Teacher's Guide

Simulating a Controlled Drug Delivery System

Grade Level: Middle and high school

Subject area(s): Biology & chemistry

Time required: (3) 50 minute classes

Learning objectives: Through experimentation, understand how drugs can diffuse over time.

Summary: In this activity, students will learn about alternative drug delivery methods and then prepare a controlled drug delivery system using sodium alginate and glucose to mimic the behavior of a controlled release drug delivery system. The purpose of this investigation is to model a controlled drug delivery system by demonstrating the rate of glucose release from alginate capsules. Students will determine the rate of diffusion through an alginate membrane, graphically represent the system, and describe how this delivery system is an appropriate model for modern drug delivery systems.

Lesson Background: In 2008 *Electronics.ca Publications*, indicated that the advanced drug delivery market was $134.4 billion was expected to increase $196.4 billion by 2014. In 2015, it was estimated to be $178.8 billion with an expected growth rate of 4.9% or $227.3 billion by 2020 (www.bccresearch.com). Certainly the field of advanced drug delivery is growing with increasing global demand for pharmaceuticals that yield greater efficacy at a lower cost and with fewer side effects. Ideally, drug delivery systems seek to achieve the minimum dose where and when a medication is needed. The challenges facing conventional methods of drug dosage modalities including oral, transdermal, and intravenous administration routes must be overcome when designing novel delivery systems. Progress has been made in this field with advances in targeted delivery and sustained release systems that represent the first and second largest global market share, respectively.

In 2009, *ScienceDaily* (8/10/09) reported the development of an effective targeted drug delivery system that uses short strands of DNA or RNA as receptors that are able to specifically bind to cancer cells and deliver the contents of liposomes carrying anti-cancer medication directly to affected cells. In 2020, targeted drug delivery is a method used to fight breast cancer (https://www.cancer.org/cancer/breast-cancer/treatment/targeted-therapy-for-breast-cancer.html) and CRISPR has led to advances in therapeutics. The common orally administered Concerta® uses osmotic pressure to control the rate of delivery of ADHD medication over 6 to 8 hours thereby increasing patient compliance by reducing dosage events. Such advances in controlled release and targeted drug delivery have advanced pharmaceuticals in the last decade and will continue to do so. We now are able deliver effective concentrations of a prescribed medication to a specific location at a sustained rate. In this activity, students will learn about alternative drug delivery methods and then prepare a controlled drug delivery system using sodium alginate and glucose to mimic the behavior of a controlled release drug delivery system.

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Drug Delivery: Delivering pharmaceuticals in the correct dosage form to reach a desired location is a formidable research and development challenge. You are probably familiar with the most common forms of pharmaceutical administration including oral, transdermal, and intravenous administration. Each form attempts to deliver a certain drug to the desired location without the risk of the drug accumulating to toxic levels in the body or being in concentrations too low to be effective. The purpose of the evolving field of pharmaceutical development is to engineer medications that will provide the prescribed drug in a minimum dose to achieve a desired effect. You may be familiar with a variety of conventional drug delivery methods including orally delivered aspirin or the delivery of insulin by injection. However, modern drug delivery systems have become more sophisticated in their design. Although conventional methods deliver the prescribed medication, they are limited in the extent to which they reach the desired levels necessary to initiate a response and they must be administered frequently to maintain an effective therapeutic level. To address the challenges arising from this single dosage model, and to increase patient compliance, innovative delivery systems have been developed to deliver medications to a targeted area while at the same time maintaining effective concentrations of the drug for a sustained period. In this activity, you will assemble alginate-glucose capsules that will serve as a glucose drug delivery vehicle to model the effects of a controlled drug delivery system.

Sodium Alginate: Alginates are a group of polysaccharide polymers derived from the cell wall of brown algae (i.e., of the class Phaeophyceae). Alginates are commonly used in the textile, pharmaceutical, and food industries and are especially common as binders in tablets and stabilizers for emulsions. Food grade alginates are predominantly used as a thickening agent in foods like Nutri-Grain bars and in the processing of the pimentos found in Spanish olives. Alginates are versatile biopolymers displaying unique properties of gelation and cross-linking when exposed to calcium chloride, and are suitable candidates for living systems. This cross-linking property promotes the formation of a semi-permeable membrane and makes alginate an ideal candidate as a delivery vehicle for pharmaceuticals as well as a versatile compound for the encapsulation of materials for medical and pharmaceutical purposes. Alginate's properties have been examined for the fabrication of controlled, injectable drug delivery products in the form of chitosan-alginate composites to generate new bone and as scaffolds for encapsulating and delivering neural stem cells to bone tissue (Journal of Cranio-Maxillofacial Surgery, 33(1): 2005; *ScienceDaily* 11/11/07).

