Biopharmaceutics and Drug Interactions

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THIRD EDITION

Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

Library of Congress Cataloging in Publication Data

Cadwallader, Donald E. (Donald Elton), 1931–
Biopharmaceutics and drug interactions.

Bibliography: p.
Includes index.
1. Biopharmaceutics. 2. Drug interactions.
I. Title. [DNLM: 1. Drug interactions. 2. Biopharmaceutics. QV 38 C126b]
RM301.4.C33 1983 615'.7 83-3278
ISBN 0-09004-7049

Second Printing, August 1985

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Preface

Members of health care teams have become increasingly aware of the importance of publications in the fields of biopharmaceutics and drug interactions. This has become very pleasantly clear from the great demand by pharmacists, physicians, nurses, educators, and students for previous editions of this book. It is apparent that health care professionals want to keep up-to-date on current pharmaceutical and medical problems; and to acquaint themselves with new concepts, procedures, and evolving subject areas pertinent to their profession.

Rapid developments in the fascinating and expanding areas of biopharmaceutics and drug interactions have led to the publication of this third edition. Sections on bioavailability testing and drug product selection have been expanded, and many new figures and tables—published recently in the scientific literature—have been added. Full citations of the original literature are presented under the figures and tables so that the reader can acquire an appreciation of the scientific work being carried out and become knowledgeable of the primary scientific literature dealing with biopharmaceutic and drug interaction phenomena.

Any member of the health care team possesses the ability and background to understand and absorb the subject material presented in this text on the basis of his academic training in the biological and physical sciences and the associated pharmaceutical and medical sciences. The areas of biopharmaceutics and drug interactions utilize and correlate all these disciplines in a manner relevant to the contemporary practice of pharmacy and medicine. The illustrations, whenever possible, relate directly to drugs and drug products familiar to the practitioner in his daily routine.

This volume is designed for the practitioner who does not have the time to master these subjects through a formal curriculum, but who wants access to information on current pharmacy and medicine. For students in any of the health care professions the book can serve as a primer on biopharmaceutics and drug interactions. My hope is that the reader will be encouraged to gain greater insight into biopharmaceutics and drug interactions by utilizing the references in the selected reading list given at the end of this book, by enrolling in independent study courses, and by attending seminars and continuing education courses on these subjects.

Donald E. Cadwallader

Acknowledgments

I would like to thank Dr. B. V. Pisha for his continuing encouragement, guidance, and editing of all three editions of this work. I am also indebted to many colleagues and friends at the College of Pharmacy, University of Georgia, for their help and advice.

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Introduction

To understand the underlying principles of biopharmaceutics and the basic principles of drug interactions, it is necessary to understand the fundamentals of drug absorption, transport (distribution), metabolism (biotransformation), and excretion. This is the common ground for discussing and correlating biopharmaceutical phenomena and drug interactions. The purpose of the discussions in this book is to develop this understanding.

Presentation of the subject material is as follows:

1. The fundamentals of a specific phenomenon, e.g., absorption and drug absorption
2. A discussion with illustrations on the biopharmaceutical relationships pertaining to the specific phenomenon, e.g., the influence of formulation on the absorption of drugs
3. Drug interactions that might or do occur with relation to the specific site, e.g., drug interactions in the gut and gut wall

The same type of format is used for transport, metabolism, and excretion phenomena. Mathematical equations have been kept to a minimum and when used are strategically placed in the text so that the reader has a clear idea of the practical applications of the subject matter before analyzing the equations.

Biopharmaceutics

You can hardly pick up a professional journal or newsletter today, or for that matter a magazine or newspaper, without reading something about generic equivalency, therapeutic efficacy, drug availability, drug substitution, or drug product selection. All these topics are part of a field of pharmacy called biopharmaceutics. The concept of biopharmaceutics has arisen out of a combination of disciplines. When drug product development research became highly active during the last 15 to 20 years, it was recognized that a great deal of background knowledge is required for studying the many factors that affect the biological activity of administered medication. It was realized that dosage form design, for example, must, in the final analysis, take these factors into account.

The term biopharmaceutics and a definition of it first appeared in print in a review article by Wagner in 1961 (4):

> Biopharmaceutics encompasses the study of the relation between the nature and intensity of the biological effects observed in animals and man and the following factors: *(a)* simple chemical modification of drugs such as formation of esters, salts, and complexes; *(b)* modification of the physical state, particle size and/or surface area of the drug available to the absorption sites; *(c)* presence or absence of adjuvants in the dosage form with the drug; *(d)* the type of dosage form in which the drug is administered; and *(e)* the pharmaceutical process or processes by which the dosage form is manufactured.

Therefore, biopharmaceutics may be defined as the study of the influence of formulation on the therapeutic activity of a drug product or of the relationships between some of the physical and chemical properties of the drug and its dosage forms and the biological effects observed following its administration in its various dosage forms. Biopharmaceutics includes: (a) all possible effects observed following the administration of the drug in its various dosage forms; (b) all possible effects of dosage forms on biological response; (c) all possible physiological factors which may affect the drug contained in the dosage form; and (d) the dosage form of the drug itself. To prevent possible confusion with other rapidly growing and closely related fields, biopharmaceutics is best defined as *the study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacological or therapeutic activity of drug products in clinical application.*

The biological availability of a drug may be greatly affected by its physical state and by the dosage form in which it is administered. A given drug may show different degrees of availability from one dosage form to another when given by the same route. For example, a drug might have different onsets of action or show different blood level concentrations depending on whether it is administered as a tablet, capsule, or suspension. Also, a given drug might show different availability from the same dosage form depending on the manufacturer; there is also the possibility of different availability from one lot of the drug to another, even when made by one manufacturer.

There are many and varied pharmaceutical factors that may alter drug availability. Some of the physicochemical factors are:

1. The particle size of the drug in solid dosage form. Some drugs, e.g., griseofulvin, are made available as the micronized form to increase their low dissolution rate. Inadequate particle size was one cause of the relatively

poor availability of several generic chloramphenicol capsules which were recalled several years ago.

2. Particle size of the dispersed phase in an emulsion.

3. Tablet disintegration. This may depend not only on the type and quality of the disintegrating agent but also on the hardness of the tablet.

4. Tablet and capsule adjuncts. Diluents, binders, and lubricants, for example, may decrease water permeability and consequently reduce drug absorption.

5. Tablet coatings. Some of these may release drugs unevenly or not at all.

6. Crystalline drug properties. The crystalline, or amorphous, form of the drug may have a profound effect on the dissolution rate of the drug after ingestion. Cortisone acetate and novobiocin are examples of drugs whose availabilities are altered by changes in their crystalline forms.

The physicochemical properties of a compound are measurable characteristics by which the compound may interact with other systems. The physical and chemical properties of a molecule are determined by the number, kind, and arrangement of the atoms. Both properties are closely interrelated, and for this reason the term "physicochemical" is the preferred expression of the properties that relate to biological action rather than either physical properties or chemical properties used singly. Some examples of physicochemical properties are solubility, pH, surface activity, hydrogen binding, and partition coefficients.

In addition to physicochemical factors, of course, drug availability is affected by various pharmacological, physiological, and biochemical factors.

Although the field of biopharmaceutics has grown rapidly during the last decade, it has only been in recent years that subject material pertaining to biopharmaceutics has been incorporated into the undergraduate pharmacy curriculum. Therefore many practicing pharmacists have never been introduced to this new and important area of pharmacy. The individual pharmacist has the responsibility of understanding biopharmaceutics. He should be able to discuss with physicians, nurses, and other professionals the effects of dosage forms on the therapeutic efficacy of a drug. The pharmacist should understand why two drug products may be different and should be able to make informed drug product selections for his patients.

Drug Interactions

Drug interaction is a phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another (or the same) drug(s). It occurs, more specifically, when the overall biological

response to the simultaneous (or nearly so) administration of two or more drugs is markedly different from the simple sum of the effect of each compound given singly. During the last several years there has been an increasing awareness of drug interactions, e.g., when one drug alters the expected therapeutic response of another drug that has been administered just prior to, simultaneously with, or just after another drug. Interest in adverse drug reactions and drug–drug interactions is currently enormous and is growing every day.

Drug interactions present a complex and profound problem. They may arise either from *alteration of the absorption, distribution, biotransformation, or excretion* of one drug by another, or from a combination of their actions or effects. With newer and more sophisticated and potent drugs, and with the proliferation of drug therapy, the problem can only get worse! Understanding the basic mechanisms by which drug interactions occur will help the members of the health team to anticipate possible drug–drug interactions. This situation gives the pharmacist an opportunity to utilize his education and training for the benefit of the patient. Knowledge of drug actions, reactions, and interactions, and communicating this information to other members of the health team, are among the most important functions of the pharmacist.

If, as one study has shown (1), the patients in our hospitals receive an average of 14 medications during their hospital stay, what are the chances that one of these drugs will affect the subject's reactivity to another drug?

Although outpatients usually take fewer medications than hospitalized patients, the risk of a drug interaction in today's world is increased by several factors:

1. The practice of polypharmacy is alive and well today. When a patient sees a physician he may expect more than one medication for an ailment. The tradition of prescribing a combination of drugs is still common. Indeed it is difficult to adequately treat many ailments with a single medication.

2. In this age of specialization, many patients see more than one physician concurrently, none of whom may be aware of the others' involvement with the patient and his drug therapy.

3. Self-medication is prevalent, and multiple-drug use is practiced by individuals who take numerous over-the-counter (OTC) medications for various ailments.

4. Many drugs used today are very potent and are given in doses that are close to their toxic level (the therapeutic index of the drug is low). Also many drugs have powerful side effects.

5. Many modern drugs are polymechanistic and may affect several or many physiological and biochemical systems of the body.

In an interesting and realistic presentation, Knyvett of the Royal Brisbane Hospital, Australia (2), pointed out that this is the era of symptomatic therapy in medicine. From the enormous amount of prescribing by physicians and self-medication by patients, it is apparent that many people seem to have a psychological need to take something for every ailment, real or imagined. If a person has a common cold, he may take some aspirin, drink plenty of fluids, and retire to bed. This is a good treatment, but how many people would be happy to pay the doctor for the same advice? Experiences indicate that if patients were treated at the physician's office or clinic, or in a hospital, they would get some or all of the drugs appearing in Table 1-1. This regimen is quite different from the self-medication therapy; however, each of these preparations has symptomatic value. Each can be justified, and in many cases several combinations might be essential to the proper management of the patient. On the other hand, each may on some occasions produce side effects, and many, if given concurrently, may give rise to drug interactions.

Of special concern to the medical community is the high potential for drug interactions in the elderly. As people grow older, they demonstrate a need for multiple-drug therapy to treat a variety of disease states. The ingestion of numerous drugs coupled with the possible decrease in physiological capabilities make the elderly particularly susceptible to adverse drug reactions and drug–drug interactions. Age is an important physiological factor in the consideration of drug reactions and interactions. Studies indicate that there is an increased incidence of adverse drug reactions in geriatric patients, and an estimate by Melmon (3) suggests that the risk of drug

TABLE 1-1. *Treatment of common cold*

Possible self-treatment
Aspirin
Hot or cold drinks
Perhaps some favorite alcoholic beverage
Bed rest
Possible physican treatment after visit
Compound codeine tablets—for aches and pains
Nose drops—to free the nasal airway
An antihistamine—to reduce nasal "allergic" congestion
An inhalant—to reduce nasal congestion
An antitussive syrup—to ease a cough, present or anticipated
Often an antibiotic—to "prevent" secondary infection
Sleeping pills—to ensure some restful nights
Sometimes a laxative—prescribed by the doctor who is aware of the constipating effects of codeine and fever

Adapted from Knyvett, A. F. (1968): The hazards of drug therapy. *Austral. J. Pharm.*, 49:394.

reaction in patients 60 to 70 years old is almost double that in adults 30 to 40 years old. Although renal and hepatic function in the elderly may be diminished, there is no evidence that these factors in general are responsible for the high incidence and severity of drug reactions and interactions in the elderly. The aging process leads to many disease states—some acute, some chronic—and one disease state may lead to another. This theme is developed in Fig. 1-1. Diabetes, arthritis and bursitis, glaucoma, emphysema, ulcers, and other gastrointestinal (GI) disorders, urinary tract problems, high blood pressure, atherosclerosis, heart failure, and stroke are only some of the diseases associated with advanced years. It is a fortunate senior citizen who suffers only one or two of these conditions. In addition to this, the eyes of the elderly are getting weak, hearing is failing, and constipation is becoming a way of life. Figure 1-1 shows that multiple diseases—in fact many single diseases (high blood pressure, for example)—lead to multiple-drug therapy; and the more drugs a patient takes into the body, the greater are the chances of adverse reactions and interactions. The geriatric patient, because of a general debilitated condition will likely have a stronger reaction or interaction to drug therapy than a younger adult.

Dispensers of drugs should be aware of the potential for lawsuits associated with harm to a patient from a drug interaction. There is growing recognition by the courts that detection of adverse drug interactions during the dispensing of medication is the responsibility of the pharmacist, and proper procedures should be utilized to monitor patients' prescriptions. Maintenance of patient medication records to assist in detecting potentially dangerous drug interactions is an increasing service provided by pharmacists. Some states mandate that patient profiles be maintained.

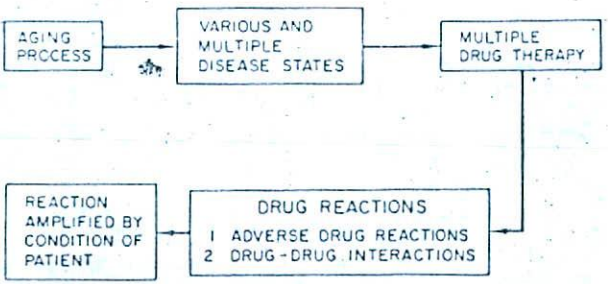

FIG. 1-1. Multiple-drug use and adverse reactions in the aged. [From Cadwallader, D. E. (1979): Drug interactions in the elderly. In: *Drugs and the Elderly—Social and Pharmacological Issues*, edited by D. M. Peterson, F. J. Whittington, and B. P. Payne, p. 81. Charles C Thomas, Springfield, IL.]

One must view drug interactions in the proper perspective. Many interactions apparently are clinically insignificant to the majority of patients. Also, to deny a patient needed therapy might not be warranted because of a possible interaction. In fact, most combinations of drugs can be safely used provided the patient is carefully counseled and monitored. Nevertheless, the physician must be informed of a potential hazard and the pharmacist should be a prime source of this information.

Drug interactions have been known for years to be a beneficial aspect of drug therapy as well as a danger. For example, the concomitant administration of probenecid (Benemid®) with penicillin products is a widely used practice for maintaining high antibiotic blood levels. Most antidote therapy for drug overdose involves nullifying the toxic drug by interaction with another drug.

The potential hazards, and the ones we need to be aware of, are those unwanted or unsuspected interactions that may cause harm to the patient. The main emphasis in this book is placed on drug interactions that result from interactions with other drugs (drug–drug interactions). Some of the important hazards that result from interactions with components of the diet, e.g., milk and tetracyclines, monoamine oxidase inhibitors (MAOI) and tyramine in aged cheese, are discussed. Possible interactions with environmental components such as cigarette smoke and some interactions with endogenous physiological chemical agents are also presented. In all these discussions a drug is "any biologically active substance," a widely accepted definition.

The means by which drug interactions occur, when they do, are varied and complex, including:

1. Action—chemical or physical—of one compound directly on another
2. Modification of GI absorption
3. Competition for protein-binding sites during transport
4. Modification of a drug's action at a receptor site
5. Acceleration or retardation of the metabolism of a given drug by modification of enzyme systems
6. Modification of the rate of urinary excretion-renal clearance.

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2

The Complex System

Whenever biopharmaceutics and drug interactions are discussed, there is always reference to systems and events or sequences of events that are very complex. The pathways and sequence of events for drug disposition can be represented by various schemes and diagrams. Drug disposition is a term used to describe the simultaneous effects of distribution and elimination. To exert their biological effect, drugs must be soluble in and transported by body fluids, pass membrane barriers, escape excessive distribution into inert body depots (where they cannot act), endure metabolic attack, penetrate to their sites of action, and act so as to cause an alteration of a particular function—termed the *action* of a drug. This action, or biological response to a drug, is a consequence of the interaction of that drug with the living system, causing some change in the biological state that was present before the drug was administered.

Figures 2-1 and 2-2 illustrate the complexity and the great amount of interplay that takes place between absorption, transport, metabolism, and excretion. When a drug is administered orally, it first must be dissolved in the GI fluids before transport can take place across a membrane into the systemic circulation. The drug is then distributed to various parts of the body where it may be stored, metabolized, exert a pharmacological action, or be excreted. As drugs may be distributed indiscriminately to all parts of the body, they sometimes exert actions that are not needed and therefore in many instances cause undesirable side effects.

The transfer of drug from the site of administration (e.g., GI tract or intramuscular injection site) to the bloodstream is called *absorption*. The absorption process can be greatly influenced by formulation factors. *Distribution* is associated with the transfer of drug from the circulating blood to other parts, or compartments, of the body (e.g., lymph fluid, muscle tissue, liver, kidneys). *Metabolism*, or biotransformation, of drugs takes place in the liver and other parts of the body. The main site of *excretion* for most drugs is the kidney. The term *elimination* refers to the combined effects of metabolism and excretion.

Arrows are used in the diagrams in this book to indicate direction of flow or transport of the drug. In many cases arrows go in both directions across membranes, and in some instances they indicate that cyclic processes are taking place, e.g., the recycling of drug back to the small intestine via the bile fluid, with its subsequent reabsorption. The Ks above the arrows indicate rates of absorption, transport, metabolism, and excretion, these rates being different for different drugs and membranes and for different conditions of the system. The purpose of the science of *pharmacokinetics* is to study the time course (rates, or Ks) of drug and metabolite concentrations and amounts in various tissues and excreta, and to construct models to interpret such

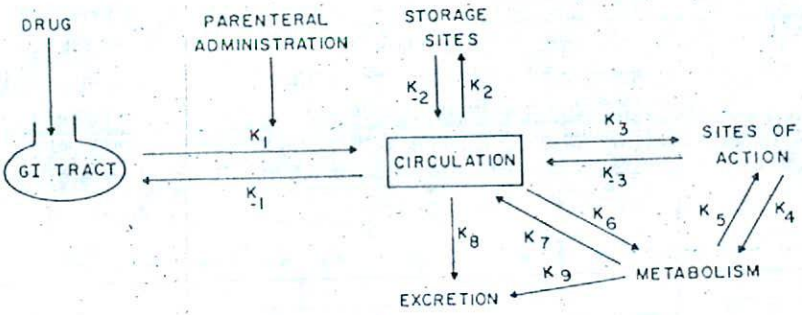

FIG. 2-1. Complex of events between drug administration and action

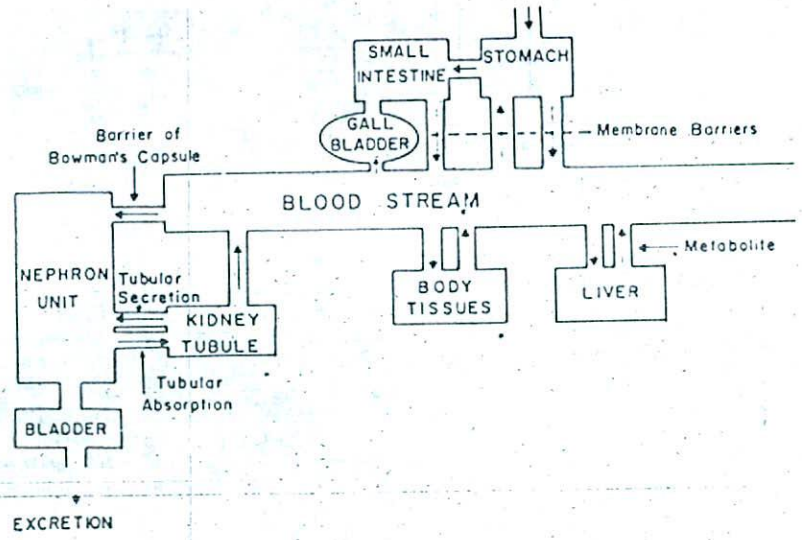

FIG. 2-2. Absorption, transport, metabolism, and excretion. [Adapted from Stuart, D. M. (1968): Drug metabolism—Part II. PharmIndex, 10:5.]

data. Pharmacokinetics is mainly concerned with the kinetics, or dynamics, of absorption, distribution, metabolism, and excretion of drugs and some endogenous substances; it includes the relationship between pharmacological response and concentrations of drugs or their metabolites in body fluids. A function of pharmacokinetics is to describe what the body does to a drug. The application of pharmacokinetics to establishing the optimum dose size and dosing intervals for an individual patient is of growing interest to the medical care team.

The fact that only a fraction of the original dose of drug taken orally may reach the systemic circulation is shown in Fig. 2-3. There are many factors that can influence the amount of drug that reaches the systemic circulation. As soon as a drug is ingested, it enters a hostile environment, where it may be destroyed by chemical and enzymatic action, be incompletely absorbed, be bound and inactivated in tissues, or be metabolized in various body compartments. The drug that finally reaches the systemic circulation is now subjected to additional binding, biotransformation, and excretion before a

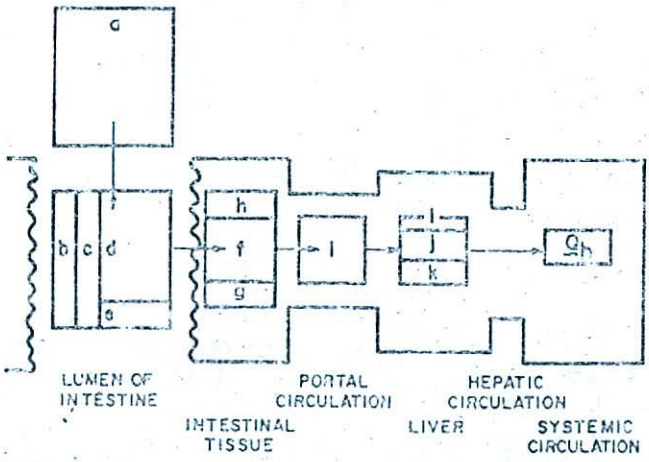

FIG. 2-3. Some factors that influence the amount of drug reaching the systemic circulation. **a** = Total drug in dosage form. **b** = Drug degraded in GI fluids (e.g., acid-catalyzed hydrolysis). **c** = Drug metabolized by GI enzymes (e.g., esterases). **d** = Drug in solution which is absorbed. **e** = Drug in solution which is not absorbed. **f** = Drug in intestinal mucosa which is transferred to the portal circulation. **g** = Drug in mucosal cell which is metabolized (e.g., glucuronide) which may pass into the lumen or the portal circulation. **h** = Drug bound in intestine (e.g., iron). **i** = Drug in portal circulation. **j** = Drug first in liver then transferred to the body. **k** = Drug in liver where it is metabolized. **l** = Drug bound in liver. Q_b = Amount of drug which finally reaches the body. [From Barr, W. H. (1968): Principles of biopharmaceutics. *Am. J. Pharm. Educ.*, 32:958.]

portion finally reaches its sites of action, where it must achieve adequate concentration to produce its characteristic effects.

It seems that a lot is expected of a drug, especially when taken orally: It must travel through the labyrinth of obstacles and hazards present in the complex system of the body, and when it finally arrives at its sites of action it is expected to elicit a pharmacological response. Why give a drug orally if so much can happen to it before it even reaches the systemic circulation? Why not give it by injection and circumvent most of the problems associated with absorption? It should be kept in mind that a complex organism such as man has few direct routes of entry for a drug, and the oral route is probably the most convenient. Fortunately, for most orally administered drugs, a sufficient amount of active ingredient does reach the sites of action. When drugs are taken orally, they are absorbed from the GI tract into the portal circulation and transported immediately to the liver (Fig. 2-4). Some drugs during this first pass through the liver may be metabolized

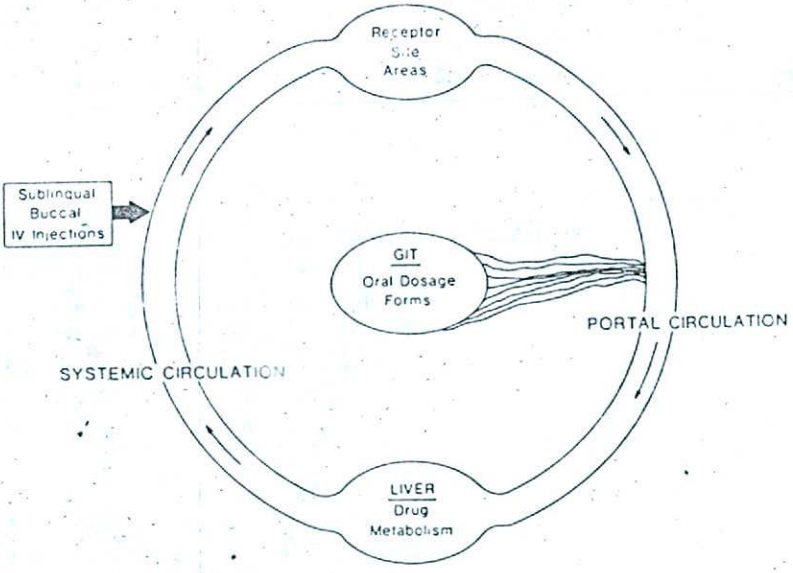

FIG. 2-4. First-pass effect. Some drugs when administered orally have a considerable fraction of their original dose metabolized by liver enzymes before they reach the systemic (general) circulation. Removal of drug during its first passage through the liver before passing into the systemic circulation is the *first-pass effect.* If the drug is administered by the buccal or sublingual route or by intravenous injection, the liver is by-passed and a larger fraction of the dose reaches the systemic circulation and eventually the receptor site areas.

extensively, with only a small fraction of the original dose reaching the systemic circulation; this results in poor bioavailability and ineffective therapy.

The direct routes of administration are oral, buccal or sublingual, alveolar, and rectal. The indirect routes of administration are by puncture (subcutaneous, intramuscular, or intravenous injection) and via the skin (percutaneous absorption). Injections, especially those given intravenously, allow efficient and rapid utilization of drugs, but they are uncomfortable for the patient and require trained personnel. Absorption of drugs through the skin is usually inefficient and slow. However, a topically applied nitroglycerin ointment (Nitroglyn®, Nitro-Bid®) is an effective dosage form, and a novel dosage form for prevention of motion sickness (Transderm-Scop®) depends on the steady delivery of scopolamine through the intact skin and into the bloodstream. A dosage form (Transderm-Nitro®) that allows the controlled passage of nitroglycerin through a membrane and into the skin and bloodstream has been recently marketed. The buccal or sublingual route is used for some hormone drugs and nitroglycerin; breakdown of these drugs is minimized by avoiding the GI tract and circumventing the first pass through the portal circulation. Some antibiotics are very efficiently absorbed by direct nebulization into the lungs. Many drugs can be administered rectally; however, the American public has never been very excited about using suppositories. Oral routes are preferred in our American society and are used whenever possible.

There are a large number of factors that affect the individual's response to drugs. Genetic composition is probably the main single cause for variability in the response to drugs. Each individual has a unique, complex system that controls the absorption, distribution, biotransformation, and elimination of drugs. Some individuals absorb orally administered drugs more efficiently than others, and normal liver and kidney functions can vary considerably from person to person. The system becomes more intricate when the impact of environmental factors is considered. Numerous environmental factors (Fig. 2-5, outer circle) can impinge on the intrinsic genetic factors and possibly modify genetically controlled functions. This helps explain why responses to the same dose of drug may differ widely in apparently similar patients. Some patients respond to a drug exactly as described in the literature, whereas others have no clinical response. Some subjects attain a high blood level of a drug and others a low level for the same dose. One patient may respond violently to a side effect or a drug interaction, whereas another who is receiving identical therapy exhibits no significant adverse response. Such is the nature of man. Individuality and

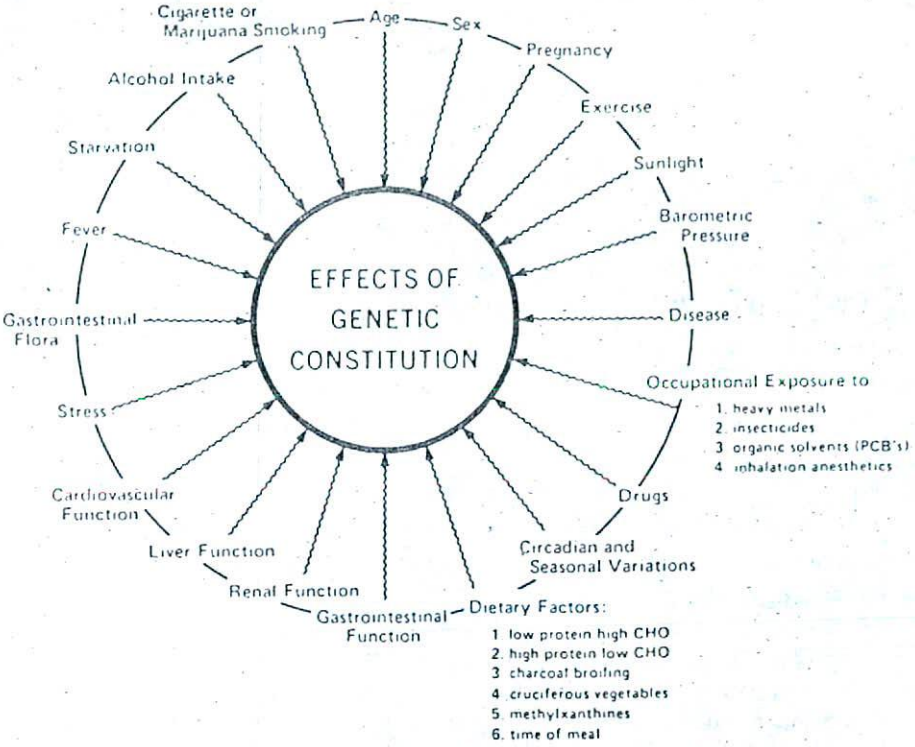

FIG. 2-5. Environmental factors affecting drug distribution in human subjects. The outer wheel shows established or suspected environmental factors that can alter genetically controlled rates of drug elimination. Lines from each environmental factor to the inner wheel are wavy, suggesting that genetically controlled rates can be modified at several levels and not necessarily at the genetic level. A line joins environmental factors to suggest that several of these factors are associated and interdependent, rather than independent. [From Vesell, E. S. (1981): The influence of host factors on drug response. VI. Hepatocellular diseases. *Rational Drug Ther.*, 15:1–8.]

variability among patients in regard to drug disposition and response as well as adverse reactions and drug interactions is the norm and should be expected.

3

Biological Half-Life, Elimination Rate Constant, and Volume of Distribution

Biological Half-Life

For most drugs the disappearance rate from the body at any time is proportional to the concentration at that time. The biological half-life is usually defined as the time required for the reduction to one-half of the initial drug activity after the drug has been absorbed and has reached a desirable level of activity. It may also be described as the time it takes for the body to eliminate half of a given dose of drug by excretion, metabolism, or a combination of the two. The biological half-life is a property of the drug itself and is not dependent on the manner in which the drug may be administered. If the biologocal half-life is known, the total drug intake for a given period of time can be calculated and adjusted to produce the dosage needed for long-term effects.

A half-life value can be readily determined for most drugs by administering a dose of the drug to a subject, taking blood samples at various time intervals, and then assaying them for drug content. Blood level data that might be obtained for a hypothetical drug under these conditions is presented in Table 3-1. If these blood concentrations are plotted against time on linear x–y graph paper, the curve shown in Fig. 3-1, an exponential curve, is obtained. A straight-line curve is obtained for the same data if the blood concentrations are plotted against time on semilogarithmic graph paper (Fig. 3-2). This is characteristic of a first-order, or exponential, process, meaning that the drug disappearance rate at any time is proportional to its concentration at that time.

If elimination of a drug follows an exponential process, the period during which the drug falls from one blood concentration to one-half this concentration is called the biological half-life. If the straight line in Fig. 3-2 is extrapolated to the y-axis, the concentration of drug in the blood immediately

TABLE 3-1. *Data for determination of biological half-life of drug*

Time after i.v. administration (min)	Blood level (mg/100 ml)
10	8.6
20	7.5
30	6.5
60	4.2
80	3.2
100	2.4
120	1.8

The drug (dose 1.0 g) was injected intravenously into a subject, and blood samples were taken at specific time intervals. Each sample was analyzed for its drug concentration.

after injection (C_0) is determined (approximately 10 mg/100 ml). One-half of this initial concentration is 5 mg/100 ml, and the time it takes for the blood concentration to fall to this level is approximately 50 min. This is the biological half-life ($t_{1/2}$) for this drug; the same time value would be obtained for an 8 mg/100 ml concentration falling to 4 mg/100 ml or 6 mg/100 ml to 3 mg/100 ml. Try this out yourself by determining the time interval between any selected concentration of Fig. 3-2 and one-half this concentration.

Figure 3-3 shows blood levels of theophylline after oral and intravenous administration. When a drug is administered by rapid intravenous injection,

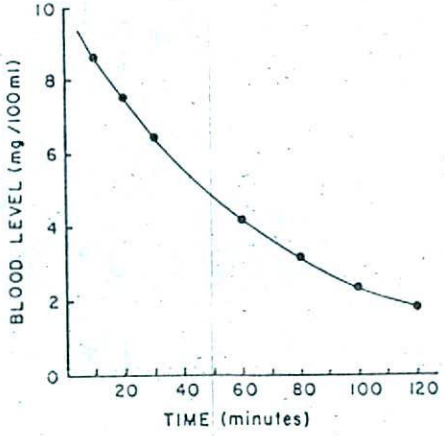

FIG. 3-1. Exponential curve for blood level data.

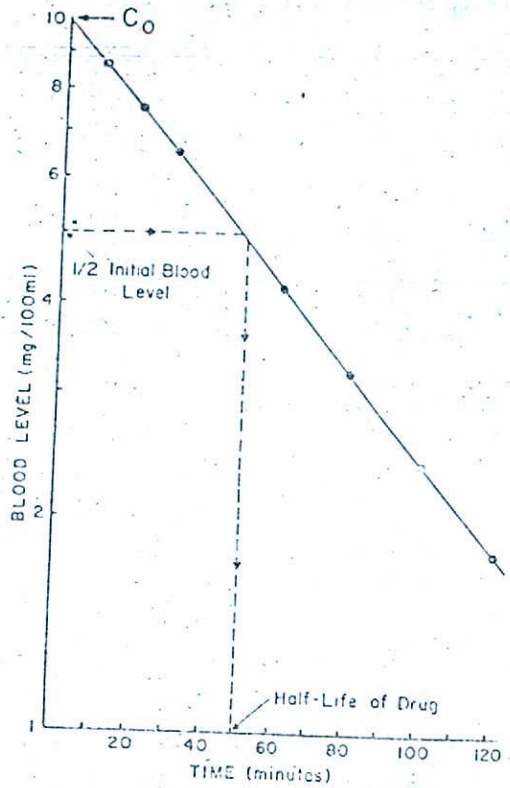

FIG. 3-2. Linear plot of blood level data and determination of drug half-life.

the maximum concentration in the blood is reached at once and begins to decline immediately, whereas with oral administration the drug levels first increase, reach a peak, and then decrease. After the peak blood level is reached, the orally administered theophylline is eliminated from the body at the same rate as the intravenously administered drug. The elimination part of the oral theophylline curve is parallel to that in the intravenous curve. The biological half-life for theophylline can be determined from this elimination curve and from the intravenous curve; it would be the same in each case. This illustrates the fact that the biological half-life of a drug is independent of the route of administration.

The biological half-life is a property of the drug as much as a melting point or a refractive index is a property of a chemical compound. The half-life is usually different for different drugs. Some half-life values for various drugs are presented in Table 3-2. The biological half-life is an important

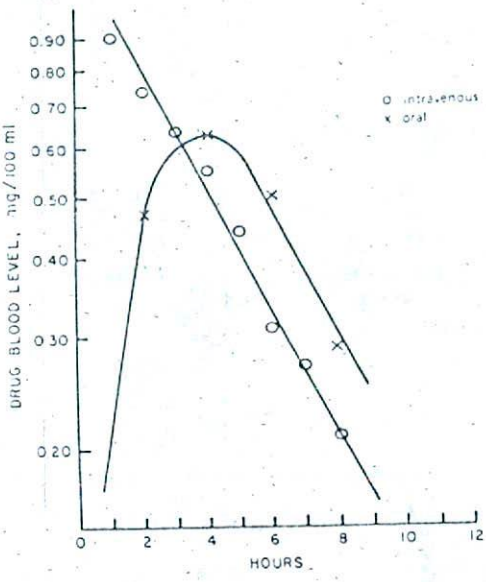

FIG. 3-3. Theophylline blood levels following intravenous and oral administration. [From Swintosky, J. V. (1956): Illustrations and pharmaceutical interpretations of first order drug elimination rate from the blood stream. *J. Am. Pharm. Assoc.*, 45:395.]

TABLE 3-2. *Some biological half-life values (human subjects)*

Drug	$t_{1/2}$ (hr)
Indomethacin	1–2
Penicillin G	<1
Salicylic acid	19
Sulfathiazole	3.5
Sulfanilamide	8.8
Sulfadiazine	16.7
Sulfadimethoxine	41
Tetracycline	8
Theophylline	3
Tolbutamide	5

Values were obtained from the following sources: Krüger-Theimer, E., and Bunger, P. (1961): *Arzneim-Forsch.*, 11:867; Swintosky, J. V. (1956): *J. Am. Pharm. Assoc.*, 45:395; Hucker, H. B., et al. (1966): *J. Pharmacol. Exp. Ther.*, 153:237; Stowers, J. M., et al. (1958): *Lancet*, 1:278.

TABLE 3-3. *Some biological half-life values for normal human subjects and patients with renal failure*

Drug	$t_{1/2}$ (hr)	
	Normal	Renal failure
Cephalexin	1.4	14.4
Colistimethate	4.8	18.0
Lincomycin	4.7	9.3
Methicillin	0.5	3.8
Insulin	2.0	5.1

From Gibaldi, M., and Perrier, D. (1972): Drug distribution and renal failure. *J. Clin. Pharmacol.*, 12:201.

drug parameter and is necessary for establishing rational dosage regimens for drugs, e.g., initial doses (priming or loading doses), maintenance doses, or doses for sustained-action dosage forms.

The biological half-life of a drug can be influenced considerably by the condition of a patient. For example, patients with impaired kidney function may excrete certain drugs much slower than normal subjects, and high blood levels of the drugs are maintained for longer periods of time. As seen in Table 3-3, the biological half-lives of some drugs are considerably greater for patients with renal failure than for normal subjects. These data can have significant implications in the treatment and dosage regimens of patients with decreased kidney function.

Elimination Rate Constant

Elimination of a drug from the body is usually a result of metabolic and excretion processes. The rate of elimination for most drugs is described by a first-order process* (Fig. 3-1). The elimination rate constant (K_e) for a first-order process can be calculated using the equation

*The equation for a first-order rate process is

$$K_e = \frac{2.3}{t} \log \frac{C_o}{C}$$

where C_o is the initial concentration, and C is the concentration at time t. When the original concentration decreases to one-half the original concentration, the equation becomes

$$K_e = \frac{2.3}{t_{1/2}} \log \frac{C_o}{C_o/2} = \frac{2.3}{t_{1/2}} \log 2 = \frac{0.693}{t_{1/2}}$$

$$*K_e = \frac{0.693}{t_{1/2}}$$

For the data presented in Fig. 3-2, the rate constant would be

$$K_e = \frac{0.693}{50 \text{ min}} = 0.0139 \text{ min}^{-1}$$

Like the drug half-life ($t_{1/2}$), the elimination constant (K_e) is an important parameter that describes the action of the body when it is disposing of a drug.

