Drug Dosage Forms

Dr. Stephanie Farrell

Introduction

Lozenges are solid drug dosage forms containing a drug along with flavoring and sweetening agents. Lozenges are formulated to be harder than ordinary pharmaceutical tablets so that they will dissolve slowly in the mouth.

Lozenges can be used for hospice or chemotherapy patients who often experience nausea. Geriatric and pediatric patients often show improved compliance with lozenges over other types of oral formulations such as tablets.

Traditional drugs that have been used in lozenge formulations are:

- Benzocaine - a topical anesthetic used in Cepacol lozenges and also in sore throat spray
- Cetylpyridinium chloride - an antimicrobial agent, used in Cepacol lozenges and also in mouthwash

Newer drugs that are now incorporated into lozenges are:

- Morphine sulfate - a narcotic analgesic used to relieve moderate to severe pain
- Clotrimazole - an antifungal agent used to treat or prevent yeast infections of the mouth or throat in susceptible individuals
- Nystatin - an antifungal agent used to treat intestinal fungal infections
- Lorazepam - a type of central nervous system (CNS) depressant, or medicine that slows down the nervous system. It is used to treat anxiety, anxiety associated with depression, or insomnia
- Diphenhydramine HCl - an antihistamine that is used help you sleep
- Haloperidol - used to treat psychotic disorders and severe behavior problems in children. It is also used to control the symptoms of Tourette's syndrome
- Dexamethasone - belongs to class of anti-inflammatory agents called corticosteroids. It is used to treat a variety of inflammatory conditions, including allergic reactions, skin diseases
- Metoclopramide HCl - increases gastrointestinal motility. It has a variety of uses, including treatment of diabetic gastroparesis, gastroesophageal reflux disease and the prevention of chemotherapy induced nausea and vomiting
- Benztropine mesylate - an anticholinergic agent used for all forms of parkinsonism

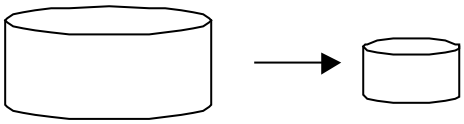
Dissolution Rates

The rate at which a lozenge dissolves is important because it is directly related to the rate at which the active drug is delivered to the body. If the lozenge dissolves too fast, some of the drug may be “lost” as it is swallowed. This would be true, for example, if the drug were a topical

anesthetic used for sore throats, one that would be effective only if it directly contacts the painful location.

Drug formulations can be *engineered* to dissolve at the desired rate. If the dissolution is too fast, the formulation is adjusted to dissolve more slowly. In this experiment, we will investigate the dissolution rate of a lozenge.

When placed in water (or in the mouth), the lozenge becomes smaller as it dissolves from the surface into the water.



initially after time t

Chemical Engineers who work on drug formulations are concerned with obtaining the desired dissolution rate. We must be able to measure the drug dissolution rate, and we must also be able to describe the drug dissolution using a mathematical model. These equations should match the experimental data.

In your experiment you will measure the concentration of drug in solution and then calculate the mass of the drug that is dissolved:

$$M_{dissolved} = C \cdot V \tag{1}$$

Where C is the drug concentration (mg/ml) and V is the volume (ml) of the solution. We wish to compare this experimental value of dissolved drug to a value predicted by a model.

The model below expresses the mass of the dissolved drug as a function of time. You will make a graph of this equation, and compare your data to it.

$$M_{dissolved} = M_0\left(1 - e^{\beta t}\right) \tag{2}$$

In this equation, $M_{dissolved}$ is the mass of drug that has dissolved into the water in mg, M_0 is the initial mass of the lozenge in mg, t is time in minutes, and β is a constant that we will learn how to determine. M_0 is found on the package label - our cough drops contain 7.6 mg of menthol. Once we find β, we can calculate the value of $M_{dissolved}$ for different values of time (t), and make a graph.

How do we find β?

