Encyclopedia of Pharmaceutical Technology

Volume 1

Editors
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ENCYCLOPEDIA OF PHARMACEUTICAL TECHNOLOGY

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VOLUME 1

ABSORPTION OF DRUGS TO BIOAVAILABILITY OF DRUGS AND BIOEQUIVALENCE

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VOLUME 1

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PREFACE

The science and technology associated with pharmacy and related biomedical disciplines has progressed enormously over the past twenty five years. Significant advances in the understanding of disease processes, related therapeutics, and an understanding of the need to optimize drug delivery in the body have brought about an increased awareness of the role of the dosage form. In turn, this has resulted in an increased sophistication and level of expertise of the design, development, manufacture, testing and regulation of drugs and dosage forms. Such activitites are embraced by the term "pharmaceutical technology" and so it is both appropriate and timely that an encyclopedia dealing with this area should now start to be published.

When first approached in 1984 by Marcel Dekker to serve as editors to such an undertaking, our initial reaction was mixed. The size of the task and the commitment of time needed were significant. However, the need was obvious and we felt that such an encyclopedia would become a valuable resource to colleagues in the pharmaceutical industry, education, and government. The appearance of this, the first volume in the series, makes the effort to date worthwhile.

Our first activity was to define the scope of the encyclopedia and put together a list of all possible topics. The scope was broadly defined as subjects pertaining to the discovery, development, regulation, manufacturing and commercialization of drugs and dosage forms. It would include disciplines such as pharmaceutics, pharmacokinetics, analytical chemistry, quality assurance, toxicology and manufacturing processes, but would not include detailed sections on, for example, organic chemistry and the pharmacological comparison of drugs.

Once a working alphabetical listing of titles was completed, we began contacting colleagues as potential contributors. Those who participated in the first volume come from the United States or Europe. However, we are conscious that advances and the development of new approaches in pharmaceutical technology are international in nature and we intend to seek contributors accordingly as the work proceeds. In this regard, we anticipate that the full encyclopedia will comprise from 10 to 12 volumes; these are projected to appear at the rate of approximately two volumes per year.

An undertaking of this kind, that extends over multiple volumes and years, requires the active support of many individuals. Rosalind and Allen Kent, as Administrative Editors with Marcel Dekker, Inc. have kept us organized and given us excellent advice and encouragement based on their prior involvement with other encyclopedias published by Marcel Dekker, Inc. The secretarial assistance of Almeda Floyd is gratefully acknowledged, as is our indebtedness to Sandra Beberman and Joseph Cacciottoli at Marcel Dekker, Inc. We must also acknowledge the contributors, without whom this encyclo-

pedia would not materialize. It is their knowledge and the desire to share this with a wider audience that has made this undertaking a reality. Finally, we must thank our wives, Pamela and Carol, for their support and forebearance.

The acceptance of this work will depend on the quality of the contributed articles and the authors. We would welcome any and all comments and criticisms, together with suggestions for topics and contributors.

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Absorption of Drugs

Drugs that have to enter the systemic circulation to exert their therapeutic effect can be administered by two major routes, enteral and parenteral. *Enteral* applies to drugs administered via the gastrointestinal (GI) tract, and *parenteral* applies to drugs given by other routes.

The Membrane

To be absorbed and distributed into organs and tissues, a drug must pass through one or more biologic membranes. Membranes are complex structures that serve many purposes. The GI epithelial lining is a membrane concerned with absorption and secretion. Membranes associated with the blood-brain barrier protect the brain from foreign substances. The membrane of the proximal kidney tubule is concerned with selective drug secretion.

Despite the diversity in membrane functions, there is a general consensus regarding their basic structure. The basic cell membrane is shown in Fig. 1 [1]. The membrane comprises a bimolecular lipid leaflet containing phospholipids, cholesterol, and fatty acid esters oriented with their hydrophobic portions inside and their hydrophilic portions facing the outside aqueous environment. Associated with the lipid molecules are globular protein molecules embedded into or passing through the membrane.