Materials:

- Stopwatch
- Glucose tablets
- Sodium alginate
- Calcium chloride
- TrueTrack™ Glucose Meters (or comparable meter)
- TrueTrack™ blood glucose test strips
- Dropper bottles (author used mustard/kitchen dispensers from discount store)
- Disposable dropper pipets
- Conical/centrifuge tubes
- Plastic cups

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- Plastic spoons
- Metal strainer
- Oversized glass slides (author used ones from small picture frames at discount store)
- Metric ruler
- Hotplate
- Permanent marker
- Balance
- 25mL or 50mL graduated cylinder
- Mixing bowl or blender (optional)

Safety Information: ***CAUTION**: All glucose monitors are pre-packaged with instruction booklet, log book, glucose control solution, lancing device, lancets, monitor, test strips, and a test strip coding chip. It is imperative that the instructor removes the lancets, lancing devices, log book, and instruction booklet prior to conducting the lab for student use. Collect the lancets and lancing devices and dispose of them at your local pharmacy (check with your local pharmacy or hospital for drop off instructions).*

General Safety Guidelines

1. Always wear proper lab safety attire including goggles and lab aprons.
2. Preparation of a 1% $CaCl_2$ solution generates heat - be careful when handling warm/hot glassware.
3. You will require a hot plate for preparing the alginate-glucose gel - be careful when handling hot glassware.
4. Clearly label all chemicals that will be located at the shared chemical station for students. Reiterate to students the importance of avoiding cross-contamination.
5. Handle all glass material with care. Reiterate to students the importance of telling the teacher when an accident has occurred.

Vocabulary and Definitions: Prior to beginning the activity, students should be presented with an introduction to drug delivery methods and systems. You may use the included PowerPoint, create your own, or view YouTube videos. Review of the meaning of the terms should be covered before starting the activity.

- *Drug Delivery:* the method or process of administering a pharmaceutical compound to achieve a therapeutic effect in humans and have been classified by drug administration route including oral, transdermal, and intravenous, although variations of these exist (From en.wikipedia.org/wiki/Drug_delivery).
- *Drug Delivery Systems:* Formulation or device that delivers therapeutic agent(s) to desired body location(s) and/or provides timely release of therapeutic agent(s). Systems have routinely been categorized as conventional or controlled release, but currently include targeted delivery systems as well (From www.drugdel.com/glossbot.htm).
- *Methods of Drug Delivery:* Due to the advances in medicine, drugs may be delivered in many different ways using many different delivery systems including: by mouth (pills or suspensions), through the vein (intravenously), and topically through the skin

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(transdermally). Other ways that medications can be delivered systemically include: through the eye (ocular), through the lungs (inhaled), by injection into the skin (subcutaneously), by injection into the muscle (intramuscularly), and under the tongue (sublingually) (From http://www.icu-usa.com/tour/procedures/drug_delivery.htm).

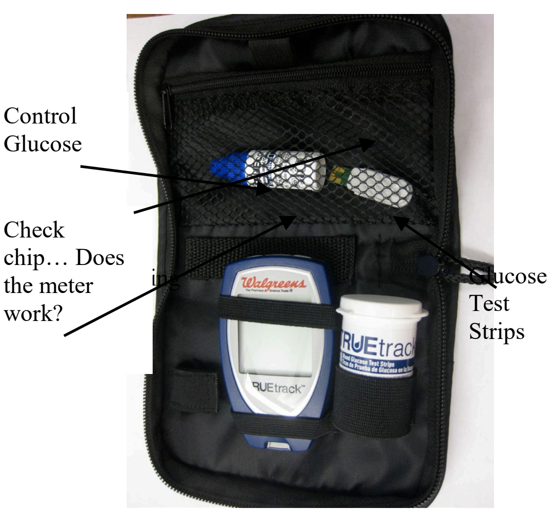
- *Controlled Release:* Based on "Time Release Technology," controlled release is also known as sustained-release (SR), extended-release (ER), or timed-release are formulated so that the active ingredient is embedded in a matrix of insoluble so that the dissolving drug has to find its way out through the holes in the matrix (From en.wikipedia.org/wiki/Controlled_release).
- *Targeted Delivery:* Delivering a drug to a specific site in the body where it has the greatest effect, instead of allowing it to diffuse to various sites, where it may cause damage or trigger side effects. (From http://www.mondofacto.com/facts/dictionary?targeted+drug+delivery)

Ask students questions to provoke thought and review what they already know:

- *What is a mg?* Milligram or 1,000th of a gram
- *What is a dL?* Deciliter of 1/10th of a liter
- *What is a mg/dL?* Milligrams per deciliter, a measurement that indicates the amount of a particular substance, such as glucose in a specific amount of blood.
- *What is a solution?* A type of homogeneous mixture composed of two or more substances. In such a mixture, a solute is a substance dissolved in another substance, known as a solvent.
- *In science, what does "concentration" refer to?* The amount of a substance in a defined space such as volume. It can also be defined as the ratio of solute in a solution to either the solvent of total solution.
- *What is a polysaccharide?* A carbohydrate whose molecules consist of a number of sugar molecules bonded together. They are long chains of monosaccharides linked by glycosidic bonds. *Give an example.* starch, cellulose, chitin, or glycogen

Advance Preparation:

1. Setup 6 glucose monitor carrying cases to include only the materials shown in the figure:



2. Use the glucose control chip and the control liquid to ensure that the monitor is working properly.
3. Insert the appropriate coding chip into each monitor prior to the investigation.
4. Setup 12 student lab stations for Day 2. Include the following materials at each station: 4 plastic cups, 1 permanent marker, 1 glucose monitor/test strip vial kit, 1 disposable transfer pipet, 1 plastic spoon, 1 metal strainer, 1 stopwatch, 1 container of alginate-glucose gel, 1 metric ruler, 1 collection tube, 1 piece of glass for sample testing.

