Experiment 14
Amount of Active Ingredient in Aspirin
(One Lab Period)

Version 5

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A sodium hydroxide solution will be standardized by titration with hydrochloric acid. The sodium hydroxide will then be used to determine the amount of active ingredient in a commercial aspirin.

Objectives

- Perform a titration.
- Perform serial dilutions to obtain desired solution concentrations.
- Employ stoichiometric relationships and titration to determine an unknown quantity.

Learning Outcomes

Students will be able to:
- Apply proper rounding rules and rules of significant figures in calculations.
- Employ dimensional analysis (factor-label method) for unit conversions.
- Evaluate chemical quantities related to compounds (mass, molar mass, moles, and molecules/formula units).
- Identify and apply the concept of solution concentration.
- Apply the concept of serial dilutions.
- Prepare and complete labs to apply practical chemical concepts.
- Master essential laboratory techniques critical for laboratory science (titration and serial dilutions).
- Use scientific reasoning skills (such as observing, measuring, inferring, and predicting) to solve a solution to a simulated real-world situation.

Definitions

- **Acid-base reaction** – see neutralization reaction
- **Acids** – molecular compounds that form hydrogen ions, H^+, in water
- **Analyte** – the component of the sample to be studied or measured
- **Bases** – substances that form hydroxide ions, OH^-, in water
- **Concentration** – a measure of the amount of solute compared to solvent, often reported in molarity, M (mol/L), moles of solute in liters of solution

- **Endpoint** – when the indicator changes color during a titration; it is an estimate of the equivalence point, but often a little different (In this reaction, the indicator, phenolphthalein, turns pink in the presence of base so the equivalence point must be passed to have excess NaOH lead to color change.)
- **Equivalence point** – the stoichiometric point of the reaction, where the reagents have reacted completely
- **Indicator** – a substance that gives a visible change to show the presence or concentration of a chemical species
- **Neutralization or acid-base reaction** – when acid reacts with a base to form water and a salt
- **Standard solution** – a solution where the concentration is known to a great precision
- **Stock solution** – a solution that has a higher concentration than needed, used to prepare working solution(s) by serial dilution(s)
- **Titrant** – reagent used to carry out a titration, often the solution of known concentration
- **Titration** – process in which a solution of known concentration is reacted completely with a chemical of unknown amount
- **Working solution** – a solution prepared from the stock solution that we want to use in the experiment

Introduction

How do we know if medicines actually have the active ingredients that they are supposed to? Often times, we cannot detect if a medicine is present or working - certainly not by looking at it. The U.S. Food and Drug Administration (FDA) has Current Good Manufacturing Practices that create standards for ensuring pharmaceutical quality. By following the standards, the identity, strength, quality, and purity of drug products is assured. However, it is up to each manufacturer to choose how the standards are implemented. In addition, it is up to each manufacturer to report their compliance with the standards. The FDA does very little testing itself. It only reviews the results provided by pharmaceutical companies.

You have just been hired as a quality control expert for Pain Be Gone, a pharmaceutical company that makes aspirin. You need to check the latest lot of your company's aspirin to verify the amount of active ingredient. How would you measure active ingredients in a commercial aspirin?

Figure 1. Old Newspaper Advertisement of Bayer Aspirin.
Photo credit: Ads in History: 1926 Bayer Aspirin[1], used under the Creative Commons license.

Aspirin

Aspirin, also known as acetylsalicylic acid, is a medication taken to temporarily relieve pain and fever. It has been promoted as pain reliever for a wide range of maladies as can be seen in the label depicted in Figure 1. Acetylsalicylic acid (see Figure 2) is a weak acid. Recall that **acids** are molecular compounds that produce hydrogen ions, H^+, in water (pH is a measurement of the concentration of hydrogen ion).
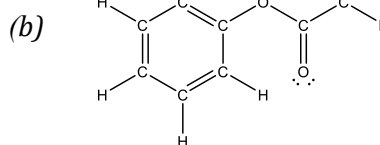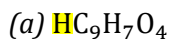
(a) $HC_9H_7O_4$ *(b)*

Figure 2. Acetylsalicylic acid.
(a) Chemical formula. (b) Structural formula. (The acidic hydrogen has been highlighted in yellow.)