Apparent Volume of Distribution

When a drug is absorbed and arrives in the general circulation, it is rapidly apportioned throughout the body. This distribution involves transfer from the circulating blood to other parts of the body (e.g., plasma, lymph fluid, muscle tissue, liver, kidneys). *Apparent volume of distribution* is a term used to describe this distribution and is defined as the volume of body fluids in which a drug appears to be dissolved. The word *apparent* is used as this is not an actual anatomical volume but a hypothetical one in which the drug appears to be uniformly distributed.

The apparent volume of distribution (V_d) can be calculated by dividing the amount of drug in the body by the blood (plasma) concentration and is expressed as —

$$V_d = \frac{\text{total amount of drug in body}}{\text{blood (plasma) concentration, } C_c}$$

When an intravenous injection is administered, the total amount of intact drug in the body immediately after injection is known, as it is the same as the dose administered. The blood concentration immediately after injection (C_0) can be determined by extrapolating the blood level curve (Fig. 3-2) to the y-axis at zero time. For the data presented in Table 3-1 and Fig. 3-2 the volume of distribution for the drug is

$$V_d = \frac{\text{total dose injected}}{\text{blood concentration, } C_o} = \frac{1000 \text{ mg}}{10 \text{ mg/100 ml}} = 10 \text{ liters}$$

The volume of distribution depends on the drug's physicochemical properties, e.g., water and lipid solubility and degree of protein binding. Patient characteristics, e.g., weight and body composition (lean or obese), also affect the volume. A larger volume of distribution (30 to 45 liters for a 75-kg male) indicates that the drug is distributed to various parts of the body with a small fraction of the drug remaining in the plasma. A relatively small volume of distribution (6 to 12 liters) indicates that a major fraction of the drug remains in the plasma probably as a result of protein binding.

The apparent volume of distribution is a valuable parameter that can be used to relate the amount of drug in the body to its blood (plasma) concentration, to determine or predict the distribution of drugs, and to compare the distribution characteristics of various drugs.

4

Bioavailability, Blood Levels, and Urinary Excretion Data

Bioavailability

Drugs are not usually administered in the form of the simple drug compound but, rather, as complex mixtures of a drug with various other ingredients required to make an effective, stable, and convenient dosage form. *Dosage form* refers to the gross physical form in which a drug is administered to or used by a patient. *Drug product* may be defined as the delivery system of the drug, consisting of the drug formulated into a suitable dosage form alone or in combination with other active ingredients. The quality of a drug product is directly related to the efficiency with which the product delivers the drug, the reliability with which delivery is achieved, and the stability and safety of the product. The availability of a drug from a particular dosage form involves both the rate and the completeness with which the drug product delivers an absorbable form of the drug to an absorption site in the body. Almost anything that is done to the drug product can alter the delivery rate and the amount of drug delivered to the desired place in the human body.

Drug availability defines the efficiency of drug products or dosage forms as drug delivery systems, and a reduction in drug availability can be considered equivalent to a reduction in dosage. The primary proof of drug availability is the quantification of the biological (pharmacological) response—the clinical efficacy. Except for very obvious and easily measured responses (e.g., changes in blood pressure, pulse rate, or temperature), it is very difficult to quantitate direct clinical responses. Even in apparently obvious cases it requires a large number of subjects to obtain reliable statistical data because of the great variability in people.

Clinical responses can be plotted against time after the administration of drug to give a clinical profile of the drug (Figs. 4-1, 4-2, and 4-3). Figure 4-1 presents clinical proof that aspirin and acetaminophen (APAP) are very

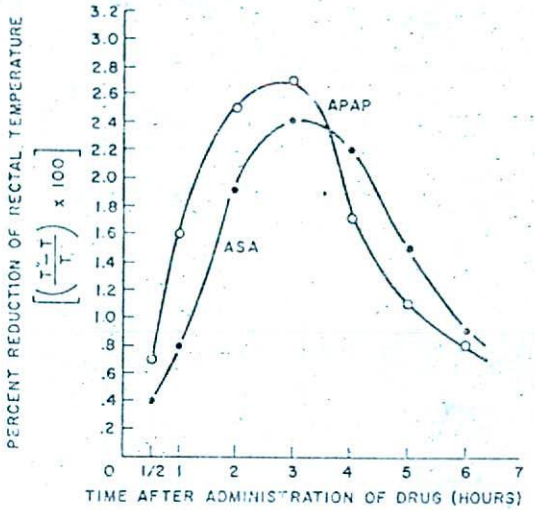

FIG. 4-1. Comparative effects of aspirin and N-acetyl paraaminophenol (APAP) in reducing fever. The graph shows the time response curve for the mean percent reduction of original temperature in 50 febrile patients receiving a single dose (based on age) of these agents. T° is the rectal temperature before medication and T the temperature at a given time after drug administration. [From Barr, W. H., and Penna, R. P. (1969): O.T.C. internal analgesics. In: *Handbook of Non-Prescription Drugs*, p. 30. American Pharmaceutical Association, Washington, D.C.]

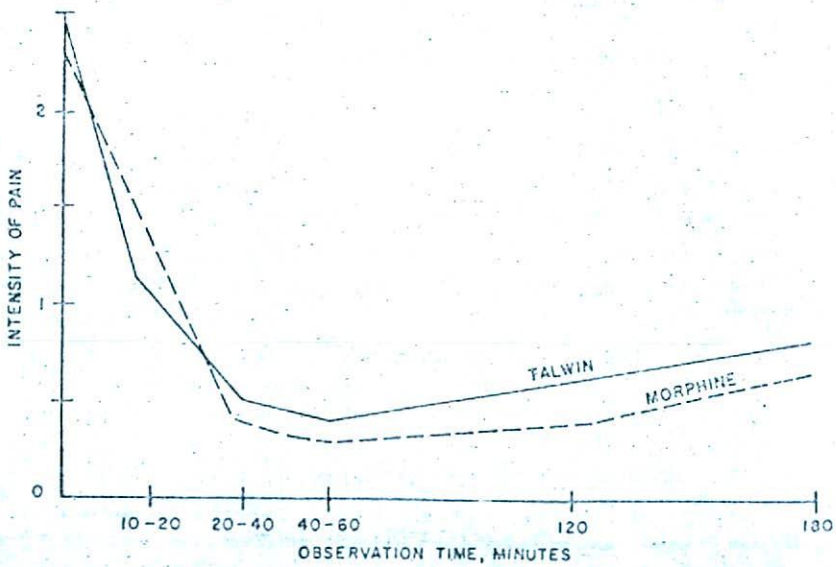

FIG. 4-2. Comparative analgesic efficiency of pentazocine (Talwin®) 30 mg and morphine 10 mg. [From *Talwin*, p. 25. Winthrop Laboratories Professional Literature, Winthrop Laboratories, 1967.]

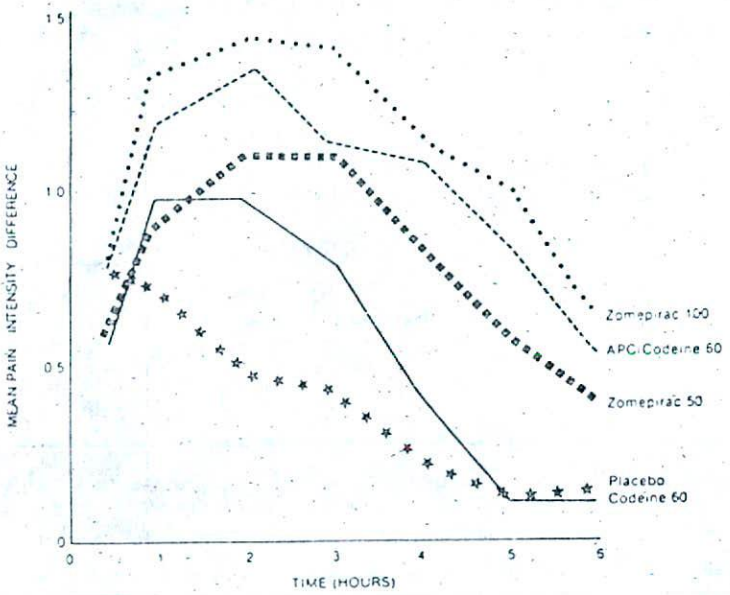

FIG. 4-3. Time-action curve of mean pain intensity difference versus time for the duration of the 6-hr study. [From Baird, W. M., and Turek, D. (1980): Comparison of zomepirac, APC with codeine, codeine and placebo in the treatment of moderate and severe postoperative pain. *J. Clin. Pharmacol.*, 20:243–249.]

effective as antifebrile agents. Figure 4-2 shows the results of a clinical study in which pentazocine (Talwin®) was compared with morphine for analgesic activity. Pentazocine 30 mg was found to be equivalent to morphine 10 mg in overall analgesic efficiency. This clinical study involved 260 patients with postoperative pain. The degrees of pain (severe, moderate, mild, or none) were determined subjectively. The results of a similar study involving the analgesic zomepirac (Zomax®) are shown in Fig. 4-3. This study used 148 patients randomly divided into five groups, and each group was given one of the following drugs: zomepirac 50 mg, zomepirac 100 mg, APC with 60 mg codeine, codeine 60 mg, and placebo. The patients were questioned about their pain just before dosing, at 30 min and 1 hr after administration, and at hourly intervals thereafter for a total of 6 hr after dosing. At each observation, patients were asked to rate their pain intensity from none to severe on a four-point scale. Each individual curve on Fig. 4-3 represents the average pain intensity differences scores computed as the difference between the subjects' initial pain intensity and each pain intensity value at subsequent hours. These examples not only illustrate the complexity

of clinical studies but also help explain the extraordinary time and expense required to carry out these studies.

This is the reason there is so little in the scientific literature on the generally accepted clinical proof or disproof of differences in the availability between drug products of the same drug entity. It would be prohibitively expensive to clinically evaluate all the manufacturers' drug products of meperidine (Demerol®), for example, to determine if they alleviate pain equally well, or if some of the products are better than others.

In addition to the primary proof of a definite response, secondary proof of drug availability is the appearance of the drug and/or its metabolites in blood or urine. This is based on the reasonable assumptions that: (a) the drug exercises its action when introduced into the body; and (b) the biological activity is related to the amount of drug that appears in the body.

It is relatively easy, rapid, and inexpensive to carry out experiments or evaluations wherein subjects are given a drug, and then their blood or urine is analyzed for drug content at various time intervals. The methods for carrying out these studies are discussed in Chapter 9.

Drug availability has been an issue of importance for the last decade, and many new terms and phrases have emerged to describe this phenomenon. Confusion arises out of the interchangeable use of such phrases as "biological availability," "physiological availability," "therapeutic equivalence," and "generic equivalence." Increased significance has been attached to the meaning of the phrases by the emergence of one of them—biological availability—as a major criterion for the continued marketing of drugs cleared by National Academy of Sciences/National Research Council (NAS/NRC) panels on the efficacy of drugs marketed before October 10, 1962. The short-hand term "bioavailability" has been suggested to cover the testing now required by the Food and Drug Administration (FDA) for the continued marketing of drugs whose efficacy has been cleared by the NAS/NRC review. Proof of bioavailability is required by the FDA for drugs already on the market, providing their New Drug Applications do not already provide such data, as well as for "me too" products, marketed on the basis of NAS/NRC statements of efficacy. In this context, bioavailability seems to mean *blood levels or similar tests that establish a significant concentration of a drug in the bloodstream or other body systems where its presence is understood to be effective.* Currently, bioavailability is the preferred term to indicate the rate and relative amount of administered drug which reaches the general circulation intact.

Blood Levels and Urinary Excretion Data

Blood level data can be plotted against time. The data in Fig. 4-4 were obtained by giving 250 mg dicloxacillin (Dynapen®) to fasting adult subjects,

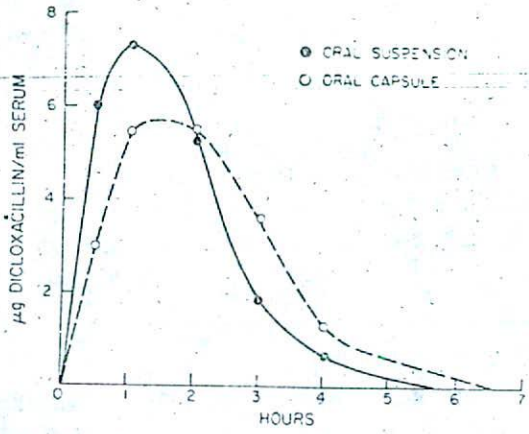

FIG. 4-4. Average levels of dicloxacillin activity in serum of fasted subjects receiving 250 mg dose. [From Doluisio, J. T., LaPiana, J. C., Wilkinson, G. R., and Dittert, L. W. (1970): Pharmacokinetic interpretation of dicloxacillin levels in serum after extravascular administration. In: *Antimicrobial Agents and Chemotherapy—1969*, edited by G. L. Hobby, p. 49. American Society for Microbiology, Bethesda.]

withdrawing blood samples 0.5, 1, 2, 3, and 4 hr after drug administration, and analyzing the samples for drug content. The blood level curves establish that a high concentration of dicloxacillin in blood is obtained rapidly after the drug is administered orally by capsule or suspension. Meaningful proof of bioavailability of another dicloxacillin drug product (whether it be another manufacturer's capsule or suspension, or a different dosage form, e.g., a suppository) can be established if similar blood level curves are obtained after its administration.

Figures obtained by plotting drug–blood concentrations against time are called drug–blood profiles or patterns. Figure 4-5 shows a typical blood profile after oral administration of a drug. Note that there is an optimum or desired therapeutic or pharmacological concentration range where the drug produces its characteristic effect. The lower level of this range is called the minimum effective concentration (MEC); this level must be achieved before a drug can have its desired effect. Drug concentrations above the minimum toxic concentration (MTC) usually produce toxic effects.

The left-hand side of the curve in Fig. 4-5 indicates the rate of absorption, and the right-hand portion shows the excretion rate of the drug. The length of time the drug level remains above the MEC is the duration of action for the dose of drug.

Urinary excretion data can be plotted against time to construct urinary profiles. Subjects are given a dose of drug, total urine samples are collected, and the samples are analyzed for drug content. Usually the cumulative

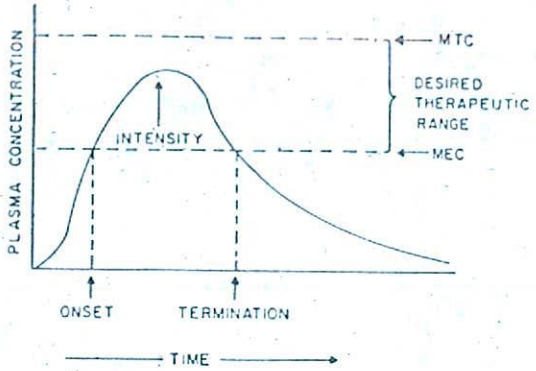

FIG. 4-5. Relationship between the blood profile and factors which effect the pharmacological activity. [Adapted from Barr, W. H. (1968): Principles of biopharmaceutics. *Am. J. Pharm. Educ.*, 32:958.]

amount of drug or its metabolite excreted in the urine is plotted against time, and the total amount of excreted drug is readily determined after any specific time period. Figure 4-6 shows cumulative urinary excretion curves for equal doses of the same drug in different tablet formulations. The excretion curves show that the drug in tablet A has a much higher cumulative value than does the drug in tablet B. Hence the drug was much better absorbed from tablet A than from tablet B. Blood (plasma) level curves corresponding to the above cumulative urinary excretion curves obtained for the same tablets are shown in the bottom part of Fig. 4-6.

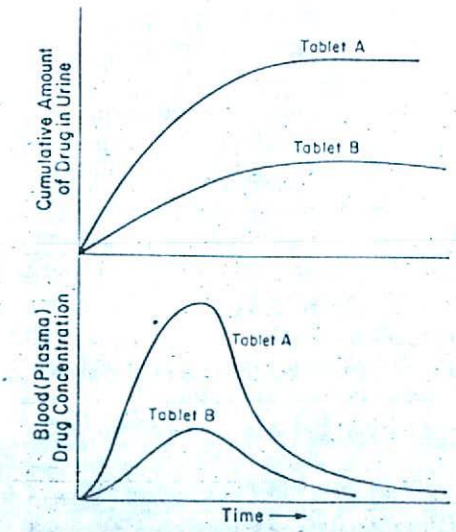

FIG. 4-6. Corresponding plots showing the cumulative urinary excretion curve *(top)* and the blood (plasma)–time curve *(bottom)* obtained following the administration of a single dose of two tablet formulations.

Biological availability of a specific drug from various dosage forms or under various conditions can be compared on the basis of how much drug is in one or more of the body compartments (blood or urine) as a function of time. Blood or urinary excretion profiles can be used to evaluate the bioavailability of drugs from drug products. The most valid application of blood concentration or urinary excretion profile data is *comparing the relative performance of a single drug*—when that drug exists, for example, in different physical forms, different dosage forms, or different size doses, or is administered via different routes or to different subjects. Blood and urinary excretion profile data are useful for comparing:

1. Different physical forms of drugs (e.g., fine powder or large granules)
2. Different dosage forms (e.g., suspension versus capsule)
3. Different size doses
4. Different dosage regimens (e.g., one tablet q 4 hr or two tablets q 6 hr)
5. Different manufacturers' products
6. Availabilities of drug in ill and normal subjects
7. Different routes of administration (e.g., intravenous versus oral)
8. Drug availability in different age and sex groups
9. The effect of adjuvants and manufacturing processes on drug availability

Most of the above comparisons would involve bioavailability testing to determine the relative bioavailability of an active ingredient in two or more formulations or regimens without regard for the actual amount absorbed from each formulation or condition. This is called *comparative bioavailability testing* and is the type of testing that drug manufacturers carry out to compare their products with those of their competitors or established standards (Chapter 9). *Absolute bioavailability testing* is used to determine the relative amount of administered drug that is absorbed from a dosage form as compared to the intravenous administration of the same dose of drug (considered to be 100% absorbed).

Examples of blood and urinary excretion are presented in Figs. 4-7 through 4-10. Figure 4-7 shows the difference in blood profiles when sulfadimethoxide (Madribon®) is administered as either tablets or a suspension. It is obvious that the suspension allows more rapid and efficient utilization of the drug. In Fig. 4-8 we see that different doses of zomepirac (Zomax®) give different plasma level curves, and the height and size of the curves are directly related to the dose of the drug administered. Figure 4-9 shows the urinary excretion data for several manufacturers of chloramphenicol capsules. It can readily be seen that products A, B, and C have lower cumulative urinary excretion rates than Chloromycetin® and therefore can be assumed

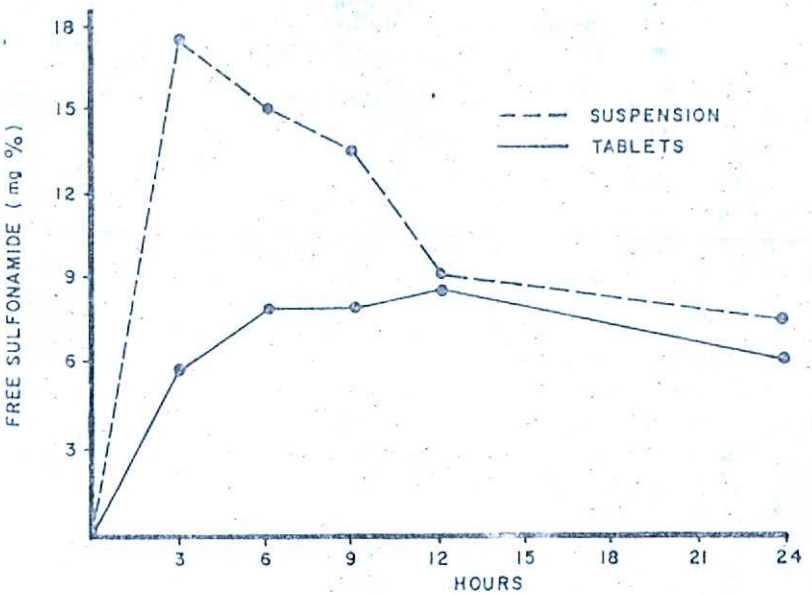

FIG. 4-7. Average blood levels of free sulfonamide in children following oral administration of sulfadimethoxine (Madribon®) (1 g/m²) in tablets and suspensions. [From Levy, G. (1963): Biopharmaceutical considerations in dosage form design and evaluation. In: *Prescription Pharmacy*, edited by J. B. Sprowls, p. 70. Lippincott, Philadelphia.]

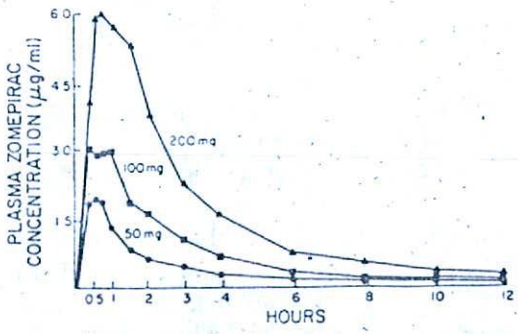

FIG. 4-8. Mean zomepirac plasma levels from 21 subjects after various doses by oral administration of zomepirac tablets. [From Nayak, R. K., et al. (1980): Zomepirac kinetics in healthy males. *Clin. Pharmacol. Ther.*, 27:395–401.]

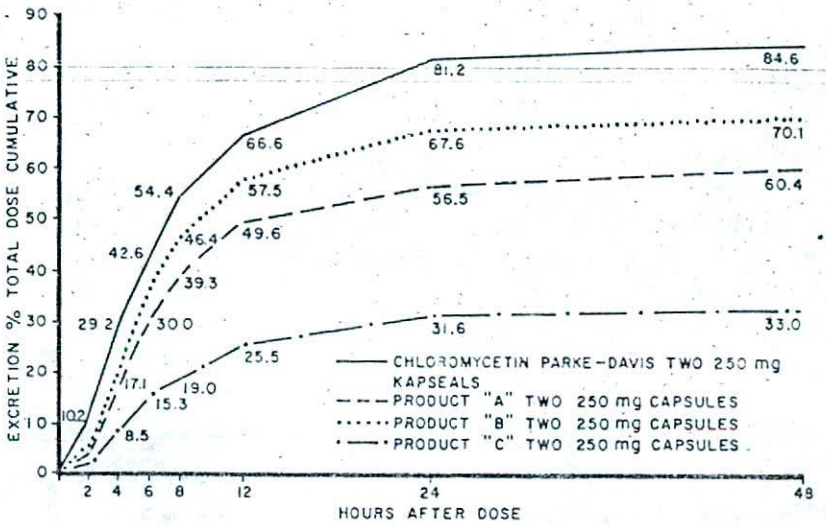

FIG. 4-9. Cumulative urinary excretion profile of four different brands of chloramphenicol. [Data are from Glasko, A. J., et al. (1968): An evaluation of the absorption characteristics of different chloramphenicol preparations in normal human subjects. *Clin. Pharmacol. Ther.*, 9:472. Figure is from *The Blue Sheet. Drug Research Reports*, Vol. 10, 1967.]

to be less efficiently absorbed. Data such as these were used as the basis for initiating drug recalls for products A, B, and C in 1968 (because of relatively poor biological availability of the drug). A comparison of the urinary excretion rates of acetaminophen after administration of the drug in various suppository formulations is seen in Fig. 4-10, which demonstrates the variability of absorption of acetaminophen from rectal dosage forms. It appears that only one suppository dosage form (C) approached the rate and extent of absorption exhibited by the oral tablet dosage form.

Bioavailability expertise has greatly expanded during recent years, and some [illegible] suggested by Wagner (1) are:

1. Determination of those formulation factors that alter the bioavailability of an active ingredient in a drug product or products
2. Establishing generic equivalence or inequivalence of two or more drug products or formulations
3. Determining the effect of food on the absorption of an active ingredient in a drug product or formulation
4. Establishing that one drug interferes with the absorption of another drug, and how to avoid the interaction

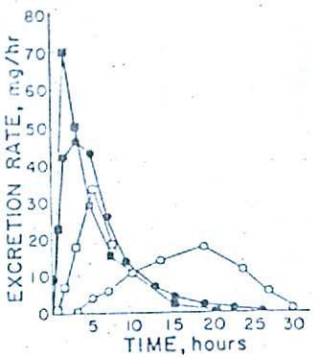

FIG. 4-10: Plot of excretion rate in one subject of apparent acetaminophen versus time for several formulations of acetaminophen: (▤) tablet; (○) suppository A; (□) suppository B; (●) suppository C. [From Feldman, S. (1975): Bioavailability of acetaminophen suppositories. *Am. J. Hosp. Pharm.*, 32:1173–1175.

5. Determining if increasing age or specific disease states influence the absorption of an active ingredient in a drug product or formulation
6. Assessment of the magnitude and variability of the "first-pass" effect with specific drugs after oral administration and the degree to which other routes of administration, e.g., rectal, nasal, or buccal administration, avoid this effect
7. As one of the tools in quantitatively assessing drug–drug interactions

Many more drug–blood and urinary excretion profiles illustrate the effect of dosage forms, drug product design and formulation, and drug interactions on the biological availability of drugs. These are discussed later in this book.

It is quite another matter, however, to compare and evaluate blood and urine profiles of drugs which are closely related chemically and therapeutically, and to make conclusions regarding their clinical usefulness. The chemotherapeutic sulfonamides, penicillins, and tetracyclines are examples. Figure 4-11 depicts the serum levels of four tetracyclines after oral administration of single 500-mg equivalents of the hydrochlorides to normal young adults. The amount of antibiotic in the blood serum was determined by microbiological assay. All of the tetracyclines attain peak blood levels at about the same times; the absorption period for demethylchlortetracycline is longer than the others. It might be erroneously assumed that the antibiotic with the highest blood level is the most useful. Other factors, e.g., the site of infection, distribution of the antibiotic, and differences among the various antibiotics against particular organisms, must also be considered. In the absence of other supporting data, the blood concentration profiles are of no value in judging their clinical efficacy. There is no relevance unless the drugs are tested in patients for specific disease states. It should be emphasized that blood level data alone present an insufficient basis on which to judge the relative merits of structurally and therapeutically related drugs. The frequent

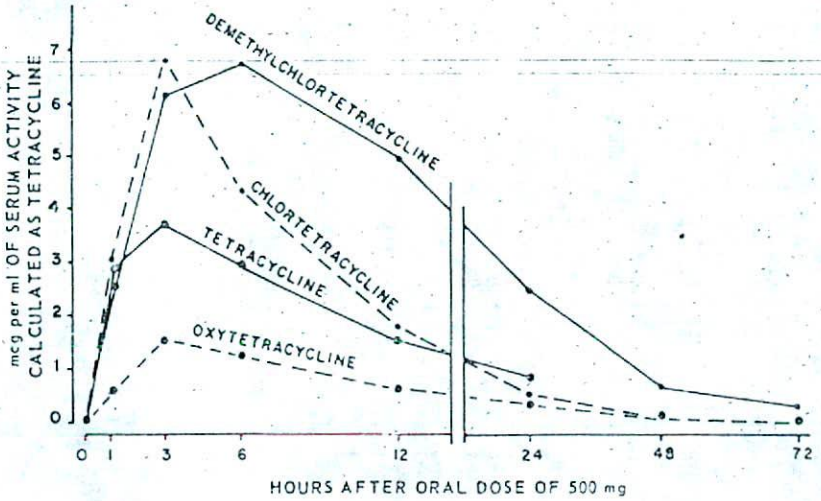

FIG. 4-11. Plasma levels of four tetracyclines expressed in terms of tetracycline activity. [From Kunin, C. M., and Finland, M. (1961): Clinical Pharmacology of the tetracycline antibiotics. *Clin. Pharmacol. Ther.*, 2:51.]

occurrence of antibiotic blood profiles in the drug promotional literature has been appropriately dubbed the "battle of the blood levels." These data should be critically evaluated with an awareness that there are a great many other factors that determine the usefulness and efficiency of drugs.

Interpretation of Drug Blood (Plasma) Level Curves

A typical single-dose drug blood level curve (serum concentration–time curve) is shown in Fig. 4-12. One can examine the curve and readily interpret the bioavailability data involving a single dose of a drug. The three main parameters used for describing a single-dose blood level curve are shown in Fig. 4-12 as peak height concentration, time of the peak height concentration, and area under the curve.

The *peak height concentration* represents the highest blood concentration attained after oral administration of a single dose of drug. This amount is usually reported in some concentration term, e.g., micrograms per milliliter (μg/ml). The height of the peak in Fig. 4-12 is 4.0 μg/ml.

The *time of peak height concentration* is the length of time it takes to attain the maximum drug concentration after oral administration. The time for peak concentration in Fig. 4-12 is 2 hr.

The *area under the curve* (AUC) is the mathematically calculated area under the blood concentration–time curve. A trapezoidal rule technique,

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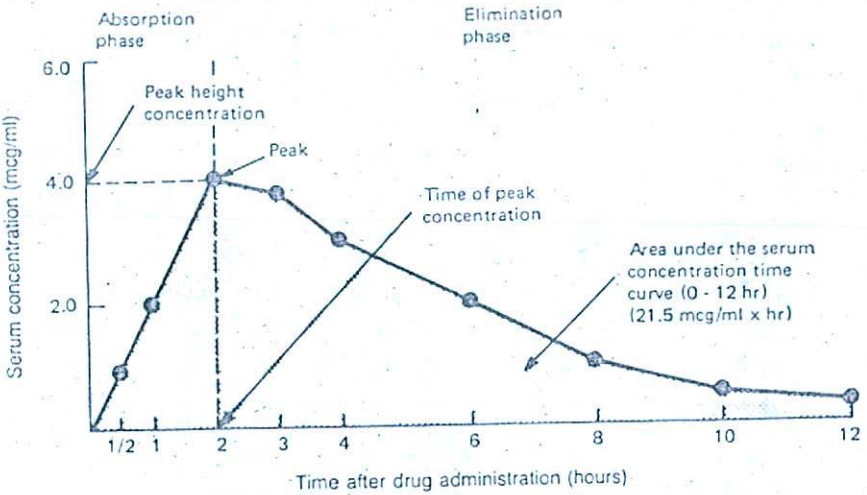


FIG. 4-12. Serum concentration–time curve following single dose of a drug that shows an absorption phase and an elimination phase. [From Dittert, L. W., and DiSanto, A. R. (1973): The bioavailability of drug products. *J. Am. Pharm. Assoc.*, NS13: 421–432.]

which involves geometrically dividing the area under the curve into parallelograms and right triangles, can be used to calculate the area. The area of each of the geometric forms is readily determined, and the total sum of these areas is the AUC. The AUC for Fig. 4-12 is 21.5 μg/ml × hours and is representative of the amount of drug absorbed after the administration of a single dose of drug. This is a very important parameter when comparing the bioavailability of the same drug administered in different formulations and dosage forms.

The blood level curve can take many shapes depending on the rate and extent of absorption of the drug. The overall height of the curve depends on the dose of the drug administered as blood levels are directly proportional to the amount of drug given. The amount of drug released and eventually absorbed from the administered dosage form affects the curve as a reduction in drug availability can be considered a reduction in dosage. A rapid or slow rate of absorption of the drug certainly affects the height and shape of the blood level profile.

Figure 4-13 illustrates several of the many results from different rates and extents of absorption from a variety of drug formulations. The blood (serum) concentration time curves represent the blood levels of equal doses of the same drug administered in different formulations.

Part I of Fig. 4-13 compares two formulations, A and B, and indicates that both formulations have approximately the same peak height time. For-

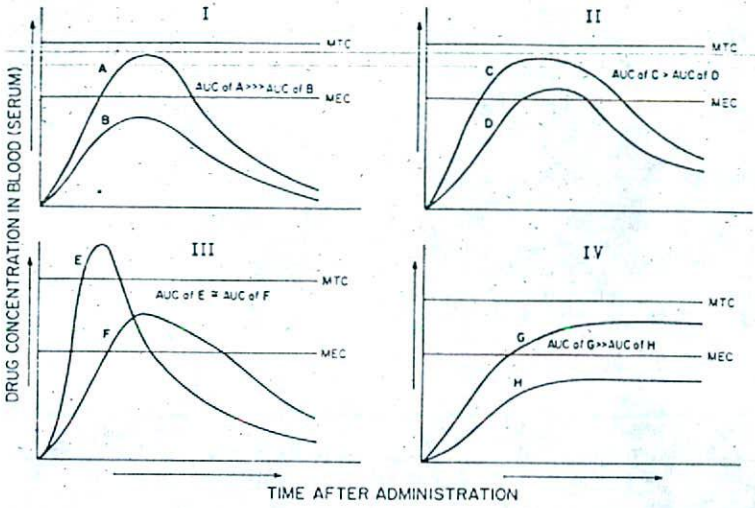


FIG. 4-13. Blood (serum)–time curves obtained following the administration of the same drug from various dosage forms.

mulation B, however, does not achieve an adequate blood level above the MEC and therefore would be an ineffective formulation.

Part II shows that formulations C and D attain effective blood levels, although formulation C has a longer duration of action than D as its blood level curve remains above the MEC for a longer period of time.

Part III indicates that formulation E would produce a toxic effect as the absorption of a significant amount of drug is very rapid, and the blood level exceeds the MTC. Formulation F gives a slower rate of absorption; however, adequate blood levels are achieved and therapeutic effectiveness is maintained for that period of time the curve remains above the MEC. Even though the two curves have different shapes, they both have approximately the same AUC, which indicates that the same amount of drug was absorbed from each formulation.

Part IV shows hypothetical curves for two sustained-release formulations. Formulation G maintains a steady blood level above the MEC and would be effective for a prolonged period of time. Formulation H gives a steady blood level, although the drug level remains below the MEC and the formulation would be ineffective.

Reference

1. Wagner, J. G. (1980): Bioavailability trials: a modern perspective. *Pharm. Int.*, 1:184–187.

5

Anatomy and Physiology of the Gastrointestinal Tract

The great majority of orally administered drugs are intended to be dissolved in and absorbed from the GI tract, and so a brief review of GI anatomy and physiology is warranted. The GI tract is a very complicated system. When an ingested drug descends through it, the drug encounters different environments with respect to pH, enzymes, electrolytes, fluidity, and surface characteristics, all of which can affect drug absorption and interactions.

Figures 5-1, 5-2, and 5-3 show the many features that make the GI tract an efficient absorption system. A copious blood supply is present, and the entire length of the tract is lined with mucous membranes through which various substances and drugs are readily transferred. The interior surface of the stomach is relatively smooth in contrast to the numerous folds and projections in the small intestine. Approximately 8 to 10 liters of fluid per day are produced by or secreted into the GI tract, and an additional 1 to 2 liters is obtained through food and fluid intake. The GI tract is highly perfused by a capillary network that allows efficient absorption and distribution of nutrients and drugs. This immediate circulation drains into the portal circulation, where the absorbed drug is carried directly to the liver and may undergo a first-pass effect (Chapter 2).

Stomach contents in man are usually in the pH range of 1 to 3.5, pH 1 to 2.5 being the most common range. Agitation of the gastric contents as a result of motor activity is mild but thorough because of the squeezing action of the gastric contractions. Materials may remain in the stomach for 30 min to several hours before moving through the pylorus to the duodenum. Transfer may be very rapid if a drug is taken on a fasting stomach or very slow if taken after a heavy, high-fat meal. The gastric emptying rate can be influenced by many factors, e.g., the type of food; volume, temperature,

FIG. 5-1. Digestive system anatomy of stomach and duodenum: anatomic relationships and variations of the stomach. [© Copyright 1959, CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from *The CIBA Collection of Medical Illustrations*, illustrated by Frank H. Netter, M. D. All rights reserved.]

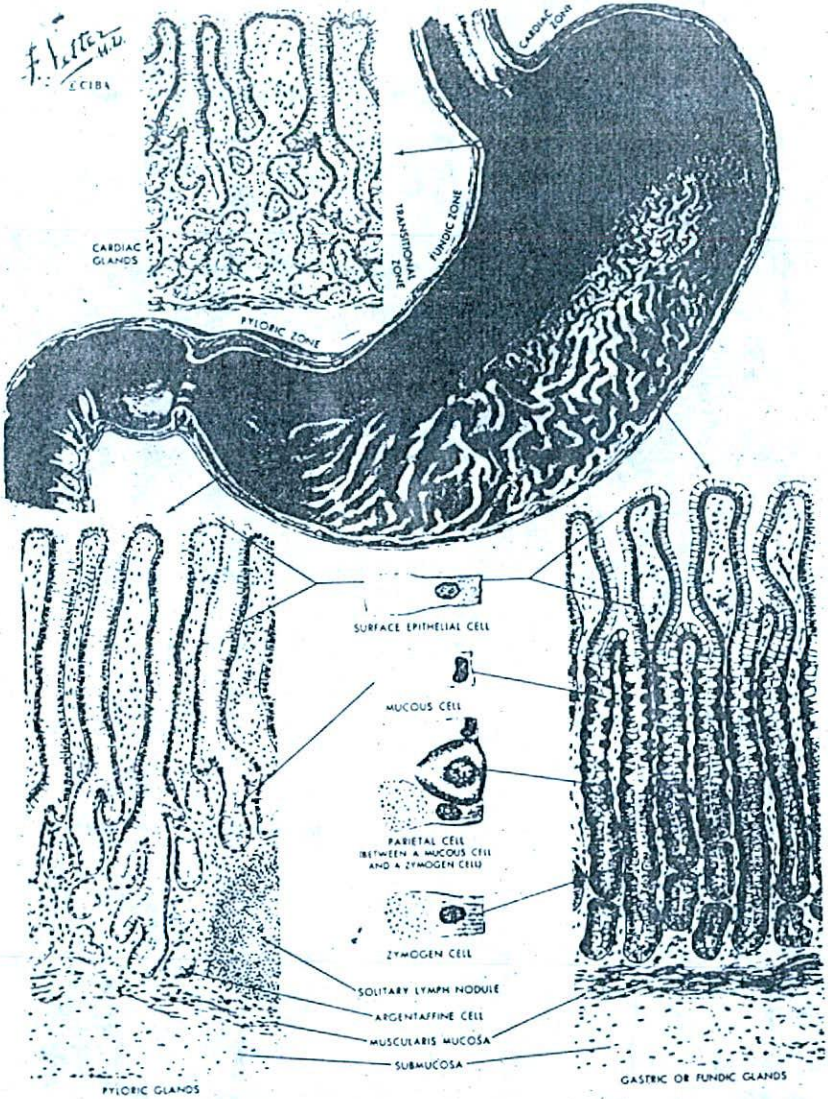


FIG. 5-2. Anatomy of stomach mucous membrane: histology. [© Copyright 1959. CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from *The CIBA Collection of Medical Illustrations*, illustrated by Frank H. Netter, M.D. All rights reserved.]

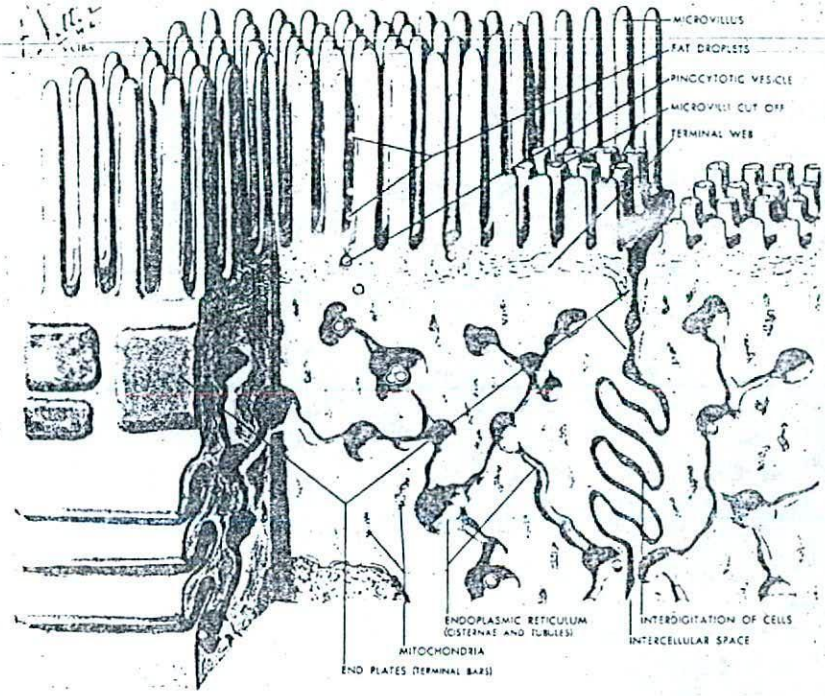


FIG. 5-3. Three-dimensional schema of striated border or intestinal epithelial cells (based on ultramicroscopic studies). [© Copyright 1962, 1979, CIBA Pharmaceutical Company, Division of CIBA-GEIGY Corporation. Reprinted with permission from *The CIBA Collection of Medical Illustrations*, illustrated by Frank H. Netter, M.D. All rights reserved.]

and viscosity of ingested contents; certain drugs; pH; buffer capacity; age; state of health; posture; and emotional condition.

