



Remington

Essentials of Pharmaceutics

Edited by Linda Felton





Essentials of Pharmaceuticals





Essentials of Pharmaceutics

Edited by Linda A. Felton, PhD
Chair, Department of Pharmaceutical Sciences
Associate Professor of Pharmaceutics
College of Pharmacy
University of New Mexico
Albuquerque, NM, USA



University of the Sciences
Philadelphia
College of
Pharmacy



Published by Pharmaceutical Press

1 Lambeth High Street, London SE1 7JN, UK

© Pharmaceutical Press 2012

(PP) is a trade mark of Pharmaceutical Press

Pharmaceutical Press is the publishing division of the Royal Pharmaceutical Society

First edition published 2013

Typeset by Newgen KnowledgeWorks, India

Printed in the United States of America by Edwards Brothers Malloy

ISBN 978 0 85711 105 0

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without the prior written permission of the copyright holder.

The publisher makes no representation, express or implied, with regard to the accuracy of the information contained in this book and cannot accept any legal responsibility or liability for any errors or omissions that may be made.

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

This book is adapted from contributions published in *Remington: The Science and Practice of Pharmacy* 22nd edition.

Contents

Preface v			
About the editor vii			
Contributors ix			
Chapter 1	Information resources in pharmacy and the pharmaceutical sciences <i>Robin H. Bogner, PhD and Sharon Giovenale, MSLS</i>	1	
Chapter 2	Analysis of medicinals <i>Raymond D. Skwierczynski, PhD</i>	9	
Chapter 3	Quality assurance and control <i>John H. Parker, PhD and John E. Enders, PhD, MBA</i>	29	
Chapter 4	Stability of pharmaceutical products <i>Allan D. Bokser, PhD and Patrick B. O'Donnell, PhD</i>	37	
Chapter 5	Bioavailability and bioequivalence <i>Steven B. Johnson, PharmD</i>	51	
Chapter 6	Dissolution <i>Vijai Kumar, MS, MBA and Praveen Hiremath, PhD</i>	63	
Chapter 7	Modern-day drug discovery and development <i>Rick G. Schnatz, PharmD</i>	81	
Chapter 8	The New Drug Approval Process <i>Linda A. Felton, PhD and Dennis W. Raisch, PhD, RPh</i>	93	
Chapter 9	Metrology and pharmaceutical calculations <i>Roger L. Schnaare, PhD and Shelly J. Prince, PhD</i>	101	
Chapter 10	Statistics <i>Sanford Bolton, PhD and Richard Hirsch, PhD</i>	133	
Chapter 11	Molecular structure, properties and states of matter <i>Thomas Rades, PhD, Keith C. Gordon, PhD and Kirsten Graeser, PhD</i>	177	
Chapter 12	Thermodynamics <i>Timothy S. Wiedmann, PhD</i>	207	
Chapter 13	Solutions and phase equilibria <i>Pardeep K. Gupta, PhD</i>	219	
Chapter 14	Separation methods <i>Lloyd V. Allen, Jr., PhD, RPh</i>	241	
Chapter 15	Ionic solutions and electrolytic equilibria <i>Barbara R. Conway, PhD</i>	257	
Chapter 16	Tonicity, osmoticity, osmolality, osmolarity <i>Andrew Ingham, MRPharmS, PhD and Cathy Y. Poon, PharmD</i>	277	
Chapter 17	Chemical kinetics <i>Rodney J. Wigent, PhD</i>	301	
Chapter 18	Complex formation <i>Thorsteinn Loftsson, MSPHarm, MSc, PhD and Marcus E. Brewster, PhD</i>	317	
Chapter 19	Interfacial phenomena <i>Paul M. Bummer, PhD and Yvonne Perrie, PhD</i>	329	
Chapter 20	Colloidal dispersions <i>Bill J. Bowman, RPh, PhD, Clyde M. Ofner III, PhD, Hans Schott, PhD and Yvonne Perrie, PhD</i>	343	
Chapter 21	Coarse dispersions <i>James Swarbrick, DSc, PhD, Joseph T. Rubino, PhD, RPh and Orapin P. Rubino, PhD</i>	371	
Chapter 22	Rheology <i>Lawrence H. Block, PhD</i>	393	
Chapter 23	Powders <i>Yi-Bo Wang and Robert O. Williams III, PhD</i>	411	
Chapter 24	Solutions, Emulsions, Suspensions, and Extracts <i>Michael M. Crowley, PhD</i>	435	
Chapter 25	Sterilization Processes and Sterility Assurance <i>James Agalloco, BEChE, MSCHE, MBA, William G. Lindboem, Jr., PhD and Russell E. Madsen, MS</i>	469	
Chapter 26	Parenteral Preparations <i>Michael J. Akers, PhD</i>	495	
Chapter 27	Pharmaceutical Compounding – USP <797> Sterile Preparations <i>Catherine Cone, PharmD, BCPS, Linda A. Felton, PhD, Amy Bachyrycz, PharmD</i>	533	
Chapter 28	Ophthalmic Preparations <i>Masood Chowhan, PhD, John C. Lang, PhD, Paul Missel, PhD</i>	541	
Chapter 29	Medicated Topicals <i>Lawrence H. Block, PhD</i>	565	
Chapter 30	Oral Solid Dosage Forms <i>Ahmed Adel Sakr, PhD and Fars K. Alanazi, PhD</i>	581	

