Drug Delivery from Swellable Tablets

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Objectives

- To define a swellable matrix drug delivery system
- To explain how the rate of drug release can be controlled in a swellable matrix
- To demonstrate the effect of drug concentration on the release rate
- To demonstrate the effect of polymer composition on the release rate
- To demonstrate the effect of polymer molecular weight on the release rate
- To compare release data with a mathematical model
- To identify the rate controlling mechanism from experimental data

Introduction

Drug delivery systems are an integral part of the development of new medicines. Chemical engineers working in the pharmaceutical field may contribute to the design of drug-delivery systems to deliver a predetermined amount of drug for a decided length of time to a particular location in the human body. Chemical engineers are able to combine their knowledge of the physical and chemical properties, chemical reactions, mass transfer rates, polymer materials, and system models that are not taught in the other disciplines, and are therefore a vital role in the pharmaceutical industry.[i] The goal of controlled drug delivery is to dispense the drug at a predetermined rate, either constant or in intervals, to the optimum target area for absorption in order to control the drug concentration in these regions. This not only minimizes negative side effects due to drugs passing through organs that do not require treatment, but similarly lowers the amount of drug needed because of direct application. Oral drug delivery systems have been widely investigated because they provide the most convenient route of administration and are capable of effecting controlled, responsive, site-specific drug release. This module focuses on drug delivery from swellable matrices (tablets) which are monolithic systems formed by direct compression of drug and swellable polymer particles.

A swellable matrix system is one in which a drug/polymer matrix contains a polymer which swells and forms a gel layer upon contact with water. The gel layer acts as a protective film for the matrix core which is susceptible to erosion.

The rate of release of a drug from a polymeric device can be controlled by Fickian diffusion through the polymer[ii], by erosion or dissolution of the polymer, or by polymer relaxation in the case of a swellable polymer. The rate of diffusion through the gel layer depends on the drug loading, solubility in the matrix, dissolution rate into the matrix and diffusivity in the matrix. Erosion control is governed by the rate of water penetration, rate of polymer erosion or dissolution, and hydrodynamic conditions. Relaxation control occurs when the concentration gradient of the drug in the gel region controls the release rate.

Ritger and Peppas present a simple model for drug release from a polymer which can be used to identify the mechanism of rate controlii.

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

Where M_t is the mass of drug released at time t, M_∞ is the mass of drug released after infinite time, F is the fraction released, k is a constant that depends on the diffusion coefficient and diffusion length, and n is an exponent which is indicative of the rate control mechanism. For Fickian diffusion in a slab, n = 0.5; for Fickian diffusion in a cylinder, n = 0.45. This short-time approximation is valid for $M_t/M_\infty \leq 0.6$. When the polymer is swellable, diffusion and/or polymer relaxation may govern the release rate.[ii,iii] For relaxation control, n = 1.0 for a slab and 0.89 for a cylinder. When n lies between the values for Fickian diffusion and relaxation control, both diffusion and relaxation contribute to rate control. A plot of ln F vs lnt will yield a line with slope equal to n and intercept equal to ln(k).

This lab will explore the drug delivery of caffeine and ultimately lead to the discovery of percent caffeine released over time. Five different caffeine tablets will be tested, each yielding slightly different results (see Table 1).

Table 1: Ingredients for Five Caffeine Pills, A-E

Ingredients	**A**	**B**	**C**	**D**	**E**
Caffeine (g)	0.12	0.24	0.36	0.24	0.24
POLYOX (g)	0.24	0.24	0.24	0.12	0.72
Lactose (g)	0.828	0.708	0.588	0.828	0.228
Magnesium Stearate (g)	0.012	0.012	0.012	0.012	0.012

These five different pills can be used to test molecular weight, polymer concentration, and drug loading. By varying the ingredients in each pill, we can see the impact each ingredient has on the delivery of the drug.

The caffeine in each pill is the intended ingredient to be delivered to the body. Caffeine is an organic white powder with molecular formula: $C_8H_{10}N_4O_2$. It has a shelf life of four years and is most commonly found in foods such as coffee, tea, soda and cocoa. When in the body, caffeine acts as a mild central nervous system (CNS) stimulant.[iv] In the medical world, caffeine is known as trimethylxanthine, and is generally used as a cardiac stimulant, although it is normally thought of as an energy stimulant. Caffeine is also an addictive drug because it uses the same mechanism as cocaine and heroin in the body. That is, they all stimulate the transmission of dopamine, a monoamine neurotransmitter formed in the brain that aids in the function of the CNS, in the shell of the nucleus accumbens. This transmission of dopamine has also been linked to causes of drug addiction. Caffeine, however, shows very little addictive properties.[v] Fresh coffee contains between 0.08 and 0.35 g of caffeine per cup. The caffeine pills that will be

made in this lab contain between 0.12-0.36 g of caffeine[vi]. Below is a chart with shows the levels of caffeine in some common dietary and pharmaceutical sources.

Table 2: Caffeine Levels in Common Products[vii]

Source	Grams
Beverages	*(per 150mL)*
Brewed Coffee	0.08
Brewed Black Tea	0.05
Brewed Green Tea	0.03
Cola	0.01 - 0.03
Cocoa	0.00 - 1.42
Over-the-counter meds	*(per tablet)*
Aspirin	0.03
Excedrin	0.06
NoDoz	1.00
ViVarin	1.00 - 2.00

POLYOX is an ingredient in these caffeine pills that regulates the rate of caffeine delivery to the body over a period of time. POLYOX polymer resin is mixed with other ingredients and pressed into a tablet form. When the tablet is contacted with a liquid (water), the POLYOX swells and forms a gel layer which acts as a protective film around the tablet. The drug is released slowly through this gel layer, and the release rate is controlled by the thickness of the gel layer.

