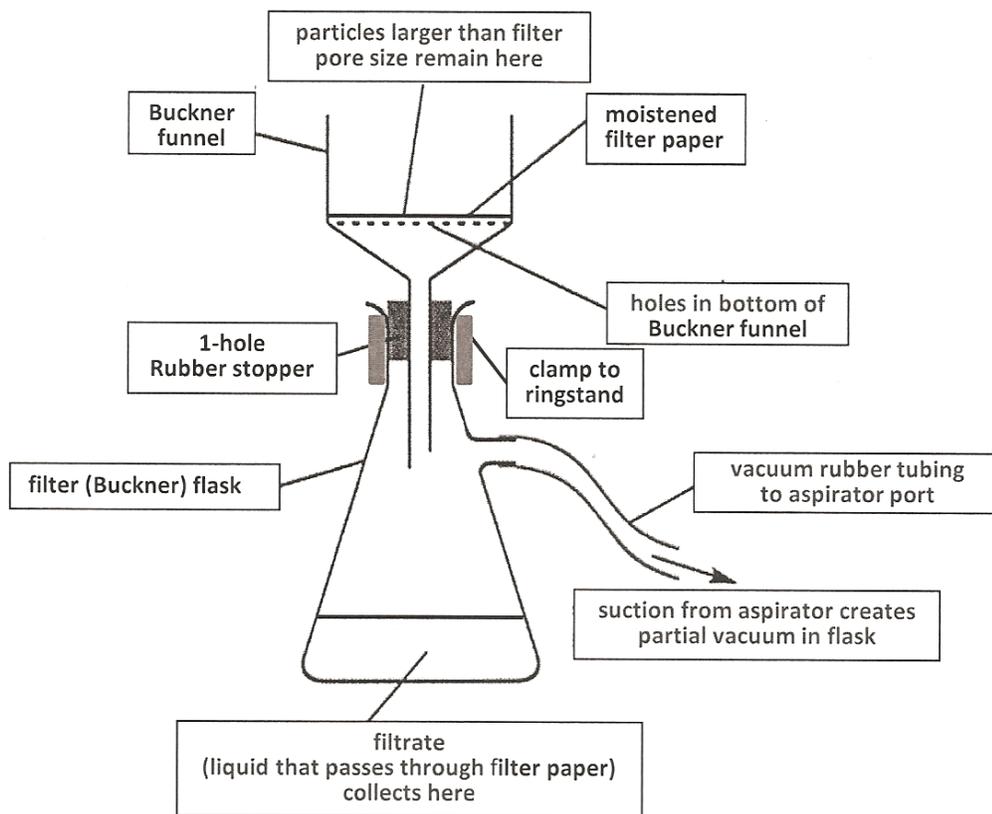
The laboratory synthesis of a compound usually requires the product to go through a series of steps to isolate it from the reaction mixture and any soluble impurities. The procedures used to accomplish these tasks in this experiment will be (1) vacuum filtration and (2) recrystallization.

Vacuum filtration:

Vacuum (suction) filtration is a commonly used procedure to separate a solid from a liquid. The apparatus used consists of a Buckner funnel, paper filter, single-hole rubber

stopper, ring stand and clamp, filter flask (sometimes called a Buckner flask), and vacuum tubing connecting the flask to an aspirator (water or air). A typical setup is shown in figure 1.

Figure 1: Vacuum Filtration System



Recrystallization:

Solid compounds synthesized in the laboratory usually contain impurities that must be separated from the product before final confirmation tests are performed. One of the most commonly used techniques is recrystallization. The recrystallization process is based on the changes in the solubility of a compound as temperature changes. In accordance with Le Chatelier's Principle, when the dissolution process is endothermic (heat is absorbed), solubility (solubility product) increases with rising temperature.

If the sample is placed in a minimal amount of a suitable solvent and then heated to near the boiling point of the solvent, the sample will dissolve completely forming a saturated solution. As the sample is allowed to cool slowly to room temperature, the compound becomes less soluble (more saturated) and crystals come out of solution. Any soluble impurities present in unsaturated amounts will remain in solution. Thus, the impurities can now be separated from the compound by vacuum filtration.

Solvents used in the recrystallization process must be matched to the compound being purified. The attributes of a suitable solvent include:

- The solute particles are generally insoluble in cold solvent, but soluble in hot solvent.

