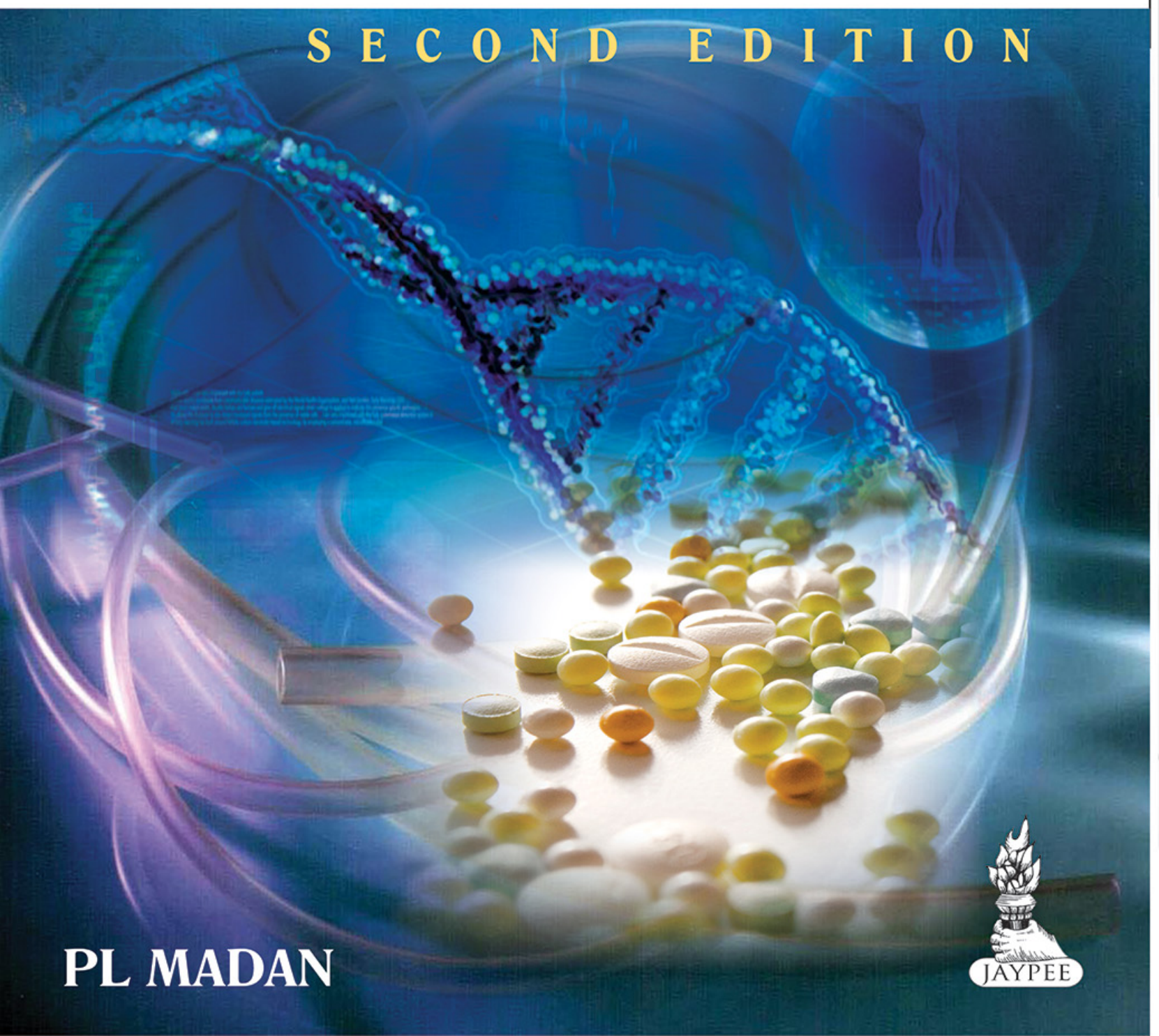
Biopharmaceutics & Pharmacokinetics

SECOND EDITION



PL MADAN

JAYPEE

CONTENTS

1. Basic Concepts 1

Biopharmaceutics 2
Pharmacokinetics 8
Pharmacodynamics 16
Pharmacogenetics 17
Toxicokinetics 19
Legal Definitions 20

2. Mathematical Concepts 26

Logarithms 26
Graphic Methods 31
Linear Regression Analysis 35

3. Rate Processes 48

Zero-Order Kinetics 49
First-Order Kinetics 55
Semi-Logarithmic Graph Paper 63

4. Drug Absorption 74

Routes of Drug Administration 77
Topical Absorption 79
Oral Administration 81
Absorption Mechanisms 82
Gastrointestinal Tract 89

5. Drug Distribution 101

Role of Proteins in Drug Distribution 104
Perfusion and Drug Distribution 108
Drug Distribution and Body Water Compartments 110
Volume of Distribution 114
Body Composition 119

6. Drug Elimination 124

Elimination of Drug 124
Routes of Drug Excretion 125
Renal Excretion 131
Glomerular Filtration 133
Urine pH and Reabsorption 137
Pharmacokinetics and Renal Excretion 143

7. Clearance 145

Factors Affecting Clearance 145
Renal Clearance 146
Drugs Eliminated Solely by Renal Excretion 155
Creatinine Clearance 157
Renal Function in Adults 159
Renal Function in Infants 164
Hepatic Clearance 168
First-Pass Effect 171
Dosage in Children 172

8. Bioavailability 177

Determination of Bioavailability 179
Relative Bioavailability 185
Determination of Area under the Curve 186
Intravenous Administration 193

