

# ORAL DELIVERY OF MACROMOLECULES FOR THE DEVELOPMENT OF THERAPEUTIC AGENTS

HYE J. LEE AND CHANMI CHOI

*Hopkins Bio Research Center, Co., Seoul, South Korea*

## 1 INTRODUCTION

Oral delivery of macromolecules as therapeutic agents is still an unthinkable project for pharmaceutical scientists. However, considering the fact that developing peptides and proteins (major macromolecules) as medicines was also a mission impossible not too long ago, delivering macromolecules orally could not be just dreaming. Currently, over 160 protein-based therapeutics are available on the U.S. market and about 400 compounds are being developed [1]. Expenditures in the protein therapeutics market are predicted to continue to expand by 15–20% annually [2]. This is astonishing progress and could be attributed to the tremendous advances in recombinant DNA (deoxyribonucleic acid) techniques and biotechnologies. The dosage forms for peptide and protein drugs rely on their parenteral injection, which requires frequent administration, and are urging the development of more convenient dosage forms for non-invasive administration. An oral dosage form is the most preferable route because of the accompanying advantages of patient comfort, ease of administration, decreased medical costs, and increased patient compliance. Significant efforts in academic and commercial laboratories have been expended, but major breakthroughs in oral peptide and protein formulation achieving predictable and reproducible drug profiles in therapeutic doses without wasting up to 99% of the drug have not been achieved yet. The major barriers to developing oral formulations for peptides and proteins

include poor intrinsic permeability, luminal and cellular enzymatic degradation, rapid clearance, and chemical and conformational stability [3]. Conventional approaches to address these barriers have not readily translated into effective peptide and protein formulations [4].

This review will provide an overview of the existing approaches, the recent advances that have been made in oral delivery as related to proteins, and some future directions to consider followed by reviewing factors affecting oral protein absorption. It is likely that effective oral formulations for peptides and proteins will remain highly compound specific, but the principal concept into preserve protein integrity before its reaches systemic circulation.

## 2 FACTORS AFFECTING ORAL PROTEIN ABSORPTION

Mechanisms of the absorption of peptides and proteins by epithelial cells are well described by Goldberg and Gomez-Orellana [5]. The process of receptor-mediated or non-receptor-mediated endocytosis (also called pinocytosis, when the material taken up is entirely soluble) is the most likely route of uptake and possible translocation of an orally administered therapeutic protein. Recent findings on many transporters add a transporter-mediated uptake as a possible absorption mechanism for proteins in addition to the paracellular absorption