Chapter 31	Coating of Pharmaceutical Dosage Forms <i>Stuart C. Porter, PhD</i>	611	Chapter 36	Pharmaceutical Excipients <i>William J. Reilly, Jr., MBA</i>	683
Chapter 32	Oral Modified-Release Drug Delivery Systems <i>Ali R. Rajabi-Siahboomi, PhD, Manish S. Rane, PhD and Linda A. Felton, PhD</i>	623	Chapter 37	Basic pharmacokinetics and pharmacodynamics <i>Raymond E. Galinsky, PharmD and Craig K. Svensson, PharmD, PhD</i>	705
Chapter 33	Aerosols <i>John J. Sciarra, PhD and Christopher J. Sciarra, BS, MS Industrial Pharmacy</i>	633	Chapter 38	Drug action and effect <i>Donald N. Franz, PhD</i>	727
Chapter 34	Biotechnology and Drugs <i>Ara H. DerMarderosian, PhD and Zhiyu Li, PhD</i>	651	Chapter 39	Drug absorption, distribution, metabolism and excretion <i>Michael R. Franklin, PhD</i>	739
Chapter 35	Pharmaceutical Packaging <i>C. Jeanne Taborsky, BSChem and Kathleen Deiss, RN</i>	667	Chapter 40	Pharmacokinetics/pharmacodynamics in drug development <i>George L. Drusano, MD</i>	755
			Index		763

Chapter 5

Bioavailability and Bioequivalence Testing

Steven B. Johnson, PharmD

INTRODUCTION 51

DISSOLUTION 51

ABSORPTION FACTORS 52

BIOEQUIVALENCE TESTING 53

METHODS FOR DETERMINING BIOEQUIVALENCE 53

MINIMIZING THE NEED FOR BIOEQUIVALENCE STUDIES 54

EVALUATION OF BIOEQUIVALENCE DATA 54

BIOEQUIVALENCE ASSESSMENT AND DATA EVALUATION 54

CRITERIA FOR BIOEQUIVALENCE 56

STUDY DESIGN 58

THERAPEUTIC EQUIVALENCE EVALUATIONS 60

INTRODUCTION

Understanding the concepts of bioavailability and bioequivalence testing is essential in the drug development process because they create the foundation for regulatory decision making when evaluating formulation changes and lot-to-lot consistency in innovator products. They also serve as the primary components to demonstrate therapeutic equivalence between generic products and the reference innovator product.