9. Bioequivalence 203

Equivalence 204
Bioequivalency of Generic Drugs 216
Therapeutic Equivalence Evaluations 217
Bioequivalence Studies 223
Oral Dosage Forms that should not be Crushed 232

10. Compartment Models 246

Compartment Modeling 247
One-Compartment Model 248

11. Intravenous Bolus Dose 256

One-Compartment Model 256
Multi-Compartment Model 259
Two-Compartment Model 261
Three-Compartment Model 270

12. Extravascular Bolus Dose 287

Plasma Profile 287
One-Compartment Model 288
Time of Maximum Concentration (T_{max}) 295
Maximum Plasma Concentration 296
Lag-Time 297
Two-Compartment Model 306

13. Multiple Dosing 330

Intravenous Administration 330
Steady-State Concentrations 342
Extravascular Administration 349

14. Loading Dose 359

Intravenous Administration 360
Extravascular Administration 367

15. Continuous Intravenous Infusion 376

Plasma Profile 378
Steady-State Concentration 386
Loading Dose followed by Continuous Infusion 396

16. Renal Impairment 404

Dosage Adjustment in Renal Impairment 405
Determination of K_{ri} 407
Dosage Regimen in the Renally Impaired 413
Dosage Adjustment in Renal Insufficiency 420

17. Therapeutic Drug Monitoring 426

Historical Background 427
Candidates for Therapeutic Monitoring 430
Factors Influencing Drug Variability 434
Presence of Other Drugs 435
Process of Therapeutic Drug Monitoring 438
Intravenous Administration 444
Extravascular Administration 453

18. Non-compartmental Methods 462

Advantages of Compartment Models 462
Disadvantages of Compartment Models 463

Non-compartmental Methods 463
Mean Residence Time 466
Methods of Determining Mean Residence Time 468
Mean Absorption Time 479
Rate Constant of Elimination 482
Rate Constant of Absorption 484
Total Body Clearance 485

Answers *493*

Appendix A: Glossary of Terms *501*

Appendix B: Nomenclature and Symbols *508*

Index *513*

CHAPTER 4

DRUG ABSORPTION

The availability of an administered dose for its systemic effect depends, among other factors, on the route of administration of the drug. For example, an intravenously administered dose is available in the blood stream at its maximum concentration immediately after administration, but an orally administered dose must release its contents in the gastrointestinal tract (e.g. from a capsule dosage form) and the drug must dissolve in the gastrointestinal fluids before it becomes available for absorption. Since absorption is not an instantaneous process, the administered dose does not appear in the plasma all-at-once immediately after administration. Thus, the peak plasma concentration of the drug is delayed. Also, the peak plasma concentration during extravascular administration, is expected to be less than that obtained after intravenous administration because appearance of drug in plasma is not as rapid as during intravenous administration. Similarly, in other extravascular routes, e.g. buccal, extravascular parenteral (intramuscular, subcutaneous, etc.) or transdermal route, the drug must diffuse through the biological membrane(s) before it can reach systemic circulation. The plasma profile in all these cases exhibits an absorption phase, very similar to the plasma profile obtained after oral administration.

In the case of orally administered drugs, the situation can become very complex. Some drugs are unstable in gastrointestinal environment and part of the administered dose is 'lost' before absorption can take place. There are instances where the drug is quite stable, but the entire administered dose is not available for absorption, i.e. the extent of absorption for these drugs is less than 100 percent. This may be due to many reasons. The main reasons for the lack of availability of drug for absorption are:

i. Incomplete dissolution of drug from the dosage form or
ii. Partial and/or slow inactivation of drug in the gastric environment.

Some drugs are absorbed completely, but their systemic availability is small because these drugs undergo enterohepatic circulation. Presystemic elimination of drugs due to first-pass effect may reduce systemic availability, even after the drug has been completely absorbed. Thus, even though the drug may have been absorbed 100 percent from the dosage form, the fraction of dose reaching systemic circulation is less than 1.

Some drugs, however, cannot be administered orally for absorption through the gastrointestinal tract because they are either not absorbed at all or they undergo rapid degradation in the environment of the gastrointestinal tract. Therefore, these drugs must be administered by routes other than the gastrointestinal tract and liver. Common routes, which bypass gastrointestinal tract are—intravenous, intramuscular or subcutaneous injection, sublingual or rectal administration or through the skin, as a transdermal patch. The choice of route of administration in these cases is dictated by the nature and physicochemical properties of the drug. When immediate response of nitroglycerin is desired, sublingual route is preferred because the drug reaches systemic circulation rapidly by this route. Unpleasant and bitter tasting drugs are not administered by sublingual route for obvious reasons. Although nitroglycerin is administered transdermally (nitroglycerin patch) for sustained release of the drug, drugs having a large molecular weight cannot be administered transdermally because they are difficult to diffuse through the skin.

JAYPEE BROTHERS

Similarly, those drugs, which are insoluble in suitable aqueous solvents, such as, water for injection, dextrose solution, normal saline, cannot be administered intravenously, but may be given as a suspension either subcutaneously or intramuscularly and drugs unstable in a solution form must be reconstituted just before administration.

A partial listing of some examples of drugs, which are administered by routes other than the gastrointestinal route is shown in Table 4-1. These drugs are either not absorbed or are very poorly absorbed through the gastrointestinal tract.

The most direct route of placement of drug in the systemic circulation is the intravascular (intravenous) route of drug administration. All other routes of drug administration, including the oral route and other extravascular routes (e.g. subcutaneous, transdermal and intramuscular routes), involve an absorption step. This step is essential for the appearance of drug into the systemic circulation.

