(b) Electrochemical Diffusion

The diffusion of uncharged molecules is called as *nonionic* diffusion, whereas diffusion of ionic molecules as a function of potential difference or electrical gradient across the membrane is termed as *electrical or ionic diffusion*. The ionic drugs cross the membrane much more slowly than do lipid soluble, uncharged molecules. Nevertheless, ionic drugs demonstrate significant absorption. Membrane is positively charged on the outside surface whereas intracellular surface is negatively charged. Due to repulsion between similarly charged molecules, the cationic drugs exhibit electrostatic repulsion on the outside surface of the membrane and only molecules with a high kinetic energy can cross the barrier. Inside the membrane, cationic drugs interact with negatively charged intracellular membrane, creating the electrical gradient, in turn causing *electrical diffusion*. An *electrochemical diffusion* is the function of both electrical field and the concentration difference across the membrane. This process continues until equilibrium is attained.

(c) Ion-pair Transport

The zwitterionic drugs ionize over the entire pH range of the GI tract, e.g. ampicillin, amoxicillin, tetracycline. As discussed above, smaller ionic drug can travel through water-filled pores. However, zwitterionic drugs are too large to pass through the water-filled pores and are too lipid insoluble to partition through lipoidal membrane. Such drugs cross the membrane by forming ion-pair with endogenous ions of the GI tract. The charge is utilized to form ion-pair and the resulting molecule gets partitioned into the lipoidal membrane. Though these drugs are ionic, they show passive absorption and exhibit maximum partition coefficient when the net charge on the molecule is at its minimum.

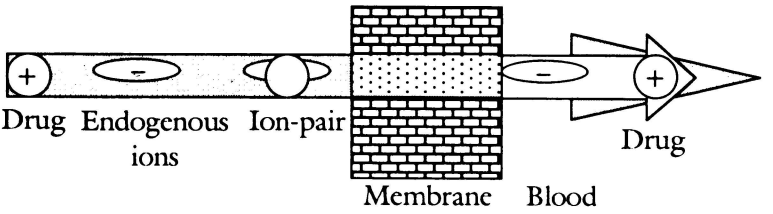

Fig. 1.4. Ion pair transport of cationic drug

5. Protein Binding

Free drug concentration in body is responsible for pharmacodynamic properties of drug. The drug bound to proteins in blood (plasma), membranes or tissue is difficult to diffuse, absorb, reach to the site of action and interact with receptors. The rate of biotransformation and elimination are also decreased because of protein binding. Albumin is the main component, which binds to a wide variety of drugs. The protein binding is usually reversible and it releases drug from the protein until drug in the extravascular water equilibrates with free drug in the plasma. Binding may be competitive where one drug displaces another drug e.g. aspirin displaces penicillin. Infants and adults show difference in plasma protein binding and tissue binding of drugs, e.g. local anesthetics, sulfaphenazole.

6. Presystemic Metabolism

Liver is the primary site of drug metabolism. In addition, presystemic metabolism of drug can occur in GI tract or in membrane. Reduction in amount of absorbed dose by biotransformation of drug in liver before its entry into blood circulation is termed as *first pass metabolism*. After oral administration of drug, almost entire absorbed dose is exposed to the liver. If a drug is subject to rapid metabolism in liver, then a reduced absorbed dose reaches in blood circulation. For some drugs bioavailability may be reduced to such an extent so as to render the GI route of administration ineffective. The examples include alprenolol, imipramine, lignocaine, pethidine, phenacitin, and propranolol.

7. Circadian Rhythm

The functions of body including body secretions and pharmacokinetics display its own time schedule per day and over entire life period; this is called as *circadian cycle*. Diseases such as bronchitis, ischemic heart attacks, rheumatoid arthritis, and allergic rhinitis display circadian dependent symptoms in early morning hours. Acidity gradually increases from 4 pm and it is maximum at mid night. Patients suffering from sleeping disorder need second dose of sedatives at around 2 am.

