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Robert Langer's Lecture Part 1:

Advances in Controlled Drug Release Technology: An Overview

Teaching Tools were prepared by Lindsay Osso & Valentina Garcia.

Contents

1. Keywords and Terms
2. Lecture Notes
3. Review Questions
4. Answers to Review Questions
5. Discussion Questions
6. Answers to Discussion Questions
7. Questions for Discussion Paper
8. Answers to Questions for Discussion Paper

1. Keywords and Terms

Desired/therapeutic range, Drug delivery systems, Controlled release, Targeted release/local delivery

2. Lecture Notes

Overview

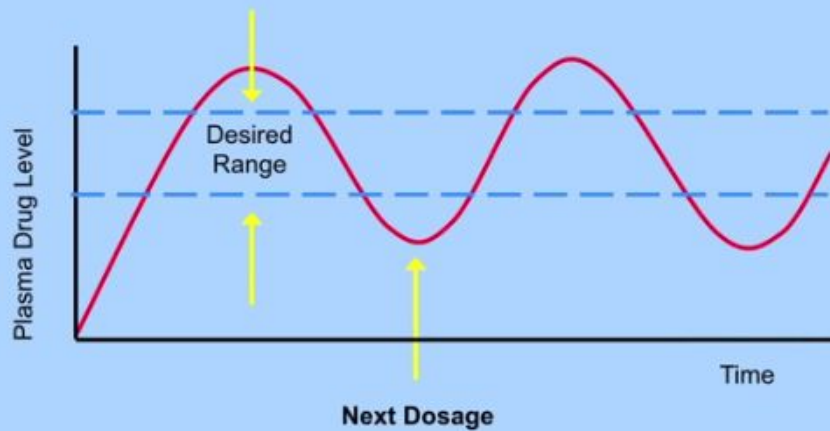
- Lecture 1: Advances in controlled release technology overview
- Lecture 2: Drug delivery technology: Present and Future
- Lecture 3: Biomaterials and Biotechnology: The development of controlled drug delivery systems and the foundation of tissue engineering



0:54-1:14

Dr. Langer discusses three major topics in his lectures. In this lecture, he discusses current drug release mechanisms, future drug delivery technologies, and new materials for drug delivery. In his second and third lecture he discusses his own lab's work in advancing these technologies.

Usual Case

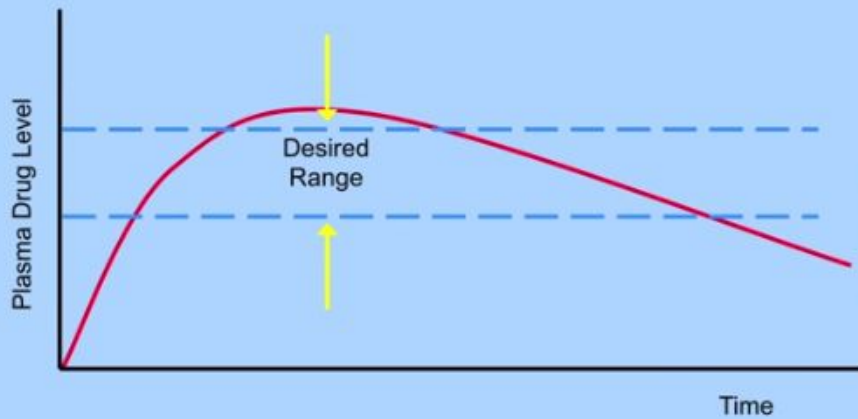


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1:15-3:28

The major issue being addressed by current drug delivery methods is how to maintain constant levels of drug within the desired (or therapeutic) range. Currently, the concentration of many medications is too high following a dose and too low between doses, which can lead to toxicity or ineffectiveness.

Sustained Release



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2:52-5:47

Sustained release

mechanisms were the first attempt to maintain constant drug levels. Here, the drug is released slowly once introduced into the body. For example, a tablet can be covered by a slowly dissolving coating. But, sustained release systems function only for a few hours and are affected by different conditions in the body.

Controlled Release – Ideal Case



4:59-5:49

Controlled release mechanisms more successfully maintain drug levels in the desired range for extended periods of time, even up to five years. These drug delivery techniques primarily use pump or polymer technologies to deliver constant or repeating doses.

