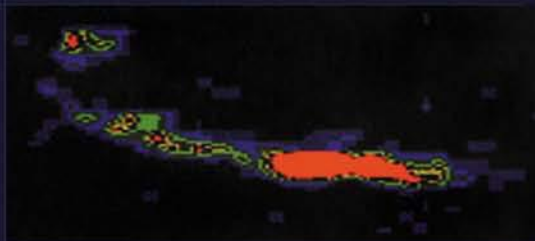


Physiological Pharmaceutics

BARRIERS TO DRUG ABSORPTION

SECOND EDITION



Neena Washington

Clive Washington

Clive G Wilson

**Also available as a printed book
see title verso for ISBN details**

Physiological Pharmaceutics

For Alexander and Sarina

With all our love

Physiological Pharmaceutics

Barriers to drug absorption

Second Edition

Neena Washington, Clive Washington and
Clive G. Wilson



First edition 1989

Second edition first published 2001 by Taylor and Francis
11 New Fetter Lane, London EC4P 4EE

Simultaneously published in the USA and Canada
by Taylor and Francis Inc,
29 West 35th Street, New York, NY 10001

Taylor and Francis is an imprint of the Taylor & Francis Group

This edition published in the Taylor & Francis e-Library, 2003.

Publisher's Note

This book has been prepared from camera-ready copy provided by the authors.

© 2001 Neena Washington, Clive Washington and Clive G. Wilson

All rights reserved. No part of this book may be reprinted or reproduced or utilised in any form or by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying and recording, or in any information storage or retrieval system, without permission in writing from the publishers.

Every effort has been made to ensure that the advice and information in this book is true and accurate at the time of going to press. However, neither the publishers nor the authors can accept any legal responsibility or liability for any errors or omissions that may be made. In the case of drug administration, any medical procedure or the use of technical equipment mentioned within this book, you are strongly advised to consult the manufacturer's guidelines.

British Library Cataloguing in Publication Data

A catalogue record is available for this book from the British Library

Library of Congress Cataloguing in Publication Data

Washington, Neena, 1961–

Physiological pharmaceuticals: barriers to drug absorption/Neena

Washington, Clive Washington, and

Clive George Wilson.—2nd ed.

p.cm.

Previous ed. Physiological pharmaceuticals: biological barriers to drug absorption/Clive George Wilson, Neena Washington.

“Simultaneously published in the USA and Canada.”

Includes bibliographical references and index.

1. Drugs—Bioavailability. 2. Drugs—Dosage forms. 3. Drugs—Physiological transport.

4. Absorption (Physiology) I. Washington, Clive, 1957– II. Wilson, Clive George. III.

Wilson, Clive George. Physiological pharmaceuticals: biological barriers to drug absorption. IV. Title.

RM301.6.W54 2000

615'.7—dc21

ISBN 0-203-48370-7 Master e-book ISBN

ISBN 0-203-79194-0 (Adobe eReader Format)

ISBN 0-748-40610-7 (hbk)

ISBN 0-748-40562-3 (pbk)

PREFACE

Considering the variety in the human race, height, weight, temperament, enzymatic capacity, it is amazing that pharmaceuticals work at all. Add environmental factors, and personal preferences, and suddenly you begin to realise the scale of the problem. Some years ago I ran a clinical trial in patients with ulcerative colitis. When I was recruiting the subjects, I asked people to keep a diary of everything that they ate. Even within the catchment area of Queen's Medical Centre in Nottingham, the diversity of food eaten, let alone the frequency of eating, was beyond comprehension. This led me to think about the world outside Nottingham, eating habits within the UK, the north/south divide (which we are assured by the Government does not exist) let alone what people eat in Africa, China, Fiji.....?? Then remember that medication is designed for sick people, who by definition have a physiology disordered in some way. So how can one pill fit all?

