AN INTRODUCTION TO DRUG DELIVERY FOR CHEMICAL ENGINEERS

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Rowan University is pioneering a progressive engineering program that uses innovative methods of teaching and learning to prepare students for a rapidly changing and highly competitive marketplace, as recommended by ASEE.[1] Key features of the program include

- Multidisciplinary education through collaborative laboratory and course work
- Teamwork as the necessary framework for solving complex problems
- Incorporation of state-of-the-art technologies throughout the curricula
- 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. In the spring semester, students are immersed in a semester-long project that focuses on the reverse engineering of a product or a process. In addition to introducing engineering concepts, the Freshman Clinic incorporates the four key features mentioned above.

This paper describes an experiment that was performed both in our Freshman Clinic to introduce students to drug delivery, and in a senior-level elective on pharmaceutical and biomedical topics to apply concepts of mass transfer and mathematical modeling. Drug delivery is a burgeoning field that represents one of the major research and development focus areas of the pharmaceutical industry today, with new drug delivery system sales exceeding $10 billion per year.[3] With projected double-digit growth, the market is expected to reach $30 billion per year by 2005.[4] Drug delivery is an inherently multidisciplinary field that combines knowledge from fields of medicine, pharmaceutical sciences, engineering, and chemistry. Chemical engineers play an important role in this exciting field by applying their knowledge of physical and chemical properties, chemical reactions, mass transfer rates, polymer materials, and system models to the design of drug-delivery systems, yet undergraduate chemical engineering students are rarely exposed to drug delivery through their coursework.

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

- *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*
- *Development of a mathematical model (in the senior level class)*

BACKGROUND

Periodic administration of a drug by conventional means, such as taking a tablet every four hours, can result in constantly changing systemic drug concentrations with alternating periods of ineffectiveness and toxicity. Controlled-release systems attempt to maintain a therapeutic concentration of a drug in the body for an extended time by controlling its rate of delivery. A comparison of systemic drug profiles estab-

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lished by conventional administration and controlled release is shown in Figure 1.

Historically, drug-delivery systems were developed primarily for traditional routes of administration, such as oral and intravenous, but recently there has been an explosion in research on delivery by so-called nonconventional routes, such as transdermal (skin), nasal, ocular (eyes), and pulmonary (lung) administration. Drug-delivery applications have expanded from traditional drugs to therapeutic peptides, vaccines, hormones, and viral vectors for gene therapy. These systems employ a variety of rate-controlling mechanisms, including matrix diffusion, membrane diffusion, biodegradation, and osmosis. To design and produce a new drug-delivery system, an engineer must fully understand the drug and its material properties as well as processing variables that affect its release from the system. This requires a solid grasp of the fundamentals of mass transfer, reaction kinetics, thermodynamics, and transport phenomena. The engineer must also be skilled in characterization techniques and physical property testing of the delivery system, and practiced in analysis of the drug-release data.

We present a simple experiment in which students are introduced to the basic concepts of drug delivery by studying the dissolution of a lozenge into water. This is the type of experiment that would be performed by a drug company to determine the rate of drug release from a dissolution-limited system. As the lozenge dissolves, the drug is released (along with a coloring agent added by the manufacturer) into the surrounding water. Students observe the increasing color intensity of the water and 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.

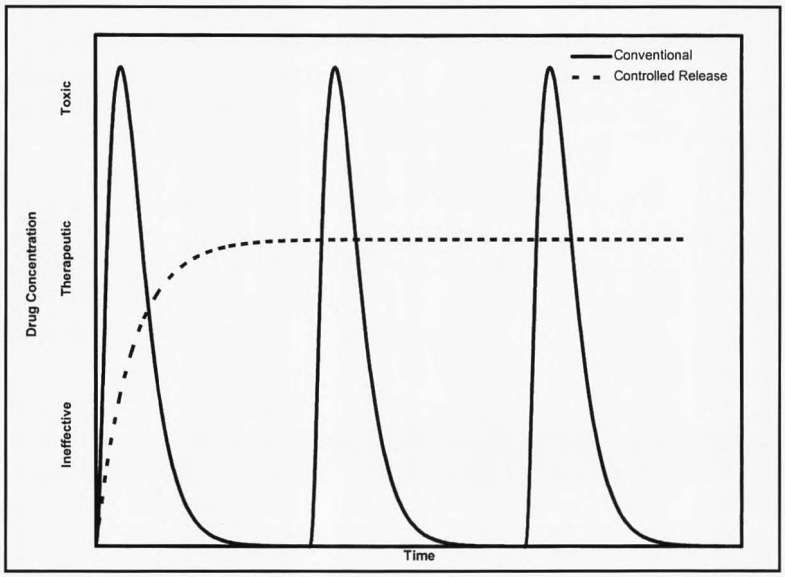

Figure 1. *A comparison of systemic drug profiles established by conventional administration and controlled release.*

Through this experiment, students are exposed to the exciting field of drug delivery and are introduced to some basic principles of chemical engineering. They perform a calibration that enables 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 evaluate what is needed to apply a model to their system, and they compare their experimental release profile to that described by the model.

