

The Use of Controlled Release Technology in Drug Delivery

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Since its humble beginnings with Edward Jenner's injection of smallpox lesions into patients to prevent the deadly disease in Europe and America, medicine has made great new strides towards disease control and prevention. The science of vaccination in particular has adapted biotechnological advances to produce vaccines that are efficacious and safe. In addition, advances in the fields of protein sequencing and genetic engineering have allowed protein therapeutics to become much more specific and precise in their mode of action. There are hundreds of protein therapeutics in development, with many currently in advanced stages of clinical testing. Due to their critical role in cellular functions, it is likely that these therapeutic proteins will be produced at an increased rate in the future.

Peptides and proteins range in molecular weight from 300 to 1,000,000. These proteins are comprised of long chains of amino acids. Proteins themselves are amphoteric (that is, they may have either a positive or a negative charge) hydrophilic polyelectrolytes that attain their weak ionic properties from the acidic and basic properties of the side chains of the constituent amino acids. As a result, their net charge can vary significantly. These properties allow the protein to be highly specific in their actions and thus have few side effects; in addition, they are very effective in low doses. A number of commercially available protein drugs and others going through clinical trial are shown in Table 1.

Proteins have many attractive properties. Unfortunately, they also have some disadvantages that may limit their clinical use. The short in vivo half lives and low oral bioavailability of proteins have resulted in frequent injections.¹ These injections are costly, painful, and inconvenient, resulting in

Table 1:Kydonieus, A. Treatise on Controlled Drug Delivery: Fundamentals, Optimization, Applications. 1992, New York, NY

Table 1: Examples of Peptide and Protein Drugs and Their Pharmaceutical Use		
Drug	Molec. Weight	Pharmaceutical Use
Human Insulin	6000	Blood Glucose Regulation
Interleukin 2	15000	Antiviral
Human interferon	20000	Immunoregulation
Tumor necrosis factor	-----	Treatment of Cancer
Epidermal growth factor	6200	Wound healing

poor patient compliance and an oscillating drug concentration in the blood. Bringing all of this together, it is clear that all of these problems can be circumvented through the use of some sort of controlled release technology.

Before continuing, it is important to answer a fundamental question: What is controlled release technology? Controlled release products provide prolonged delivery of a drug while maintaining its blood concentration within therapeutic limits. It is a relatively new field, and, as a result, research in the field has been extremely fertile and has produced many discoveries. Traditionally, the most popular form of drug delivery has been injection and ingestion in tabular form. The justification for a controlled release dosage form over a conventional tablet is either to circumvent problems in drug absorption or metabolism, or to optimize therapy itself. The variety of routes available for drug delivery corresponds to the list of biological membranes in the human body: nasal, gastrointestinal tract, the eye, skin, and even the vaginal mucosa. To this list should be added implants and targeted delivery.

Here at MIT, in the Langer lab, targeted delivery has been studied extensively. One method, specifically, that has become widespread is the microencapsulation of proteins. These proteins are made in injectable depot formulations and are released over time from microspheres. It may be necessary to clarify that the best way to think of these microspheres is to think of a bar of soap randomly containing sand particles within it. The sand particles are the protein and the soap is the polymer. The sand resides in little pockets called micropores or microspheres. The advantage of this method of delivery over the injectable solution form is that the protein is administered less frequently, is protected from degradation, and can be delivered to specific sites. In addition, these systems allow for the dose and release rates to be varied by changing the parameters of the system itself.

By releasing small amounts of macromolecules over sustained periods of days and even

years, polymeric controlled-release systems greatly improve the effect of the proteins. As the microsphere degrades, the protein is released by desorption and diffusion. Desorption is assumed to originate with protein that is initially contained on the sphere surface and in mesopores connected to the outside surface of the microsphere. In contrast, protein diffusion is delayed by a period of time that is determined by how long it takes the micropores to coalesce and the pro-

