INTRODUCING FRESHMEN TO DRUG DELIVERY

Stephanie Farrell and Robert P. Hesketh
Chemical Engineering Department
Rowan University
201 Mullica Hill Road
Glassboro, New Jersey 08028-1701

Abstract

Drug delivery is an exciting multidisciplinary field in which chemical engineers play an important role. Chemical engineers apply their knowledge of mass transfer, rates and dynamic systems, and polymer materials to the design of drug delivery systems.

This paper describes a simple experiment that exposes students to basic principles of drug delivery and chemical engineering. First, students are introduced to different types of dosage formulations using as examples over-the-counter-medications that are already familiar to the students. The mechanism of drug release is different for each type of formulation, and students learn how each different dosage form works. The students then perform an experiment that involves the release a drug from a lozenge formulation, which is an example of a matrix-type drug delivery system.

Students study the dissolution of a lozenge into water. As the lozenge dissolves, the drug is released, along with a coloring agent, into the surrounding water. Students observe the increasing color intensity of the water, and they are able to measure the increasing drug concentration periodically using a spectrophotometer. After calculating the mass of drug released at any time t, they plot a release profile. They must calculate by material balance the mass of drug remaining in the lozenge at any time. They are also able to compare their data to a model after evaluating a single parameter in the model.

Through this experiment, students are exposed to the exciting field of drug delivery, and they are introduced to some basic principles of chemical engineering. They perform a calibration to enable them to determine the concentration of drug in their samples. A spreadsheet is used to perform calculations necessary to determine the release profile, and a plot of the release profile of drug from their lozenge is created. Finally they determine the parameter necessary to apply a model to their system, and they compare their experimental release profile to that described by the model.

Introduction

Rowan University is pioneering a progressive and innovative Engineering program that uses innovative methods of teaching and learning to prepare students better for a rapidly changing and highly competitive marketplace, as recommended by ASEE[1]. Key features of the program include: (i) multidisciplinary education through collaborative laboratory and course work; (ii) teamwork as the necessary framework for solving complex problems; (iii) incorporation of state-

of-the-art technologies throughout the curricula; and (iv) creation of continuous opportunities for technical communication[2]. The Rowan program emphasizes these essential features in an eight-semester, multidisciplinary Engineering Clinic sequence that is common to the four Engineering programs (Civil, Chemical, Electrical and Mechanical).

A two-semester Freshman Clinic sequence introduces all freshmen engineering students to engineering at Rowan University. The first semester of the course focuses on multidisciplinary engineering experiments using engineering measurements as a common thread.

This experiment introduces engineering students to chemical engineering principles and their application to the exciting field of drug delivery. Students are introduced to concentration measurements and simple analysis of rate data. Through this experiments students explore many concepts and tools that they will use throughout their engineering careers:

- Novel application of chemical engineering principles
- Concentration measurement
- Calibration
- Material balances
- Use of spreadsheets for calculations and graphing
- Parameter evaluation
- Semi-log plots and trendlines
- Comparison of experimental concentration data to predicted concentrations
- Testing a transient model at the limits of initial time and infinite time

Drug Delivery

The experiment begins with a short lecture on drug delivery, in which students are introduced to the two main objectives to drug delivery: (1) to deliver a drug to the desired location in the body and (2) to deliver a drug at a desired rate for a desired length of time. These two objectives are illustrated through familiar examples of drug delivery systems, and the important role of chemical engineers in designing drug delivery systems is explained to the students.

The objective of drug targeting, or the delivery of a drug to a desired location in the body is illustrated by enteric-coated aspirin. Enteric-coated aspirin accomplishes a drug targeting objective by avoiding dissolution of the aspirin in the stomach where it can cause irritation. The enteric coating (such as hydroxypropyl methylcellulose or methacrylic acid copolymer) is specifically designed to prevent dissolution in the low pH of the stomach, so that the aspirin tablet passes intact to the intestine. In the more neutlkaline environment of the stomach, the coating dissolves, allowing the aspirin to dissolve as well. The absorption of drugs in the small intestine is usually quite good due to the large surface area available. The function of the enteric-coating is illustrated by placing one enteric-coated aspirin tablet in an environment simulating the pH of the stomach (Hydrochloric Acid, pH 2), and another enteric-coated aspirin tablet in an environment simulating the pH of the intestine (Sodium Hydroxide, pH 8). Students see that within about 30 seconds the tablet in the intestine environment has begun to dissolve, but the tablet in the stomach environment remains intact. Within a couple of minutes, the tablet in the intestine environment has essentially disintegrated, but the other tablet remains completely unchanged for the entire class period (and for several weeks thereafter).