The experiment begins with a short lecture of drug delivery in which students are introduced to the two main objectives to drug delivery: drug targeting (to deliver a drug to the desired location in the body), and controlled release (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 release mechanism of three commercial drug-delivery systems are explored in the lecture: enteric coated aspirin, Efidac® 24-hour-nasal decongestant, and Contac® 12-hour cold capsules. The experiment explores drug release from an analgesic throat lozenge.

The objective of drug targeting is illustrated by enteric-coated aspirin, which 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 neutral environment of the intestine, 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 stomach (hydrochloric acid, pH 2), and another enteric-coated aspirin tablet in an environment simulating the intestine (sodium hydroxide, pH 8). Students see that within about thirty seconds the tablet in the intestine environment has begun to dissolve, while the tablet in the stomach environment remains intact. Within a couple of minutes, the tablet in the intestine 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 or controlled release (or the release of a drug at a desired rate for a desired time) is illustrated through famil-

iar 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 to the students, and a brief description of each is included here. For more details the reader is referred to a comprehensive text on drug delivery such as Robinson and Lee[5] or Mathiowitz.[6]

Contac is a capsule that contains many tiny beads of different colors. Each bead contains the drug in a core region that is surrounded by a coating material. While the coating material is biodegradable, the rate at which it degrades is slow compared with the rate at which the drug is released through the coating material. Hence, the coating controls the drug's rate of release and is therefore considered a rate-controlling membrane. Some beads have coatings that allow rapid release of the drug for immediate relief of cold symptoms. Some coatings allow release at an intermediate rate, and others effect a slow diffusion rate for extended release, providing relief for up to twelve hours.

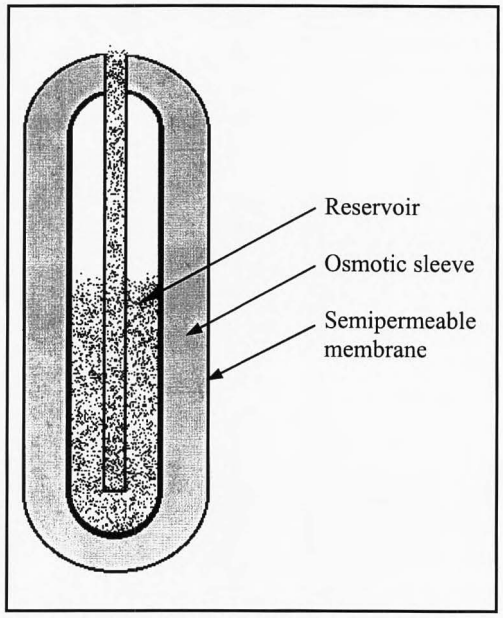

Figure 2. *The osmotic pump. Adapted from Robinson and Lee.*[5]

The osmotic pump developed by Alza exploits osmosis to achieve a constant drug-release rate for an extended time. This technology has been applied to implant systems for delivery of drugs for treatment of diseases such as Parkinson's and Alzheimer's, cancer, diabetes, and cardiovascular disorders. Efidac 24-hour nasal decongestants are an example of an oral system that uses the same technology.

The osmotic pump comprises three concentric layers: an innermost drug reservoir contained within an impermeable membrane, an osmotic solution, and a rigid outer layer of a rate-controlling semipermeable membrane (see Figure 2). As water from the body permeates through the outermost membrane and into the osmotic "sleeve,", the sleeve expands and compresses the innermost drug reservoir, squeezing the drug out of the reservoir through a delivery portal.[7]

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 most familiar lozenge formulation is used to deliver topical anesthetics to relieve sore throat pain. But lozenges are also an important formulation used to deliver a wide range of very powerful drugs used to treat very serious ailments, such as 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 Parkinson disease.

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 or the specified target site. If the target site is the throat, as is the case with a topical anaesthetic, fast dissolution could result in the drug being "lost" if it were swallowed before acting to numb the irritated throat. Drug formulations can be engineered to dissolve at the desired rate. 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. A mathematical model can be developed to express the amount of drug released as a function of time, in terms of quantities that can be measured experimentally. We begin with a rate expression for the dissolution rate of the lozenge