Lactose is a beneficial excipient because it acts as a soluble filler that adds bulk to powders. It is also inert, innocuous and inexpensive. The average particle size for spray dried lactose is 100µ, which is large even when compared to other bulk fillers of 70 - 90 µ.[viii] This bulk will be able to vary the time required for the tablet to be dissolved and therefore the time required for the drug to be released into the body. It also allows the particles to mix together well when being compressed into a tablet.[8] The large pore diameter of lactose pellets increases the crushing strength of the tablet as well as the available surface area. However, changes in pH cause the pore diameter of lactose to decrease and consequently slow drug release.[ix]

Lubricants are often added to pharmaceutical tablets to prevent them from attaching to the die and punches of a tablet press. The most commonly used lubricant is magnesium stearate. However, in addition to acting as a lubricant, magnesium stearate decreases interparticle bonding. This decreases the tensile strength of the tablet by decreasing the density of the powder.[x]

After a tablet is made with the ingredients described above, the release of drug can be investigated experimentally. The tablet is placed in a beaker containing a large volume of water (representing the body). Samples are taken at regular intervals from the water,

and the concentration of caffeine is analyzed using a spectrophotometer. A spectrophotometer measures the absorbance of light by a sample. When there is more caffeine present in a sample, the sample will absorb more light. To find the relationship between absorbance the percent of caffeine released, a caffeine curve must be made. Figure 1 shows the caffeine curve to be used for the laboratory calculations. It was constructed by taking samples of a distilled water and caffeine mixture at different concentrations, and measuring the absorbance of each sample. A linear trendline fit (shown on the graph) provides the caffeine calibration equation. This equation can be used to find the concentration of caffeine released by only knowing the absorbance.

Below is a sample calculation to find the mass of caffeine in a one liter solution using the caffeine calibration equation for an experiment done where the absorbance was found to be 1.65.

$$C = 0.0209 * (1.65) - 0.0040 = 0.0305 \frac{g}{L} \tag{2}$$

$$Mc(g) = 0.0305 \frac{g}{L} * (1L) = 0.0305g \tag{3}$$

In the example shown there was 0.0305g of caffeine in the one liter solution. This information was found using only the absorbance from the spectrophotometer and the caffeine curve (equation 5).

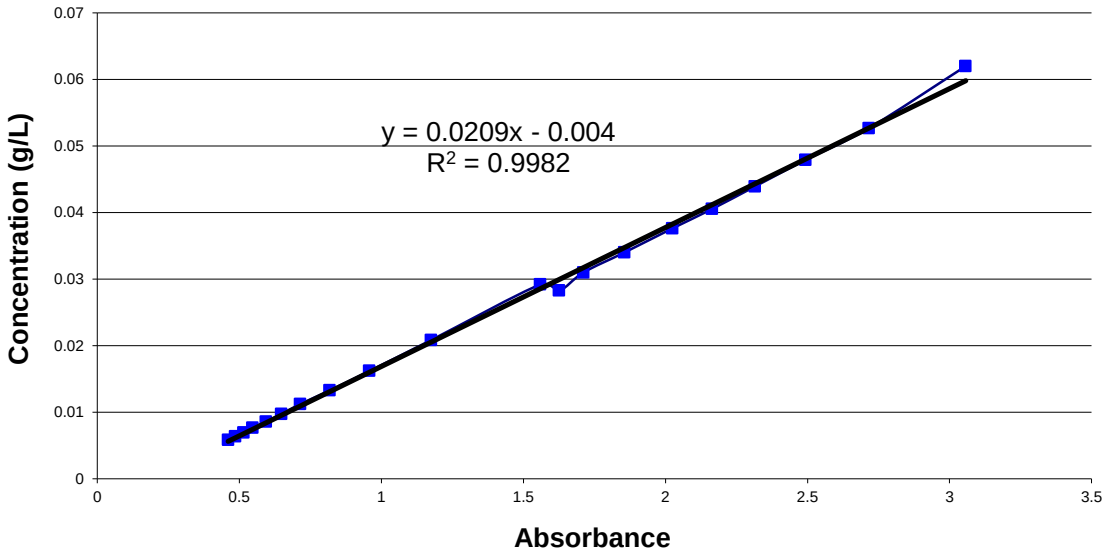

Figure 1. Caffeine calibration curve.

Laboratory Procedure

Equipment and Materials

Hot plate
Stir bar
Beaker
2,000 mL of distilled water
1 caffeine tablet
5,000μL Micropipetter
Quartz Cuvette
Spectrophotometer set to 273 nm
Tea bag holder
Stopwatch

Making the tablet

The Carver "Mini C" hydraulic press will be used to make the tablets. Components to the hydraulic press can be found below and may be seen in Figure 1:

- Top Bolster
- Bottom Bolster
- Gauge
- Pump Arm
- Release Valve

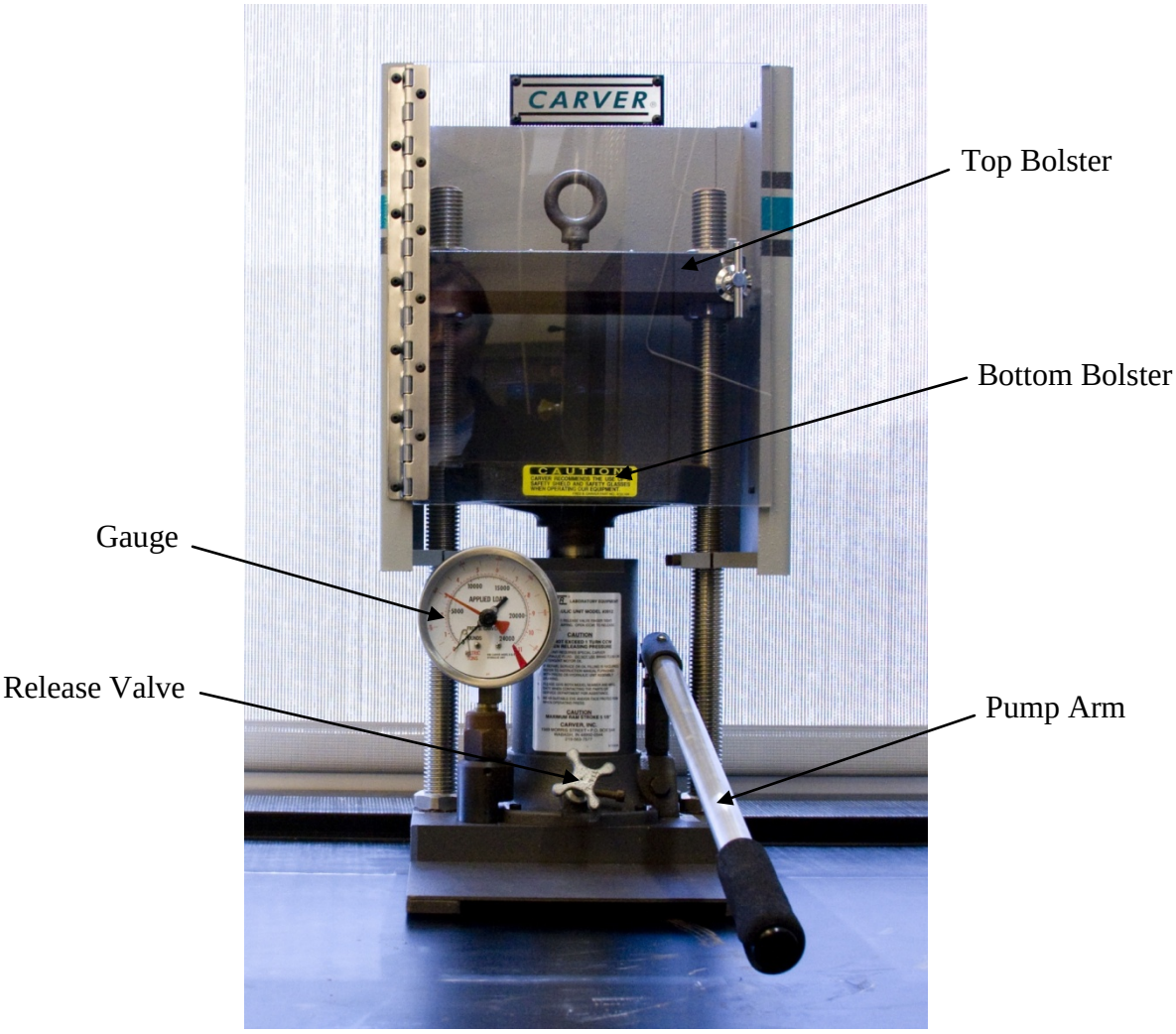

Figure 2. Carver Mini C Hydraulic Press

Below is an enlargement of the gauge, in order to show increments and units.

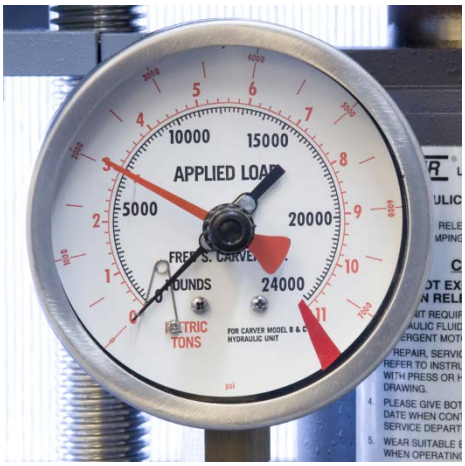

Figure 3. Pressure gauge on the tablet press.

The die that will be used to press the pills has four parts (see Figure 2):

- Upper Punch – the upper punch has a long stem with the bottom most part being a smoothed surface that will physically form the top of the pill
- Die – the die is a small tubular piece with a top and a bottom. The bottom has a small neck that has a smaller outer diameter than the top of the die
- Lower Punch – the lower punch has a short stem with the top most part being a smoothed surface that will physically form the bottom of the pill
- Ejector Die – this die is only used after the pill is pressed to eject the pill (Figure 3)

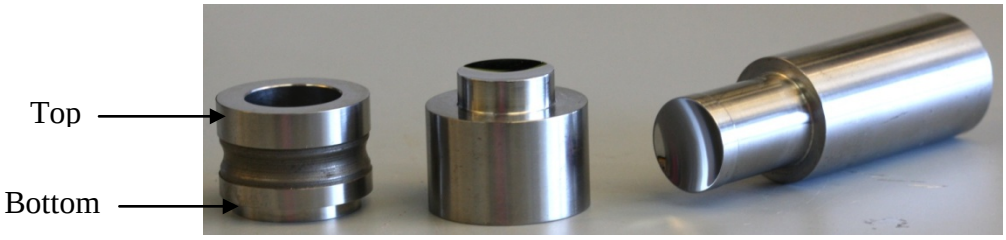

Figure 4. From left to right, die, lower punch and upper punch.