As membranes are lipoidal in nature, fat-soluble compounds tend to cross readily. Weak acids and bases cross membranes more readily when they are un-ionized. Some drugs cross membranes more efficiently than one would predict from their concentration-gradients and fat-solubility measurements, which suggests specialized transport. Specialized transport can be separated into passive facilitated diffusion and active transport. Facilitated diffusion differs from passive diffusion in that it depends on binding to a membrane carrier and is saturable. Active transport is also saturable and utilizes cellular energy for the drug to cross the membrane, even against a concentration gradient.

Active transport is more common than passive facilitated diffusion but does not occur very frequently in drug absorption. Examples of active membrane transport are renal and biliary excretion of some acids and bases and excretion of some acids from the central nervous system.

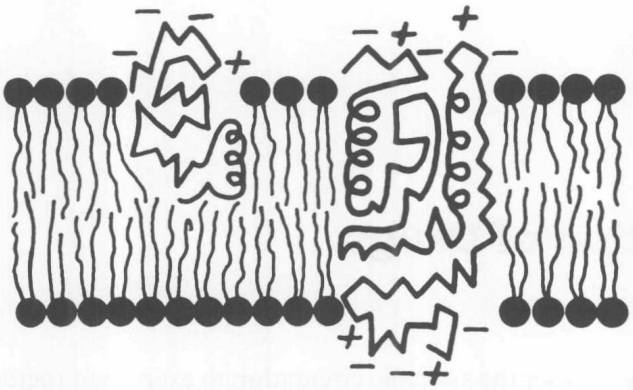

FIG. 1. The lipid-protein model of membrane structure: schematic cross-sectional view. The phospholipids are arranged as a discontinuous bilayer with their ionic and polar heads in contact with water. Proteins are shown as globular molecules partially embedded in, and partially protruding from, the membrane. The protruding parts have on their surfaces the ionic residues (– and +) of the protein, and the nonpolar residues are largely in the embedded parts. The degree to which the integral proteins are embedded and, in particular, whether they span the entire membrane thickness depend on the size and structure of the molecules. Reprinted from Ref. 1, p. 72.

Parenteral Drug Absorption

Parenteral routes of drug administration are generally used only when the oral route is inappropriate, e.g., with drugs that are unstable in the GI tract. Parenteral routes may also be used when prompt drug action is required.

Intravenous Injection

Intravenous administration is used to introduce drugs directly into the circulation. The complete systemic availability of drugs makes this route extremely useful for investigating the absorption efficiency of drugs administered by other routes.

The intravenous bolus route is useful when prompt drug effect is required [2]. A good example is the use of intravenous lidocaine for cardiac arrhythmia. A disadvantage of intravenous administration is that the dose, once injected, cannot be withdrawn. Drugs are generally administered slowly over a period of several minutes to avoid high initial drug levels. Continuous drug therapy may be obtained by intravenous drip or an infusion pump.

Intramuscular Injection

Intramuscular injection may also be used for drugs not absorbed orally. Drugs given intramuscularly include the aminoglycosides, insulin, and mephentermine. Most compounds are reliably absorbed from intramuscular doses. However, slow or

incomplete absorption from intramuscular sites has been reported for a number of compounds, including chlordiazepoxide, diazepam, digoxin, phenobarbital, and promethazine. Factors that may be responsible for this include degradation of the drug in muscle tissue and slow absorption of a portion of the injected material, which yields low and possibly undetectable blood levels after the bulk of the drug has been absorbed. Drugs may also precipitate out at the injection site, producing slow absorption.

Absorption of lipophilic compounds is generally independent of molecular size, but absorption of water-soluble drugs is inversely related to molecular size. Small water-soluble molecules are absorbed into the circulation via the capillaries at the injection site. Larger molecules enter the circulatory system indirectly via the lymphatics. Blood flow through muscular tissue varies from approximately 0.02 to 0.07 ml/min per gram of muscle tissue. The higher the flow rate, the faster the drug is cleared from the injection site. The absorption rate of lente insulin has been shown to be faster from arm muscle than from thigh muscle, probably because of the greater vascular perfusion and smaller mass of arm muscle.

Drug absorption from intramuscular injections may be influenced by the type of solvent. Drugs with low aqueous solubility can be dissolved in nonaqueous vehicles such as sesame or other suitable unsaturated oils. Drugs administered in oily vehicles may precipitate at the injection site to cause slow absorption. Small injection volumes generally result in faster absorption than large volumes.

