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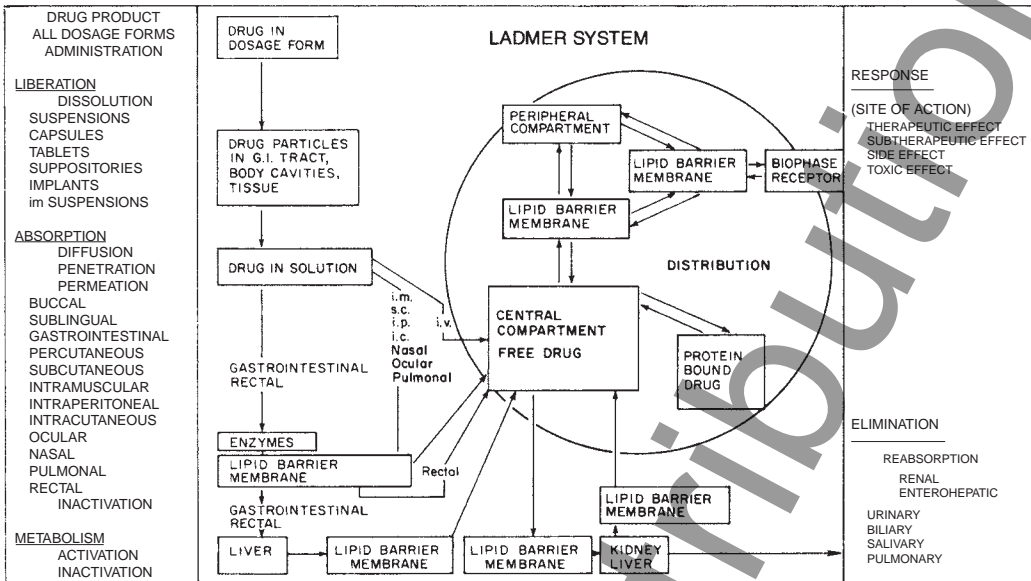
# The LADMER System

## Liberation, Absorption, Distribution, Metabolism, Elimination, and Response

In the relationship between dose and effectiveness, or dose–response, not only the amount of drug administered and the pharmacologic effect of the drug are of importance; many other factors are responsible for the entrance of a drug into the body. These factors are based on the physical and chemical properties of the drug substance and of the drug product. What happens to the active ingredient in the body after administration of a drug product in its various dosage forms? This entire cycle of processes is termed *fate of drugs*. Whether a blood-level curve will reach its peak rapidly or slowly depends on the route of administration; the dosage form; the liberation rate of the drug from the dosage form; diffusion, penetration, and permeation of the drug; its distribution within the body fluids and tissues; the type, amount, and rate of biotransformation; recycling processes; and elimination. Other factors are also involved, depending on the individual disposition, diseases, and so on.

The fate of drugs is described in the leading literature on biopharmaceutics and pharmacokinetics by the LADMER system, showing that liberation, absorption, distribution, metabolism, and elimination are involved to elicit the response. Liberation is the first step in determining onset of action, rate of absorption, availability, and so on. This is true for all drug products by all routes of administration, except intravenous (IV) and the peroral use of true solutions. Liberation is controlled by the characteristics of the drug product.

Figure 2-1 presents a schematic diagram of the LADMER system. On the sides of the diagram (underlined) are the five processes: liberation, absorption, metabolism, elimination, and response. A drug administered in a dosage form by any route of administration must be released from the dosage form (except IV, and true solutions for other routes). In order for a drug to be absorbed, it must be present in the form of solution; therefore, dissolution becomes the first and sometimes rate-limiting step. Upon administration of suspensions, capsules, tablets, suppositories, implants, and intramuscular (IM) suspensions, we find drug particles in the gastrointestinal (GI) tract, in body cavities, or in tissue. After dissolution, the drug diffuses to the site of absorption (e.g., buccal, sublingual, gastrointestinal, percutaneous, subcutaneous, intramuscular, intraperitoneal, intracutaneous, ocular, nasal, pulmonary, rectal). Some of the drug will already be inactivated before it can be absorbed. Only drugs administered intravenously in solution enter the circulatory system immediately. With all



**Figure 2-1.** Diagram of LADMER system showing the complex interrelationships among drug, drug product, and body.

other routes of administration, the drugs must pass membranes that act as lipid barriers. Different transport mechanisms are employed to penetrate into and to permeate through these membranes. Most of the drugs are absorbed or transported by passive diffusion, which depends on the  $pK_a$  value of the drug, the pH of the solution, and the lipid solubility of the unionized form.

Drugs passing through the lipid barrier may directly enter the central compartment, i.e., after intramuscular, subcutaneous, intraperitoneal, intracutaneous, nasal, ocular, and pulmonic, and, partly, after rectal administration. Drugs administered orally and some of the drugs administered rectally are confronted with enzymes as they pass through the liver with the blood flow. In the liver, the main place of metabolism, some drugs are inactivated and metabolized during the first pass; other drugs are activated here. Most drugs are at least partially bound to protein in the bloodstream. Only the free, unbound form of the drug is available for action. The protein-bound fraction is not permanently trapped but is in equilibrium and will be released from the protein as the free drug is eliminated from the plasma.

The drug may enter the peripheral compartment by again passing a lipid barrier until it finally reaches the biophase (process of distribution, characterized by the circle in Figure 2-1). This is a cell, or even a cell component, where the final interaction between drug and receptor takes place. After release of the drug from its receptor binding, the drug again passes through a lipid barrier and enters the central compartment, from which the drug, by again passing a lipid barrier, is metabolized in the liver or kidney or in the tissue or plasma. It then either passes via biliary excretion into the intestines or passes through the kidney, where it will be either reabsorbed or finally excreted into urine. Elimination is not only by urinary and biliary means but also through the salivary glands, the milk glands, the sweat glands, and the lungs. Reabsorption takes place not only in the kidney by tubular

reabsorption but also in the intestine after enterohepatic cycling if the drug or its metabolite is in absorbable form. All these factors are involved in determining whether the drug administered will produce a therapeutic effect, yield only a subtherapeutic effect, or even show toxic effects.

Knowledge and understanding of the LADMER system enable the scientist to design a drug product controlling these factors. Onset of action, intensity of effect, and duration of effect are controllable. The sum of all these phenomena is the quantitative characteristic of a drug product's effect.

For most drug products, a relatively rapid and quantitative absorption and a slow elimination are required in order to maintain a therapeutic drug concentration for a long period of time. In some cases this goal may easily be achieved: if the drug is soluble and highly unionized, is absorbed by passive diffusion, and has a long elimination half-life. If this is not the case, many manipulations are necessary to create a drug product with the desired characteristics.

The LADMER system is key to the following tasks:

- Development of new active compounds, analogs, or derivatives;
- Development of dosage forms with desired release characteristics;
- Determination of pharmacokinetic parameters and pharmacokinetic drug product profiles;
- Determination and evaluation of bioavailability;
- Selection of the most appropriate route of administration;
- Determination of effective dose sizes; and
- Adjustment of dosage regimen to achieve a desired therapeutic concentration of drug in the body based on physiologic (e.g., body weight, age, sex) and pathologic (e.g., renal, hepatic, or heart failure; obesity; malnutrition) factors.