# AC 2011-1049: DRUG DELIVERY EDUCATION USING MICROSPHERE TECHNOLOGY

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# Controlled drug delivery using microspheres: An experiment for chemical engineers


## Abstract

Controlled release drug delivery has recently become a major research and development focus area of today's pharmaceutical industry. New drug delivery systems are continually being designed to dispense a drug at a predetermined rate, either constant or in intervals, to a target area in order to maintain a therapeutic concentration of drug at a desired location in the body. Rowan University is currently working with the Engineering Research Center for Structured Organic Particulate Systems (ERC-SOPS) of Rutgers University to develop educational materials involving drug delivery technology. The current materials being developed are freshman level experiments involving drug release from microspheres. The microspheres are made with an alginate loaded with a model drug. The experiments involve measuring and analyzing the release rate of the drug from the microspheres. The purpose of the experiment is to provide engineering students with basic skills relevant to the drug delivery field. These experiments will also allow engineering students to grasp basic knowledge of mass transfer and hydrogel properties.


## Introduction

Drug delivery is an important part of the pharmaceutical aspect of chemical engineering. Although it is the pharmacists' and chemists' job to combine the chemicals necessary to treat illnesses, chemical engineers are able to design the drug-delivery systems. These systems are engineered to deliver a predetermined amount of drug for a decided length of time, often 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, polymeric materials, and system models that are not taught in the other disciplines, and are therefore a vital role in the pharmaceutical industry. Controlled drug delivery is the method of administering a predetermined optimal dosage of drug to a human in order to cure or control the present condition as quickly and conveniently as possible.

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[1]. To work with drug delivery systems, an engineer must fully understand the drug and material properties and the processing variables that affect the release of the drug from the system. Drug delivery is an essentially multidisciplinary field that combines knowledge from fields of medicine, pharmaceutical sciences, engineering and chemistry. Chemical engineers play an important role in this fast-paced field by applying their knowledge to the design of drug delivery systems, yet undergraduate chemical engineering students are rarely exposed to drug delivery through their coursework. At Rowan University, a two-semester Freshman Clinic

sequence introduces all freshmen engineering students to basic engineering principles. This paper describes an experiment that will be implemented into Rowan University's Freshman Clinic in order to introduce students to drug delivery systems that use fairly new technologies.

This experiment introduces freshman engineering students to drug delivery by studying the use of microspheres as a controlled release system. Students are introduced to concentration measurements and analysis of rate data. Through this experiment 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
- Comparison of experimental concentration data to predicted concentrations

**Background Information**

**Conventional Drug Delivery Methods**

The most common methods of administration of a drug are by ingestion and injection[2]. In recent years, several other routes of adiminstration have been explored, including pulmonary- through the lung, transdermal- though the skin, transmucosal - through a mucous membrane, and transepithelial- a combination of transdermal and transmucosal**Error! Bookmark not defined.**.

Injections and oral drug delivery are still widely used because of ease of administration and convenience. However, conventional methods of drug delivery are associated with blood level profiles that are characterized by peaks and valleys which increases patient exposure to side effects[3]. The need for delivering large molecules such as therapeutic proteins has also driven the quest for alternative delivery methods. Research on injections is currently leading researchers to "patient-friendly" injections that can administer drug at a constant rate and target the delivery to a specific location in the body.

**Controlled Release Systems**

A conventional drug such as a tablet would be taken periodically, resulting in cyclical periods of ineffectiveness, effectiveness, and possibly toxicity. Sustained release delivery forms

are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time. Controlled drug delivery systems are more advanced than sustained release systems because they are able to control the release rate and duration in order to achieve a specific release rate profile. 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. With targeted drug delivery, the drug is delivered to a desired type of cell or location in the body, while avoiding systemic administration which could harm other types of cells which are not the desired target. Some advantages of controlled release delivery systems include the reproducibility of the release rate, less frequent required administration, decreased side effects, and smaller quantity drug needed.