After a material passes from the stomach to the duodenum, it is subjected to a drastic change of environment. The duodenal contents have a pH of 5 to 7, and many enzymes are present that were not in the gastric juices. There is a gradual increase in the alkalinity along the length of the GI tract, so that ultimately the pH may be 7 to 8 in the lower ileum (Fig. 5-4). The duodenum, jejunun, and upper regions of the ileum are the most efficient areas in the GI tract for absorption. The villi (Fig. 5-3) present a fantastically large surface area for transport and assimilation of substances into the systemic circulation. The capillary network in the villi and microvilli is the primary pathway by which most drugs reach the systemic circulation.

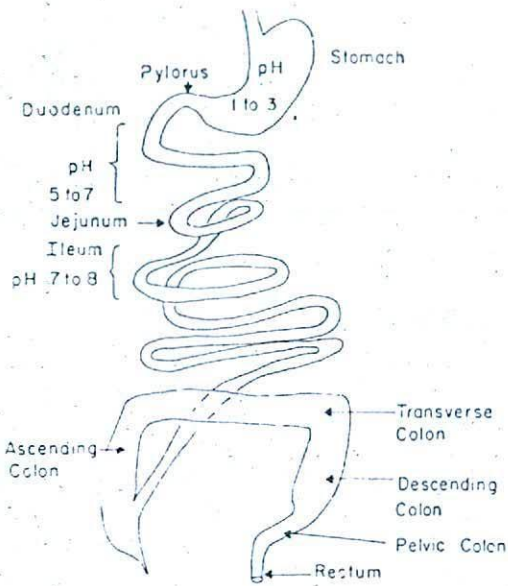


FIG. 5-4. GI tract showing the variations in pH.

Some drugs are absorbed better from the stomach than the intestine and vice versa; however, even those drugs that are compatible with gastric absorption are only partially absorbed (10 to 30%) from the stomach before passing on to the small intestine. The short residence time in the stomach and the limited surface area of this region restrict the amount of drug absorbed. For some drugs there are even specialized absorption sites where the drug is most efficiently absorbed. Therefore orally administered drugs should be in a physiologically available form (e.g., in solution rather than solid) by the time they reach their respective absorption sites. Because of the differences between the absorption properties of the stomach and intestine, any unusual decrease in the emptying time or delay in the transfer of a drug from stomach to intestine may affect the rate of absorption and thereby the onset of therapeutic activity. The absorption of relatively slowly absorbed drugs, e.g., digoxin and the tetracyclines, might be influenced by intestinal motility. The total amount of drug absorbed might be substantially decreased if passage through the intestine is rapid.

6

Mechanism of Drug Absorption

When a drug is introduced into the body by oral administration, it must gain access to the bloodstream where distribution processes take it to sites of action as well as to other parts of the body. For absorption to take place the drug must first pass through a membrane.

The Cell Membrane: The Gastrointestinal Barrier

The structure of the cell membrane is shown in Fig. 6-1. This model illustrates the lipoprotein theory of membrane structure where a lipid layer is sandwiched between protein layers. The lipid layer is the backbone of the membrane and is made up of complex lipid molecules (e.g., cholesterol and phospholipids) arranged so that the nonpolar end (lipid protein) of each molecule is directed inward and its polar end faces toward the outer surfaces. The layers of protein impart strength and elasticity to the membrane. The lipid membrane is discontinuous and penetrated at intervals by fluid-filled channels, or "pores." Water-soluble substances of small molecular size (less than 4 Å), e.g., urea, are absorbed by simple diffusion through the water-filled channels. Most drug molecules, however, are too large to be absorbed by this process. For most drugs it is possible to explain absorption on the basis that the cell membrane is a lipid layer through which drug molecules can pass. There are several mechanisms of absorption; the two main processes available for drug absorption from the GI tract after the drug is in solution are *passive diffusion* and *carrier transport*.

Passive Diffusion

The membrane plays a passive role in passive diffusion, or passive transfer, not actively participating in the transfer process. Most drugs pass through membranes by this mechanism, and the rates of transfer are determined by the physicochemical properties of the solute, the membrane, and the concentration gradient.

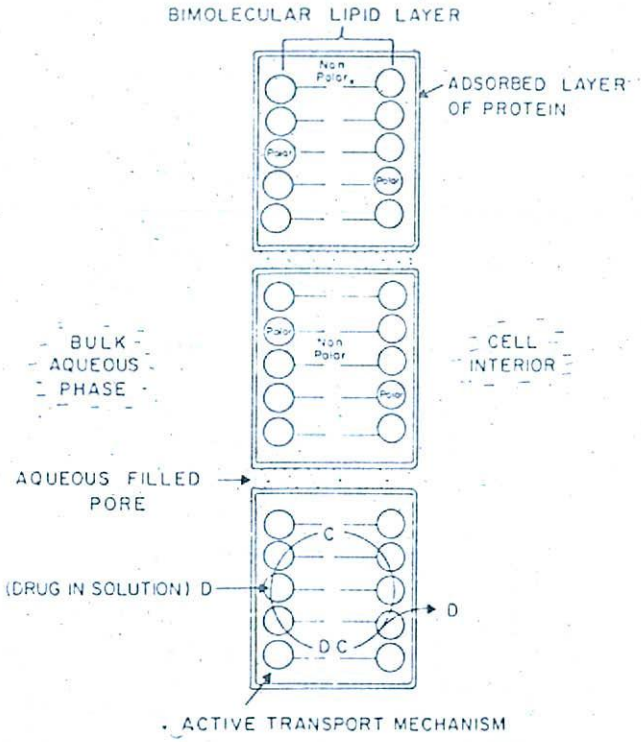


FIG. 6-1. Structure of the cell membrane.

The driving force for movement of drug from the GI fluids to the blood is the concentration gradient—the difference between the concentration of drug in the GI fluids and in the bloodstream. The drug molecules pass through a membrane from an area of high drug concentration to an area of low drug concentration. There is always an appreciable concentration gradient between the GI tract and bloodstream to effect drug transfer. The reason for this is illustrated in Fig. 6-2, which shows drug passing from the GI tract into the rapidly circulating bloodstream where it is diluted and immediately distributed to sites of excretion and metabolism. Proteins in the blood may bind the drug molecules and thereby prevent reabsorption of the free drug into the GI fluids. Because of these processes there is always an effective gradient. This phenomenon is called a "sink" condition for absorption, which means that a relatively small drug concentration is present in the circulation.

The passive transfer process follows first-order kinetics, which means that the transfer rate is proportional to the concentration of the drug at the

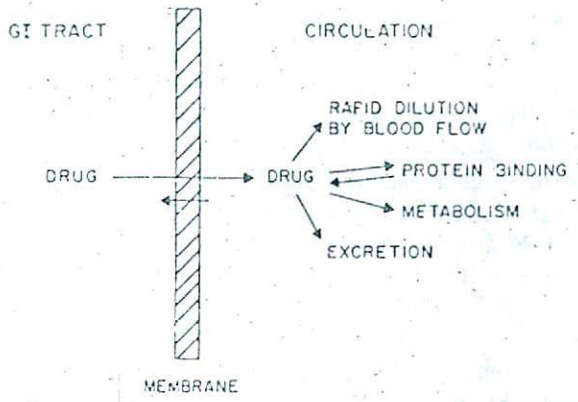


FIG. 6-2. Drug being diluted and distributed in the bloodstream.

absorption site; i.e., doubling the dose doubles the transfer rate (Fig. 6-3). Fick's law of diffusion mathematically describes the passive diffusion process and is discussed at the end of this chapter.

Carrier Transport

With carrier transport, a chemical carrier in the membrane combines with the drug and carries it through the membrane to be discharged on the other side (Fig. 6-1, bottom). The most important type of carrier transport for drug transport is *active transport*. The membrane plays an active role in this process as there is a need for the temporary combination of drug molecules with a carrier to mediate the transfer. Chemical energy is needed for active transport. Drug molecules can be transferred against a high concen-

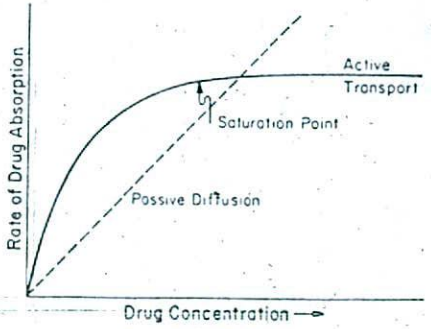


FIG. 6-3. Relationship between drug concentration at the absorption site and absorption rate for a passive process and active transport.

tration gradient to areas of high drug concentration with this form of transport. The greatest difference between this process and passive transfer is the fact that active transport is saturable and obeys laws of saturation kinetics. This means that the rate of absorption does not necessarily increase with large doses of drug. As shown in Fig. 6-3, the rate of absorption associated with passive diffusion increases as the drug concentration increases, whereas the rate of absorption of an active process reaches a saturation point where further increases in drug concentration do not result in further increases in rates of absorption. With active transport the carrier molecule is usually highly selective, and competition may occur between drugs of similar structure for the carrier compounds in the membrane.

Another carrier-mediated transport system, *facilitated transport*, is similar to active transport but does not require chemical energy and transport does not proceed against a higher concentration. This system is not an important process for the absorption of drugs, although the absorption of vitamin B_{12} from the GI tract is dependent on this transport method. Vitamin B_{12} first forms a complex with intrinsic factors produced by the stomach wall, after which this B_{12}-intrinsic factor complex combines with a specific carrier for transport and absorption.

Many body nutrients (e.g., sugars and amino acids) are transported across the GI membranes by the carrier processes. Vitamins such as thiamine, niacin, riboflavin, and B_6 require an active transport system. The anticancer drug 5-fluorouracil (Fluorouracil®), methyldopa (Aldomet®), and nicotinamide are absorbed by active transport.

pH Partition Theory of Drug Absorption

The basic principles governing absorption of most drugs from the GI tract are presented in Table 6-1, which is a summary of the pH partition theory of drug absorption. This theory is based on the demonstrated relationship between lipid solubility, the ionization constant (pK_a), and the degree of absorption. The theory requires that the drug be absorbed from the GI tract by passive transfer of the un-ionized, lipid-soluble drug molecules across a lipid membrane.

Most weakly acidic drugs (e.g., salicylic acid, aspirin) are absorbed to some extent from the stomach. The high acidity of the stomach ensures that the acids are essentially un-ionized and in their lipid-soluble form. On the other hand, weak basic drugs (e.g., atropine, dextromethorphan) are not absorbed to any significant degree from the stomach as they are completely ionized in the stomach fluids and are not lipid-soluble. When basic drugs reach the small intestine, where the pH is between 5 and 6, efficient absorption of these drugs can take place. The higher pH allows the basic drugs to be present in their un-ionized and lipid-soluble forms. Strong acids and

bases are poorly absorbed from the GI tract because they remain highly ionized in the GI fluids even at the low and high pH levels of the stomach and small intestine.

A primary physicochemical property of a drug that influences its ability to cross biological membranes is the oil/water partition coefficient of the drug. The higher the oil/water coefficient of a drug, the greater is its lipid solubility. The amount of lipid-soluble (un-ionized) weakly acidic or basic drug in the GI tract is governed by the pK_a of the drug and the pH of the immediate environment. The pK_a of a weakly acidic or basic drug is an important parameter as it determines its aqueous solubility, dissolution rate, and rate of transport across lipoidal barriers. Table 6-2 lists pK_a values for selected drugs of common use. The Henderson-Hasselbalch[1] equation can be used to relate pK_a of a drug and pH to the membrane transport of a weakly acidic or basic drug. Using the appropriate equations, the proportion of ionized aspirin (pK_a 3.5) in stomach fluid at pH 2.5 is calculated to be:

$$\frac{\text{ionized aspirin}}{\text{un-ionized aspirin}} = 10^{(pH - pK_a)} = 10^{(2.5 - 3.5)} = 10^{-1} = \frac{1}{10}$$

Ten times as much un-ionized aspirin as ionized drug is present in gastric fluid at pH 2.5. In the small intestine at pH 6.5, the proportion of ionized to un-ionized aspirin is calculated to be:

$$10^{(6.5 - 3.5)} = 10^3 = 1{,}000$$

There is 1,000 times more ionized aspirin than un-ionized aspirin at pH 6.5. For a basic drug having a pK_a of 6.5 there are equal portions of un-ionized and ionized drug in the small intestine at pH 6.5:

$$10^{(pH - pK_a)} = 10^{6.5 - 6.5} = 10^0 = 1$$

The absorption behaviors of neutral compounds (no pK_a value) and very weak bases such as caffeine (pK_a 0.8) are not appreciably influenced by changes in pH.

---

[1]According to the Henderson-Hasselbalch equation, the proportion, or ratio, of un-ionized to ionized drug at the absorption site can be determined for weak acids utilizing the following expressions:

$$\log \frac{\text{(ionized drug)}}{\text{(un-ionized drug)}} = pH - pK_a \text{ or } \frac{\text{(ionized drug)}}{\text{(un-ionized drug)}} = 10^{(pH - pK_a)}$$

For weak bases the following expressions are used:

$$\log \frac{\text{(un-ionized drug)}}{\text{(ionized drug)}} = pH - pK_a \text{ or } \frac{\text{(un-ionized drug)}}{\text{(ionized drug)}} = 10^{(pH - pK_a)}$$

TABLE 6- . *Absorption from the GI tract*

1. The GI memb[illegible]e acts as a lipoid sieve barrier.
2. The barrier preferentially allows passage of the un-ionized (lipid-soluble) forms of acids and bases.
3. The gastric contents have a low pH (pH 1–2).
4. The duodenal contents have a pH of about 5.5.
5. Most drugs are absorbed by a passive transport mechanism.
6. Rate of absorption is related to the oil/water partition coefficient of the drug. In general, the more lipid-soluble a drug is the more rapidly it is absorbed.
7. The lowest pK_a of an acid compatible with rapid absorption is about 3.
8. The highest p[illegible] base compatible with rapid absorption is about 7.8.
9. In general, ac[illegible]ugs but not basic drugs are absorbed fro[illegible]ch.

Adapted from Wagner, J. G. (1964): Biopharmaceutics: gastrointestinal absorption aspects. *Antibiot. Chemother. Adv.*, 12:53–84.

It should be emphasized that the pH partition theory does not explain all drug absorption processes or why certain drugs are absorbed and others are not. Also, drug absc[illegible]'s a relative thing, not an all-or-nothing phenomenon. Most drugs a[illegible]orbed to some extent from both the stomach and intestine. In fact, most [illegible]ugs, regardless of their pK_a values, are best absorbed from the sma[illegible]stine. Although weakly acidic drugs are absorbed from the stomach, a drug is usually not in the stomach long enough for a large amount to be absorbed; also, the surface area of the stomach is relatively small. When an acidic drug reaches the upper portions of the

TABLE 6-2. *Ionization constants of some selected drugs*

Drug	Acid or base	pK_a
Amitriptyline	Base	9.4
Amphetamine	Base	9.8
Aspirin	Acid	3.5
Atropine	Base	9.8
Caffeine	Base	0.8
Codeine	Base	6.0
Ethacrynic acid	Acid	3.5
Nalidixic acid	Acid	6.7
Phenobarbital	Acid	7.2
Propranolol	Base	9.4
Secobarbital	Acid	7.9
Tolbutamide	Acid	5.4

intestine, it is efficiently absorbed. The surface area for absorption here is very large, and the pH of the tract is still on the acidic side (pH less than 7).

Other Factors Affecting Gastrointestinal Absorption

There are several factors that may affect GI absorption of drugs (Table 6-3). The GI tract exhibits variations in absorptive power for drugs in different areas. Figure 6-4 shows the different blood level patterns obtained when tetracycline was administered to different sites in a dog's GI tract. The most efficient absorption took place in the duodenum, which would probably also be true for human absorption of tetracycline. There are specific areas in the human GI tract where particular drugs are most efficiently absorbed (for example, ferrous iron, riboflavin, and vitamin B_{12} are absorbed at specific sites in the ileum and upper small intestine).

Some drugs may have limited intrinsic absorption from the GI tract. In 1981 the FDA requested all manufacturers of chlorothiazide and chlorothiazide in combination with other drugs to voluntarily withdraw the 500-mg products from the market. Studies had indicated that the bioavailability of chlorothiazide is limited and not proportional to the dose administered, and so a 500-mg oral dose does not deliver more drug to the systemic circulation or promote greater diuresis than a 250-mg dose. This phenomenon is not due to a limited dissolution rate but appears to be associated with some mechanism that limits the inherent absorption rate of the drug. Actually, the optimum dose for chlorothiazide may be less than 250 mg, and appropriate blood level studies should be able to define the optimal dosage in the future.

TABLE 6-3. *Factors involved in GI absorption*

1. Variations in absorptive power along the tract
2. Gastric emptying rate
3. Drug interaction with contents of the tract
4. Metabolic changes in drugs in the tract
5. Dose size effects
6. Age and individual variations (sex, weight, allergies, idiosyncrasies)
7. Effect of disease
8. Effect of other drugs (drug interactions)
9. Motility and blood flow in the intestine and stomach
10. Effect of fluid and food intake

Adapted from Wagner, J. G. (1964). Biopharmaceutics: gastrointestinal absorption aspects. *Antibiot. Chemother. Adv.*, 12:53–84.

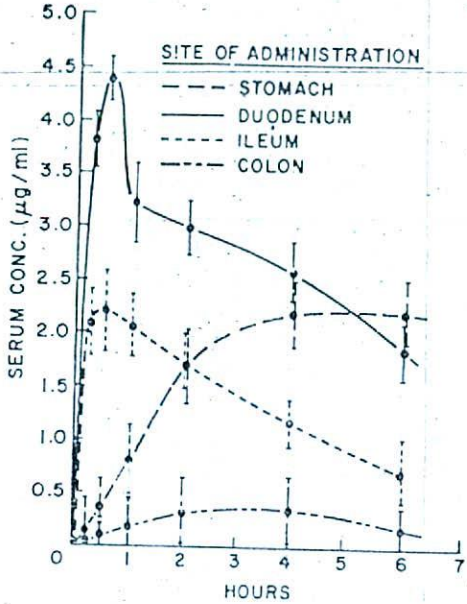


FIG. 6-4. Tetracycline absorption in dogs. [From Pindell, M. H., et al. (1959): Absorption and excretion studies on tetracycline. *J. Pharmacol. Exp. Ther.*, 125:287.]

Anything that slows the emptying rate of the stomach [e.g., anxiety or stress, or the intake of certain drugs such as atropine, propantheline (anticholinergics), imipramine and other tricyclic depressants, or narcotic analgesics (codeine, morphine)] can affect the onset of action of most drugs, especially those that are rapidly absorbed from the small intestine, e.g., weakly basic compounds. Drugs that are acid-unstable (e.g., penicillins and erythromycin) might decompose extensively if their stay in the stomach is prolonged.

Any chemical change due to pH, complexation, and enzymatic action that reduces the bioavailability of the drug should be prevented or minimized. Protein or polypeptide drugs, e.g., insulin, corticotropin (ACTH), vasopressin, and oxytocin, are readily destroyed by enzymes in the GI tract, and so are administered by injection, thereby avoiding the GI tract. Hormones (e.g., progesterone, testosterone, and aldosterone) which are partially destroyed in the GI tract and further broken down by liver enzymes during a first-pass effect are frequently administered by injection (implants, intramuscular depot) or by the buccal or sublingual route.

Tetracycline antibiotics form insoluble complexes (chelates) with di- and trivalent metals. This effect is minimized by combining tetracyclines with

nontherapeutic agents that tie up endogenous metals, e.g., calcium and magnesium. This is the reason for combining tetracycline with agents such as glucosamine (Tetracyn®) or phosphates (Panmycin®, Sumycin®, Tetrex®).

The GI tract contains a large quantity of mucin, a high-molecular-weight polysaccharide, which might bind and prevent absorption of some drugs (e.g., streptomycin).

Several antibiotics are highly unstable in the hydrochloric acid of the stomach. Penicillin per se is very unstable, but the phenoxymethyl derivative penicillin V has greater acid stability and therefore greater efficacy when taken orally. Chemical modification of erythromycin is used to yield compounds (prodrugs) that are not rapidly inactivated by gastric acidity. To prevent acid hydrolysis, salts of erythromycin that are not wetted by gastric fluids are used in drug products. Erythromycin stearate (Erythrocin®) and erythromycin estolate (Ilosone®) are not solubilized in stomach fluids (a requisite for hydrolysis to take place) and pass into the intestine where they are efficiently absorbed. After erythromycin stearate reaches the intestine, the salt dissociates giving free erythromycin, which is readily absorbed. Erythromycin estolate is absorbed intact from the intestine, and free erythromycin is released into the bloodstream after hydrolysis of an ester linkage. Safe passage through the stomach can also be accomplished by using an enteric-coated drug product (E-Mycin®).

A seriously ill or debilitated patient may absorb drugs differently than a moderately ill or healthy person because of changes in body chemistry. The blood flow and the motility of the GI tract can be affected by disease, pressure and stress, medication, exercise, food, drink, and other factors.

The amount of fluid intake which accompanies an orally administered drug can effect the dissolution and absorption of the drug. In general, more efficient and reliable drug absorption takes place when an oral dosage form is ingested with a relatively large fluid volume—a full glass rather than a few swallows of water. The type of food ingested can influence absorption. Figure 6-5 illustrates how a variety of diets can greatly affect the bioavailability of griseofulvin. The ingestion of griseofulvin along with food having a high fat content can significantly increase the amount of drug in the blood.

GI absorption of many drugs is affected by the presence of food. Figure 6-6 shows the average levels in serum after administration of dicloxacillin (Dynapen®) capsules on a fasting stomach 1 hr before a standard meal and with a standard meal. Dicloxacillin showed the greatest availability when it was administered on a fasting stomach. Most drugs are best absorbed on an empty stomach. It is common practice to administer drugs to fasting subjects in bioavailability studies in order to reduce the variability in the

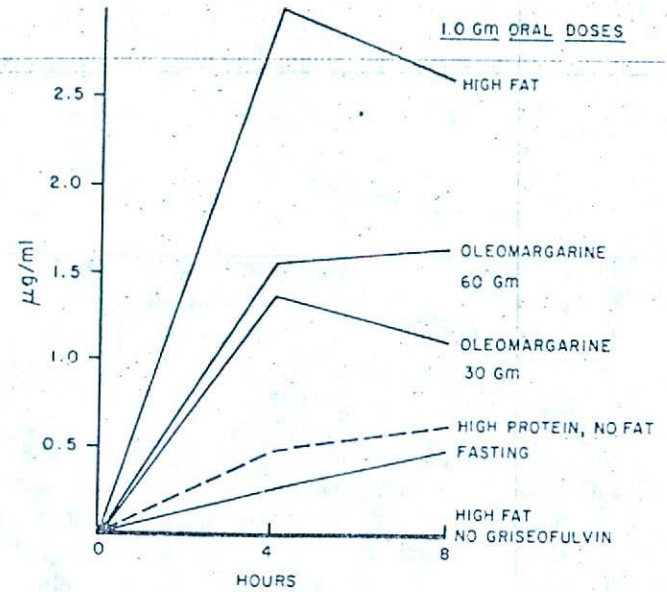


FIG. 6-5. Effects of various types of food intake on the serum griseofulvin levels following a 1-g oral dose. [From Crounse, R. G. (1961): Human pharmacology of griseofulvin: the effect of fat intake on gastrointestinal absorption. *J. Invest. Dermatol.*, 37:529.]

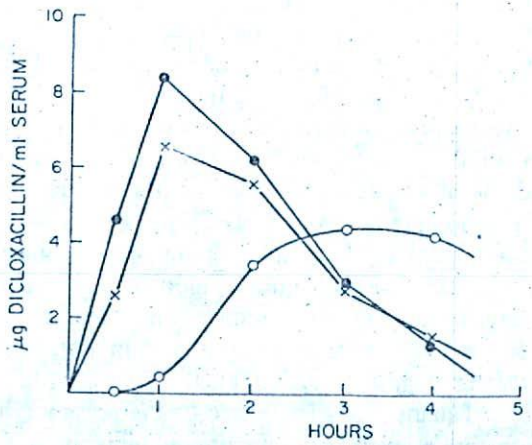


FIG. 6-6. Average levels of dicloxacillin activity in serum of adults receiving a 250-mg capsule after an overnight fast (•), 1 hr before a standard breakfast (X), and with breakfast (O). [From Doluisio, J. T., LaPiana, J. C., Wilkinson, G. R., and Dittert, L. W. (1970): Pharmacokinetic interpretation of dicloxacillin levels in serum after extravascular administration. In: *Antimicrobial Agents and Chemotherapy—1969*, edited by G. L. Hobby, p. 49. American Society for Microbiology, Bethesda.]

absorption phase. Drug products should be taken before meals whenever possible except for those drugs that may be highly irritating to some patients' stomachs (aspirin, iron salts, phenylbutazone) or very unstable in stomach fluids (penicillin, erythromycin).

Drug manufacturers are aware of the effect of food on drug absorption and recommend appropriate instructions based on bioavailability data. For example, captopril (Capoten®) should be taken 1 hr before meals because food in the GI tract reduces absorption by 30 to 40%.

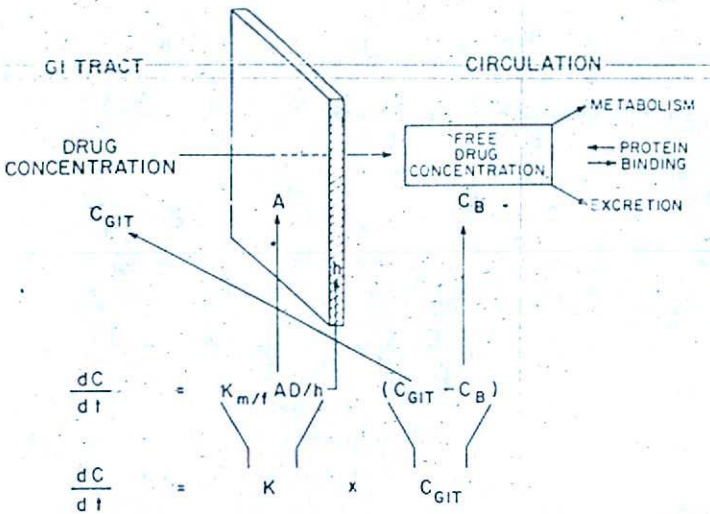
Fick's Law and Drug Absorption

As discussed earlier in this chapter, passive diffusion involves the passage of drug molecules from a region of high drug concentration to a region of low drug concentration. The driving force for diffusion of drug across a membrane is the difference in effective drug concentration on opposite sides of the membrane (the concentration gradient). *Fick's law of diffusion* mathematically describes the mechanism of membrane diffusion, the equation for which is presented in Fig. 6-7 along with a diagram of the various components of the equation.

The expression for Fick's law of diffusion indicates that the rate of absorption is directly related to the surface area (A) of the membrane and the distribution coefficient ($K_{m/f}$) and diffusion coefficient (D) of the drug. According to Fick's law, a region with a large surface area (e.g., the small intestine) should be a very efficient site for absorption. The upper portion of the small intestine, in fact, exhibits the most rapid drug absorption. A drug that has a higher degree of lipid solubility will have a higher distribution coefficient and should have a faster rate of absorption. As was discussed earlier, the pH of the immediate environment can change the partition coefficient of weakly acidic and basic drugs. The diffusion coefficient can also be changed by pH.

The diffusion coefficient defines a drug's ability to diffuse across a membrane and is a specific constant for each drug. The distribution coefficient is also a constant for a specified drug. The thickness (h) and surface area of the GI tract of a biological system such as man can be considered relatively constant. Therefore, for the GI tract membrane system in man and a specific drug, the expression $K_{m/f}AD/h$ can be combined into one overall constant (K), called the specific permeability coefficient.

During drug absorption the driving force for diffusion across the membrane is maintained because the effective drug concentration in the blood remains considerably lower than the concentration in the GI tract. Gastric and intestinal fluid volumes are relatively small compared to the circulating blood volume, so that any drug entering the bloodstream is rapidly diluted.



$\frac{dC}{dt}$ = rate of appearance of drug in blood

$K_{m/f}$ = partition coefficient of the drug between membrane (lipid) and GIT fluids (aqueous)

A = surface area of membrane

D = diffusion coefficient of the drug

h = thickness of membrane

C_{GIT} = drug concentration in GIT fluids

C_B = free drug concentration in blood at membrane

$C_{GIT} - C_B$ = concentration gradient across the membrane

K = specific permeability coefficient

FIG. 6-7. Fick's law of diffusion.

Also, the binding and excretion processes constantly reduce the free drug concentration. So long as the drug concentration in the GI tract (C_{GIT}) remains much higher than the blood drug concentration (C_B), the C_B term can be removed from the equation; hence the final expression becomes $dc/dt = KC_{GIT}$. This equation describes a first-order kinetic process which predicts that the rate of drug absorption is dependent on the drug concentration in the GI tract. This concentration, of course, is influenced by the dose of drug administered (see Fig. 4-8, p. 28).

7

Dissolution and Drug Absorption

Dissolution Rate

A basic principle of drug absorption is that absorption takes place only after a drug is in solution. This means that drugs given orally in solid form must dissolve in the GI fluids before absorption occurs (Fig. 7-1).

The dissolution process is shown in Fig. 7-2. When solid particles are in the GI tract, an essentially saturated solution of the drug builds up very quickly on the surfaces of the particles and in the liquid immediately surrounding them. The drug passes through these diffusion layers and into the GI contents. The drug molecules then diffuse through the GI contents to the lipoid sieve barrier where absorption takes place.

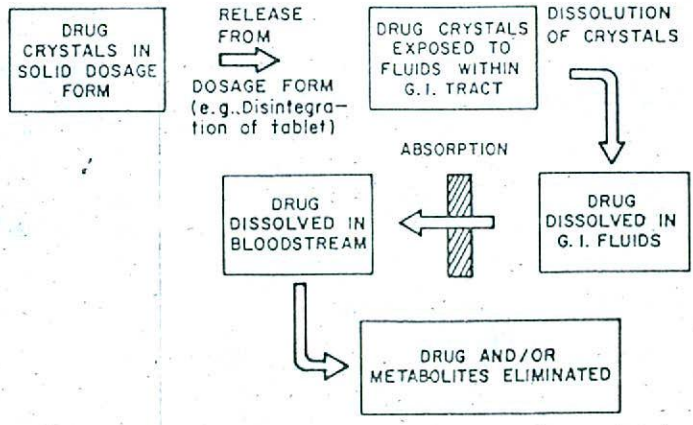


FIG. 7-1. Some of the steps involved in the absorption of drugs orally administered as typical solid dosage forms. [From Ballard, B. E. (1968): Teaching biopharmaceutics at the University of California. *Am. J. Pharm. Educ.*, 32:938.]

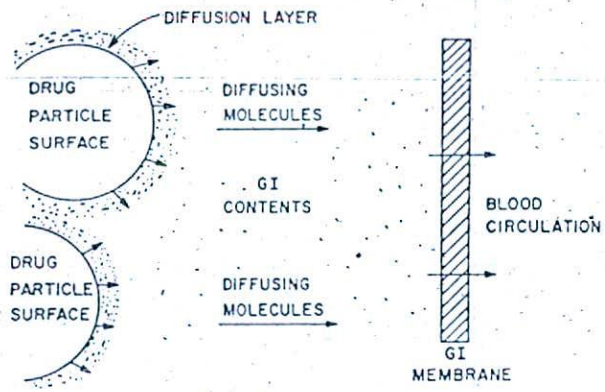


FIG. 7-2. Dissolution process.

Most drugs are absorbed and reach the systemic circulation by one of the following processes:

1. Absorption from solution or following rapid dissolution of solid particles. In this process the absorption rate is controlled by the rate of diffusion of drug molecules in GI fluids and/or through the membrane barrier.

2. Absorption following slow dissolution of solid particles. In this process the appearance of drug in the blood is controlled by the rate of availability of the drug from the solid particles in the GI tract.

The majority of drugs are sufficiently soluble in water, or water-soluble salts can be prepared that are readily soluble. These drugs are absorbed by the first process, and usually no problem is encountered in their bioavailability.

Some drugs, however, have slow dissolution rates, and then the dissolution process becomes a rate-limiting step in the absorption process. That is, the rate of absorption and bioavailability is dependent on how fast the drug dissolves in the GI fluids. Generally, the rate of absorption can be increased by increasing the rate of dissolution. The dissolution, and ultimately the bioavailability, of slowly soluble drugs may be influenced by several factors.

Factors That Affect Dissolution Rate

Some of the more important factors that affect the dissolution rate of slowly soluble substances are the surface area of the dissolving solid, the solubility of the drug in the diffusion layer, the crystal form of the drug, and the state of hydration of the drug molecule. By controlling one or more of these factors, the formulator may be able to control dissolution and ultimately the bioavailability of the drug.

Surface area. The more surface area of a substance that is in contact with solvent, the faster is the solubility. Therefore the smaller the particles of a drug, the faster is the dissolution rate. The effect of particle size on the dissolution rate and bioavailability of several drugs is shown in Figs. 7-3 through 7-7.

Figure 7-3 illustrates the difference in dissolution rate between micronized and nonmicronized norethisterone acetate in 0.1 N hydrochloride acid. The micronized form dissolved much faster than the nonmicronized material. These findings seem to agree with clinical studies in which a micronized norethisterone acetate preparation was almost five times as active as the nonmicronized form when used for hormone therapy. The micronized form of sulfadiazine gave higher blood levels than the United States Pharmacoepia (USP) material when both were administered to human subjects (Fig. 7-4).

Usually drugs with very low aqueous solubilities (e.g., digoxin, griseofulvin, and spironolactone) have absorption problems, and particle size can be an important factor in controlling the adequate dissolution of these com-

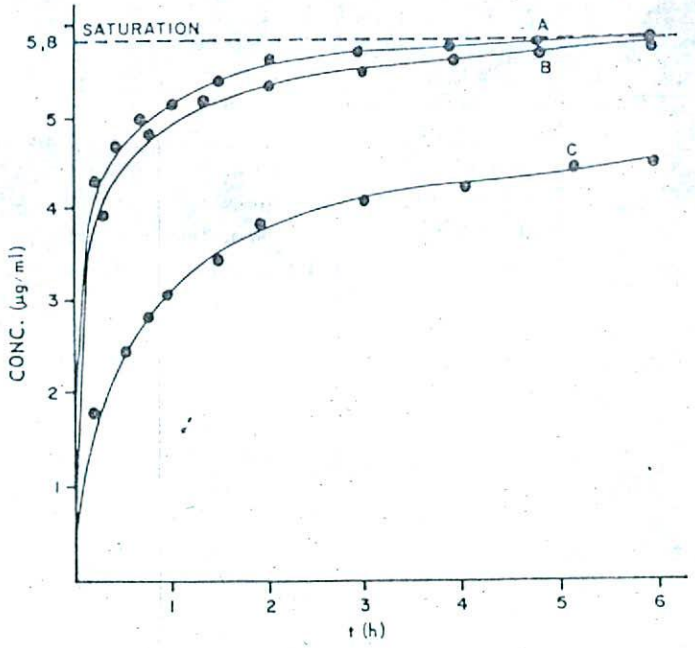


FIG. 7-3. Rate of dissolution of norethisterone acetate in 0.1 N HCl at 37°C. A. Micronized material. B. Micronized material in coated tablet form. C. Nonmicronized material in coated tablet form. [From Gibian, H., et al. (1968): Effect of particle size on biological activity of norethisterone acetate. *Acta Physiol. Latinoam.*, 18:323.]

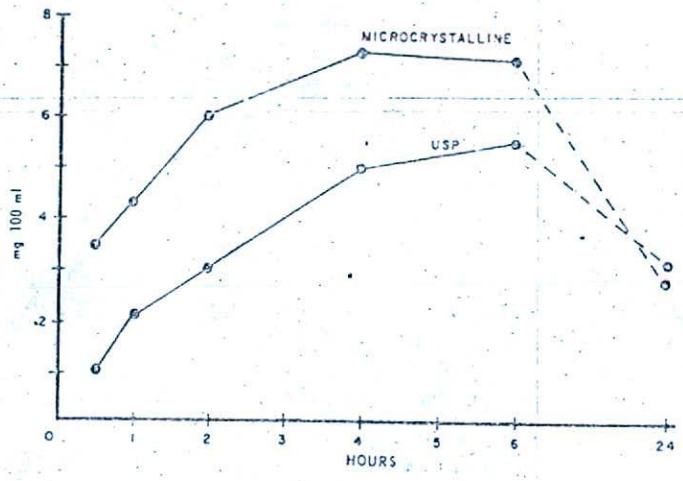


FIG. 7-4. Blood levels in humans after one 3-g dose of sulfadiazine. [From Reinhold, J. G., et al. (1945): A comparison of the behavior of microcrystalline sulfadiazine with that of ordinary sulfadiazine in man. *Am. J. Med. Sci.*, 210:141.]

pounds. Particle size greatly influences the solubility rate of griseofulvin, a poorly soluble drug. Figure 7-5 shows how an increase in the surface area (decrease in particle size) of the material increases the bioavailability of the drug. Using the ultramicronized form of griseofulvin in drug products (Fulvicin P/G®, Grisactin Ultra®, Gris-PEG®) gives higher blood levels and allows smaller doses than the micronized griseofulvin products (Grifulvin V®, Grisactin®, Fulvicin U/F®) for treating fungal infections.

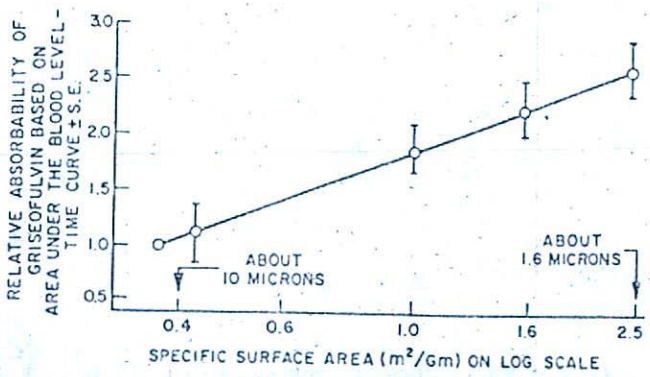


FIG. 7-5. Effect of specific surface area on bioavailability of griseofulvin. [From Wagner, J. G. (1964): Biopharmaceutics: gastrointestinal absorption aspects. *Antibiot. Chemother. Adv.*, 12:53–84.]

The blood profiles of four chloramphenicol products are shown in Fig. 7-6. Product A displayed bioavailability superior to that for the other three products. *In vitro* tests indicated that products B, C, and D went into solution more slowly than A. The slower dissolution rates were probably due to differences in particle size.

Figure 7-7 shows the effect of particle size on absorption and resultant blood levels following oral administration of chloramphenicol in rabbits. Peak blood levels occurred much faster with the smaller particles than the larger ones. These observations emphasize the need for caution in assuming that absorption characteristics are the same for different chloramphenicol preparations containing identical amounts of drug.

