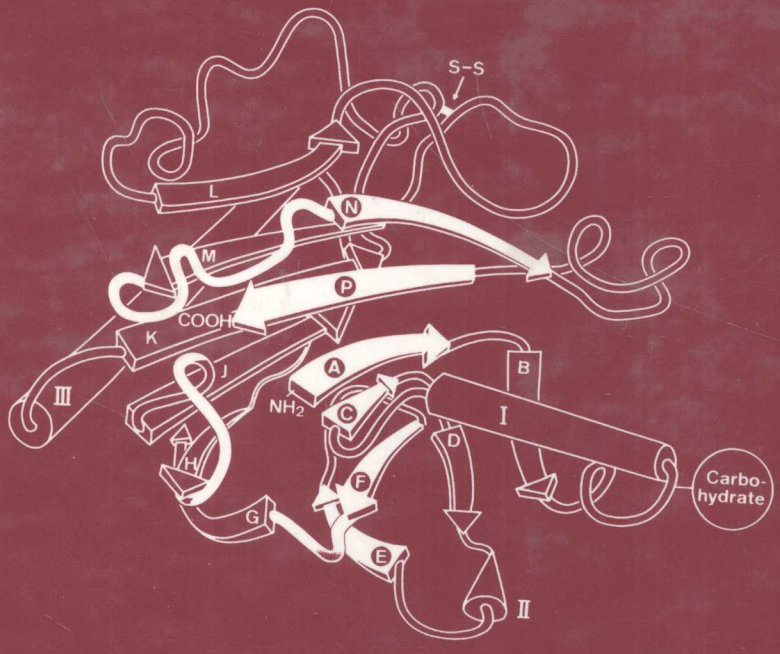
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 84

Pharmaceutical Enzymes



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Pharmaceutical Enzymes

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Preface

Almost two decades have passed since the second edition of *Pharmaceutical Enzymes* was published in 1978. In fact, the need for such a volume never waned; the book was out of print a few years after its initial publication. Since that time, there has not been any monograph or book covering the field. Thanks to continuing demand by many colleagues in industry and academia, we decided to compile an entirely new edition. The scope of pharmaceutical enzymology has expanded over a broad spectrum of scientific fields, and this book is a reflection of these advances. Of paramount importance was the need to tackle the subject in an interdisciplinary fashion so as to appeal to researchers active in drug companies, universities, and pharmaceutical regulatory affairs as well as graduate students and professionals in pharmaceutical sciences and medicine.

Molecular and biochemical data concerning pharmaceutical enzymes are presented together with robust methods of measurement and evaluation, and when relevant information is known, emphasis is placed on pharmacology and clinical impact. Special attention is given to practical, often previously unpublished background information and material not readily found in standard textbooks and other reference works.

This book consists of 15 chapters and is divided into four major sections. Part One addresses the actual knowledge of bioavailability of pharmaceutical enzymes. Part Two presents the spectrum of different chemical approaches for tailoring enzymes to improve therapeutic effectiveness. It features a stepwise and practical guide to molecular modeling of important pharmaceutical targets, including flowcharts, examples, and references to further sources of information in databases and the literature.

Part Three reviews representative multienzyme compositions, such as pancreatin, as well as promising recent developments with glucocerebrosidase, deoxyribonuclease and protein inhibitors of elastase. This part integrates biochemical, experimental, and clinical data of therapeutic enzymes, such as asparaginase, bromelain, hyaluronidase, and cysteine proteinases, about which

pharmaceutical information in a pharmaceutical context is rarely available in the literature.

The last part brings together a completely updated and elaborate description of the methods of assay of pharmaceutical enzymes, reflecting the output of sustained collaborative work between universities and industries in the framework of the Commission on Pharmaceutical Enzymes of the Fédération International Pharmaceutique during the last two decades.