When ingested, acetylsalicylic acid remains intact in the acidic stomach but in the basic medium of the upper intestinal tract, it forms the salicylate and acetate ions.[2] Aspirin selectively inhibits the production of cyclo-oxygenase 1 and cyclo-oxygenase 2, which are enzymes responsible for inflammation and pain[3]. (It is interesting to note that historical accounts related to treating illnesses by ingesting extracts of salicylate-containing plants date back thousands of years. For example, about 2400 years ago, Hippocrates recommended treating eye diseases and pain with juices of poplar tree and willow bark, respectively, both of which are salicylate-containing plants.[4])

Different strengths of aspirin are based on the amount of acetylsalicylic acid present. In this experiment, you will measure this amount by using a quantitative technique known as titration. The process of titration allows determination of the concentration of an unknown acid or base by adding the exact amount of a base or acid to neutralize the other. A **neutralization** or **acid-base reaction** happens when an acid reacts with a base to form water and a salt. The balanced molecular equation for the reaction of acetylsalicylic acid and sodium hydroxide is shown in Equation 1 and in Figure 3.
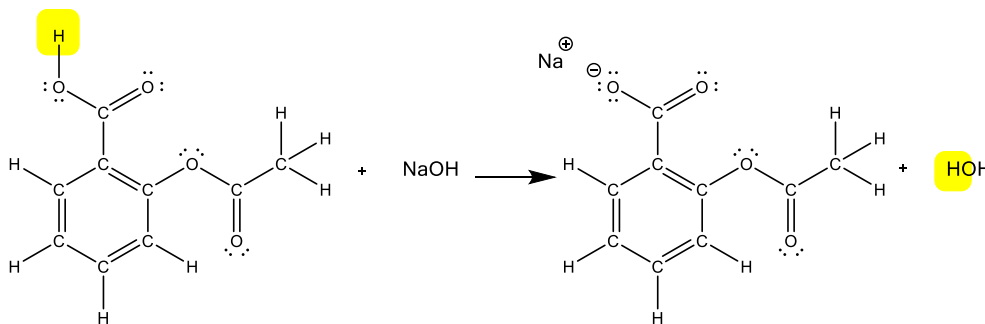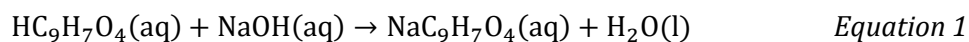
$$HC_9H_7O_4(aq) + NaOH(aq) \rightarrow NaC_9H_7O_4(aq) + H_2O(l) \qquad \textit{Equation 1}$$

Figure 3. Structural representation of the reaction of acetylsalicylic acid with sodium hydroxide.

Titration

To determine the amount of acetylsalicylic acid present in an aspirin tablet, the easiest process would be to dissolve a tablet and titrate it with a base. **Titration** uses a solution of known concentration to react completely with an analyte to determine its concentration or amount. Titrations are usually set up with the solution of known concentration in a buret as seen in Figure 4 (though in Part A of this experiment the solution of unknown concentration will be in in the buret). The solution of unknown concentration, the analyte, is usually placed in an Erlenmeyer flask. Therefore, you might dissolve the aspirin tablet in water and slowly add 0.200 M NaOH to it until you reach the stoichiometric ratio, the **equivalence point** of the reaction. The **endpoint** of the titration, is shown with an indicator that changes color. From the known concentration and its volume used to reach the end point, the moles of the known solution are calculated,

Buret: contains **titrant**, the solution of known concentration.

Graduations allow precise measurement of the volume added.

Erlenmeyer flask: contains **analyte**, the solution of unknown concentration.

Indicator is added to show the endpoint of the titration with a color change.

Figure 4. Components of a Titration

then the mole-to-mole ratio from the balanced reaction is used to determine the moles of the active ingredient. Finally, the mass of the active ingredient is found from its moles by use of its molar mass. Exercise 1 below, illustrates this process.

Exercise 1: A solution of magnesium hydroxide was titrated with a hydrochloric acid solution. What was the mass of $Mg(OH)_2$ in the solution if the titration required 71.10 mL of 0.150 M HCl?