**Microsphere Technology**

Drug targeting strives to create a desirable pharmaceutical response at a specified area of the body without causing undesirable interactions with other areas of the body. Drug targeting is conventionally accomplished with two methods. The first approach involves using a compound that is chemically modified to activate only at the target site; the second approach involves the use of carriers to direct the drug to the target site. The different carriers used can include liposomes, microspheres, nanoparticles, antibodies, cellular carriers, and macromolecules.[4]

Microspheres are microscopic beads that comprise a polymer matrix which contains a drug. The polymer may be in the form of a solid bead throughout which the drug is dissolved or dispersed, or the drug may be encapsulated within a polymeric shell. Polymer microspheres have been used in controlled release and drug targeting to organs such as the liver, spleen, lung, and kidney[4]. Microspheres made from biocompatible natural and synthetic polymers can be used as drug delivery systems for administration by injection, intramuscular, and through the nasal route[5]. Microspheres can easily be modified and are compatible with many drugs, allowing them to be easily developed to contain a desirable drug. Moreover, the size of microspheres is easily controllable by modification of the preparation method.

**Mass Transfer and Crosslinking**

The rate of release of a drug from a microsphere can be controlled by diffusion through the polymer. The diffusion depends on the molecular weight of the drug molecule and the cross-linking density of the microspheres[2]. A small drug molecule will diffuse relatively freely through the polymer network, resulting in rapid release. The diffusion of a large molecule will be hindered by its size, which results in slower release of the drug.

A very simple and non-toxic procedure to produce microspheres involves mixing a drug, or model drug, in an alginate solution that is combined with calcium chloride solution. One important property of alginate is the ability to form gels by ionic crosslinking with divalent calcium ions. When alginate solution is combined with calcium chloride in aqueous solution,

ionic crosslinking of alginate chains occurs instantaneously. This crosslinking results in a matrix at the interface between the two solutions[2]. When drops of alginate solution are added to the calcium chloride, polymerization occurs at a spherical interface resulting in a polymer shell that encapsulates a solution of drug in calcium chloride.

**Microsphere experiment**

**Objectives**

In this experiment, freshman students produce drug-containing alginate spheres and investigate the factors which affect the rate of release of the drug from the polymeric microspheres. (Technically the spheres produced are not microspheres since their diameter is about 1-3 millimeters). The model drug used in this experiment is food coloring. Drug release studies are performed by placing the drug-loaded microspheres in a beaker containing water. Concentration measurements are made periodically by measuring absorbance of the surrounding solution (into which dye has been released) using a spectrophotometer. The release rate of the drug from the microspheres is analyzed using an Excel spreadsheet. The learning objectives of the experiment are:

1. **Define** a hydrogel.
2. **Define** the chemical structure and ionic crosslinking of alginate to form hydrogels.
3. **Explain** the role of hydrogels in drug delivery.
4. **Determine** the effect of surface area on the release rate of the drug
5. **Determine** the effect of drug loading on the release rate of the drug
6. **Explain** the role of a chemical engineer in designing controlled release system

**Microsphere preparation**

*Materials*

- Alginate Solution (Water and Alginic Acid, Sodium Salt; Acros Organics)
- Calcium chloride
- Food coloring (model drug)
- Blunt tip needle (JG18-0.5x; Jensen Global) and Luer-Lok Syringe

*Procedure*

1. Alginate solution is prepared by combining approximately 20 ml of DI water and 0.2 g of alginate. A 1% alginate solution will be made.