The potential sites for drug absorption following oral administration are:

i. The buccal cavity
ii. The gastrointestinal tract.

Absorption of drugs from the gastrointestinal tract can occur from the stomach, small intestines, large intestines and the rectum.

The small intestine is a common area for drug absorption. Once absorbed in the gastrointestinal tract, the drug is channeled through the portal vein to the liver and then gains access to the systemic circulation for delivery to the site of action. Because the liver and the intestinal walls are the major sites of biotransformation of the drug, all or part of the administered dose may undergo degradation at these sites. That is, a portion of the extravascularly administered dose may not reach systemic circulation. In these situations, the fraction of the administered dose absorbed (referred to as the F value) is less than 1.0. If the F value of an extravascularly administered drug is very low (much less than 1.0), it indicates poor bioavailability of the drug.

It should be mentioned, however, that not all drugs are biotransformed into inactive metabolites. The metabolites of some drugs are active and exert pharmacologic effects. For example, the antianxiety drug prazepam (Centrax) metabolizes in part, to oxazepam (Serax), which also has antianxiety effects. Similarly, in some instances, a pharmacologically inactive drug (usually referred to as the prodrug) may be administered for the known effects of its metabolites.

A relatively high proportion of drug administered in the buccal cavity and rectum is absorbed and drained into the venous circulation, thereby avoiding (bypassing) the initial biotransformation

Table 4-1 Examples of drugs administered by routes other than the oral route

Drug	*Usual Route of Administration*	*Drug*	*Usual Route of Administration*
Amikacin	IV, IM	Dopamine	IV
Azlocillin	IV	Gentamicin	IM
Aztreonam	IV, IM	Insulin	IV, IM, SC
Cefazolin	IM	Kanamycin	IM
Cefotaxime	IV, IM	Methicillin	IV, IM
Cefoxitin	IV, IM	Mezlocillin	IV, IM
Ceftizoxime	IV, IM	Moxalactam	IV, IM
Cefuroxime	IV, IM	Netilmicin	IV, IM
Cephacetrile	IV, IM	Sisomicin	IV, IM
Cephalothin	IV, IM	Streptomycin	IV, IM
Dobutamine	IV	Ticarcillin	IV, IM

IV = intravenous, IM = intramuscular, SC = subcutaneous

JAYPEE BROTHERS

step. In general, low bioavailability of drugs administered by oral route is caused not only by the poor water-solubility and poor intestinal permeability of the drug, but also due to biodegradation of drug in the upper portion of the digestive tract.

Many drugs are absorbed completely, i.e. 100 percent of the extravascularly administered dose is absorbed and is able to appear in systemic circulation. These drugs have an F value equal to 1.0. The symbol F stands for—fraction of dose absorbed. However, a large number of drugs exhibit F values, which range from almost zero to slightly less than 1.

Table 4-2 lists examples of some drugs and their F values following oral administration. The data presented in this Table have been extracted from a large number of publications and listed as the mean data. As can be seen from this Table, while some drugs are absorbed completely, others are absorbed to a very small extent.

Table 4-2 Fraction of dose absorbed (F) of some important drugs

Drug	*F*	*Drug*	*F*	*Drug*	*F*
Acetazolamide	1.0	Clonazepam	0.9	Fenfluramine	0.65
Amobarbital	1.0	Digitoxin	0.9	Methotrexate	0.65
Amodiaquine	1.0	Disopyramide	0.9	Atenolol	0.6
Amphetamine	1.0	Disulfiram	0.9	Digoxin	0.6
Antipyrine	1.0	Ethosuximide	0.9	Furosemide	0.6
Butobarbital	1.0	Isoniazid	0.9	Haloperidol	0.6
Carbenoxolone	1.0	Levodopa	0.9	Hydromorphone	0.6
Cefadroxil	1.0	Meprobamate	0.9	Nortryptine	0.6
Cephradine	1.0	Minocycline	0.9	Penicillin V	0.6
Chloroquine	1.0	Penbutalol	0.9	Ranitidine	0.6
Chlorpropamide	1.0	Phenobarbital	0.9	Prazocin	0.57
Clofibrate	1.0	Phenytoin	0.9	Nifedipine	0.56
Desipramine	1.0	Secobarbital	0.9	Papaverine	0.53
Diazepam	1.0	Sulfadiazine	0.9	Ampicillin	0.5
Diazoxide	1.0	Sulfaethidole	0.9	Cloxacillin	0.5
Glutethimide	1.0	Sulfamerazine	0.9	Codeine	0.5
Hexobarbital	1.0	Sulfamethazine	0.9	Diphenhydramine	0.5
Hydrocortisone	1.0	Valproate	0.9	Flucloxacillin	0.5
Ibuprofen	1.0	Warfarin	0.9	Griseofulvin	0.5
Indomethacin	1.0	Acetaminophen	0.85	Imipramine	0.5
Lithium	1.0	Flucytosine	0.85	Meperidine	0.5
Methocarbamol	1.0	Lorazepam	0.85	Nafcillin	0.5
Naproxen	1.0	Procainamide	0.85	Pentazocine	0.5
Oxazepam	1.0	Acetyldigoxin	0.8	Metoprolol	0.45
Pentobarbital	1.0	Cimetidine	0.8	Oxprenolol	0.45
Phenprocoumon	1.0	Clonidine	0.8	Chlorpheniramine	0.4
Phenylbutazone	1.0	Dicloxacillin	0.8	Erythromycin	0.4
Probenecid	1.0	Dicumarol	0.8	Lincomycin	0.4
Protriptyline	1.0	Doxycycline	0.8	Nadolol	0.4
Pseudoephedrine	1.0	Ethambutol	0.8	Propranolol	0.35
Pyrimethamine	1.0	Flunitrazepam	0.8	Chlorpromazine	0.32

Contd...

