

## **A Three-Week Hands-On Introduction to Biotransport & Drug Delivery for First-Year Engineering Students**

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### Abstract

In their first semester at Bucknell, all engineering students enroll in Exploring Engineering which is an introductory course designed to provide the students with an introduction to Bucknell's six engineering disciplines as well as overarching concepts such as engineering design, ethics and teamwork. In one component of the course, each student participates in two three-week seminars which provide a more in-depth and hands-on introduction to the disciplines. To complement the new biomedical engineering major at Bucknell, we have implemented a new biotransport seminar with a focus on drug delivery. The goal of the seminar is to expose the students to the fundamental concepts associated with drug delivery and to provide the opportunity to implement these concepts in a hands-on environment.

The ten lectures and three labs in the seminar are presented in an order which is analogous to the simple pathway of an orally ingested drug. While the early lectures focus on the possible routes of entry of a drug into the body and basic dissolution mechanics, the first lab experiment involves quantifying the dissolution of a throat lozenge under varying levels of heat and agitation (Farrell and Hesketh, 2002). Following dissolution, the lectures focus on simple diffusion in order to describe the transport of the drug from the stomach into the bloodstream. Next, the seminar examines the mechanics of blood flow with the corresponding lectures providing a basic introduction to cardiac fluid mechanics including cardiac physiology, Bernoulli's equation, Reynolds number and flow resistance. In the associated fluid mechanics lab, the students utilize an assortment of fluid flow equipment to design and build a recirculating flow system for examining how pressure and flow resistance in a tube is affected by flow rate, tube length and degree of constriction. In the last lab session, the students merge the first two experiments into a single experiment which examines the effects of the recirculating flow on the dissolution and transport of the dissolving lozenge. Overall, this seminar provides an introductory, hands-on experience into the fundamental concepts associated with biotransport and drug delivery.

## Introduction

With the implementation of a new major in biomedical engineering at Bucknell University, faculty from the biomedical engineering program have become an integral part of the introductory engineering course required of all first-year engineers. This course, ENGR 100 Exploring Engineering, is designed to provide the students with an introduction to Bucknell's six engineering disciplines as well as overarching concepts such as engineering design, ethics and teamwork. This is accomplished by dividing the course into 4 components including a group design project assessing wheelchair accessibility on campus, two student-chosen topical seminars and the reading and analysis of engineering related books. As the topical seminars are used to provide the students with a more detailed and hands-on introduction to two of the six engineering disciplines offered at Bucknell, biomedical engineering was included in this component of the course. For this purpose, a three week seminar was designed with a focus on drug delivery as the focus of the new major is the area of biotransport. The objectives of the seminar included:

1. To introduce the students to drug delivery as an example of biotransport and biomedical engineering
2. To introduce the students to concepts such as dissolution, mass diffusion, mechanical energy balance as related to fluid mechanics, and pressure-flow relationships
3. To provide the students with a hands-on learning environment
4. To require the students to utilize teamwork skills in a lab environment
5. To introduce the students to basic engineering methodologies such as proper graphing, report writing, and data analysis
6. To introduce the students to open-ended laboratory exercises in a teamwork environment.

The overall order in which material is presented in the seminar was based upon the general pathway of drug delivery into the human body. This pathway includes the following general components: 1) route of drug introduction; 2) dissolution of a drug in solid form; 3) diffusion of the drug into the bloodstream; and 4) transport of the drug throughout the circulation. These general components were utilized to demonstrate the application of fundamental engineering principles to the drug delivery process. To provide a hands-on experience, three 2-hour laboratory sessions were included in the seminar along with 10 lecture periods. In these lab sessions, students were required to carry out a series of experiments of which the first was well-defined, the second contained both well-defined and open-ended components, and the third was completely designed, constructed and analyzed by the students themselves. We have divided the seminar into 5 parts for ease of discussion as presented below.

### Part 1: Introduction to Drug Delivery

Before introducing the students to the direct ways in which engineering concepts can be applied to drug delivery, one lecture was spent relaying some general information and facts about drug delivery. The first major concept covered was drug targeting which describes the methods used to delivery a drug to a desired location within the body. As drug targeting can become a very complex topic, this seminar primarily focused on the first step of drug targeting which is the route of entry of a drug. The second major drug delivery concept presented was controlled

release methodologies utilized in drug delivery. By comparing time dependent profiles of drug concentrations in the bloodstream, the students were shown the differences between controlled release technologies such as intravenous injection, machine regulated constant infusion and orally ingested pills. Finally, the lecture reviewed the advantages and disadvantages of the various routes of entry and methods of controlled release<sup>1</sup>. After discussing these drug delivery concepts at a fundamental level, the class as a whole assisted in outlining the general pathway for a drug which is ingested orally in pill form. This pathway consisted of the following steps:

