CHEMICAL ENGINEERING SENIOR LABORATORY
CHEG 4139

Controlled Drug Delivery Using Alginate Beads

Objective:
The objective of this experiment is to determine what factors control the release of a drug (simulated by the dye tartrazine) from hydrogel beads. You must determine what conditions lead to the greatest fraction of dye being transferred from the beads to the body (represented by a stirred beaker of water) as well as the rate of drug release for each condition. Several variables may contribute to the rate of drug release, including (but not limited to) bead size, bead cross-linking time, bath stirring rate, and alginate concentration.

Major Topics Covered: Mass transport, polymer kinetics, spectrophotometry

Theory:
Alginate is a polymer commonly used in drug delivery studies due to its biocompatibility. When sodium alginate is exposed to calcium ions, certain monomer linkages in the polymer will fold around the calcium ion, allowing a hydrogel to form through a mechanism known as cross-linking. In drug delivery studies, a drug can be mixed in with the alginate solution before cross-linking, suspending the drug within the hydrogel where it can be dispersed. For pertinent theory and equations describing the rate of drug delivery, refer to references 1-3. To analyze the concentration of dye that has diffused out of the beads, you will be analyzing samples of the immersion bath with a spectrophotometer. Recall that concentration of dye will be directly proportional to the absorbance. For tartrazine, peak absorbance is observed at 427 nm.

Safety Precautions:
1. Calcium chloride is an irritant. Avoid getting it on your skin or in your eyes. In the event of eye contact, flush eyes with water for 15 minutes.
2. Be careful when working with tartrazine. It is an irritant, and it will stain clothes and skin.
3. Do not dump alginate down the sink!!! There will be a container for alginate waste. If alginate is poured down the sink, immediately pour NaCl solution down the drain.

Available variables: Bath stir rate, bead size, bead cross-linking time, number of beads, temperature, dye concentration, alginate concentration, alginate molecular weight, pH

Procedure:

Solution Production:
Make sure to properly label your bottle(s) with full chemical names as well as group numbers and initials.
1. Create 1L of a solution that is 0.5g/L tartrazine.
2. Make the alginate solution.
   - Add 0.1 g alginate per 10 mL of 0.5 g/L tartrazine solution. You will likely need approximately 300mL.
   - Stir vigorously until a smooth, uniform yellow solution is formed. Your group may choose to have two flasks of the alginate solution. This solution should be fully dissolved by the next lab period.

3. Prepare a stock solution of 6 wt% calcium chloride; you will likely need approximately 500mL.
    - Be aware that you may be using calcium chloride dehydrate or hexahydrate.
    - Dissolving the calcium chloride in tartrazine solution helps avoid unwanted tartrazine diffusion when making beads.

Spectrophotometer Calibration:

1. Set the spectrophotometer wavelength to 427nm
2. Zero the spectrophotometer using DI water
3. Take a reading of 3-5 solutions of known tartrazine concentrations. You will need to dilute your stock solution.

Bead Production:

1. Carefully pour the calcium chloride solution into a large weigh boat. Make sure to use a new weigh boat for each set of beads.
2. Load 3 mL alginate into a disposable syringe by immersing the tip of the syringe into the solution and pulling back on the plunger.
3. Slowly dispense the alginate into the weigh boat containing the calcium chloride stock solution. Make sure to record the cross-linking time. Push slowly enough to assure drop-wise dispensing into the calcium chloride. Avoid drops falling on top of other drops. This method should produce approximately 70-100 beads in about 60 seconds.
    - If using a needle tip, be cautious of the needle orientation as different orientations produce different bead sizes.
4. Separate the beads from the calcium chloride solution by filtration. Rinse the beads with DI water after filtration.

Measurement of Dye Release:

Make sure the spectrophotometer is set to 427nm!

1. Fill a 150 mL beaker with 100 mL deionized water.
2. Add the alginate beads to the deionized water and set your stir rate.
3. Remove samples with a Pasteur pipette every 2 minutes for the first 10 minutes. Do not withdraw any beads with your sample. Measure the absorbance with a spectrophotometer. Return the sample to the beaker after measurement to maintain constant volume.
4. Remove samples with a Pasteur pipette every 5 minutes for the next 20 minutes. Do not withdraw any beads with your sample. Measure the absorbance with a spectrophotometer. Return the sample to the beaker after measurement to maintain constant volume.
5. Remove samples with a Pasteur pipette every 10 minutes for the last 30 minutes. Do not withdraw any beads with your sample. Measure the absorbance with a spectrophotometer. Return the sample to the beaker after measurement to maintain constant volume. The full test should last no more than an hour.

Pro Tips:

1. Alginate beads will continue to cross-link even after they have been removed from the calcium solution. It is advised to use any beads you make during the laboratory period and not save any overnight.
2. When calibrating the spectrophotometer, be sure to use a blank of DI water.
3. Alginate is a swellable polymer, so bead swelling may become release rate governing[2,3]. It might be wise to measure a few beads before and after each test.

Analysis:
Your analysis **must** include:

1. Determination of fraction of dye released (F) from the gel as a function of time
2. Determination of the normalized rate of release (*dF/dt*) as a function of time
3. Determination of the rate control mechanism constant (*n*). Note that for Fickian diffusion in a sphere, *n* is expected to be 0.43.

Report:
Describe the design of your experiments and results obtained, **including error analysis**. Provide thoughtful and quantitative discussion of results, explaining trends using physical principles (i.e. why certain parameters will either increase or decrease amount of dye distributed). Be sure to thoroughly explain any deviations from your expected results. Provide suggestions for improvement, including what parts of your procedure worked well and what parts did not.

References

1) **Ritger, Phillip L. and Nikolaos A. Peppas, A simple equation for description of solute release I. Fickian and non- fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs, Journal of Controlled Release, 5(1), 1987, 23-36.**
2) **Ritger, Philip L. and Nikolaos A. Peppas, A simple equation for description of solute release II. Fickian and anomalous release from swellable devices, Journal of Controlled Release, 5(1) 1987, 37-42.**
3) **Peppas, Nikolaos A. and Jennifer J. Sahlin, A simple equation for the description of solute release. III. Coupling of diffusion and relaxation, International Journal of Pharmaceutics, 57, 1989, 169-172.**