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24 to 48 hours prior to the investigation:

Prepare Sodium alginate-glucose gel (this recipe will make 600mL of the alginate-glucose gel which can be divided into 50mL units to accommodate 12 groups of 2 students). This will take 20-30 minutes to prepare.

1. Add 48 glucose tablets to 600mL of distilled water. This is the equivalent of 12g of glucose and therefore a 2% glucose solution. The tablets will easily dissolve in the water, but the insoluble tablet binder will float to the top of the solution. You can either scoop it out using a spoon, or you could strain the solution for a more homogeneous solution.
2. Measure 12 grams of sodium alginate.
3. Incorporate this into 600mL of glucose solution by manually stirring the mixture at room temperature. Alternatively, to increase dissolving time, use a hot plate to warm up the mixture, and stir continuously. The sodium alginate will clump, so you may consider using a magnetic hot plate with stir option to accomplish this step. Mix until the solution displays a uniform consistency.
4. Divide the 600mL alginate-glucose gel into 12, 50mL volumes to be poured into 12 ketchup/mustard dispensers for student workstations.
5. Properly label each container before setting up student workstations.

Prepare 1% Calcium Chloride solution (this recipe will make 1L of $CaCl_2$ solution, and can be reused if cross-contamination has been avoided). This will take 15 minutes to prepare.

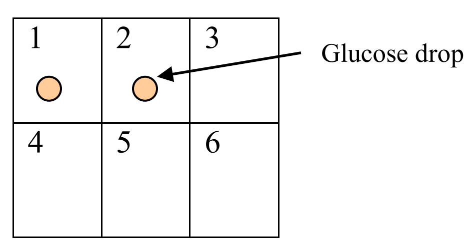
1. Measure 10g of $CaCl_2$.
2. Dissolve the 10g of $CaCl_2$ into 1L of distilled water. Allow solid to dissolve sufficiently.
3. Adding $CaCl_2$ to water initiates an exothermic reaction, so the chemical storage bottle will become warm to the touch.

Prepare glucose meter cases. This part will take 20 minutes to prepare.

1. Each glucose monitor kit that is purchased from the local pharmacy will contain lancets and lancing devices in addition to the monitor and a starter vial of test strips.
2. Remove all items from the kit. Insert the control chip (this is flat) into the device to ensure that the monitor works. Then, open the glucose test strip vial and insert the coding chip that corresponds to the test strip vial that accompanies each glucose monitor kit. Insert a test strip. Use the glucose control solution to check that the monitor works properly (the concentration in the control solution should match the "level" that the test strip vial is labeled).
3. Discard the used test strip.
4. For each carrying case, place a glucose monitor and corresponding test strips in the main part of the case. The control solution and control chip should be placed in the zipper part of the case.
5. Assign a number to each case using masking tape.

Prepare Glass Piece for testing glucose sample. This will take 10 minutes to prepare.

1. Obtain 12 wallet-sized frames.
2. Remove the glass from each frame.
3. Use a permanent marker and ruler to divide the glass into a 2 X 3 grid.
4. Number each grid cell. These areas will be used to



Glass substrate where glucose samples will be tested using the glucose monitor

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perform the glucose test during the investigation.

Prepare "Pharm Cards". You can either use the images that supplement this activity, or you may choose to select your own images. Option 1 will take 20-30 minutes (add an additional 20 minutes for laminating).

1. Print 12 sets of the "Pharm Cards" that supplement this activity.
2. Cut them out and place each set in a plastic bag or secure them with a rubber band. Laminating is optional, but recommended if you intend to use conduct this investigation more than once.

Teacher Preparation for the Day of the Investigation

Prepare Student Workstations

1. Student workstations should be setup prior to the execution of the activity.
2. Each student workstation should include an assigned glucose monitor kit with test strips, a disposable transfer pipet, a plastic spoon, a ketchup/mustard dispenser containing 50mL of alginate-glucose gel, a stopwatch, an empty collection tube, a piece of prepared glass, 4 plastic cups, a metal strainer, and metric ruler.
3. The $CaCl_2$ stock solution and distilled water should be located in a common area for students as they conduct the experiment.

Suggested Teaching Strategies or Troubleshooting Tips: The investigation as presented in this form is designed for lab groups of 2 students. However, if cost is a factor, the investigation could be performed with lab groups of 4 students. The instructions have been written for a class of 24 students.

