Past, Present, and Future Technologies for Oral Delivery of Therapeutic Proteins

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ABSTRACT: Biological drugs are usually complex proteins and cannot be orally delivered due to problems related to degradation in the acidic and protease-rich environment of the gastrointestinal (GI) tract. The high molecular weight of these drugs often results in poor absorption into the periphery when administered orally. The most common route of administration for these therapeutic proteins is injection. Most of these proteins have short serum half-lives and need to be administered frequently or in high doses to be effective. So, difficulties in the administration of protein-based drugs provides the motivation for developing drug delivery systems (DDSs) capable of maintaining therapeutic drug levels without side effects as well as traversing the deleterious mucosal environment. Employing a polymer as an entrapment matrix is a common feature among the different types of systems currently being pursued for protein delivery. Protein release from these matrices can occur through various mechanisms, such as diffusion through or erosion of the polymer matrix, and sometimes a combination of both. Encapsulation of proteins in liposomes has also been a widely investigated technology for protein delivery. All of these systems have merit and our worthy of pursuit. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:2497–2523, 2008

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INTRODUCTION

Proteins perform many important physiological and biological processes of the host. Protein ligands bind their receptors that result in actions or changes due to sometime distant signals. Enzymes are involved in many biotransformational reactions or *de novo* generation or catalysis of a multitude of substrates. Antibodies can actively participate in neutralizing toxins or host factors (e.g., TNF-α). The knowledge and translation of the human genome, has greatly increased the desire to discover new proteins and understand their function, usefulness as a therapy as well as to devise drug delivery systems (DDSs) for these molecules. While designing novel DDSs is not essential for successful and efficacious protein drug delivery, effective DDSs would enable these therapeutic proteins to be delivered via mucosal routes to increase efficacy and patient compliance

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as well as reduce medical errors in administration (e.g., intravenous delivery).

DDSs should be designed to reduce adverse reactions while achieving site-specific delivery, convenient administration, improved patient compliance, and increase product shelf-life. Over the past few decades, interest in developing effective DDSs for biologicals has grown considerably as the number of recombinant proteins being investigated for therapeutic applications has increased.[1] Success of these new therapeutics hinges on efficient DDSs that allow drug access to their target site(s) at the right time, duration and dose. Four factors must be considered to create these conditions: route of administration, drug release pattern, delivery method, and fabrication/formulation.

Unfortunately, most protein drugs are therapeutically useful only when a regimen requiring multiple injections is followed without tissue targeting (Fig. 1). Such therapies are frequently administered under close medical supervision. This necessitates novel technologies to refine and control therapeutic protein delivery. In addition, the biochemical and structural complexity of proteins compared to conventional drug-based pharmaceuticals makes formulations design for biologicals a formidable task. In this regard, the development and evaluation of effective DDSs for therapeutic proteins must consider the biophysical, biochemical, and physiological characteristics of proteins, including their molecular size, biological half-life, immunogenicity, conformational stability, dose requirement, site and rate of administration, pharmacokinetics, and pharmacodynamics.[2]

Several technologies have been used to deliver complex molecules. Although the concepts of microencapsulation and sustained release are well established, the convergence of these concepts and their applications to control release from polymeric microspheres occurred <15 years ago. Somatostatin encapsulation in poly-lactic glycolic acid (PLGA) microspheres and thyroid releasing hormone microspheres were successfully prepared by spray drying techniques.[3,4]

Microparticles comprised of biodegradable and non-biodegradable polymers have been investigated for sustained release. Non-biodegradable polymers pose problems of toxicity, ease of removal or degradation and achieving a constant rate of release.[5] To overcome some of these problems investigations into biodegradable polymers for sustained release and the development of parenteral DDSs began in the early 1970s. Yolles et al.[6] was one of the first to report the use of polypeptides in parenteral DDSs. These methods were developed for two reasons. Surgery was required to remove drug-depleted DDSs made with non-biodegradable polymers since non-removal posed toxicological problems. Second, diffusion-controlled systems, although an excellent means of achieving predetermined rates of drug delivery, were limited by polymer permeability and drug characteristics. With the basic mechanism of non-biodegradable devices being diffusion, drugs having either a high molecular weight (>7500 Da) or poor polymer solubility are not amenable to classic diffusion-controlled release.

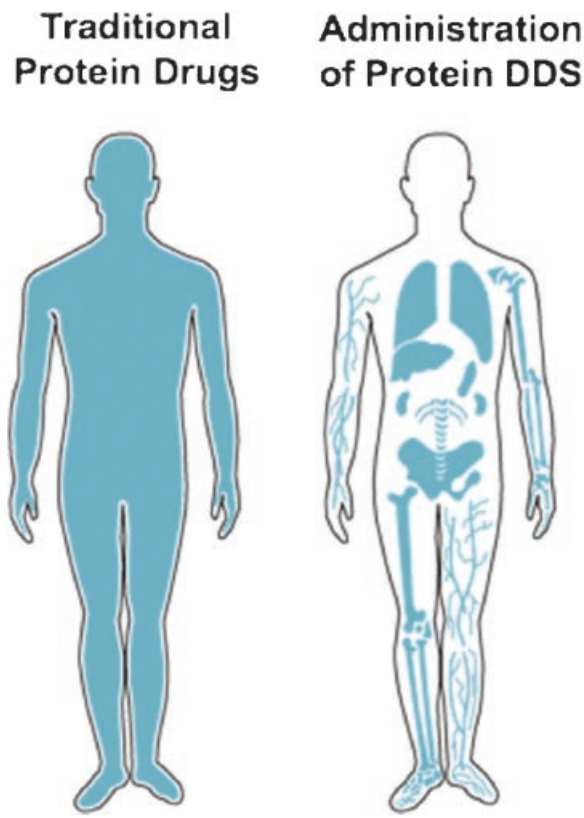

Figure 1. Protein drug delivery. An ideal oral protein drug delivery system (DDS) should provide multi-functionality for targeting and controlled release. This in turn will yield improved therapeutic drug index, lower toxicity, and targeted delivery of protein drugs in a site-specific fashion by multiple routes of administration, including *per os*.

In the last decade, there have been major advancements using biodegradable polymers. The most notable is for prostate cancer treatment, where a single (once-a-month) injection has replaced 30 daily injections of luteinizing hormone-releasing hormone agonist. Additional promis-

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