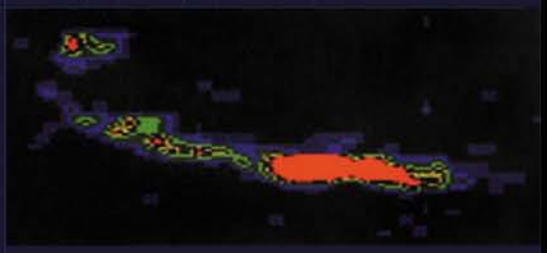
Physiological Pharmaceutics

BARRIERS TO DRUG ABSORPTION

SECOND EDITION



Neena Washington
Clive Washington
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Physiological Pharmaceutics

For Alexander and Sarina

With all our love

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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.

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 pharmaceutics: barriers to drug absorption/Neena Washington, Clive Washington, and Clive George Wilson.—2nd ed.
p.cm.
Previous ed. Physiological pharmaceutics: 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 pharmaceutics: 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

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