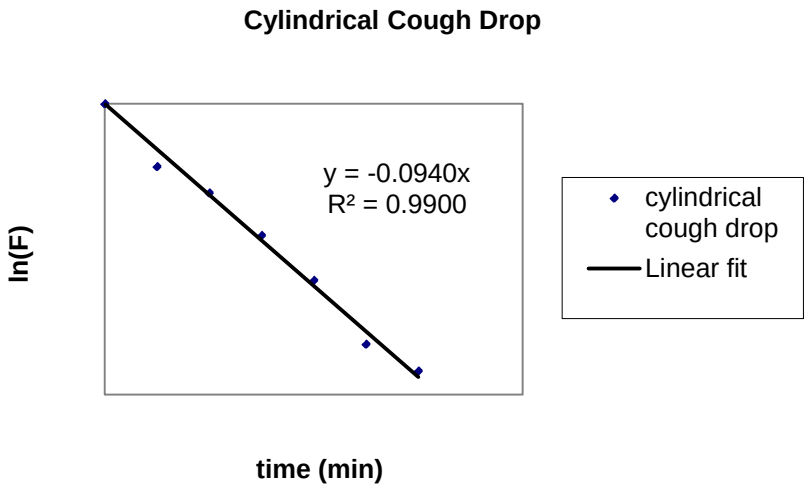
With some manipulation of Equation 1 (again, don't worry about the details), we can write an equation that allows us to determine β.

$$\ln\left[\frac{M_o - M_{dissolved}}{M_o}\right] = \beta t \tag{3}$$

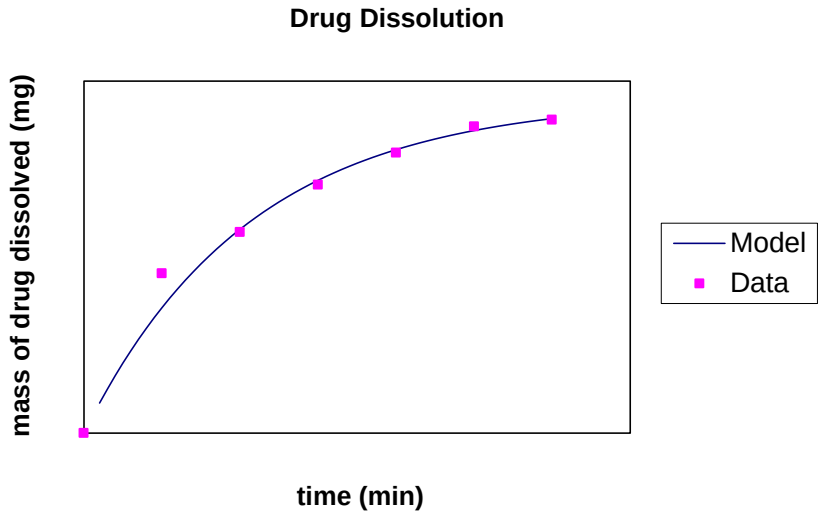
This can be written in a simpler form by renaming the expression in brackets with "F":

$$\ln[F] = \beta\, t \qquad (4)$$

In this equation, F is the fraction of total drug that remains in the undissolved lozenge. F is simply $(M_0\text{-}M_{dissolved})/M_0$, or the mass of undissolved drug divided by the initial mass of drug. (Note that F decreases as time increases and the lozenge dissolves). If we call the term on the left side of the equation "y", and plot it vs. time on the x axis, the slope will be equal to β. This is shown in the plot below, where the "trendline" feature of Excel was used to find the slope of the graph. In the graph below, the slope, -0.094 (min^{-1}), is equal to β.



Once we know β, we can make the plot of $M_{dissolved}$ vs. time using Equation (1).



You will make these two graphs using your experimental data together with the predictive model.

Spectrophotometry

Beer's Law (named after a person, not the beverage) states that the amount of light that a sample absorbs is proportional to its concentration and the path length (the sample thickness through which the light travels). The more concentrated it is, the more light it absorbs. The "thicker" the sample is, the more light it absorbs.

