Controlled Release Drug Delivery from Hydrogels

Teacher's Guide

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1 Overview

The objective of this project is to introduce students to the concepts of diffusion, polymers and polymerization reactions, and enzyme mediated reactions by designing and testing a controlled release drug delivery system. These types of systems are also referred to as localized drug delivery because an implant that releases drugs is placed directly into diseased tissue. Here, we use Jell-O©as a drug delivery vehicle and food dye as a model drug. Physiological conditions are simulated by placing a cube of the drug delivery system into a test tube with varying ionic and enzymatic conditions.

2 Subjects

This project was developed for and implemented in high school chemistry courses of all levels. The rate of diffusion and degradation of a model drug (food dye) is determined for different polymerization conditions of a hydrogel (Jell-O®). However, drugs and how they are delivered certainly can be taught under the auspices of system and organ biology. Furthermore, the concept of enzymes and their role in the body is appropriate for either chemistry or biology courses.

3 Audience

High school chemistry courses are the target audience for this project. Students in grades 10-12 and remedial through advanced levels have

participated in the piloting of the curriculum. The only specialized piece of equipment is a spectrophotometer for determining the concentration of the model drug. Otherwise, all supplies can be found at a grocery store.

4 Time Required

A minimum of two class periods (50 minutes) is needed to start the project. Following the second lab period students can take data for up to a week to determine the release profile of the model drug from the hydrogel. The time required to take the data is 5-10 minutes. During the piloting of the curriculum, we found it particularly useful to add an additional background lesson preceding the laboratory activities. The background lesson allowed for introduction of new concepts and terminology as well as discussing the relevance of drug delivery to students' lives. In an effort to incorporate student directed inquiry, we have asked students to come up with other variables that may affect the release kinetics. Temperature, pH, and molecular size are student ideas that have been used as an extension of the core lesson. These additional variables can be included in the original lesson or as a separate exercise.

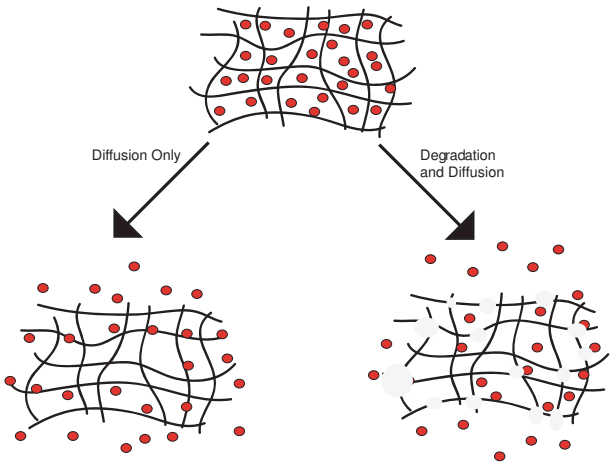
5 Background

Controlled release drug delivery is a new way to treat illnesses. Over the last 20 years it has become more popular as a way to treat diseases such as cancer and diabetes. It generally involves implanting an engineered polymer directly into the organ or system that is affected by a disease. Since the polymer is implanted directly into the tissues affected by disease, the side effects are often small compared to systemic drug delivery (i.e. taking a pill or getting a shot). Brain diseases are particularly good candidates for controlled release techniques because of a physiological feature known as the blood-brain barrier. The blood-brain barrier refers to a tight sheath of cells that surround the blood

vessels in the brain. These cells make sure that only specific types of molecules get into the brain. More specifically, only small (molecular weight less than 1000 g/mol), water insoluble molecules can get into the brain. Consequently, the types of drugs that are developed for brain disease must fit this criteria, which is unfortunate because many promising drugs are water soluble or large. The use of controlled release techniques has led to tremendous breakthroughs in treating brain diseases.

There are two ways that a drug can be released from a polymer implant: 1) Diffusion through the implant and into the surrounding tissue. 2) Degradation of the implant by enzymes, water, or acidic/basic conditions coupled with diffusion (Figure 1). Some systems are designed not to degrade and release is controlled only by diffusion. However, these systems may require an extra surgery to remove the implant. Biodegradable systems only require one initial surgery and are ultimately digested by the body.