Controlled Release Polymeric Systems

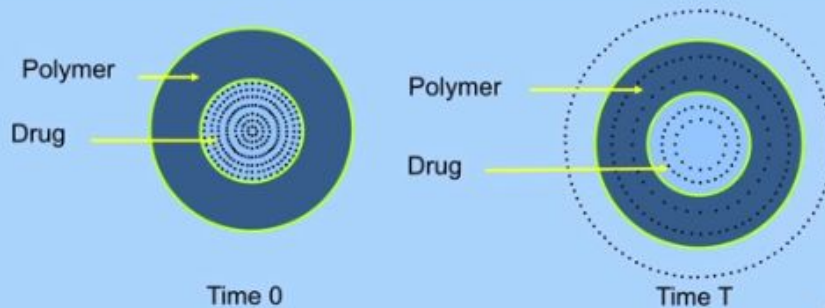
- > Diffusion Controlled
 - ◆ Reservoir Systems
 - ◆ Matrices
- > Chemically Controlled
 - ◆ Bioerodible
 - ◆ Pendant Chain
- > Solvent Controlled
 - ◆ Swelling
 - ◆ Osmosis
- > Externally Activated or Modulated



6:47-37:44

(Overview): The lecture describes controlled release mechanisms. In diffusion controlled systems, drug diffuses from a polymer. Chemical release methods rely on specific reactions. Solvent methods use the flow of water to alter the shape of a drug delivery device leading to drug release. Externally activated systems depend on signals to trigger drug release.

Reservoir System



- > Forms — Capsules, Microcapsules, Hollow Fibers, Membranes
- > Most Commonly Polymers — Silicone, EVA, Hydrogels

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8:10-9:59

The reservoir system uses a drug reservoir encapsulated in permeable polymer. The drug slowly diffuses out of the polymer into the body. A drawback of this system is the possibility of ruptures or leaks, releasing a large dose of drug at once. If the drug is toxic in high doses, this system cannot be used.

Non-Erodible Matrix System

Drug Dispersed in Polymer

Time 0

Drug Dispersed in Polymer

4:09

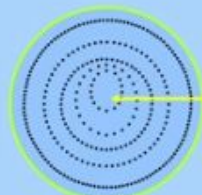
10:34 / 37:44

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10:00-10:54

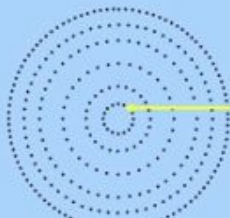
The second diffusion based system is the non-erodible matrix. The drug is dispersed throughout a polymer that permits it to slowly diffuse out through small circuitous openings. This system mitigates the dangers of a leak that are a concern for the reservoir system, since there is no concentrated reservoir of drug. However, release is less consistent.

Bioerodible Matrix System



Time 0

Drug Dispersed in Polymer



Time T

Drug Dispersed in Polymer



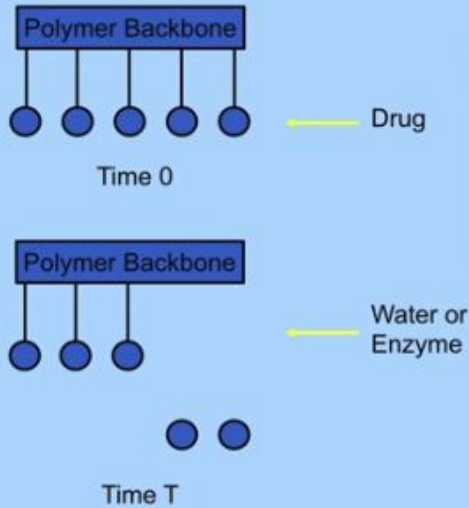
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10:55-11:59

Bioerodible matrix

systems similarly disperse drug throughout a polymer. In contrast to their non-erodible counterparts, this chemically controlled system releases drug contained within the polymer as the polymer degrades. Since it degrades, the polymer does not have to be removed at the completion of treatment.

Polymers with Pendent Drugs



Primary Advantage
> Very high drug loadings

Primary Disadvantage
> New chemical entity

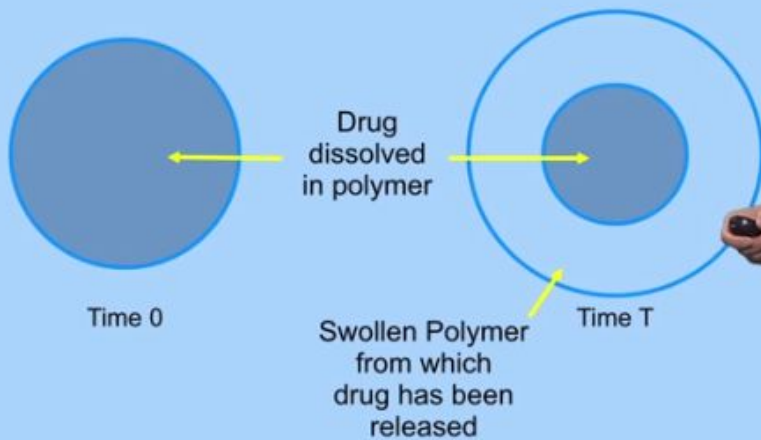


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12:00-12:41

Pendent drugs are another method of chemically controlled drug delivery. Drugs are chemically altered to attach to a polymer backbone. A molecule of drug is released when its pendent is cut by water or an enzyme.