The balanced equation for this reaction is:

$$Mg(OH)_2(s) + 2\ HCl(aq) \rightarrow MgCl_2(aq) + 2\ H_2O(l)$$
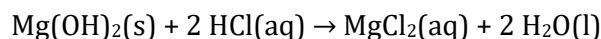
Solution:

a) Find moles of HCl that reacted by using the molarity equation:

Concentration is usually reported in molarity, M:

$$M = \frac{amount\ of\ solute\ (in\ mol)}{volume\ of\ solution\ (in\ L)}$$

Equation 2

Rearranging equation 2 to solve for moles:

$$?\ moles\ HCl = M_{HCl} \times Volume\ HCl_L = \frac{0.150\ mol}{L} \times 0.07110\ L = 0.010\underline{6}65\ mol\ HCl$$

b) Find mass of $Mg(OH)_2$:

$$?\ g\ Mg(OH)_2 = 0.010\underline{6}65\ mol\ HCl \times \frac{1\ mol\ Mg(OH)_2}{2\ mol\ HCl} \times \frac{58.326\ g\ Mg(OH)_2}{1\ mol\ Mg(OH)_2} = 0.311023 = 0.311\ g$$

Titrating the Aspirin

There are a few steps that will lead to analysis of the aspirin. First, you need to standardize a NaOH solution (approximate concentration of 0.1 M) by titration with hydrochloric acid (HCl). A standard solution of HCl (approximately 0.15 M) will be provided; its exact concentration will be written on the carboy or bottle. (A standard solution is a solution whose concentration is known with a high precision.) Finally, you will dissolve the aspirin and titrate it with the NaOH solution you prepared to determine the amount of acetylsalicylic acid per tablet.

These steps lead to the following series of chemical and mathematical equations.

1) Standardize NaOH using standard HCl:

$$NaOH(aq) + HCl(aq) \rightarrow H_2O(l) + NaCl(aq)$$
Equation 3

2) Titrate the acetylsalicylic acid in the aspirin with sodium hydroxide. See Equation 1.
3) Calculate the mass of acetylsalicylic acid present in the aspirin. See Equation 8.

The analyses will be performed in triplicate. Report the mean and standard deviation using correct units and correct significant figures (see Appendix 8). Average or mean ($\bar{x}$) can be calculated by adding together values for all trials and dividing by the number of trials, as seen in Equation 4. Standard deviation will measure precision by showing the variation in a set of values around the mean. Equation 5 below has the formula for standard deviation.

$$\text{Mean:} \quad \bar{x} = \frac{x_1 + x_2 + x_3 + \cdots + x_n}{n}$$
Equation 4

$$\text{Standard deviation:} \quad s = \sqrt{\frac{\sum(x_i - \bar{x})^2}{n-1}}$$
Equation 5

where: n is the number of trials
x_i is the individual result of each trial
Note: Standard deviation is usually reported to the same decimal places and unit of measure as the mean.

In addition, you will calculate the relative standard deviation (RSD, see Equation 6 and Appendix 8), and the relative percent error (see Equation 7 and Appendix 8).

$$RSD = \frac{s}{\bar{x}} \times 100 = \%$$
Equation 6

(If *RSD*<5%, you were precise in your measurements.)

$$Relative\ \%\ error = \left| \frac{true\ value - experimental\ value}{true\ value} \right| \times 100 = \%$$
Equation 7

where: *true value* is the expected or theoretical value
experimental value is the calculated value based on data.

If relative % error ≤ 5%, the amount of active ingredient is acceptable.

Techniques

- [Technique 1](): Cleaning glassware
- [Technique 3](): Transferring liquids
- [Technique 5](), [Video Tech. 5](): Using a volumetric pipet
- [Technique 11](): Disposing chemical waste
- [Technique 16,]() [Video Tech. 16](): Filtration by gravity
- [Technique 22,]() [Video Tech. 22](): Titration
- [Technique 23](): Fan-Folding Flat Filter Paper

- [Technique 2](): Using a balance
- [Technique 4](): Using a graduated cylinder

Techniques

List of Chemicals

- 0.10 M NaOH
- 0.15 M HCl
- Phenolphthalein indicator

- 95% Ethyl alcohol
- Commercial Aspirin, several brands

List of Equipment and Glassware

- one 15-mL volumetric pipet
- pipet bulb
- one 50-mL beaker
- one 150-mL beaker
- one 250-mL beaker
- four watch glasses
- 6 Parafilm squares, or 3 watch glasses
- six 125- or 250-mL Erlenmeyer flasks
- one magnetic stir bar
- one buret

- one mortar and pestle
- one small funnel
- three medium-sized funnels
- three fluted filter paper (or three flat filter papers)
- one 10-mL or 25-mL graduated cylinder
- one buret stand
- one buret clamp
- one magnetic stirrer

Experimental Procedure

Procedure summary: You will determine the concentration of an NaOH Solution by titration using the standardized HCl solution provided as titrant. Then you will use the NaOH Solution to determine the amount of acetylsalicylic acid in a commercial aspirin tablet.