There are times when fine particle size and rapid dissolution are not desirable. A case in point is nitrofurantoin (Furadantin®), an agent that may cause gastric irritation and nausea when taken orally. These side effects are attributed to the rapid dissolution of nitrofurantoin crystals, which results in a high concentration of drug in the gastric fluids. Increased GI tolerance is claimed for a drug product (Macrodantin®) which utilizes larger, slower-dissolving crystals of nitrofurantoin in a capsule dosage form.

Solubility in diffusion layer. If the solubility of drugs can be appreciably increased in the diffusion layer (in the immediate area surrounding the drug particles), then the molecules can rapidly escape from the main particles

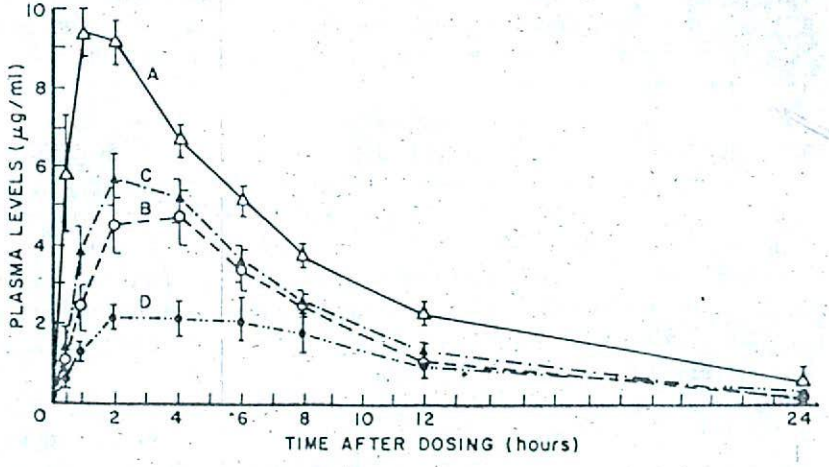


FIG. 7-6. Mean plasma levels for groups of 10 human subjects receiving single 0.5-g oral doses of chloramphenicol preparations A, B, C, or D. Vertical lines represent 1 SE on either side of the mean. [From Glasko, A. J., et al. (1967): An evaluation of the absorption characteristics of different chloramphenicol preparations in normal human subjects. *Clin. Pharmacol. Ther.*, 9:472.]

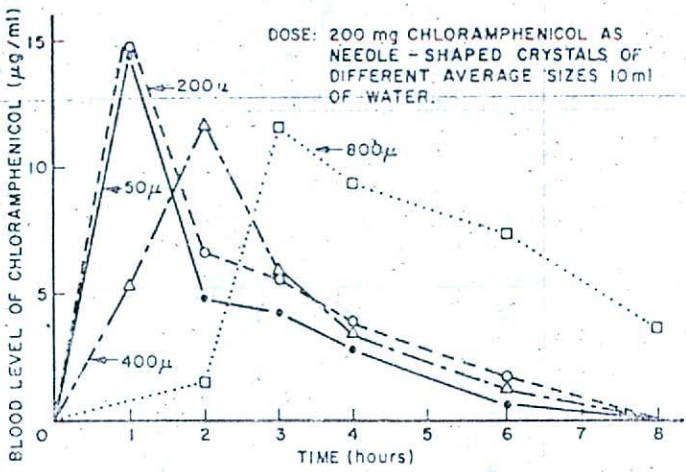


FIG. 7-7. Effect of particle size on absorption and resultant blood levels of chloramphenicol in rabbits. [From Kakemi, K., et al. (1962): Absorption and excretion of chloramphenicol. *Symposium on Drug Absorption, Metabolism and Excretion*, Paper B-IV. Preprints of Papers, Scientific Section of the American Pharmaceutical Association, Las Vegas.]

and travel to the absorption sites. Consideration of this phenomenon is used to increase the solubility of weak acids in the stomach. The solubility of a weak acid increases with an increase in pH because the acid is transformed into its ionized, or dissociated, form, which is very soluble in the aqueous GI contents. Several methods that can be and are used to raise the pH of the diffusion layer are as follows:

1. *Use a highly water soluble salt of a weak acid.* This is the most effective means of attaining higher dissolution rates. The salt acts as its own buffer and raises the pH of the immediate environment. The ionized molecules rapidly diffuse from the drug particles into the highly acidic gastric contents. Even if the ionized molecules precipitate in the gastric fluid—and they will if the free acid is not very soluble—they do so as very fine particles. These particles have a very large surface area and dissolve rapidly—much more rapidly than if the free acid per se had been administered. This process is shown in Fig. 7-8.

The administration of soluble salts of penicillin V result in much higher blood levels than the administration of the free acid (Fig. 7-9). The highly soluble sodium salt of penicillin G gave poor blood levels because of its greater instability in gastric fluid than the V form of the antibiotic.

The effect of the dissolution rate on the bioavailability of tolbutamide (Orinase®) and its sodium salt from compressed tablets is shown in Fig. 7-

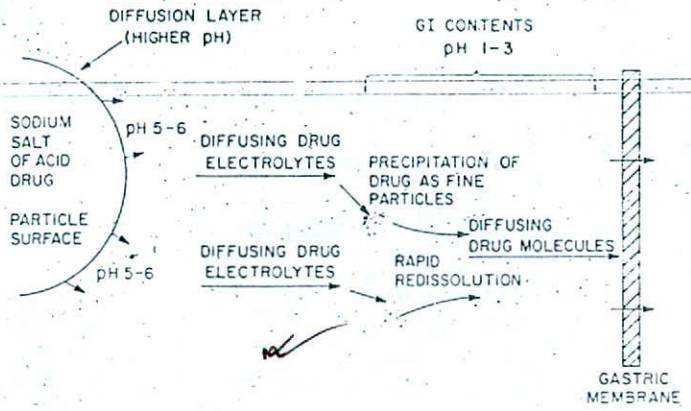


FIG. 7-8. Dissolution process in the stomach from the surface of a highly water soluble salt.

10. After administration of sodium tolbutamide, there is a very rapid decrease in the blood sugar level followed by a rapid recovery. Tolbutamide causes a much slower drop in the blood sugar level, and a steady, lower sugar level is maintained for a long period of time. The gradual decrease in blood sugar levels, and not the sharp dip and recovery (which could be dangerous to diabetic patients), is the preferred clinical response. Therefore the slower

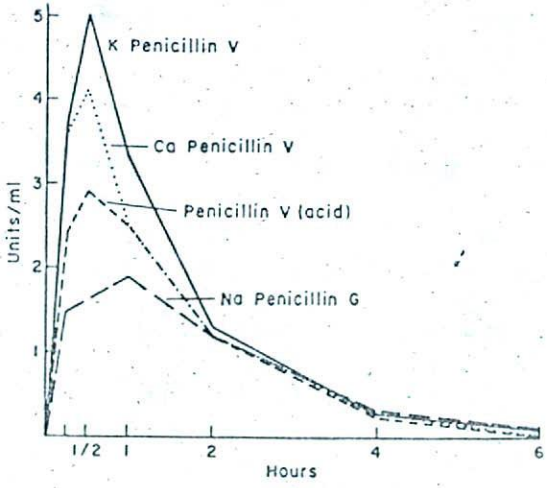


FIG. 7-9. Average penicillin levels in the plasma of 10 fasting subjects following oral administration of 400,000 units of penicillin in the different forms. [From Juncher, H., and Raaschou, F. (1957): The solubility of oral preparations of penicillin V. *Antibiot. Med. Clin. Ther.*, 4:497.]

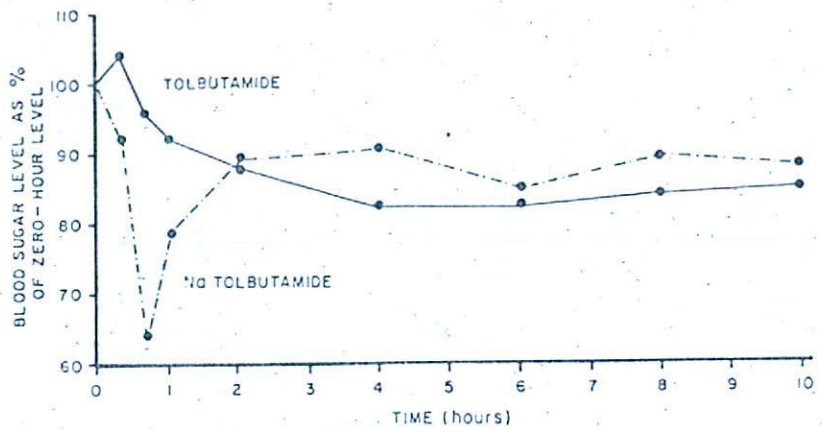


FIG. 7-10. Effect of dissolution rate on the absorption and biological response of tolbutamide (1.0 g) and sodium tolbutamide (1.0 g equivalent) when formulated in compressed tablets. [From Wagner, J. G. (1961): Biopharmaceutics: absorption aspects. *J. Pharm. Sci.*, 50:359. Reproduced with permission of the copyright owner.]

dissolving and more slowly and uniformly absorbed free-acid form is used in tolbutamide products.

2. *Mix and combine a basic substance (e.g., sodium bicarbonate or calcium carbonate) with the weak acid in a dosage form.* This increases the pH in the immediate environment of the weak acid particles. The relatively small amounts of buffer compounds that are usually combined with acidic drugs certainly do not raise the pH of the stomach contents but they do raise the pH in the immediate area surrounding the acidic drug particles. Buffered aspirin, salicylic acid, and para-aminosalicylic acid (PAS) products use one or a combination of basic ingredients to increase their dissolution rate and to decrease gastric irritation. Other examples of basic ingredients are sodium citrate, magnesium oxide, and magnesium carbonate. Bufferin® (buffered aspirin) utilizes a combination of aluminum dihydroxyaminoacetate and magnesium carbonate. The value of these buffering agents is demonstrated in Fig. 7-11, where Bufferin® is shown to have faster and greater bioavailability than a plain tableted aspirin product.

3. *Increase the pH of the entire dissolution medium.* Antacids could be administered in relatively large doses to raise the pH of the gastric contents. However, this is rather drastic treatment, and the disadvantages of antacid therapy would not warrant its general use to increase the dissolution of weakly acidic drugs.

Crystalline form. Many drugs can exist in more than one crystalline form and so are said to be *polymorphic*. The various crystalline forms usually

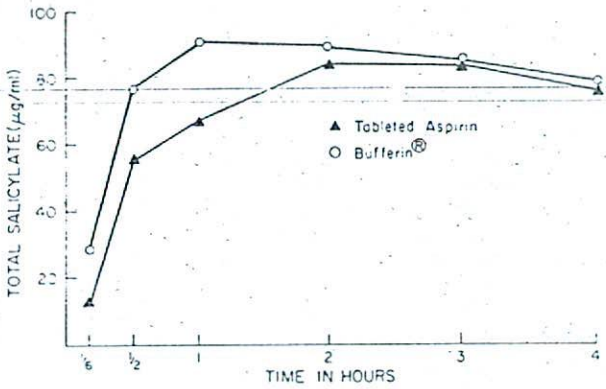


FIG. 7-11. Comparison of two preparations of aspirin in regard to serum concentrations of total salicylate over a 4-hr period. [Adapted from Hollister, L. E. (1972): Measuring measurin: problems of oral prolonged-action medications. *Clin. Pharmacol. Ther.*, 13:1.]

have different solubilities as well as differences in other physical properties. As a result of different solubilities, the polymorphic forms may also exhibit differences in their dissolution rates and, ultimately, their bioavailability. There are at least five crystalline forms of cortisone acetate. Examination of several brands of cortisone acetate tablets has shown that some of the products contain one form and others a different form. These various forms differ in their solubilities and dissolution rates, factors which probably account for differences in bioavailability.

Some drugs have the property of existing in either a crystalline or an amorphous form. As the amorphous form is always more soluble than the crystalline form, there is the possibility that there will be significant differences in their bioavailabilities. The amorphous form of the antibiotic novobiocin is 10 times more soluble than the crystalline form and has similar differences in dissolution rate. The data in Table 7-1 show that the crystalline form of novobiocin is not absorbed when given orally to dogs, whereas the amorphous form is readily absorbed and gives high blood levels.

The amorphous forms of chloromycetin palmitate and stearate are readily absorbed, whereas the crystalline forms are not absorbed at all and are therefore therapeutically inactive. These fatty acid derivatives of chloramphenicol provide a tasteless form of the drug that may be used in liquid dosage forms. The amorphous forms of these antibiotics are hydrolyzed in the GI tract to give absorbable chloramphenicol. These amorphous forms must be administered as finely divided suspensions so adequate dissolution takes place, which is a prerequisite to hydrolysis.

chloramphenicol palmitate — 4 polymorphs:
3 crystalline forms — A, B & C.
1 amorphous form.

TABLE 7-1. *Novobiocin plasma levels in dogs following oral administration of different solid forms*[a]

Hours after dose	Sodium novobiocin, (μg/ml plasma)	Amorphous novobiocin (acid) (μg/ml plasma)	Calcium novobiocin (μg/ml plasma)	Crystalline novobiocin (acid)
½	0.5	5.0	9.0	N.D.[b]
1	0.5	40.0	16.4	N.D.
2	14.6	29.5	26.8	N.D.
3	22.2	22.3	19.0	N.D.
4	16.9	23.7	15.7	N.D.
5	10.4	20.2	13.8	N.D.
6	6.4	17.5	10.0	N.D.

From Mullins, J. D., and Macek, T. J. (1960): Some pharmaceutical properties of novobiocin. *J. Am. Pharm. Assoc.*, 49:245.

[a]Dose = 12.5 mg/kg.

[b]Not detectable.

State of hydration. The state of hydration of a drug molecule can affect some of the chemical, physical, and biological properties of the drug. One of the physicochemical properties that is significantly influenced by the state of hydration is the aqueous solubility of the drug. Usually the anhydrous form of an organic compound is more soluble than the hydrate. An excellent study was carried out in 1968 on ampicillin, a penicillin derivative that is available as the anhydrous form (Omnipen®) and the trihydrate (Polycillin®). The results of this study are shown in Figs. 7-12 through 7-17. The anhydrous ampicillin was shown to be more soluble and to have a faster dissolution rate than the trihydrate (Figs. 7-12 and 7-13). The two forms of ampicillin were then administered to beagle dogs as suspensions or in capsules. The results (Figs. 7-14 and 7-15) demonstrate that the absorption of the anhydrous form is much greater than that of the trihydrate in dogs. Finally, the ampicillins were administered to human subjects; the results (Figs. 7-16 and 7-17) indicate that the anhydrous form of ampicillin has greater bioavailability than the trihydrate. A modification of Fig. 7-16 is used in the professional literature (Fig. 7-18) to illustrate the superior bioavailability of a suspension drug product containing anhydrous ampicillin.

A very important aspect of the above study, in addition to demonstrating the superior bioavailability of anhydrous ampicillin (compared to the trihydrate), was the correlation among physicochemical properties in the animal and human studies. The bioavailability of ampicillin after oral administration to laboratory animals and human subjects correlated positively with the physicochemical characteristics of solubility and dissolution

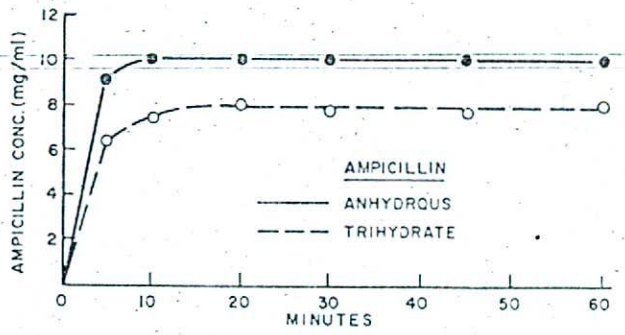


FIG. 7-12. Solubility of ampicillin in distilled water at 37°C. [From Poole, J. (1968): Physicochemical factors influencing the absorption of the anhydrous and trihydrate forms of ampicillin. *Curr. Ther. Res.*, 10:292–303.]

rate. The greater aqueous solubility is probably the major factor responsible for the enhanced *in vitro* and *in vivo* availability of this form of ampicillin. The correlation noted between the results in laboratory animals and human subjects suggests that the beagle dog is a useful species for the preliminary evaluation of dosage forms of ampicillin intended for human use. Also, the observed bioavailability correlated with the dissolution test utilized as a measure of *in vitro* availability.

When a therapeutic agent exists in two or more forms, each possessing different physicochemical properties, it is reasonable to expect that the different forms will exhibit differences in bioavailability. Standards that

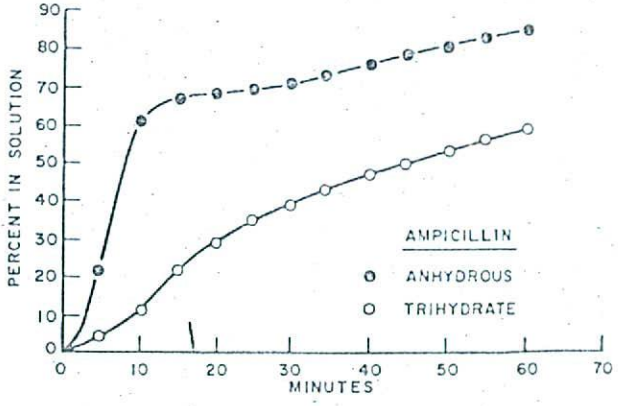


FIG. 7-13. Dissolution of ampicillin in distilled water at 37°C from trade capsule formulations. [From Poole, J. (1968): Physicochemical factors influencing the absorption of the anhydrous and trihydrate forms of ampicillin. *Curr. Ther. Res.*, 10:292–303.]

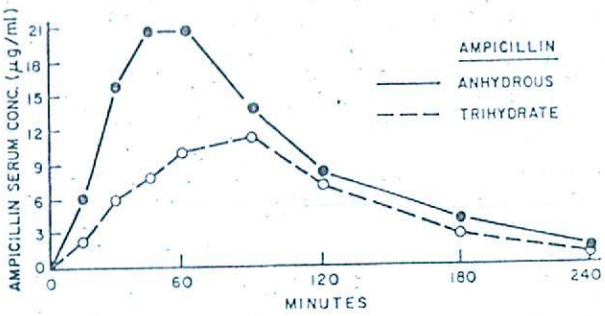


FIG. 7-14. Mean blood serum concentrations of ampicillin in dogs after oral administration of 250-mg doses of trade oral suspensions. [From Poole, J. (1968): Physicochemical factors influencing the absorption of the anhydrous and trihydrate forms of ampicillin. *Curr. Ther. Res.*, 10:292–303.]

distinguish between crystalline, amorphous, hydrated, and anhydrous forms of drugs in cases where the various forms exhibit significantly different bioavailability due to differences in dissolution rate have been incorporated into recent revisions of the *United States Pharmacoepia/National Formulary* (USP-NF), and additional standards will be added in the future.

The importance of dissolution rates and tests, especially as they pertain to solid dosage forms (as compressed tablets and capsules) is discussed in Chapter 8.

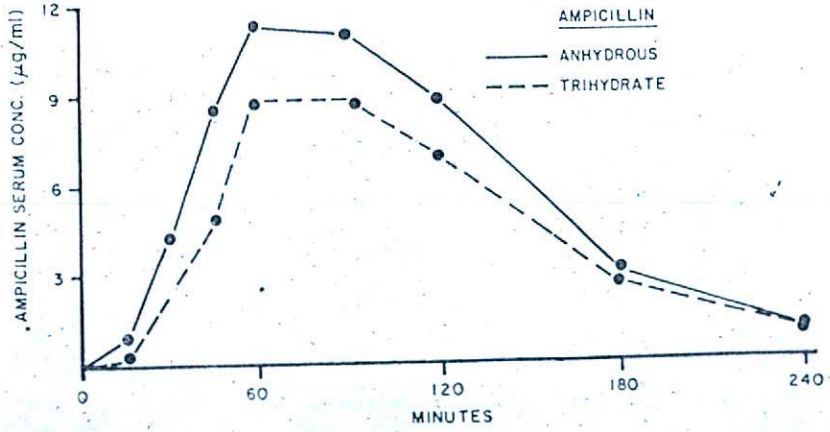


FIG. 7-15. Mean blood serum concentrations of ampicillin in dogs after oral administration of 250-mg doses of trade capsules. [From Poole, J. (1968): Physicochemical factors influencing the absorption of the anhydrous and trihydrate forms of ampicillin. *Curr. Ther. Res.*, 10:292–303.]

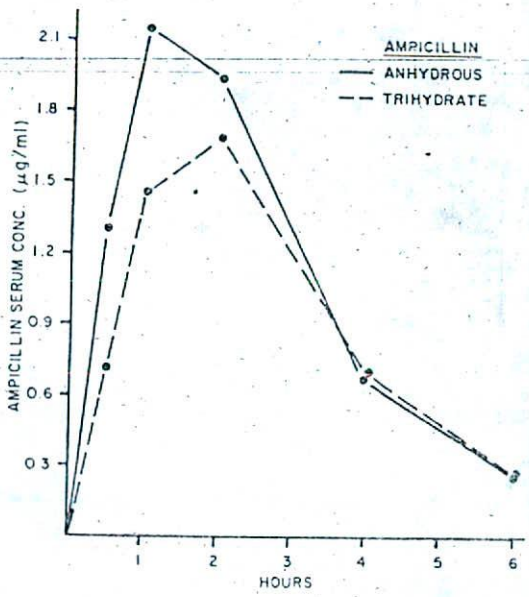


FIG. 7-16. Mean blood serum concentrations of ampicillin in human subjects after oral administration of 250-mg doses of the oral suspensions. [From Poole, J. (1968): Physicochemical factors influencing the absorption of the anhydrous and trihydrate forms of ampicillin. *Curr. Ther. Res.*, 10:292–303.]

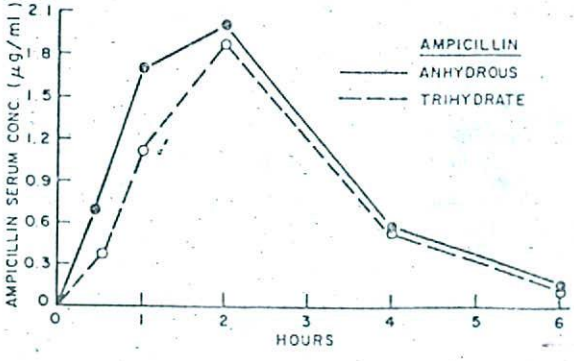


FIG. 7-17. Mean blood concentrations of ampicillin in human subjects after oral administration of 250-mg doses of trade capsules. [From Poole, J. (1968): Physicochemical factors influencing the absorption of the anhydrous and trihydrate forms of ampicillin. *Curr. Ther. Res.*, 10:292–303.]

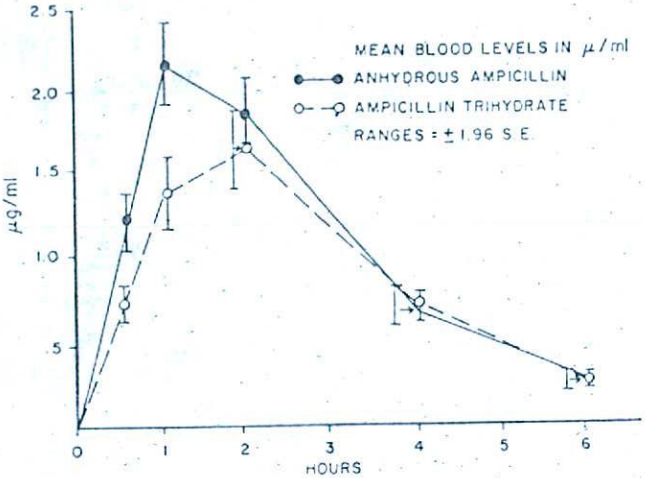


FIG. 7-18. Mean blood serum concentrations of ampicillin in human subjects after oral administration of 250-mg doses of trade suspensions. [Courtesy of Wyeth Laboratories, Philadelphia.]

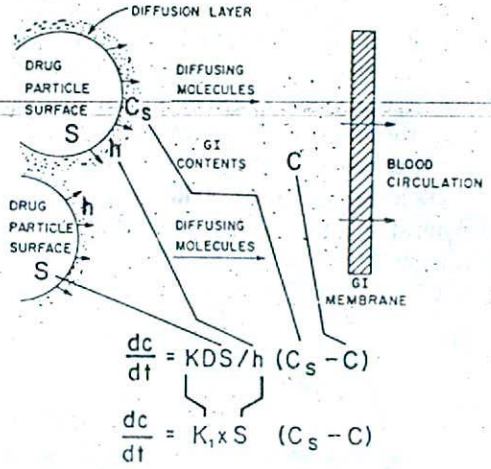
Noyes-Whitney Equation and Drug Dissolution

The expression for the *Noyes-Whitney dissolution rate law* is presented in Fig. 7-19. This law was developed at the turn of the century from the careful observation of dissolution behavior of solids in solvent systems. The equation is similar to the expression for Fick's law of diffusion (Chapter 6); the Noyes-Whitney equation can in fact be derived from Fick's law.

The Noyes-Whitney equation generally governs the dissolution rates of solid drugs. The dissolution rate (dc/dt) of a drug in the GI tract is dependent on the diffusion coefficient (D) of the drug in GI fluids, the surface area (S) of the undissolved solid drug, the saturation solubility of the drug in the GI fluids (C_S), and the thickness of the diffusion layer around the dissolving drug particles (h). The concentration of drug in GI fluids (C) is not a significant factor as the removal of drug by absorption does not allow a significant concentration of drug to build up.

For a specific drug under a given set of conditions (e.g., dissolution in the GI tract), the diffusion coefficient and diffusion layer thickness will be constant and can be incorporated into a specific dissolution rate constant (K_1). Therefore the two main variables governing dissolution of a drug in the GI tract are: (a) surface area of the solid drug; and (b) the saturation solubility of the drug in GI fluids (C_S) as shown in the simplified equation.

$$dC/dt = K_1 S (C_s - C)$$



$\frac{dc}{dt}$ = Rate of concentration change (dissolution rate)

K = Dissolution rate constant

D = Diffusion coefficient

h = Thickness of diffusion layer

S = Surface area of solid

C_S = Solubility of drug in solvent

C = Concentration of drug in GIT fluids or other solvent

$C_S - C$ = Concentration gradient

K_1 = Specific dissolution rate constant

FIG. 7-19. Noyes-Whitney dissolution rate law.

This equation explains the techniques discussed earlier in this chapter that can be used to alter the dissolution behavior of drugs in the GI tract. The particle size of a drug can be controlled to give a total surface area that allows a faster or slower dissolution rate. The solubility of a drug can be controlled by proper selection of a very soluble inorganic salt or less-soluble free acid or base, or using different crystal forms or hydrated forms of the same drug entity in the drug formulation. Solubilities of weakly acidic drugs can be controlled by the proper use of buffer ingredients in the dosage form.

The specific dissolution rate constant (K_1) is a constant for a specific set of conditions, although it is dependent on temperature, agitation, volume of solvent, and even the physical shape of the environment. In an *in vitro* situation (e.g., drug dissolution testing carried out under different conditions), the temperature, rate of stirring, volume of solvent, type of solvent (artificial gastric or intestinal juice), and vessel size and shape can all influence the rate constant and dissolution rate of a drug. Dissolution testing is discussed in Chapter 8.

8

Effect of Drug Product Design and Manufacture on Drug Availability

The Dosage Form

The dosage form and the formulation of a drug product may have very little effect on drug availability, or they may have beneficial or adverse effects. It is important that health care professionals be aware of the existence and importance of factors that give rise to bioavailability difficulties.

The various direct and indirect routes of drug administration were presented in Chapter 2. The oral route is the most popular method of direct drug administration, and there are many dosage forms utilized for this purpose. The major pharmaceutical dosage forms for oral, internal use are listed in Table 8-1 in the order of general availability of their active ingredients.

When rapid, efficient absorption of drug is desired, aqueous solutions represent the oral dosage form of choice. Drugs in suspension are readily absorbed because of the large available surface area of the dispersed solids. The various factors that influence the bioavailability of powders (e.g., particle size and other particle characteristics) have already been discussed. These factors retain their importance when the powdered drugs are incorporated into more compact dosage forms. As the dosage forms become more compact, the availability of their active ingredients usually decreases.

Soft elastic capsules have been shown to be efficient and reliable dosage forms, and their use has grown in recent years. The ingredients of soft gelatin capsules must be carefully selected and controlled so that the capsules do not harden on storage and become less soluble. Hard gelatin capsules have been used for many years and have always been thought of as a reliable dosage form. In fact, preliminary clinical studies by drug manufacturers have been routinely carried out utilizing hard gelatin capsules containing the active ingredient and a lactose diluent. Experiences have indicated that

TABLE 8-1. *Dosage forms for oral use*

Fastest availability	Aqueous solution (includes elixirs, syrups, etc.)
	Emulsion
	Suspension
	Soft gelatin capsule (for appropriate drugs)
	Hard gelatin capsule (questionable rate)
	Tablet
	Coated tablet
	Enteric-coated tablet
Slowest availability	Sustained-action (controlled-release) formulations

hard gelatin capsules might not be as reliable a dosage form as it was once considered; erratic dissolution and unreliable availability have been observed. Although hard gelatin capsules usually readily dissolve in gastric fluids, their erratic behavior might be due to flotation of the capsules in the stomach or a coating of mucus enveloping the dosage forms.

Erratic release behavior of enteric-coated tablets has usually been attributed to poor disintegration of the enteric coating, and in some cases passage of the intact tablet through the GI tract. Because of their complicated formulations, sustained (controlled) release dosage forms are subject to variable release patterns. The FDA considers sustained release products as new drugs, and they must undergo extensive bioavailability evaluation before being allowed on the market.

Blood level patterns after single doses of an antibiotic in three dosage forms are shown in Fig. 8-1. The top curve was obtained with an aqueous suspension of a water-insoluble derivative of the antibiotic, and the lowest

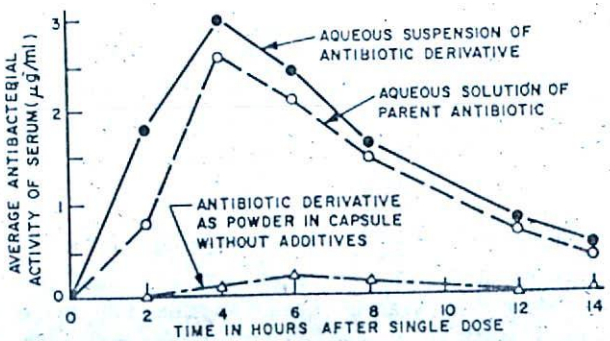


FIG. 8-1. Average antibacterial activity in the serum of normal human volunteers following oral administration of equal single doses of an antibiotic in three forms. [From Wagner, J. G. (1968): Biopharmaceutics part 3. *Drug Intell.*, 2:115.]

curve was obtained when the antibiotic derivative was administered as a powder in a hard gelatin capsule without additives. It is obvious that there was a very large difference in bioavailability of the antibiotic derivative between the capsule and suspension dosage forms. The effect of dosage form on serum levels of indoxole (an experimental anti-inflammatory agent) is shown in Fig. 8-2. Blood profile data were obtained after the first and sixth doses were administered in four dosage forms. The curves were very similar for the emulsion form and a soft elastic capsule form (the drug was dissolved in polysorbate 80, a wetting and emulsifying agent, and placed in the capsules). However, when indoxole was administered as an aqueous suspension or as a fine powder in a hard gelatin capsule, the blood levels were very much lower. This type of bioavailability study provides an excellent method of ranking several formulations or dosage forms of a given drug.

The mean plasma levels of procainamide found at each of the sample times for two procainamide formulations—a regular USP capsule and a sustained-release tablet—are shown in Fig. 8-3. Although significant differences were occasionally found at certain times, it appears that the 500-mg sustained-release formulation given every 6 hr is as effective as a 250-mg USP capsule given every 3 hr. Figure 8-4 illustrates how the absorption rates and resultant bioavailabilities of the alkaloid noscapine, obtained in the same person, depend on the method of administration. A single 250-

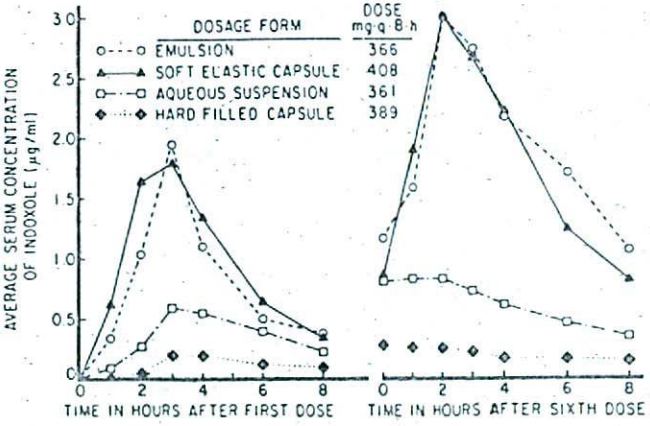


FIG. 8-2. Average serum concentrations of indoxole observed in eight volunteers following oral administration of the indicated doses every 8 hr. [From Wagner, J. G., et al. (1966): The effect of dosage form on serum levels of indoxole. *Clin. Pharmacol. Ther.*, 7:610.]

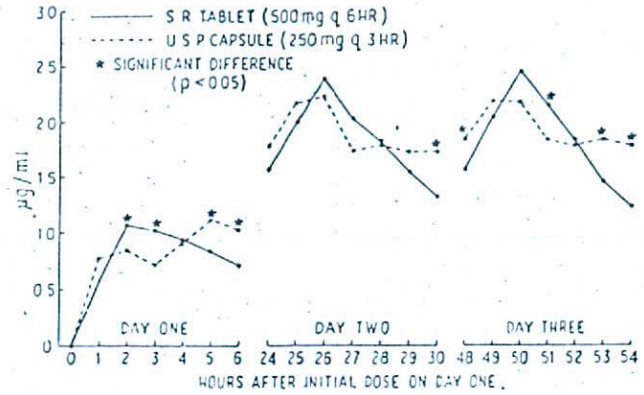


FIG. 8-3. Mean plasma levels of procainamide during 6 hr following first daily dose on days 1, 2, and 3. [From Smith, T. C., and Kinkel, A. W. (1980): Plasma levels of procainamide after administration of conventional and sustained-release preparations. *Curr. Ther. Res.*, 27:217–228.]

mg tablet dose was rapidly absorbed and eliminated. When the dose was divided into 16 aliquots and administered in solution at the rate of one aliquot every 10 min, the time to reach a peak level was slower, but an effective blood level was maintained for a longer period of time. When an equivalent 250-mg dose was administered in the form of a resin complex

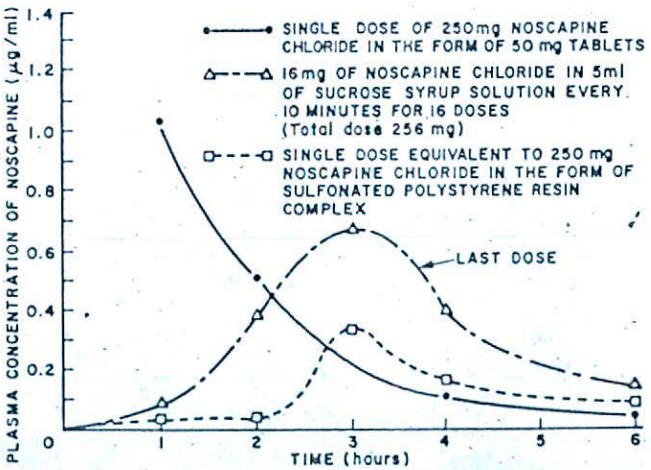


FIG. 8-4. Absorption and resultant plasma concentrations of noscapine obtained in the same person. [From Vedsø, S. (1961): Absorption and excretion of noscapine. *Acta Pharmacol. Toxicol. (Copenh.)*, 18:157.]

(a sustained-action formulation), the plasma level data indicated a reduced bioavailability of the alkaloid and a 2-hr lag time before a significant amount of drug reached the systemic circulation.

Figure 8-5 shows the cumulative urinary excretion curves for salicylamide metabolites excreted after oral administration of the drug in solution, suspension, or compressed pellets. The curves indicate that absorption of salicylamide from the pellets was relatively poor compared with solution and suspension dosage forms.

In light of the above examples, it is obvious that the dosage form and its formulation can greatly influence the therapeutic effectiveness of the active ingredient.

Compressed Tablets, Disintegration Time, and Dissolution Rate

Compressed tablets are the most widely prescribed dosage forms dispensed by the pharmacist. Most of the problems and arguments concerning generic equivalence and therapeutic equivalence center around compressed tablets. For this reason it is important that the pharmacist recognize the problems that pertain to the bioavailability of the active ingredients.

When a drug is formulated into a compressed tablet, there is a drastic decrease in the available surface area of the active ingredient because of

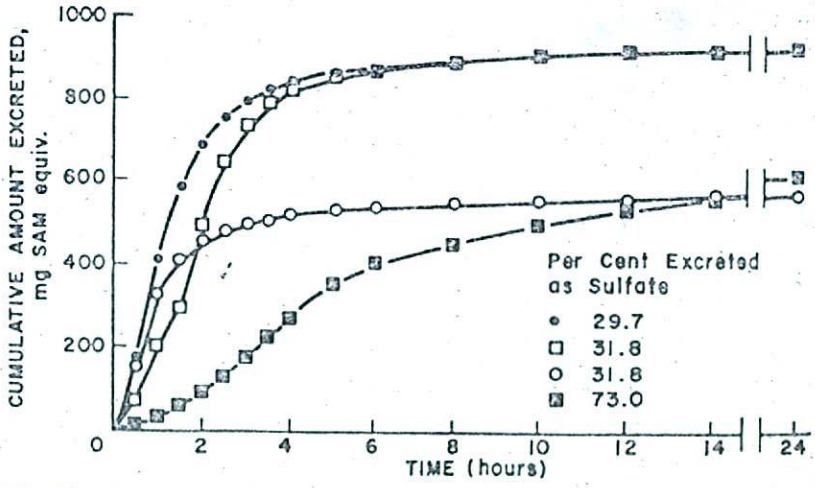


FIG. 8-5. Effect of dosage form on cumulative urinary excretion of salicylamide metabolites and on percent of 1.0-g dose of salicylamide excreted as salicylamide sulfate in a subject. (●)1.0 g in solution; (□) 1.0 g in suspension; (○) 600 mg in solution; (▨) 1.0 g in pellets. [From Levy, G., and Matsuzawa, T. (1967): Pharmacokinetics of salicylamide elimination in man. *J. Pharmacol. Exp. Ther.*, 156:285.]

compression of the drug particles. This loss of effective surface area of the drug is the main problem associated with compressed tablets. The intact tablet itself offers very little surface area for dissolution to take place. Therefore the tablet must readily and completely disintegrate when it comes in contact with gastric fluids.