The development work is aimed at the "average" patient. Is there such a thing as an average patient? Is the "average" person really a 70 kg man? In the U.K. 41% of males and 20% of females are overweight. Even the "average" healthy woman may be excluded from pharmacokinetic trials not only due to the risk of potential genetic damage to reproductive tissue but also a tacit admission that the menstrual cycle may affect not only gastrointestinal transit, but also a wide range of physiological processes. This leaves basic data concerning the behaviour of drugs in women largely undiscovered until they are treated as patients.

The realisation that the USP dissolution test bore little resemblance to dosage form behaviour in the body, particularly for the new sophisticated dose forms, led to the first edition of this book being written ten years ago. Over the past 30 years, a predominant focus of drug delivery has been the development of sustained and controlled release formulations, whose interaction with the body is even more critical and complex than that of 'ordinary' tablets. In 1996 there were 35 pharmaceutical products based on advanced drug delivery with a worldwide sales often million US dollars each or higher; this was 11 more than in 1994. In these two years total sales had increased from 5.5 to 6.5 billion dollars. Four products were responsible for more than half of the total sales in 1996; these were ProcardiaXL (nifedipine), Lupron (leuprolide), Cardizem (diltiazem) and Zoladex (goserelin).

The primary goals are usually to minimise the dose of drug administered and to optimize the delivery of the drug, to achieve an 'ideal' plasma-concentration time profile. An added advantage is that simplification of the dosage regimen leads to increased patient compliance by reducing the number of daily doses. With the new requirement to deliver drugs to precise locations of the gastrointestinal tract came the need to study physiological variations in gastrointestinal transit, such as those brought about by eating, levels of physical activity and chronobiological effects. The focus on once-a-day dosing necessitated larger payloads of drugs per unit than conventional counterparts. Premature release of the drug could have potentially disastrous effects, so prediction of dosage form behaviour needs to be accurate.

With the leap in the number of sophisticated technologies reaching the market place the amount of literature which has become available since 1990 is considerable, and hence the second edition of "Physiological Pharmaceutics" is a complete re-write and not just an update. We are very aware that people placed advance orders for this book and we would like to thank them for buying it on faith. We also would like to thank them for their patience and we hope that they feel that the wait was worthwhile. We would like to thank our

publishers, who I am sure, at times, thought the manuscript was a figment of the imagination (either theirs or ours). Ironically, the first draft of the manuscript was delivered to them 3 years *to the day* late. By way of an explanation for the tardiness of this book, I would like you to realise that this book was written in “our spare time”, as if scientists with full time jobs and a young family have “spare time”! The university obsession with the research assessment exercise has made the production of textbooks a rather low priority, so much of the volume has been written after 11 at night!

For this very reason I would like to thank our children, Alex (9 years) and Sarina (4 years) for their patience whilst mummy was writing or daddy was drawing diagrams, and Alex for ‘helping’ with the diagrams...We are painfully aware that it is they who have suffered as we have had virtually no time for them, particularly over the last year. As I write this, they know that the “end of book” promised trip to LegoLand is coming closer! I also must thank my friends and colleagues, Drs Caroline Herd, Mike Nassim, Gerry Hooper and Carol Astbury for their caring and support. I would also like to thank my husband, who saw the vast amount of work which needed to be done on the book and mucked in. In acknowledgement of his substantial contribution, we made him a full author on this edition. Without him, the book would probably have been 6 years late!

Neena Washington 14th February 2000

FIGURE ACKNOWLEDGEMENTS

Fig 1.13 is reprinted from Volkheimer G et al., Gut 1969; 10:32–3. with the permission of the BMJ Publishing Group.

Fig 3.4 is reprinted from Sanford PA, Digestive System Physiology (1982) with the permission of Arnold.

Fig 3.5 is reprinted from Pimlott & Addy, Oral Surg. Oral. Med. Path. 1985; 59:145–8. with the permission of Mosby.

Fig 3.6 is reprinted from Squier CA & Johnson NW, British Medical Bulletin 1975; 31:169 with the permission of Christopher A Squier.

Fig 3.8 is reprinted from Wilson CG et al., Int J Pharm 1987; 40:119–123 with the permission of Elsevier Science.

