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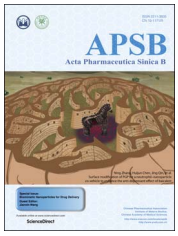

REVIEW

# Designing the new generation of intelligent biocompatible carriers for protein and peptide delivery

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**Abstract** Therapeutic proteins and peptides have revolutionized treatment for a number of diseases, and the expected increase in macromolecule-based therapies brings a new set of challenges for the pharmaceutics field. Due to their poor stability, large molecular weight, and poor transport properties, therapeutic proteins and peptides are predominantly limited to parenteral administration. The short serum half-lives typically require frequent injections to maintain an effective dose, and patient compliance is a growing issue as therapeutic protein treatments become more widely available. A number of studies have underscored the relationship of subcutaneous injections with patient non-adherence, estimating that over half of insulin-dependent adults intentionally skip injections. The development of oral formulations has the potential to address some issues associated with non-adherence including the interference with daily activities, embarrassment, and injection pain. Oral delivery can also help to eliminate the adverse effects and scar tissue buildup associated with repeated injections. However, there are several major challenges associated with oral delivery of proteins and peptides, such as the instability in the gastrointestinal (GI) tract, low permeability, and a narrow absorption window in the intestine. This review provides a detailed overview of the oral delivery route and associated challenges. Recent advances in formulation and drug

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delivery technologies to enhance bioavailability are discussed, including the co-administration of compounds to alter conditions in the GI tract, the modification of the macromolecule physicochemical properties, and the use of improved targeted and controlled release carriers.



## 1. Introduction

Since the entrance of insulin as the first FDA-approved commercially available recombinant protein drug in 1982, protein and peptide drugs have become one of the fastest growing classes of new therapeutics. Because of the size and their stability, protein and peptide drugs are typically administered *via* injection. Most have short serum half-lives and, thus, need to be administered frequently or in high doses to be effective.

Alternative methods of administration which do not require injection or intravenous access are highly desirable. The oral route is the most desirable administration method for drugs as it is easy for patients and does not require injection. However, there are several significant challenges to the successful development of oral protein drug formulations: the instability of protein drugs in the gastrointestinal (GI) tract, the low permeability of protein drugs, and a narrow absorption window in the intestine. The activity of the therapeutic must be retained through the GI tract, and the active drug must reach the bloodstream at levels high enough to provide therapeutic efficacy. An oral delivery system must protect the drug from acid and enzymes in the stomach, but release the protein in the neutral environment of the small or large intestine.

This review is divided into six major sections to review the motivation, approach, and materials studied in literature to enable the oral delivery of therapeutic proteins and peptides. Detailed overviews of the oral delivery route, mechanisms, associated advantages, and major challenges are provided. Recent advances in formulation and drug delivery technologies to enhance bioavailability are discussed, including the co-administration of compounds to alter conditions in the GI tract, the modification of the macromolecule physicochemical properties, and the use of improved targeted and controlled release carriers.

## 2. Protein and peptide therapeutics

Protein and peptide drugs have become the fastest growing class of new pharmaceutics since the FDA approval of recombinant insulin in 1982. The field of protein and peptide therapeutics has experienced tremendous growth (Fig. 1) in part due to recombinant biotechnology but also the inherent advantages over small drugs. Proteins carry out complex functions, interact with biomolecules specifically with reduced risk of side effects, and have low immunogenicity[1].

The first accounts of protein drugs in the treatment of diseases were in the form of tissue extracts. For example, the first protein-based vaccine was developed in 1796 for small pox by Jenner using extracts from cowpox blisters of milkmaids. Over a century later in 1922, the first protein drug, insulin, was discovered by Banting et al.[2] in treatment of diabetes in humans with pancreatic extracts from dog. A method for extraction of pure insulin from bovine pancreas extracts was later developed. The safety, quantity, and activity of these insulin extracts were determined by quantifying its effects on rabbit blood glucose levels. Manufacturing of insulin by synthetic chemical means was made possible by the work of Fred Sanger on sequencing insulin during the mid-1940s and -1950s.

It was not until the 1970s that the foundation for modern protein therapeutic production and engineering was established. In 1977, somatostatin was the first protein to be cloned into *Escherichia coli* by insertion of the somatostatin gene into the pBR322 plasmid[3]. A year later, the first recombinant protein, insulin, was reported by Genentech. Goeddel et al.[4] synthesized insulin from two separately cloned polypeptide chains demonstrating for the first time synthetic recombinant technology to produce a therapeutic protein. Over the next decade, protein therapeutics including human growth hormone and interferon-$\alpha$ were reported. Meanwhile, several other major breakthroughs notably the discovery of polymerase chain reactions (PCR) for DNA amplification and the development of chemical DNA sequencing methods transformed biotechnology. These technologies along with the 1982 FDA approval of the recombinant form of insulin set the stage for protein drug development.

Recombinant DNA technology has had a significant impact on the discovery of new drugs but has also contributed to the safety and efficacy of protein drugs. For example, recombinant production of protein drugs reduced supply and immunological issues associated with protein drugs, which were previously harvested, then purified from blood or tissues. Moreover, protein engineering has led to improved drug half-lives and activity over native forms. The impact of biotechnology is already apparent in the more than 130 protein drugs approved by the Food and Drug Administration (FDA)[1]. Protein-based pharmaceutics are expected to continue to expand. It is estimated that by 2015 the protein drug market will exceed $150 billion US dollars (Global Industry Analysts, Inc.).

## 3. Advantages and challenges to oral delivery

While protein drugs have revolutionized treatment for a number of diseases, the expected increase in protein-based pharmaceutics brings a new set of challenges for the pharmaceutics field. Due to their instability, size, and poor transport, therapeutic proteins are predominantly administered by either intravenous or subcutaneous injection. Patient compliance, the extent to which a patient adheres to the treatment, is already a huge issue in diabetes treatment with insulin and is likely to become a growing issue as protein drug treatments become more widely used. A number of studies have underscored the relationship of traditional subcutaneous injections with patient non-adherence, and it is estimated that over half of insulin-dependent adults intentionally skip injections[5,6].

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