DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 105

Oral Drug Absorption

Prediction and Assessment

edited by
Jennifer B. Dressman
Hans Lennernäs

Oral Drug Absorption

Prediction and Assessment

edited by

Jennifer B. Dressman

Institute of Pharmaceutical Technology
Johann Wolfgang Goethe University
Frankfurt on Main, Germany

Hans Lennernäs

Biopharmaceutics Group
Department of Pharmacy
Uppsala University
Uppsala, Sweden

MARCEL DEKKER, INC. NEW YORK • BASEL

ISBN: 0-8247-0272-7

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-261-8482; fax: 41-61-261-8896

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

1

Gastrointestinal Transit and Drug Absorption

Clive G. Wilson
Strathclyde Institute for Biomedical Sciences, University of Strathclyde, Glasgow, Scotland, United Kingdom

I. INTRODUCTION

The human gut has evolved over many thousands of years to provide an efficient system for the extraction of nutrients from a varied diet. Functionally, the gut is divided into a preparative and primary storage region (mouth and stomach), a secretory and absorptive region (the midgut), a water reclamation system (ascending colon), and finally, a waste-product storage system (the descending and sigmoid colon regions and the rectum). The organization of the upper gut facilitates the controlled presentation of calories to the systemic circulation allowing the replete person to perform physical work, to undergo social activities, and to go to sleep. In spite of this wondrous organization it is still necessary, or at least desirable, in a modern lifestyle to take three meals a day. On the other hand, most of us wish to take our medications only once a day.

Although the human race has relied on medicines for an indeterminate number of years, the physiology of the digestive process is less than convenient for the efficient absorption of many of the modern therapeutic entities we wish to administer. The influence of feeding and temporal patterns on gastrointestinal transit, therefore, is of great relevance in attempting to optimize drug absorption. In this chapter, we will consider how data from recent experiments might have an influence on how we think about dosing issues.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

We will start with swallowing a medicine and finish with transit through the large intestine.

II. ESOPHAGEAL TRANSIT

After the dosage form leaves the buccal cavity, which is a relatively benign environment, transit through the esophagus is normally complete within 5–15 s, depending on posture. It has been known for many years that disorders of normal motility (dysphagia), left-sided heart enlargement, or stricture of the esophagus can result in impaired clearance of formulations. In some cases this can lead to damage of the esophageal wall. The elderly have a decreased ability to swallow large dosage forms, a phenomenon that may be related to the loss of secondary peristaltic mechanisms. Impairment of the ability to swallow with advancing age has been identified as a major health care problem in an aging population. Radiological studies of an asymptomatic group of 56 patients, mean age 83 years, showed that a normal pattern of deglutition was present in only 16% of individuals (1). Oral abnormalities, which included difficulty in controlling and delivering a bolus to the esophagus following ingestion were noted in 63% of cases. Structural abnormalities capable of causing esophageal dysphagia include neoplasms, strictures, and diverticula, although several workers have commented that only minor changes of structure and function are associated with aging. The difficulty, therefore, appears to relate to neurological mechanisms associated with the coordination of tongue, oropharynx, and upper esophagus during a swallow.

In scintigraphic studies of transit rates of hard gelatin capsules and tablets, elderly subjects were frequently unable to clear the capsules (2,3). This appears to be due to the separation of the bolus of water and capsule in the oropharynx, resulting in a ''dry'' swallow. As a result, capsule adherence occurred in the lower third of the esophagus. In this region, adherence is not sensorially detected: subjects were unaware of sticking. The importance of buoyancy in capsule formulation has hitherto been ignored and may be an additional risk factor in dosing the elderly.

III. GASTRIC RETENTION

Our understanding of the behavior of dosage forms in the stomach has been gained largely from scintigraphic studies in which phases of a meal and formulations are labeled with different radionuclides, particularly technetium-99m

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.