Fig 3.9 is reprinted from Davis SS et al, In: Modern Concepts in Nitrate Delivery Systems, Goldberg AAJ & Parson DG (eds) pp29–37 (1983) with the permission of Pharmaceutical Press.

Fig 4.6 is reprinted from Wilson CG et al., Int. J. Pharm. 1988; 46:241–46 with the permission of Elsevier Science.

Fig 4.7 is reprinted from Kikendall JW et al., Dig. Dis. Sci. 1983; 28:174–182 with the permission of Kluwer Academic/Plenum Publisher.

Fig 4.8 is reprinted from Weinbeck M et al, Bailliere's Clin. Gastroenterol. 1988; 2:263–274 with the permission of Harcourt Publishers Ltd.

Fig 5.1 is reprinted from Sanford PA, Digestive System Physiology (1982) with the permission of Arnold.

Fig 5.6 is reprinted from Johnson LR (ed), Gastrointestinal physiology, 3rd edition (1985) with the permission of W.B.Saunders.

Fig 5.7 is reprinted from Sanford PA, Digestive System Physiology (1982) with the permission of Arnold.

Fig 5.11 is reprinted from Sanford PA, Digestive System Physiology (1982) with the permission of Arnold.

Fig 5.13 is reprinted with thanks to Dr Wright of the Department of Surgery, Queen's Medical Centre, Nottingham, UK.

Fig 5.15 is reprinted from Goo RH et al, Gastroenterol. 1987; 93:515–518 with the permission of W.B. Saunders.

Fig 5.17 is reprinted from O'Reilly S et al., Int. J. Pharm. 1987; 34:213–216 with the permission of Elsevier Science.

Fig 5.19 is reprinted from O'Reilly S et al., Int. J. Pharm. 1987; 34:213–216 with the permission of Elsevier Science.

Fig 5.20 is reprinted from Meyer JH et al., Gastroenterol. 1985; 88:1502 with the permission of W.B. Saunders.

Fig 6.1 is reprinted from Moog F., The lining of the small intestine. Scientific American 1981; 245:154–158 with the permission of Carol Donner.

Fig 6.2 is reprinted from Weiner D, Chapter 43 in: Biological Foundations of Biomedical Engineering, Kline J (ed) (1976) with the permission of Lippincott Williams & Wilkins and D Weiner.

Fig 6.4 is reprinted from Sanford PA, Digestive System Physiology (1982) with the permission of Arnold.

Fig 6.5 is reprinted from Johnson LR (ed), *Gastrointestinal Physiology*, 3rd edition (1985) with the permission of W.B.Saunders.

Fig 6.7 is reprinted from Davis SS et al., *Int. J. Pharm.* 1987; 34:253–8 with the permission of Elsevier Science.

Fig 6.8 is reprinted from Davis SS et al., *Gut* 1986; 27:886–892 with the permission of the BMJ Publishing Group.

Fig 6.10 is reprinted from Fischer W et al, *Pharm. Res.* 1987; 4:480–485 with the permission of Kluwer Academic/Plenum Publisher.

Fig 6.11 is reprinted from Bechgard H et al., *J. Pharm. Pharmacol.* 1985; 37:718–721 with the permission of Pharmaceutical Press.

Fig 6.12 is reprinted from Schinkel AH, *Adv. Drug Deliv. Rev* 1999; 36:179–194 with the permission of Elsevier Science.

Fig 7.1 is reprinted from Sanford PA, *Digestive System Physiology* (1982) with the permission of Arnold.

Fig 7.2 is reprinted from Krstic RV, *Human Microscopic Anatomy* (1991) with the permission of Springer-Verlag.

Fig 7.3 is reprinted from Stephen AM et al., *Br. J. Nutr.* 1986; 56:349–361 with the permission of CABI Publishing.

Fig 7.4 is reprinted from Washington N et al., *Moderation of lactulose induced diarrhoea by psyllium: effects on motility and fermentation* *Am. J. Clin. Nutr.* 1998; 67:317–321 with the permission of The American Society for Clinical Nutrition.