The intramuscular site is ideal for sustained or controlled drug release. Sustained release from intramuscularly implanted devices has recently been reviewed by Chien [3]. Vehicles for intramuscular sustained drug release include aqueous suspensions, oily formulations in which drug release is controlled by partitioning between the vehicle and the surrounding medium, and complex formation with materials such as methylcellulose or polyvinylpyrrolidone.

Other methods currently being investigated for sustained drug release from intramuscular injections are the use of biodegradable polymers, such as polylactic acid, and microencapsulation.

Absorption Via the Skin

The skin is generally considered to be a barrier to most substances [4]. However, absorption of drug substances through the skin can be very effective. As indicated in Fig. 2, there are three major regions in the skin: the epidermis, dermis, and subcutaneous tissue. Major resistance to drug penetration is provided by the outer horny layer of the epithelium, the stratum corneum. If this region is intact, penetration of the drug into the body via the skin is usually slow. If this region is disrupted, by burns or other injury, permeability is increased.

Drugs penetrate the epidermis by the transepidermal route, in which compounds pass through or between epidermal cells, and the transappendageal route, e.g., hair follicles or sebaceous glands. Although the appendageal route is probably more efficient, the transepidermal route is more important because of the small percentage of skin surface made up of hair follicles and sweat glands.

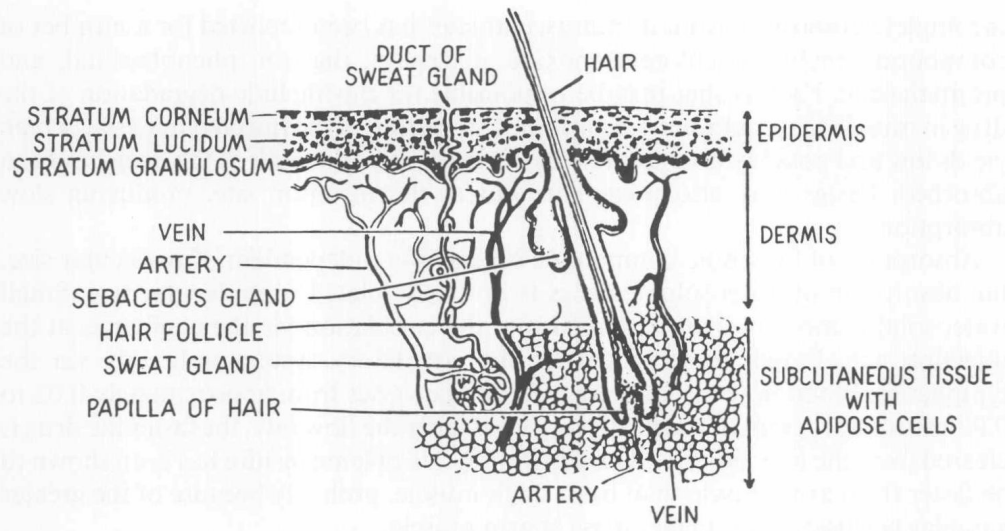

FIG. 2. Cross-section through human skin.

Subcutaneous Injection

Subcutaneous injection bypasses the epidermis and dermis and generally ensures efficient systemic drug absorption. Compounds given this way include insulin, local anesthetics, and vaccines.

Because of the lower capillary density in subcutaneous connective tissue compared with intramuscular tissue, absorption is slower by this route but is increased by rubbing and by exercise [5,6]. The effect that exercise may have on insulin absorption is indicated in Fig. 3.

The use of subcutaneous implants and similar techniques is a rapidly expanding area for sustained-release medication. Commercial implants are available for steroid hormones, gold salts, and sulfonamides.

Intradermal Injection

Intradermal injections are generally intended for local effect, but this route also has potential for systemic activity, particularly for vaccines. For example, an intradermal injection of 0.1 ml of an Asian influenza vaccine produces an effect comparable to a l-ml subcutaneous injection of the same vaccine [7]. The intradermal route may cause less irritation than the subcutaneous route.