The disintegration process and its effect on dissolution are presented in Fig. 8-6. Disintegration involves the break-up of the tablet into its constituent granules, followed by disintegration of the granules into small, primary particles. As surface area controls the dissolution rate of slowly soluble drugs, it is especially important for this class of drugs that the small, primary particles be made available by a disintegration process. At this point, it should be kept in mind that the dissolution rate and bioavailability of the primary particles may be significantly influenced by one or more of the

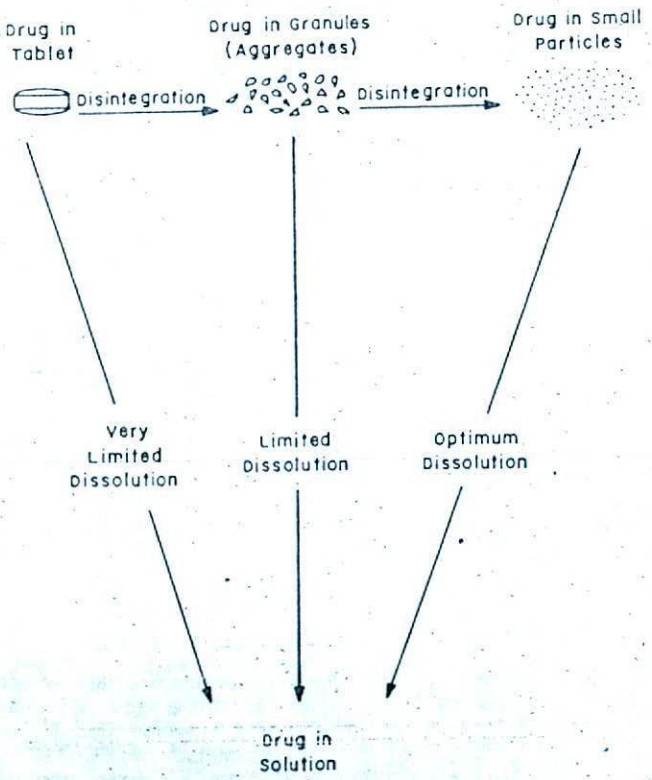


FIG. 8-6. Disintegration process.

TABLE 8-2. *Disintegration, dissolution, and GI absorption values for a series of commercial aspirin tablets*

Product	Average USP disintegration time (secs)	Average amount dissolved in 10 min (mg)	Amount excreted in urine[a] (mg)	
A	256	242	24.3	Study I[b]
C	<10	165	18.1	
E	<10	127	15.9	
B	35	205	18.5	Study II[b]
D	13	158	13.6	
E	<10	127	12.1	

From Levy, G. (1961): Comparison of dissolution and absorption rates of different commercial aspirin tablets. *J. Pharm. Sci.*, 50:388.

[a]In terms of apparent salicylic acid, 1 hr after administration of two 0.3-g tablets.

[b]Studies I and II were carried out with different test subjects and under somewhat different conditions.

From Levy, G. (1963): Biopharmaceutical considerations in dosage form design and evaluation. In: *Prescription Pharmacy*, edited by J. B. Sprowls, p. 75. Lippincott, Philadelphia.

physicochemical properties previously discussed (pH, hydration, polymorphism, etc.).

For many years the accepted laboratory standard for the release of the active ingredient from a compressed tablet was the disintegration time. This term represents the number of minutes required for the tablet, exposed to an aqueous solvent under standard agitation, to crumble into fragments small enough to pass through a No. 10 mesh screen. However, during recent years it has become apparent that the disintegration test is not in itself a wholly adequate criterion. As pointed out in previous discussions, there are many other factors that can influence the availability of some drugs. A tablet may rapidly crumble into fine particles, but the active ingredients may be slowly or incompletely available. Also, the disintegration test is not designed to determine the relative size of aggregates and particles. A tablet can be shown to disintegrate rapidly into granules, but this does not mean that the granules will disintegrate into fine particles or that the drug particles will dissolve and be absorbed adequately.

The present USP and NF disintegration test measures physical break-up of the tablet, but this does not necessarily correlate with drug availability. The lack of correlation between tablet disintegration time and rate of GI absorption of the active ingredient is shown in Table 8-2. These excellent studies dramatically demonstrate that dissolution rate rather than disinte-

gration time is indicative of the rate of absorption of aspirin from compressed tablets. In studies I and II (Table 8-2) the slowest disintegrating tablets had the fastest dissolution rates and produced the highest urine drug levels. It is clear that a rapid disintegration time does not indicate the true solubility rate and availability of the active ingredient.

If a tablet does not disintegrate within a reasonable period of time (more than 30 min), it is valid to assume that its active ingredient is only slowly available. Figure 8-7 illustrates the different plasma profiles for phenylindanedione tablets, which rapidly disintegrated in water, and tablets of the same drug, which remained intact after submersion in water for over 30 min.

A direct correlation between dissolution rate and bioavailability is shown in Figs. 8-8 and 8-9. The *in vitro* dissolution rate data correlate quantitatively with the human absorption rate data. Those aspirin tablets with the fastest dissolution also demonstrated the fastest bioavailability of their active ingredients. Figures 8-10 and 8-11 also illustrate a good rank-order correlation between bioavailability data (plasma levels) for five phenytoin preparations and *in vitro* dissociation data using a rotary basket dissolution apparatus (described in *USP XIX*).

The dissolution profiles of different brands of phenylbutazone tablets are shown in Fig. 8-12. There are large differences among the dissolution

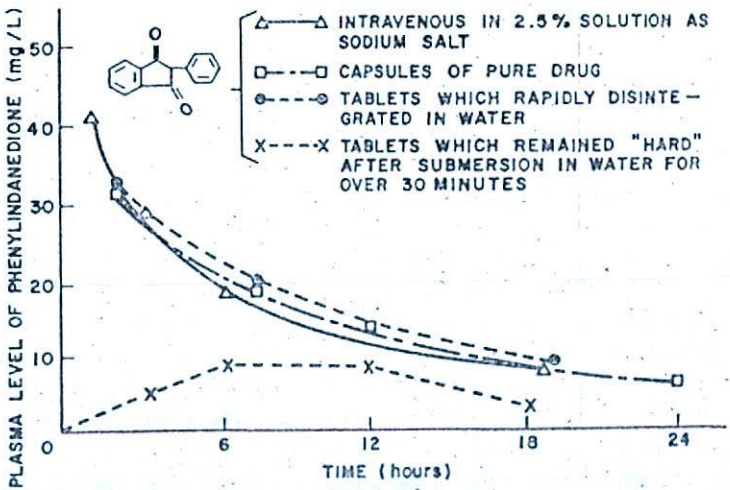


FIG. 8-7. Plasma levels of phenylindanedione following administration of the same dose (400 mg) to the same subject in different dosage forms. [From Wagner, J. G. (1964): Biopharmaceutics: gastrointestinal absorption aspects. *Antibiot. Chemother. Adv.*, 12:53–84.]

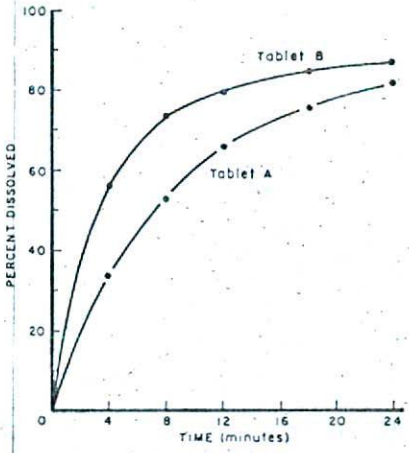


FIG. 8-8. *In vitro* dissolution of aspirin from two tablet formulations, A and B. [From Levy, G. (1964): Effect of dosage form on drug absorption—a frequent variable in clinical pharmacology. *Arch. Int. Pharmacodyn. Ther.*, 152:59.]

behaviors of the various tablets, and generally those tablets that displayed poor dissolution characteristics had relatively poor bioavailability of their active ingredients.

A dissolution test is much more discriminating than the disintegration test. A number of academic, government, and industrial scientists have developed dissolution rate tests that have been used to correlate *in vitro*

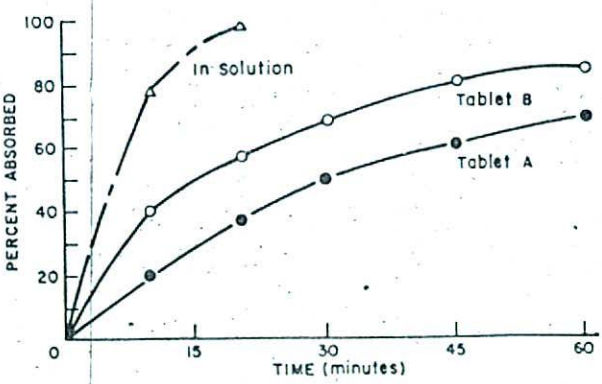


FIG. 8-9. Percent of the administered dose absorbed at various times after oral administration of 0.65 g aspirin. [From Levy, G. (1964): Effect of dosage form on drug absorption—a frequent variable in clinical pharmacology. *Arch. Int. Pharmacodyn. Ther.*, 152:59.]

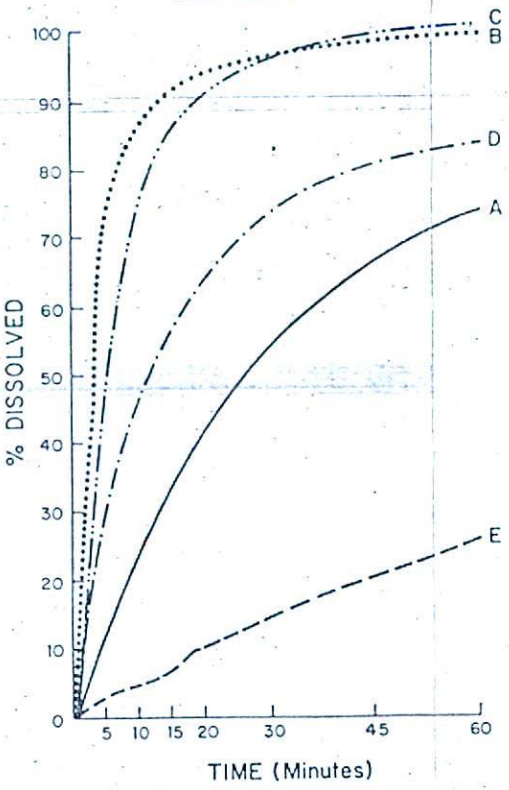


FIG. 8-10. Dissolution rates of phenytoin preparations A–E *in vitro*. [From Brandau, R., and Wehnert, H.-U. (1979): Lösungsgeshwindigkeit und Bioverfügbarkeit von Phenytoin-Zubereitungen. *Arzneim. Forsch.*, 29:552–555.]

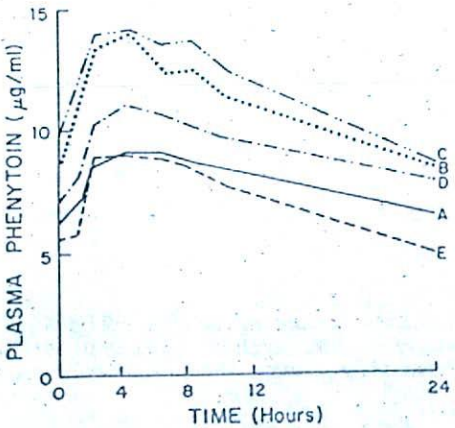


FIG. 8-11. Plasma concentrations of phenytoin, preparations A–E, at the end of a 2-week period of taking phenytoin 300 mg daily. [From Brandau, P., and Wehnert, H.-U. (1979): Lösungsgeshwindigkeit und Bioverfügbarkeit von Phenytoin-Zubereitungen. *Arzneim. Forsch.*, 29:552–555.]

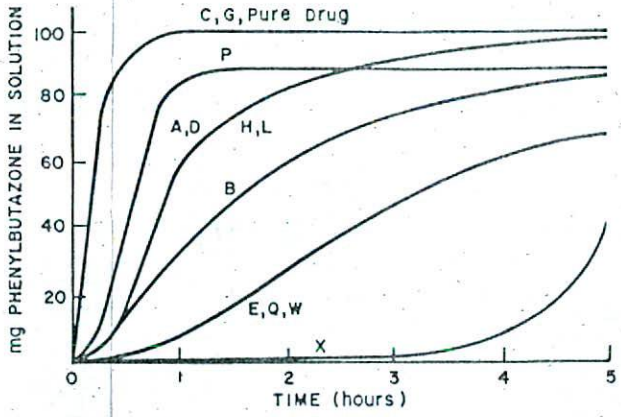


FIG. 8-12. Dissolution profiles for pure phenylbutazone and for 12 brands (A–E, G, H, L, P, Q, W, X) of phenylbutazone tablets in simulated intestinal juice. [From Searle, R. O., and Pernarowski, M. (1967): The biopharmaceutical properties of solid dosage forms 1. *Can. Med. Assoc. J.*, 96:2.]

drug dissolution with *in vivo* drug availability. Some of the methods developed are shown in Fig. 8-13. All of these methods measure the rate of appearance of dissolved drug in an aqueous fluid in which the dosage form has been immersed under conditions of carefully controlled agitation. After careful consideration, the National Formulary Drug Standards Laboratory recommended a tablet and capsule dissolution test which was included in the *National Formulary XIII (NF XIII)*. Two methods were made official for the determination of dissolution rates, the first method (method I) being a rotary basket method (Fig. 8-14) and the second method (method II) a modification of the USP-NF tablet disintegration method (basket-rack assembly in Fig. 8-13). Method I is applicable to those drugs that are not readily soluble, where the solubility is less than one dosage unit per 100 ml. Method II is applicable to those drugs where the solubility is greater than one dosage unit per 100 ml. These two methods were retained in the *NF XIV*, and the rotary basket method was also included in the *USP XIX*. The two procedures were again retained in the *USP XX/NF XV* and a third method added, called the USP paddle method. The new apparatus includes a round-bottom 1,000-ml container and a flat blade (paddle) held in a horizontal position. A dissolution system containing six individual paddle method setups is shown in Fig. 8-15. This dissolution system is typical of the type of equipment used in industry to perform large numbers of dissolution tests.

The USP rotary basket method (designated apparatus 1 in *USP XX*) is preferred by the USP and its use specified in most USP monographs which

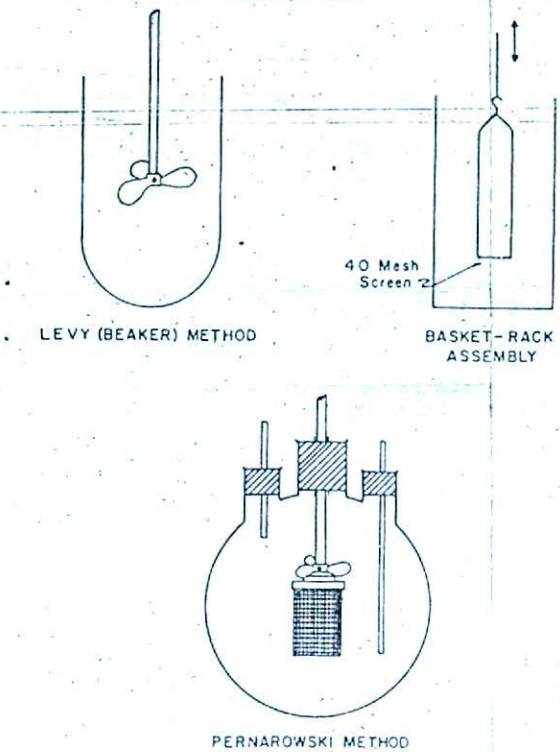


FIG. 8-13. *In vitro* methods of determining dissolution rate.

have dissolution requirements. The paddle method (apparatus 2 in *USP XX*) is indicated in seven USP monographs and is widely used by industry and the FDA for testing and evaluating tablet products. The modified disintegration apparatus (apparatus 3 in *USP XX*) is indicated in three USP tablet monographs (indomethacin; oxyphencyclimine hydrochloride; and theophylline, ephedrine hydrochloride, phenobarbital).

The *in vitro* dissolution test per se is not designed to ensure or measure the safety or effectiveness of the drug being tested. The safety and effectiveness of a specific formulation must be initially demonstrated through appropriate *in vivo* studies and clinical evaluation. The dissolution test does provide, however, an objective means of determining the dissolution characteristics of a solid dosage form, although it is recognized that by correlating *in vivo* test data and clinical evaluation more precise *in vitro* dissolution limits might subsequently be established. As drug absorption and bioavailability often are largely dependent on the drug being in the dissolved state, suitable dissolution characteristics can be an important property of a satis-

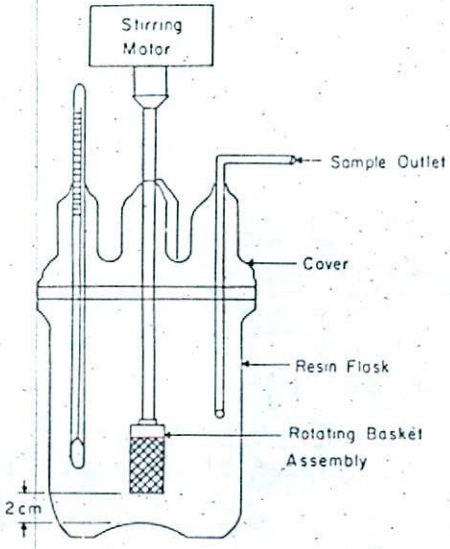


FIG. 8-14. Apparatus for dissolution testing, method I. This rotary basket method was retained in the *NF XIV* and adopted in *USP XIX* and retained in *USP XX/NF XV*. [From *The National Formulary*, 13th ed., p. 802. American Pharmaceutical Association, Washington, D.C., 1970.]

factory drug product. On this basis, specific test conditions and dissolution limits were first provided in certain *NF XIII* and *USP XVIII* tablet or capsule monographs. USP and NF drug products which originally had dissolution rate requirements included in their monographs are given in Table 8-3. All of these original drug products plus 40 additional tablets and capsules have dissolution requirements in the *USP XX*. Some of the important additions are colchicine, digoxin, digitoxin, lithium carbonate, and quinidine sulfate. The dissolution requirement for each of these tablets provides a control for ensuring that a tablet formulation containing the specific drug has the same dissolution as the batch of tablets shown originally to be bioavailable and effective. Products which meet USP requirements must dissolve within the time prescribed and under the specific conditions stated in the monograph. For example, the USP dissolution requirement for digoxin tablets is that not less than 65% of the labeled amount of digoxin dissolves within 60 min in 500 ml dilute hydrochloric acid using the rotating basket apparatus at a stirring rate of 120 rpm. A drug product that has met USP dissolution requirements will be absorbed as expected. Dissolution testing is also used as a control procedure during the manufacturing process to maintain uniformity among production batches.

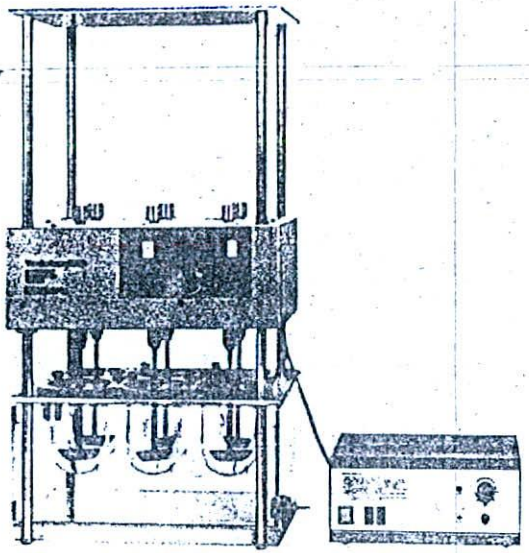


FIG. 8-15. Six spindle dissolution tester with paddles (USP method II). Vandercamp 600 apparatus. [Courtesy of Van-Kel Industries, Inc.]

Many studies have been carried out over the last 20 years in an attempt to correlate *in vitro* dissolution tests with *in vivo* bioavailability data. Some studies have found significant correlation, whereas others have been unsuccessful in attempts to find satisfactory *in vitro* conditions (e.g., type of apparatus, dissolution medium, stirring rate, pH, volume) that correlate with *in vivo* absorption and bioavailability data. As seen in Fig. 8-8 through 8-11, good rank-order correlations were found for the dissolution rates of aspirin and phenytoin and their human absorption rate data after adminis-

TABLE 8-3. *Drugs for which dissolution rate requirements were originally included in the* USP XVIII *and* NF XIII

NF XIII drugs	*USP XVIII* drugs
Acetohexamide (Dymelor®)	Hydrochlorothiazide (Esidrix®)
Indomethacin (Indocin®)	Meprobamate (Miltown®, Equanil®)
Methandrostenolone (Dianabol®)	Nitrofurantoin (Furadantin®)
Methylprednisolone (Medrol®)	Prednisone (Deltasone®)
Sulfamethoxazole (Gantanol®)	Prednisolone (Delta Cortef®)
Theophylline, ephedrine HCl and phenobarbital (Tedral®)	Sulfisoxazole (Gantrisin®)
	Tolbutamide (Orinase®)

tration of different product formulations. These correlations are very specific to the experimental conditions used in the studies, and any change in the type of dissolution apparatus, rate of stirring, type of dissolution medium, etc. would probably change the degree of correlation and could even reverse the rank order. Many carefully planned and tedious studies must be carried out before a significant relationship can be established between an *in vitro* dissolution test and previously determined absorption and bioavailability data. *In vitro* testing may or may not correlate with *in vivo* bioavailability data, and the current state of the art is such that it will be some time in the future, indeed if ever, that dissolution tests will be used routinely to predict and assess bioavailability. The greatest value of *in vitro* dissolution testing lies in the areas of (a) helping to identify formulations that may present potential bioequivalence problems and (b) ensuring batch-to-batch bioequivalence once a formulation has been shown to be bioavailable.

Formulation and Processing Factors

There are numerous reports describing the effects of formulation and processing variables on the dissolution and bioavailability of active ingredients from drug products. Some of the materials and processes which can influence dissolution rate and drug availability are diluents (fillers), binders (excipients), disintegrating agents, lubricants (glidants), surfactants, suspending agents, compaction and compression pressures, coating ingredients, and coloring agents.

Adsorption of some drugs, especially vitamins, on diluents such as kaolin, Fuller's earth, or bentonite can occur in capsule and tablet dosage forms. This physical adsorption can retard the availability of the drug. Calcium sulfate and dicalcium phosphate are extensively utilized as capsule and tablet fillers. Their original use in tetracycline capsule formulations, however, resulted in poor bioavailability of the antibiotic because a poorly absorbed complex formed between calcium and tetracycline when the capsule ingredients were dispersed in the GI fluids; replacement of the calcium fillers by suitable inert diluents prevented this phenomenon.

In Australia several years ago, changing the excipient of a phenytoin (diphenylhydantoin) capsule formulation from calcium sulfate to lactose apparently resulted in greater bioavailability of the drug. This formulation change was suggested to be the reason for an unusually large number of patients with signs of phenytoin overdosage during that period of time. Currently there are two *USP XX* phenytoin sodium capsules: Prompt Phenytoin Sodium Capsules, a rapid-release type, and Extended Phenytoin Sodium Capsules (Dilantin Kapseals®), a slower-release type. The "prompt"

capsule has a much faster dissolution requirement than the extended-dosage form. The difference in dissolution rates is a result of formulation manipulation to prolong the dissolution rate of phenytoin sodium. Because there are these different types of capsule on the market, and differences in dissolution rates and bioavailabilities may exist among different brands, patients should be maintained on one manufacturer's product during phenytoin therapy.

Natural and synthetic gums (e.g., acacia, methylcellulose) are commonly used as tablet binders, and they usually form viscous solutions when they come in contact with gastric fluids. This may slow down dissolution by delaying disintegration and forming a mucilaginous layer around dissolving drug particles. When these same gums are utilized as suspending agents, they may delay or prevent the availability of some drugs by interacting with the drug to form less-soluble or insoluble substances.

The concentration of disintegrant in a tablet can greatly influence the dissolution and bioavailability of the active ingredients. The dissolution rate is usually increased when the concentration of starch is increased in a tablet formulation. This effect is shown in Fig. 8-16 for salicylic acid tablets. Figures 8-17 and 8-18 illustrate how changing the concentration of disintegrant (Veegum®) in a tolbutamide tablet formulation can greatly alter bioavailability. Two formulations were administered to healthy, nondiabetic subjects. One formulation was a commercial product (Orinase®) and the other was identical in all composition and manufacturing respects except for halving the amount of disintegrant (Veegum®). The commercial product (A) displayed higher blood levels and greater ability to lower blood glucose than the experimental product (B).

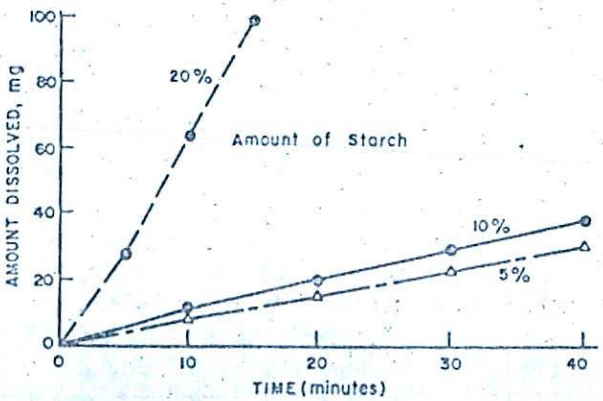


FIG. 8-16. Effect of starch content of granules on dissolution rate of salicylic acid contained in compressed tablets. [From Levy, G., et al. (1963): Effect of certain tablet formulation factors on dissolution rate of ingredients II. *J. Pharm. Sci.*, 52:1047. Reproduced with permission of copyright holder.]

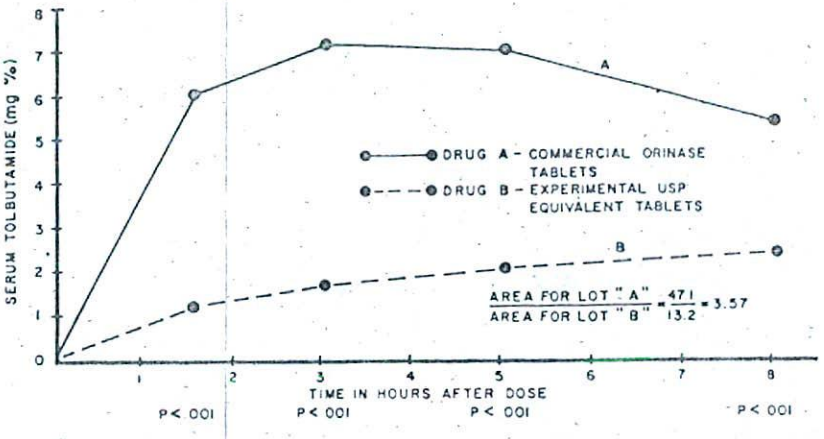


FIG. 8-17. Serum tolbutamide levels after administration of commercial tolbutamide (Orinase) (A) and experimental drug (B). [From Varley, A. B. (1968): The generic inequivalence of drugs. *JAMA*, 206:1745.]

The dissolution of salicylic acid from tablets can be affected by the type of starch used as a disintegrant in the tablet formulation (Fig. 8-19). The dissolution of the drug was considerably faster from tablets formulated with a specially treated, directly compressible starch.

Generally, the dissolution rate is slowed when high compression pressures are used to prepare tablets. This is probably due to the more difficult dis-

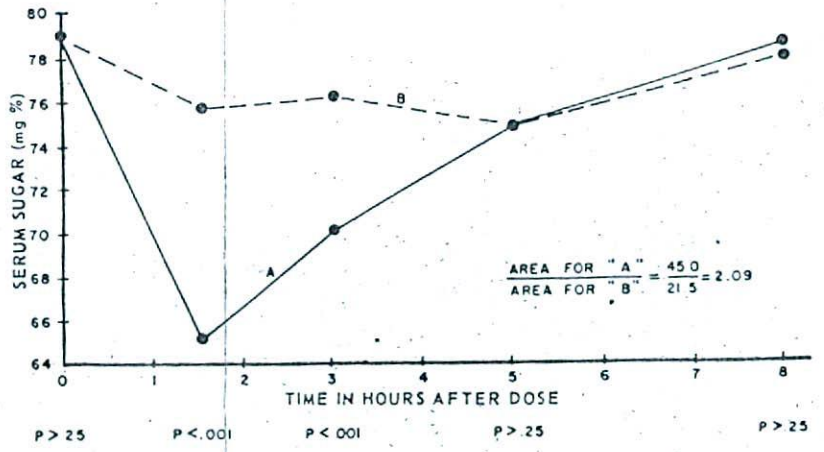


FIG. 8-18. Serum glucose levels after administration of commercial tolbutamide (Orinase) (A) and experimental drug (B). [From Varley, A. B. (1968): The generic inequivalence of drugs. *JAMA*, 206:1745.]

* Increasing the amount of disintegrant may overcome the retarding effect of lubricants on dissolution.

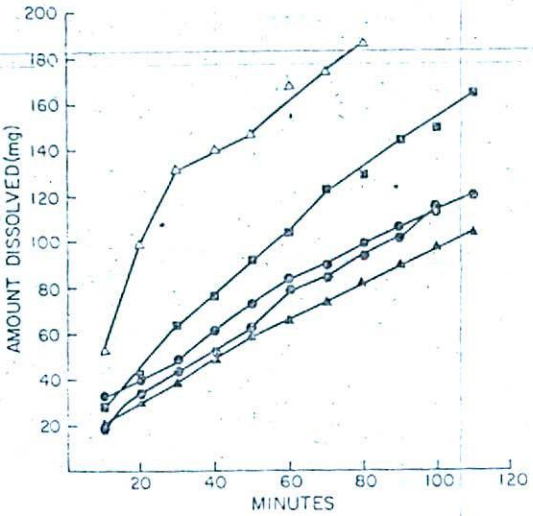


FIG. 8-19. Dissolution rates of salicylic acid from tablets containing various starches using the flask method (59 rpm) at 37°C. (●) Cornstarch; (■) potato starch; (▲) rice starch; (◆) arrowroot starch, and (Δ) compressible starch. [From Underwood, T. W., and Cadwallader, D. E. (1972): Influence of various starches on dissolution rate of salicylic acid from tablets. *J. Pharm. Sci.*, 61:239. Reproduced with permission of the copyright owner.]

integration of highly compressed granules. Very tightly compacted powders in hard gelatin capsules is a possible cause for erratic release of active ingredients from this dosage form.

Tablet lubricants (e.g., magnesium stearate and mineral oil) are water-insoluble and water-repellent. Their hydrophobic nature can prevent contact between the dosage form solids and GI fluids and thereby cause slow dissolution of the drug. Figure 8-20 shows how magnesium stearate retards the dissolution of salicylic acid from tablets. On the other hand, tablets prepared using sodium lauryl sulfate (a soluble, hydrophilic, wetting agent) as a lubricant gave very rapid dissolution of salicylic acid.

Many substances (sugars, natural gums, synthetic gums and polymers, shellac, cellulose derivatives, and waxes) are used as tablet coatings. Improper coating or possible reactions (e.g., polymerization) during storage could result in unreliable release of the medicaments, or perhaps even the passage of the intact dosage form through the alimentary tract.

Figure 8-21 presents the blood concentration curves of sulfathiazole obtained following administration in the absence and presence of a coloring agent, FD & C Blue No. 1. From these data it is apparent that during the first 3 hr, the sulfathiazole concentrations in the presence of the dye were

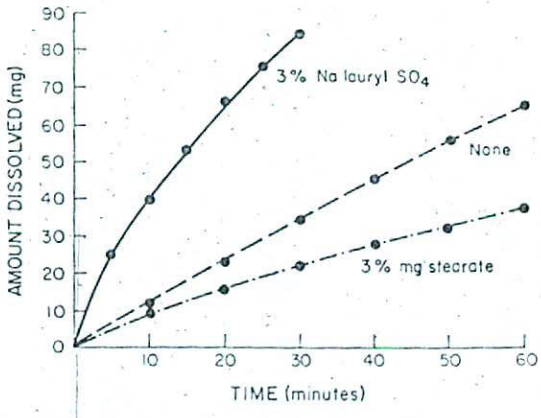


FIG. 8-20. Effect of lubricant on dissolution rate of salicylic acid contained in compressed tablets. [From Levy, G., and Gumtow, R. H. (1963): Effect of certain tablet formulation factors on dissolution rate of the active ingredient III. *J. Pharm. Sci.*, 52:1139. Reproduced with permission of the copyright owner.]

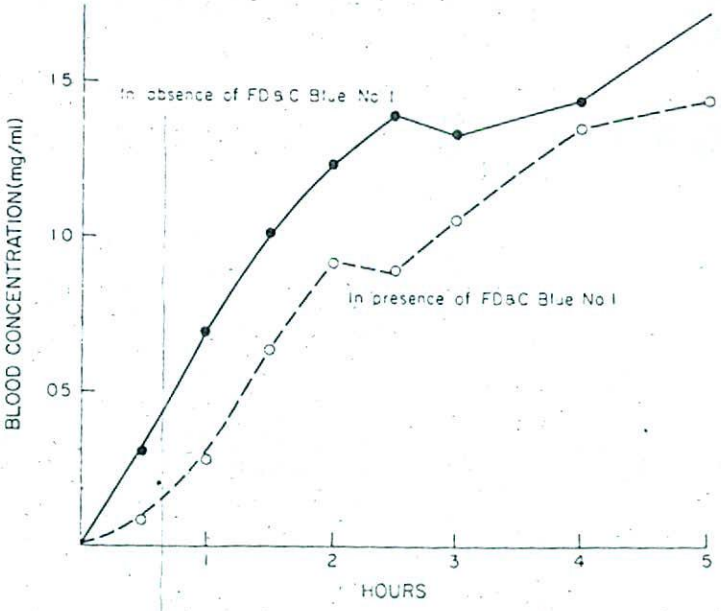


FIG. 8-21. Blood concentrations of free sulfathiazole following oral administration of 1 g sulfathiazole crystals to adult human subjects. [From Tawashi, R., and Piccolo, J. (1972): Inhibited dissolution of drug crystals by certified water soluble dyes: in vivo effect. *J. Pharm. Sci.*, 61:1857. Reproduced with permission of the copyright owner.]

lower than those in the absence of the dye. These blood level data were in good agreement with *in vitro* dissolution rate data, and this agreement suggests that a small concentration of Blue No. 1 could significantly delay the absorption of sulfathiazole through dissolution inhibition.

It is apparent from the foregoing discussion that the bioavailability of medications from drug products can be significantly influenced by many and sometimes seemingly minor pharmaceutical formulation and processing variables. The members of the health team should be aware that changing from one brand of a particular drug to another may result in a change in the bioavailability of the drug and patient response to the drug because of differences in their formulations.

9

Bioavailability Testing and Drug Product Selection

Extensive bioavailability testing is carried out by drug manufacturers because of an enlightened self-interest to ensure the quality of its products. It is important to the manufacturer that a given drug product is appropriate to get the therapeutic agent to its site of action. Drug manufacturers must fulfill the FDA requirements for new drug applications (NDAs) and specific requirements for drug products, including *in vivo* and *in vitro* testing. A drug manufacturer often wants to compare its drug product with another or with a set of established standards to confirm the bioequivalence of its products. This last type of specific bioavailability testing is called *bioequivalence testing*, and the results of such studies are usually made available to health care practitioners for evaluation.

Bioavailability testing is also carried out by academic and government research institutions to study the absorption, distribution, and elimination characteristics of drugs and to evaluate dosage form variables and dosage regimens (Chapter 4) as well as to test drug products for regulatory purposes.

The FDA may request that certain drug products meet specific *bioequivalence requirements*. Obviously those drug products that have been shown, through well-controlled studies, to be bioinequivalent or not therapeutically equivalent would be good candidates for bioequivalence requirements. A product which contains an active drug ingredient that, because of some physicochemical or formulation property (Chapter 8) has low water solubility or a slow dissolution rate, should have appropriate bioequivalence requirements. If the active drug is rapidly metabolized or excreted, bioequivalence requirements may be imposed to ensure rapid dissolution and absorption. Drug products that are specially formulated to maintain the stability (e.g., enteric-coated tablet) or prolong the release (e.g., sustained-action dosage form) of the active ingredient should meet requirements that ensure adequate absorption.

Bioavailability requirements are not relevant to certain drug products (e.g., topically applied ointments, creams, and lotions intended for local effect) and are not required by the FDA. Drug products such as antacids and laxatives contain ingredients not intended for absorption and therefore do not need bioavailability testing. Intravenous solution products that have the same drug concentration and solvent system as the FDA-approved product do not need additional bioavailability testing. This is also generally the case for those liquid drug products that contain the active ingredient in a solubilized form (oral solutions, elixirs, syrups, etc.) in the same concentration as the drug product that has been approved by the FDA via an NDA.

Methods for Determining Bioavailability

Bioavailability in humans may be determined by several *in vivo* methods. The method used depends mainly on the availability of a good analytical method for measuring low concentrations of drug in human fluids. Clinical trials or measurement of a pharmacological effect can be used when suitable. When an analytical method is available, the method of choice for routine bioavailabilty studies is the measurement of drug and/or its metabolites in blood or other body fluids.

Clinical trials. Well-controlled clinical trials in humans are used to establish the efficacy and safety of drugs and drug products, and many such studies must be carried out by drug manufacturers before a new product is finally approved for marketing. As pointed out earlier (Chapter 4), these studies usually involve a large number of patients and are very expensive. In addition, a clinical trial is the least sensitive of methods for verifying drug bioavailability in humans. Although this method would give an adequate estimation of drug in body fluids, it would not be used for bioavailability studies unless an adequate assay could not be developed. Because of the high costs, this method would not be used for routine bioequivalence studies.

Quantification of pharmacological effect. Use of pharmacological response data to establish bioavailability is warranted when assay methods are not available for detecting small quantities of drug in body fluids. This method assumes that a given intensity of response is associated with a particular drug concentration at the site of action. Figure 9-1 shows how the variation of miotic response intensity can be directly related to the oral dose of chlorpromazine. Pupil size is monitored, and the test subjects do not have to undergo an invasive technique to obtain blood samples. Un-

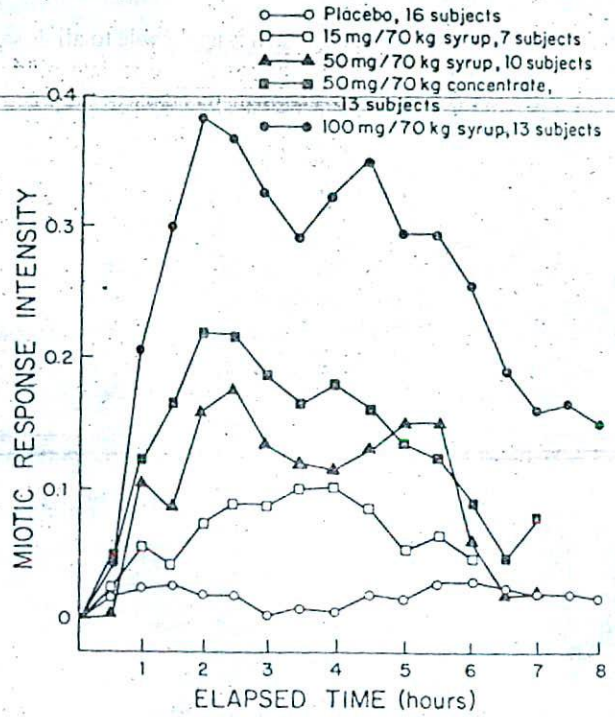


FIG. 9-1. Time variation of average miotic response intensity observed following oral placebo and chlorpromazine syrup and liquid concentrate dosing of up to 13 normal human subjects. [Adapted from Smolen, V. F., et al. (1975): Pharmacological response data for comparative bioavailability studies of chlorpromazine oral dosage forms in humans. I. Pupilometry. *J. Clin. Pharmacol.*, 15:734–750.]

fortunately, the monitoring of pharmacological data is not as easy as it appears, and precision and reproducibility are very difficult to establish for routine use. There are only a limited number of pharmacological effects, e.g., heart rate, blood pressure, blood sugar levels, body temperature (see Fig. 4-1, p.22), and electrocardiograph (ECG) changes, that might be applicable to this method.

Measurement of drug and/or its metabolites in blood and urine. The measurement of the drug or its metabolite in blood or urine is the method of choice for routine bioavailability studies because it is relatively easy to carry out and requires a limited number of human subjects. Blood level or urinary excretion data can be used to evaluate and establish the bioavailability of drug products and compare the performance of a single drug entity under

many conditions (Chapter 4). This approach is applicable to all dosage forms that are intended to deliver the drug to the systemic circulation: oral dosage forms, buccal and sublingual dosage forms, injectables, suppositories, inhalation dosage forms, and even some topical applications. This method is used by drug manufacturers to compare their product with another product or with an established standard. This specific type of study is appropriately called a bioequivalence study, or bioequivalence testing, as the drug manufacturer is attempting to prove that its product is bioequivalent to a competitor's product or to a recognized standard.