Changes in bioavailability can be thought of in terms of changes in exposure to the drug. If these changes are substantial, then they can alter the safety and efficacy profile of the compound in question. The bioavailability of orally administered drugs can be affected by numerous factors. These include food or fed state, differences in drug metabolism, drug–drug interactions, gastrointestinal transit time, and changes in dosage form release characteristics (especially for modified release products).

Bioequivalence is an important consideration in ensuring lot-to-lot consistency, including whenever evaluating changes in a marketed product's formulation, manufacturing process, and dosage strength. Bioequivalence is also critical in regulatory authority decision making when determining whether a generic product is therapeutically equivalent to the original innovator product.

In addition, chemical equivalence, lot-to-lot uniformity of physicochemical characteristics, and stability equivalence are other factors that are important, as they too can affect product quality. In this chapter, bioavailability and bioequivalence topics are emphasized for solid oral dosage forms. However, many of the general concepts can also be applied to other dosage forms, including biologics.

GENERAL CONCEPTS

The terms used in this chapter require careful definition, since, as in any area, some terms have been used in different contexts by different authors.

Bioavailability is a term that indicates measurement of both the rate of drug absorption and the total amount (extent) of drug that reaches the systemic circulation from an administered dosage form. It is specific to the parent or active drug substance as contrasted to metabolites.

Equivalence is more a general and relative term that indicates a comparison of one drug product with another. Equivalence may be defined in several ways:

- **Bioequivalence** indicates that a drug in two or more similar dosage forms reaches the systemic circulation at the same relative rate and extent (i.e., the plasma level

profiles of the drug obtained using the two dosage forms are the same).

- **Chemical equivalence** considers that two or more dosage forms contain the same labeled quantities (within specified limits) of the drug.
- **Clinical equivalence** occurs when the same drug from two or more dosage forms gives identical *in vivo* effects as measured by a pharmacological response or by control of a symptom or disease.
- **Pharmaceutical equivalence** refers to two drug products with the same dosage form and same strength.
- **Therapeutic equivalence** implies that two brands of a drug product are expected to yield the same clinical result. The FDA specifically uses the term “therapeutic equivalence” in the evaluation of multi-source prescription drug products (generic drugs).

Area under the Concentration–Time Curve (AUC) is the integral of the concentration–time curve after administration of a single dose of drug or after achieving a steady state. The calculated area under the serum, blood, or plasma concentration–time curve is reported in amount/volume multiplied by time (e.g., $\mu\text{g/mL} \times \text{h}$ or $\text{g}/100 \text{ mL} \times \text{h}$) and can be considered representative of the amount of drug absorbed. Several variants of AUC exist, including AUC_{0-t} , $\text{AUC}_{0-\infty}$, and $\text{AUC}_{\tau, \text{SS}}$, corresponding to the calculated area from time zero to a truncated time point (e.g., AUC_{0-48}), the total area under the curve, and the area when steady state has been achieved.

Peak-height Concentration (C_{max}) is the peak of the blood level–time curve and represents the highest drug concentration achieved after drug administration.

Time of Peak Concentration (T_{max}) is the measured length of time necessary to achieve the maximum concentration (C_{max}) after drug administration.

DISSOLUTION

For a drug to be absorbed, it must first go into solution. In Figure 5-1 the steps in the dissolution and subsequent absorption process of a tablet or capsule dosage form are outlined. Similar profiles could be obtained for any solid or semisolid dosage form, including oral suspensions, parenteral suspensions, and suppositories. The theory and mechanics of drug dissolution rate are described in detail in Chapter 6. The physical characteristics of the drug and the composition of the tablet (dosage form) can have an effect on the rates of disintegration, deaggregation, and dissolution of the drug. As such, these can affect the rate of absorption and resultant blood levels of the drug.

