4. Separation and Purification of the Components of an Analgesic Tablet

J.R. Mohrig,	Chapters 10 (extraction) and 11 (drying agents)
C.N. Hammond,	142-147 (general introduction)
and P.F. Schatz:	147-149 (acid-base)
	144 (partition/distribution coefficient)
	152-158 (microscale extraction and general information)
	158-163 (density, sources of confusion)
	163-169 (drying agents)

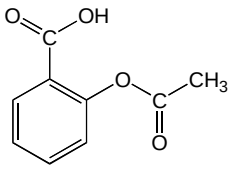
This procedure and material has been adapted from the microscale procedure described in *Macroscale and Microscale Organic Chemistry Experiments* by Kenneth L. Williamson and *Experiments in Organic Chemistry* by Louis F. Fieser.

In a nutshell

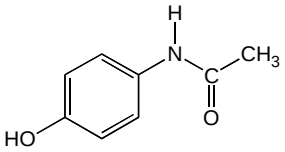
In this experiment, you will separate a strong organic acid, a weak organic acid, a weak base and a neutral substance. Solubility, which complicates the experiment, will be a key factor to understanding the full scope of the separation and purification of the analgesic tablet.

Background

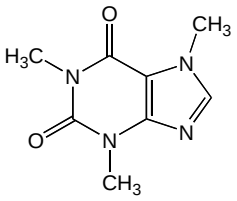
Analgesic tablets may contain a mixture of aspirin, acetaminophen, and caffeine, along with a binder, and are common pain relievers. The binder, a neutral substance usually made of silica gel, starch or microcrystalline cellulose, is used to hold the tablet together after packaging, shipping and while it is being swallowed. The binder is not soluble in water or common organic solvents.



aspirin
(acetylsalicylic acid,
2-acetoxybenzoic acid)
mp 138-140 °C
MW 180.15

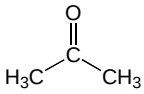


acetaminophen
(4-acetamidophenol,
4'-hydroxyacetanilide)
mp 169-172 °C
MW 151.16

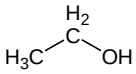


caffeine
mp 234-236.5 °C
MW 194.19

hexanes
(mixture of isomers)
d 0.672 bp 68-70 °C
MW 86.18



acetone
(propanone)
d 0.791 bp 56 °C
MW 59.08



ethanol
(ethyl alcohol)
d 0.816 bp 78 °C
MW 46.07

Aspirin was first synthesized by 1859 by Herman Kolbe, and Rudolph Schmidtt modified Kolbe's synthesis in 1885, which led to its mass production at a low price (P.Y. Bruice, *Organic Chemistry* Prentice-Hall, Upper Saddle River, NJ, 1995, p 835). It introduced to the market in 1899 and has analgesic (reduce pain), antipyretic (reduce fever), anti-inflammatory (reduce swelling) properties (*Concise Encyclopedia of Chemistry*, Walterde Gruyter, Berlin, 1994). It has come into more recent notice because of its affects in reducing the occurrence of heart attacks (http://www.cardioaspirin.com/en/hh/hh_prevention.html; *MacMillan Encyclopedia of Chemistry*, J.J. Lagowski, Ed., Vol. 1, Simon and Schuster MacMillan, New York, 1997, p. 145). Acetaminophen is also a drug, which acts in a similar way as aspirin but was "approved by the FDA in 1951" (http://www.medicinenet.com/acetaminophen/article.htm). If you can believe the hype, caffeine is a stimulant and known as one of the most "widely consumed psychoactive substances" (http://en.wikipedia.org/wiki/Caffeine). It is a known cerebral vasoconstrictor, diuretic and perhaps the active ingredient in previous diet pills (*MacMillan Encyclopedia of Chemistry*, p. 280).

If you take one look at the components, it looks like this experiment is similar to the one that we performed last week. The pK_a for aspirin is 3.49 (similar to benzoic acid), and the pK_a is 9.71 for acetaminophen. So you could treat the ground up tablet with an organic solvent, filter off the binder and then use a three-prong extraction system. At first glance, it looks like it would be the combination of the separation of the strong and weak organic acids and an organic base from a neutral organic compound. Unfortunately, there is a solubility issue.