1. Drug is orally ingested
2. Drug dissolves or is released into stomach/intestines as a specific rate
3. Drug is absorbed into the blood at a specific rate
4. Drug is transported throughout the body via the circulation
5. Drug is transported from blood into cells throughout the body
6. Drug is removed or broken down over time by liver and/or kidneys
7. Drug concentration in the bloodstream returns to zero

Knowing this pathway, the students were then informed that they were going to be applying engineering concepts to the steps of drug dissolution, drug transport into the blood, and the transport of the blood throughout the body via the circulation.

## Part 2: Drug Dissolution

When a patient ingests a drug orally in pill form, the drug may be released from the pill into the stomach or intestines via a variety of mechanisms including dissolution or membrane controlled release. While the latter provides for more regulated release and is more complex, simple dissolution was chosen as the focus of this seminar due to the ease of implementing it into this first-year engineering course. In this part of the seminar, the students were exposed to the dissolution of a solid in an aqueous medium through both lab and lecture activities. A significant portion of this part of the seminar was based on the work of Farrell and Hesketh (2002) where the authors provide an excellent description of a dissolving lozenge experiment as an introduction to drug delivery<sup>2</sup>.

In the lecture component, students were introduced to the use of differentials as a way to express rates of mass change and factors that might affect dissolution rates such as temperature, surface area, drug and surrounding fluid composition. Conservation of mass concepts were utilized to relate the rate at which the drug dissolves into the liquid regions near the pill to the rate at which the drug is transported to areas far away from the pill. Following the overview of dissolution mechanics, the students were provided with an in-class activity where their three person lab groups were assembled in order to carry out some initial planning for the first lab session. In this planning session, the groups were given a memo from a fictitious drug company requesting them to design experiments which will help analyze the dissolution of a new throat lozenge. The students were restricted to using a equipment from the following list:

- heating/stirring plate with magnetic stir bar
- laptop pc with Vernier temperature probe and colorimeter for measuring concentration
- supply of prototype lozenges

- mass balance
- beakers
- syringes
- water supply.

At the end of the hour, the students were required to submit an experimental plan including the following:

- A general description of the types of experiments to be run.
- A description of what experimental factors will be examined
- A description of what combinations of factors will be examined
- A possible method for analyzing the results to determine the optimal dissolution conditions.

While there were a few groups who devised creative experiments not thought of by the instructor, most of the student planning produced the same general experimental approach which was to examine the effects of different levels of heating and agitation on the dissolution of the lozenges. It is these experiments which were carried out in the first laboratory session.

For the first laboratory session, the students were provided with a detailed protocol to guide them in performing the exercises. The level of guidance in this lab was high as it was intended to familiarize the students with the equipment in addition to giving them some insight on how one might construct and perform a set of experiments. The goal of the lab was for the students to determine how heating and agitation affect the dissolving of a common throat lozenge in a beaker of water. One important preliminary exercise in this lab was the calibration of the Vernier colorimeter. As this device quantifies the concentration of a dye in a solution, the students were required to take readings from provided standards in order to create their calibration plots that relate measured absorbance with actual mass concentrations. As each lozenge consists of a coloring agent and the drug (menthol), the students were instructed to assume that the release of the coloring agent and the drug were proportional. After acquiring enough data to construct their calibration curves, the students used the provided equipment to set up their experimental system. Each group was required to choose two heating levels and two agitation levels within specified ranges. With the constructed system, the students ran 4 separate experiments of which each is a different combination of the heating and agitation parameters.

For each experiment, the students set the agitation and heating levels to the desired settings and drop in two lozenges. It is important to note that the students examined different heat settings on the hot plates and did not examine fixed temperatures. At each three minute time mark, the groups recorded the temperature of the solution and also removed a ~2.5 ml sample of the solution for immediate analysis in the colorimeter. After the analysis was complete, the sample was returned to the beaker so as to maintain a constant volume throughout the experiment. The sampling continued until a final measurement is taken after the lozenges have dissolved.

For the memo style group report for this lab exercise, the students were given detailed instructions on analyzing their data. They were give five general tasks:

1. Devise a method to determine what percentage of the lozenge is menthol
2. Create a calibration curve relating the absorbances measured by the colorimeter with the actual concentration of lozenge mass.
3. Create properly formatted and labeled graphs of the temperature, lozenge concentration and menthol concentration in the solution as a function of time.
4. Perform the following analysis steps and provide supporting evidence and reasoning:
  - a. Analyze the graphs to determine which combination of parameters promoted the fastest dissolution.
  - b. Compare the graphs to see if all experiments ended with the same final concentration. Would that be an expected result?
  - c. How did changing the heating setting alter the temperature profile of the solution?
  - d. Provide a physical interpretation for the slope of the concentration vs. time graph between any two time points.