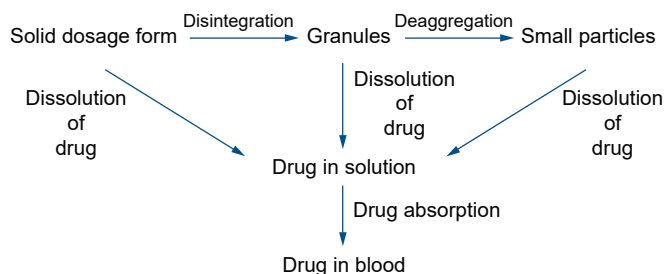


Figure 5-1. Sequence of events involved in the dissolution and absorption of a drug from a solid oral dosage form.

An important aspect of product quality for marketed oral solid dosage forms relates to dissolution testing. The dosage forms actually used by patients will be from lots that have not directly undergone human bioavailability testing. Once adequate product quality has been established by bioavailability testing, subsequent batches manufactured using the same formulation, equipment, and process are likely to be bioequivalent to the original batch tested in humans. This is an important concept in the regulatory control of product quality and is where *in vitro* testing such as assay, content uniformity, tablet hardness, and dissolution are important. Among these several *in vitro* tests, dissolution testing is probably the most important, related to bioavailability. As part of the drug approval process, a dissolution test procedure is established for all oral solid dosage forms. These dissolution tests are incorporated into the United States Pharmacopeia (USP) and apply both to innovator and generic drug products. All marketed batches of these drug products must meet the Abbreviated New Drug Application (ANDA)/New Drug Application (NDA)/USP dissolution tests throughout the shelf-life of the product. Products failing their approved dissolution test and/or a USP dissolution test must be removed from the market.

PROPERTIES OF THE DRUG

The physical characteristics of the drug that can alter bioavailability are discussed in Chapter 39 and consist of the polymorphic crystal form, choice of the salt form, particle size, hydrated or anhydrous form, wettability, and solubility of the drug. These factors should be investigated during product development and should not, therefore, affect the bioavailability of the drug product.

PROPERTIES OF THE DOSAGE FORM

The various components of the solid or semisolid dosage form, other than the active ingredient, are discussed in Chapter 30. Only an overview, for tablet dosage forms, is given here. In addition to the active ingredient, a tablet product usually will contain the following types of inactive ingredients:

- *Glidants* are used to provide a free-flowing powder from the mix of tablet ingredients so that the material will flow when used on a tablet machine.
- *Binders* provide cohesiveness to the tablet. Too little binder will produce tablets that do not maintain their integrity; too much may affect adversely the release (dissolution rate) of the drug from the tablet.
- *Fillers* are used to give the powder bulk so that an acceptably sized tablet is produced. Most commercial tablets weigh from 100 mg to 500 mg, so it is obvious that for many potent drugs the filler constitutes a large portion of the tablet. Binding of drug to the fillers may occur and affect bioavailability.
- *Disintegrants* are used to cause the tablets to disintegrate when exposed to an aqueous environment. Too much will produce tablets that may disintegrate in the bottle because of atmospheric moisture, and too little may be insufficient for disintegration to occur and may therefore

alter the rate and extent of release of the drug from the dosage form.

- *Lubricants* are used to enhance the flow of the powder through the tablet machine and to prevent sticking of the tablet in the die of the tablet machine after the tablet is compressed. Lubricants are usually hydrophobic materials such as stearic acid, magnesium, or calcium stearate. Too little lubricant will not permit satisfactory tablets to be made; too much may produce a tablet with a water-imperious hydrophobic coat, which can inhibit the disintegration of the tablet and dissolution of the drug.

ABSORPTION FACTORS

A significant factor related to drug bioavailability is the fact that many drugs are administered, not as a solution, but as a solid dosage form. Optimal bioavailability might be expected from a solution, since a solid drug must first dissolve to be absorbed, but considerations such as drug stability, unpalatable taste, and the desired duration of action (for controlled-release drug products) may prevent the development of solution-based dosage form.

In the dose titration of any patient the objective is, in conceptual terms, to attain and maintain a blood level that exceeds the minimum effective level required for response but does not exceed the minimum toxic (side-effect) level. This is shown graphically in Figure 5-2. There are several absorption factors that can affect the general shape of this blood-level curve and thus drug response.