Part A Determination of NaOH(aq) concentration using standardized HCl(aq)

Record the data of Part A in Data Table 1.

1. **Prepare the HCl Standard samples that will be titrated.**
   a) Pour approximately 80 mL of the HCl Standard solution into a 150-mL beaker. Label and cover it with a watch glass. Record the concentration of the standardized HCl solution.
   b) Obtain three 125-mL or 250-mL Erlenmeyer flasks (if there are no more Erlenmeyer flasks available, use beakers), and a 15-mL volumetric pipet. Label the flasks as HCl Trial 1, HCl Trial 2, and HCl Trial 3.

   Technique 3
   Technique 5
   Video Tech. 5

   c) Using the 15-mL volumetric pipet (condition it first), deliver 15.00 mL of the HCl standard into each of these three Erlenmeyer flasks. Add 2-3 drops of phenolphthalein indicator. Cover with Parafilm or watch glasses, and set aside for now.

2. **Titration set-up.**
   a) Pour approximately 150 mL of the 0.10 M NaOH solution into a 250-mL beaker. Label and cover it with a watch glass.
   b) Obtain a buret, a buret stand, buret clamp, a small funnel, a magnetic stirrer, and one magnetic stir bar.

   Technique 22
   Video Tech. 22

   c) Place the buret clamp on the stand and position the magnetic stirrer so that the buret may be suspended as close as possible over the center of the magnetic stirrer (if using a magnetic stirrer/hot plate unit, make sure the heating element is off). See Figure 5.
   d) Condition the buret with the NaOH Solution (use a funnel to pour the NaOH into the buret). Then add NaOH Solution to the buret until the bottom of the meniscus is close to the 45-mL gradation mark. Suspend the buret with the clamp, and place the NaOH Solution underneath it. Open the buret valve so the tip fills up with the solution. Do not allow it to completely empty out. Look closely just below the valve. If there is an air bubble, tap the buret while the valve is open, to see if it comes out. If not, ask your professor for help.

   Golden Lab Rule: Place funnel in a beaker or on a watch glass after use.

   e) Add NaOH Solution into the buret until it is close to the 0 mL mark. Remove the funnel.

3. **Titrate the samples of HCl Standard using the NaOH Solution.**
   a) Add a magnetic stir bar into the HCl Standard - Trial 1 (Part A-1), place it on the magnetic stirrer, and turn the stirrer on so it mixes the solution quickly without splattering (or mix manually after each addition if not using the stirrer). Lower the buret until its tip is barely below the rim of the Erlenmeyer flask.
   b) Make the initial NaOH volume reading. Read the buret to a precision of ± 0.01 mL and record in Data Table 1.
   c) Start titrating: Add the NaOH into the HCl sample while continually mixing. As the endpoint nears, drip the NaOH solution into the HCl sample until the endpoint, which is when the solution turns pale pink and persists for at least 30 seconds. Stop titrating. Make

the final NaOH volume reading. Read the buret to a precision of ± 0.01 mL and record in Data Table 1.

d) Refill the buret with the NaOH Solution. Repeat Step A3 with HCl Trials 2 and 3.