$$Absorbance = a * C$$

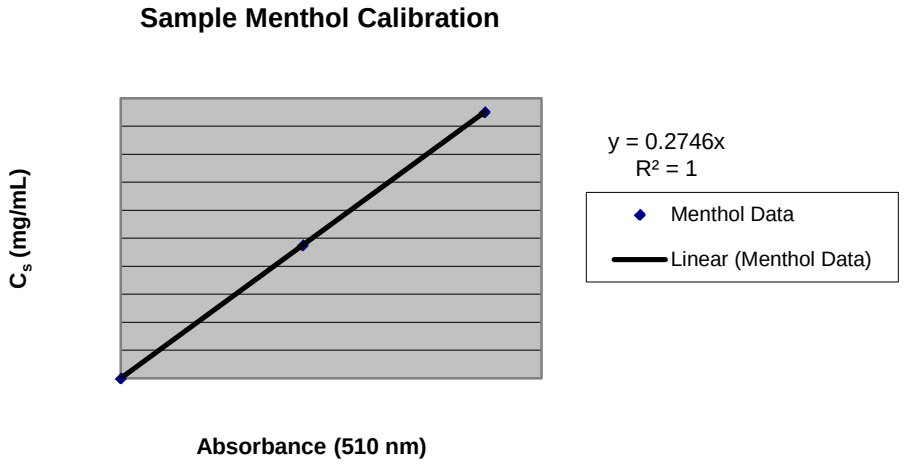
Thus, there is a linear relationship between absorbance and concentration. We will use this relationship to calculate concentration of drug in our samples.

If we make a plot of Concentration vs. Absorbance, this allows us to determine the concentration of a sample if we measure the absorbance. A calibration plot shown below shows that the concentration of menthol in the water is proportional to the absorbance reading at 510 nm, and that they are related by the equation

$$C_s = (\boldsymbol{m}\ \text{mg/ml})*(\text{Absorbance}) \qquad (5)$$

Where ***m*** is the slope of the calibration plot, with units of mg/ml.

For this plot, both the concentration and the proportionality constant have units of mg/ml.



Objectives

1. To measure the concentration of a drug in solution using a spectrophotometer
2. To use a model to describe a drug release profile of a drug from a lozenge
3. To obtain an experimental drug release profile of a drug from a lozenge

Procedure

Choose one or two group members to work on data analysis using an Excel spreadsheet and graphs. The rest of the team members will execute the experiment. The data analysts will set up the spreadsheet, and the experimenters will give them data as they collect it. This will allow you to complete the entire assignment as you go along so that you don't have to do it at home! Halfway through the experiment, the data analysts should switch with the experimentalists, so that everyone gets a turn with both aspects of the project.

Experiment

1. Make a table with the following column headings in your laboratory notebook, and use it for recording your data:

Elapsed time (min)	**Absorbance (at 510 nm)**

2. Fill a small beaker with 80 ml water
3. Place a small stir bar in the beaker, and place the beaker on a magnetic stir plate
4. Set the stirring speed dial to 1 or 2 (to achieve good, but not too vigorous, mixing). Record the stirrer speed setting.
5. Using a dropper, fill a spectrophotometer cuvette with water from the beaker.
6. Obtain an absorbance reading on the spectrophotometer and record it as the initial (t=0) absorbance reading.
7. Replace the liquid from the cuvette back into the beaker.
8. Place a lozenge in the beaker and record the time. Keep track of time beginning now.
9. After approximately 5 minutes remove a sample for analysis. When you remove the sample, record the time (elapsed time since you put the lozenge in the beaker).
10. Obtain and record an absorbance reading.
11. Repeat this sampling procedure at 5 minute intervals (approximately), until the lozenge dissolves completely.

Data Analysis

Set Up Your Spreadsheet (Show units on all physical quantities: on spreadsheet column headings, graph axis labels, and sample calculations).

1) Create an excel spreadsheet for your experimental data. In Column A, make a column heading called "time". Include the units of time.
2) In Column B, make a column heading for called "Absorbance"

3) In Column C, make a column heading for the experimental values of C_s and include the units in the column heading.
   - Values of C_s in this column will later be calculated from equation (5).
4) In Column D, make another column heading for the <u>experimental</u> values of $M_{dissolved}$. Label this column M_d (expt), and indicate the units in the column heading.
   - The values in this column will later be determined from your data using equation (1).
5) In Column E, make a column heading for $M_{undissolved}$, the mass of drug that has not yet dissolved. Label the column heading M_u and include the units.
   - The values in this column will later be calculated using the equation:

$$M_{undissolved} = M_o - M_{dissolved}$$

   Where M_o is the initial amount of drug in the lozenge, 7.6 mg.
6) In Column F, create a column heading for the *fraction* of drug remaining in the undissolved lozenge, F. Label the column heading F.
   - The values in this column will later be calculated using the equation:

$$F = M_{undissolved}/M_o$$

7) In Column G, make a column heading for quantity $\{\ln[F]\}$. Label this column $\{\ln[F]\}$.
8) In Column H, make another column heading on for the mass of dissolved drug, <u>as predicted by your model</u>. Label this column heading M_d (predicted). Include the units.
   - These values will later be calculated using equation (2)

$$M_{dissolved} = M_0\left(1 - e^{\beta t}\right).$$

Entering Equations and Graphing Data

1) Enter your time data in Column A and the absorbance data in Column B.
2) On a new worksheet, make a calibration plot for the concentration of dissolved drug by doing the following.
   a) In the first column, enter the initial absorbance measurement in the first row and final absorbance measurement in the second row.
   b) In the second column, enter the initial and final concentrations in the first and second rows respectively. The initial concentration is 0 mg/ml and the final concentration is 7.6 mg/80 ml = 0.095 mg/ml
   c) Create a plot with concentration on the y-axis and absorbance on the x axis.
   d) Fit a trendline through the plot. Set the intercept equal to zero and show the equation of the trendline on the graph.
   e) The equation of the plot is your calibration equation which is equivalent to Equation (5).

3) Go back to the first worksheet, and go to the column for Concentration. Enter your calibration equation from the previous step to calculate C_s. The values of Absorbance in the equation should be obtained from Column B.

4) Go to the column for M_d (expt). Enter an equation to calculate $M_{dissolved}$ by using the equation:

$$M_{dissolved} = C_s * 80 \text{ ml.}$$

5) Make a plot of the experimental values of $M_{dissolved}$, M_d(expt) versus time.

   a) Remember, this shows your values of $M_{dissolved}$ obtained from data, so name this data series "data" when you make your graph.

   b) You should include $M_{dissolved}$ and its units on the y-axis label.

   c) You should include time and its units on the x-axis label.

6) Go to the column for M_u and enter the equation to calculate $M_{undissolved}$

$$M_{undissolved} = M_o - M_{dissolved}$$

   Where M_o is the initial amount of drug in the lozenge, 7.6 mg.

7) Go to the column for F and enter the following equation to calculate F

$$F = M_{undissolved}/M_o$$

8) Go to the column for $\{\ln[F]\}$ and enter the equation to calculate the natural log of F. In Excel, the function =LN(x) calculates the natural log of x.

9) Make a chart of $\{\ln[F]\}$ versus time (min).

   a) Label the y-axis ln(F)

   b) Label the x-axis time, and include the units for time on the x-axis label.

   c) Do not connect your data point markers with a line.

10) Add a linear trendline to the chart in step 9, and obtain the slope of the trendline and display it on the chart.

   a) Choose the trendline options "set intercept equal to zero" and "display equation on chart".

   b) From the relationship, $\ln[F] = \beta t$, we know that the slope of the line you just plotted should be equal to (β).

11) Go to the column for M_d (predicted).

   a) Enter the equation to calculate the predicted value of M_d from your model.

   b) $M_{dissolved} = M_0\left(1 - e^{\beta t}\right)$.

   You will have to use the value of (β) that you obtained from step 10. In Excel, the function =EXP(x) finds the exponential of x, or e^x.

12) To the same plot you made in step 5, you will add another data series to show the values of $M_{dissolved}$ (predicted) vs. time.

a) Add this series this by choosing chart, source data, and then click "add" under the box labeled series.

b) The y values will be $M_{dissolved}$ (predicted). The x values will be time.

c) Name this series "predicted", because these are the values of $M_{dissolved}$ that you predict from your model. Use a continuous line to represent the model; do not use data markers.

Assignment (one per team)

1) Standard Freshman Clinic report

2) Submit your yellow laboratory data sheet.

3) Include three graphs in the results section:

   a) Your calibration graph.

   b) Your graph of $\{\ln[F]\}$ versus time (min).

   c) The plot showing your drug release profiles (from data and from the model). This is the chart you made in steps 5 and 12 above.

4) Answer the following questions in the results and discussion

   a) Looking at the graph of your release data, how long does it take for the drug to be completely released?

   b) Check your model to make sure it makes sense by showing the following calculations. Plug t=0 into Equation (2) and solve for $M_{dissolved}$. Does the value you calculate make sense? Now plug in a large value for time (for example, 100 minutes). Does this value make sense? It is always a good idea to check your model this way.