The teaching strategies that are employed during this investigation include small group collaboration as student teams sort "Pharm Cards" into appropriate categories. The structure of this warm up activity should provide students with the necessary context to explore the broad concept of drug delivery. Student readiness should also be evaluated prior to performing this lab. Basic chemistry definitions and concepts should be reviewed and described before the guided inquiry and subsequently applied during the lab investigation. Teachers electing to carry out this investigation may discover that it has been designed as a lab activity that can be easily implemented as the first lab activity of the year. As such, the structure of this 3-day lesson permits students to apply their prior knowledge, assimilate new content, and then apply this content in a novel way.

Before conducting the lab, students should be aware of common technical and procedural issues to avoid while preparing for the lab and during data gathering. In order to successfully carry out this investigation, students should be reminded that cross-contamination must be avoided throughout this experiment. This is particularly an issue during the straining and rinsing steps of the investigation. It is also easy to mistake a used test strip for an unused one. Take care to keep used and unused test strips separated.

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Students should also be advised that glucose monitors can only be used with the designated test strips because of the coding chip embedded within the device. Therefore, no sharing of test strips from other monitor carrying cases is permitted..

Lastly, students should be encouraged to ask questions when procedural or technical aspects of the activity require clarification. For instance, if a student group attempts to test a glucose sample at a designated time, and obtain an error reading, the instructor must be notified so that the teacher designated monitor can be used as a backup. Similarly, students should be instructed to use only the number of test strips allotted to their group.

Suggested Instructional Sequence:

Day 1: Introduction to drug delivery (45 minutes)

Warm-up (10 minutes)

Present student groups of 2 with the "Pharm Cards". Follow Warm-up instructions according to the PowerPoint that supplements this activity.

Introduction (30 minutes)

Before conducting this investigation, students will require background information about how pharmaceuticals are delivered, the trends in engineering innovative drug delivery systems. The PowerPoint that supplements this activity explores this content in general terms, appropriate for a 9^{th} grade audience. As homework, have students watch one or two of the suggested YouTube videos on encapsulation or read one of the online sources.

Day 2: Conducting the investigation (45 minutes)

Prelab Quiz (5 minutes)

In order to determine the readiness of students to perform the investigation, a 10 question prelab quiz will be assigned prior to conducting the investigation. This may also be used as a post-lab quiz to see how much they have learned.

Review Procedural, Technical, and Cleanup strategies (10 minutes)

Students should be advised of all safety requirements and any points during the procedure where error can be avoided. This includes a reminder about cross contamination and the sharing of glucose test strips between groups who are not using the same glucose monitor. Additionally, students should be made aware that if a test strip reads "Error" that the teacher should be informed so that a new test can be immediately performed using a teacher designated device.

Collect Data (25 minutes)

Students will perform the investigation and collect data every 5 minutes for a 20 to 25 minutes period, depending on the time constraints.

Cleanup (5 minutes)

Students will strain alginate-glucose capsules and dispose of them in the waste receptacle. $CaCl_2$ will be returned to the "USED" $CaCl_2$ solution bottle. Pipet, collection tube, plastic cups,

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plastic spoon, and glass will be rinsed with water and dried using a paper towel. Lab stations will be checked for tidiness.

Day 3: Using Excel (45 minutes)

- *Review results (15 minutes):* A discussion regarding the results should begin this lesson. Ideally, student data should demonstrate a linear trend resulting from an increase in glucose concentration over time with an explanation about what substance diffused and why. A complete explanation of using Excel can be found in the Student Worksheet with answers (below).
- *Using Excel and Determining rate of release (slope) (20 minutes)*
- *Review components of lab report and assign lab report due date (10 minutes):* Review with students how they will be assessed, and use this time to generate ideas about the benefits and challenges of conventional, controlled release, and targeted drug delivery systems.

Directions for the Activity: These are in the Student Guide with answers below.

Resources:

For current and up to date resources, Google advances in drug delivery or the specific drug delivery method including gene therapy and CRISPR therapeutics.

https://en.wikipedia.org/wiki/Targeted_drug_delivery Review of targeted drug delivery.

http://www.azonano.com/details.asp?ArticleID=1538 Recent advances in drug delivery are described. Technical distinctions between passive and active targeted drug delivery are provided along with more sophisticated approaches to designing drug delivery vehicles. Old but still interesting.

https://jbiomedsci.biomedcentral.com/articles/10.1186/s12929-019-0571-4 Smart polymers for cell therapy and precision medicine in the Journal of Biomedical Science.

https://www.advancedsciencenews.com/smart-polymers-biomedical-applications/ Smart Polymers for Bioimedical Apllication at Advanced Science News.

http://www.sciencedaily.com/releases/2009/08/090806112359.htm Describes the formation of a liposome with aptamer labels that provide the vehicle for delivering powerful anti-cancer medication to specific cancer cells while sparing unaffected cells.

https://www.sciencedaily.com/releases/2020/01/200128114720.htm Nanoparticle chomps away plaque that causes heart attacks at Science Daily.

http://www.webmd.com/pain-management/guide/spinal-drug-delivery-systems Describes an implantable, spinal drug delivery system for the treatment of chronic pain.

http://www.sciencedaily.com/releases/2007/11/071109191538.htm A use for sodium alginate as a scaffold for delivering neural stem cells to specific regions in the body.

http://www.electronics-ca.com/products/Advanced-Drug-Delivery-Systems%3A-New-Developments%2C-New-Technologies.html Provides a market analysis of current and future trends in advanced drug delivery systems.