DOSE ADMINISTERED

The blood levels will rise and fall in proportion to the dose administered.

AMOUNT OF DRUG ABSORBED

Blood levels achieved are also dependent on the amount of drug absorbed. For example, the effect of having only one-half of the drug absorbed from a dosage form is equivalent to lowering the dose (Figure 5-3).

RATE OF ABSORPTION

If absorption from the dosage form is more rapid than the rate of absorption that gave profile C in Figure 5-4, minimum toxic (side-effect) levels may be exceeded. If absorption from the dosage form is sufficiently slow, minimum effective levels may never be attained, as in profile B in Figure 5-4.

In either instance, the time course and extent of clinical response to the drug may be altered because of changes in dose or rate and extent of absorption.

Both factors, rate and extent of drug absorption, can be affected by the dosage form in which the drug is contained. The

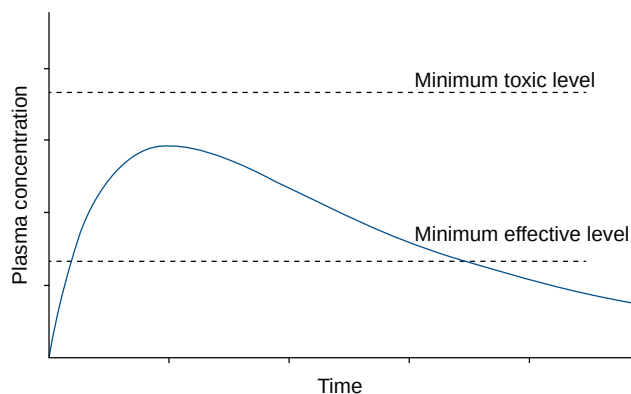


Figure 5-2. Typical plasma-level curve of a drug with effective and toxic (side-effect) profile levels defined.

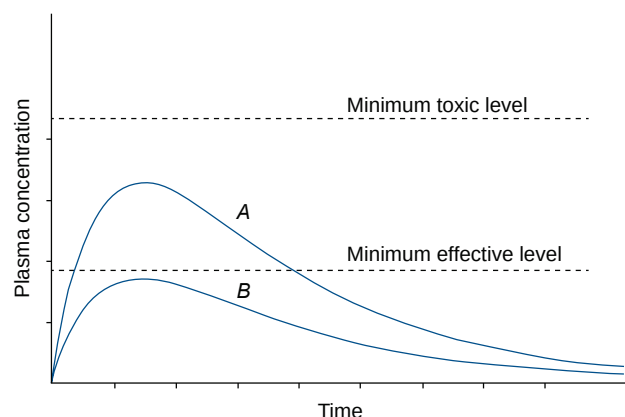


Figure 5-3. Effect of the extent of drug absorption from a dosage form on drug-plasma levels and efficacy. The extent of absorption from dosage form B is 50% of that from dosage form A.

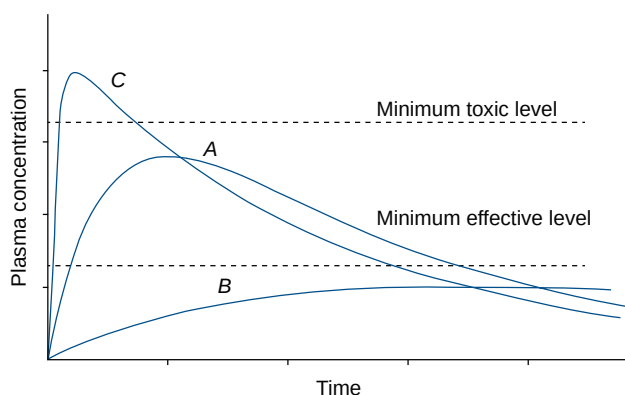


Figure 5-4. Effect of the rate of drug absorption from a dosage form on the plasma-level profile and efficacy. The rates of absorption from dosage forms B and C are 1/10 and 10 times those from dosage form A.

effect of rate of absorption may be intentional, as in controlled-release products, or unintentional, for example, as brought about by a change in the composition and/or method of manufacture of the dosage form.