As editors, we owe thanks to many for advice, encouragement, and help: first to the contributors, for sharing their expertise; to many colleagues around the world, for their willing cooperation and extensive collaborative work in the development of the methodological aspects of this volume; to the former and present members of the International Commission on Pharmaceutical Enzymes, for their continuous support during more than three decades; to Dr. M. van Sande, for being a constant source of support throughout the writing of the book; to Ms. L. Pelosi, M. Snoeckx and K. Wullsert for excellent assistance during the production of this book.

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Biopharmaceutical Aspects of Enzyme Absorption

Joseph Demeester
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I. INTRODUCTION

Enzymes as therapeutic products are not only very diverse but also very complex. They are proteins, a large group of pharmacologically active molecules that also includes monoclonal antibodies, cytokines, growth factors, hemostatic and thrombostatic agents, and vaccines.

Problems in the therapeutic application of proteins are caused by host contaminants, species specificity, cross-reactivity, immunogenicity, and the difficulty of targeting the right location in the human body. Moreover, the rate at which proteins reach the plasma compartment depends upon the route of administration: intravenous or subcutaneous injection and sometimes pulmonary delivery.

The gastrointestinal tract is the most appropriate route for drug delivery. However, for enzymes, other proteins, and peptides, this way of administration is a new challenge for many research groups. Indeed, the parenteral route is often the preferred one for protein and peptide administration. Despite current opinion that the gut is completely impermeable to proteins and peptides, progress has recently been made in the elucidation of possible routes of penetration through the intestinal barriers. There is now evidence that small quantities of peptides and proteins can be absorbed intact from the gut.

This chapter will discuss some biopharmaceutical aspects of enzyme absorption, although most studies have been performed using other proteins or peptides. Small molecules are predominantly metabolized in the liver, but proteins and peptides are degraded by enzymes present in most compartments of the body.

II. GASTROINTESTINAL PATHWAYS FOR DRUGS

A. Oral Cavity

The oral cavity has little importance in the liberation of most drugs. Mastication mainly causes mechanical destruction and size reduction. A salivary volume of about 0.5–1.5 L, a pH of 6, and a surface tension of 15–20 mN/m are important factors for drug delivery; the membrane surface pH is 6.7. No peptide bond–splitting enzymes are present.

In optimizing peptide or protein delivery, buccal administration is sometimes preferred. The buccal membrane is a stratified squamous epithelium, and the intercellular spaces are filled by cellular extrusion products.

B. Esophagus

The esophagus has a pH of 5–6, and its absorptive capacity is negligible.

C. Stomach

Epithelial cells secrete hydrogen carbonate ions, which have a cytoprotective action. They neutralize the hydrochloric acid secreted by the parietal cells (about 0.87 M) in the mucus layer, creating a neutral to slightly alkaline pH at the stomach wall. About 2–3 L of fluid are produced per day with a pH of about 0.8–2.0. After food intake, the pH rises to about 4–5, but further gastric secretion restores a strongly acid pH within 30–45 minutes [1]. In about 40% of patients above 65 years old, achlorhydria is observed, which increases the pH. In neonati, the pH is neutral to slightly alkaline. The acidic conditions denature protein molecules, exposing them to hydrolysis by endogenous pepsin, which is an endopeptidase unable to cause complete proteolysis. It is an aspartic proteinase that is most active at pH 2–3 and inactivated at pH above 5. Very large polypeptides with molecular weights of several thousand are mainly formed that are not absorbed in the stomach. This inactivation can be reduced by administration of antacids, such as sodium hydrogen carbonate, or by H_2-receptor antagonists such as Cimetidine®. The administration of pepsin-containing drugs improves food digestion. Other enzyme preparations are often administrated using coatings that resist stomach fluid.

D. Stomach Emptying

How long drugs stay in the stomach can influence their bioavailability. Rapid stomach transit can be achieved by administrating the drug in a large volume of liquid that is warm, isotonic, and slightly alkaline and that is taken ambulatory on