Gel bead and encapsulation videos:

https://www.youtube.com/watch?v=dyQnFS39nTg

https://www.youtube.com/watch?v=afIT1vZMivM

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https://www.youtube.com/watch?v=1gNl88DCyLA
https://www.youtube.com/watch?v=Ro_qvq6RqY0
https://www.youtube.com/watch?v=JcwUNAjmU_g
https://www.youtube.com/watch?v=aQp1mC9GGfA

Assessment: You will be evaluated on your lab technique and your written formal lab report for this investigation. The rubric for both criteria are listed below:

Rubric for Lab Technique	
Category	**Points**
Participation in lab	20 points
Accuracy of data	10 points
Adherence to safety rules	10 points
Cleaning of equipment and lab station	10 points

Rubric for Evaluating Lab Reports	
Component	**Points**
1. Attribution	2
2.Title	3
3. Introduction	5
4. Purpose	2
5. Materials	3
6. Safety	5
7. Procedure	10
8. Results	10
9. Calculations (when applicable)	10
10. Graphs	10-20
11. Discussion	20
12. Conclusion	5
13. Works Cited	5

Next Generation Science Standards:

Cross Cutting Concept:

Cause and Effect (HS-LS2-8 & HS-LS4-6)

System and System Models (HS-LS1-2)

Science and Engineering Practices

Developing and Using Models (HS-LS1-2)

Planning and Carrying out Investigations (HS-LS1-3)

Constructing Explanations and Designing Solutions (HS-LS1-1)

Optional Engineering Design Extension:

If you would like to extend this investigation to students as an engineering design challenge, consider the following:

1. How does altering the time in the $CaCl_2$ bath change the rate of glucose release;
2. How can this system be designed to achieve a zero order release;
3. Can this system be redesigned to release glucose at a lower rate based on the health of an individual (i.e., diabetic vs. non-diabetic);
4. Can other materials be encapsulated in this manner and then tested using an alternative to the glucose monitor and test strips?

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Student Guide

(with answers in red)

Simulating a Controlled Drug Delivery System

Introduction:

Do you use an inhaler to control your asthma? Have you ever taken a cough suppressant to stop your nagging cough? Have you ever used eye drops? Can you think of how all of these “devices” are related? All of these are examples of drug delivery systems; important advances in chemical and biomedical engineering that promote better health through prevention and treatment of diseases and disorders. In developing drug delivery systems, scientists must determine what the body does to the drug and also what the drug does to the body. Significant drug delivery systems including transdermal patches, inhalers, and enteric coating for oral tablets have been in development since the 1970s. But, recent advances in the engineering and design of pharmaceuticals as controlled release and targeted drug delivery systems show promise beyond these conventional systems because they can deliver effective concentrations of a prescribed medication to a specific location at a sustained rate. In this activity, you will learn about alternative drug delivery methods and then prepare a controlled drug delivery system using sodium alginate and glucose to mimic the behavior of a controlled release drug delivery system.

Pre Lab Questions:

Scientists are constantly thinking about how to improve experimental designs to overcome challenges and to achieve more profound results. In this investigation you will consider the field of advanced drug delivery as a model for thinking like a scientist.

- What do you think will happen to the concentration of sugar in your body after you eat a candy bar? *It increases.*
- Does the sugar in your body stay at this concentration? *No.* Why? *Because your body metabolizes it.*
- Now consider this, if you had a nagging cough, would you prefer that your cough medicine work with several doses or with a single dose and for a longer time? *One dose for convenience.* Why?
- Now, consider your answer as you make your own controlled drug delivery system. Would you design a cough drop that behaves in the same way? *Yes, because the same amount of medication will be in my body to suppress my cough for a longer period.*

Materials:

- Laminated Pharma cards
- Prepared alginate-glucose gel in dispenser
- Permanent marker

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- Metric ruler
- Small metal strainer
- Plastic spoon
- Disposable pipette
- Glass piece 2.5x35. in.
- 2 plastic cups labeled 1% $CaCl_2$
- 2 plastic cups labeled water
- Stopwatch or similar device
- 1 collection tube with 20mL of water
- Truetrack™ glucose monitor
- 6 Truetrack™ glucose test strips
- Access to Excel application

Procedure:

Day 1: An introduction to drug delivery

1. Your group will be provided with a set of "Pharm Cards". Your teacher will provide you with prompts as you attempt to sort the image cards into categories that you and your partner have agreed upon.
2. Be prepared to discuss the categories that you applied to your selection of cards.
3. You and your classmates will explore advanced drug delivery through the presentation of a PowerPoint slide show. You will discover the design and application of the images on the "Pharm Cards" that you initially sorted.

Day 2: Performing the investigation

1. If you would like to record your experiment using digital photography, feel free to use a digital camera or cellphone. This is optional, but enriches your lab report.
2. Your lab station will be equipped with the materials you will need to carry out this investigation (refer to Figure 1).