- The solvent should have a steep solubility vs temperature curve for the solute.
- The boiling point of the solvent must be **less than** the melting point of the solute.
- The solvent should not react with the solute.
- The solubility of an organic compound is a function of the polarities of both the solvent and the solute. Thus, the term “Like Dissolves Like” indicates that:
 - ▲ Polar solvents dissolve polar solutes.
 - ▲ Nonpolar solvents dissolve nonpolar solutes.

Pre-Lab Report & Notebook:

Download from the department data base to your hard drive or flash drive a copy of the lab report template and the data summary table for the Aspirin experiment:

<http://chem.gmu.edu/templates>

Print the summary results table for the Aspirin experiment.

Prepare the Pre-lab report according to instructor’s instructions.

Materials & Equipment:

<u>Materials</u>	<u>Equipment</u>
Distilled Water	Ring Stand
Acetic Anhydride	Clamp
Salicylic Acid	Medicine Dropper
Conc Sulfuric Acid	Spatula
1% FeCl ₃	Glass Stirring Rod
Ethanol	2 400 ml Beakers
	150 ml Beaker
	125 ml Erlenmeyer Flask
	Watch Glass
	Buckner Funnel
	Filter Flask
	Vacuum Tubing
	3 Small Test Tubes
	Hot Plate
	Electronic Balance
	Calculator
	Fume Hood

Reagents:

The compound names, formulas, molecular weights, and densities for the substances mentioned in this experiment are given in table 5.1 below. CRC Handbook (89th Ed.)

Table 5.1: Literature Information for Reagents Used in Aspirin Synthesis Experiment

Table 1			
Compound	Formula	Molecular Weight	Density (g/ml)
Salicylic Acid	C ₇ H ₆ O ₃	138.12	–
Acetic Anhydride	C ₄ H ₆ O ₃	102.09	1.0820
Acetyl Salicylic acid	C ₉ H ₈ O ₄	180.17	–
Methanol	CH ₄ O	32.04	0.7914
Acetic acid	C ₂ H ₄ O ₂	60.05	1.0492
Sulfuric Acid	H ₂ SO ₄	98.079	1.84

Procedure:

Hazard: Acetic anhydride is a corrosive liquid and quite flammable. Avoid breathing vapors and carry out all transfers in the fume hood.

Concentrated sulfuric acid is also highly corrosive and must be handled with care.

Avoid contact on skin or clothing. Wash with copious amounts of water if a spill occurs. Notify Instructor.

1. Half-fill 400 ml beaker with tap water and heat it on a hot plate to temperature of 45-50°C. This will serve as a hot bath for the reaction. It is important that the temperature of the water bath be steady before heating the reactants.
2. Tare weight a plastic weighing tray to the nearest 0.001 g.
3. Add approximately 2 g of Salicylic Acid and determine its mass to the nearest 0.001 g.
4. Transfer the salicylic acid to a 125 mL Erlenmeyer flask.
5. Take the flask to the fume hood.
6. Add approximately 5 mL of acetic anhydride (Density – 1.08 g/mL) to a small graduated cylinder and determine its volume to the nearest 0.01 ml.

Note: Compute the mass of acetic anhydride from its volume & density.

7. Add the acetic anhydride to the flask containing the salicylic acid and swirl.

8. Carefully add 4 drops of concentrated sulfuric acid catalyst to the reaction mixture.
9. Swirl the mixture gently.
10. Heat the flask in the hot water bath for 10 minutes, stirring with a glass stirring rod or metal spatula until the salicylic acid dissolves completely.
11. Prepare an ice-water bath in a 400 ml beaker (about 50 ml tap water, 50 g ice)
12. Remove the flask from the hot water bath and allow the reaction mixture to cool in the ice-water bath until no more precipitation occurs.

Note: Particles of the acetylsalicylic acid (Aspirin) product should begin to recrystallize out of solution as the mixture cools. Swirl the mixture if recrystallization does not start.
13. After the precipitation is complete, add 20 mL of cold distilled water to the reaction flask in 5 mL increments (wash off stirring rod), swirl to mix, and again cool the mixture in the ice bath.

