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REVIEW

# A review on the strategies for oral delivery of proteins and peptides and their clinical perspectives

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**Abstract** In the modern world, a number of therapeutic proteins such as vaccines, antigens, and hormones are being developed utilizing different sophisticated biotechnological techniques like recombinant DNA technology and protein purification. However, the major glitches in the optimal utilization of therapeutic proteins and peptides by the oral route are their extensive hepatic first-pass metabolism, degradation in the gastrointestinal tract (presence of enzymes and pH-dependent factors), large molecular size and poor permeation. These problems can be overcome by adopting techniques such as chemical transformation of protein structures, enzyme inhibitors, mucoadhesive polymers and permeation enhancers. Being invasive, parenteral route is inconvenient for the administration of protein and peptides, several research endeavors have been undertaken to formulate a better delivery system for proteins and peptides with major emphasis on non-invasive routes such as oral, transdermal, vaginal, rectal, pulmonary and intrauterine. This review article emphasizes on the recent advancements made in the delivery of protein and peptides by a non-invasive (*peroral*) route into the body.



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**Contents**



## 1. Introduction

Proteins and peptides are the building blocks of life and are now evolving as a very promising brand of therapeutic entities. Once a rarely used subset of medical treatments, therapeutic proteins have increased dramatically in number and frequency of use since the introduction of first recombinant protein therapeutic viz. human insulin, 25 years ago. Therapeutic proteins and peptides hold a significant role in almost every field of medicine, but this role is still only in its infancy. The foundation for the popularity of protein therapeutics was laid down with the regulatory approval of recombinant insulin by the US Food and Drug Administration (FDA) in 1982, which became the first commercially-available recombinant protein and a source of major therapy for patients suffering from diabetes mellitus (Leader et al., 2008). Three decades have passed since the inauguration of approval of first recombinant protein i.e. insulin by the FDA, and its clinical success has inspired the field of therapeutic proteins into a wider horizon ever since, with more than 130 different proteins or peptides already approved for clinical use by the FDA till 2008 alone, and many more in the development pipeline.

A better understanding of molecular biology and biochemistry behind the macromolecular endogenous proteins, peptides and peptidergic molecules, and their role in various body functions and pathological conditions has led to the realization of the enormous therapeutic potential of proteins and peptides in the last few decades. Consequently, a variety of new therapeutic proteins have been developed showing therapeutic benefits in the treatment of ailments like diabetes, cancer which offer several advantages over the conventional small-molecule drugs. Firstly, proteins often serve a highly specific and complex set of functions in the body that cannot be mimicked by simple chemical compounds. Secondly, since the action of proteins is highly specific, there is often less potential for therapeutic protein to interfere with normal biological processes and cause adverse effects. Thirdly, because the body naturally produces many of the proteins that are used for therapeutic purpose, these agents are often well-tolerated and are less likely to elicit immune responses. Fourthly, for diseases in which a gene is mutated or deleted, protein therapeutics can provide an effective replacement for the treatment without the need for gene therapy, which is not currently available for most genetic disorders. Fifthly, the clinical development and FDA approval time of protein therapeutics may be faster than that of small-molecule drugs. A study published in 2003 showed that the average clinical development and approval time was more than one year faster for 33 protein therapeutics approved between 1980 and 2002 than for 294 small-molecule drugs approved during the same time period. Lastly, because proteins are unique in form and function, companies are able to obtain far-reaching patent protection for protein therapeutics. The last two advantages make proteins