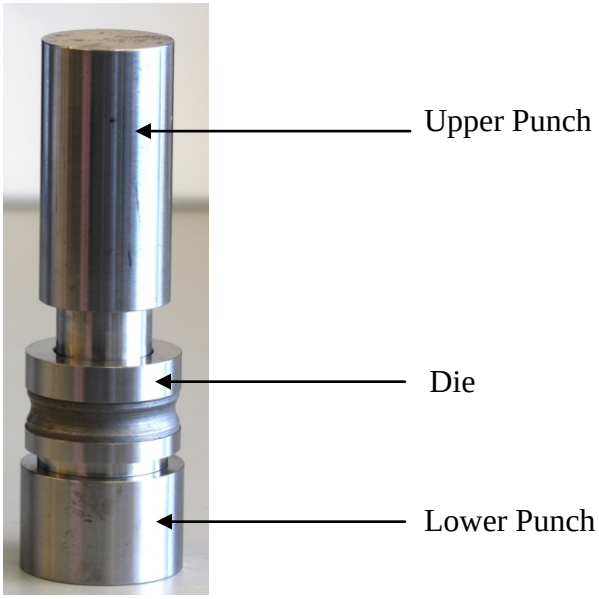

Figure 5. Assembled punch and ejector die

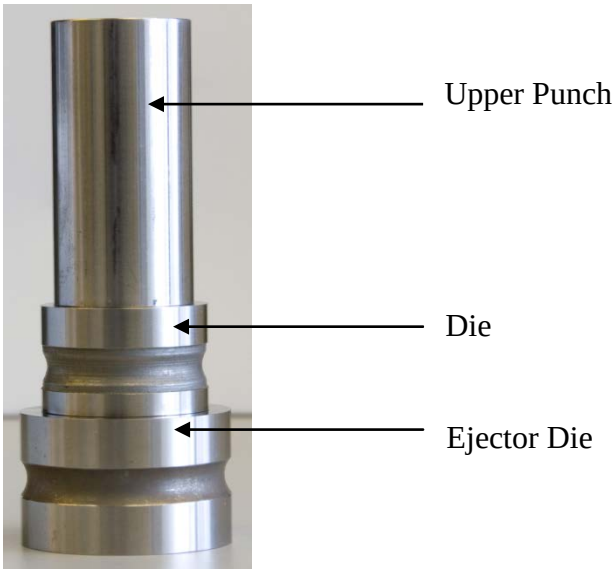

Figure 6. Assembled punch and die

Figure 8 shows the lower (left) and upper (right) punches lying on an angle. From this view, it is easy to see the very smooth, rounded sides that will compress the powder matrix into a tablet.

Figure 7. Punches.

Figure 8 shows the fully assembled punches and die on the tablet press, ready for hydraulic pressure to be applied to the bolsters via the pump arm therefore forming a tablet. It also shows part two of tablet making, the assembled die and ejector die in which to eject the formed tablet from the die.

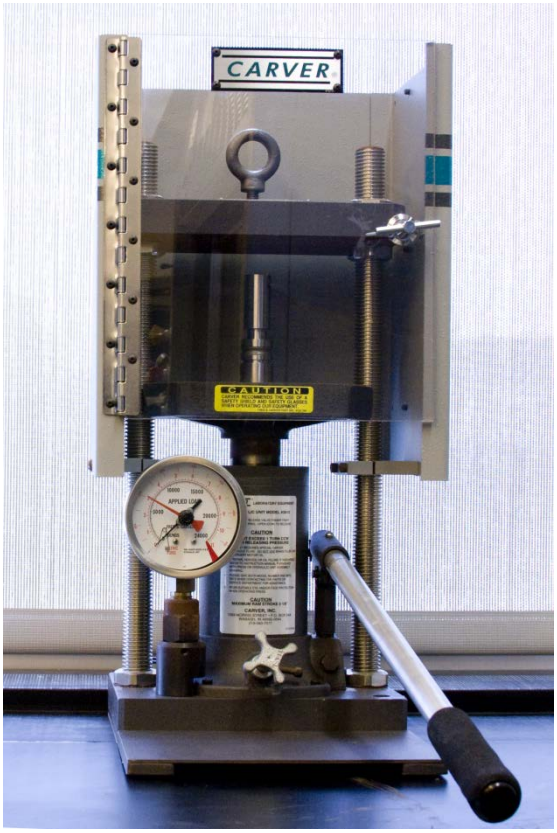

Figure 8. Punches and die on the tablet press prior to compression.

The procedure for the pill press follows:

1. Weigh specified amount of powder that will be used to make a tablet. (Note: The final tablet weight will be less than the weighed amount of material, as it is very

likely some of the material will be lost when transferring material from the weight boat to the punch and die.)

2. Insert lower punch into the bottom of the die. Pour the powder into the die.
3. Place upper punch into the top of the die and press down. The upper punch should move up and down in the die. See compression diagram in Figure 6 to ensure tooling is assembled properly.
4. Wipe the bottom of the punch so that the punch will sit flat on the bottom bolster of the carver press.
5. Open safety shield of the carver press and place the punch and die in the center of the bottom bolster.
6. Check that the release valve is closed.
7. Before applying force to the punch and die assure that the punch and die are centered.
8. Close safety shield and begin pumping the hydraulic press to raise the bottom bolster until the top bolster touches the top of the upper punch.
9. Apply specified amount of force to the punch and die. The force is measured on the gauge in both metric and English units. Once the initial amount of force is applied check the gauge to ensure that the force remains constant, as the press may need more force applied to maintain the specified pressure.
10. Lower the bottom bolster by turning the release valve counter clockwise.
11. Open the safety shield and remove the punch and die.
12. Place cotton or tissue into the ejector die. The ejector die is used to catch the tablet when it comes out of the tooling.
13. Remove the lower punch from the die.
14. Place the upper punch and die on the ejector die. Press the upper punch down to release the tablet. See the ejection diagram in Figure 6.

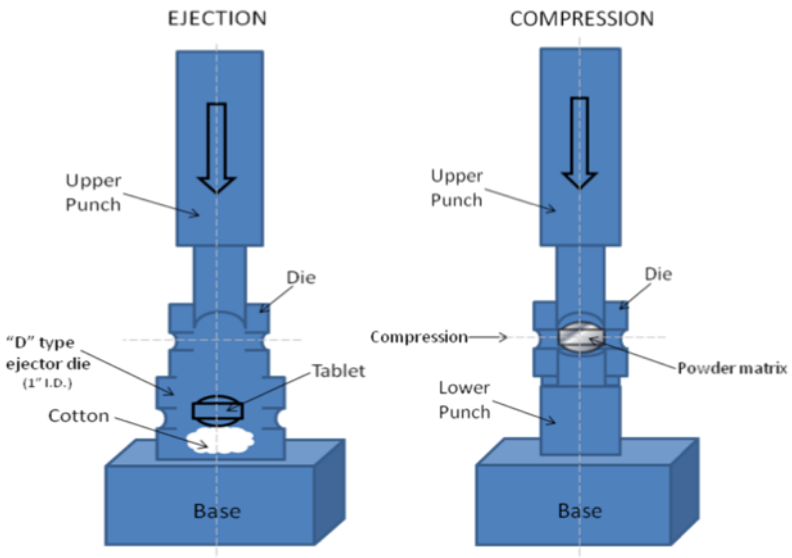

Figure 9. Compression and ejection.