Swelling Controlled Matrix

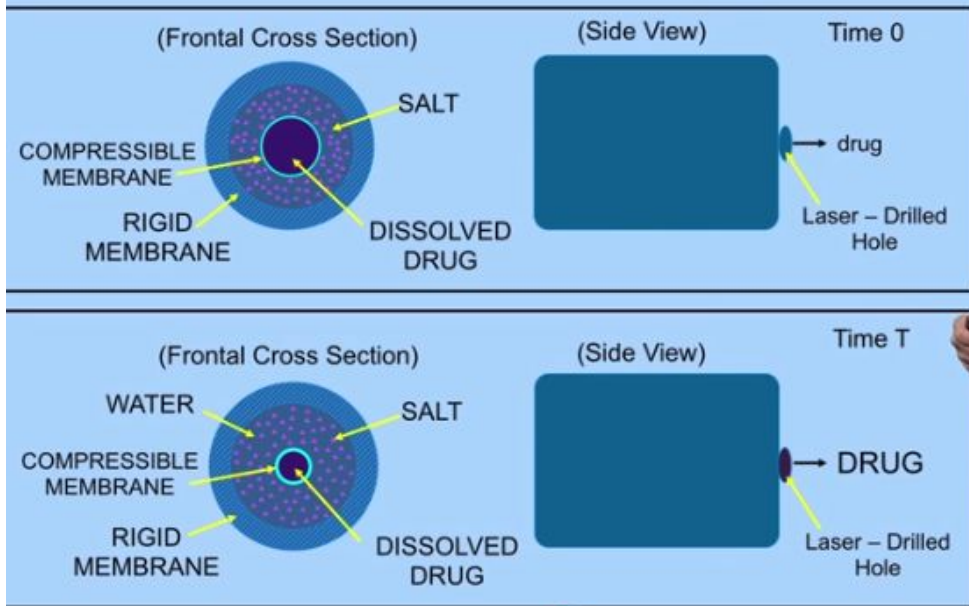


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12:42-13:44

The first solvent controlled system Dr. Langer discusses is the swelling controlled matrix. Like the non-erodible matrix system, drug is dissolved in a non-biodegradable polymer. Drug is released from the polymer as the polymer swells from absorbing water.

Osmotic System



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13:45-19:03

The osmotic pump is also a solvent controlled system. Drug is contained in an inner flexible membrane. There is a salt layer between the inner membrane and an outer rigid water-permeable membrane. Osmotic pressure causes water to pass through the rigid membrane to dilute the salt. This compresses the flexible membrane, forcing drug out of the device through a hole.

Ocular applications

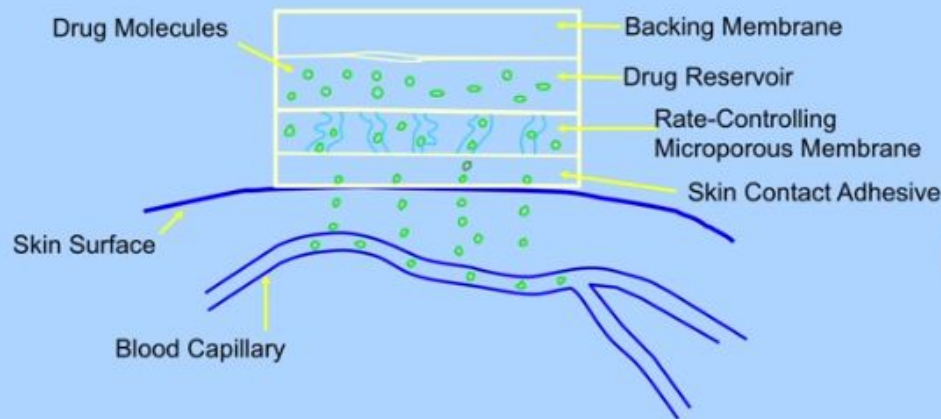
- Glaucoma
- Artificial tears



19:04-30:09

Dr. Langer explains a number of circumstances under which controlled release is used. These include therapies for type II diabetes, schizophrenia, glaucoma, and periodontal and reproductive diseases. Contraceptives, artificial tears, and blood vessel stents also employ controlled release devices.