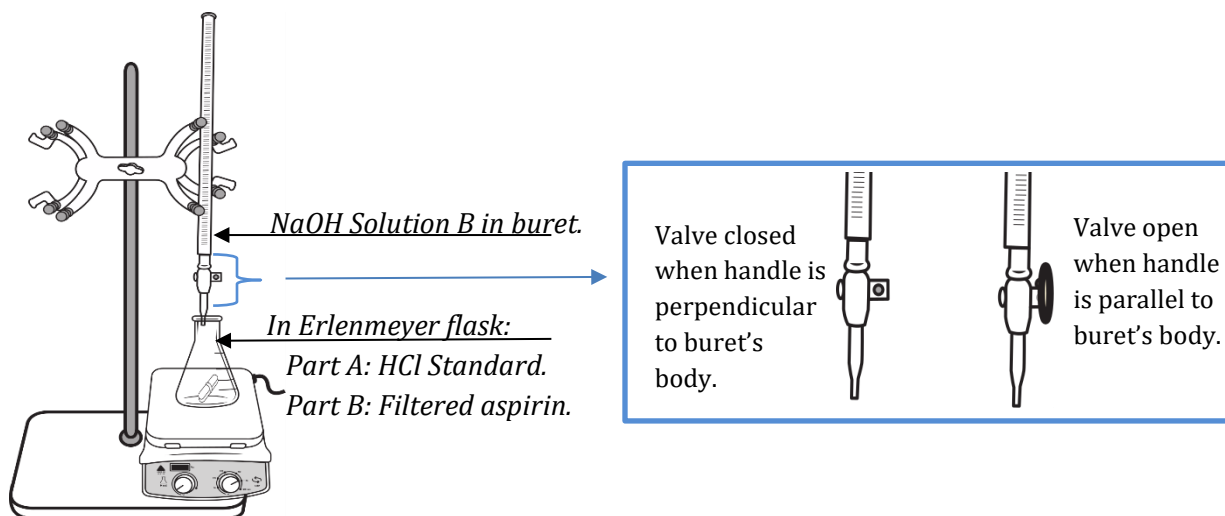Leave the titration set up. You will use it in Part B.

NaOH Solution B in buret.

In Erlenmeyer flask:
Part A: HCl Standard.
Part B: Filtered aspirin.

Valve closed when handle is perpendicular to buret's body.

Valve open when handle is parallel to buret's body.

Figure 5. Titration setup (setup on left side of stand if left-handed).

Part B Determination of the amount of acetylsalicylic acid in aspirin by titration with NaOH

Record the data of Part B in Data Table 2.

1. **Prepare the aspirin sample Trial 1.**
   a. Select an aspirin brand. Record brand and amount of active ingredient on Data Table 2.
   b. Remove one tablet from the selected brand and weigh it. Record in Data Table 2 Trial 1.
   c. Pulverize the weighed tablet using a mortar and pestle.

   Technique 2

   d. Tare a boat (or weighing paper) on the balance. Carefully transfer as much powdered sample into the boat as possible. Record the mass (record all digits from the analytical balance). You will need to determine the actual mass titrated in order to correct for the mass loss.
   e. Transfer the weighed powder into a clean Erlenmeyer flask (125-mL or 250-mL). Rinse the boat with DI water over the flask to ensure the sample is completely transferred into the flask. Label the flask as Aspirin Trial 1.
   f. Pour about 30 mL of ethyl alcohol (also called ethanol) into a 50-mL beaker. Label the beaker and cover with a watch glass.
   g. Using a graduated cylinder, add 10.0 mL of ethyl alcohol to the Erlenmeyer flask and stir for about 30 seconds with a glass rod. Then add 25.0 mL of water to the flask and stir again for another 30 seconds. The tablet will not completely dissolve due to inert ingredients (fillers and binding agents) in the tablet; the solution will be turbid. It will be necessary to filter it. (Remember to properly label your sample.)

h. Clean the three Erlenmeyer flasks used in Part A, and rinse with DI water. Shake out excess water. You do not need to dry them inside.

i. Place a funnel in one of the clean Erlenmeyer flasks (125-mL or 250-mL). See Figure 6a. (Note: If the funnel touches the bottom of the flask, suspend it above the flask using a support ring clamp and, if needed, a clay triangle (Figure 6b) held on a stand.)

Technique 16
Video Tech. 16

a   b
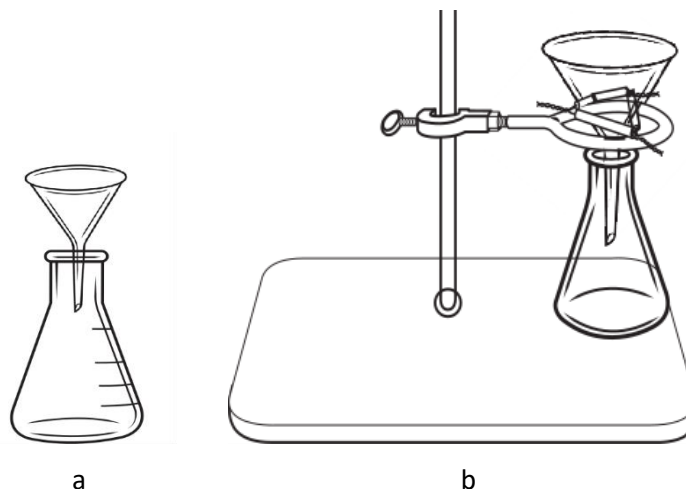
Figure 6. Funnel over Erlenmeyer flask

j. Obtain a fluted filter paper (Fisherbrand Qualitative P8-Flute 09-790-14E) <u>or</u> fan fold a flat filter paper (Whatman #1 Qualitative). Open it (Figure 7).