Fig 7.5 is reprinted from Davis et al., *Relationship between the rate of appearance of oxprenolol in the systemic circulation and the location of an oxprenolol Oros 16/260 drug delivery system within the gastrointestinal tract as determined by scintigraphy.* *Br. J., Clin. Pharmacol.* 1988; 26:435–443 with the permission of Sage Publications Inc.

Fig 7.6 is reprinted from Hardy JG et al., *J. Pharm. Pharmacol.* 1985; 37:874–877 with the permission of Pharmaceutical Press.

Fig 7.7 is reprinted from Hardy JG et al., *J. Pharm. Pharmacol.* 1985; 37:874–877 with the permission of Pharmaceutical Press.

Fig 7.9 is reprinted from Tozer, T.N., *Kinetic perspectives on colonic delivery.* *Proc. Int. Symp. Cont. Rel. Bioact. Mat.* 1990; 17:126 with the permission of the Controlled Release Society.

Fig 7.11 is reprinted from Tukker J, Ph.D thesis, University of Leiden 1983 with the permission of J Tukker.

Fig 7.12 is reprinted from Wood E et al., *Int. J. Pharmaceut.* 1985; 25:191–197 with the permission of Elsevier Science.

Fig 7.13 is reprinted from van Hoogdalem E.J., de Boer A.G. and Briemer D.D., *Pharmacokinetics of rectal drug administration. Part I—general considerations and clinical applications of centrally acting drugs.* *Clin. Pharmokinet.* 1991; 21:11–26 with the permission of Adis International Ltd.

Fig 7.14 is reprinted from van Hoogdalem E.J., de Boer A.G. and Briemer D.D., *Pharmacokinetics of rectal drug administration. Part II—Clinical applications of peripherally acting drugs and conclusions.* *Clin. Pharmokinet.* 1991; 21:110–128 with the permission of Adis International Ltd.

Fig 9.3 is reprinted from Hussain A.A., *Intranasal drug delivery.* *Advanced Drug Delivery Reviews* 1998; 29:39–49, with the permission of Elsevier Science.

Fig 9.4 is reprinted from Fisher A. et al, *The effect of molecular size on the nasal absorption of water-soluble compounds in the albino rat.* *J. Pharm. Pharmacol.* 1987; 39:357–362 with the permission of Pharmaceutical Press.

Fig 9.5 is reprinted from Jackson SJ et al., *J. Pharm. Pharmacol* 1997; 49: suppl 84 with the permission of Pharmaceutical Press.

Fig 9.6 is reprinted from Ridley D. et al., The effect of posture on the nasal clearance of starch microspheres. *STP Pharma Sciences* 1995; 5:442–446 with the permission of Editions de Sante.

Fig 9.7 is reprinted from Hehar SS et al. *Clin. Otolaryngology* 1999; 24:24–25 with the permission of Blackwell Science.

Fig 9.8 is reprinted from Huang C. et al., *J. Pharm. Sci.* 1985; 74:550–552 with the permission of John Wiley & Sons.

Fig 9.9 is reprinted from Washington N et al., *Int. J. Pharm.* 2000; 198:139–146 with the permission of Elsevier Science.

Fig 10.2 is reprinted from Bell GH, Emslie-Smith D and Paterson CR, *Textbook of Physiology*, 10th edn. (1980) with the permission of W.B.Saunders/Churchill-Livingstone.

Fig 10.3 is reprinted from Vander AJ, Sherman JH & Luciano DS, *Human Physiology* (1975) with the permission of Tata McGraw-Hill Publishing Company.

Fig 11.1 is reprinted from Mitra AK, *Ophthalmic Drug Delivery Devices* (P.Tyle ed) Marcel Dekker, New York (1993) with the permission of Marcel Dekker Inc.

Fig 11.5 is reprinted from Greaves JL and Wilson CG, Treatment of diseases of the eye with mucoadhesive delivery systems. *Advanced Drug Delivery Reviews* 1993; 11:349–383 with the permission of Elsevier Science.