2. A 6% calcium chloride solution is prepared in a separate container. The experiment requires approximately 20 mL of the calcium chloride solution.
3. Red food coloring is added to the alginate solution until food coloring is 5% by vol. *note: this concentration of food coloring will make the solution opaque, this is expected.
4. A blunt tip is screwed on the Luer-Lok syringe which is then loaded with the alginate-food coloring solution.
5. The alginate-dye solution is dripped into the calcium chloride solution. The syringe is squeezed slowly and continuously until all of the alginate-dye solution is used. Observations are made and recorded.
6. The microspheres are filtered out. The microspheres should not stay in the calcium chloride solution for more than a few minutes. Observations are made on the appearance of the beads.
7. The beads are blotted to remove the remaining calcium chloride solution. They are then placed in an open vial and stored in vacuum dryer at room temperature.

**Measuring Release Rate of Dye**

Materials

- Dye loaded microspheres
- 1000-mL capacity Beaker, de-ionized water, stir bar, and stir plate
- Spectrophotometer (Spectronic 20; Genesys)
- Disposable polystyrene spectrophotometer cuvette (Sigma Aldrich)
- Disposable Pasteur pipette (Sigma Aldrich)

Procedure

1. 100 ml of de-ionized water is placed in a beaker with a stir bar and placed on a stir plate.
2. 50 dye loaded alginate beads are placed into beaker and stirring begins.
3. Absorbances of water-dye solution are measured every 10 min:
    a. 2 ml of solution are removed using a Pasteur pipette and placed in cuvette
    b. Absorbance is measured at the appropriate wavelength (for red dye use 504 nm)
    c. Solution is returned to the beaker after measuring absorbance (to maintain a constant volume)
4. Absorbance values are measured over a 2 hour period.
5. Trials are run simultaneously to investigate the effect of drug loading and surface area on the release rate.

**Sample student results**

After the experiment is completed, the students are required to use Excel spreadsheet to analyze the data. The students should convert the recorded absorbance measurements into

concentration values using the provided equation from the absorbance curve given in Figure 1. Calibration data are provided with the lab instructions. Students are guided toward using only the linear portion of the calibration data; when this range is exceeded, an increase in concentration will not result in a proportionate increase in absorbance.

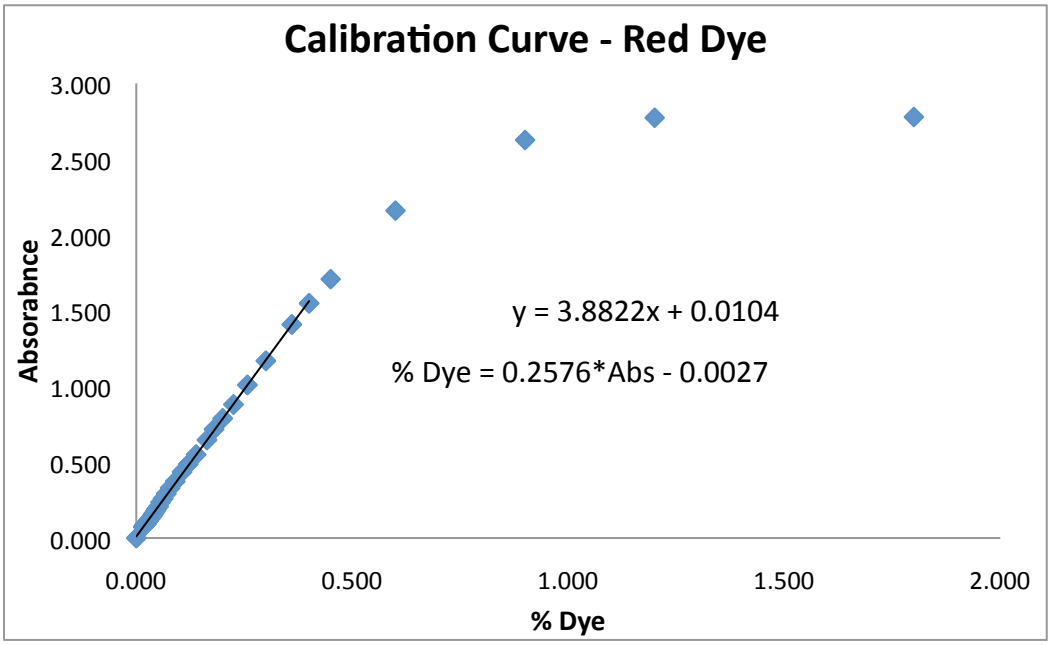


**Figure 1. Calibration plot for red dye**

With absorbance data converted to concentration values, the students create graphs that demonstrate drug concentration as a function of elapsed time as shown in Figure 1. By comparing the release data from different trials, students explore the effects of surface area and drug loading on the release of the drug.