$$\frac{dM}{dt} = -k\alpha A\left(C_s - C_{aq}\right) \qquad (1)$$

where M is the mass of drug remaining in the lozenge (mg), t is time (s), k is the mass transfer coefficient (cm/s), α is the mass fraction of drug in the lozenge, and A is the surface area of the lozenge (cm^2). The lozenge is a sugar-based matrix, and its rate of dissolution is proportional to the concentration driving force across a boundary layer in the liquid adjacent to the solid matrix. The concentration difference is assumed to be $C_s - C_{aq}$, where C_s is the saturation concentration of sugar in water and C_{aq} is the concentration of sugar in the bulk water. C_{aq} is assumed to be negligible since the solubility of sucrose in water at 25°C is 674 g/L[8], while the maximum sucrose concentration from a completely dissolved cough drop of pure sucrose would be 46 g/L in this experiment. The shape of the lozenge is approximated as a cylinder, and the surface area can therefore be expressed in terms of radius r and height h:

$$A = 2\pi r^2 + 2\pi rh \qquad (2)$$

To simplify the model solution and analysis, the area of the sides ($2\pi rh$) was neglected. The mass of drug remaining in the lozenge can similarly be represented in terms of r:

$$M = M_0 \frac{\pi r^2 h}{\pi r_0^2 h} \qquad (3)$$

where M_0 is the amount of drug present in the lozenge ini-

tially (known) and r_0 is the radius of the lozenge initially. Combining Eq. (1-3) and integrating from time 0 to time t results in an intermediate expression for the mass of drug remaining in the lozenge as a function of time:

$$M = M_0 \exp\left[-\frac{A_0 C_s k\alpha}{M_0} t\right] \quad (4)$$

A plot of $\ell n\,(M/M_0)$ vs t should yield a line with a slope of $-A_0C_sk/M_0$. The amount of drug released from the lozenge, M_d, is related to the amount remaining, M, by the material balance

$$M_0 = M + M_d \quad (5)$$

Combining Eqs. (4) and (5), an expression for the amount of dissolved drug at time t is obtained by

$$M_d = M_0\left[1 - \exp\left(\frac{-A_0 C_s k}{M_0} t\right)\right] \quad (6)$$

Equation (4) is adequate for describing mass transfer in the lozenge system since it provides an expression for the amount of drug remaining in the lozenge, but the expression for M_d provided by Eq. (6) is more meaningful for two reasons: the amount of *released* drug is directly related to systemic drug concentrations in the body, and the concentration of released drug will be measured in the experiment. In the transport phenomena course where model development is emphasized, this expression for area in Eq. (2) was retained. When it is substituted into Eq. (1), the resulting differential equation contains two time-dependent spatial variables (r and h) that are independent of one another. The equation can be solved by splitting the equation into two differential equations and solving each separately. This is an interesting exercise for advanced chemical engineering students, but is not necessary to achieve good agreement between the model and the data.

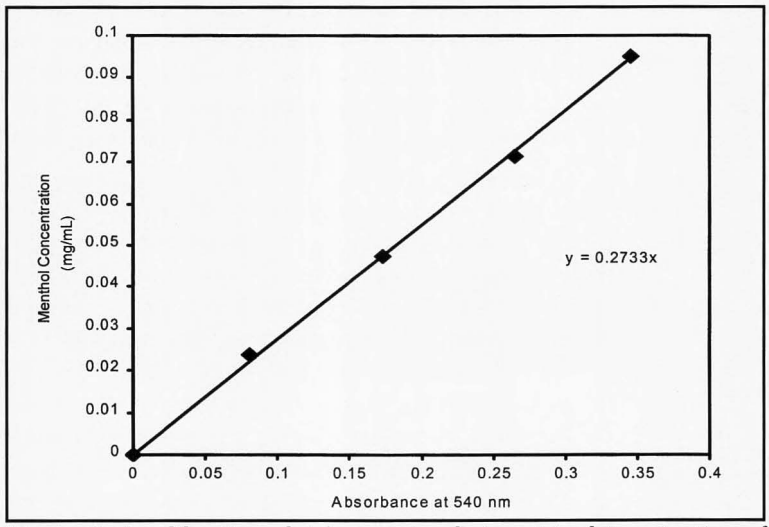

Figure 3. *A calibration plot for spectrophotometric determination of menthol concentration. The coloring in the lozenge serves as a marker that is released in proportion to the drug, menthol, as the lozenge dissolves.*

The experiment involves the release of a drug from a lozenge formulation, which is an example of a matrix-type drug-delivery system.

EXPERIMENTAL SET-UP

The dissolution experiment is simple to implement. Each group is provided with

- *One magnetic stir plate*
- *One magnetic stirrer*
- *One graduated cylinder*
- *One 100-ml beaker*
- *One cuvette*
- *One dropper or Pasteur pipette*
- *One 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 to obtain a background reading for the solution. 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[9,10] 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 through indirect measurement of the concentration of dissolved drug in solution as a function of time, using red dye as a marker. The red dye used in the manufacturer's formulation provides a convenient method of analysis. As the drug dissolves, it is released into the surrounding aqueous solution along with the coloring agent present in the lozenge. Since the drug and dye are considered to be evenly distributed throughout the matrix, the dye can be used as a marker for indirect spectrophotometric determination of drug concentration present in samples.