Fig 12.3 is reprinted from Krstic RV, *Human Microscopic Anatomy* (1991) with the permission of Springer-Verlag.

The authors and publishers have made every effort to contact authors/copyright holders of works reprinted from in *Physiological Pharmaceutics 2nd ed.* This has not been possible in every case, however, and we would welcome correspondence from those individuals/companies we have been unable to trace.

Table of Contents

1. Cell Membranes, Epithelial Barriers and Drug Absorption	1
INTRODUCTION	2
THE PLASMA MEMBRANE	2
The phospholipid bilayer	3
Dynamic behaviour of membranes	4
Modulation of membrane fluidity by sterols	5
Models of cell membranes	5
Membrane proteins	7
Membrane asymmetry	7
EPITHELIA	7
Cell junctions	8
TRANSPORT ACROSS CELL MEMBRANES	12
Passive diffusion	12
Facilitated and carrier mediated diffusion	14
Cotransport	14
Uptake of macromolecules and particles	15
INTERCELLULAR ROUTES OF ABSORPTION	16
PERSORPTION	16
MUCUS	17
CONCLUSIONS	18
REFERENCES	18
2. Parenteral Drug Delivery	19
INTRODUCTION	20
INTRAVENOUS DELIVERY	20
Physiology	20
Advantages and disadvantages of intravenous delivery	21
Formulation considerations	23
Devices and technologies	23
Injected particulates	24
Intravenous oxygen carriers	25
INTRAMUSCULAR DELIVERY	26
Physiology	26
Pharmacokinetics	26
Formulation considerations	28
SUBCUTANEOUS DELIVERY	28
Physiology	28
Subcutaneous colloidal delivery systems	29
TISSUE DAMAGE AND BIOCOMPATIBILITY	29
DRUG DISTRIBUTION FOLLOWING PARENTERAL ADMINISTRATION ...	30
PROTEIN BINDING	31
THE BLOOD-BRAIN BARRIER	32
Physiology	32
Uptake by diffusion	32
Receptor-mediated transport	33
Colloidal delivery	33
REFERENCES	34

3. Drug Delivery to the Oral Cavity or Mouth	37
ANATOMY AND PHYSIOLOGY	38
The oral cavity	38
The palate	38
The tongue	39
The teeth	39
Organisation of the oral mucosa	39
Functions of the oral mucosa	41
Salivary secretion	41
MIGRATION AND CLEARANCE OF SUBSTANCES FROM THE ORAL CAVITY	43
ABSORPTION OF DRUGS ACROSS THE ORAL MUCOSA	44
Disadvantages of oral mucosal delivery	44
Effect of position on drug delivery	45
Gingival penetration	46
Improving penetration through the mucosa	47
MEASUREMENT OF ORAL MUCOSAL DRUG ABSORPTION	48
DOSAGE FORMS FOR THE ORAL CAVITY	48
Chewable formulations	49
Fast-dissolving dosage forms	50
Bioadhesive dosage forms	51
Dental systems	53
DRUGS ADMINISTERED VIA THE ORAL MUCOSA	53
Nitrates	53
Steroids	53
Analgesics	54
Antibiotics	54
Antifungals	54
Others	55
CONCLUSIONS	55
REFERENCES	55
4. Oesophageal Transit	59
INTRODUCTION	60
ANATOMY AND PHYSIOLOGY	60
Oesophagus	60
Gastro-oesophageal junction or cardia	61
MOTILITY OF THE OESOPHAGUS	61
OESOPHAGEAL TRANSIT OF DOSAGE FORMS	63
Measurement	63
Typical transit times	64
OESOPHAGEAL ADHESION OF DOSAGE FORMS	65
Factors predisposing formulations to adhere	66
CONSEQUENCES OF ADHESION OF DOSAGE FORMS	67
Delay in drug absorption	67
Oesophageal damage	67
EFFECT OF AGEING	68
PATIENT PREFERENCE AND EASE OF SWALLOWING	69
EFFECT OF DISEASED STATES ON TRANSIT	69
TARGETING THE OESOPHAGUS	70
CONCLUSIONS	71
REFERENCES	71
5. The Stomach	75
ANATOMY AND PHYSIOLOGY	76
Organisation of the stomach	76
Gastric secretion	80
Digestion and absorption	82