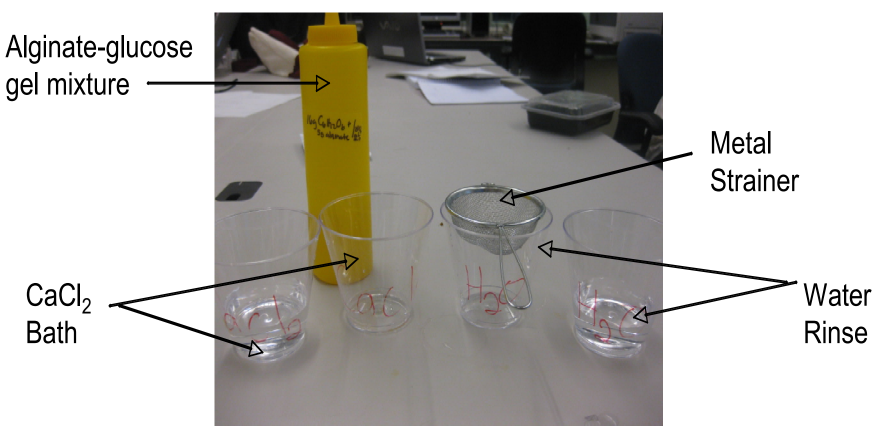

Figure 1. Student Workstation for Microcapsule formation

3. Label 2 of the plastic cups "$CaCl_2$" and the other 2 "water."
4. Obtain 200mL of 1% $CaCl_2$ solution from the chemical station, and pour it into one of the cups labeled $CaCl_2$.

5. Similarly, obtain 200mL of water from the chemical station, and pour it into one of the plastic cups labeled water.

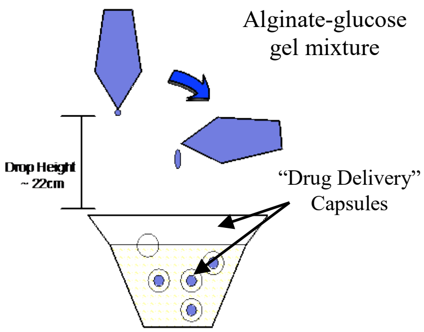

Figure 2. Demonstrating the method for drop formation in $CaCl_2$

6. Hold the container labeled "alginate-glucose" in a vertical position and from a height of approximately 22cm over the cup labeled "$CaCl_2$" and gently squeeze the container until you observe the formation of a drop from the tip of the container. Then, rotate your container 90 degrees so that it is parallel with the cup containing $CaCl_2$. Allow the drop that was forming to fall into the $CaCl_2$ solution (refer to Figure 2).
7. Immediately start your stopwatch. Gently stir the drop in the $CaCl_2$ for 30 seconds.
8. When 30 seconds up, place the small metal strainer on top of the second empty cup labeled "$CaCl_2$." Pour the contents of the first $CaCl_2$ solution with the recently formed capsule into the second cup.
9. Place the strainer containing the capsule on top of the empty cup labeled "water."
10. Rinse the capsule by pouring the water from the full cup of water into this apparatus.
11. Use the plastic spoon to collect the capsule and place into a collection tube (Note: **Do Not** add water to the collection tube until all capsules have been formed).
12. Repeat this procedure 7 more times for a total of 8 capsules.
13. You will be sharing your glucose monitor with another lab group. Make sure that the glucose test strips are used properly and **ONLY** with the glucose monitor at your station. Your group will be provided with 5 test strips to collect your data. If you obtain and "Error" reading, please notify your teacher so you can use the teacher designated backup monitor.
14. When all the capsules have been formed and placed into the collection tube, add 20mL of water to the collection tube and IMMEDIATELY start your stopwatch. Continue to gently agitate the contents of the collection tube for 5 minutes.
15. After 5 minutes has elapsed, withdraw a sample of the liquid from your collection tube. Place a drop of the sample onto the glass grid labeled "1".
16. Insert an unused test strip into the glucose monitor. Wait for the blood drop icon to flash. When you see this, the machine is ready to test.
17. Hold the glucose monitor in a vertical position, and place the tip of the test strip directly into the liquid sample. Wait for the monitor to determine the glucose concentration in your sample drop.
18. Record this numerical value in the data table provided.
19. Continue to agitate the contents of the collection tube while waiting for the next 5-minute interval to elapse. Repeat steps 16-18 until 20 minutes has passed. This will ensure that you and your partner will have recorded a minimum of 4 data points. If time is not a constraint, continue recording measurements until you reach "HI" as a data point. Record this as >600mg/dL in your data table.

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Cleanup:

1. Alginate-glucose capsules and leftover mixtures should be strained and disposed of into a compost or common waste receptacle.
2. Do not pour the $CaCl_2$ solution down the sink. Return the USED $CaCl_2$ to the stock container labeled "USED $CaCl_2$" to avoid cross-contaminating the unused batch. $CaCl_2$ can be saved and reused.
3. Rinse all cups, pipets, and collection tubes with water and let dry.
4. Dispose of glucose test strips in a common waste receptacle.
5. Return glucose monitor and test strip vial to its carrying case.
6. Wipe down your station.
7. If you were borrowing a digital camera, download your photos, delete them from the camera, and store the camera properly.