JAYPEE BROTHERS

Contd...

Quinine	1.0	Methadone	0.8	Metformin	0.32
Rifampin	1.0	Methaqualone	0.8	Azidocillin	0.3
Sotalol	1.0	Methenamine	0.8	Fentanyl	0.3
Sulfisoxazole	1.0	Metronidazole	0.8	Mianserin	0.3
Theophylline	1.0	Nitrazepam	0.8	Penicillin G	0.3
Tolbutamide	1.0	Primidone	0.8	Tolamolol	0.3
Trimethoprin	1.0	Sulfisomidine	0.8	Vincamine	0.3
Dapsone	0.9	Tetracycline	0.8	Zimelidine	0.3
Pindolol	0.9	Oxytetracycline	0.8	Doxepin	0.27
Practolol	0.9	Atropine	0.75	Hydralazine	0.22
Sulfinpyrazone	0.9	Oxtriphylline	0.75	Verapamil	0.22
Tocainide	0.9	Quinidine	0.75	Propoxyphene	0.2
Zomiprac	0.9	Timolol	0.75	Mebendazole	0.17
Amoxicillin	0.9	Guanethidine	0.7	Ketamine	0.16
Carbamazepine	0.9	Methacycline	0.7	Chlorothiazide	0.14
Cefaclor	0.9	Oxacillin	0.7	Phenacetin	0.13
Cephalexin	0.9	Thyroxine	0.7	Propantheline	0.1
Clindamycin	0.9	Amitriptyline	0.65	Alprenolol	0.01

ROUTES OF DRUG ADMINISTRATION

Drugs intended for systemic circulation are administered by various routes of administration. Broadly speaking, the various routes of drug administration may be classified into the following two major categories. i. intravascular route and ii. extravascular route. In the intravascular route of administration, the drug is placed directly into the blood stream. In the extravascular route, the drug undergoes an absorption process before it reaches systemic circulation. Although intravascular route has the advantage that the drug is placed directly into the blood stream, its main disadvantages are that besides causing discomfort to the patient, the dosage form must be sterile, pyrogen-free and free of particulate matter. Also, these dosage forms are relatively more expensive (because of stringent requirements for the manufacture of parenteral products) and require a physician or a trained health-care professional for administration. The most common intravascular route is intravenous administration. The drug may be given as a single bolus dose, or as continuous infusion over a period of time, which may range from a few hours to more than 24 hours. The most popular and common extravascular route of administration is the oral route. The oral route suffers from the disadvantage of potential first-pass effect, which causes a portion of the drug not being available for absorption. Other commonly used extravascular routes include intramuscular, subcutaneous and transdermal routes. The various routes of drug administration and the types of dosage forms commonly used for these routes are shown in Table 4-3.

Choice of Route of Administration

Of the various routes of drug administration, the most common routes of drug administration are the intravenous route and the extravascular route. The intravenous route is preferred when the drug must be placed directly into the systemic circulation for immediate effect (e.g. in emergency situations), because administration of drugs by extravascular route involves absorption of drug into the systemic circulation. If the drug is absorbed slowly, then there would be a possible delay in the onset of action. Even if the drug is absorbed relatively rapidly, one would expect some

JAYPEE BROTHERS

Table 4-3 Dosage forms and routes of drug administration

Route	*Site*	*Commonly* used dosage forms*
Parenteral		
Intra-arterial	Artery	Solutions
Intra-articular	Joint	Solutions, suspensions
Intra-cardiac	Heart	Solutions
Intradermal	Skin\	Solutions, suspensions
intramuscular	Muscle	Solutions, suspensions
intrasynovial	Joint-fluid	Solutions
Intrathecal	Spine	Solutions
Intravenous	Vein	Solutions
Subcutaneous	Under skin	Implants, solutions, suspensions
Aural	Ear	Solutions, suspensions, ointments
Conjunctival	Conjunctiva	Ointments
Intranasal	Nose	Inhalants, ointments, solutions, sprays
Intraocular	Eye	Solutions
Intrarespiratory	Lung	Aerosols
Oral	Mouth	Capsules, elixirs, emulsions, gels, lozenges, magmas, powder, solutions, suspensions, syrups, tablets
Rectal	Rectum	Ointments, solution, suppositories, tablets
Sublingual	Under the tongue	Lozenges, tablets
Transdermal	Skin	Aerosols, creams, lotions, ointments, patches, powders
Urethral	Urethra	Solutions, suppositories
Vaginal	Vagina	Inserts, ointments, solutions, suppositories, tablets

*Only the most commonly used dosage forms are listed here.

delay before the plasma concentration of drug reaches the minimum effective concentration of drug in order to exhibit its therapeutic action.

Among the many extravascular routes of drug administration, the oral route is preferred by everybody involved in the treatment with the drug. This includes the pharmaceutical manufacturer, the wholesale distributor, the patient, the physician, the pharmacist and the health care attendant. The reason for the preference of oral route is that this route of administration offers many advantages. Some of these advantages include the following:

a. Patients prefer oral route because of ease of administration of drug and self-medication with the drug.
b. The pharmacists prefer dosage forms intended for oral administration because it offers convenience in storage, handling and dispensing.
c. The prescribers favor this route because orally administered dosage forms offer relative accuracy of dose and patient compliance.
d. The manufacturers like it because these dosage forms are less expensive to manufacturer and are more economical in packaging, storage and shipping than other dosage forms.