A good analytical procedure that accurately detects very small quantities of drug in blood, serum, or urine is essential to this type of testing. During the last several years newer, sophisticated techniques, e.g., high-performance liquid chromatography (HPLC), radioimmunoassay (RIA), and gas chromatography-mass spectroscopy (GC-MS), have been developed to detect drug and drug metabolite concentrations in micro (parts per million, or 10^{-6}), nano (parts per billion, or 10^{-9}), and even pico (parts per trillion, or 10^{-12}) quantities. Thus drugs that could not be studied *in vivo* a few years ago are now subject to routine evaluation.

Methods and Criteria for Bioavailability Testing

The general method of bioavailability testing involves administering a drug to healthy human subjects, obtaining serial blood or urine samples over a period of time, analyzing them for drug content, and tabulating and graphing the results. Examples of methods and criteria for the bioavailability testing of warfarin, nitrofurantoin, and digoxin are presented in Tables 9-1 through 9-3, respectively. Note that the comparative bioavailability tests are conducted in a crossover design to minimize the effect of individual subject variation to a drug. A crossover study design means that each subject receives each of the dosage forms to be tested during the testing period. A minimum of 12 healthy human subjects is recommended, although usually 18 to 24 subjects are used to increase the data base for statistical analysis. Informed, written consent must be obtained from each of the individuals, and adequate examinations and laboratory tests (hematology, blood chemistry, and urinalysis) are carried out to establish them as healthy volunteers. Although the weight range for subjects is rather wide (120 to 220 lb), the individual weights of subjects sould be close to the desirable weight for height, frame, and age. The subjects should not be taking drugs prior to the test and should not take any other drugs during the study. Usually the volunteers fast overnight, and the drug is taken first thing in the morning with a prescribed amount of water. Ordinarily, comparison of a drug product with an appro-

TABLE 9-1. *Criteria for bioavailability tests: warfarin products*

1. Tests should be conducted in a two-way crossover design.
2. At least 12 subjects should be utilized. The subjects should not receive barbiturates or other known enzyme-inducing agents for 30 days prior to the study and no medication other than the prescribed medication for 7 days preceding and during the study. Subjects should be fasted overnight and for 4 hr after drug administration. On the mornings of drug administration, each subject should drink 240 ml water within the first hour after arising and 240 ml water when the tablets are ingested. Tablets should be swallowed whole.
3. Healthy subjects should weigh between 55 and 95 kg and should be selected on the basis of medical history, physical examination, urinalysis, and clinical pathology screening, including liver, kidney, and hematology function tests.
4. At least 3 weeks, equivalent to about 10 average serum warfarin half-lives, should separate crossover tests.
5. The test product should be compared with a standard reference tablet product of the same strength (e.g., Endo warfarin sodium).
6. Serum warfarin concentrations should be determined at 0, 0.5, 1, 4, 8, 12, 24, 48, 72, and 96 hr after dosing.
7. Blood data should include drug levels at each collection period, peak drug levels, time of peak level, and area under the serum level–time curve.
8. The data obtained at each sampling time should be analyzed by analysis of variance to test for differences between formulations.

From Benya, T. J. (1978): Warfarin (bioavailability monograph). In: *The Bioavailability of Drug Products*, pp. 113–116. American Pharmaceutical Association, Washington, D.C.

priate standard of another drug product involves only a single dose of drug. Sometimes food and liquid intake is kept uniform among subjects by requiring standardized meals and regulating fluid intake. Statistical tests are utilized to determine if any differences observed during the study were due to chance occurrence or if in fact the differences were due to the differences in treatment.

Presentation of Bioequivalence Data

Bioequivalence study data should be presented so that the important factors of peak height time, peak serum concentration, and area under the curve can be readily and adequately evaluated. This usually involves a format that includes tabulated data and a drug concentration versus time figure. A typical format for presentation of a single-dose bioequivalence study is shown in Fig. 9-2. Note that the following factors are included in this clear and concise format.

TABLE 9-2. *Criteria for bioavailability tests: nitrofurantoin products*

As the USP dissolution test for nitrofurantoin does not yet appear to be a reliable indicator of *in vivo* bioavailability, pharmacists should use bioavailability data to make judgments on nitrofurantoin products from non-innovator companies. The following criteria should be looked for when assessing bioavailability data.

1. Tests should be conducted in a two-way crossover design.
2. A minimum of 12 subjects should be used. Subjects fed a light, standard meal should be used for single-dose bioavailability studies.
3. Healthy subjects should be selected on the basis of medical history, physical examination, urinalysis, and other laboratory tests that establish the presence of normal kidney function and rule out previous or current genitourinary disease.
4. When possible the subjects' weights should be within 55 and 95 kg.
5. A 48-hr interval should separate the crossover tests.
6. The test product should be compared with a standard reference tablet product (Eaton Laboratories' brand of nitrofurantoin, Furadantin).
7. Data should be in one of the following forms:
   a. Cumulative urinary excretion curves (cumulative amount of drug versus time).
   b. Tabulation of 24-hr urinary recovery from test subjects (percent of drug recovered after 24 hr for each test subject).
8. The test should be conducted for 24 hr.
9. Urine samples should be obtained during the periods 0–2, 2–4, 4–6, 6–8, 8–12, and 12–14 hr. All subjects should ingest approximately the same amount and type of fluids and food during the test period.
10. The data at each sampling time should be analyzed by analysis of variance to test differences between the two formulations.

From Cadwallader, D.E. (1978): Nitrofurantoin (bioavailability monograph). In: *The Bioavailability of Drug Products*, pp. 63–66. American Pharmaceutical Association, Washington, D.C.

1. Name and manufacturer of drug
2. Dosage form and dose of drug
3. Number of volunteers and number of each sex
4. Analytical procedure used in study (microbiological)
5. Type of study (randomized crossover)
6. Sampling intervals
7. Drug concentrations at each sampling interval
8. Average of individual peak serum concentrations
9. Average of the times of peak serum concentration

TABLE 9-3. *Criteria for bioavailability tests: digoxin tablets*

Although the FDA has set specific requirements for the marketing of digoxin tablets (*Fed. Register*, 39:2471, 1974), pharmacists still need to be concerned about bioavailability information on the diogoxin tablets they dispense, particularly digoxin products of a non-innovator company. The following criteria for bioavailability tests are based on those used by FDA:

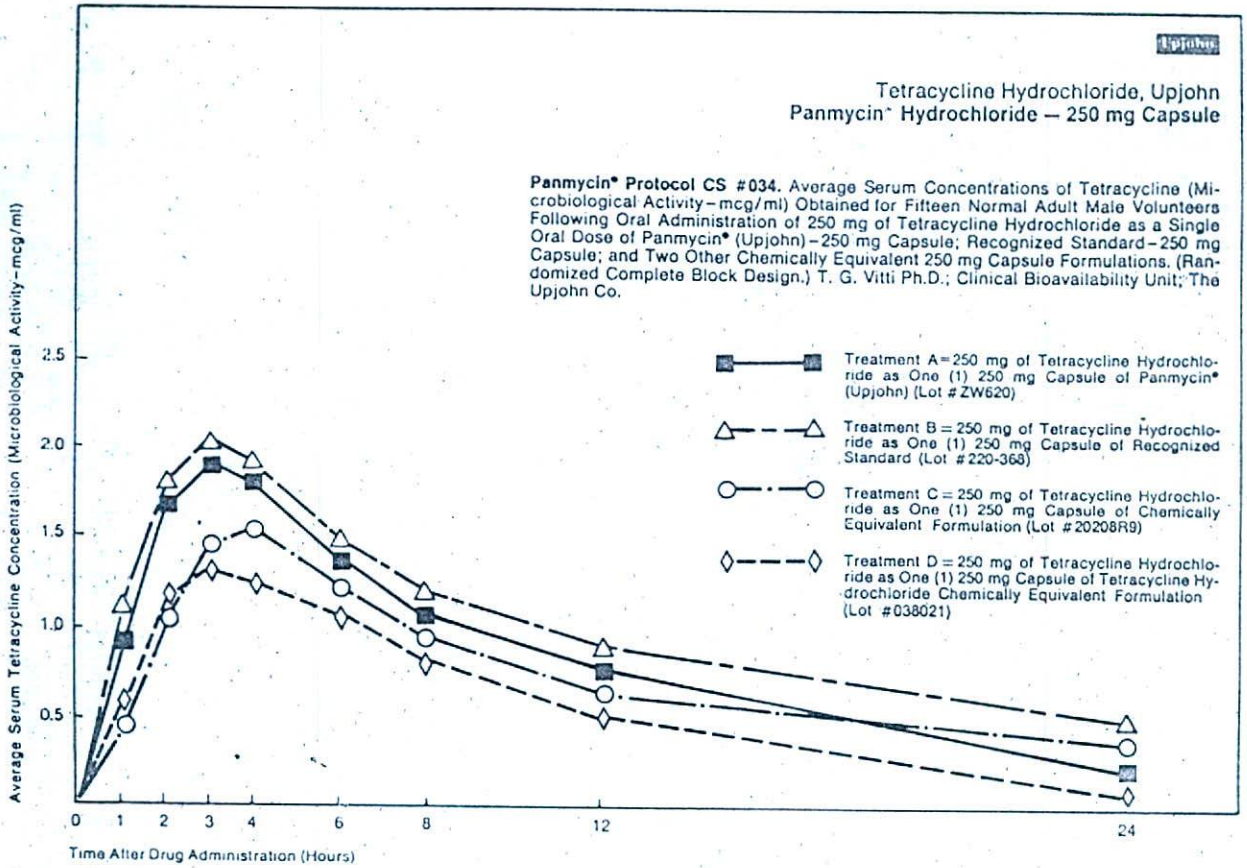
1. Tests should be conducted in a three-way crossover design.
2. A minimum of 12 subjects should be used.
3. Subjects should undergo adequate clinical pathology screening, including liver, kidney, and hematology function tests, and electrocardiograms.
4. When possible, subjects should weigh between 55 and 95 kg.
5. Two weeks should separate the crossover tests.
6. The test product should be compared to:
   a. A standard reference tablet product (Burroughs Wellcome brand of digoxin, Lanoxin®) *and*
   b. An aqueous solution administered orally
7. Data should be in the form of serum level–time profiles and urinary excretion data for 0–24, 24–48, 48–72, and 72–96 hr.
8. The test should be conducted for a minimum of 5 hr, preferably 96 hr.
9. Blood level determinations should be made at 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, and 5 hr and preferably at 12, 24, 48, 72, and 96 hr.
10. Renal clearance of digoxin should be calculated for each subject.
11. AUC $0-\infty$ (0 to infinite time) should be estimated for each subject after each treatment.
12. Relative absorption efficiencies should be calculated for each subject by correcting for changing renal clearances based on the equation developed by Till et al. (*J. Pharmacokinet. and Biopharm.*, 2:529, 1974).
13. Plasma levels at each sampling time and the area under the curve should be evaluated according to analysis of variance for a crossover design.

From Collaizzi, J. L. (1978): Digoxin (bioavailability monograph). In: *The Bioavailability of Drug Products*, pp. 41–44. American Pharmaceutical Association, Washington, D.C.

10. Area under the curves for the various time intervals
11. Statistical method used to evaluate data (ANOVA)
12. The results of statistical evaluation (no significant difference between the two products)

The graph portion of Fig. 9.2 allows the evaluator to compare the overall performance of the two drug products, and the table portion clearly presents the numerical data.

Average Serum Concentrations of Tetracycline Hydrochloride (Microbiological Activity—mcg/ml) and Related Parameters



Tetracyline	Treatment A
	Panmycin® (Upjohn)
	250 mg Capsule
	Lot #ZW620
	Dose = 250 mg
		Treatment B
		Recognized Standard
		250 mg Capsule
		Lot #220-620
		Dose = 250 mg
			Treatment C
			Chemically Equivalent Formulation
			250 mg Capsule
			Lot #20208 R9
			Dose = 250 mg
				Treatment D
				Chemically Equivalent Formulation
				250 mg Capsule
				Lot #03021
				Dose = 250 mg
					Statistics
					ANOVA† (Among Treatments)
						Tukey's** Allowable Difference (Between Treatments)
						A & B
							A & C	A & D	B & C	B & D	C & D

Average Serum Concentration at: 1.0 Hours (mcg/ml)	0.96	0.99	0.44	0.55	p<.001	–	+	+	+	+	–
2.0 Hours	1.67	1.69	1.02	1.08	p<.005	–	+	+	+	+	–
3.0 Hours	1.91	1.96	1.39	1.36	p<.05	–	–	–	±	±	–
4.0 Hours	1.73	1.87	1.50	1.32	n.s.*	–	–	–	–	–	–
6.0 Hours	1.29	1.39	1.16	1.06	n.s.	–	–	–	–	–	–
8.0 Hours	1.04	1.10	0.95	0.83	n.s.	–	–	–	–	–	–
12.0 Hours	0.72	0.77	0.67	0.57	n.s.	–	–	–	–	–	–
24.0 Hours	0.27	0.34	0.29	0.25	n.s.	–	–	–	–	–	–
Peak of the Average Serum Concentration Time Curve (mcg/ml)	1.91	1.96	1.50	1.36	n.s.	–	–	–	–	–	–
Average of the Individual Peak Serum Concentrations (mcg/ml)	1.99	2.01	1.63	1.54	n.s.	–	–	–	–	–	–
Time of the Peak of the Average Serum Concentration Time Curve (hours)	3.0	3.0	4.0	3.0	–						
Average of the Individual Peak Times (hours)	2.67	3.07	3.27	3.15	n.s.	–	–	–	–	–	–
Average of the Areas Under the Individual Serum Concentration Time Curves: (mcg x hours/ml) 0-6 Hours	8.41	8.83	6.25	6.04	p<.025	–	–	–	–	+	–
0-24 Hours	20.22	21.76	17.39	15.64	n.s.	–	–	–	–	–	–

†ANOVA = Analysis of Variance for Complete Crossover Design

*n.s. = Not statistically significant at the .05 level of confidence ($p > .05$)
**Tested only at the .05 level of confidence; (+) = ($p < .05$), (–) = ($p > .05$)

FIG. 9-2. Bioavailability data for tetracycline hydrochloride (Panmycin® Hydrochloride) 250 mg capsule. [From professional product information, The UpJohn Company.]

Crossover Design

A suitable crossover design should be utilized in bioavailability testing so that subjects' daily variations are distributed equally among all dosage forms or drug products being tested. A four-way crossover design is shown in Table 9-4, which was used to evaluate intrasubject variability of digoxin bioavailability for tablet and capsule dosage forms. Twelve healthy, nonobese male subjects were randomly assigned a number (1 through 12), and then each signed a written informed consent form. They were instructed not to take any drugs for a period of 30 days before the start of the study or alcoholic beverages 7 days prior to the study and during the study. Their diets were carefully controlled.

Two 0.25-mg standard reference tablets (Lanoxin®) or two 0.2-mg soft gelatin capsules were given on two occasions according to Table 9-4, where treatment phases A_1 and A_2 represent the tablets and treatments B_1 and B_2 represent the capsules. In each case the drug product was administered with 240 ml water on the morning after an overnight fast (about 10 hr). Food was allowed 4 hr after administration of the drug. Serial blood samples were collected for a period of 48 hr following administration of the drug. After centrifugation of the blood sample, the plasma was collected and frozen until assay by a radioimmunoassay procedure. A washout period of 2 weeks was allowed between consecutive treatment phases. The foregoing illustrates the utilization of a crossover design as part of a carefully planned bioavailability study.

Appropriate crossover designs are shown in Tables 9-5 and 9-6 according to the criteria presented in Tables 9-1 through 9-3. A two-way crossover

TABLE 9-4. *Four-way crossover study design*

Group no.	Subjects in group	Treatment order (phase no.)[a] I	II	III	IV
1	1,2,3	A_1	B_1	A_2	B_2
2	4,5,6	A_1	A_2	B_1	B_2
3	7,8,9	B_1	A_1	B_2	A_2
4	10,11,12	B_1	B_2	A_1	A_2

From Yacobi, A., et al. (1981): The assessment of the intrasubject variability in digoxin absorption in man from two oral dosage forms. *J. Clin. Pharmacol.*, 21:301–310.

[a] A_1 and A_2—0.5 mg tablets; B_1 and B_2—0.4 mg capsules.

TABLE 9-5. *Crossover design for a bioequivalency study of two products*

Group	First week	Second week
I (6 subjects)	Product A	Product B
II (6 subjects)	Product B	Product A

TABLE 9-6. *Crossover design for a bioequivalency study of two products and a standard solution*

Group	First week	Third week	Fifth week
I (6 subjects)	Product A	Product B	Solution C
II (6 subjects)	Product B	Solution C	Product A
III (6 subjects)	Solution C	Product A	Product B

design (Table 9-5) would be suitable for carrying out bioequivalence studies on warfarin or nitrofurantoin, whereas a three-way crossover study (Table 9-6) would be needed for studying the bioequivalence of digoxin products. These study designs allow each subject to act as his or her own control, thereby minimizing the effect of subject-to-subject variability. For example, in a two-way crossover study one-half of the volunteers take product A and the other half product B. Then after a suitable waiting period, each group reverses its position and takes the other drug product. To minimize subject selection bias and sampling lag times, the subjects are randomly selected for each group and the sequence of drug administration is randomly assigned.

A waiting period of 1 week between drug treatments is usually an adequate period of time to allow for elimination of the drug. This interval between drug administrations is known as a *washout* period and should be a minimum of at least 10 half-lives of the administered drug. Theophylline has a half-life of approximately 3 hr, and more than 99% of the drug is eliminated at the end of 30 hr. Most commonly used drugs have half-lives of 1 to 12 hr, and a washout period of 7 days is more than adequate for a bioequivalence study. If a drug has a relatively long half-life, then a longer interval is needed between drug administrations. Digoxin has a half-life of approximately 36 to 44 hr, and a 2-week washout period is recommended.

Acceptability of Bioavailability Data

The prevailing methods and criteria for bioavailability testing have been presented, and a general set of rules for judging the acceptability of bio-

TABLE 9-7. *Summary of guidelines for judging acceptability of bioavailability data*

I. Study design for comparative bioavailability studies
   a. Was the study a completely randomized crossover?
   b. Was an appropriate recognized standard used? (Usually the innovator's or original manufacturer's product.)
   c. Was the study clearly labeled single or multiple dose?
   d. Were a sufficient number of samples taken to fully define the peak and area values for the given dosage form? (No less than five points for single-dose blood, serum, or plasma studies, not including the zero-hour values.)
   e. Was sampling conducted long enough? (Usually until blood, serum, or plasma levels are 1/10 to 1/20 of the peak concentrations.)
   f. Were a sufficient number of subjects used? (Usually at least 10 to 12 subjects are desirable for studies involving two to four treatments.)
   g. Were factors such as age range, weight range, and the number of males and females used specified? [No abnormally large people (over 215 lb) or abnormally small (less than 105 lb) should be used in a study as they may give rise to unusual blood levels in a given study, making data analysis extremely difficult. Sex factors may be quite influential in studies involving many drugs, e.g., hormonal agents or steroids.]
   h. Were analytical considerations specified, e.g., the type of analysis procedure employed (microbiological, etc.)?
   i. Did the study measure a response in serum, plasma, whole blood, or urine?
   j. What was the dose administered and the strength and type of dosage form used?
   k. Were any *in vitro* assay potency and content uniformity values given for the brands that were compared?
   l. Were the expiration data cited for all drug studies?
   m. Were the drugs from production or research lots?

II. Presentation and analysis of comparative bioavailability data
   a. Are both tabulated and graphic data presented? (Graphic data can be misleading; tabulated data may be essential in making comparisons of treatments in a study.)
   b. Were average and/or individual drug concentrations at all sampling times presented?
   c. Was the average area under the serum concentration–time curve calculated for each treatment?
   d. Were average peak concentrations (for blood level studies) presented?
   e. Was statistical evaluation of the data presented to establish if differences found are statistically meaningful (ANOVA, Tukey's)?

From Summary of guidelines for judging acceptability of bioavailability data. *Que Newsletter*, Issue No.2, The UpJohn Co., 1974.

equivalence data can be established. A comprehensive summary of important questions to ask when bioavailability data and studies are reviewed is presented in Table 9-7.

Drug Product Selection

With every passing day the pharmacist is assuming more responsibility for the selection of drug products that he dispenses. The expanding responsibility in drug product selection is a result of several trends that have grown rapidly in the last 10 years. The vast majority of states have passed legislation to repeal or modify previously existing antisubsitution laws. In essence the repeal of antisubstitution laws allows the pharmacist, when he receives a prescription order for a brand name, to dispense an equivalent drug product. Some states have adopted the use of state formularies which allows the pharmacist to select an equivalent drug product from those listed in the formulary. Hospital formulary systems are in wide use, and the lists of equivalent drugs are usually the responsibility of Pharmacy and Therapeutic Committees, comprised of members of the health team. Third-party payment systems at all levels stipulate quality drug products at the lowest possible cost and are based on the principle of generic prescribing. The public is demanding lower cost of prescription drugs. Hence the physician is finding himself more and more in the position where he must write generically, with certain explicit exceptions (e.g., "do not substitute"), or his prescription order must, by law or institutional regulation, be interpreted by the pharmacist as a generic prescription. Authority for the pharmacist to engage in drug product selection is usually implied on prescriptions by telephone unless the physician expressly forbids it. The laws of many states provide for a two-line prescription system, under which the physician must sign either a line saying "product selection permitted" or one saying "dispense as written." With these current trends, the pharmacist is in a position to influence the selection of drug products he dispenses. Proper selection of multisource drug products is a major role and responsibility of the pharmacist and offers a tremendous opportunity for professional input into health care team decisions. Informed estimates indicate that more than two out of every three prescriptions have drug product selection potential. In accepting the responsibility of product selection, the pharmacist should be able to apply those principles discussed in the preceding chapters to the proper selection of drug products. All health practitioners should be aware that biopharmaceutical principles can provide a sound basis for rational drug product selection.

It was established in the preceding chapters that drug products from different manufacturers which contain the same amount of active ingredient

may perform differently in patients. Differences in formulation, some of them seemingly unimportant, can cause significant differences in the bioavailability of the drug. Most of the problems concerning the "generic equivalents" are usually associated with the more compact powder dosage forms, e.g., capsules and tablets. There are few, if any, specific regulations for the formulation of solid dosage forms. Manufacturing processes and materials used in the formulation of drug products can vary considerably from one drug manufacturer to another. Therefore it is not surprising that the various drug products of the same drug entity may exhibit different bioavailability characteristics.

The safety of the drug and the chemical equivalence (amount of drug in the dosage form) are ensured by official standards regulating drug manufacture. The FDA has initiated bioequivalence requirements for those drugs which have well-documented evidence that an actual or potential bioequivalence problem exists. The FDA has published a list of therapeutically equivalent products (1) in an attempt to document individual product acceptability. There is some contention that the list is not infallible, and the FDA certainly is not assuming any liabilities that may result from substitution of approved products. From a legal standpoint, however, as a result of recent court decisions, FDA approval is the only guarantee that two products are bioequivalent. The practitioner must make sure that each product dispensed is covered by an FDA-approved Abbreviated New Drug Application (ANDA) or New Drug Application (NDA). In addition, efforts should be made to make sure the drug product is not infringing on the patent rights of the innovator product. As ascertaining FDA approval and patent status can be difficult, it is important that the pharmacist know the manufacturer or distributor and substantiate the responsibility and reliability of the firm.

It was explained in Chapter 4 how blood level and urinary excretion data can be used to compare the bioavailability of a specific drug from various dosage forms and under various conditions. Blood level curves and urinary excretion profiles can be used to evaluate the bioavailability of a specific drug from different drug products. Probably the best data on which to base drug product equivalence are the results of well-designed bioequivalence studies, as discussed earlier in this chapter.

The type of data a practitioner should be looking for to prove bioequivalence of the drug products that will be selected for dispensing warrants further discussion. Figure 9-2 is an excellent example of the type of bioavailability data that experienced and responsible manufacturers can make available to health practitioners. Figure 9-3 is an example of bioavailability data that drug product manufacturers should readily provide to members of the health team. Note that the methodology used for the bioavailability testing is also provided, an important feature of this information. The data

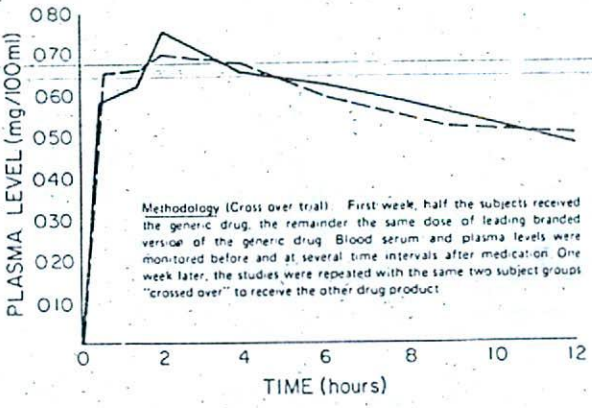


FIG. 9-3. Blood level curves for meprobamate drug products; 400 mg dose; average of 14 subjects. *Solid line*, SK-Bamate®; *dashed curve*, standard reference product. [From Promotional drug literature—bioavailability booklet. SK-Line Pharmaceuticals, Smith, Kline and French Laboratories, Philadelphia, 1972.]

in Fig. 9-3 indicate that the manufacturer's drug product is equivalent to the standard reference product against which it has been tested; the blood levels of the two products are essentially superimposable. An adequate number of subjects have been used in the study (normally 10 to 30 healthy adult subjects should be used in bioavailability studies). The standard reference product employed in these studies should be the most widely used brand-name counterpart, which is usually the innovator of the drug product. The same type of bioavailability data is shown in Fig. 9-4 for two brands of tetracycline HCl. This study shows that the drug product tested compares favorably with the leading proprietary counterpart.

When the drug concentration time curves for the drug products are superimposable, there is no problem deducing that the two products are bioequivalent. Exact superimposability is a rare occurrence, however, and much of the data received from various manufacturers of generic drugs usually show curves that are essentially superimposable or very similar. If blood level curves for two drug products of the same active ingredient are significantly different, there is then the question of how much difference is allowed before one of the drug products can be judged bioinequivalent to the standard product and unacceptable for substitution. The FDA currently proposes a 75/75 requirement for bioequivalency studies for certain drug products. The requirement essentially is that the relative bioavailability of the test product, when compared to the bioavailability of a reference product, must be greater than or equal to 75% for 75% of the subjects: In at least 75% of the subjects administered the drug, the test drug product has a bioavailability of greater than 75% relative to the AUC and/or peak height

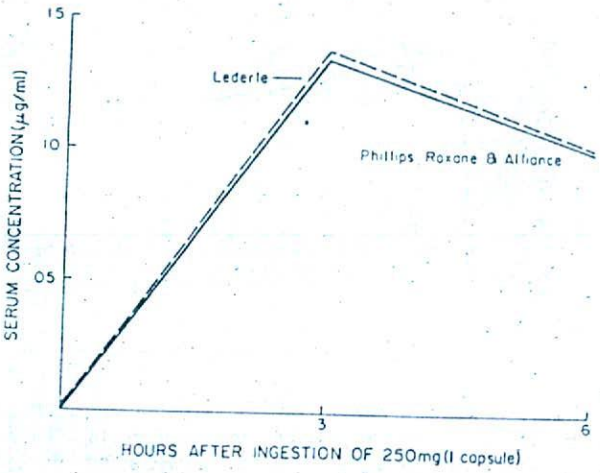


FIG. 9-4. Serum levels following oral ingestion of tetracycline hydrochloride capsules, 250 mg; average of 10 subjects. [From professional product information, Alliance Laboratories, Inc., 1972.]

of a reference standard. This 75/75 specification is subject to some controversy, and it will be interesting to see if adjustments are made in the future. A 25% difference in products should be looked at with some concern. For some drugs with a wide margin of safety, e.g., penicillin, a 25% difference might not significantly affect the clinical outcome after 1 to 2 weeks of therapy. On the other hand, for drugs with a narrower margin of therapeutic effectiveness and safety (e.g., digoxin, warfarin), a 25% decrease in bioavailability could cause significant adverse therapeutic effects. Judgments will have to be made on an individual basis about whether a 25% reduction in dosage will reduce the overall efficacy for the drug.

However, from a practical standpoint, will practitioners be forced to make such a decision? The answer is probably not for the vast majority of drugs. There is a lot of competition in the world of generic drug products, and so conscientious and reliable drug manufacturers design and manufacture products that closely duplicate standards rather than merely meet minimum requirements.

As a rule, the results of studies providing bioinequivalence of drug products are usually found in scientific journals, where the data have been published to inform members of the health care community of bioavailability problems associated with certain drugs. Figure 9-5 shows the blood levels of four digoxin products. It is readily seen that products C and B_2 gave significantly lower blood levels than product A (Lanoxin®). Although prod-

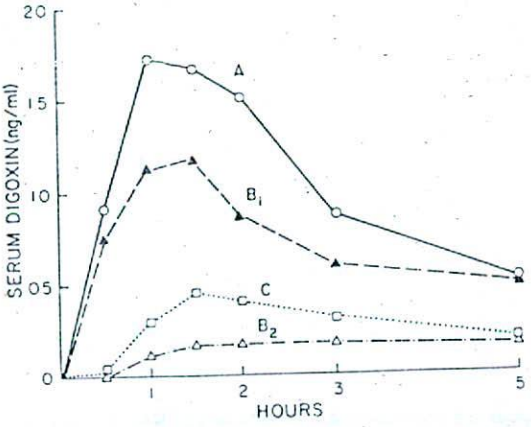


FIG. 9-5. Mean serum digoxin levels over a 5-hr period after oral administration of four digoxin products (0.5 mg digoxin as two 0.25-mg tablets) to four volunteers. Each line represents the mean of four curves. [From Lindenbaum, J., Fellow, M. H., Blackstone, M. O., and Butler, V. P. (1971): Variation in biologic availability of digoxin from four preparations. *N. Engl. J. Med.*, 285:1344.]

uct B_1 gave a lower level than A, the authors state that the difference was not statistically significant. The observed variability in absorption of digoxin preparations represents a potential hazard to the patient. Changes in the source of manufactured digoxin (or even from lot to lot of the same manufacturer, as with products B_1 and B_2) may occur without the knowledge of physician or patient, and result in toxicity or underdigitalization depending on the product substituted. Because of these bioavailability problems, the FDA instituted a mandatory batch-to-batch (lot-to-lot) certification for digoxin tablets which has recently been replaced by compendial *in vitro* dissolution requirements. Although the specifications for digoxin tablets are rigid, it is still prudent to start and maintain patients on a single brand of digoxin and if for some reason a brand change is made to carefully monitor the patient.

The plasma levels of phenylbutazone after administration of several drug products are shown in Fig. 9-6. The data indicate that brand A is readily absorbed as it has a blood level curve similar to that of the control solution of phenylbutazone. The blood level curve for brand E indicates that the drug is poorly absorbed and certainly is bioinequivalent to brand A. Figure 9-7 illustrates the bioavailability of two cimetidine products. Cimetidine 300-mg tablets (Tagamet®) and sustained-action 300-mg capsules were compared in a blind crossover study among 12 healthy subjects. Cimetidine was found to be significantly less available from the sustained-release capsule

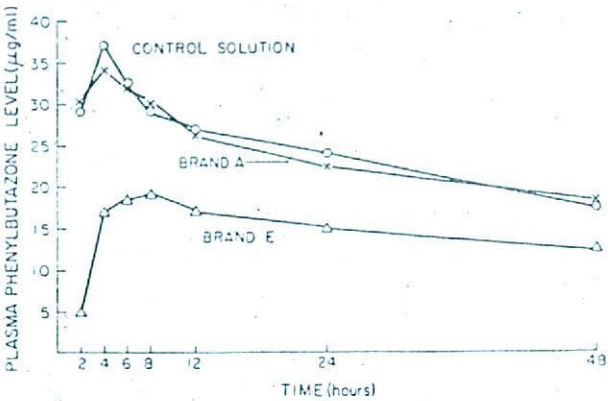


FIG. 9-6. Mean plasma level of phenylbutazone following administration of a 200-mg dose contained in the control solution (○), brand A tablets (X), and brand E tablets (Δ). [From Van Petten, G. R., Feng, H., Withey, R. J., and Lettau, H. F. (1971): The physiologic availability of solid dosage forms of phenylbutazone. I. In vivo physiologic availability and pharmacologic considerations. *J. Clin. Pharmacol.*, 11:177.]

than from the tablets, with the result that subtherapeutic blood levels of cimetidine were obtained with the capsule formulation at times when the tablet still produced therapeutic levels. In addition, the capsule product did not have the sustained-release property claimed by its manufacturer. Reports

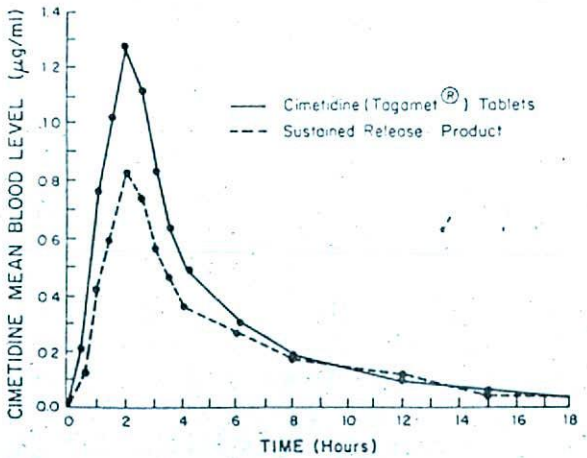


FIG. 9-7. Mean cimetidine blood levels at individual sampling times. [Adapted from Ortega, E., Querol, J., and Garza, H. H. (1980): Comparative bioavailability of cimetidine from two marketed formulations. *Curr. Ther. Res.*, 28:692–697.]

such as these continue to remind us that formulation factors can cause significant bioavailability problems.

The act of drug product selection carries with it a legal responsibility. Professional responsibility is achieved if the practitioner selects products on the basis of proper evaluation of bioequivalence data. However, care must be taken to ensure that the product has been approved by the FDA and that there is no patent infringement. Although most major manufacturers provide liability idemnification to pharmacists in suits arising from proper dispensing of their product, this should in no way deter the practitioner from carrying out a thorough evaluation of bioavailability data (Table 9-7) before selecting a drug product.

For many products, good bioavailability data may be made available by several, indeed many, pharmaceutical manufacturers. Therefore other manufacturing considerations should be taken into account when selecting a manufacturer of drug products. Some important criteria for manufacturing procedures are presented in Table 9-8. The obligations associated with manufacturing procedures are part of a set of guidelines published by the

TABLE 9-8. *Guidelines for selecting pharmaceutical manufacturers*

1. Upon request of the pharmacist, the supplier should furnish analytical control, sterility testing and bioavailability data, descriptions of testing procedures for raw materials and finished products, or any other information which may be indicative of the quality of a given finished drug product. This information should be supplied at no charge.
2. There should be no history of recurring product recalls indicative of deficient quality control procedures.
3. The company should permit visits (during normal business hours) by the pharmacist to inspect its manufacturing and control procedures.
4. All drug products shipped to the hospital should conform to the requirements of the most recent USP-NF criteria unless otherwise specified by the pharmacist. Items not recognized by the USP-NF should meet the specifications set forth by the pharmacist.
5. All single-unit packages of drugs should conform to the Guidelines for Single Unit Packages of Drugs of the American Society of Hospital Pharmacists (see footnote).
6. The name and address of the fabricator of the final dosage form should be present on the product labeling.
7. Expiration dates should be clearly indicated on the package label and, unless stability properties warrant otherwise, should be dated January or July.

From Guidelines for selecting pharmaceutical manufacturers and distributors. *J. Am. Soc. Hosp. Pharmacists*, 33:645–646, 1976.

American Society of Hospital Pharmacists intended as an aid to pharmacists to ensure that their patients receive drug products at the lowest cost consistent with high quality. The complete set of guidelines also includes other factors that should be considered, e.g., product costs and distribution, sales, and credit policies of the manufacturer. After weighing all the evidence and selecting a drug product, be sure to follow through on your professional responsibility and inform the patient of your product selection whenever you dispense a multiple-source prescription drug.

Sometime in the future, health care practitioners will have reliable national and/or state formulary systems to assist them in the selection of quality drug products. Until that time they must rely on their own judgment about the bioavailability of the drug products they dispense. Most judgments will be based on the combination of an evaluation of drug manufacturers' bioavailability data and information found in professional journals, e.g., *American Pharmacy*, *American Journal of Hospital Pharmacy*, *Clinical Pharmacology and Therapeutics*, *Current Therapeutic Research*, *Drug Intelligence and Clinical Pharmacy*, *Journal of the American Medical Association*, *Journal of Clinical Pharmacology*, and *Journal of Pharmaceutical Sciences*. Also, most pharmacists, through experience, observation, and consultation, have formed opinions about the general quality of drug manufacturers and the reliability of the products they provide. Many practitioners have developed their knowledge and expertise in drug product selection through self-instruction and participation in seminars. By applying some of the principles discussed in this book, the practitioner should be able to analyze the data and make a decision about a drug product. Whenever possible, decisions concerning drug product selection should include evaluation of bioavailability data.

Reference

1. *Approved Prescription Drug Products with Therapeutic Equivalence Evaluations*. U.S. Department of Health and Human Services, FDA, Bureau of Drugs, 1980.

10

Terminology Associated with Drug Interactions

A drug interaction occurs when the action of one drug is modified by another. One drug may alter the pharmacokinetics of another by changing the drug's absorption, distribution, metabolism, or urinary excretion behavior; or a drug may change the pharmacological response to another by various antagonistic effects or by additive and synergistic effects (Table 10.1). Drug interactions may occur in the GI tract, although the majority of interactions take place after the drug has been absorbed and is being distributed, metabolized, and excreted. To understand drug interactions and their significance, the practitioner should be familiar with the terminology. The terms used to described the effects of drug interactions are often ambiguous. The various terms used to describe the combined effects of drugs, presented in Table 10-1, describe the combined effects in terms of mechanism and locus of action. Although these terms may be the preferred and/or the correct way of describing drug interactions, they are not necessarily always used in the same context as presented in Table 10-1.

In the scientific and drug promotional literature synergism or synergistic effect is often used to describe any combined effect of the drugs that is greater than the possible additive or summation effect. Although potentiation is not a recommended term for drug interactions because it could erroneously convey a connotation of clinical superiority, it is widely used as a synonym for synergism to describe the effects of drug combinations.

Generally, drug interactions—alteration of the effects of one drug by another—result in either (a) a diminution of therapeutic efficacy or (b) an increase in drug activity and possible toxic drug reactions. Some of the mechanisms that may contribute to drug interactions are presented below.

Mechanisms that may contribute to diminution of therapeutic efficacy:

Chemical and physical antagonisms. Many drug interactions in the GI tract are due to chemical reactions (complex formation) and physical antagonisms (adsorption of drugs on kaolin). Protamine sulfate (a specific

TABLE 10-1. *Terms used to describe the combined effects of drugs*

- **Homergic**—two drugs produce the same overt effect
  - **Summation**—if the combined effects are equal to the sum of their individual effect
  - **Additive**—if combined effects are equal to those expected for drugs acting by the same mechanisms
  - **Synergism**—has various meanings and is best avoided for homergic drugs
- **Heterergic**—only one of a pair of drugs produces an effect
  - **Synergism**—combined effects of heterergic drugs that are greater than those of the active component alone
  - **Potentiation**—often a synonym for synergism; should be abandoned
  - **Antagonism**—combined effects of heterergic drugs that are less than that of the active component alone
    - **Chemical antagonism**—interaction of an agonist and an antagonist to form an inactive complex (e.g., EDTA and lead; BAL and As and Hg; protamine sulfate and heparin sodium)
    - **Competitive antagonism**—antagonist acts reversibly at the same receptor site as the agonist (e.g., atropine and acetylcholine)
    - **Nonequilibrium antagonism**—receptor antagonist acts irreversibly
    - **Noncompetitive antagonism**—agonist and antagonist act at different receptor sites
    - **Physiological or functional antagonism**—antagonism between drugs having overtly opposite effects (e.g., amphetamine and barbiturate)

Adapted from Goodman, L. S., and Gilman, A. (1970): *The Pharmacological Basis of Therapeutics*, p. 25. Macmillan, New York.

antidote) neutralizes the anticoagulant activity of heparin sodium by direct chemical reaction in the bloodstream.