Day 3: Using Excel®

1. Now that you have collected some data, you will be compiling it into a form that is more easily interpreted.
2. Open a new spreadsheet from the Excel program on your computer.
3. Type the title of your investigation in the spreadsheet for reference.
4. Insert the Time (minutes) and record the time intervals vertically by starting with "0". Repeat this in the adjacent column for Glucose (mg/dL) and record the glucose values you measured.
5. Highlight the content of both columns and then click on the "chart" icon in the Excel® toolbar. This will open another window. Select the scatter plot graph option and click XY (scatter) chart type and the scatter plot graph with just data points as your chart sub-type. Click "Next".
6. The screen will display a graph of your data points. Click "Next".
7. The screen that appears should display chart options for title, x-axis, and y-axis. Fill in these labels as appropriate, including units.
8. Click on the toolbar option entitled "legend" and click off the "show legend" mode.
9. Click "next" and the "Finish" to complete your graph.
10. Your graph should appear on the spreadsheet with your data. Feel free to move the graph over if it is obscuring your data table.
11. Use the Excel toolbar to select "Chart" and then "Add Trendline" in the drop down menu.
12. Once in this dialogue box, click on the "Linear trend/regression" line. Then, select "Options" from the menu bar in this window. Once there, click on the "Display equation on chart" and "Display R-squared value in chart". This will display the slope of your best fit line as well as how well this equation describes the data (R^2).
13. Click "OK" and the dialogue box will disappear and the final graph will appear on your spreadsheet.
14. Save your spreadsheet to a thumb drive, email it to yourself, or print it to a local printer so that you can include it in your lab report.

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Record your Observations:

Monitoring Glucose Concentration

Time (minutes)	Glucose Concentration (mg/dL)
0	
5	
10	
15	
20	
25	
30	
35	
40	

Analyze the Results:

The only analysis that will be conducted will be in the determination of the rate of glucose release. The common formula for a linear equation is $y = mx + b$; where m and b designate constants. Students should recognize that x and y are values that were measured during the lab activity, while b represents the point at which the line crosses the y-axis. The slope of the line, represented by m, is a derived value based on the data points gathered. There is a direct relationship between the slope of the line and the rate of release (i.e., the greater the slope value, the higher the rate at which glucose is released from the "drug delivery" vehicle).

Students should also recognize that a controlled release drug will eventually reach a "zero order release". Zero order release refers to the ability to deliver a drug at a rate independent of time and the concentration of the drug (http://www.colorcon.com/formulation/app/tailoring-release-profiles/zero-order-releasebe). This ensures that a steady concentration of the desirable drug will be released continuously and at the therapeutic dose.

When data points are analyzed in this context, students may wonder where the plateau in their graphs is located. Challenge them to consider why a plateau was not achieved in this simulation. Answers should immediately identify the limitations of the equipment used in this investigation. More specifically, the glucose monitor does not detect concentrations over 600mg/dL and therefore only a predicted plateau or zero order can be achieved.

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Student groups should compare the graphs that they generated and further compare them to the profiles of conventional and controlled release drug delivery systems. They should conclude that conventional methods of delivering medications are limited due to the frequent doses required by an individual to achieve therapeutic levels of the drug. Consequently, the conventional drug dosage form will be graphically represented by drastic fluctuations in concentrations over time which corresponds to the administration of single doses. Students should also observe that the line that best fits their data resembles the controlled release profile with the exception of the plateau.

Draw Conclusions:

1. What part of this experiment did you purposely change or manipulate? *The time interval.*
2. What variable changed as a result of the variable in #1? *Glucose concentration.* How much did that responding variable change? *Answers will vary depending on meter readouts; concentrations have ranged from 200mg/dL to >600mg/dL over the course of the experiment.*
3. Does this investigation have a control? *There is no tested control in this experiment, but students could use a test strip to test the concentration of glucose in distilled water.* If yes, identify it.
4. What did you keep the same during this experiment? In other words, what were the constants in your experiment? *The constants in this experiment include the glucose monitor and test strips, amount of water, number of alginate-glucose capsules, time interval for testing concentration, etc. Any part of the investigation that does not vary during the experiment is considered a constant.*
5. What is the slope of your line? Compare the slope of your line with that of 3 other groups. Provide a reason for any apparent differences. *The slope is the coefficient that appears in front of the x in the linear equation y = mx + b. This value is measured in mg/dL and will vary by group. Although the trend in data between groups shows a direct relationship between time and glucose concentration, most of the differences in data points can be attributed to glucose monitor error.*
6. What is the relationship between the slope of your line and the rate of glucose release? *There is a direct relation ship between the slope of the line and the rate of glucose release. The steeper the slope, the higher the rate of glucose release.*
7. If we continued recording measurements, what do you predict would happen to your slope? Explain. *Eventually the concentration of glucose would level off as similar measurements of glucose concentration are recorded. This would be illustrated by a plateau in the glucose concentration graph and described exponentially.*
8. Predict what would happen to the slope of the line if you increased the concentration of glucose in the alginate capsule? *The slope of the line would increase suggesting an increase in the rate of release.* Decreased the concentration of glucose in the alginate capsule? *The slope of the line would decrease suggesting a decrease in the rate of release.*