Technique 23
video starting at 1:04

Figure 7. Open fluted (or fan-folded) filter paper

k. Place the filter paper inside the funnel and seal it by wetting it with a small amount DI water. (You can leave this water in the Erlenmeyer flask.) Filter the aspirin sample prepared above. Once all the solution has gone through, rinse the filter paper and precipitate with a few milliliters of deionized water. Allow all the water to drain into the receiving flask. Rinse two more times.

l. Remove funnel and cover flask with Parafilm or a watch glass.

2. **Prepare the aspirin sample Trials 2 and 3.**
   a. Wipe the mortar and pestle with a paper towel to remove residue left from first tablet.
   b. Prepare two more trials: obtain two additional tablets of the same aspirin brand and repeat steps B1b – B1l; wipe mortar and pestle after each use, use a new filter paper and new flask each time. Label as Aspirin Trial 2 and Aspirin Trial 3.

3. **Titrate the aspirin samples.**
   a. Refill the buret with the NaOH solution.
   b. Add 2-3 drops of phenolphthalein indicator and a magnetic stir bar to the filtered aspirin sample Trial 1. Lower the buret until its tip is barely below the rim of the Erlenmeyer flask.
   c. Make the initial NaOH volume reading. Read the buret to a precision of ± 0.01 mL and record in Data Table 2.
   d. Start titrating: Add the NaOH into the aspirin sample while continually mixing. As the endpoint nears, drip the NaOH solution into the aspirin sample until the endpoint, which is when the solution turns pale pink and persists for at least 30 seconds (titrate slowly – it takes longer for the aspirin sample to react with the NaOH near the endpoint). Stop titrating. Make the final NaOH volume reading. Read the buret to a precision of ± 0.01 mL and record in Data Table 2.
   e. Repeat Part B steps 3a-3d with aspirin Trial 2.
   f. Repeat Part B steps 3a-3d with aspirin Trial 3.

Part C Calculations

Data Table 1:
1. Calculate the concentration of NaOH Solution in each trial:
   a. Calculate the moles of HCl Standard used in each Trial using Equation 2. Remember that the volume of the sample of HCl titrated was 15.00 mL.
   b. Use the balanced equation, Equation 3, to calculate the moles of NaOH that reacted with the moles of HCl in each Trial.
   c. Calculate the volume of NaOH delivered (final – initial buret readings).
   d. Calculate the molar concentration of NaOH Solution from each Trial (see Equation 2).
2. Calculate the mean molar concentration of the NaOH Solution and its standard deviation using Equation 4 and Equation 5, respectively. Also, calculate the relative standard deviation using Equation 6.

Data Table 2:
1. Calculate the active ingredient in the aspirin in each trial:
   a. Calculate the volume of NaOH added and the moles of NaOH.
   b. Calculate the moles of acetylsalicylic acid that reacted with the NaOH in the titrated sample using Equation 1.
   c. Calculate the grams of acetylsalicylic acid in the titrated sample using the molar mass acetylsalicylic acid.
   d. Determine milligrams of acetylsalicylic acid (asa) in the <u>whole tablet</u> using Equation 8.

$$mg_{\text{asa per tablet}} = mg_{\text{asa in sample}} \times \left(\frac{mass\ tablet}{mass\ pulverized\ sample} \right) \qquad \textit{Equation 8}$$

e. Calculate the mean $mg_{\text{asa } per\ tablet}$ and its standard deviation. Also, calculate the relative standard deviation.

f. Calculate the relative percent error between the experimental mean and theoretical value (the value on label) for the $mg_{\text{acetylsalicylic acid } per\ tablet}$.

g. Finally, state if the brand analyzed contained an acceptable mass of acetylsalicylic acid per tablet. (Acceptable industry tolerance for this type of product ranges within 5% of the value stated on the label.)