The second objective of drug delivery, controlled release, or the release of a drug at a desired rate for a desired time, is illustrated through familiar controlled release products such as Contac® 12-hour cold capsules and Efidac 24-hour nasal decongestants. Contac is a membrane-based controlled release system, and Efidac® is an oral osmotic (OROS®) pump device. Both mechanisms of controlled release are explained.

The experiment that the students perform uses a lozenge formulation, and the short introduction to drug delivery concludes with an explanation of lozenge formulations and their applications. The familiar lozenge formulation is used to deliver topical anesthetics that relieve sore throat pain. However, lozenges are an important formulation also used to deliver a wide range of very powerful drugs that are used to treat very serious ailments such as those associated with cancer and AIDS. These include pain relief medication, antifungal agents, central nervous system depressants (used to treat anxiety, depression and insomnia), anti-psychotic drugs, antiflammatory agents, and anticholinergic agents used to treat Parkinsonism.

Lozenge Dissolution

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 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.

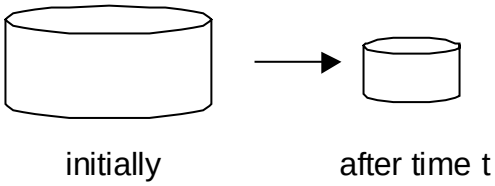


Figure 1: Dissolution of a lozenge

Experimental Set-up

The dissolution experiment is simple to implement. Each group is provided with the following equipment and supplies:

- 1 magnetic stir plate
- 1 magnetic stirrer
- 1 graduated cylinder
- 1 100 ml beaker
- 1 cuvette
- 1 dropper or Pasteur pipette

- 1 lozenge (cherry flavor)

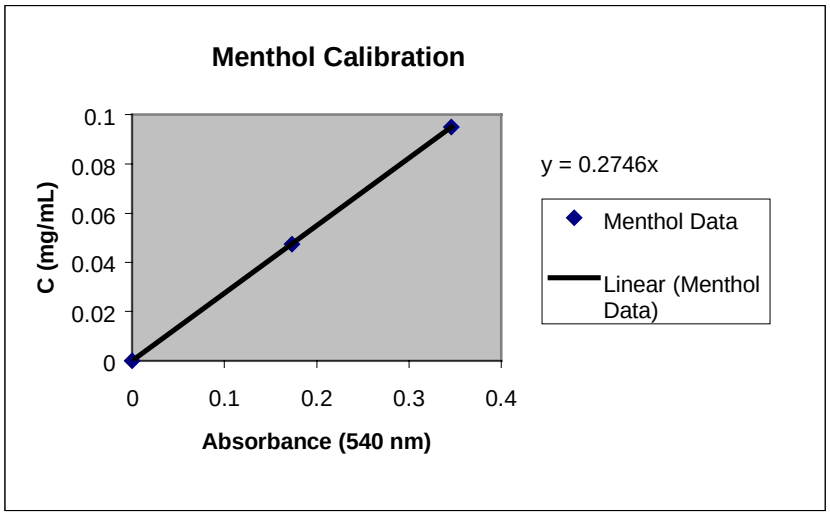
The beaker is filled with 80 ml of water and placed on a magnetic stir plate. Before the lozenge is introduced, the first sample (t=0) is taken and analyzed spectrophotometrically as described below. After analysis, the sample liquid is returned to the beaker. The magnetic stirrer and the lozenge are then placed in the beaker, the solution is agitated gently, and samples are taken at intervals of approximately 5 minutes.

Similar experimental set-ups have been developed[3, 4] to investigate mass transfer between a solid and a surrounding liquid using a dissolving candy. The experiment described here introduces the application of mass transfer principles to drug delivery and the measurement of concentration (instead of solid mass determination) in dissolution analysis.

Concentration Measurement

The release profile of the drug, or amount of drug released as a function of time, is obtained by measuring the concentration of dissolved drug in solution as a function of time. As the drug dissolves, it is released into the surrounding aqueous solution along with the coloring agent present in the lozenge. The coloring agent acts as a marker, allowing the spectrophotometric determination of drug concentration present in samples.

A simple calibration plot may be prepared using a lozenge (containing a known amount of drug) dissolved in a known amount of water. Dilutions may be prepared for the purposes of calibration. The absorbance of each drug concentration is measured and a calibration plot is prepared as shown below. The calibration plot (or calibration equation) may be used to determine drug concentrations of samples taken during the experiment.