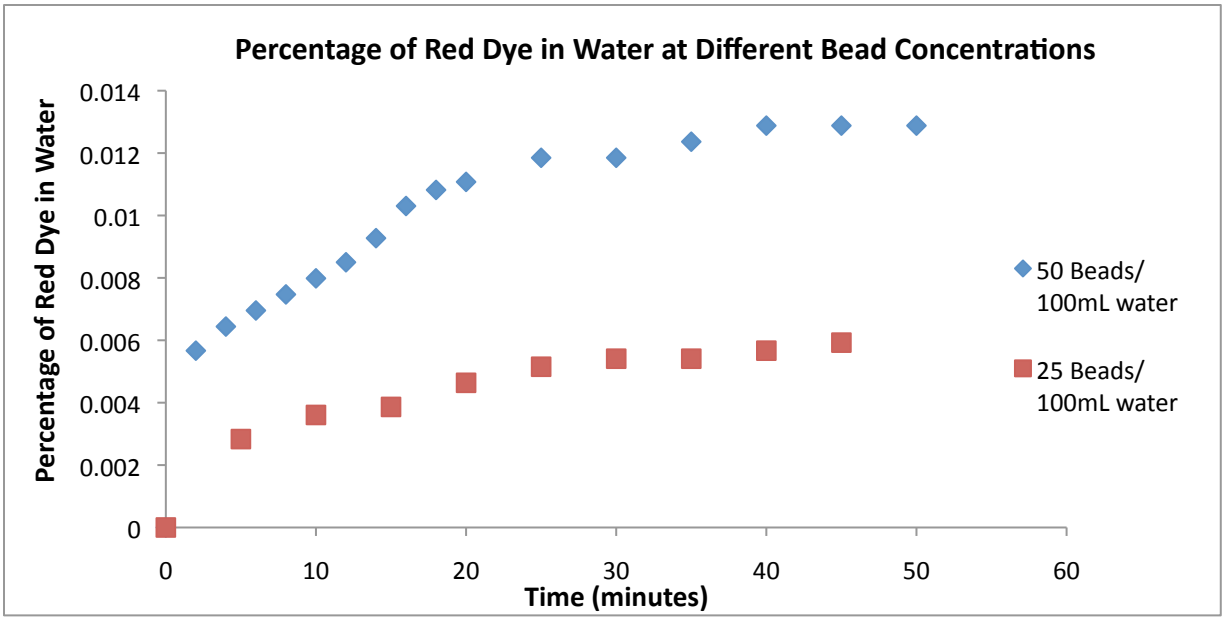


**Figure 2. Drug release profile for spheres loaded with red dye, showing the effect of the amount of beads used.**

## Future Work

Model drugs of different molecular weights can be used, and a comparison of their release rates can be made. Bovine Serum Albumin (BSA) will be used as a model protein with a large molecular weight. Different size microspheres or beads will also be used to determine the effect of size on release rate. This experiment can be used for more advanced courses (mass transfer, transport phenomena, elective courses) by incorporating mass transfer models to describe drug release.

## Summary

This paper examines an experiment that introduces freshman engineering students to drug delivery using polymeric microspheres. By producing alginate microspheres loaded with a model drug and then investigating the factors that affect the release rate, students learn about polymer materials and controlled drug delivery. This experiment will be piloted in the spring semester Freshman Engineering course at Rowan University.

## Acknowledgements

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