Percutaneous Absorption

Percutaneous absorption occurs when a drug is administered to the skin surface. The drug has to cross the entire skin thickness, including the stratum corneum, before it reaches the systemic circulation. However, if a suitable compound can be retained at the skin surface for a sufficiently long period of time, and the skin is kept in a

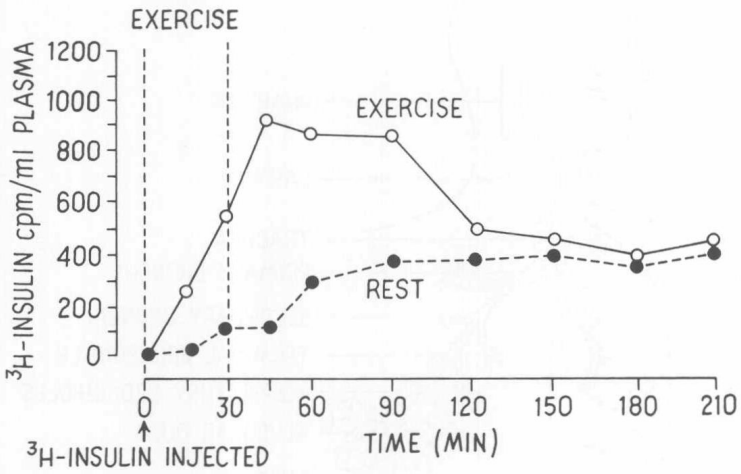

FIG. 3. Effect of exercise on plasma concentrations of intact ^{3}H-insulin following subcutaneous injection of ^{3}H-insulin into the leg of a juvenile patient. Reprinted from Ref. 5, p. 53.

hydrated condition, percutaneous absorption may be quite efficient. Percutaneous administration for systemic effect is suitable only for drugs given in very small doses.

Percutaneous absorption is used for sustained-release dosage forms of antianginal agents such as nitroglycerin. Slow absorption of the drug, partly as a result of slow release from the topical device, gives rise to low circulating drug concentrations that may provide prophylaxis against angina. The percutaneous route has considerable potential for controlled drug release, and much more will be heard of this route of administration.

Inhalation

When a substance is inhaled, it is exposed to membranes of the mouth or nose, pharynx, trachea, bronchi, bronchioles, alveolar sacs, and alveoli [8]. These membranes, illustrated in Fig. 4, comprise a large absorptive surface area. Drugs may be inhaled as gases or aerosols. Examples of the former are the general anesthetics ether and chloroform. The alveolar-capillary membrane offers no significant resistance to gases, and absorption is very rapid.

Drugs in aerosols are usually suspended in a liquid propellant system. Upon inhalation, the drug may deposit in different regions of the respiratory tree. Particles larger than 10 μ deposit almost entirely in the nasopharyngeal region, while smaller particles penetrate deeper into the respiratory tree. The sedimentation rate is related to particle density and size. Thus, both impaction and sedimentation tend to remove heavier, larger particles in the upper respiratory tract. Smaller particles penetrate deeper and are more efficiently absorbed.

Inhalation aerosols are used primarily for local effect, e.g., metaproterenol in acute asthma, and to a lesser extent for systemic effects, e.g., some antibiotics and corticosteroids.

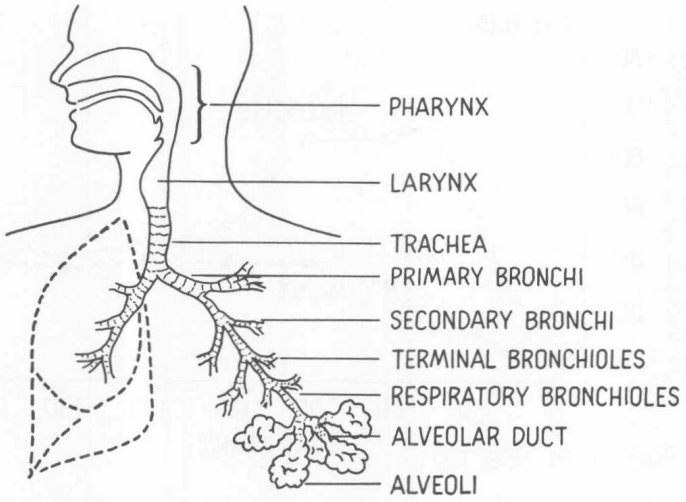

FIG. 4. Bronchial tree.