Among the dosage forms available for oral administration, the solid dosage forms are most preferred. Liquid dosage forms are more popular with those who are not comfortable with solid dosage forms, e.g. pediatric and geriatric patients (for obvious reasons). Liquid dosage forms are not popular with adult patients because of inconvenience in carrying the day's supply, handling and measuring the dose and administration of the dose.

The many extravascular routes of drug administration may be classified into two major groups:

i. Parenteral route
ii. Non-parenteral route.

The more popular extravascular parenteral routes are intramuscular and subcutaneous injections and the more popular non-parenteral routes include oral, rectal, vaginal and more

JAYPEE BROTHERS

recently, topical administration. In general, the non-parenteral extravascular routes are preferred because dosage forms intended for administration by a non-parenteral extravascular route offer the following advantages:

a. They are relatively less expensive because all parenteral dosage forms must be sterile, free of particulate matter and pyrogen and manufacturing conditions for these dosage forms are stringent.
b. They are relatively painless during administration because skin-penetration is not required.
c. They exhibit better patient compliance because they offer the advantage of ease of administration.
d. They afford feasibility of self-administration.

Although oral route has been and continues to be the most preferred route of drug administration for systemic action, the rectal and vaginal routes are used for both systemic as well as topical effect of the drug. Not too long ago, topical application of drugs was intended exclusively for local effect of drug at the site of application. For example, topical application of analgesic creams, ointments, liniments and lotions has been a standard practice for local effect of the drug, although it has also been known for some time that topical application of a drug does not necessarily mean that the drug will not be absorbed through skin. For example, rectal absorption of glucocorticoids (hydrocortisone, prednisolone or betamethasone) following their administration as an enema or suppository has been reported to range from 25% to 50%. In recent years, traditional topical route (skin) of administering drugs for local effect has gained popularity as a route of administering drugs for systemic effect (transdermal delivery) due to successful administration of such drugs as nitroglycerin, clonidine, estradiol, nicotine and scopolamine. Transdermal delivery of other drugs is being investigated by many companies as an alternative to optimizing drug therapy.

TOPICAL ABSORPTION

Compared to absorption by other routes of administration, topical absorption of drugs is limited mainly due to anatomical structure of the skin. Historically, skin has seldom been regarded as a suitable route for systemic absorption of drugs, because it has always been thought of as the most impenetrable tissue of the body, serving the primary function of a protective barrier. Recent studies have shown that although not all drugs permeate through the skin, those that do exhibit skin permeation differ in their rate and extent of permeation. The rate and extent of permeation of drugs through the skin appears to depend primarily upon two factors:

i. The physico-chemical properties of the drug and
ii. The anatomical nature of the skin.

Studies have demonstrated that the differences observed in the rate and extent of skin permeation are not only drug-related, but these differences are also related to the specific absorption sites. For example, several studies have shown that the rate and extent of absorption of nitroglycerin is more predictable and reproducible when the drug is applied on the chest area. Similarly, the earlobe appears to be a better site for the transdermal delivery of scopolamine and the upper arm is suggested for the application of nicotine patch. Based on the various studies involving transdermal delivery of drugs the following observations have been made:

a. Skin permeability is a passive process rather than a biologically active property,
b. Permeation of drugs through intact skin can be regarded as a process of dissolution and molecular diffusion of drug,
c. The principle barrier to permeation is stratum corneum, which is 3 to 5 orders of magnitude less permeable than dermis, making permeability of the entire epidermis more or less indistinguishable from that of stratum corneum *per se*,
d. Stratum corneum is the rate-limiting layer of skin penetration and may be regarded as a two phase lipid/protein heterogeneous membrane in which lipid is continuous and

JAYPEE BROTHERS

e. The membrane permeability of drug correlates with aqueous solubility and lipid/protein partition coefficient of the specific drug.

From a comparative stand-point and in order to distinguish drug absorption through the skin and through the gastrointestinal mucosa (lining of the gastrointestinal tract, mouth and rectum), the following observations can be made:

a. The skin is much less permeable to drugs than the mucosa.
b. Absorption of drugs through gastrointestinal mucosa depends on lipid/water partition coefficient, but permeation of drugs through skin is a function of lipid/protein partition coefficient of the drug.
c. The surface area of the entire skin in an adult is only 1.73 m^2 compared to the absorbing surface area of lung (about 70 m^2) or surface area of the gastrointestinal tract (120–200 m^2). Table 4-4 lists the surface area of various anatomical sites and parts of the human body.

The relatively large absorbing surface area of the gastrointestinal tract and the ease of oral administration of drugs is perhaps the reason for the popularity of oral administration of drugs. Compared to oral drug therapy, transdermal application of drugs for systemic effect has the following potential advantages: avoiding biochemical degradation in gastrointestinal tract, avoiding presystemic metabolism in the gut wall and liver and provide long periods of drug action for relatively short-acting drugs. The transdermal route is also recommended for potent, lipophilic drugs with short half-lives.

Rate and Extent of Absorption

The rate and extent of absorption of a drug from a topically applied dosage form (transdermal delivery system) depends on many factors. Some of these factors may be related to the site of application of the delivery system, while some of the factors may be related to the delivery system itself. The following is a listing of some of these factors:

1. Concentration of drug in the delivery system.
2. Nature of vehicle containing the drug. If the vehicle used for the delivery of drug has greater affinity for the drug, it will have a tendency to retard the rate of release of drug from the delivery system.
3. Surface area of the film of drug applied to the skin. Larger the surface area of film containing the drug, greater is the rate and extent of release of drug from the delivery system.