Figure 1: Mechanisms of Drug Release



In this activity controlled release drug delivery will be simulated using gelatin hydrogels. Hydrogels are a special type of mesh like polymer that have the ability to absorb large amounts of water. In addition, hydrogels mimic many of the chemical and physical properties of tissue, making them more biocompatible than other types of polymers.

Here, the gels will be loaded with a known concentration of a food dye which acts as the drug molecule. Following gelation, 5 mm^3 cubes of gel will be cut with razors and placed into three different aqueous solutions. The first solution is plain water, which simulates a non-degradable polymer matrix. Here release is due to diffusion through the implant only. The other two solutions will contain a low (1 mg/ml) and high concentration (5 mg/ml) of meat tenderizer which degrade the gelatin. In these second two cases release will be due to both diffusion and degradation. To quantify the release of the dye molecules from the gels we will use spectrophotometry.

6 Learning Objectives

- Students will learn the mechanism behind polymerization reactions.
- Students will learn that enzymes act as catalysts in biological reactions.
- Students will demonstrate that molecular structure of polymer implants and the rate of diffusion dictates drug release.
- Students will manipulate the gel density to achieve a specific release behavior and degradation rates.
- Students will show that diffusion is dependent on temperature, molecular size, ionic conditions, and the resistance a molecule encounters.

7 National Science Education Standards addressed

- Physical Science, Content Standard B: Structure of atoms, structure and property of matter, Chemical reactions
- Science and Technology, Content Standard E: Abilities of technological designs-identify a problem or design an opportunity, pro-

pose designs and choose between alternative solutions, evaluate solution and its consequences

- Science and Technology, Content Standard E: Understandings about science and technology-technological design driven to meet human need and solve human problems
- Science as Inquiry, Content Standard A: Abilities Necessary to do Scientific Inquiry: 1) Design and conduct scientific investigations

8 Assessment Strategy

The student worksheet includes two types of follow-up questions: 1) Comprehension questions regarding the concepts of diffusion and enzymatic degradation. 2) Analysis questions which require deeper scientific insight as well as providing a starting point for student directed inquiry. An extension of this activity is to have students design their own experiment to consider the affects of other variables such as temperature, pH, and drug size.

9 Teaching Tips and Potential Problems

A good way to start this lesson is to make the problem at hand relevant to students' lives. Start out by asking students to write down all of the drugs they have ever used and how they took them (i.e. oral, intravenous, etc.). Write the list (which generally contains 20-50 drugs) on the board to illustrate how ubiquitous drugs are in our everyday life. Student's are then asked to come up with the drawbacks of systemic drug delivery and to propose better methods. The ensuing discussion sets the stage for why scientists and engineers are developing more advanced drug delivery systems. Follow-up this discussion with a brief overview of some the newest drug delivery technologies and define any new terminology or concepts contained in the lesson. A good resource is the biomedical engineering website at Texas A & M University (http://biomed.tamu.edu/biomaterials/DrugDelivery.htm). More

specifically, introduce hydrogels and their properties, the concepts of controlled release, and mechanisms of release(Peppas et al., 2000).

The are a few steps in the experimental procedure that may cause problems. The most common problem is the addition of the gelatin to the hot water. This step needs to be done slowly otherwise the gelatin tends to aggregate into clumps that are difficult to dissolve. The best way to perform this step is on a hot plate with a stirrer. However, the same results can be achieved with stir rod given that the students are patient. Another issue involves the use of the spectrophotometer. Often students do not go through the entire calibration procedure or forget to change the wavelength, which leads to erroneous absorbance readings. This can be avoided by supervision and having written instructions next to the spectrophotometer.

References

N.A. Peppas, P. Bures, W. Leobandung, and H. Ichikawa. Hydrogels in pharmaceutical formulation. *European Journal of Pharmaceutics and Biopharmaceutics*, 50:27–46, 2000.

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