Intraarterial Administration

Intraarterial injection is used predominantly for delivery of drugs to specific organs or tissues. Intraarterial injection increases drug delivery to the organs or tissues supplied by the artery and reduces access, at least initially, to the systemic circulation.

Intraarterial administration is limited by its potential dangers. Complications such as embolization and local drug toxicity are common, and care is necessary when using this route of administration.

Intrathecal Injection

Intrathecal administration is the term used when a drug is injected directly into the cerebrospinal fluid to ensure complete drug availability to the central nervous system. It is useful for the treatment of central nervous system infections such as meningitis. Intrathecal injection is used also for spinal anesthesia with agents such as mepivacaine and prilocaine and for the treatment of brain tumors [9].

Intrathecally administered drugs are generally injected directly into the lumbar spinal subarachnoid space or into the ventricles. The site of injection can markedly affect penetration of the drugs into different regions of the central nervous system.

Intraperitoneal Administration

The *peritoneal cavity* is that part of the body that contains the viscera. The cavity is lined by the peritoneal membrane. This membrane provides an efficient absorbing surface. Compounds introduced into the peritoneal cavity are often absorbed quite efficiently into the circulation.

Intraperitoneal drug dosage is not common. It has been used to treat tumors that have extensive peritoneal involvement, e.g., cancer of the stomach and colon. If the peritoneal permeability of drugs is slower than their plasma clearance, intraperitoneal dosing may lead to substantially higher drug concentrations in the peritoneal cavity than in plasma.

A novel aspect of intraperitoneal drug administration has developed recently with the introduction of continuous ambulatory peritoneal dialysis (CAPD) for patients with renal impairment [10,11]. Peritoneal dialysis is not as efficient as hemodialysis, but because of its continuous nature it works well. A disadvantage of self-administered CAPD is the occurrence of peritonitis. CAPD-induced peritonitis is often associated with positive blood cultures, so that it is important to achieve therapeutic antibiotic levels in the systemic circulation and the peritoneal cavity.

In cases of peritonitis, drugs may be given orally or by vascular injection to achieve adequate plasma levels in the hope that adequate levels are achieved in the peritoneal cavity. Alternatively, drugs may be administered into the peritoneal cavity in the hope that sufficient drug diffuses across the peritoneum to produce adequate systemic levels.

Vaginal Administration

The vaginal dosage route is used mostly for local effect. However, vaginal administration may provide rapid and complete systemic absorption, hence the vaginal controlled-release contraceptives. An example of vaginal drug absorption is given in Fig. 5, which shows plasma levels of estrone and estradiol following oral and vaginal doses of conjugated equine estrogens [12]. Levels of both estradiol and estrone are much higher following the vaginal dose than after the oral dose.

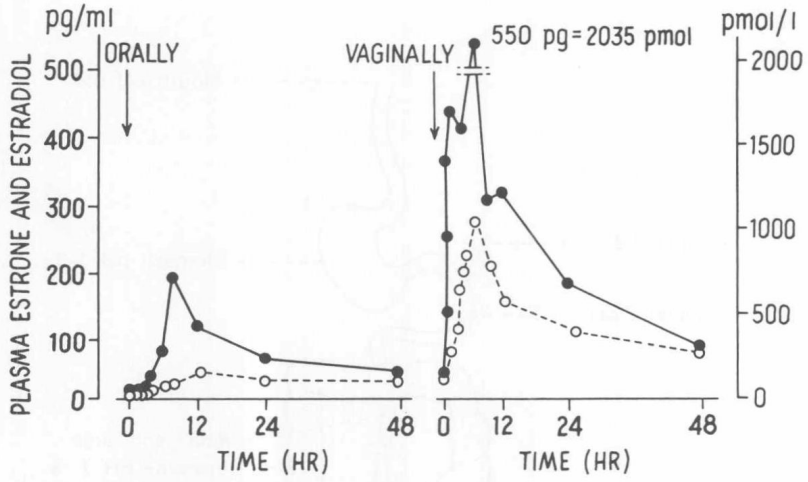

FIG. 5. Plasma estrone (—) and estradiol (--) concentrations following 1.25-mg oral and vaginal doses of conjugated equine estrogens in a 53-year-old woman. Reprinted from Ref. 12, p. 547.