Once the concentration of dissolved drug, C, is known, the mass of dissolved drug may be calculated as the product of the concentration C and the volume of solution (80 ml). The amount of drug remaining in the lozenge at any time t may then be determined by material balance:

$$M = M_0 - M_d$$

Where M is the amount of drug remaining in the lozenge, M_0 is the amount of drug initially present in the formulation, and M_d is the mass of dissolved drug.

Model

Chemical Engineers who work on drug formulations are concerned with obtaining the desired dissolution rate. They must be able to measure the drug dissolution rate, and they must also be able to describe the drug dissolution using a mathematical model. The concentrations by the model should match the experimental data.

The following equation represents a simplified model of the mass of dissolved drug as a function of time:

$$M_d = M_0\left(1 - e^{\beta t}\right) \qquad (1)$$

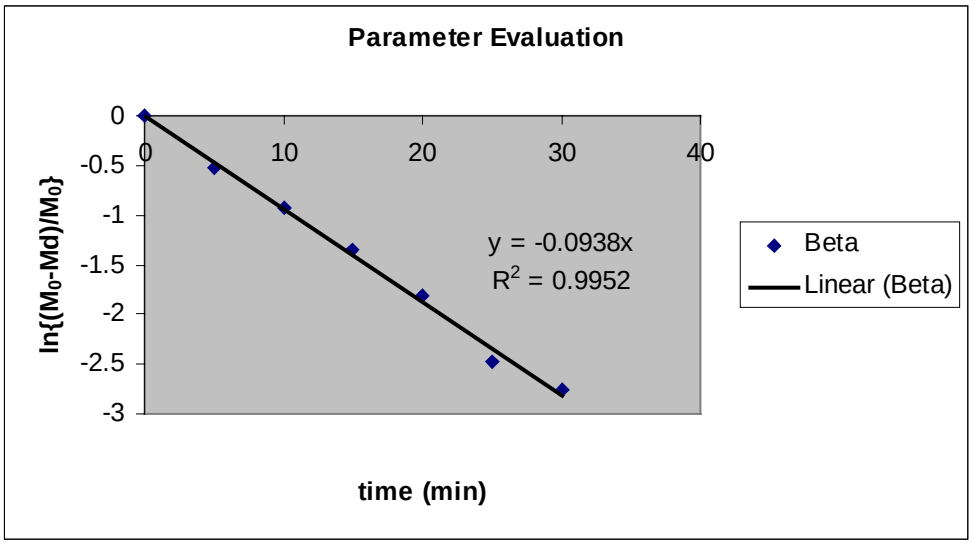
In this equation, M_d is the mass of drug that has dissolved into the water in mg, M_0 is the initial mass of drug in the lozenge in mg, t is time in minutes, and β is a constant that will be determined from the experimental data. M_0 is found on the package label - our Eckerd brand cough drops contain 7.6 mg of menthol. After determining the value of β, M_d can be predicted using Equation (1).

Parameter Evaluation

Equation (1) can be rearranged into the following form:

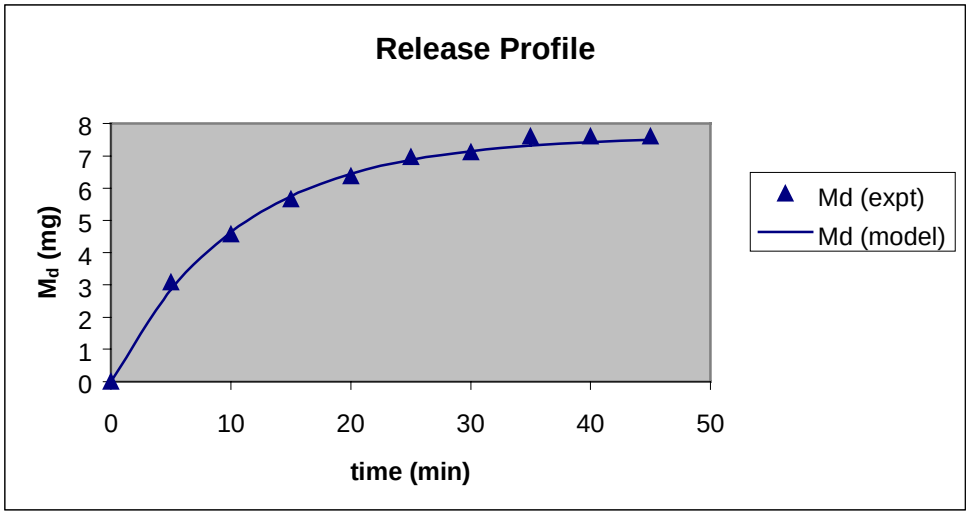
$$\ln\left[\frac{M_o - M_{dissolved}}{M_o}\right] = \beta t$$