Vacuum Filtration I:

14. Set up the Vacuum Filtration apparatus.
 - a. Place a paper filter in the Buckner funnel
 - b. Insert Buckner funnel securely into the neck of the filtration flask.
 - c. Attach vacuum tubing to flask and vacuum source
 - d. Moisten filter paper with distilled water.
 - e. Turn the vacuum on and insure the moistened filter paper forms a seal with the bottom of the funnel.
15. Transfer the reaction mixture to the Buchner funnel and continue to pull vacuum until all liquid is transferred from the funnel to the flask.
16. Use the liquid in the filtration receiving flask to rinse more product from the reaction flask and continue the filtration.
17. Rinse the product in the funnel with small increments of cold distilled water.
18. Continue to draw air through the filtration apparatus until the crystals are relatively dry.

Recrystallization:

19. Transfer the product crystals to a 150 mL beaker
20. Add 8 mL of ethanol.
21. Warm the beaker in the water bath until the crystals dissolve completely.
22. Add 17 mL of distilled water.
23. Cover the beaker with a watch glass and set aside to cool to room temperature.
24. Place the beaker in the ice-water bath to complete recrystallization.

Vacuum Filtration II:

25. Setup the vacuum filtration apparatus again with a new moistened filter.
26. Transfer the recrystallization mixture to the Buckner Funnel and filter the purified product.

Note: Do not rinse the product in the funnel with any additional alcohol.
Simply scrape the beaker with a spatula to transfer as much of the product crystals as possible to the Buchner Funnel.

27. Transfer the crystals to a paper towel for drying.
28. Pat dry the crystals with a new piece of filter paper.
29. Transfer the dried crystals to a pre-weighed watch glass.

Ferric Chloride Color Test:

30. Determine if any unreacted Salicylic Acid is present in the “purified” aspirin product.
 - a. Obtain 3 small test tubes.
 - b. In the first test tube place about 5 mL distilled water and a pen-tip size amount of aspirin product.
 - c. In the second test tube place about 5 mL distilled water and a pen-tip size amount of Salicylic Acid.
 - d. Into the third test tube place about 5 ml of the filtrate from the synthesis procedure
 - e. To each test tube about 10 drops of 1% Ferric Chloride (FeCl_3) and stir.
 - f. Compare the color in the three test tubes.

Computations:

1. Determine the mass of salicylic acid by difference or tare weight
2. Compute the mass of acetic anhydride from its volume and density
3. Compute the moles of salicylic acid and acetic anhydride
4. Compute the actual molar ratio of salicylic acid : acetic anhydride
5. Determine the limiting reagent
6. Compute the theoretical yield
7. Determine the mass of the aspirin product by difference.
8. Compute the percent (%) yield from the product mass and the theoretical yield.
9. Compute the average % yield for the class
10. Compute the standard deviation of % yield for the class

Analysis and Conclusions:

1. Discuss your yield (probably not 100%) in terms of the following:
 - a. Experimental process
 - b. Equilibrium constant
2. Compare the colors in the three tests from the ferric chloride test. Explain your results.

Data Processing:

Use the printed Pre-lab report as a notebook to record the experimental results in the results section of the applicable procedure.

Enter the experimental results into the printed “Aspirin” summary results table and attach to report.

In the summary table show all calculations. Equations must be typed if the final report is completed using the electronic report template. It is recommended that the MS Word equation editor be used. Click on “Insert” and “Object” in the Menu bar. From the scroll down menu select “Microsoft Equation 3.0. Equations can be constructed and inserted into the document, including tables, and resized as necessary.

If required by the instructor, transfer the laboratory results to the electronic files and finalize the laboratory report.

Spreadsheet Processing:

Input Results into Laboratory Excel Database

Use one of the laboratory computers and the web-based data entry forms shown in Figure 6.1 below to enter the Aspirin lab results into an Excel spreadsheet.

Figure 6.1: Input Screen for entering Aspirin results into Excel database

GMU General Chem: Aspirin Synthesis

Clear

Enter Your ID:

Enter last 4 digits of G No.:

Data:

Enter only the numerical values, **not the units**

Mass Salicylic Acid g

Volume Acetic Anhydride mL

Mass Final Product g

After entering all the data, click the Submit button.
If the data has been successfully stored, you will receive a confirmation page

Submit Data

Retrieve Class Data:

Retrieve class data for Aspirin experiment from website

<http://chem.gmu.edu/results> (select "Aspirin")

Copy the data presented on the screen and insert into a spreadsheet (Excel, Google, other) and save the spreadsheet on your hard drive or flash drive with an appropriate file name.