Table 4-4 Surface area of body parts and anatomical sites

Site	*Surface area (m^2)*	*Body part*	*Surface area (m^2)*
Skin	1.73	Index finger	0.006
Head	0.1	Hand + 5 fingers	0.05
Trunk	56	Lower arm (includes hand, but does not include fingers)	0.07
Lung	70	Upper arm	0.1
Mouth cavity	0.02	Thigh	0.2
Stomach	0.1 – 0.2	Lower leg	0.1
Small intestine	120 – 200	Foot	0.05
Large intestine	0.5 – 1		
Rectum	0.05		
Glomeruli (both kidneys)	1.16		

JAYPEE BROTHERS

4. Thickness of film of drug applied to the skin. A thicker film of drug acts like a reservoir, thereby prolonging release of drug from the delivery device.
5. Presence or absence of occlusion over drug reservoir.
6. Presence or absence of permeation enhancers in the dosage form. Permeation enhancers are used to increase permeability of drug through the skin.
7. Nature of skin to which dosage form is applied. Nature of skin includes the following factors:
   a. Anatomical region of body. Different regions of the body offer different types of resistance to transport of drug and therefore affect the rate and extent of absorption of drug.
   b. Age of the patient. Skin permeability changes with age due to physiological changes.
   c. Sex of the patient. It has been reported that there are differences in drug permeability from identical sites of application in males and females.
   d. Thickness of skin. Greater the thickness of skin, slower the rate of permeability of drug, because the drug has to travel a longer distance to permeate.
   e. Multiple applications at the same site. The permeability of a drug tends to increase if the same site is used for multiple applications, probably due to occlusion and/or due to inflammation caused by adhesive used in the fabrication of delivery system.
   f. Miscellaneous factors. These include: presence of skin pigmentation, psoriasis, dermatitis and hydration. These factors are equally important in considering transdermal absorption of drugs, because permeation of drugs changes in the presence of these factors.

In addition to the factors listed above, there are other factors, which also affect rate and extent of transdermal absorption of drugs. These include the following:

1. Metabolism of drug in skin. Some drugs undergo rapid metabolism in the skin, while others do not.
2. Binding of drug to epidermis. In the case of drugs, which bind to epidermis, initial applications of drug are lost in the epidermis. Since binding is a reversible process, the bound drug is ultimately released after application of drug is terminated.
3. Blood supply affected by the presence of drug. Drugs, which affect blood supply will also affect their rate and extent of absorption soon after their first application.
4. Effect of first dose on absorption of subsequent doses. Some drugs influence their own absorption once they appear in systemic circulation, e.g. by enzymes induction.

ORAL ADMINISTRATION

Although oral ingestion of a dosage form not only represents the most popular route, it also represents the most frequently used route of administration. However, the oral route of drug administration also poses many problems to efficient drug therapy. Most of these problems are primarily due to two main reasons:

i. Dosage form considerations or
ii. Physiological variables.

In order to achieve the best therapeutic results, a rapid rate of absorption of drug from the administered dose is of utmost importance (except in the case of modified release dosage forms). Some of the reasons for the desirability of rapid rate of drug absorption are as follows:

1. Rapidly absorbed drugs provide maximal concentration in plasma, assuring rapid onset of action and maximum pharmacologic response.
2. Rapid absorption means less time for exposure of drug to the gastrointestinal fluids, thereby reducing drug interactions with the components of these fluids and minimizing drug degradation.
3. Rapid absorption generally assures uniform and predictable pharmacologic response, thus reducing undesirable variability.

JAYPEE BROTHERS

In order for a drug to be absorbed through a biological membrane and reach systemic circulation, it must be released from the dosage form and be available as an aqueous solution at the absorption site. The release of drug from the dosage form depends on three major factors:

1. Physicochemical properties of the drug
2. Physicochemical properties of the dosage form and
3. Physicochemical factors of the human body at the site of administration or absorption.

The formulation of dosage form is the most important factor in obtaining proper release of drug from the dosage form. The drug released from a dosage form may not necessarily be absorbed if drug molecule is bound to mucosa. If the drug is bound to the surface of mucosa by hydrogen bonding, ion binding or van der Waals forces, the process is termed adsorption and if the drug permeates through capillary walls and enters systemic circulation, the process is called absorption. In oral administration, the drug usually must permeate more than one membrane (e.g. in lumen of gastrointestinal tract) before the drug molecule passes from outside into a capillary. However, the only rate controlling factor appears to be the rate of permeation through epithelial cells. Other factors the which affect, rate of drug permeation include vascularity and rate of blood flow at absorption site. This is also true for drugs administered rectally and topically.

ABSORPTION MECHANISMS

There are six accepted mechanisms of drug absorption. These, in order of their importance are:

1. Passive diffusion
2. Active transport
3. Facilitated transport
4. Convective transport
5. Ion-pair transport and
6. Pinocytosis.

A prerequisite for absorption is that the drug must be present in a solution form at the absorption site. This is valid for all absorption mechanisms, except absorption by pinocytosis.

Passive Diffusion

Passive diffusion is transport through a semi-permeable membrane. In this transport mechanism, drug molecules diffuse through a membrane by first dissolving in the aqueous portion of the membrane and then by dissolution in the lipid portion of the membrane. The solubility of a drug in the aqueous portion and in the portion of the membrane is governed by the partition coefficient of the drug. After entering the membrane, the drug molecules leave the lipid portion of the membrane and dissolve again in the aqueous portion of the membrane, but this time on the other side of the membrane and according to the concentration gradient. Once the drug enters the blood stream, it is now available for elimination. Since, the concentration of drug at the absorption site is almost always greater than its concentration in the blood stream, the concentration gradient always favors absorption. The rate of absorption by passive diffusion is given by the following relationship:

$$\text{Rate of Absorption} = \frac{DAK\Delta C}{h} \qquad (4\text{-}1)$$

In equation (4-1), D = diffusion coefficient of drug, A = surface area of absorbing membrane, K = partition coefficient of the drug, ΔC = concentration gradient and h = thickness of absorbing membrane.