Students prepare a simple calibration plot using a lozenge (containing a known amount of drug) dissolved in a known amount of water (see Figure 3). The calibration plot (or calibration equation) can be used to determine drug concentrations of samples taken during the experiment.

The amount of drug that has dissolved from the lozenge can be calculated once the menthol concen-

tration is determined.

ANALYSIS

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 describe the drug dissolution using a mathematical model. The concentrations by the model should match the experimental data.

To use Eq. (6) to describe the experimental data, the parameter

$$\beta = -\frac{A_0 C_s k \alpha}{M_0} \tag{7}$$

must be evaluated.

PARAMETER EVALUATION

Equation (6) can be rearranged to

$$\ell n\left(\frac{M_0 - M_d}{M_0}\right) = \beta t \tag{8}$$

In this equation, the term in parentheses 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, which can be determined using the "trendline" feature of Excel. In Figure 4, the slope of -0.0938 (min^{-1}) is equal to β. It is important to emphasize that the parameter 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 can be emphasized by having the students make both plots.

The amount of drug initially contained in the lozenge, M_0, is found on the package label. The Eckerd-brand cough drops used in our laboratory contain 7.6 mg of menthol.

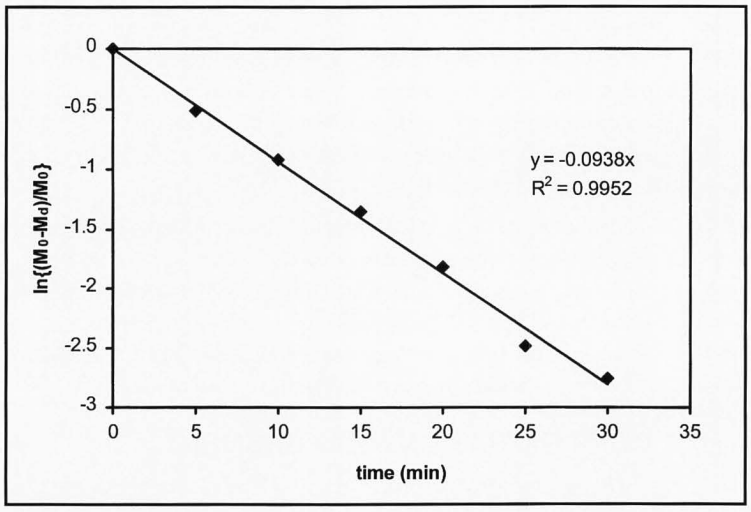

Figure 4. *Parameter evaluation. The parameter β is determined from the slope of the line.*

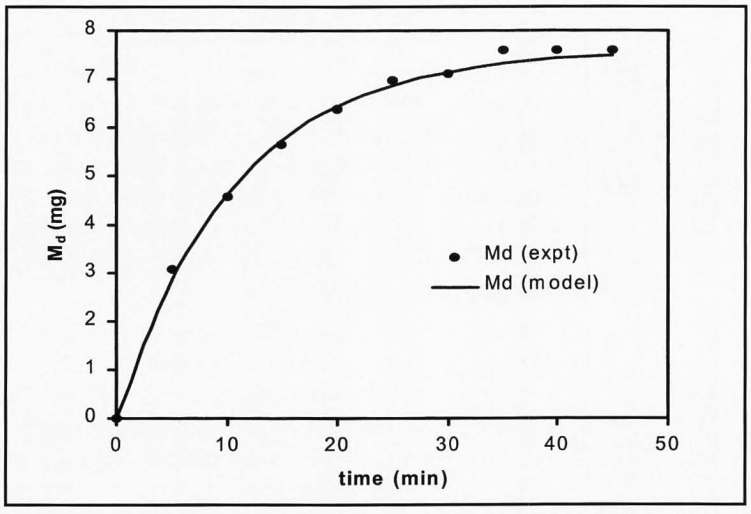

Figure 5. *Comparison of the experimental release data to that described by the model.*

COMPARISON OF MODEL TO EXPERIMENTAL DATA

After determining the value of β, Eq. (6) can be used to describe the experimental release data (see Figure 5). Students are asked to observe the agreement between the model and the data. Freshman students are stepped through the basic steps of the model development, testing 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 can 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 of 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 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 a 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 both 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.

Through this experiment and lecture, students are introduced to the role that chemical engineers have in the area of drug delivery and pharmaceutical production. This experiment has also been used in senior-level courses such as transport phenomena and as an elective in drug delivery. Here, students develop their own model, compare their experimental results to those described by the model, and examine the validity of their simplifying assumptions.

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