The choice of the inactive ingredients (excipients) used to prepare a dosage form is up to the individual manufacturer. It is through these changes in composition and manufacturing technique that unintended changes in bioavailability and bioequivalence may occur. Revalidation of bioequivalence may be needed for major changes in the manufacturing process, whereas small changes may not raise significant bioavailability concerns. In situations involving minor changes in the manufacturing process, comparative dissolution testing of the original and reformulated product provides adequate documentation of continued product quality, if the resulting dissolution profiles are similar. These considerations apply to all drug manufacturers, both innovator and generic companies.

BIOEQUIVALENCE TESTING

The awareness of the potential for clinical differences between otherwise chemically equivalent drug products has been brought about by a multiplicity of factors that include, among others:

- better methods for clinical efficacy evaluation
- development of techniques to measure microgram or nanogram quantities of drugs in biological fluids

- improvements in the technology of dosage form formulation and physical testing
- awareness of reported clinical differences from the literature in otherwise similar products
- increased cost of classical clinical evaluation
- objective and quantitative nature of bioavailability tests
- an increase in the number of chemically equivalent products on the market because of patent expirations and the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), which established the generic drug approval procedures that are in place today.

The increase in the number of drugs that are available from multiple sources frequently has placed people involved in the delivery of healthcare in the position of having to select one from among several marketed products. As with any decision, the more data available, the more comfortable one is in arriving at the final decision. The need to make these choices, in light of the potential failure to demonstrate *in vivo* equivalence between products or different batches of the same product, has increased the demand for quantitative data. Bioequivalence testing represents a bridging alternative to clinical testing for efficacy and safety in such cases and is the means by which generic drugs are approved for marketing. In addition, this is also the means by which the quality of all drug products is maintained in situations involving major changes in formulation or manufacturing process.

Requirements for bioequivalence data on drug products should be applied reasonably. The reason for bioequivalence testing should not be overlooked (i.e., it is used as a surrogate, in certain situations, for the clinical evaluation of drug products). In some instances, bioequivalence data cannot reliably be obtained if the bioanalytical methodology is not available. However, in such cases pharmacodynamic data may provide a more sensitive, objective evaluation of a product's therapeutic equivalence and may be explored as an alternative evaluation method in the absence of relevant bioanalytical methodology.

Basic pharmacokinetic evaluation of bioavailability data is not necessary to show bioequivalence of two drug products. Pharmacokinetics has its major utility in the prediction or projection of dosage regimens and/or in providing a better understanding of observed drug reactions or interactions that result from the accumulation of drug in some specific site, tissue, or compartment of the body. The basis for the conclusion that two drug products are bioequivalent must be that the drug concentrations measured in a biological matrix, or alternatively the pharmacological response, for one drug product are essentially the same for the second drug product. The more straightforward decisions in the evaluation of bioequivalence between two drug products are those in which the two products are exactly superimposable (definitely bioequivalent). Those in which the two products differ in their bioequivalence parameters by a large amount, such as 50% or more, are most definitely not bioequivalent. Statistical evaluation of the data is necessary for all situations, particularly for data that exist between these two extremes.

METHODS FOR DETERMINING BIOEQUIVALENCE

Bioequivalence usually involves human testing but sometimes may be demonstrated using an *in vitro* bioequivalence standard, especially when such an *in vitro* test has been correlated with human *in vivo* bioavailability data. In other situations, bioequivalence may be demonstrated through comparative clinical trials or pharmacodynamic studies.

The FDA has categorized (21CFR320.24) various *in vivo* and *in vitro* approaches that may be utilized to establish bioequivalence. These are, in descending order of accuracy, sensitivity and reproducibility,