Thus, the rate of drug transport via passive diffusion is directly proportional to diffusion coefficient of the drug, partition coefficient of the drug, surface area of the absorbing membrane, and concentration gradient of the drug. As seen in equation (4-1), the rate of drug transport is

JAYPEE BROTHERS

inversely proportional to the thickness of absorbing membrane. Because transport via passive diffusion is limited to the non-ionized or undissociated species of the drug, therefore, the rate of absorption also depends on dissociation constant of the drug and the pH of the biological fluids on either side of absorbing membrane. Thus, the extent of drug diffusion through the absorbing membrane is a function of the degree or the extent of ionization of the drug. The fraction of drug non-ionized in a given pH environment can be estimated using Henderson-Hasselbalch equation. The equation relating pH, dissociation constant and ratio of ionized to non-ionized species of an acidic drug is given by the following Henderson-Hasselbalch equation:

$$pH = pK_a + \log \frac{[\text{ionized}]}{[\text{non-ionized}]} \quad (4\text{-}2)$$

The corresponding equation for basic drugs is:

$$pH = pK_w - pK_b + \log \frac{[\text{non-ionized}]}{[\text{ionized}]} \quad (4\text{-}3)$$

In these equations, the brackets indicate that concentrations of the ionized and the non-ionized species are expressed in the units of moles per liter, not in the units of milligrams per milliliter, or milligrams per liter, etc. Examples of drugs, which undergo passive diffusion include those drugs that are weak organic acids and weak organic bases, organic non-electrolytes (e.g. alcohol, urea and aminopyrine) and some cardiac glycosides.

Example 4-1 The pK_a of aspirin is 3.5. Calculate fraction of dose available for absorption at pH = 1.0.

Solution

Because aspirin is an acidic drug, equation (4-2) should be used. From equation (4-2)

$$pH = pK_a + \log \frac{[\text{ionized}]}{[\text{non-ionized}]}$$

Substituting the value of pH = 1.0 and pK_a = 3.5 into equation (4-2),

$$1.0 = 3.5 + \log \frac{[\text{ionized}]}{[\text{non-ionized}]}$$

This, upon rearrangement yields the following relationship:

$$\text{Log} \frac{[\text{ionized}]}{[\text{non-ionized}]} = 1.0 - 3.5 = -2.5$$

$$\frac{[\text{ionized}]}{[\text{non-ionized}]} = \text{Inverse log of} -2.5 = -0.00316 = \frac{0.00316}{1}$$

Since the ratio [ionized]:[non-ionized] = 0.00316:1, therefore

$$\text{Percent [ionized]} = \frac{\text{Fraction}[\text{ionized}]}{\text{Fraction}[\text{ionized}] + \text{Fraction}[\text{non-ionized}]} \times 100\%$$

$$\text{Percent [ionized]} = \frac{0.00316}{0.00316 + 1} \times 100\% = 0.32\%$$

Similarly,

$$\text{Percent [non-ionized]} = \frac{\text{Fraction}[\text{non-ionized}]}{\text{Fraction}[\text{ionized}] + \text{Fraction}[\text{non-ionized}]} \times 100\%$$

$$\text{Percent [non-ionized]} = \frac{1}{0.00316 + 1} \times 100\% = 99.68\%$$

$$\text{Fraction available for absorption} = \text{Fraction [non-ionized]} = \frac{99.68\%}{100\%} = 0.9968$$

JAYPEE BROTHERS

Example 4-2 The pK_b of a drug is 6.9. Calculate fraction of dose available for absorption at pH = 7.0.

Solution

Because the drug is a basic drug, equation (4-3) should be used. From equation (4-3)

$$pH = pK_w - pK_b + \log \frac{[\text{non-ionized}]}{[\text{ionized}]}$$

Substituting the value of pH = 7.0 and pK_b = 6.9 into equation (4-3),

$$7.0 = 14 - 6.9 + \log \frac{[\text{non-ionized}]}{[\text{ionized}]}$$

This, upon rearrangement gives

$$\log \frac{[\text{non-ionized}]}{[\text{ionized}]} = 7.0 - 14 + 6.9 = -0.1$$

$$\frac{[\text{non-ionized}]}{[\text{ionized}]} = \text{inverse log}\,(-0.1) = 0.7943 = \frac{0.7943}{1}$$

$$\text{Percent [ionized]} = \frac{\text{Fraction}[\text{ionized}]}{\text{Fraction}[\text{ionized}] + \text{Fraction}[\text{non-ionized}]} \times 100\%$$

$$\text{Percent [ionized]} = \frac{1}{0.7943 + 1} \times 100\% = 55.73\%$$

$$\text{Percent [non-ionized]} = \frac{\text{Fraction}[\text{non-ionized}]}{\text{Fraction}[\text{ionized}] + \text{Fraction}[\text{non-ionized}]} \times 100\%$$

$$\text{Percent [non-ionized]} = \frac{0.7943}{1 + 0.7943} \times 100\% = 44.27\%$$

$$\text{Fraction available for absorption} = \text{Fraction [non-ionized]} = \frac{44.27\%}{100\%} = 0.4427$$

Active Transport

This mechanism utilizes carriers under expenditure of energy, i.e. utilization of adenosine triphosphate (ATP). To be absorbed by active transport, each drug or a group of drugs needs a specific carrier. The carriers are located on the external surface of the membrane and appear to be enzymes or at least proteinaceous materials. The carriers bind to the drug molecules to form a complex and this complex moves across the membrane utilizing energy provided by ATP. Once transported, the drug-carrier complex dissociates, releasing drug molecules and the carrier thus released from the complex returns to the original site of the absorbing membrane to continue the transport process. The binding of carrier and drug molecules follow drug-receptor theory. When more than one drug is present at the site of absorption, the drug, which possesses relatively higher affinity for the carrier can competitively inhibit or displace the drug, which has a relatively lower affinity for the carrier (competitive inhibition). Similarly certain substances, which interfere with cell metabolism (e.g. cyanides, fluorides, etc.) can also non-competitively inhibit active transport of drugs.