Protein-binding effects during transport. Displacement of a drug from protein-binding sites in plasma can result in increased metabolism and excretion of the displaced drug.

Enzyme induction effects. The ability of numerous drugs to stimulate the production of drug-metabolizing enzymes in the liver can result in increased metabolism of the administered drug as well as other related or even unrelated drugs.

Antagonism at receptor sites. Drug interactions can occur when an agent occupies the receptors normally used by an active drug or when the agent acts on another site, either producing an opposite effect or blocking the effect of the drug.

Renal clearance effects. Changes in urinary pH can increase the excretion of weakly acidic and basic drugs.

Mechanisms that may contribute to increases in drug activity:

Additive and synergistic effects. The concurrent or sequential administration of two or more agents possessing similar pharmacological actions or

side effects may give rise to drug interactions by the additive or synergistic effect of these properties. An additive effect, for example, would be produced by the concurrent administration of the two barbiturates phenobarbital and secobarbital. The concurrent administration of central nervous system (CNS) depression (e.g., barbiturates and tranquilizers) or the administration of a sympathomimetic drug (e.g., amphetamine) with an adrenergic sensitizer [e.g., imipramine (Tofranil)] can produce additive or synergistic effects that may be dangerous. The effects of combining CNS depressants with alcohol have been called "additive," "synergistic," or "potentiated" by various authors. Because alcohol is so widely used in our society, adverse interactions resulting from concomitant ingestion of a drug and alcohol are considered true drug interactions.

Protein-binding during transport. Displacement of a drug from protein-binding sites in plasma can result in high, possible toxic, blood levels of displaced drug.

Enzyme inhibition effects. The ability of some drugs to inhibit production of drug-metabolizing enzymes can result in high blood levels and prolonged activity of the more slowly detoxified drug. Also, two drugs may compete for the same metabolizing enzyme systems.

Biochemical effects. The administration of one drug with the potential to alter the basic mechanism of action of another drug can result in a drug interaction. The interaction is not a simple additive effect but is the result of drug-induced changes in the patient. For example, thiazide diuretics (Esidrix®, HydroDiuril®), by producing potassium loss, can predispose patients to toxic reactions from cardiac glycosides, which affect ionic transfer in cardiac cells.

Renal clearance effects. Changes in urinary pH can decrease the renal clearance of weakly acidic and basic drugs.

Although the above mechanisms are more fully discussed elsewhere in this book, no attempt is made to present comprehensive lists or tables of all drug interactions. Excellent compilations of known drug interactions have been published and can be found in references named in the "Reading and Resource Material" section at the end of the book.

Diagnostic laboratory tests may be altered by a patient's drug therapy, leading to false positive or negative clinical test values. These drug-laboratory test interactions may result from either (a) direct interference of the drug in the serum or other body fluid with the analytical measurement or (b) the phamacological action of the drug causing an increase or decrease in the parameter being measured. An excellent comprehensive review and listing of drug effects on clinical laboratory tests is presented in Hansten's *Drug Interactions* (see "Reading and Resource Material").

11

Drug Interactions in the Gastrointestinal Tract

Adsorption of toxins on activated charcoal or kaolin could be called a useful drug interaction, and in fact these substances are used as antidotes and antidiarrheals because of their adsorptive properties. However, when these substances are administered concurrently with certain drugs, there is the possibility of drug interactions that may result in reduced bioavailabilty of the active ingredients. Figure 11-1 shows how a kaolin-pectin mixture (Kaopectate®) interferes with the absorption of lincomycin (Lincocin®). A large portion of the antibiotic is apparently adsorbed on the kaolin and passes through the GI tract. There is less interference when the Kaopectate® is given several hours before or after the administration of lincomycin. The bioavailability of promazine (Sparine®) is also reduced when taken with kaolin-pectin mixtures, and chlorpromazine (Thorazine®) bioavailability is decreased by concomitant antacid therapy. Table 11-1 shows that plasma chlorpromazine levels were lower in all subjects receiving concomitant antacid therapy than following the administration of chlorpromazine alone.

Complexation of tetracycline antibiotics may occur when these drugs are administered along with dairy products or aluminum, calcium, and magnesium antacid products. Figure 11-2 illustrates the greatly decreased bioavailability of demethylchlortetracycline (Declomycin®) when it is administered with aluminum hydroxide gel and with whole milk. Ferrous sulfate has been shown to impair the absorption of tetracycline, oxytetracycline (Terramycin®), methacycline (Rondomycin®), and doxycycline (Vibramycin®). Iron absorption is also decreased. It is established that the absorption of doxycycline or minocycline (Minocin®) is not markedly influenced by simultaneous administration of food or milk, although simultaneous administration of antacids and ferrous sulfate has been shown to decrease their absorption. If gastric irritation occurs when taking these tetracycline products, it is recommended that they be given with food or milk.

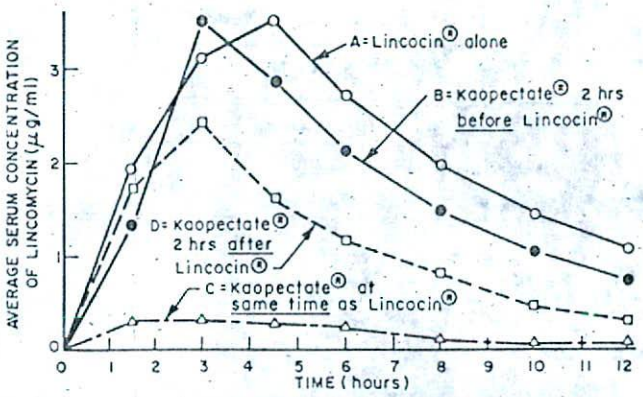


FIG. 11-1. Average serum concentrations of lincomycin following a 0.5-g dose of lincomycin in capsule form orally. [From Wagner, J. G. (1966): Design and data analysis of biopharmaceutical studies in man. *Can. J. Pharm. Sci.*, 1:55.]

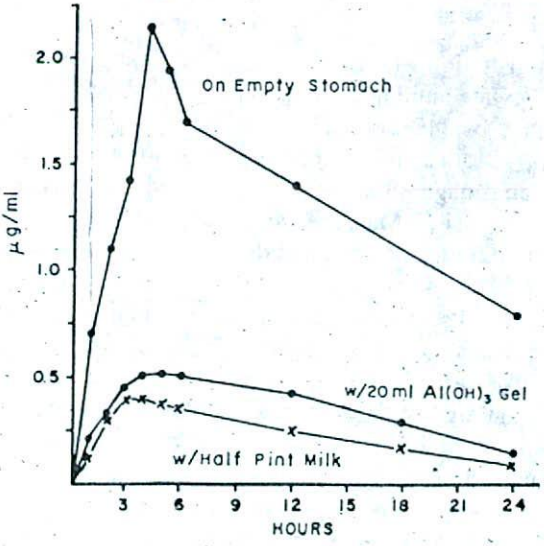


FIG. 11-2. Serum concentrations after a single oral dose of 300 mg of demethylchlortetracycline. [From Levy, G. (1963): Biopharmaceutical considerations in dosage form design and evaluation. In: *Prescription Pharmacy*, edited by J. B. Sprowls, p. 80. Lippincott, Philadelphia.]

TABLE 11-1. *Plasma chlorpromazine levels 2 hr after oral chlorpromazine alone and with gel antacid*

Subject no.[a]	Chlorpromazine levels (ng/ml)	
	Chlorpromazine alone	Chlorpromazine + antacid[b]
1	153	106
2	173	83
3	101	77
4	76	70
5	159	150
6	212	188
7	302	250
Average	168 ± 28	132 ± 25

From Fann, W. E., et al. (1973): Chlorpromazine: effects of antacids on its gastrointestinal absorption. *J. Clin. Pharmacol.*, 13:388–390.

[a]Subjects 1 and 6 are the same patient, with the test procedure repeated after several intervening days.

[b]Magnesium trisilicate-aluminum hydroxide-type gel (Gelusil®).

Oral coadministration of 250-mg tetracycline capsules and 60 ml of a bismuth subsalicylate antidiarrheal mixture (Pepto-Bismol®) reduced tetracycline absorption by 34% (Fig. 11-3). The mechanism of action was probably an adsorptive rather than a complex formation phenomenon.

Aluminum- and magnesium-containing antacid products, e.g., Amphogel®, Di-Gel®, Gelusil®, Maalox®, and Mylanta®, can interfere with the absorption of digoxin (Lanoxin®) and digitoxin. Kaolin antidiarrheal products (Kaopectate®) can also reduce absorption of digitalis glycosides. Figure 11-4 shows the results of a single-dose bioavailability study involving 10 normal human volunteers administered 0.75 mg digoxin (Lanoxin®) alone and with 60 ml of various antacid suspensions or a kaolin-pectin mixture. Reduced bioavialability of digoxin in patients who must maintain a regular heart beat could be dangerous, and it is recommended that there be an interval of at least 5 to 6 hr if both medications must be taken.

Drug interactions involving complexation can occur when cholestyramine (Cuemid®, Questran®) or cholestipol hydrochloride (Cholestid®), ion-exchange resins used to form complexes with bile acids in the GI tract, are administered with other medications. Because these compounds have the ability to form complexes with other drugs given orally and thereby prevent their absorption, it is recommended that they be given at least several hours after the administration of other drugs. Figure 11-5 illustrates how the plasma

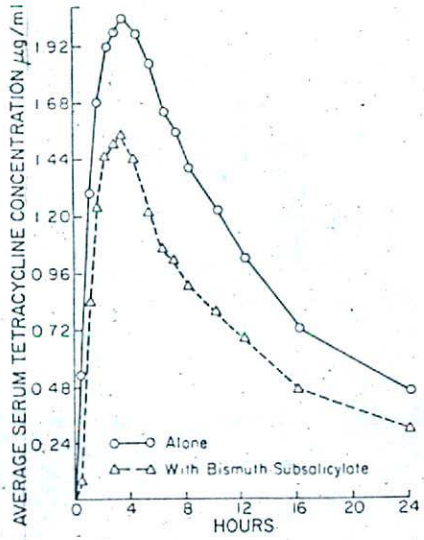


FIG. 11-3. Effects of bismuth subsalicylate antidiarrheal mixture on serum tetracycline levels following concomitant administration of both drugs. [From Albert, K. S. et al. (1979): Decreased tetracycline bioavailability caused by a bismuth subsalicylate antidiarrheal mixture. *J. Pharm. Sci.*, 68:586–588. Reproduced with permission of the copyright owner.]

levels of warfarin are decreased by the concurrent and remote administration of cholestyramine.

As a general rule, patients taking antacids, adsorbent-type antidiarrheal preparations, or resin-type complexing agents should take these medications 1 to 2 hr before taking any other oral drug product. The assumption is made that adsorbent and complexing agents will interact to some extent with most drugs, and the easiest way to prevent bioavailability problems is to avoid concomitant administration whenever possible.

Tetracyclines taken orally decrease the bacterial flora of the intestinal tract. Vitamin K synthesis by intestinal bacteria can be inhibited by this alteration of the GI flora, which may result in an increased anticoagulant effect in patients taking oral anticoagulants. Changes in the intestinal flora by antibiotic therapy may markedly alter the state of digitalization. This interesting phenomenon occurs in a minority of patients who have the ability to substantially convert digoxin to cardioinactive metabolites in the gut. The digoxin is inactivated by GI bacteria, and the coadministration of erythromycin or tetracycline appears to reduce this process. The urinary excretion of digoxin metabolites (digoxin reduction products; DRPs) is drastically reduced (Fig. 11-6), and the digoxin serum levels are much higher.

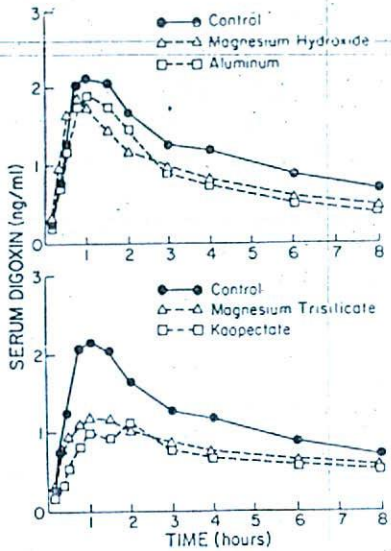


FIG. 11-4. Time course of serum digoxin concentration after administration of 0.75 mg digoxin by mouth to 10 healthy adult subjects. Each point represents ± SE for all subjects. [From Brown, D. D., and Juhl, R. P. (1976): Decreased bioavailability of digoxin due to antacids and kaolin-pectin. *N. Engl. J. Med.*, 295:1034–1036. Reproduced with permission of *The New England Journal of Medicine*.]

As discussed in Chapter 4, drugs are generally absorbed better and faster in the small intestine. Figures 11-7 and 11-8 illustrate how drugs that influence gastric emptying may delay or accelerate adsorption of another drug. Propantheline (Pro-Banthine®), an anticholinergic agent, slows gastric emptying, and the rate of paracetamol (acetaminophen) absorption is considerably delayed (Fig. 11-7). Delayed gastric emptying of drugs that are unstable in gastric fluids (e.g., penicillin G, erythromycin) could decrease the amount absorbed. Delayed absorption of a hypnotic drug may delay the onset and intensity of action. Gastric emptying into the intestine is accelerated by metoclopramide (Reglan®), and the rate of acetaminophen absorption is increased (Fig. 11-8). Irritant laxatives can shorten the GI transit time and possibly prevent adequate drug absorption, especially of slow-release products, e.g., Theo-Dur® (theophylline) or Slow-K® (potassium chloride).

Drugs and certain foods may affect enzyme transport systems and thereby alter intestinal absorption of specific drugs. The Zyloprim® (allopurinol) package insert states that allopurinol and iron preparations should not be administered simultaneously as allopurinol blocks the enzyme system which prevents iron absorption. Overabsorption and an iron overload in patients

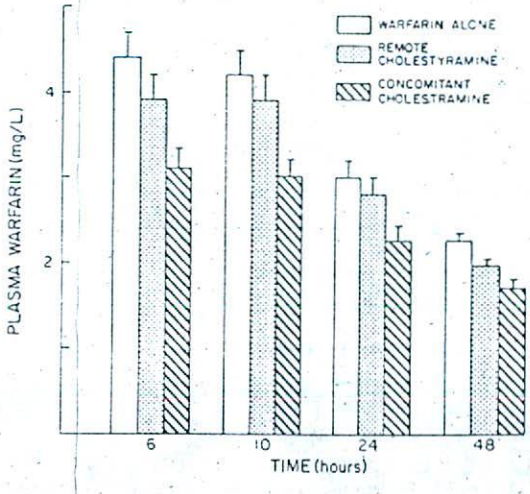


FIG. 11-5. Mean plasma warfarin concentrations of six subjects at 6, 10, 24, and 48 hr after administration of single dose of warfarin 40 mg are shown for three conditions: (a) warfarin alone (control); (b) cholestyramine 12 g in three divided doses in which the first dose precedes the warfarin dose by 3 hr, and the subsequent two doses follow the warfarin by 3 and 6 hr (remote); and (c) cholestyramine 12 g in three divided doses in which the first dose coincides with the warfarin and the subsequent two doses follow at 3-hr intervals (concomitant). Compared to control values the decreases in plasma warfarin concentrations due to cholestyramine ingestion were significant ($p < 0.05$) by Student's *t*-test for paired data for all comparisons except for 10 and 24 hr with remote administration of the resin. [From Robinson, D. S., Benjamin, D. M., and McCormack, J. J. (1971): Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin. Pharmacol. Ther.*, 12:491.]

may occur resulting in hemosiderosis (insoluble hematin deposits in tissue). It appears, however, that this recommendation is based on limited animal studies and theoretical assumptions. A review of the evidence (1) indicates that no added precautions are required when allopurinol and iron preparations are taken concurrently, although the precaution remains in the package insert.

Some drugs when administered concurrently with timed-release, sustained-action, or repeat action drug products may alter the release of the drug from these dosage forms. Tablet coatings sensitive to changes in pH (enteric coatings) may be prematurely disintegrated or dissolved if the drug product is taken concurrently with antacids, e.g., aluminum or magnesium hydroxides. Bisacodyl (Dulcolax®) has an enteric coating which is dissolved by antacids, releasing the very irritating laxative drug in the stomach and causing irritation and nausea. Wetting agents, e.g., dioctyl sodium sulfosuccinate (Colace®), may increase the drug-release rates of erosion and

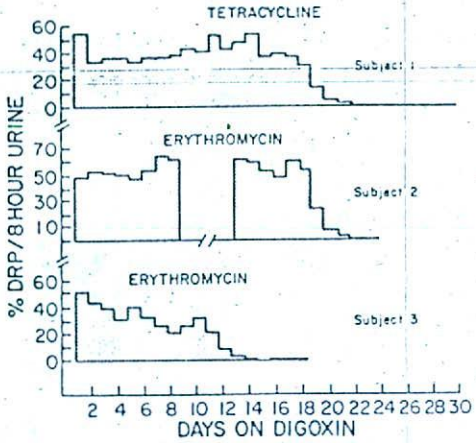


FIG. 11-6. Daily urinary excretion of digoxin reduction products (DRPs) between midnight and 8 a.m. Three subjects who were excretors were given two 0.25-mg digoxin tablets for 22 days (subject 3) or 29 days (subjects 1 and 2). (Because subject 2 temporarily left the study, collections of his urine were interrupted on days 9 to 12 of the preantibiotic period, although he continued to take digoxin.) DRP excretion fell markedly in each subject during a 5-day course of oral antibiotics. Urinary reduced metabolites remained at very low or undetectable levels during the week after antimicrobial treatment. [Adapted from Lindenbaum, J., et al. (1981): Inactivation of digoxin by the gut flora: reversal of antibiotic therapy. *N. Engl. J. Med.*, 305:789–794. Reproduced with permission of *The New England Journal of Medicine*.]

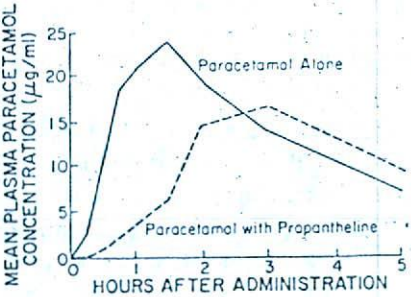


FIG. 11-7. Inhibitory effect of propantheline on paracetamol (acetaminophen) absorption in six patients. [From Nimmo, J., Heading, R. C., Tothill, P., and Prescott, L. F. (1973): Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol absorption. *Br. Med. J.*, 1:587–589.]

solution-type drug products (Gradumet®, Durabond®). Many timed-release or sustained-action drug products depend on erosion or moisture permeability of a lipid or cellulose coating (Spansule®, Measurin®). Because these coating materials are very soluble in organic solvents (e.g., alcohol), the simulta-

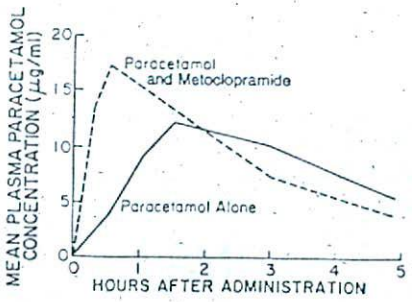


FIG. 11-8. Increased rate of paracetamol (acetaminophen) absorption after metoclopromide in five healthy volunteers. [From Nimmo, J., Heading, R. C., Tothill, P., and Prescott, L. F. (1973): Pharmacological modification of gastric emptying: effects of propantheline and metoclopramide on paracetamol absorption. *Br. Med. J.*, 1:587–589.]

neous intake of alcoholic beverages with these dosage forms can significantly increase the release rate of the total active ingredients. Amphetamines, barbiturates, and antihistamines are commonly used in sustained-action dosage forms at two or three times the single dosage level. The sudden release of these high amounts of drug in combination with alcohol could lead to serious central nervous system adverse reactions.

Reference

1. Ascione, F. L. (1975): Allopurinol and iron. *JAMA*, 232:1010.

12

Drug-Interactions During Transport

Transport of Drugs in the Bloodstream

Binding of endogenous chemicals to serum proteins is a normal physiological process which solubilizes and ties up hormones and metabolites and allows their slow and steady release at receptor and excretion sites. This process is also useful for transporting drugs that are relatively insoluble in body fluids at pH 7.4. These drugs are transported in the bloodstream to various sites of action, metabolism, and excretion as weak complexes bound to plasma proteins.

Although little work has been done to show exactly which proteins are responsible for drug transport, the most likely candidates seem to be the albumin fraction and the alpha- and beta-globulins. These protein substances contain many chemical groups capable of forming complexes with drugs.

Some drugs are more likely to be bound than others—some are more strongly bound than others. Strongly acidic drugs (e.g., salicylates, warfarin, phenylbutazone, and sulfonamides) are usually associated with strong-to-moderate protein binding (greater than 90% of drug is bound). Bound drug is pharmacologically inert as drug action depends on the adsorption of the free drug by an active receptor site.

There are various equilibrium processes taking place between the free and the bound drug. Figure 12-1 diagrams these equilibrium processes. The drug on the receptor is in equilibrium with the free drug in the bloodstream. Therefore the response to a drug is determined in part by the concentration of free drug in the plasma, which in turn is dependent on a number of factors, an important one being the amount of bound drug.

The free drug in the plasma is also in equilibrium with bound drug in the plasma and in the tissues. The binding of a drug may take place at several sites other than the bloodstream (connective tissue, adipose tissue, intracellular spaces, transcellular areas, etc.). These bound drugs act as a reservoir; and as the free drug is metabolized, accumulated in other tissues,

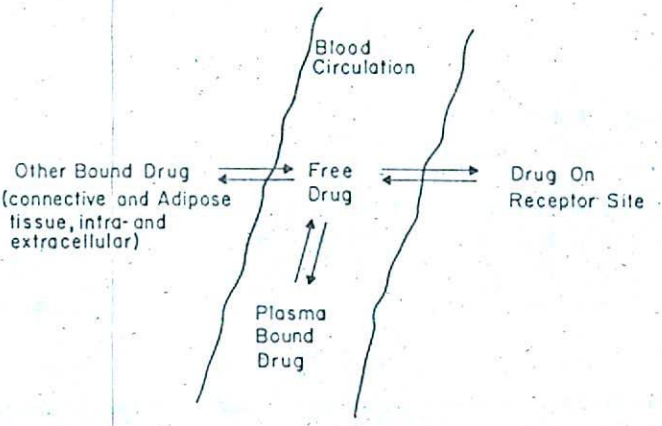


FIG. 12-1. Protein-binding processes.

or excreted, additional drug is obtained via release of the bound form. Hence there is a continuous dynamic equilibrium process in which a constant proportion of drug exists in the free state (unbound).

As a result of binding, effective plasma levels of many drugs are maintained for long periods of time, and their pharmacological effects are correspondingly maintained. The long-acting sulfonamides (e.g., Midicel®, Sulla®) have a long duration of action (long half-life) because of their strong protein-binding characteristics.

Drug–Drug Interactions During Transport

Many drugs are reversibly bound to plasma and tissue proteins. As only free drug exerts pharmacological action, displacement of a drug from protein-binding sites may produce increased pharmacological effects or possibly toxic effects, depending on the nature of the drug. A drug interaction may occur when two concurrently administered drugs compete for a common binding site, or when a drug already bound to plasma proteins is displaced by a second drug that has entered the bloodstream (competitive displacement). If a very highly bound drug (greater than 99% bound) is given with or after a moderately bound drug (greater than 90% bound), the moderately bound drug is displaced and its activity increased because of the increase in plasma drug concentration. For example, a moderately bound drug (e.g., warfarin) may be 97% bound to plasma proteins with 3% free in blood and tissue fluids, whereas a strongly bound drug may be 99.8% bound with only 0.2% in the free form. When the strongly bound drug competitively displaces only a relatively small proportion of the moderately bound drug,

so that the drug ratio becomes 94% bound and 6% free, there will actually be a 100% increase in the amount of free drug in the body tissues. Because a larger amount of drug is available in its active form, overdosage may result before the drug can be metabolized or excreted. For a drug that is poorly bound (only 50 to 60%), a similar 3% increase in the already 40 to 50% free drug level would be clinically insignificant.

Because the amount of bound drug determines to some extent the duration of action, the addition of some displacing agent can also have the effect of shortening the action of the drug. The release of free drug into the circulation facilitates the drug's metabolism and excretion. The drug has to be free to be metabolized either in the liver or other tissues. Usually only free drug is filtered through Bowman's capsule in the kidney; hence there would be more drug to be filtered into the kidney and excreted. The combined effects of increased metabolism and excretion could shorten the duration of action of a normally bound, long-acting drug. In general, this type of interaction is difficult to detect and is clinically insignificant.

Some typical interactions that occur in transport are presented in Table 12-1. Sulfonamides, salicylates, and phenylbutazone derivatives are very strongly bound drugs and displace many moderately bound drugs. Only those drugs that are highly bound have the potential for significant clinical effects due to displacement. These effects are usually encountered only when a competitive drug is given in large doses, competes for the same binding site as the moderately bound drug, and has a high affinity for the protein. Most clinically significant drug–protein interactions appear to involve strongly complexed acidic agents, e.g., salicylates, nonsteroidal anti-inflammatory agents, oral antidiabetic agents, anticoagulants, and long-acting sulfonamides. Serious bleeding episodes and hypoglycemic reactions have been associated with displacement of warfarin and oral antidiabetic agents by strongly bound drugs. Significant interactions may occur when a patient on a maintenance dose of warfarin or an oral hypoglycemic agent begins to take a new drug that displaces the first drug and raises its blood or tissue concentration to toxic levels. Warfarin–phenylbutazone interactions are well documented, and the initial increase in anticoagulant activity persists longer than usual for a drug displacement interaction because phenylbutazone also inhibits warfarin metabolism (Chapter 13). When highly protein bound drugs must be used together, the patient should be carefully monitored and dosage adjustments made if needed.

An interesting binding interaction is the one associated with concomitant administration of furosemide and chloral hydrate (1). One patient on chloral hydrate when given furosemide (Lasix®) was reported to exhibit diaphoresis, hot flashes, variable blood pressure including hypertension, and uneasiness.

TABLE 12-1. *Interactions during transport*

Strongly bound drug (A)	+	Moderately bound drug (B)	→	Possible effect due to increased concentration of B
Sulfonamides (long-acting) Phenylbutazone (Butazolidin®) Salicylates		Tolbutamide (Orinase®)		Hypoglycemia
Oxyphenylbutazone (Tandearil®) Phenylbutazone Sulfinpyrazone (Anturane®)		Warfarin (Panwarfin®, Coumadin®)		Hemorrhage
Sulfonamides Salicylates		Methotrexate		Cytopenia, blood dyscrasias
Quinacrine (Atabrine®)		Pamaquin		GI distress; anemias
Pyrimethamine (Daraprim®)		Quinine		Cinchonism, neutropenia
Phenylbutazone		Sulfaethidole (Sul-Span®)		Shortens duration of action
Ethacrynic acid (Edecrin®)		Oral antidiabetics		Hypoglycemia

Displacement of protein-bound trichloracetic acid (the metabolic breakdown product of chloral hydrate) by furosemide was suggested as the first step in a possible mechanism of action. The free trichloracetic acid then either competes with the thyroxine–protein complex, freeing the thyroxine, or lowers the pH of the serum so that the thyroxine-binding abilities of specific thyroxine-binding proteins are inhibited. A rapid rise in blood thyroxine level may account for the hypermetabolic state observed. A retrospective study of this type of reaction indicated that it was not a common occurrence; however, the combination of furosemide plus chloral hydrate should be administered with caution or avoided (2).

Sulfonamides, salicylates, and other acidic drugs should not be given to neonates, or at least should be used with extreme caution, because these strong protein binders are able to displace bilirubin from plasma albumin. The high concentration of free, unconjugated bilirubin (highly soluble in lipids) can pass the brain–plasma barrier, resulting in irreversible brain damage and possible death (kernicterus).

References

1. Malach, M., and Berman, N. (1975): Furosemide and chloral hydrate adverse drug interaction. *JAMA*, 232:638–639.
2. Pevonka, M. P., et al. (1977): Interaction of chloral hydrate and furosemide. *Drug Intell. Clin. Pharm.*, 11:332–335.

13

Drug Interactions Associated with Metabolism

Drug Metabolism

Many drugs are highly lipid-soluble and weak electrolytes. Such compounds are readily reabsorbed in the kidney tubules and are poorly excreted. They remain in the body until they are converted by metabolic processes into more water soluble compounds. The main function of metabolism (biotransformation) is to transform these drugs into more polar compounds that are readily excreted by the kidneys. Biotransformation usually results in inactivation of the drug, and the rate and extent of metabolism determine the length of time such drugs remain active in the body. In several instances the metabolites of the parent compound (e.g., propranolol, diazepam, some oral hypoglycemics) retain pharmacological activity.

The chemical reactions drugs may undergo in the body are presented in Table 13-1. These biotransformation processes are either nonsynthetic reactions (e.g., oxidation, reduction, hydrolysis) or synthetic reactions which involve conjugations between the drug and endogenous substrates (glycine, glucuronic acid, acetic acid, etc.).

Some representative metabolic reactions are presented in Figs 13-1 through 13-4. Note that all of the reactions produce metabolites having polar groups (hydroxyl or amine) or water-soluble conjugates (glucuronides). These metabolites are not reabsorbed by the kidney tubules and are readily excreted. Many drugs are metabolized by more than one chemical pathway, whereas others involve only a single process.

Drug metabolism involves a large number of enzyme systems. Biotransformation of drugs takes place mainly in the liver, although some occurs in plasma, kidney, and other tissues. The enzyme systems concerned in the biotransformation of drugs (oxidative, hydrolysis, and conjugating enzymes) are located mainly in the hepatic endoplasmic reticulum (the location of

TABLE 13-1. *Types of metabolic reactions*

Oxidation
Reduction
Replacement reactions
Hydrolysis
Acetylation
Methylation
Conjugation (condensation)
Sulfuric acid
Glucuronic acid
Glycine
Glutamine
Ornithine
Cysteine and acetylcysteine
Thiocyanate formation

From Wilson, C.O., Gisvold, O., and Doerge, R.F., editors (1966): *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 5th ed., p. 69. Lippincott, Philadelphia.

OXIDATION OF GROUPS SUBSTITUTED IN THE 5-POSITION

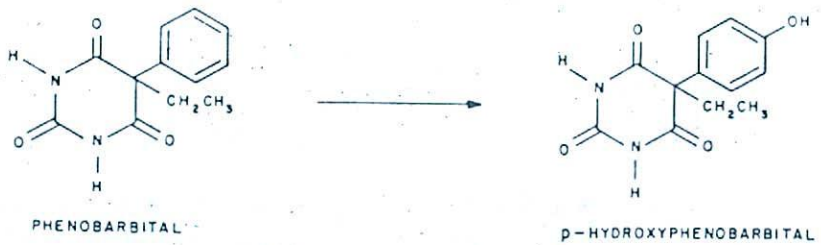


FIG. 13-1. Metabolic change of phenobarbital. [From Wilson, C. O., Gisvold, O., and Doerge, R. F., editors (1966): *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 5th ed., pp. 69, 76, 83, 103. Lippincott, Philadelphia.]

microsomes). It is the microsomal enzymes that catalyze the various drug biotransformations.

The activity of the drug-metabolizing enzymes in liver microsomes, as well as the structure and amount of endoplasmic reticulum and even the size of the liver, are influenced to a great extent by the administration of drugs and hormones, and by age, sex, temperature, nutritional status, and psychological and pathological state of the subject. It may well be that variations of drug metabolism in the liver is a substantial cause for variation of drug effect in different patients: why a good clinical response is obtained in one patient and a poor response in another; why pediatric and geriatric dosing is difficult.

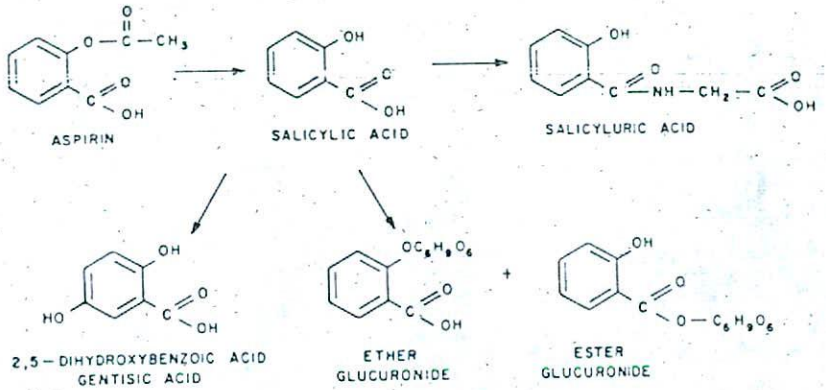


FIG. 13-2. Metabolic changes of aspirin. [From Wilson, C. O., Gisvold, O., and Doerge, R. F., editors (1966): *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 5th ed., pp. 69, 76, 83, 103. Lippincott, Philadelphia.]

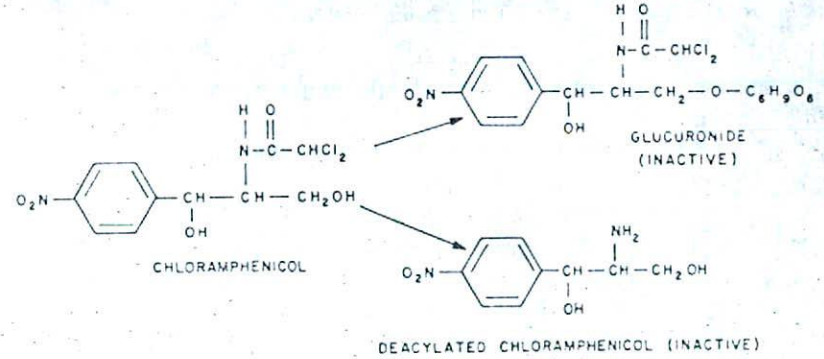


FIG. 13-3. Metabolic changes of chloramphenicol. [From Wilson, C. O., Gisvold, O., and Doerge, R. F., editors (1966): *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 5th ed., pp. 69, 76, 83, 103. Lippincott, Philadelphia.]

Drug Interactions by Accelerated Metabolism

Prior treatment of experimental animals with various drugs has been shown to increase the rate of metabolism and to shorten the duration of action for subsequent drugs administered. This same type of phenomenon occurs in human subjects. Chronic administration of one drug can reduce the pharmacological activity of itself or another drug by stimulating their metabolic breakdown. This effect, produced by increasing the amount of drug-metabolizing enzymes in the liver microsomes, is called enzyme induction. The mechanism of enzyme induction is an increase in the number of molecules of a specific enzyme as a result of either an increase in enzyme

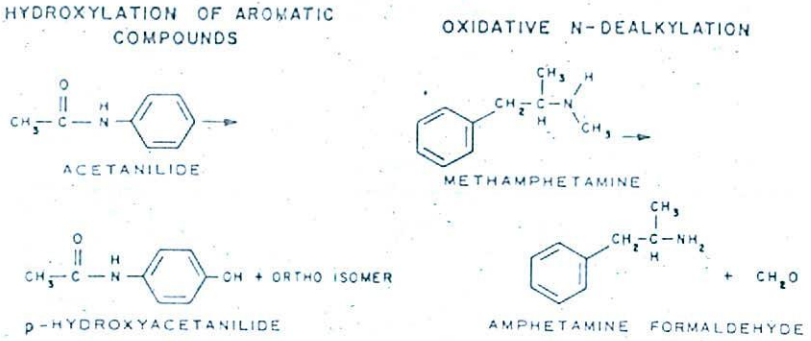


FIG. 13-4. Metabolic changes of acetanilide and methamphetamine. [From Wilson, C. O., Gisvold, O., and Doerge, R. F., editors (1966): *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 5th ed., pp. 69, 76, 83, 103. Lippincott, Philadelphia.]

synthesis or a decrease in the rate of enzyme degradation. Some drugs stimulate their own metabolism (e.g., antihistamines, barbiturates, phenytoin, glutethimide, meprobamate, phenylbutazone, probenecid, tolbutamide); some accelerate the biotransformation of other drugs (Table 13-2); and others do both. Some of the classes of drugs which have been found to enhance metabolism are the sedatives, tranquilizers, analgesics, and antihistamines. These drugs are used frequently in clinical practice and often administered concomitantly with other drugs. Induction of the hepatic enzyme systems can lead to increased drug clearance, reduced plasma levels of active drug, and possible therapeutic failure. The main consequence of most clinically significant enzyme induction interactions is a decrease in therapeutic effectiveness which is usually not immediately evident. These results might not be as dramatic as toxic drug reactions, but they are certainly as important and should be given the same concern. Phenobarbital, one of the mose widely prescribed drugs, is probably the most notorious of the enzyme-inducing drugs. Table 13-3 shows the results of experiments to study the effect of phenobarbital on digitoxin metabolism. In each subject (taking 0.1 mg digitoxin per day) who received phenobarbital (60 mg t.i.d. for 12 weeks), the steady-state concentration of digitoxin in plasma fell approximately 50% when the drugs were administered concurrently, and returned to control values (control 2) when phenobarbital was discontinued. Figure 13-5 shows how the disappearance of dexamethasone from the plasma was considerably faster in asthmatic patients who had taken 120 mg phenobarbital (30 mg q.i.d.) for 3 weeks than in the same subjects before phenobarbital therapy.

As a result of increased metabolism, larger than usual amounts of drug would have to be administered to obtain the desired pharmacological effect.

TABLE 13-2. *Drugs that stimulate metabolism of other drugs*

This drug	Enhances the metabolism of	This drug
Alcohol		Phenytoin Tolbutamide (Orinase®) Warfarin
Aminopyrine		Androstenedione Estradiol Hydrocortisone Pentobarbital (Nembutal®)
Antihistamines (many)		Phenobarbital Progesterone Testosterone
Phenytoin (Dilantin®)		Corticosteroids
Phenobarbital and other barbiturates		Aminopyrine Bishydroxycoumarin (Dicumarol®) Corticosteroids Digitoxin Phenytoin (Dilantin®) Griseofulvin (Fulvicin®, Grifulvin®) Hexobarbital (Sombulex®) Phenylbutazone (Butazolidin®) Progesterone Testosterone Warfarin (Coumadin®, Panwarfin®)
Phenytoin Glutethimide (Doriden®) Griseofulvin Meprobamate (Equanil®, Miltown®)		Bishydroxycoumarin Warfarin

The doses of drugs that induce their own metabolism might have to be increased as the patient develops a tolerance. If a patient is on a chronic drug therapy and then begins to take an enzyme-inducing second drug, the first drug might be metabolized more rapidly and result in a significant decrease in the established therapeutic response. The dose of the first drug would have to be increased. For example, there are several possible implications of the interaction between phenobarbital and bishydroxycoumarin (Dicumarol®). The anticoagulant effectiveness is reduced by concurrent administration, thereby increasing the risk of thrombus formation. This can be offset by increasing the dose of anticoagulant. In a clinical situation where the prothrombin time is determined daily, the anticoagulant dosage can be adjusted upward as needed. However, if the patient is discharged

TABLE 13-3. *Influence of phenobarbital on the plasma concentration of digitoxin*

Treatment	No. of observations	Plasma digitoxin (mμg/ml)
Subject 1		
Control 1	7	12.5 ± 1.2
Phenobarbital	10	6.5 ± 0.4
Control 2	9	10.9 ± 0.3
Subject 2		
Control 1	8	11.7 ± 0.6
Phenobarbital	7	5.8 ± 0.4
Control 2	9	11.4 ± 0.6

From Solomon, H. M., and Abrams, W. B. (1972): Interactions between digitoxin and other drugs in man. *Am. Heart J.*, 83:277.