Table 1. **Solubilities of the analgesic compounds in water, ethanol, chloroform, and diethyl ether**.
(K.L. Williamson, M*acroscale and Microscale Organic Chemistry Experiments*, D.C. Heath and Company, Lexington, Mass, 1989, p 215 and *Lange's Handbook of Chemistry*, J.A. Dean, Ed., 13th Edition, McGraw-Hill Book Company, New York, 1985, pp. 7-90, 7-84, 7-194.)

Compounds	Water	Ethanol	Chloroform*	Diethyl ether
Aspirin	0.33 g/100 mL (25 °C) 1 g/100 mL (37 °C)	20 g/100 mL	6 g/100 mL	7.7 g/100 mL
Acetaminophen	0.56 g/100 mL (25 °C)	29 g/100 mL	0.27 g/100 mL	5 g/100 mL
Caffeine	2.2 g/100 mL (25 °C) 18.2 g/100 mL (80 °C) 67 g/100 mL (100 °C)	1.5 g/100 mL (25 °C) 4.5 g/100 mL (60 °C)	18.2 g/100 mL	0.2 g/100 mL

*Assume the solubilities of aspirin, acetaminophen and caffeine in chloroform are similar to their solubilities in dichloromethane.
All data above have been converted to solubility/100 mL.

Because they are insoluble in dichloromethane, the binder and acetaminophen will be separated from the other two components by treatment of the solid with hot dichloromethane. The acetaminophen is soluble in hot ethanol. The other two components can then be separated using a standard acid/base extraction.

After completing this experiment, you should understand and/or perform the following.
1) write your own extraction scheme for separation of a strong acid, a weak acid, a base and a neutral compound.
2) understand solubilities
3) an aqueous workup

Notebook notes.
You **MUST** write out a flowchart of the experimental procedure in your notebook so that you can follow where you are in the extraction.

This procedure has been adapted from the microscale procedure described in M*acroscale and Microscale Organic Chemistry Experiments* by Kenneth L. Williamson.

Experiment

A. Recovery of the Acetaminophen and Binder.

Add 700 mg of the solid sample (contains acetaminophen, binder, aspirin and caffeine) to a small Erlenmeyer flask (label as ***E.F. 1***), followed by 4 mL of dichloromethane. Gently warm the mixture. Vacuum filter the resulting solution and rinse the solid remaining on the filter paper with dichloromethane.

A1. Treatment of the Filtrate. Place the filtrate (liquid) in a small reaction tube (label as ***R.T. 1***). This will become the organic layer used in step **B1**, so save it!

A2. Treatment of the Solid. Remove the solid from the filter paper, transfer it to another Erlenmeyer flask (label as ***E.F. 2***), and add 3 mL of ethanol. Add a boiling stick and heat the mixture to reflux (boiling point of solvent). Gravity filter the hot solution through filter paper inserted into a funnel and rinse with hot ethanol.

A2a. Recovery of the Binder. The binder is what remains on the filter paper in the funnel. Collect, dry, and weigh the binder.

A2b. Recovery of the Acetaminophen. Concentrate the ethanol solution to dryness (evaporate off the ethanol) and recrystallize the residue with water to obtain the acetaminophen. Collect, dry and weigh the acetaminophen.

B. Recovery of the Aspirin and Caffeine.

Add a 1 mL portion of 3 M sodium hydroxide to the filtrate from above **(Part A1; *R.T. 1*)**. Cap the reaction tube and shake the solution. Extract the aqueous layer with a pipette and place into a small beaker (label as ***Beaker 1***). Repeat this process with a second 1 mL portion of 3 M sodium hydroxide and add the extracted rinse to ***Beaker 1***. Follow the two sodium hydroxide extractions by rinsing with 1 mL of water and adding this extract to ***Beaker 1*** as well. You will need this solution for **Part B2**.

B1. Aqueous Layer (Recovery of the Aspirin). To the combined aqueous layers in ***Beaker 1***, add 3 M hydrochloric acid dropwise, stirring between additions, until the pH is acidic. This will be determined using pH paper. Add a boiling stick, heat the mixture, and add water if necessary to dissolve the solid. Do not boil longer than 5 minutes. Cool to room temperature, and then place in an ice bath. Vacuum filter, dry, and weigh the resulting solid.

B2. Organic Layer (Recovery of the Caffeine). Dry the organic layer in ***R.T. 1*** with sodium sulfate and gravity filter into a small beaker (***Beaker 2***). Discard the filter paper. Add a boiling stick and concentrate the organic layer to dryness in the hood. Recrystallize the resulting solid from acetone-hexanes. Filter, dry, and weigh the solid.