GASTRIC pH	83
Circadian rhythm of acidity	84
pH and gender	85
pH and age	85
pH and smoking	85
GASTRIC MOTILITY	85
The fasted state	85
The fed state	86
Physiological factors which influence gastric emptying	92
Effect of disease on gastric emptying	93
DISPERSION OF DOSAGE FORMS IN THE STOMACH	94
Hard gelatin capsules	94
Soft gelatin capsules	94
GASTRIC EMPTYING OF DOSAGE FORMS	95
Time of dosing relative to a meal	98
Retention of formulations in the stomach	98
Posture effects	101
Drug-induced effects on gastric emptying	102
GASTRIC pH AND ENTERIC COATINGS	102
DRUG/FORMULATION INDUCED ULCERATION	102
ANIMAL MODELS FOR GASTRIC EMPTYING	103
REFERENCES	103

6. Drug Absorption from the Small Intestine

ANATOMY AND PHYSIOLOGY OF THE SMALL INTESTINE	109
Gross morphology	110
Mucosa	110
Organisation of the mucosa	111
The gastrointestinal circulation	113
The lymphatic system	114
Secretions into the small intestine	116
Secretion and absorption of water	117
Digestion and absorption of nutrients	118
PATTERNS OF MOTILITY IN THE SMALL INTESTINE	120
Stagnation at the ileocaecal junction	121
SMALL INTESTINAL TRANSIT TIMES	122
Methods for measuring small intestinal transit	122
Small intestinal transit times of food	123
Physiological and pathophysiological effects on small bowel transit	123
Small intestinal transit time of dosage forms	124
Density and small intestinal transit	127
ABSORPTION OF DRUGS	127
Absorption and delivery of macromolecules	128
Intestinal pH	129
Solvent drag and intestinal permeability	129
P-glycoprotein	130
Cytochrome P450 3A4 (CYP3A4)	131
Intestinal reserve length	132
Interaction with food	133
First-pass metabolism	134
RELATIONSHIP BETWEEN DRUG ABSORPTION AND POSITION OF DOSE FORM	135
Radio controlled capsule	135
Absorption of drugs and foreign substances through the lymphatic system	136
DRUG INDUCED DAMAGE	136
REFERENCES	137

7. Drug Delivery to the Large Intestine and Rectum	143
INTRODUCTION	144
ANATOMY AND PHYSIOLOGY OF THE COLON	144
Interspecies differences in structure	145
Colonic structure	146
Gut wall metabolism	147
Blood supply	147
Nervous and humoral control	148
Colonic environment	149
Colonic motility	151
Drug absorption from the colon	157
DRUG DELIVERY	157
Transit	158
Dietary factors	161
Temporal factors	161
Targeting the proximal colon	161
Effect of disease and co-medication on colonic drug absorption	165
RECTAL ADMINISTRATION OF DRUGS	166
Drug absorption and avoidance of first-pass metabolism	166
Dosage forms for rectal delivery	167
Adjuvants and enhancers	167
Spreading of rectal dosage forms	168
Therapeutic agents administered rectally	169
Rectal irritation and damage	173
CONCLUSIONS	174
REFERENCES	174
8. Transdermal Drug Delivery	181
INTRODUCTION	182
STRUCTURE OF THE SKIN	182
Epidermis	183
Dermis	184
Subcutaneous fat layer	184
Hair and nails	184
Sebaceous glands	185
Eccrine sweat glands	185
Surface characteristics	185
PASSAGE OF DRUG THROUGH THE SKIN	185
Model systems for skin	185
Routes of absorption	186
Advantages and disadvantages of transdermal delivery	187
FACTORS AFFECTING PERCUTANEOUS ABSORPTION	188
Individual variation	188
Age	188
Site	188
Occlusion	188
Temperature	188
Race	189
Disease	189
VEHICLES AND DEVICES	189
PENETRATION ENHANCERS	191
IONTOPHORESIS	192
ELECTROPORATION	193
SONOPHORESIS	194
CONCLUSIONS	194
REFERENCES	195