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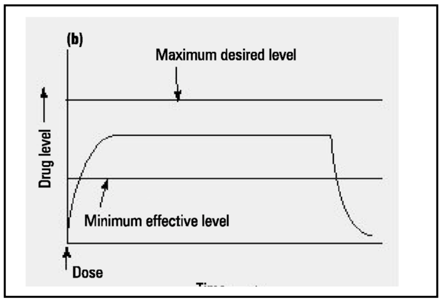
9. Compare the graph of your data with the conventional and controlled release drug delivery profiles below. Identify which graph your data most closely represents and why.



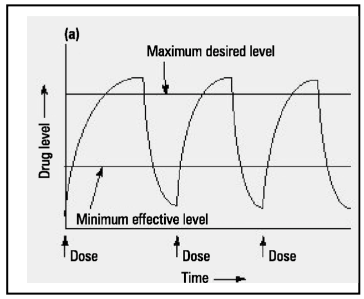


Image Source: http://www.emeraldinsight.com/fig/1560070504001.png

Students should identify that the controlled release profile most closely represents the data that they gathered with the exception of the plateau (zero order release).

10. Is this simulation an accurate representation of how a controlled release drug delivery system behaves? Why or why not? *Scientific models are approximations of a real system that omits all but the essential variables in the system. As such, this simulation provides an accurate, albeit limited depiction of how a controlled drug delivery system behaves without mimicking it in real time.*
11. Identify at least 3 sources of error in this investigation, and explain how this error could affect your results. *Glucose meters – international standards allow for as much as 20% error in glucose readings; Cross-contamination – inadvertently mixing the $CaCl_2$ and water would cause the alginate-glucose capsules to become more firm and therefore may impact the diffusion of glucose; Not mixing the collection tube with alginate-glucose capsules sufficiently – the water in the collection tube will not be sufficiently mixed to accurately measure the concentration of glucose.*

Enhancing understanding:

1. What diffused in this investigation? *Glucose.* How do you know? *The concentration of glucose in the collection tube increased over time.*
2. Was your answer to #1 the only material that diffused in this investigation? *Not likely. It is true that glucose moved from an area of high concentration in the alginate-glucose capsules to low concentration in the collection tube, but water from the collection tube diffused across the semi-permeable membrane of the alginate-glucose capsules as well due to osmotic pressure. This can be observed by the increase in capsule size from the beginning of the experiment to the end.* Explain.
3. What other variables could you test in this experimental design? *Temperature, pH, size of molecule entrapped in the capsule, concentration of calcium chloride used for cross-linking, cross-linking time (i.e., time in calcium chloride bath).*
4. Create your own experiment using this system and a variable you identified in the previous question. Provide a possible question, and then design a potential experiment that could be designed to test your idea. *Answers will vary. Accept all appropriate responses.*

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Review the findings with students:

The findings suggest the following:

1) The concentration of glucose increases over time due to the movement of glucose molecules from the interior of the alginate capsule to the external aqueous solution. This occurs as a result of diffusion; the movement of material from high to low concentration. In this instance diffusion occurred across a semi-permeable polymer membrane.
2) The line of best fit for the data gathered in this investigation is comparable to the drug release profile illustrated in a controlled release drug delivery system. That is, the drug of interest is released in a rapid burst followed by a zero order release (not confirmed by data).
3) The line of best fit for the data gathered in this investigation is not consistent with the drug release profile illustrated by conventional drug dose modalities. That is, the drug of interest in this investigation (glucose) does not have to be administered constantly to achieve the desired drug delivery effect.

Going Further

1. In order to design a new drug delivery system, what questions might a bioengineer consider before initiating its development? *How much drug is needed? At what delivery rate? Over what period of time? With what bioavailability? Acting at which sites or on what cells?*
2. Assume that the glucose represents a new prescription medication. Construct a print advertisement that accurately represents your results. *Answers will vary. Accept all appropriate responses.*
3. What are the benefits of controlled release drug delivery over conventional forms? *Greater patient compliance with controlled release systems; drug can be wasted when it dips below therapeutic range in conventional systems; toxicity is possible above therapeutic range in conventional systems; controlled and targeted release systems can improve therapy by developing environmentally-responsive systems; manufacturing costs will decrease due to fewer dose events.*

Engineering Design Extension: If you would like to extend this investigation to students as an engineering design challenge, consider the following:

1. How does altering the time in the $CaCl_2$ bath change the rate of glucose release;
2. How can this system be designed to achieve a zero order release;
3. Can this system be redesigned to release glucose at a lower rate based on the health of an individual (i.e., diabetic vs. non-diabetic);
4. Can other materials be encapsulated in this manner and then tested using an alternative to the glucose monitor and test strips?

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