

fourth edition



{LEON SHARGEL / ANDREW B.C. YU}

R M Find authenticated court documents without watermarks at <u>docketalarm.com</u>.

APPLIED Biopharmaceutics &Pharmacokinetics

fourth edition

Leon Shargel, PhD Vice President and Technical Director National Association of Pharmaceutical Manufacturers Ronkonkoma, New York

Adjunct Associate Professor School of Pharmacy University of Maryland Baltimore, Maryland

Andrew Yu, PhD Associate Professor of Pharmaceutics Albany College of Pharmacy Albany, New York*

*Present affiliation HFD-520 CDER, FDA, Rockville, MD. (The contents of this book reflect the personal views of the authors and not that of the FDA.)

McGraw-Hill Medical Publishing Division

New York St. Louis San Francisco Auckland Bogotá Caracas Lisbon London Madrid Mexico City Milan Montreal New Delhi San Juan Singapore Sydney Tokyo Toronto

Find authenticated court documents without watermarks at docketalarm.com.

McGraw-Hill

A Division of The McGraw-Hill Companies

Applied Biopharmaceutics & Pharmacokinetics, Fourth Edition

Copyright © 1999 by Appleton & Lange. All rights reserved. Printed in the United States of America. Except as permitted under the United States Copyright Act of 1976, no part of this publication may be reproduced or distributed in any form or by any means, or stored in a data base or retrieval system, without the prior written permission of the publisher.

Previous editions copyright © 1993 by Appleton & Lange; copyright © 1985, 1980 by Appleton-Century-Crofts.

4567890 HPC/HPC 0987654321

ISBN: 0-8385-0278-4 (domestic)

Library of Congress Cataloging-in-Publication Data

Shargel, Leon, 1941–
Applied biopharmaceutics and pharmacokinetics / Leon Shargel,
Andrew Yu. —4th ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-8385-0278-4 (case : alk. paper)
I. Biopharmaceutics. 2. Pharmacokinetics. I. Yu, Andrew B. C.,
1945– II. Title
[DNLM: 1. Biopharmaceutics. 2. Pharmacokinetics. QV 38 S531a
1999]
RM301.4.S52 1999
(16/7) - 4.01

615'.7—dc21 DNLM/DLC for Library of Congress

98-49079

Editor-in-Chief: Cheryl L. Mehalik Production Service: York Production Services Art Coordinator: Eve Siegel Cover Design: Aimee Nordin Illustrator: Wendy Beth Jackelow

ISBN: 0-8385-0321-7 (international)

Exclusive rights by The McGraw-Hill Companies, Inc. for manufacture and export. This book cannot be re-exported from the country to which it is consigned by McGraw-Hill. The International Edition is not available in North America.

CONTENTS

Preface / XIII

REVIEW OF MATHEMATICAL FUNDAMENTALS / 1
 Estimation and the Use of Calculators and Computers / 1
 Calculus / 6

Graphs / 9

Units in Pharmacokinetics / 16

Measurement and the Use of Significant Figures / 17

Units for Expressing Blood Concentrations / 18 Statistics / 18

Rates and Orders of Reactions / 21

Frequently Asked Questions / 26

Learning Questions / 26

References / 28

Bibliography / 28

2. INTRODUCTION TO BIOPHARMACEUTICS AND PHARMACOKINETICS / 29

Biopharmaceutics / 29
Pharmacokinetics / 30
Clinical Pharmacokinetics / 30
Pharmacodynamics / 31
Toxicokinetics and Clinical Toxicology / 31
Measurement of Drug Concentrations / 32
Basic Pharmacokinetics and Pharmacokinetic Models / 36
Frequently Asked Questions / 43
Learning Questions / 43
References / 44
Bibliography / 45

3. ONE-COMPARTMENT OPEN MODEL / 47

Intravenous Route of Administration of Drug / 47 Elimination Rate Constant / 48

DOCKE

Apparent Volume of Distribution / 49 Clearance / 52 Calculation of k from Urinary Excretion Data / 58 Clinical Application / 62 Frequently Asked Questions / 63 Learning Questions / 64 Bibliography / 66

4. MULTICOMPARTMENTAL MODELS / 67

Two-Compartment Open Model / 69 Three-Compartment Open Model / 85 Determination of Compartment Models / 88 Frequently Asked Questions / 95 Learning Questions / 95 References / 98 Bibliography / 98

5. PHYSIOLOGIC FACTORS RELATED TO DRUG ABSORPTION / 99

Nature of the Cell Membrane / 99 Passage of Drugs Across Cell Membranes / 101 Route of Drug Administration / 108 Frequently Asked Questions / 125 Learning Questions / 126 References / 127 Bibliography / 128

6. BIOPHARMACEUTIC CONSIDERATIONS IN DRUG PRODUCT DESIGN / 129

Rate-Limiting Steps in Drug Absorption / 130 Pharmaceutic Factors Affecting Drug Bioavailability / 131 Physicochemical Nature of the Drug / 133 Formulation Factors Affecting Drug Dissolution / 135 *In Vitro* Dissolution Testing / 138 Compendial Methods of Dissolution / 140 Methods for Testing Enteric-Coated Products / 143 Meeting Dissolution Requirements / 143 Unofficial Methods of Dissolution Testing / 144 Problems of Variable Control in Dissolution Testing / 145

DOCKET A L A R M



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.