Clean up/Disposal

- Use a magnetic retriever (long plastic covered bar with a magnetic end) to remove magnetic stir bars. The retriever is usually hanging inside of the hood.
- Dispose all solutions into the waste container for liquids/aqueous solutions.
- Place pulverized solid tablet, and the filter paper with the precipitate in the waste *Technique 11* container for solids.
- Rinse pipets and buret several times with small amounts of deionized water. Collect rinses into a waste beaker, transfer to waste container for liquids/aqueous solutions.
- Place pipets and buret, tip up, in the designated canisters.

References:

1. Hanneman, J. *Adds in History: 1926 Bayer Aspirin*. Treasured Lives [Online] May 1, 2016. https://treasuredlives.us/2016/05/01/ads-in-history-1926-bayer-aspirin/ (accessed July 3, 2018).

2. Beran, J. A. *Laboratory Manual for Principles of General Chemistry*, *10th ed.,* John Wiley & Sons: Hoboken, NJ, 2014; p 237.

3. Rainsford, K. D. Pharmacology and Biochemistry of Salicylates and Related Drugs. In *Aspirin And Related Drugs*, Rainsford, K. D. Ed.; CRC Press, Sheffield, UK, 2004; p 266.

4. Rainsford, K. D. History and Development of the Saicylates. In *Aspirin And Related Drugs*, Rainsford, K. D. Ed.; CRC Press, Sheffield, UK, 2004; p 2.

Pre-lab

1. The titration of a 25.00 mL sample of NaOH required 28.25 mL of a 0.200 M HCl solution to reach the end point. What was the molar concentration of the sodium hydroxide solution?

2. A group obtained the following results:

Trial #	1	2	3
Amount active ingredient/tablet (mg)	598	583	587

    Based on these results, report the following using correct units and correct significant figures.

    a. mean

    b. standard deviation

    c. relative standard deviation (RSD)

3. A tablet of Pain Be Gone Aspirin, which had a mass of 1.213 g, was pulverized and 1.159 g were dissolved in 10.0 mL of ethyl alcohol and 25.0 mL of DI water. The titration of this solution with 0.1052 M NaOH required 15.62 mL to reach the phenolphthalein endpoint.

    Answer questions a – d below.

    a. Determine the moles of NaOH that reacted with the acetylsalicylic acid.

    b. Determine the mass, in grams, of acetylsalicylic acid in the sample analyzed.

    c. Determine the mass, in milligrams, of $HC_9H_7O_4$ in the tablet.

    d. The manufacturer claims that each tablet contains 325 mg $\pm$ 10 mg of acetylsalicylic acid. Is the actual amount of acetylsalicylic acid in the tablet acceptable?

Post-lab

In the data/calculations section:

1. Include the completed data tables.

2. In the calculations section show calculations requested.

Experiment 14: Amount of Active Ingredient in Aspirin
Experimental Data and Calculations

Name: _____ **Date:** _____

Lab Partner: _____ **Section:** _____

Data Table 1. Determination of NaOH Concentration.

	Trial 1*	Trial 2	Trial 3
1) Concentration of HCl Standard solution			
2) Volume of HCl sample			
3) Moles HCl			
4) Moles of NaOH			
5) Initial buret reading			
6) Final buret reading			
7) Volume NaOH added			
8) Molar concentration of NaOH Solution			

9) Mean molar concentration of NaOH Solution	
10) Standard deviation	
11) RSD	

* Show calculations for Trial 1, standard deviation, and RSD. (Continue on back of sheet if needed.)

Data Table 2. Determination of Acetylsalicylic Acid in Aspirin.

	Trial 1*	Trial 2	Trial 3
1) Aspirin Brand (and amount of acetylsalicylic acid on label)			
2) Mean molar concentration of NaOH (from Table 1)			
3) Mass of aspirin tablet			
4) Mass of pulverized aspirin sample			
5) Initial buret reading			
6) Final buret reading			
7) Volume of NaOH added			
8) Moles of NaOH			
9) Moles of acetylsalicylic acid in sample			
10) Mass of acetylsalicylic acid in sample			
11) Amount of acetylsalicylic acid per tablet			

12) Mean amount of acetylsalicylic acid per tablet	
13) Standard deviation for acetylsalicylic acid per tablet	
14) RSD for acetylsalicylic acid per tablet	
15) Relative percent error	
16) Is the mean amount per tablet acceptable? (Yes or no.)	

*Show all calculations related to Trial 1, standard deviation, RSD, and relative % error.