where

C_1 and C_2 are the drug concentrations on each side of the membrane and

P is a permeability coefficient or constant.

The term C_1 is customarily used to represent the compartment with the greater concentration of drug, and thus the transport of drug proceeds from compartment 1 (e.g., absorption site) to compartment 2 (e.g., blood).

The concentration of drug at the site of absorption (C_1) is usually much greater than on the other side of the membrane because of the rapid dilution of the drug in the blood and its subsequent distribution to the tissues, so for practical purposes, the value of $C_1 - C_2$ may be taken simply as that of C_1 and the equation written in the standard form for a first-order rate equation:

$$-\frac{dc}{dt} = PC_1$$

The gastrointestinal absorption of most drugs from solution occurs in this manner in accordance with *first-order kinetics*, in which the rate depends on drug concentration; that is, doubling the dose doubles the transfer rate. The magnitude of the permeability constant depends on the diffusion coefficient of the drug, the thickness and area of the absorbing membrane, and the permeability of the membrane to the particular drug.

Because of the lipoid nature of the cell membrane, it is highly permeable to lipid-soluble substances. The rate of diffusion of a drug across the membrane depends not only on its concentration but also on the relative extent of its affinity for lipid and rejection of water (a high lipid partition coefficient). The greater its affinity for lipid and the more hydrophobic it is, the faster will be its rate of penetration into the lipid-rich membrane. Erythromycin base, for example, possesses a higher partition coefficient than other erythromycin compounds, for example, estolate and gluceptate. Consequently, the base is the preferred agent for the topical treatment of acne where penetration into the skin is desired.

Because biologic cells are also permeated by water and lipid-insoluble substances, it is thought that the membrane also contains water-filled pores or channels that permit the passage of these types of substances. As water passes in bulk across a porous membrane, any dissolved solute with small enough molecules to traverse the pores passes in by *filtration*. Aqueous pores vary in size from membrane to membrane and thus in their individual permeability characteristics for certain drugs and other substances.

Most drugs today are weak organic acids or bases. Knowledge of their individual ionization or dissociation characteristics is important, because their absorption is governed to a large extent by their degrees of ionization as they are presented to the membrane barriers. Cell membranes are more permeable to the un-ionized forms of drugs than to their ionized forms, mainly because of the greater lipid solubility of the un-ionized forms and the highly charged nature of the cell membrane, which results in binding or repelling of the ionized drug and thereby decreases cell penetration. Also, ions become hydrated through association with water molecules, resulting in larger particles than the undissociated molecule and again decreased penetrating capability.

The degree of a drug's ionization depends both on the pH of the solution in which it is presented to the biologic membrane and on the pK_a, or dissociation constant, of the drug (whether an acid or base). The concept of pK_a is derived from the Henderson-Hasselbalch equation.

For an acid,

$$pH = pK_a + \log \frac{\text{ionized conc.(salt)}}{\text{un-ionized conc.(acid)}}$$

For a base,

$$pH = pK_a + \log \frac{\text{un-ionized conc.(base)}}{\text{ionized conc.(acid)}}$$

Because the pH of body fluids varies (stomach, pH 1; lumen of the intestine, pH 6.6; blood plasma, pH 7.4), the absorption of a drug from various body fluids will differ and may dictate to some extent the type of dosage form and the route of administration preferred for a given drug.