NSAID, theophylline, nifedipine, oral nitrates, and propranolol have been reported to have higher C_{max} and shorter t_{max} when administered in the morning than evening. It was correlated with the

exists in unionized form, which has better absorption. When drug enters in blood it exists almost entirely in an ionized form.

For bases

(*i*) $$\log [BH^+]/[B] = pK_a - pH$$
$$= 8 - 1.2 = 6.8$$

Therefore,

$$\log [BH^+]/[B] = \text{antilog } (6.8) = 6.31 \times 10^6$$

(*ii*) $$\log [BH^+]/[B] = pK_a - pH$$
$$8 - 7.4 = 0.6$$

Therefore,

$$\log[BH^+]/[B] = \text{antilog } (0.6) = 3.981$$

It indicates that majority of drug remains in ionized state in gastric fluid.

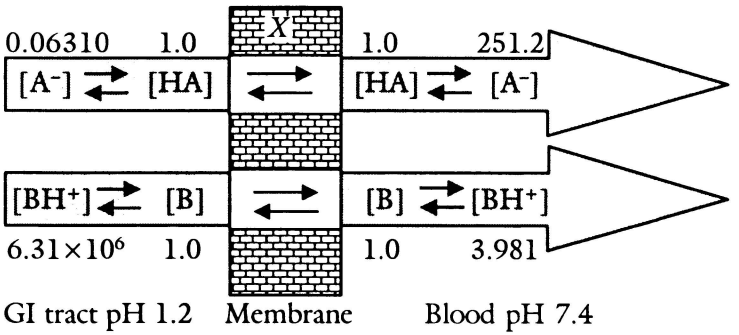

Fig. 1.10. pH- partition hypothesis

Limitations of pH-partition Theory

1. The pH-partition theory is based on assumption of attainment of equilibrium distribution between unionized and ionized forms of a drug. However, due to blood circulation the drug is continuously swept away maintaining *sink condition*. Therefore, it is the biggest failing of this hypothesis to calculate absorption from equilibrium distribution.
2. The hypothesis is more suitable in describing absorption of weak acids and weak bases.
3. The ionization of drug in the lumen is similar to that in the blood and little ion trapping occurs.

The order of dissolution of various crystal forms is:

Amorphous > metastable/anhydrous > stable

Therefore, the rate of conversion of soluble form to the less soluble form should be monitored during processing and storage of the dosage form.

7. **Solid Dispersion:** Solid dispersions are dispersion of one or more drug(s) in an inert carrier to produce solid-state molecular dispersion. It is prepared by various techniques such as solvent evaporation, fusion or combination of these. The carriers employed include, polyethylene glycol (PEG), polyvinyl pyrrolidone (PVP), citric acid and urea. The increased dissolution rate of solid dispersion is attributed to formation of molecular dispersion of the drug. The various observations are as follows:

   (*i*) A solid dispersion containing highly energetic forms of the drug possess higher dissolution rates, e.g. griseofulvin-PVP dispersion.

   (*ii*) The presence of amorphous form and metastable polymorphs can increase the dissolution rates, e.g. lack of crystalline structure increases dissolution rates of sulphathiazole-PVP dispersion; formation of indomethacin II, a metastable polymorph in dispersion with PEG 6000 by fusion method.

   (*iii*) The increased wettability, e.g. use of bile salts such as cholic acid, cholesteryl esters.

   (*iv*) Increase in aqueous solubility due to microenvironmental solubilization of drug in the gastric fluid layer surrounding the dissolving dispersion, e.g. paracetamol-urea.

   (*v*) Formation and liberation of colloidal particles or crystals from the dispersion, e.g. b-carotene -PVP.

(C) Pharmaceutical Factors

1. Additives

Dosage form is a blend of the drug component with non-drug components produced in definite physical shape, which is convenient to administer by particular route of administration. Additives are added in dosage forms for a particular function, viz. to make bulk (diluent, filler, vehicle, base), physical stabilizer (co-solvent, wetting agent, suspending agent, emulsifying agent), chemical stabilizer