In this equation, the term in brackets represents the fraction of total drug that remains in the undissolved lozenge. A plot of the left hand side of the equation as a function of time yields a straight line with a slope of β, as shown in Figure 2 below. 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. It is important to emphasize that the paramter β is evaluated using experimental data. Students can make this plot by calculating values of the fraction of drug remaining, or by generating a semilog plot. The equivalence of these two methods may be emphasized by having the students make both plots.



Comparison of Model to Experimental Data

Once the value of the parameter β has been determined, Equation (1) may be used to describe the drug release data.



Analysis

After plotting the experimental drug release profile and that described by the model, students should observe the agreement between the model and the data. Freshmen students are unfamiliar with mathematical models, and are not presented with the development of the model they use. However, they must test the validity of the model at short times and at long times. They discover that the model predicts $M_d = 0$ for $t = 0$, and $M_d = M_0$ for $t \rightarrow \infty$, and this is in agreement with "common sense". Thus, the point is emphasized that models may easily be tested for simple or limiting cases.

Conclusions

This paper describes a simple experiment that exposes students to basic principles of drug delivery and chemical engineering. The experiment involves the release a drug from a lozenge formulation, which is an example of a matrix-type drug delivery system.

Students study the dissolution of a lozenge into water. As the lozenge dissolves, the drug is released, along with a coloring agent, into the surrounding water. Students observe visually the increasing dissolved drug concentration as reflected by the increasing color intensity of the water, and they are able to measure the drug concentration spectrophotometrically. They create the calibration plot that enables them to determine the drug concentration from their absorbance measurement. They perform a material balance to determine the fraction of drug released and perform an experimental parameter evaluation. Using a spreadsheet they perform calculations necessary to determine the release profile, and they generate plots of the experimental release profile and that described by the model. Finally they test the validity of their model for the limiting cases of initial and long times.

References

1 *Engineering Education for a Changing World*, Joint project report by the Engineering Deans Council and Corporate Roundtable of the American Society for Engineering Education, Washington, DC, 1994.

2 Rowan School of Engineering – A Blueprint for Progress, Rowan College, 1995.

3 Fraser, D.M., "Introducing Students to Basic ChE Concepts – Four Simple Experiments," *Chem. Eng. Education*, 33(3), 1999.

4 Sensel, M.E. and K.J. Myers, "Add Some Flavor to Your Agitation Experiment," *Chem. Eng. Ed*., 26(156), 1992.

Stephanie Farrell is Associate Professor of Chemical Engineering at Rowan University. She received her B.S. in 1986 from the University of Pennsylvania, her MS in 1992 from Stevens Institute of Technology, and her Ph.D. in 1996 from New Jersey Institute of Technology. Prior to joining Rowan in September, 1998, she was a faculty member in Chemical Engineering at Louisiana Tech University. Stephanie has research expertise in the field of drug delivery and controlled release, and she is currently focusing efforts on developing laboratory experiments related to membrane separations, biochemical engineering,and biomedical systems, for all level students at Rowan. Stephanie won the ASEE Outstanding Campus Representative Award in 1998, and she currently serves as Newsletter editor of the Mid-Atlantic Section of ASEE .

Robert Hesketh is Associate Professor of Chemical Engineering at Rowan University. He received his B.S. in 1982 from the University of Illinois and his Ph.D. from the University of Delaware in 1987. After his Ph.D. he conducted research at the University of Cambridge, England. Prior to joining the faculty at Rowan in 1996 he was a faculty member of the University of Tulsa. Robert's research is in the chemistry of gaseous pollutant formation and destruction related to combustion processes. Nitrogen compounds are of particular environmental concern because they are the principal source of NOX in exhaust gases from many combustion devices. This research is focused on first deriving reaction pathways for combustion of nitrogen contained in fuel and second to use these pathways to reduce NOX production. Robert employs cooperative learning techniques in his classes. His teaching experience

ranges from graduate level courses to 9th grade students in an Engineering Summer Camp funded by the NSF. Robert's dedication to teaching has been rewarded by receiving several educational awards including the 1999 Ray W. Fahien Award, 1998 Dow Outstanding New Faculty Award, the 1999 and 1998 Joseph J. Martin Award, and four teaching awards.