Testing the tablets

Three different tablets will be distributed among the class (A, B, and C). When all of your data are collected, trade with the rest of the class because data from every group is required in the write-up.

Read all of the procedures before beginning this lab. Fill a beaker with 2,000mL of distilled water, and use a magnetic stirrer to achieve a stirring rate of 60 rpm. Put the caffeine pill in a tea bag holder, and suspend the tea bag holder about 1 cm from the bottom, making sure that it does not contact the stir bar. As soon as the pill is surrounded by water, start the stopwatch. A sample must be taken every five minutes. After the first five minutes, take the first sample using the micropipetter, and put the sample into the cuvette. The exact amount of the sample in the cuvette is not important, but make sure the cuvette is approximately 2/3 full. Carefully clean the sides of the cuvette with a Kimwipe and put the sample into the spectrophotometer. Check to make sure the reading is taken at the wavelength 273. Record the absorbance and the time elapsed since the beginning of the experiment (minutes) and put the sample back into the beaker. Continue these readings for 2 hours.

Instructions for Data Analysis

In Excel, create two columns for the original raw data showing time (min) and absorbance. Create two additional columns for calculated quantities of mass released (g) and time$^{1/2}$ (min$^{1/2}$). Perform the calculations according to the equations found in Appendix A. Prepare the following graphs for each tablet:

1. Mass of caffeine released vs. time
2. Mass of caffeine released vs. time^{½}.

Questions

1. Each graph should show an initial period during which the mass of drug released is increasing with time (or square root of time). Do you expect that the mass of drug released will continue to increase indefinitely?

2. Use the graph of mass released vs. time^{½} to determine the final amount of drug released from the tablet after a very long time. Identify the tablet that produced each curve on the graph.

3. Use the graph of mass released vs. time^{½}, and consider only the portion of the curve that is increasing linearly. What is the value of the slope of this portion of the curve? What factors affect the slope of this curve?

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Different factors will affect the release rate of the drug such as the total amount of caffeine present, and to what extent the powdered caffeine was mixed with the other ingredients.

Appendix A: Sample Calculations

The following shows an interpretation of a single sample point using tablet A in 2,000 mL of distilled water

Absorbance reading: 1.5131
Time: 26.5 minutes

The concentration can be found using the caffeine calibration curve. This curve reveals a linear relationship between concentration (y-axis) and absorbance (x-axis). The concentration, C has units of mass per volume such as grams per liter. The absorbance, A has no true units as it is a ratio of light intensities. Plug the absorbance reading into the equation to find the concentration.

Caffeine curve equation:

$$C = 0.0209 * A - 0.004 \tag{4}$$

Solve for concentration (C), as in equation (3):

$$C = 0.0209 * (1.5131) - 0.004 = 0.0276 \frac{g}{L}$$

The concentration is 0.0276 g/L or mg/mL.

To find the mass of caffeine released (Mc), as in equation (4):

$$\text{Mc}\,(g) = 0.0276 \frac{g}{L} * 2L = 0.0552 g$$

Perform these calculations on all of your data using Excel and then make plots of the amount of caffeine released vs. time and the square root of time. From this data you should be able to determine which tablets are A, B, and C.

Appendix B: Comparisons

For other tests the pills shown back in Table 1 were made both with a POLYOX N10 (MW = 100k), and a POLYOX 303 (MW = 7 million). This allowed other comparisons between tablets to be made, such as polymer molecular weight, polymer concentration, and drug loading. To test these effects, an A tablet was made with POLYOX N10, and another was made with POLYOX 303. The following data was collected as shown below in Figure 11:

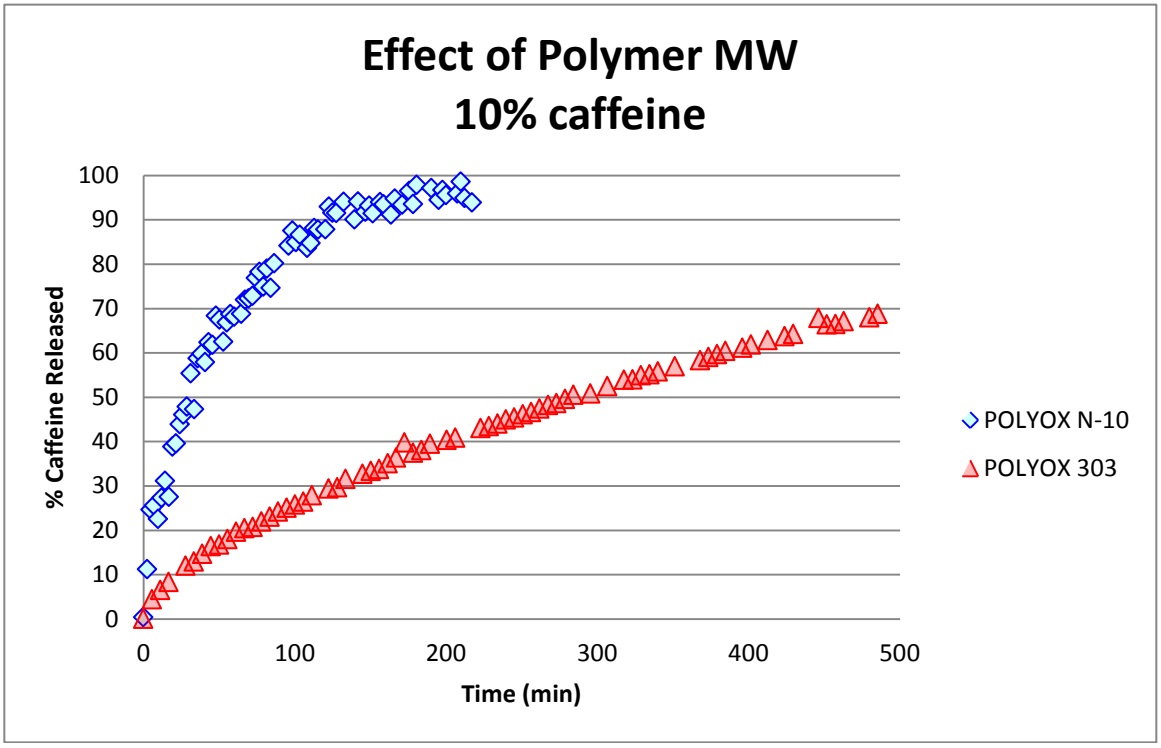

Figure 10. Effect of polymer molecular weight using formulation A (10% caffeine, 20% polymer). One tablet was made with Polyox N-10 and the other made with Polyox 303.

This graph shows that caffeine is released faster through the matrix system when POLYOX N10 is used. POLYOX 303 has a higher molecular weight than POLYOX N10, and reduces the release rate. This is because a higher molecular weight increases the gel strength, which decreases the diffusivity of caffeine through the gel.

The affects of polymer concentration were tested using tablets B and D. Tablet B has 20% caffeine and 10% Polyox 303; tablet D has 20% caffeine and 20% Polyox 303. The results are shown below in Figure 13:

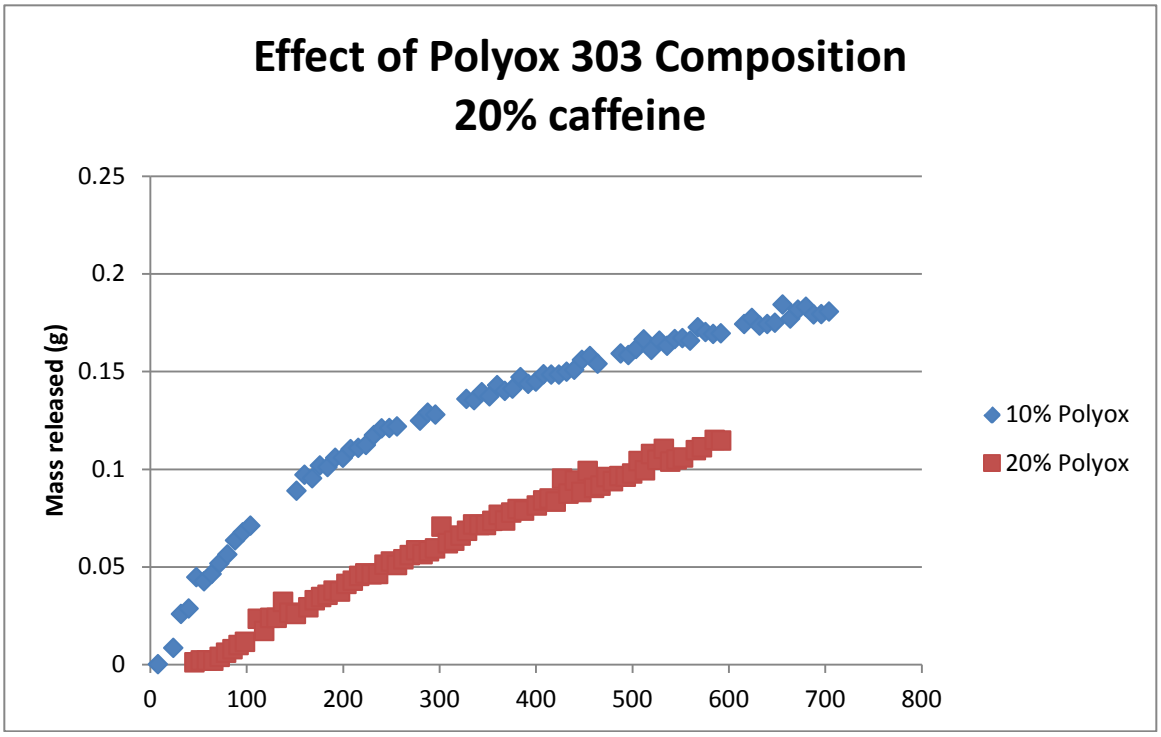

Figure 11. Effect of Polyox composition on release rate using Tablet D (20% caffeine and 10% Polyox) and Tablet B (20% caffeine and 20% Polyox).

Notice that tablet D had the faster release rate and also had the smallest amount of POLYOX (See Table 1). Therefore, when the polymer concentration is increased, the release rate is slowed. This is because the more POLYOX present, the greater the viscosity of the gel layer, which slows the diffusion of caffeine.

Drug loading was tested by varying the amount of caffeine in each tablet while keeping the amount of POLYOX constant. This was performed using tablets A and C, and the following results shown in Graph 7 were found:

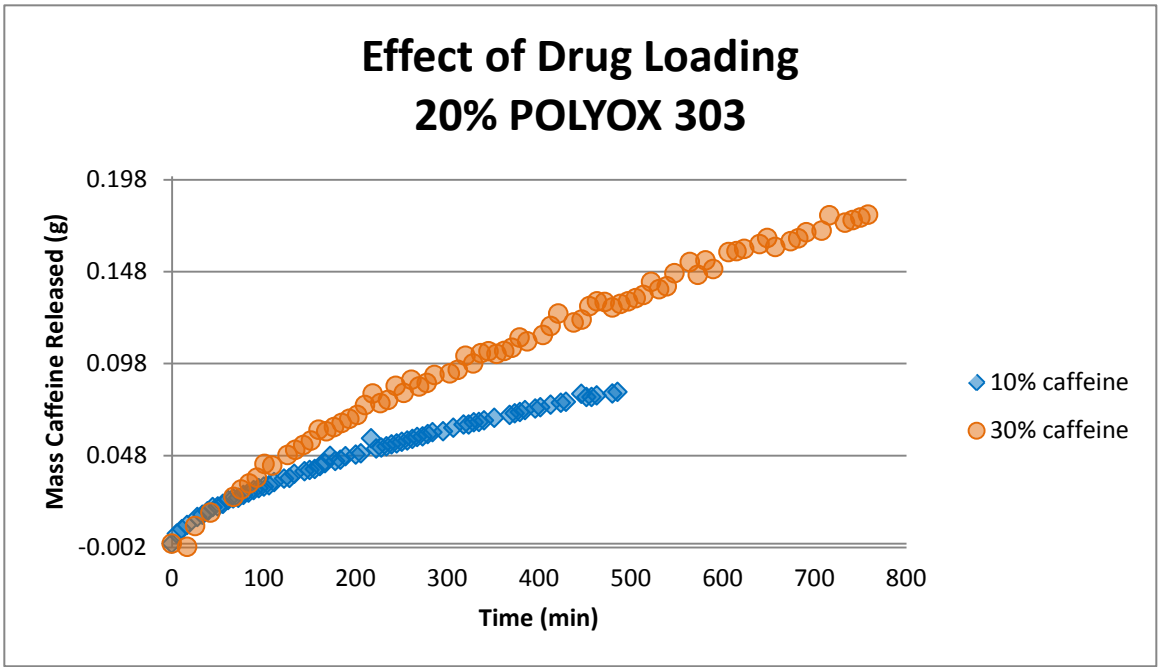

Figure 12. Effect of drug loading using Tablets A (10% Caffeine and 20% Polyox) and Tablet C (20% Caffeine and 20% Polyox)

The lower drug loading in tablet A (10%) results in a slower rate of drug release than tablet C which has 30% caffeine.

Mechanism of Rate Control

Figure 16 shows the effect of caffeine loading on the mechanism of drug release. With the low (10%) loading, the diffusion front moves faster and diffusion is more important (n=0.63. With the higher loading (20%), the diffusion front moves more slowly and relaxation becomes more important (n=0.79).

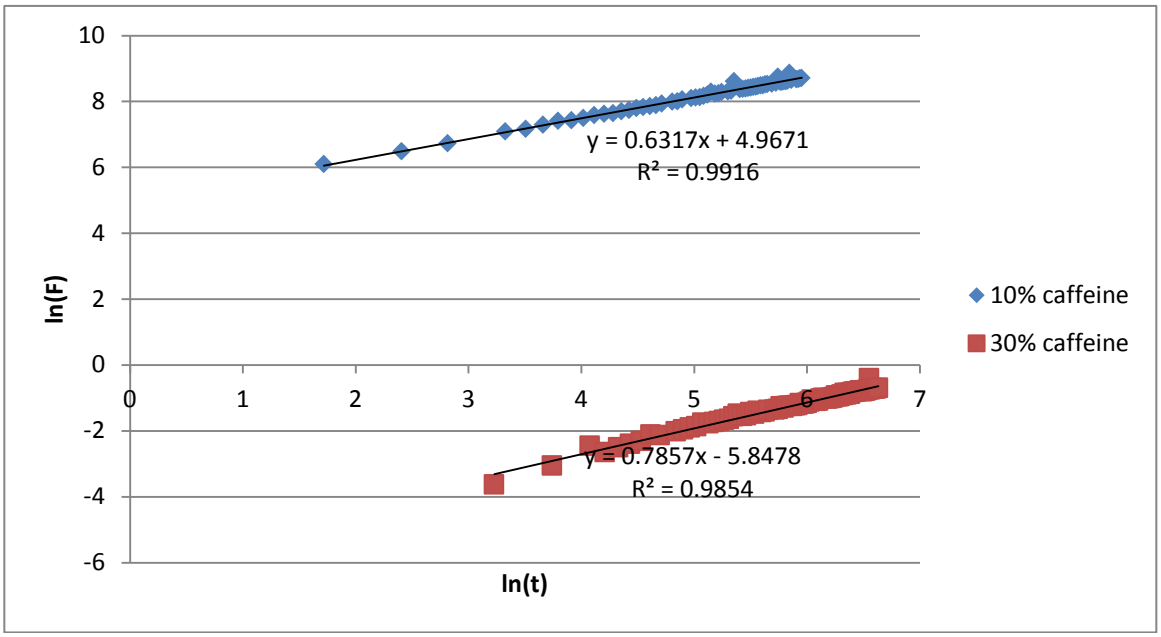

Figure 13. Effect of caffeine loading on mechanism of drug release

In Figure 17 the effect of Polyox composition on the release mechanism is shown. The lower Polyox composition (10%) results in a less viscous gel layer through which diffusion can occur freely (n=0.6). The higher Polyox composition (20%) results in a higher viscosity gel layer through which diffusion is slower, and swelling becomes more important (n=1.0).