Overall, this part of the seminar provided the students with some initial experience in the laboratory setting as well as experiences in creating proper data graphs, brief memo style reports, working with new team members, and understanding the physical interpretations which can be found in the analyzed data.

### Part 3: Diffusion into the Blood Stream

Following the dissolution of the pill in the patient's stomach or intestines, the next step in the process is for the drug to be transported into the bloodstream. In the interest of simplicity, an assumption was made that simple diffusion is the only mechanism responsible for this transport step. In lecture, single molecule discussions were followed by the application of the theory to a group of molecules resulting in Fick's Law of Diffusion. Through the determination of the units of flux, the students were encouraged to gain an understanding of the physical significance of the mass flux. A series of in-class and homework problems were assigned which not only helped familiarize the students with using the governing equation but also required the students to understand the importance of each term in the equation and the impact of variations of each parameter.

### Part 4: Blood Circulation and Fluid Mechanics

After the drug has been transported into the bloodstream, convective transport processes dominate as the drug is then circulated about the body. This mechanism of transport lends itself well to the introduction of basic energy balances and fluid mechanics. Before presenting material on fluid mechanics, a brief overview of cardiovascular physiology was provided so that the students were familiar with the anatomy and physiology of the primary pump for the circulating blood. Following the physiological discussions, basic mechanical energy balances were utilized to derive Bernoulli's Equation. Once the students had a grasp on the conservation of energy principles, the lecture proceeded to discuss how the equation can be applied between two points on a streamline and how that equation can be applied to simple fluid mechanics problems such as flow in a straight, rigid, circular pipe. This discussion then led to a basic analysis of the frictional forces in pipe flow and their impact on the energy balance and flow resistance. Finally, the students were introduced to the Reynolds number as an example of an

important dimensionless parameter. Again, a series of in-class and homework problems were assigned in order to reinforce the use and physical interpretation of the governing equations.

For the second laboratory component of the seminar, the students were guided in using some basic equipment to create an experimental model of the circulatory system in order to explore concepts such as how flow and pressure are related, what parameters can be used to characterize fluid flow and how to examine the resistance to fluid flow. They were provided with the following equipment:

- Vinyl tubing
- Assorted tubing connectors
- 2 pressure transducers
- Fluid pump
- Rotameter
- Pulse dampener
- Mass balance
- Beakers
- Stopwatch
- Deionized water supply
- Measuring calipers
- Tube clamps
- Tubing cutters.

Before constructing the recirculating system, the students needed to verify the flow rates of the pump using a specified subset of the equipment listed above. While they were told what equipment they could use, they were not told how to do it. Generally, the students realized that by pumping water from one beaker to another and timing the transfer, they can find the mass of the water transferred in order to determine the volume transferred in a set amount of time. Each group was asked to document their procedure for this aspect of the experiment.

Following the verification of the pump flow rates, the students were given the task of creating their own recirculating system which would enable them to perform the following experiments:

1. Examine the relationship between pressure drop and flow rate in a fixed length of straight tubing for three flow rates,
2. Examine the relationship between pressure drop and tube length for fixed flow rates in four different length tubes,
3. Examine the effects of varying degrees of constrictions of the tubes.

While the students were guided in their designs based upon the types of experiments they needed to be able to run, each group was free to design and construct their system as they chose. This aspect of the lab required the team members to work together to think through and assemble their systems in an efficient manner in order to get the exercises completed.

For the memo-style report, the students were again given fairly detailed analysis instructions including:

1. Pressure Drop vs. Flow Rate
  - a. Create and interpret a graph of average pressure drop vs. volume flow rate. What does this reveal about the relation between the two parameters?
  - b. Create and interpret a graph of average pressure drop vs. Reynolds number.
  - c. Relate the results in these experiments to blood flow in the human body.
2. Pressure Drop vs. Tube Length
  - a. Create and interpret a graph of average pressure drop vs. tube length. What does this reveal about the relation between the two parameters?
  - b. Create and interpret a graph of average resistance vs. tube length. What does this graph reveal about resistance to flow in tubes?
  - c. Relate the results in these experiments to blood flow in the human body.
3. Pressure Drop and Constrictions
  - a. Create and interpret a graph of average pressure drop vs. tube constriction. What does this reveal about the relation between the two parameters?
  - b. Create a graph of average resistance vs. tube constriction. What does this graph reveal about resistance to flow in constricted tubes?
  - c. Relate the results in these experiments to blood flow in the human body.
4. Experiments and Theory
  - a. Apply Bernoulli's Equation to the length of tubing between the pressure transducers. Focus on what terms are important and which can be canceled but be sure to provide reasons for canceling terms. After canceling terms, provide a discussion of the important energy types in this problem and how energy is conserved.

