or at a low rate and low level if the drug is not readily absorbed from its route of entry. The pH of the drug's current environment influences the rate and degree of its further distribution because under one condition of pH it becomes more or less un-ionized and therefore more or less lipid penetrating than under another. If an un-ionized molecule is able to diffuse through the lipid barrier and remain un-ionized in the new environment, it may return to its former location or go on to a new one. However, if in the new environment it is greatly ionized because of the influence of the pH of the second fluid, it likely will be unable to cross the membrane with its former ability. Thus, a concentration gradient of a drug usually is reached at equilibrium on each side of a membrane because different degrees of ionization occur on each side. A summary of the concepts of dissociation and ionization is found in Physical Pharmacy Capsules 4.8 and 4.10.

It is often desirable for pharmaceutical scientists to make structural modifications in organic drugs and thereby favorably alter their lipid solubility, partition coefficients, and dissociation constants while maintaining the same basic pharmacologic activity. These efforts frequently result in increased absorption, better therapeutic response, and lower dosage.

Specialized Transport Mechanisms

In contrast to the passive transfer of drugs and other substances across a biologic membrane, certain substances, including some drugs and biologic metabolites, are conducted across a membrane through one of several postulated *specialized transport* mechanisms. This type of transfer seems to account for substances, many naturally occurring as amino acids and glucose, that are too lipid insoluble to dissolve in the boundary and too large to flow or filter through the pores. This type of transport is thought to involve membrane components that may be enzymes or some other type of agent capable of forming a complex with the drug (or other agent) at the surface membrane. The complex moves across the membrane,

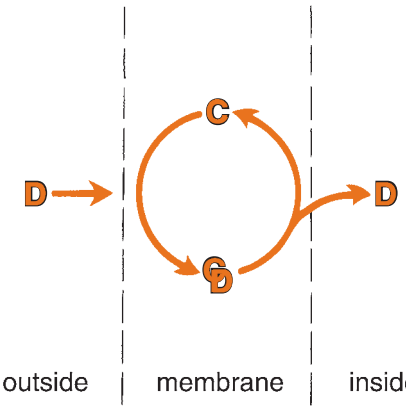

FIGURE 5.2 Active transport mechanism. D, drug molecule; C, the carrier in the membrane. (Adapted with permission from O'reilly WJ. Biological Factors in Dosage Design I: Membranes and Drug Absorption. Aust J Pharm 1966;47(Supp 42):S51.)

where the drug is released, with the carrier returning to the original surface. Figure 5.2 presents the simplified scheme of this process. Specialized transport may be differentiated from passive transfer in that the former process may become saturated as the amount of carrier for a given substance becomes completely bound with that substance, resulting in a delay in transport. Other features of specialized transport include the specificity by a carrier for a particular type of chemical structure, so that if two substances are transported by the same mechanism or carrier, one will competitively inhibit the transport of the other. Furthermore, the transport mechanism is inhibited in general by substances that interfere with cell metabolism. The term *active transport* as a subclassification of specialized transport denotes a process with the additional feature of the solute or drug being moved across the membrane against a concentration gradient, that is, from a solution of lower concentration to one of a higher concentration, or if the solute is an ion, against an electrochemical potential gradient. In contrast to active transport, *facilitated diffusion* is a specialized transport mechanism having all of the described characteristics except that the solute is not transferred against a concentration gradient and may attain the same concentration inside the cell as on the outside.