Transdermal system



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30:10-37:44

Transdermal systems deliver drug through the skin using a diffusion-based reservoir that adheres to the skin in an easy-touse patch. Drug delivery through the skin is a challenge due to the thick layers of lipids and skin cells. This limits the types of drugs that can be delivered transdermally. Fortunately, there are methods to increase the penetration of drug through the skin.

3. Review Questions

1. What is a polymer? How is it used for drug delivery?

2. What are dosage peaks and troughs? Why are they an issue?
3. What is the purpose of using controlled release devices to deliver a drug?
4. Which property of water allows osmotic drug delivery systems to exist?
5. Which controlled drug delivery system is used to treat periodontal disease?
6. How does the transdermal drug delivery system function? What are the factors that are limiting its widespread use for numerous types of drugs? What steps are being taken to overcome these limits?

4. Answers to Review Questions

1. A polymer is a large molecule that consists of many repeating units. Polymers have many applications in drug delivery. They are often used to contain a drug in a reservoir. They can also be used to make matrices that contain drug throughout them. These polymers release the trapped drug by either degrading over time or having the drug escape through small circuitous paths to the surface.
2. (1:15-3:28) Dosage peaks and troughs are when the drug is either above or below its desired concentration range, respectively. The concentration is often too high (peak) soon after taking a drug. This is problematic because a high concentration of certain drugs can have toxic side effects. The drug level will eventually fall into the desired range for a short period of time. This is the range at which the drug will have its desired effects but will not be toxic. Then, the drug will fall to a concentration that is too low (trough) to have the target therapeutic effect.
3. The drug release technologies discussed by Dr. Langer in this lecture attempt to maximize the period of time that the drug's concentration is in the desired range relative to the time at which the level is above or below this therapeutic range. Furthermore, these drug release systems aim to increase the absolute time that drug is being released from a single device, to decrease the frequency at which a drug needs to be taken by a patient.
4. Osmosis is the movement of a solvent across a semipermeable membrane toward a higher concentration of solute, for the purpose of equalizing the concentration of solute on either side of the membrane. In biological systems, the solvent is typically water. To equalize the concentrations of solute on either side of the membrane, the solvent (water) must move since the solute is unable to pass through the membrane.

Water, on the other hand, is smaller and able to pass through the membrane. Drug delivery systems that use osmosis exploit the size difference between solutes and water molecules to design membranes through which only water can diffuse. In drug delivery systems, osmosis is used to create pressure or swelling, causing drug release.

5. (24:30-26:14) Tetracycline is an antibiotic that is used to treat periodontal disease. It has uncomfortable gastrointestinal side effects when taken systemically. Therefore, a local delivery system was ideal. The system originally used consisted of a hollow porous rod filled with a reservoir of drug. The drug would diffuse through the porous polymer. After the occurrence of leaks, a new system was developed. Tetracycline was fused into a non-erodible polymer to create a diffusion-controlled matrix system.
6. (30:10-37:44) The transdermal drug delivery system is a diffusion based system. Drug sits in a reservoir separated from the air by an impermeable membrane. It diffuses through a porous membrane between the reservoir and the skin. The drug passes into the body through the skin. A major limit to delivering drug transdermally is the barrier of the skin, the stratum corneum. It is made up of dead keratinocytes packed tightly together, with thick lipid bilayers acting like grout between cells. Large drug molecules are unable to penetrate this wall. This restricts transdermal delivery to mainly small and lipid-soluble drugs. Various technologies aim to surmount this issue. Physical techniques such as electroporation and ultrasound increase permeation by creating temporary holes in the stratum corneum allowing drug to pass through it. Iontophoresis, another physical technique, uses an electrical field to accelerate the flow of drugs across the barrier. Chemical techniques are also used. One method to increase penetration chemically is to alter the drug to make it more lipid-soluble. Finally, sometimes combining a chemical (a penetration enhancer) with the drug of interest can improve its penetration.

5. Discussion Questions

1. Why is drug delivery design an important field of study for advancing therapeutics?
2. In the last minute of his lecture, Dr. Langer suggests that drug delivery technology is imperative to expand the scope of possible therapeutics to include DNA, RNA, and gene editing. Why is the method of delivery particularly important for these therapeutic options?