Absorption of drug by active transport becomes saturated, if more drug molecules are present than the carriers available for transporting the drug. Since this transport mechanism requires expenditure of energy, it can proceed against a concentration gradient and in the case of ions, against an electrochemical potential. This means that the drug can be transported from regions of low concentration to regions of high concentration. The process of active transport occurs in unidirectional manner across the membrane. In the case of intestines, active transport proceeds from the mucosal side to the serosal side. Some of the important characteristics of absorption by active transport may be summarized as follows:

JAYPEE BROTHERS

a. Transport process shows specificity for a particular type of chemical structure, i.e. a carrier molecule may be highly selective for a specific drug molecule. For example, L-amino acids and monosaccharides are actively absorbed by different carrier systems.
b. Carriers can be poisoned.
c. If two structurally similar substances are transported by the same carrier mechanism, they (the drugs) may compete with each other for adsorption sites on the carrier, i.e. one will competitively inhibit the transport of the other.
d. Carrier can be saturated if the concentration of drug molecules exceeds the number of carriers available for transport.
e. Actively absorbed substances are usually absorbed from a specific site in the gastrointestinal tract, which is located in a limited segment of the small intestine. For example, bile acids are actively absorbed from ileum.

The rate of absorption by active transport can be determined by applying the equation used for Michaelis-Menten kinetics:

$$\text{Rate of drug absorption} = \frac{[C] \times V_{max}}{K_m + [C]} \quad (4\text{-}4)$$

In this equation,

$[C]$ = Concentration of drug available for absorption,
V_{max} = Maximal rate of absorption at high drug concentration and
K_m = Affinity constant of drug for the carrier.

Hence, the rate of drug absorption by active transport depends on three factors. These are:
a. Concentration of drug at the site of absorption
b. Affinity constant of drug for the carrier, and
c. Maximal rate of absorption of drug at high drug concentration.

Because the maximal rate of drug absorption at high drug concentration may be considered constant, therefore, the two factors that govern the rate of drug absorption by active transport are:
i. Concentration of drug at the site of absorption and
ii. Affinity constant of drug for the carrier.

Relationship between K_m and C

The effect of drug concentration and affinity constant of drug on the rate of drug absorption by active transport can be considered based on the following two possibilities:
i. The affinity constant of the drug is much greater than the concentration of drug at the site of absorption and
ii. The concentration of drug at the site of absorption is much greater than the affinity constant of drug for the carrier.

K_m>>>C: (Affinity constant of the drug is greater than the concentration of drug at the site of absorption).

There are two probable situations when the affinity constant of drug for the carrier may be much greater than the concentration of drug at the site of absorption. These are:
i. When a drug is administered at a very low dose providing a relatively low concentration at the site of absorption, and
ii. If the affinity constant of drug for the carrier is inherently much greater than the concentration of drug available at the site of absorption.

When the affinity constant of the drug is much greater than the concentration of drug available at the site of absorption (i.e. when K_m>>>C), the numerical value of the term (K_m + [C]) in the denominator of equation (4-4) approaches a numerical value equal to the numerical value

JAYPEE BROTHERS

Biopharmaceutics & Pharmacokinetics

Emphasizing relevancy of the subject, clarity of presentation and utilizing practice-oriented examples, *Biopharmaceutics and Pharmacokinetics* is the ideal learning tool for students, faculty, and researchers who want to sharpen their skills.

Containing the right blend of mathematics, equations, graphs, and other pertinent information, this book provides a unified perspective that creates greater overall understanding of the subject. Each chapter adheres to an effective problem-solving structure providing sample examples with accompanying solutions and additional practice problems at the end of each chapter. Answers to these problems are provided at the end of the chapters.

With its comprehensive content, efficient size, and reader-friendly format, this book would be a valuable resource for researchers, students, as well as the faculty teaching these courses.



PL Madan PhD is Professor, Department of Pharmaceutical Sciences and Industrial Pharmacy, St John's University, Queens, New York, USA. An alumnus of Birla College, Pilani, he earned his MS and PhD degrees from University of Georgia, USA. Dr Madan started his teaching career at Northeastern University, Boston (USA) and joined St John's University in 1975. He has been teaching Biopharmaceutics and Pharmacokinetics to undergraduate and graduate students since 1973.

Dr Madan has been an invited speaker at many national and international scientific conferences. He has authored more than 150 scientific articles dealing with controlled release, microencapsulation, targeted release, buccal delivery, and non-CFC propellants published in national and international journals. His research group is currently focused on the design and evaluation of controlled- and targeted-release delivery systems. He serves as a reviewer for journals publishing research articles dealing with the science and technology of drug delivery.

Available at all medical book stores
or buy directly from Jaypee Brothers through online shopping
at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Shelving
Recommendations
PHARMACOLOGY,
PHARMACY

ISBN 978-93-5090-851-8