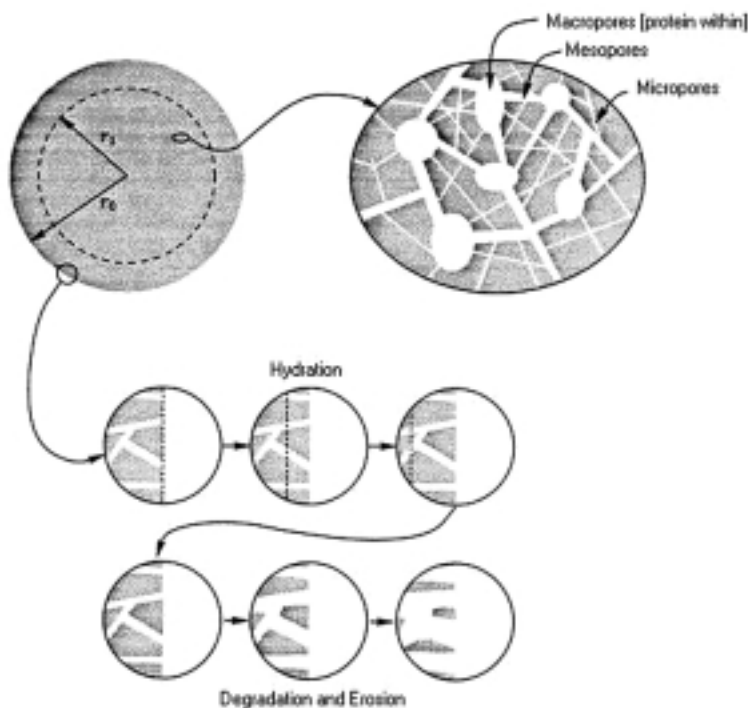


Figure 1: A microsphere with radius r going through hydration, degradation, and erosion.

Figure 1: Langer, R., A Theoretical Model of erosion and Macromolecular Drug Release from Biodegrading Microspheres, J. Pharm. Sci., 86(12), 1464 (1997)

tein to pass out of the inner portions of the macropores, forming the polymeric matrix as water makes contact with the protein, causing it to degrade.² (See Figure 1.) The aforementioned mechanism of action was supported by multiple studies, one of which incorporated electron paramagnetic resonance (EPR) spectroscopy and magnetic resonance imaging (MRI).³ This study focused on attempting to shed light on the proposed mechanism of degradation and erosion in vivo and in vitro. The MRI was used to monitor water content, tablet shape, and response of the biological system such as encapsulation. EPR helped to show that diffusion of solubilized drug molecules inside the delivery system prior to their release is an important factor as well. This study indicated that erosion occurs by the mechanism outlined above in vivo and in vitro.

The very first polymeric controlled-release delivery vaccination systems were developed

merely to use a polymer matrix to achieve a desired release profile. Subsequent efforts reduced the size of the spheres from millimeters to microns and used bioerodible polymers like poly(lactic-glycolic acid) (PLGA). (See Figure 2.) For example, Eldridge used a PLGA microsphere system for staphylococcal enterotoxin B toxoid. In this system the group used both small (1–10 m) and larger (20–50 m) particles together to produce a large immune response.⁴ When the small and large particles were tested individually, a significantly smaller immune response was detected, leading to the rationale that smaller particles were taken up by macrophages to generate the immune response. In contrast, the larger spheres, which cannot be phagocytosed, illicit a long-term response because they release their encapsulated material much slower. In another study, a pulsatile release pattern was attained with a single injection using tetanus toxoid.⁵ These two cases clearly indicate the ability to control response to a satisfactory level and help to

illustrate the promise of controlled release methods in the future.

In order to ensure the success of this method of controlled drug delivery, there are several obvious problems that have to be overcome. The stability of the protein is a limiting factor. A stable protein is needed prior to approval for

clinical use. A protein is suitable if it remains stable during three different stages: 1) during the purification and storage of finished product; 2) encapsulation; and 3) administration in vivo. Another concern is site-specific delivery. However, it should be noted that within the last decade great advances have been made in this field. Various polymers have been bound to portions of toxoids, such as tetanus toxin fragment C, to allow for site-specific delivery. One challenge for the future may be to bind microspheres to some toxoid fragment or other carrier and deliver the encapsulated protein to a specific part of the body.

Suggested Readings

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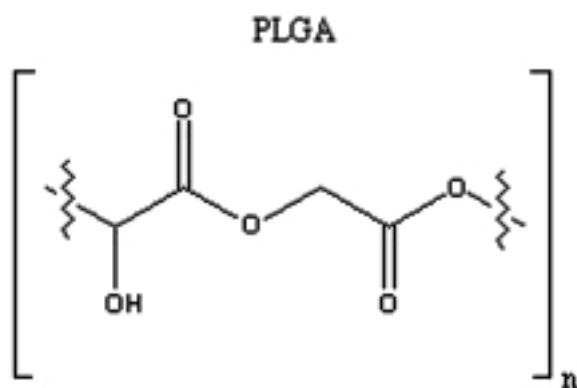


Figure 2