3. What are some remaining issues with the drug delivery systems discussed in this lecture?

6. Answers to Discussion Questions

1. There are numerous reasons why drug delivery design is necessary for advancing treatments. Firstly, as discussed at the beginning of Dr. Langer's lecture, advanced drug delivery methods allow for release of drug at a more consistent rate. Furthermore, drugs can be delivered over longer periods of time to decrease the frequency at which drugs must be administered, decreasing treatment burden to improve treatment compliance. Local or targeted delivery reduces side effects that occur from systemic delivery of certain drugs that have toxic effects on physiological systems or cell types other than those they are targeting for treatment. Due to overwhelming side effects, certain drugs with fantastic therapeutic effects are not currently being taken by patients. Targeting these drugs to a particular location or cell type will allow patients to take advantage of these beneficial therapeutics.
2. Nucleic acid therapeutics are promising for their specificity and ability to directly regulate protein sequence and expression in the cell. The main issue with delivery of nucleic acids is that they are not stable in the environment of the body, particularly the blood. Thus, they need to be protected from nucleases until they reach the cell. Nucleic acids also activate the immune system, which may be problematic for vulnerable patient populations. Furthermore, nucleic acids are negatively charged and hydrophilic. This makes it difficult for them to pass through the hydrophobic lipid bilayer to enter the cell. Finally, the effect of DNA, RNA, or gene editing is often robust. Off target effects are unpredictable and may have terrible consequences. Thus, delivery devices for nucleic acids must satisfy a number of challenging criteria (stability, safety, cellular permeation, and specificity) before they are able to be used for therapy. (The answer for this question comes primarily from the following article: Delivery systems for siRNA drug development in cancer therapy. Cong-fei Xu, Jun Wang. Asian Journal of Pharmaceutical Sciences (2015) 10 (1), 1-12.)
3. One present issue with these methods is that they are not targeted toward specific systems, cell types, or organs. For example, these systems would not be able to target tumors as opposed to healthy cells in cancer treatment. An issue with systems that are not biodegradable is that they need to be removed when empty.

7. Questions for Discussion Paper

Near-infrared-actuated devices for remotely controlled drug delivery.

Brian P Timko, Manuel Arruebo, Sahadev A Shankarappa, J B McAlvin, Obiajulu S Okonkwo, Boaz Mizrahi, Cristina F Stefanescu, Leyre Gomez, Jia Zhu, Angela Zhu, Jesus Santamaria, Robert Langer, and Daniel S Kohane.

Proceedings of the National Academy of Sciences (2014) 111, 1349-1354.

1. What is the unfilled need in drug delivery that this paper is attempting to address?
2. How is the drug released from the reservoir in this design?
3. Compare this drug delivery device to injections. Which method for drug delivery is a better treatment for diabetes? Is this true in all instances?
4. How would you change or add to this product in order to apply this concept to another disease or advance its use for diabetes?

8. Answers to Questions for Discussion Paper

1. (Introduction) The controlled drug release technologies currently on the market can release drug either over short or long periods of time. There are even triggered release technologies that can release a burst of drug in response to a stimulus. However, there is not yet a triggered drug release system that can release drug continuously or in repeated doses with clean on-off kinetics. This paper develops a reservoir-based system, where release is controlled by a continuous-wave near-infrared. In this system, release can be either continuous or pulsatile.
2. (Figure 2A and "Membrane Formulation") The drug is maintained in a reservoir. The membrane enclosing the drug is made up of three main components. Gold nanoshells are the first component. They respond to infrared radiation by increasing in temperature. The second component is a thermosensitive polymer mix formed into beads. This polymer reversibly shrinks when exposed to temperatures above body temperature. These two components are dispersed within a water-repellent third component, ethylcellulose. Under normal body temperature, this membrane is impermeable and drug cannot be released. But upon infrared stimulation, the gold nanoshells increase in temperature, heating the membrane, causing the thermosensitive polymer beads to shrink to 1/10th of their size. The area that the

full-sized polymer beads used to occupy becomes pores through which the drug exits the reservoir. As the temperature decreases back to body temperature, the polymer expands again, blocking the drug's escape route.

3. (Figure 5E) The device decreases blood glucose levels at a slower rate than an injection, and the minimum blood glucose level achieved for the device is half of what occurs with an injection. The device also maintains a lower blood glucose level for longer. For typical usage, the device is a better treatment for diabetes as it causes more consistent blood glucose levels. However, unlike an injection, it takes much longer to decrease blood glucose levels – which would be a huge disadvantage in an emergency.
4. This question is intended to be open-ended. Some possible answers are provided here.

While a remote-operated system is a huge advance for the field of diabetes treatment, a patient still needs to monitor their blood glucose levels and remotely activate or inactivate the device accordingly. Ideally, a device would be capable of both of these tasks, eliminating the burden put on the patient. This device could sense blood glucose levels, and then automatically open or close the drug reservoirs entirely without the patient's involvement. It would be as if there was a fully functioning pancreas just underneath the patient's skin.

Other answers could include decreasing leak release, or decreasing irradiation power needed to open the reservoir, among others.