Your default "sheet" should be renamed (RawData) and have the following columnar format:

Row Col	A	B	C
1	m_salicylic_acid	V_acetic_anhydride	m_product
2			
3			

Column Definitions:

Sheet #1 (RawData) – Lab results entered during lab (all students)

Col A – Initial mass of salicylic acid (g)

Col B – Initial Volume of acetic anhydride (ml)

Col C – Mass of acetylsalicylic acid (aspirin) product

Create Computation Sheet

Open a new sheet and rename it “Results.”

Follow the instructions below to define the columns and setup the appropriate computational algorithms. The final form should look something like the following.

Row Col	A	B	C	D
1				
2	Salicylic Acid (moles)	Acetic Anhydride (moles)	Theoretical Yield (g)	% Yield
3				
4				
x+2			Average =	
x+3			Standard Dev =	

Column Definitions:

Col A – Salicylic Acid (moles)

Col B – Acetic Anhydride (moles)

Col C – Theoretical yield (g)

Col D – % Yield

Enter info and algorithms into “Results” sheet

Compute moles of salicylic acid and acetic anhydride, respectively

Enter your algorithm into Cell A3
 Enter your algorithm into Cell B3
 Compute the theoretical yield of your product
 Enter your algorithm into Cell C3
 Compute the % yield of your product
 Enter your algorithm into Cell D3
 Copy algorithms for class results into rows A4:Ax; B4:Bx; C4:Cx; D4:Dx
 Select cells B3:Ex (x presents row number of last student)
 From "Editing" box under "Home" on the Menu bar select "Fill Down"
 For Google: Press Ctrl D
 Note: This computes the results for all students
 Compute average of % yield results
 Enter into cell Cx + 2 "Average = " (Adjust cell size if necessary)
 Enter your algorithm into cell Dx + 2
 Compute standard deviation of % yield results
 Enter into cell Cx + 3 "Std. Dev. =" (Adjust cell size if necessary)
 Enter your algorithm into cell Dx + 3

Create Histogram of % yield results

Open Aspirin spreadsheet from Lab data base
 Select "Results" sheet (assumed created)
 Select Data (Student, % yield)
 Select Cells A3:Ax and D3:Dx
 Create histogram
 Select "Insert Chart" from menu bar
 Click on "Column" (Chart is created)
 Modify Titles
 Under "Chart Tools Layout" select "Chart Title"
 Select "Above Chart"
 Enter text for chart title
 Right click on text box adjust font, size and orientation as desired
 Under "Chart Tools Layout" select "Legend"
 Select "Turn off legend" (optional)
 Under "Chart Tools Layout" select "Axis Titles"
 Select "Primary Vertical Axis"

Enter Text for the axis label

Right click on text box and adjust of font, size and orientation

Copy table and insert into report

Results Summary Table:

Synthesis of Aspirin

Chemical Equation for Synthesis of Aspirin:

Show calculations where applicable:

<u>Reagent Mass</u>	<u>Volume</u>	<u>Density</u>	<u>Calculation</u>
salicylic acid			= _____ g
acetic anhydride	_____ ml	_____ g/ml	= _____ g
<u>Moles</u>			
salicylic acid	Type (equation editor) or Print Algorithm Here		= _____ mol
acetic anhydride	Type (equation editor) or Print Algorithm Here		= _____ mol
Molar Ratio	Stoichiometric	Actual Ratio (show calc)	
salicylic acid	_____	$\frac{\text{Actual moles salicylic acid}}{\text{Actual moles acetic anhydride}}$	= _____
acetic anhydride			
<u>Limiting Reagent:</u>			

<u>Theoretical Yield:</u>	Type (equation editor) or Print Algorithm Here		= _____ g
<u>Actual Yield:</u>			= _____ g
<u>Percent Yield:</u>	Type (equation editor) or Print Algorithm Here		= _____ %

Ferric Chloride Test for Presence of Unreacted Salicylic Acid

<u>Test Reagents</u>	<u>Test Result (Color)</u>	<u>Salicylic Acid Present?</u>
Test tube #1 (aspirin) + FeCl ₃	_____	_____
Test tube #2 (salicylic acid) + FeCl ₃	_____	_____
Test tube #3 (filtrate) + FeCl ₃	_____	_____