9. Nasal Drug Delivery	199
ANATOMY AND PHYSIOLOGY	200
Nasal epithelia	201
Nasal lymphatic system	202
Nasal secretions	202
The nasal cycle	203
Mucociliary clearance of inhaled particles	203
Pathological effects on mucociliary function	204
External factors affecting mucociliary clearance	206
Chemical-induced changes	207
INTRANASAL ADMINISTRATION OF DRUGS	208
Drugs administered for local action	208
Drugs administered for systemic effect	209
DRUG DELIVERY SYSTEMS AND DEPOSITION PATTERNS	210
Mechanisms to increase nasal residence time of formulations	212
Excipient and drug effects on clearance	213
Effect of formulation pH	214
INTERSPECIES COMPARISONS	216
CONCLUSIONS	216
REFERENCES	217
10. Pulmonary Drug Delivery	221
STRUCTURE AND FUNCTION OF THE PULMONARY SYSTEM	222
The lung	222
Upper airway	222
Structure of the tracheo-bronchial tree	223
Epithelium	225
Lung permeability	227
Lung mucus	227
Lung defenses	228
Lung surfactant	228
Blood supply	229
Lymphatic system	229
Nervous control	229
Biochemical processes which occur in the lung	230
Breathing	230
Respiratory disease	230
DOSAGE FORMS FOR PULMONARY DRUG DELIVERY	232
Pressurized inhalation aerosols	232
Dry powder inhalers	234
Nebulizers	235
Spacer devices and ancillary equipment	236
ASSESSMENT OF DEPOSITION BY GAMMA SCINTIGRAPHY	237
Choice of radiolabel	237
Labeling inhalation formulations	238
Labeling dry powder inhalers	239
Validation	239
FACTORS AFFECTING PARTICLE DEPOSITION IN THE LUNG	239
Physicochemical properties	239
Deposition patterns from different dose forms	241
Physiological variables	241
DRUG ABSORPTION	242
PHARMACOKINETICS	243
DRUGS ADMINISTERED VIA THE PULMONARY ROUTE	243
Anti-allergy agents	243
Beta receptor agonists	243

Adrenocorticosteroids	244
Leukotriene inhibitors	244
Other bronchodilating agents	244
Mucolytics	244
Systemically-absorbed drugs	245
REFERENCES	245
11. Ocular Drug Delivery	249
INTRODUCTION	250
STRUCTURE OF THE EYE	251
The cornea	251
The conjunctiva and sclera	252
The choroid and retina	252
The aqueous humor	252
The eyelids	253
The precorneal tear film	253
Blood-eye barriers	256
FACTORS AFFECTING DRUG PERMEATION	257
Ionization and pH	257
Protein binding	258
Pigmentation and drug effects	258
Drug distribution in the eye	259
Drug penetration through the sclera and conjunctiva	259
FACTORS INFLUENCING DRUG RETENTION	260
Proper placement of the eyedrops	260
Influence of instilled volume	261
Preservatives	261
Effect of systemically administered drugs	262
ROUTES OF DRUG ADMINISTRATION	262
Topical administration	262
Intraocular drug delivery	266
Systemic administration	268
CONCLUSIONS	269
REFERENCES	269
12. Vaginal and Interuterine Drug Delivery	271
ANATOMY AND PHYSIOLOGY	272
Mucosa	273
Blood and nerve supply	275
Uterine and vaginal fluid	275
pH	275
Enzymatic activity	276
Mucus	276
Menstruation	276
Menopause	277
Disorders of the vagina	277
DRUG ABSORPTION THROUGH THE VAGINA/UTERUS	277
DRUG DELIVERY	277
Vaginal	277
Intrauterine Devices	279
CONCLUSION	280
REFERENCES	280
GLOSSARY	283
INDEX	299