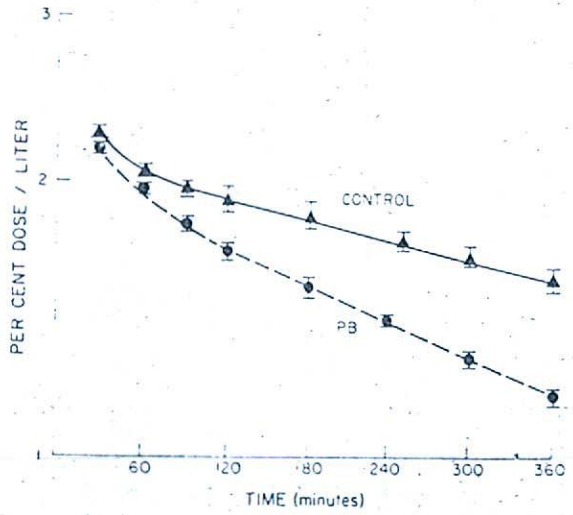


FIG. 13-5. Disappearance curves for dexamethasone for 11 subjects before and after phenobarbital (PB). [From Brooks, S. M., et al. (1972): Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *N. Engl. J. Med.*, 286:1127.]

and the sedative stopped, the enzyme-stimulating effect will cease and the anticoagulant will no longer be metabolized as rapidly. The result may be an increase in the prothrombin time and possible hemorrhaging.

Alcohol ingestion has been implicated in causing changes in the metabolism of numerous drugs. Chronic administration of alcohol can cause en-

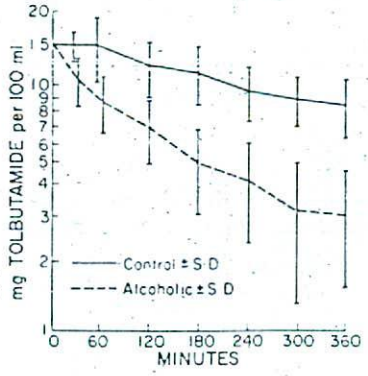


FIG. 13-6. Plasma disappearance curves of tolbutamide, derived from the mean plasma concentration at each time interval, with standard deviations, in control and alcoholic groups. [From Kater, R. M. H., Tobon, F., and Iber, F. L. (1969): Increased rate of tolbutamide metabolism in alcholic patients. *JAMA*, 207:363–365. Copyright 1969, American Medical Association.]

zyme induction and reduce the pharmacological action of a drug. Figure 13-6 illustrates the drug plasma time curves of tolbutamide (Orinase®) in 20 alcoholics and 10 nonalcoholic controls. The effectiveness of treatment would be decreased in diabetic patients who continue their drinking habits.

Tobacco smoking is one of the most recently identified factors that cause decreased effects of many drugs by enzyme induction. The enzyme-inducing components of tobacco smoke increase the metabolic breakdown of propranolol, caffeine, and theophylline. The plasma theophylline concentration–time relationship in smokers and nonsmokers is shown in Fig. 13-7.

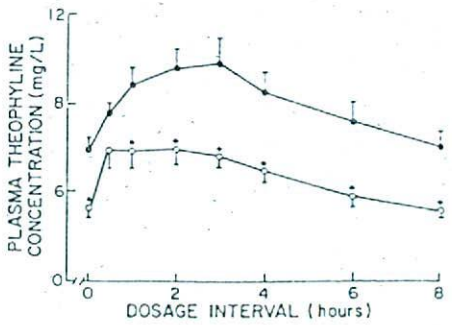


FIG. 13-7. Plasma theophylline concentration–time relationship under steady-state oral dosing conditions in smokers (○) and nonsmokers (●). Asterisks indicate differences in plasma theophylline concentration between the groups ($p < 0.005$). [From Grygiel, J. J., and Birkett, D. J. (1981): Cigarette smoking and theophylline clearance and metabolism. *Clin. Pharmacol. Ther.*, 30:491–496.]

The plasma theophylline concentration in smokers was significantly lower than that in nonsmokers.

Pyridoxine (vitamin B_6) enhances (by direct biochemical intervention rather than enzyme induction) the rapid and complete metabolic breakdown of levodopa (Laradopa®) in the peripheral areas of the body. As a result, none of the drug crosses the blood barrier into the brain where it has its antiparkinsonian effect. This interaction was discovered when the antiparkinsonian effect was lost in patients on levodopa therapy who started taking multivitamin supplements containing vitamin B_6. A multivitamin product without B_6 (Larobec®) is now marketed specifically for patients on levodopa therapy.

Drug Interactions by Inhibited Metabolism

A number of drug reactions are based on the inhibition of metabolism of certain drugs by other drugs. The result of such interactions is an increase in the duration and intensity of pharmacological activity. The suppression of metabolic breakdown is probably caused by irreversible inhibition (by mechanisms unclear) of an enzyme responsible for the biotransformation of a drug or by one drug competing with another for the same enzyme.

Some of the drugs that have been reported to inhibit metabolism of other drugs are presented in Table 13-4. The potentiation of the effects of anticoagulants and the toxic effects of 6-mercaptopurine (Purinethol®) and azothioprine (Imuran®) could lead to serious consequences. Allopurinol, a xanthine oxidase inhibitor used in the treatment of gout, significantly increases the activity of 6-mercaptopurine and azothioprine. These purine analogs are inactivated by xanthine oxidase, and the allopurinol blocks this metabolic process. Patients taking these purine drugs should have their dosage regimen reduced to about one-third the usual dose while allopurinol is being taken.

Evidence indicates that cimetidine (Tagamet®) can inhibit microsomal enzymes in the liver, and it has been shown to decrease the clearance of diazepam (Valium®) (Table 13-5). Cimetidine and diazepam are two of the most widely prescribed drugs and are frequently used together. The half-life of diazepam is considerably increased, and the resulting prolonged sedative action is of clinical relevance as the margin of safety of diazepam is decreased. Other benzodiazepine drugs, e.g., chlordiazepoxide (Librium®), might also be affected in the same way. Patients should be closely monitored if benzodiazapines and cimetidine are coadministered.

Phenylbutazone (Butazolidin®) and oxyphenylbutazone (Tandearil®) prolong tolbutamide (Orinase®) and warfarin activity by inhibiting their metabolism. Displacement of tolbutamide or warfarin by either of the anti-

TABLE 13-4. *Drugs that inhibit metabolism of other drugs*

This drug	Inhibits the metabolism of	This drug
Allopurinol (Zyloprim®)		6-Mercaptopurine (Purinethol®), azothioprine (Imuran®)
Cimetidine (Tagamet®)		Benzodiazapines (Valium®, Librium®)
Chloramphenicol		Hexobarbital, phenytoin
Desipramine (Pertofrane®)		Amphetamine
Isoniazid		Phenytoin
Methandrosteneolone (Dianabol®)		Oxphenylbutazone
Monoamine oxidase inhibitors		Tyramine in foods
Para-aminosalicylic acid		Hexobarbital
Oxyphenylbutazone (Tandearil®)		Bishydroxycoumarin
Phenylbutazone (Butazolidin®)		Tolbutamide, warfarin
Methylphenidate (Ritalin®)		Many drugs including coumarin anticoagulants, anticonvulsants, and tricyclic antidepressants

TABLE 13-5. *Pharmacokinetic variables of diazepam in six healthy volunteers after a single dose[a] before and after treatment with cimetidine*

Variable	Mean ± SD		*p*
	Before cimetidine	After cimetidine	
Half-life of distribution (hr)	1.1 ± 0.6	1.3 ± 0.7	NS
Half-life of elimination (hr)	33.5 ± 10.2	51.3 ± 13.3	0.012
Total plasma clearance (ml/min)	19.9 ± 8.2	11.4 ± 4.2	0.034
Volume of distribution during elimination phase (liter/kg)	0.82 ± 0.32	0.74 ± 0.16	NS
Volume of distribution at steady state (liter/kg)	0.71 ± 0.35	0.51 ± 0.10	0.091
Volume of the central compartment (liter/kg)	0.22 ± 0.17	0.07 ± 0.04	0.044
Plasma protein binding (%)	97.8 ± 1.0	98.2 ± 0.3	NS

From Klotz, U., and Reimann, I. (1980): Delayed clearance of diazepam due to cimetidine. *N. Engl. J. Med.*, 302:1012–1014. Reproduced by permission of *The New England Journal of Medicine.*

NS = not significant (paired Student's *t*-test was used for statistical analysis).

[a]Diazepam was given in a single dose of 0.1 mg/kg i.v.

inflammatory agents also contributes to increased pharmacological activity of these drugs (Chapter 12).

Theophylline toxicity in children has occurred soon after initiating erythromycin therapy in these patients. It is postulated that theophylline blood levels are considerably increased as a result of enzyme inhibition by the antibiotic.

The possible interactions between bishydroxycoumarin (Dicumarol®) and tolbutamide (Orinase®) are shown in Fig. 13-8. The anticoagulant inhibits the metabolism of the antidiabetic agent and increases the hypoglycemic effect. Simultaneously, tolbutamide displaces the anticoagulant from protein-binding sites and potentiates its anticoagulant effect. This example illustrates how the concurrent administration of two drugs may result in two types of drug interaction at the same time.

Generally, enzyme inhibition interactions can be minimized by reducing the dosage of the inhibited drug, especially for those drugs where relatively small changes in blood levels are critical (e.g., warfarin, phenytoin, 6-mercaptopurine, theophylline).

The combination of levodopa and carbidopa (Sinemet®) is a good example of a useful drug interaction in which a drug, carbidopa, is used to inhibit the peripheral metabolic breakdown of the active drug, levodopa. Levodopa (Laradopa®) is effective in the treatment of parkinsonism; however, toxicity often limits the dose that can be administered. Nausea, vomiting, confusion, and abnormal movements are some of the more common side effects. The antiparkinsonian effect of levodopa is dependent on its ability to penetrate the blood–brain barrier, and very large doses must be used to achieve therapeutic levels in the brain. Unfortunately, up to 95 to 99% of the levodopa is metabolized in the liver, intestine, and other parts of the body before it has a chance to cross the blood–brain barrier. The metabolic breakdown products also cause certain adverse reactions. Carbidopa inhibits this metabolic process and allows lower doses of levodopa to be used to achieve better therapeutic levels and fewer side effects.

Monoamine oxidase inhibitors (Marplan®, Parnate®, Niamid®, Nardil®) were widely used as antidepressants several years ago; however, they have been essentially replaced by the safer tricyclic antidepressant drugs (Elavil®, Pertofrane®, Tofranil®, Vivactil®, Sinequan®). There have been many reports of palpitations, severe headaches, and hypertensive crises in patients being treated with monoamine oxidase inhibitors (MAOIs) following the ingestion of foods having a high tyramine content (e.g., aged cheeses, some beers and wines, bananas, broad beans, and pickled herring). Foods which are subjected to extensive bacterial fermentation or spoilage and are rich in precursor amino acids, or already contain significant amounts of tyramine,

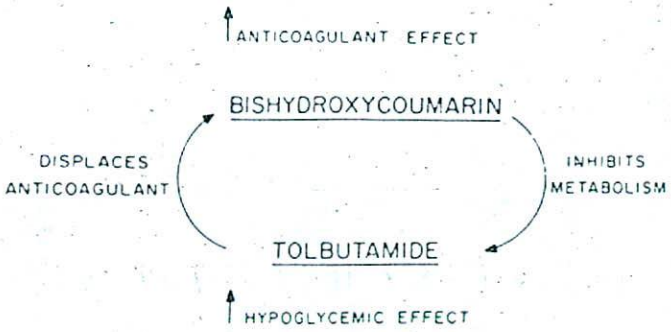


FIG. 13-8. Interactions between bishydroxycoumarin and tolbutamide which may occur in man. [From Solomon, H. M. (1968): Displacment of drugs from plasma binding sites as a factor in drug toxicity. In: *Safer and More Effective Drugs*, edited by S. W. Goldstein, p. 57. American Pharmaceutical Association-Academy of Pharmaceutical Sciences, Washington, D.C.]

are the main source of tyramine. MAOI drugs inhibit the enzymatic activity of monoamine oxidase (MAO); MAO is widely distributed throughout the body and is responsible for (a) the detoxification of monoamines (e.g., tyramine) that are absorbed from the GI tract and (b) the metabolism of endogenous amines, e.g., norepinephrine and epinephrine. Tyramine in food is normally "chewed up" by the MAO in the intestinal wall and liver. However, when a patient is on MAOIs, tyramine readily passes into the circulation and accumulates in the body. The tyramine then triggers the release of large quantities of norepinephrine that have built up in special nerve endings (adrenergic neurons) as a result of MAO inhibition. The result is an unusual rise in blood pressure and possible hypertensive crisis. Intravenous phentolamine (Regitine®), a short-acting alpha-adrenergic blocker, is recommended for treatment of these severe hypertensive reactions. Other drugs that have some MAOI activity but are not used as antidepressants are Eutonyl®, Furoxone®, and Matulane®. The interaction with tyramine does not occur with tricyclic antidepressants as they have a different mechanism of action and do not have MAOI activity. Other types of drug interaction associated with MAOI drugs are discussed in Chapter 14.

14

Drug Interactions at the Receptor Site

The pharmacological action of a compound is ultimately due to the drug's adsorption onto a specific area, or reactive site, in a cell or organism which is called a receptor site. This combination is responsible for the observed drug effects. Although the actual biochemical and biophysical mechanisms are not well known, it seems likely that most receptors are proteins, probably enzyme systems, which react with the drug to form a complex and produce a response.

Some drugs combine with receptors to form complexes that elicit a response; these are called agonists. The degree of response depends on the concentration of the drug and its affinity for the receptor sites. Other drugs combine with receptors (are adsorbed on the receptor sites) and elicit no response; these are called antagonists. Drug interactions can occur when a drug that does not give a response occupies the receptor sites normally used by an active drug. If two such compounds are administered simultaneously, they antagonize each other because they compete for the same receptor site, but only one compound can produce the response (competitive antagonism). If the concentration of the antagonist drug or its affinity to react with the receptor site is higher than that of the agonist drug, no pharmacological response takes place. Drug interactions can also occur when agonist and antagonist drugs act on different receptor sites (noncompetitive antagonism).

Several agonist–antagonist drug interactions are presented in Table 14-1. In these examples the antagonist drug usually crowds out the agonist, and the normal function of the agonist drug is prevented. A patient using a cholinergic ophthalmic solution (e.g., pilocarpine) for glaucoma may experience difficulty in the control of intraocular pressure if an anticholinergic drug (e.g., Probanthine®) is prescribed for a GI disorder.

If an antagonist drug reacts irreversibly at the receptor site, the antagonism is termed nonequilibrium. A dangerous nonequilibrium antagonism may occur in persons taking cholinergic drugs [i.e., those that destroy cholinesterase such as isofluorophate (Floropryl®) or demecarium bromide (Hu-

TABLE 14-1. *Interactions at the receptor site*

Antagonist drug	Agonist drug
Atropine	Acetylcholine
Gallamine (Flaxedil®)	Succinylcholine (Anectine®)
Amphetamine and methylphenidate	Guanethidine (Ismelin®)
Imipramine (Tofranil®) and other tricyclic antidepressants	Guanethidine (Ismelin®)
Propranolol (Inderal®)	Isoproterenol (Isuprel®, Norisodrine®)
Anticholinergics (atropine, Banthine®, Probanthine®, etc.)	Pilocarpine

morsol®)] and who are exposed to organophosphorus-type insecticides (Parathion®, Malthion®). The insecticides also act by destroying cholinesterase, and the combined action of the agents could lead to serious consequences.

Many additive and synergistic effects are due to the combined actions of two or more drugs at the same receptor area. Dangerous central nervous system depression effects can occur when any of the barbiturates, tranquilizers, antihistamines, narcotic analgesics, and alcohol are coadministered. The phenothiazine tranquilizers, meperidine (Demerol®), tricyclic antidepressants, antihistamines, and trihexyphenidyl (Cogentin®) are drugs that have different primary pharmacological effects, but each of these drug types has an anticholinergic (atropine-like) side effect that is additive when two or more of the drugs are used concurrently. The excessive anticholinergic effect is usually minor (dry mouth and nose, constipation), although in older patients dangerous adverse effects, e.g., acute glaucoma or urinary retention, can occur.

Interactions at the Adrenergic Nerve Ending (Adrenergic Neuron)

During the last several years many important drugs have been introduced for the treatment of hypertension, mental depression, and other mental disorders. The actions of these drugs are often complex and usually cannot be explained by some simple, single pharmacological process; they are polymechanistic drugs. However, many of the actions and drug interactions associated with these drugs can be explained on the basis of "what happens at the adrenergic nerve endings," especially those interactions that may result in exaggerated changes in blood pressure.

A simplified diagram of the adrenergic nerve ending is shown in Fig. 14-1. Norepinephrine (NE) is synthesized in the adrenergic neurons and stored in special granules or depots. While it is in these storage granules, the NE

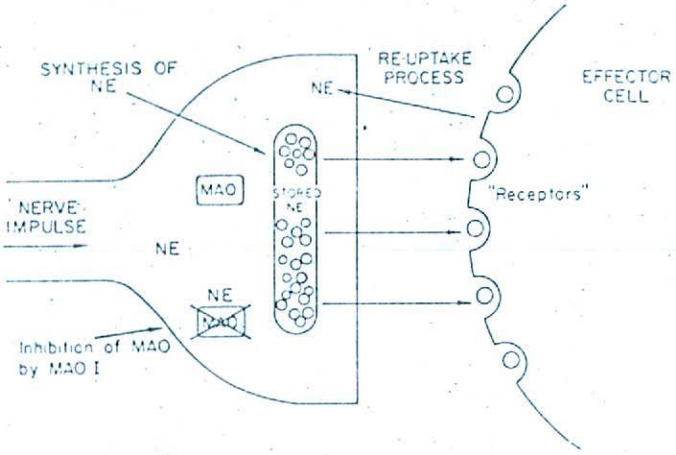


FIG. 14-1. Adrenergic neuron and receptor. [Adapted from Schoepke, H. G. (1971): Introduction to drug interactions (part II). *Louisiana Pharmacist*, Dec.: 10.]

cannot be enzymatically attacked by MAO. A nerve impulse triggers the release of NE from the granules which then rapidly travels to the synapse. The released NE exerts its action on the effector cells (receptors). If the effector cells are in the arteries, the response consists in vasoconstriction and an increase in blood pressure. The NE at the synapse is taken back up into the nerve endings by a reuptake process. This active transport process is very economical and results in the recycling of NE with little loss of the transmitter into the systemic circulation. This process is the main mechanism by which NE concentration is reduced at the synapse and receptor areas. The NE taken up into the nerve ending is dispersed throughout the cytoplasm of the nerve terminal, where some of it is deactivated by the MAO, some is taken into the storage granule, and some remains in the cytoplasm.

Those drug–drug interactions that are associated with MAOI drugs and their possible mechanism of interaction are presented in Table 14-2. MAOI drugs are no longer as widely used as they were several years ago and are considered second-line antidepressant drugs—after the tricyclic antidepressants. However, the number and variety of drug interactions associated with MAOI drugs dramatically point out the complex problems that arise in modern drug therapy. To prevent possible adverse reactions in patients who must be given levodopa, MAOI therapy should be stopped 2 weeks before initiating the new drug.

Tricyclic antidepressants have essentially replaced the MAOI drugs in the treatment of mental depression. Several drugs that may interact with these

TABLE 14-2. *Drugs that may interact with MAOIs to give an exaggerated rise in blood pressure and possible hypertensive crises*

Drug	Probable mechanism of action
Amphetamines, ephedrine, methylphenidate (Ritalin®), tyramine	Trigger the release of unusually large amounts of NE stored in the adrenergic neuron as a result of MAO inhibition (Chapter 13).
Sympathomimetic drugs (e.g., phenylephrine, phenylpropanolamine, isoproterenol)	Probably have higher than normal fluid and tissue concentrations because of decreased MAO activity. These drugs, like NE, activate the effector cells.
Tricyclic antidepressants (dibenzazepine derivatives)	Usually large amount of NE at synapse due to combined effects of drugs. Tricyclics block the *reuptake process*, and NE accumulates at synapses. Additional NE keeps coming into synapses as it is not destroyed by MAO.
Guanethidine (Ismelin®)	Blocks the process that stores NE in the granules. Normally the MAO would inactivate the NE; however, if the MAO is inhibited the excess NE spills into the synapse.
Levodopa (Laradopa®)	Increases production of precursors for NE synthesis. This combined with MAO inhibition allows a large NE buildup.

antidepressants are presented in Table 14-3. To prevent adverse reactions, it is recommended that at least a 2-week interval should lapse before a patient on a MAOI drug is switched to a tricyclic antidepressant. This allows the MAO activity of the body to return to normal. Administration of prescription or over-the-counter cough and cold preparations containing ephedrine, phenylephrine, or phenylpropranolamine could cause an exaggerated blood pressure response.

Guanethidine (Ismelin®) is an effective hypotensive agent and is prescribed mainly for patients with severe or sustained high blood pressure. Several drugs that may decrease the hypotensive action of guanethidine are shown in Table 14-4. Doxepin (Sinequan®) is a less-potent antagonist of

TABLE 14-3. *Drugs that may interact with tricyclic antidepressants to give an exaggerated blood pressure rise and possible hypertensive crises*

Drug	Probable mechanism of action
Amphetamines, ephedrine, methylphenidate (Ritalin®)	Trigger the release of NE from the adrenergic neuron. There is already a large amount of NE at the synapse because the reuptake process is blocked by the tricyclic drug.
Sympathomimetic drugs (e.g., phenylephrine, phenylpropranolamine, isoproterenol)	Combined effect of these drugs and NE on the receptors.
MAOI drugs	See Table 14-2.

TABLE 14-4. *Drugs that antagonize the hypotensive action of guanethidine (Ismelin®)*

Drug	Probable mechanism of action
Tricyclic antidepressants (Sinequan®, Elavil®, Pertofrane®, Tofranil®, Vivactil®)	Inhibit the mechanism that allows the guanethidine to concentrate in the adrenergic neuron. Antagonistic effect.
Chlorpromazine (Thorazine®)	Probably the same mechanism as for the tricyclic antidepressants.
Amphetamines, ephedrine, methylphenidate (Ritalin®)	Inhibit the mechanism that allows guanethidine to concentrate in the adrenergic neuron. Also, trigger the release of guanethidine from storage areas and allow NE to reoccupy these sites.
MAOI drugs	See Table 14-2.

guanethidine than other antidepressants and if used in normal doses probably has little effect on the activity of guanethidine. The antagonist effect of tricyclic antidepressants is developed over a 2- to 3-day period, and it takes 5 to 7 days after stopping the antidepressant for the guanethidine activity to return.

15

Drug Interactions Associated with Renal Excretion

Renal Excretion

Most drugs are excreted largely by the kidneys as either free drugs or water-soluble metabolites. Figure 15-1 shows the functional unit of the kidney, the nephron. Each human kidney contains approximately one million of these nephron units. The urine is collected by the collecting tubules and carried to the renal pelvis. From the renal pelvis, the urine is carried by way of the ureter to the bladder.

The first step in urine formation, and therefore drug excretion, is filtration of the blood. For a normal adult human being, a volume of blood equal to the total blood volume passes through the renal circulation within 4 to 5 min. Urine formation begins as the arterial blood enters the glomeruli and is filtered by a passive process. The glomerular filtrate contains many substances, e.g., water, glucose, electrolytes, amino acids, urea, creatinine, uric acid, and possibly drug and drug metabolites. The filtrate travels to the proximal convoluted tubule where much of the water and crystalloidal material necessary for normal metabolism (e.g., glucose, amino acids) is reabsorbed. Additional reabsorption takes place in the distal convoluted tubules. Tubule reabsorption and secretion are highly selective functions, and the amounts of essential substances retained are in accordance with body needs.

Glomerular filtration of a drug is a simple filtration process of free drug (drug that is not bound to plasma proteins) and is not appreciably affected by other drugs. There is the possibility that a highly protein bound drug that is displaced by a second drug would be excreted much faster than usual and its plasma half-life significantly decreased.

Drugs that are excreted passively at the glomerulus may be reabsorbed from the tubules if the drug is in its lipid-soluble form (not ionized). If the drug is an ionizable substance, then tubular reabsorption, which is a passive

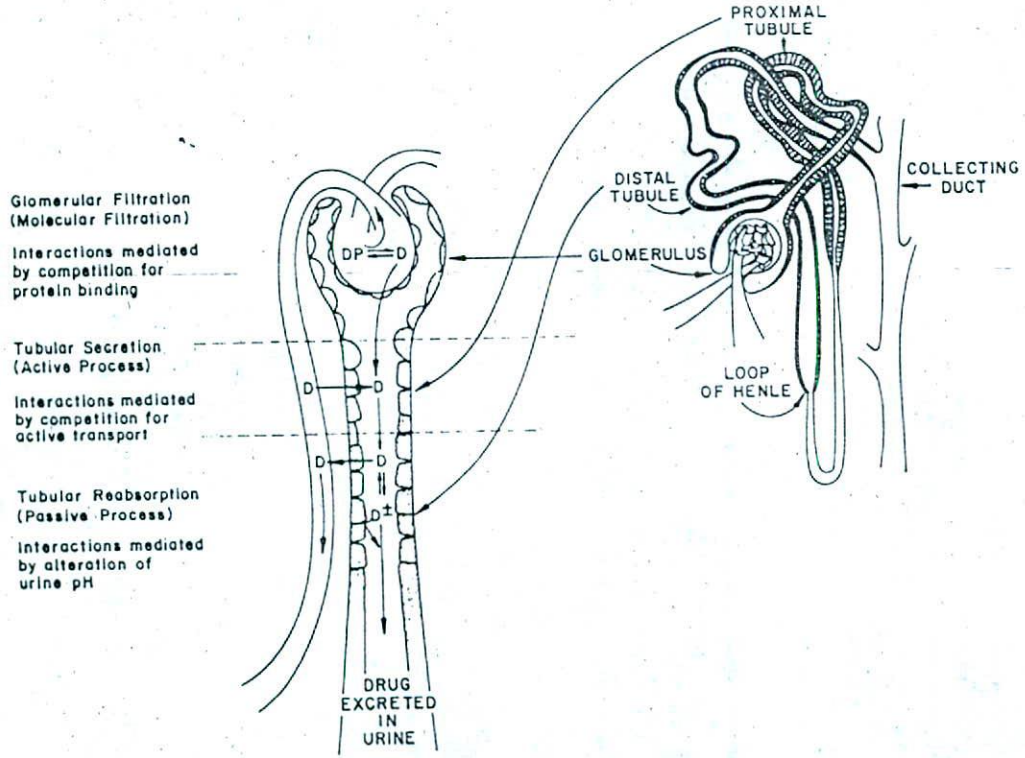


FIG. 15-1. Nephron unit and potential sites of drug interactions. [From Cadwallader, D. E. (1980): Drug interactions. 4. Drug interactions associated with renal excretion. *Mod. Med. Can.*, 35:684–686.]

absorption process, can be influenced by the pH of the tubular fluids. The drug molecules being reabsorbed from the renal tubules by passive transport must be un-ionized and lipid-soluble to cross the lipid membrane of the tubules.

The efficiency of renal excretion of a drug (or any substance for that matter) can be expressed as the volume of plasma in the circulatory system that is cleared of drug per unit time. Clearance of a drug from the plasma by the kidney is called *renal clearance* and is mathematically expressed as

$$\text{Renal clearance} = \frac{\text{excretion rate of drug}}{\text{drug plasma concentration}} = \frac{\text{amount/minute}}{\text{amount/milliliter}} = \frac{\text{milliliter}}{\text{minute}}$$

Drugs that are cleared very rapidly by the kidney would have relatively large values, 300 to 400 ml/min, whereas drugs with slow clearance rates would be 40 to 50 ml/min. Low clearance rates are indicative of tubular reabsorption of the drug. The maximum clearance rate for any drug could only be as fast as the normal renal plasma flow, approximately 500 to 650 ml/min.

Drug Interactions by Altered Urinary Excretion

Interactions which influence renal excretion of drugs are clinically significant only when the drug or its active metabolite is appreciably eliminated by the kidneys. Urinary pH can influence the activity of a drug by altering the rate of renal clearance. When a drug is in its un-ionized form, it more readily diffuses from the glomerular filtrate back into the blood. Thus for a basic drug such as amphetamine, a larger proportion of drug is in the un-ionized form in a basic (or less acidic) urine than is a normally acidic urine (pH 5.0 to 5.5). The result is that more amphetamine is reabsorbed back into the blood from the basic urine, resulting in prolonged activity. Figure 15-2 shows the cumulative urinary excretion of amphetamine under normal, alkaline, and acidic conditions. Note the very slow elimination in alkaline urine due to a decrease in the degree of dissociation and the rapid elimination of amphetamine in acidic urine. It has been observed that the effects of a single dose of amphetamine can last for several days if the urinary pH remains sufficiently alkaline by the concurrent administration of sodium bicarbonate.

Acidic drugs (e.g., salicylic acid, sulfonamides, and phenobarbital) are excreted faster when the urinary pH is alkaline. Therefore the concurrent administration of drugs that increase the pH, e.g., carbonic anhydrase inhibitor diuretics (Diamox®, Cardrase®) or systemic antacids (sodium bicarbonate), can cause rapid clearance of acidic drugs. Increasing the pH of

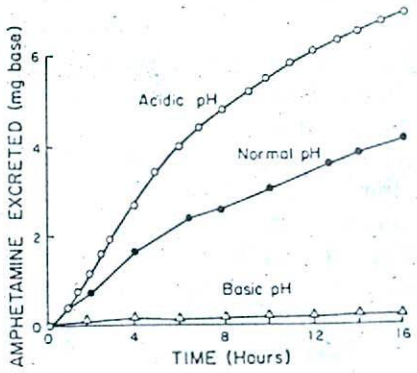


FIG. 15-2. Cumulative urinary excretion of amphetamine under normal, alkaline, and acidic conditions after oral administration of 15 mg amphetamine. [From Beckett, A. H., and Rowland, M. (1965): Urinary excretion kinetics of amphetamine in man. *J. Pharm. Pharmacol.*, 17:628–639.]

urine can be a useful procedure to increase renal elimination of an overdose of phenobarbital or methotrexate when it is used in high doses to treat tumors. Even the ingestion of nonsystemic acids (e.g., magnesium hydroxide, aluminum and magnesium hydroxide, and calcium carbonate-glycine suspensions) may increase the urinary pH by 0.5 to 0.9 pH unit, and these antacids in normal doses have the potential to influence the elimination kinetics of amphetamine and other drugs. On the other hand, basic drugs (e.g., antihistamines, meperidine, and imipramine) are excreted faster when the urinary pH is acidic; this acidification may be brought about by the administration of ammonium chloride or glutamic acid hydrochloride. Some acidic and basic drugs whose renal clearances are influenced by urinary pH are presented in Table 15-1. In general, if the drug remains ionized in the urine, the half-life is decreased and vice versa.

Methenamine products (Mandelamine®, Hiprex®, Urex®) are used in the prophylaxis and treatment of chronic urinary tract infections. Methenamine

TABLE 15-1. *Influence of pH on drug excretion*

High renal clearance when urine is acidic	
Amitriptyline (Elavil®)	Mecamylamine (Inversine®)
Amphetamines	Meperidine (Demerol®)
Antihistamines	Quinacrine (Atabrine®)
Imipramine (Tofranil®)	
High renal clearance when urine is basic	
Aspirin	Salicylic acid
Nalidixic acid (NegGram®)	Streptomycin
Nitrofurantoin (Furadantin®)	Sulfonamides
Phenobarbital	

requires an acidic pH (pH 5.5 or less) for the drug to be hydrolyzed to the active bactericidal agent formaldehyde. The drug is ineffective in patients whose urinary pH is 6 or higher as a result of antacid therapy and bland or low-protein diets. As it is usually difficult to maintain an adequately low pH in these patients, nitrofurantoin (Furadantin®) or trimethoprim-sulfamethoxazole (Bactrim®, Septra®) can be used instead of methenamine. Sulfonamides and methenamine should not be coadministered as some sulfonamides precipitate with formaldehyde in the urine.

Some drugs, e.g., penicillin, probenecid (Benemid®), salicylates, ethacrynic acid (Edecrin®), thiazide diuretics, phenylbutazone (Butazolidin®), and indomethacin (Indocin®), are excreted via active transport processes, probably involving enzyme systems in the kidneys. These drugs are transported from the blood across the proximal tubular cells into the tubular urine by an active transport system. These types of drugs, when taken concurrently, can interfere with one another's elimination. Probenecid and salicylates can inhibit the excretion of indomethacin. An example of a useful interaction is when probenecid is given with penicillin to delay the excretion of penicillin and maintain high blood levels of the antibiotic. Phenylbutazone (Butazolidin®) increases the hypoglycemic effect of acetohexamide (Dymelor®) possibly by interfering with the renal excretion of its active metabolite hydroxyhexamide. As a result of higher-than-normal drug blood levels, plasma insulin is increased and blood glucose decreased.

Some drugs that have been reported to interfere with one another during the active excretion process at the kidney tubule are listed in Table 15-2. Note that certain drugs inhibit the excretion of others. For example, salicylates inhibit the excretion of probenecid, whereas furosemide (Lasix®) interferes with the excretion of salicylates. Drug–drug interactions mediated by active transport systems in the kidneys appear to be very specific.

Although digoxin and quinidine have commonly been administered together for more than 50 years, recent information indicates that toxic reactions can occur with the concomitant use of these two drugs. Quinidine has been shown to appreciably increase serum digoxin levels when given to patients already on digoxin. The results of a pharmacokinetic study involving healthy subjects receiving 1.0-mg doses of intravenous digoxin alone and with quinidine bisulfate tablets substantiate the fact that coadministration of quinidine increases digoxin serum levels (Fig. 15-3). Several mechanisms of action have been proposed for this interaction, the most prevalent being that quinidine induces a decrease in digoxin renal clearance and reduces the binding of digoxin at peripheral sites (a reduced volume of distribution). Patients taking both drugs should be closely monitored for clinical symptoms of digoxin toxicity. Toxic results of this interaction can be minimized by

TABLE 15-2. *Some drugs that compete for active transport systems in kidney tubules*

Drug	Drug inhibited	Ref.[a]
Probenecid (Benemid®)	Indomethacin (Indocin®)	1
	Penicillins	2
	Naproxen (Naprosyn®)	3
Salicylates	Probenecid	4
	Phenylbutazone	5
	Sulfinpyrazone	6
	Indomethocin	7
Oxyphenylbutazone (Tanderil®)	Penicillin	8
Bishydroxycoumarin (Coumarin®)	Chlorpropamide (Diabinese®)	9
Phenylbutazone (Butazolidin®)	Acetohexamide (Dymelor®)	10
Sulfinpyrazone (Anturane®)	Salicylates	6

[a]References: 1. Skeith, M. D., Simkin, P. A., and Healy, L. A. (1968): The renal excretion of indomethacin and its inhibition by probenecid. *Clin. Pharmacol. Ther.*, 9:89–93. 2. Gibaldi, M., and Schwartz, M. A. (1968): Apparent effect of probenecid on the distribution of penicillins in man. *Clin. Pharmacol. Ther.*, 9:345–349. 3. Runkel, R., et al. (1978): Naproxen-probenecid interaction. *Clin. Pharmacol. Ther.*, 24:706–713. 4. Pascale, L. R., et al. (1955): Inhibition of the uricosuric action of Benemid® by salicylate. *J. Lab. Clin. Med.*, 45:771–777. 5. Pascale, L. R., Dubin, A., and Hoffman, W. S. (1952): Therapeutic value of probenecid (Benemid®) in gout. *JAMA*, 149:1188–1194. 6. Yu, T. F., Dayton, P. G., and Gutman, A. B. (1963): Mutual suppression of the uricosuric effects of sulfinpyrazone and salicylate: a study of interactions between drugs. *J. Clin. Invest.*, 42:1330–1339. 7. Kaldestad, E., Hansen, T., and Brath, H. K. (1975): Interaction of indomethacin and acetylsalicylic acid as shown by the serum concentrations of indomethacin and salicylate. *Eur. J. Clin. Pharmacol.*, 9:199–207. 8. Leger, F., and Bracharz, H. (1968): Zur frage des einflusses der oxyphenbutason therapie auf den penicillin-blutspiegel beim menchen. *Med. Welt*, 19:1253–1255. 9. Kristensen, M., and Hansen, J. M. (1968): Accumulation of chlorpropamide caused by dicoumarol. *Acta Med. Scand.*, 183:83–86. 10. Field, J. B., et al. (1967): Potentiation of acetohexamide hypoglycemia by phenylbutazone. *N. Engl. J. Med.*, 277:889–894.

stopping digoxin therapy 2 to 4 days before initiating quinidine, then restarting digoxin at half the previous dose. Serum digoxin levels may decline when quinidine is discontinued in patients previously well controlled on digoxin–quinidine therapy. The dose of digoxin should be adjusted upward to maintain adequate digoxin levels.

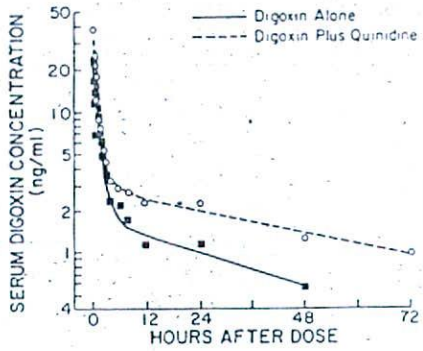


FIG. 15-3. Serum digoxin concentrations and pharmacokinetic functions for a representative subject following intravenous administration of digoxin in the control state and during coadministration of quinidine. [From Ochs, H. R., Bodem, G., and Greenblatt, D. J. (1981): Impairment of digoxin clearance by coadministration of quinidine. *J. Clin. Pharmacol.*, 21:396–400.]

Uricosuric agents, e.g., probenecid (Benemid®), and sulfinpyrazone (Anturane®), reduce the production of or promote the excretion of uric acid. Salicylates taken in relatively low doses (1 to 2 g aspirin per day) with these uricosuric agents cause uric acid retention and negate the intended treatment of hyperuricemia (gout). The salicylates possibly interfere with uric acid clearance at the renal tubular level.

Interactions Associated with Sodium- and Potassium-Depleting Diuretics

Diuretics used in the treatment of hypertension [thiazides (Hydrodiuril®, Diuril®, Esidrix®), furosemide (Lasix®), ethacrynic acid (Edecrin®)] promote the excretion of sodium and potassium. In digitalized patients, the excessive loss of potassium by intensive diuretic therapy sensitizes the heart to digitalis activity and brings about digitalis intoxication, the first signs of which are usually poor appetite and nausea. The primary candidates for this interaction are those patients on 0.25 mg digoxin and taking more than 40 mg furosemide or 50 mg hydrochlorthiazide (Hydrodiuril®). Excessive potassium loss can be corrected by taking potassium supplements (Slow-K®, Kaon®, Kay Ciel®, K-lyte®) or by eating foods rich in potassium (oranges, bananas).

Lithium toxicity may develop when lithium is coadministered with sodium- and potassium-depleting diuretics, e.g., the thiazides. It appears that thiazides increase the reabsorption of lithium in the proximal renal tubule, causing a reduction in lithium clearance. Concurrent administration of thia-

zide diuretics and lithium products should be avoided except in those cases where high lithium levels are desired.

The potassium-losing diuretics given with corticosteroids may result in enhanced potassium loss. Patients receiving this combination should be monitored for signs of excessive loss of potassium.

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Subject Index