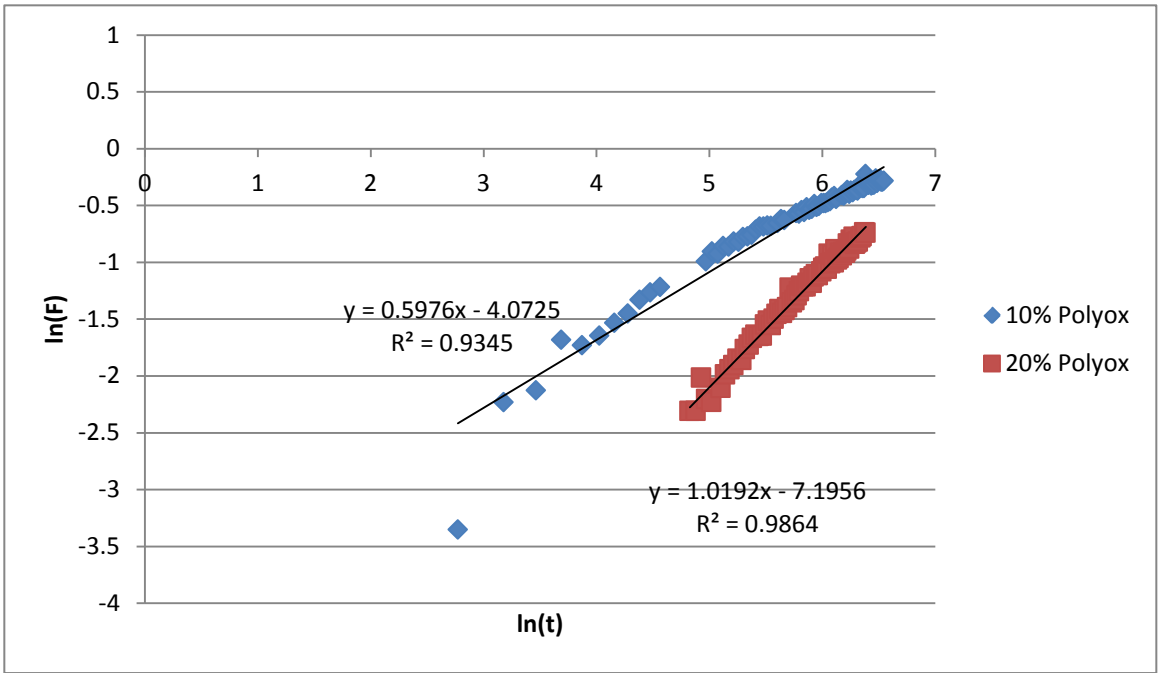

Figure 14. Effect of Polyox composition on release mechanism.

Figure 18 shows the effect of polymer molecular weight on the release mechanism from the matrix. Both the Polyox 303 resin (MW – 7 million, n=0.62) and the Polyox N-10 (MW = 100k, n=0.58) show anomalous release with contributions from both diffusion and swelling.

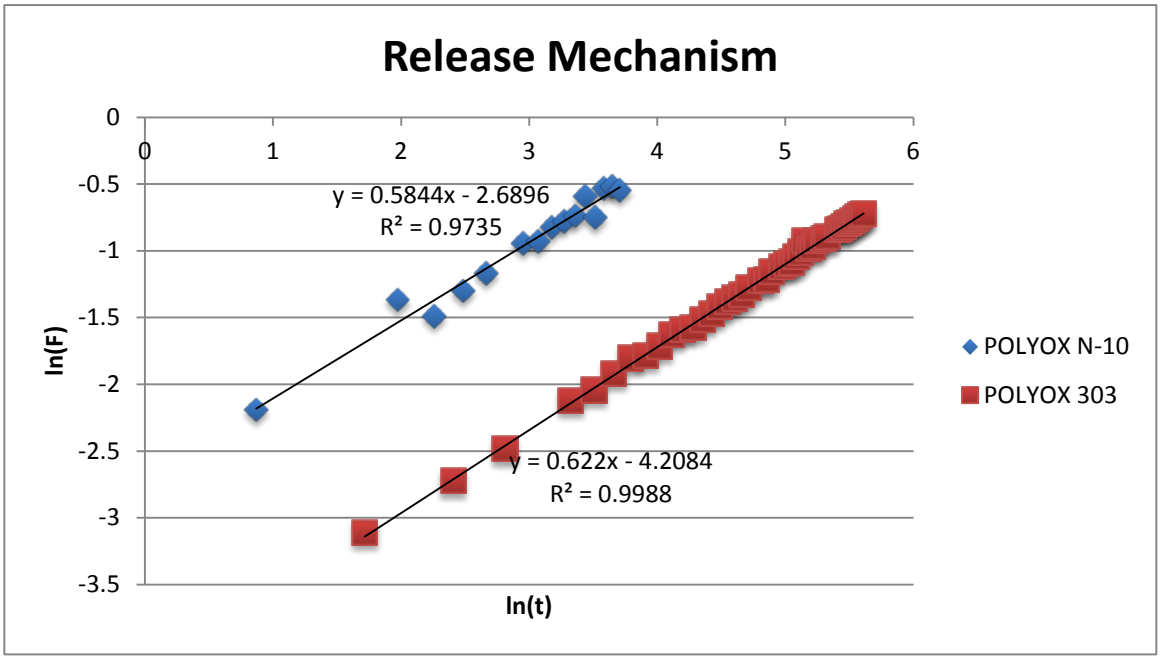

Figure 15. Effect of polymer molecular weight on the release mechanism.

Appendix C: Ordering Information

Item	Catalog #	Website	Amount	Vendor (Phone)	Price (Date)
Caffeine, Anhydrous, USP	CA105-07	Caffeine	125g	Gallade Chemical (714) 546-9901 x124	$64.29 (7/7/08)
Lactose, Monohydrate, Powder, NF	627003	Lactose	500g	Gallade Chemical (714) 546-9901 x124	$68.09 (7/7/08)
Magnesium Stearate, NF	MA130-10	Magnesium	500g	Gallade Chemical (714) 546-9901 x124	$71.87 (7/7/08)
POLYOX 303	17006883	POLYOX	1000g	DOW (215) 669-7733	$192.23 (7/9/08)
POLYOX N10	17006881	POLYOX	1000g	DOW (215) 669-7733	$192.23 (7/9/08)

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[ii] Ritger, Phillip L. and Nikolaos A. Peppas, A simple equation for description of solute release I. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs, Journal of Controlled Release, 5(1), 1987, 23-36.

[iii] Peppas, Nikolaos A. and Jennifer J. Sahlin, A simple equation for the description of solute release. III. Coupling of diffusion and relaxation, International Journal of Pharmaceutics, 57, 1989, 169-172.

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[v] Di Chiara, Gaetano. "Drug addiction as dopamine-dependent associative learning disorder." European Journal of Pharacology 13(1999): 1-3.

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