Overall, this part of the seminar introduced the students to energy balances, fluid mechanics and cardiovascular physiology as well as provided the students with a lab experience which required open-ended design and experiment planning.

#### Part 5: Open-ended Group Experiment on Dissolution, Diffusion and Circulation

The final component of this three-week seminar was centered around the students utilizing their experiences from the previous lectures and labs to plan, design, construct, carry out and analyze the results from their own series of experiments. The students were instructed that the overall goal of the last set of experiments was to creatively integrate the dissolving lozenge experiment and the recirculating flow experiment in order to create a simple model of drug delivery. This task required the students to devise a method to interface the recirculating system with the dissolving lozenge system without simply inserting inlet and outlet flow lines into the dissolution beaker. The students were told that they should design a system where the dissolution beaker represents the stomach and the recirculating flow path represents the blood circulation. Furthermore, this system should allow them to examine how the variations in a parameter of their choice affects the concentration of the drug in both the beaker and the recirculating liquid.

From the instructor's point of view, the primary objective of this component was to expose the students to a nearly completely open-ended experimental problem. In the lecture prior to the lab, the students worked in their lab groups to answer questions such as:

- What is the primary objective of the experiments?
- How would you integrate the two systems in order to allow the drug to transfer into the recirculating flow?
- What parameters are important for this final study and why?
- What parameters will you control in the final experiments?
- What parameters will you monitor in the final experiments?

At the end of the planning period, the students were asked to show their answers to the following questions to the instructor:

- A sketch of the proposed experimental system
- A listing of the parameters to be controlled and those to be monitored/measured
- An outline of the experiments to be run with the system
- A list of the major equipment needed
- A description of the types of data that might be obtained
- A description of potential data analysis techniques
- A description of how the best combination of parameters could be determined.

In both of the final lab sessions, most groups utilized the first hour for assembling and testing their systems with the final hour used to run from 2 to 4 experiments. Although this experimental session did not generate as much data for analysis as the first two labs, the exposure to designing and carry out open-ended experiments was felt to be more valuable to the goals of the seminar. In general, most groups were able to run two experiments where they could examine the effects of changing one variable on the concentration of the drug in both the beaker (stomach) and in the recirculating flow (bloodstream).

Following the final laboratory session, each group was required to submit a final memo-style report which documented the design and construction of their experimental system, the reasoning behind their choice of experiments to be run, and an analysis of the data they acquired. For this report, the students were required to choose which analysis techniques from the previous labs were appropriate for this final report.

## Results and Conclusions

Through the design and implementation of this new seminar at Bucknell University, first-year engineering students now have the opportunity to gain hands-on insight into the field of biomedical engineering and more specifically the area of biotransport. In their numerical evaluations, the students generally expressed their satisfaction with this seminar. The seminar was found to be well-organized (4.76 out of 5), the laboratory component was valuable (4.73 out of 5) and the students would likely recommend this seminar to others (4.26 out of 5). When asked if the seminar stimulated their interest in the area, the students gave a score of 4.17 out of 5. Finally, the students as a whole felt the workload was reasonable in the seminar (4.12 out of



5). While a number of students expressed in their written evaluations their satisfaction and appreciation for the open-ended components of the seminar, others expressed a desire for more guidance in the seminar, especially the labs. Additionally, a number of students stated that they enjoyed the structure of the seminar especially the fact that the lectures and labs tied together nicely.

As this seminar will be offered again in the 2004-2005 academic year, a number of improvements are planned including:

1. Increasing the level of quantitative correlation between the lecture and lab components
2. Identifying the optimal parameter ranges within which students should design their experiments
3. Provide enhanced guidance for the students in the areas of data analysis
4. Include more discussion of modern drug delivery technologies.
5. Further enhance the open-endedness aspects of the seminar while also providing adequate guidance.

Overall, we feel that this seminar was a success in its first year at Bucknell. While work needs to be done to fine tune the laboratory exercises and streamline the lecture material, we believe that the objectives of the seminar have been met to a reasonable level. As this seminar did not require any equipment which typically cannot be found at most engineering programs, it is likely that this idea for a three-week introduction to drug delivery and biotransport can be implemented at other universities where appropriate.

#### Bibliography

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