The pH-partition hypothesis

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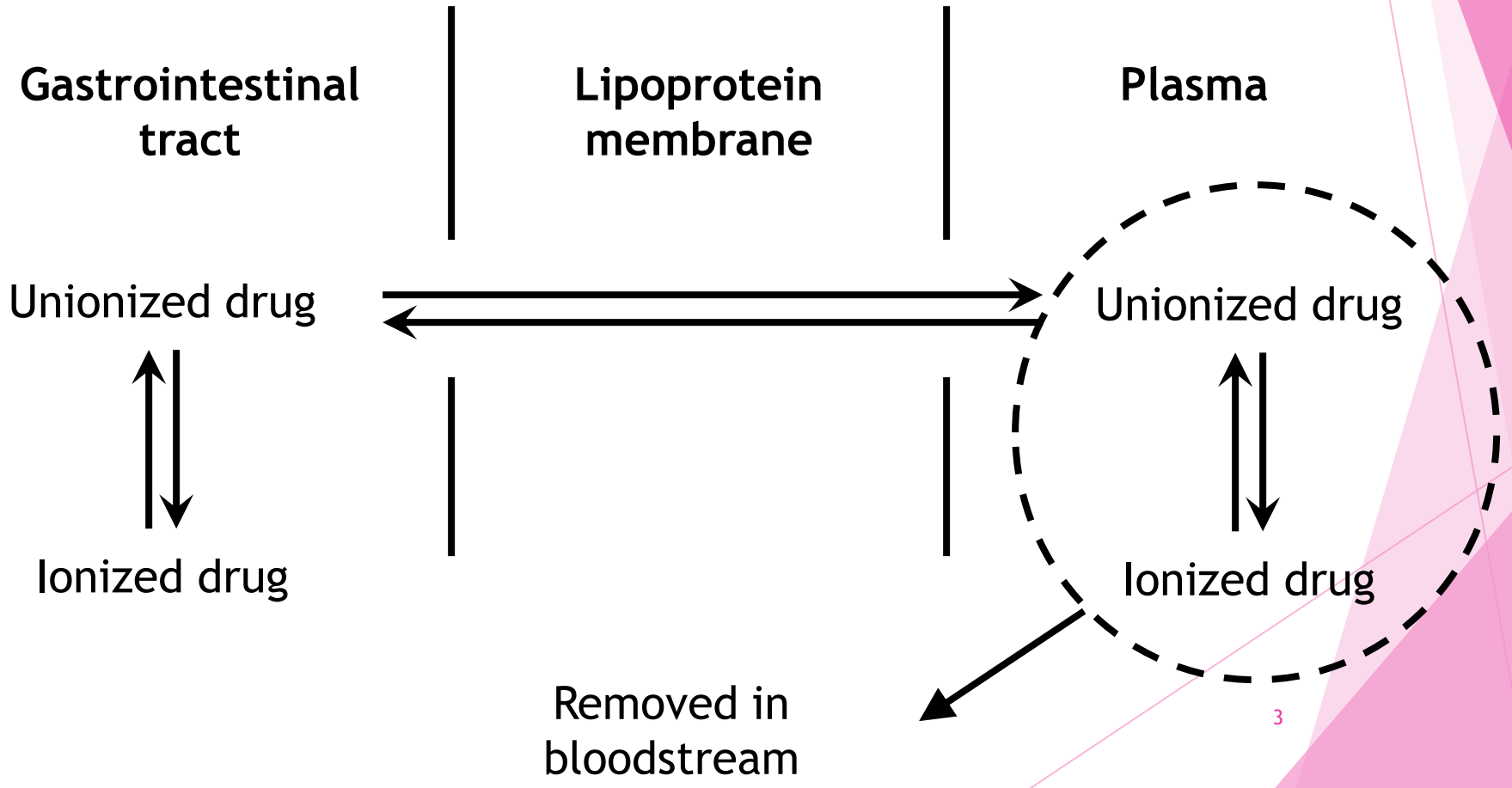
pH-partition hypothesis of drug absorption

- According to the pH-partition hypothesis, the gastrointestinal epithelia acts as a lipid barrier towards drugs which are absorbed by passive diffusion, and those that are lipid soluble will pass across the barrier.
- As most drugs are weak electrolytes, the unionized form of weakly acidic or basic drugs (i.e. the lipid-soluble form) will pass across the gastrointestinal epithelia, whereas the gastrointestinal epithelia is impermeable to the ionized (i.e. poorly lipid-soluble) form of such drugs.
- Consequently, according to the pH-partition hypothesis, the absorption of a weak electrolyte will be determined chiefly by the extent to which the drug exists in its unionized form at the site of absorption

pH-partition hypothesis of drug absorption



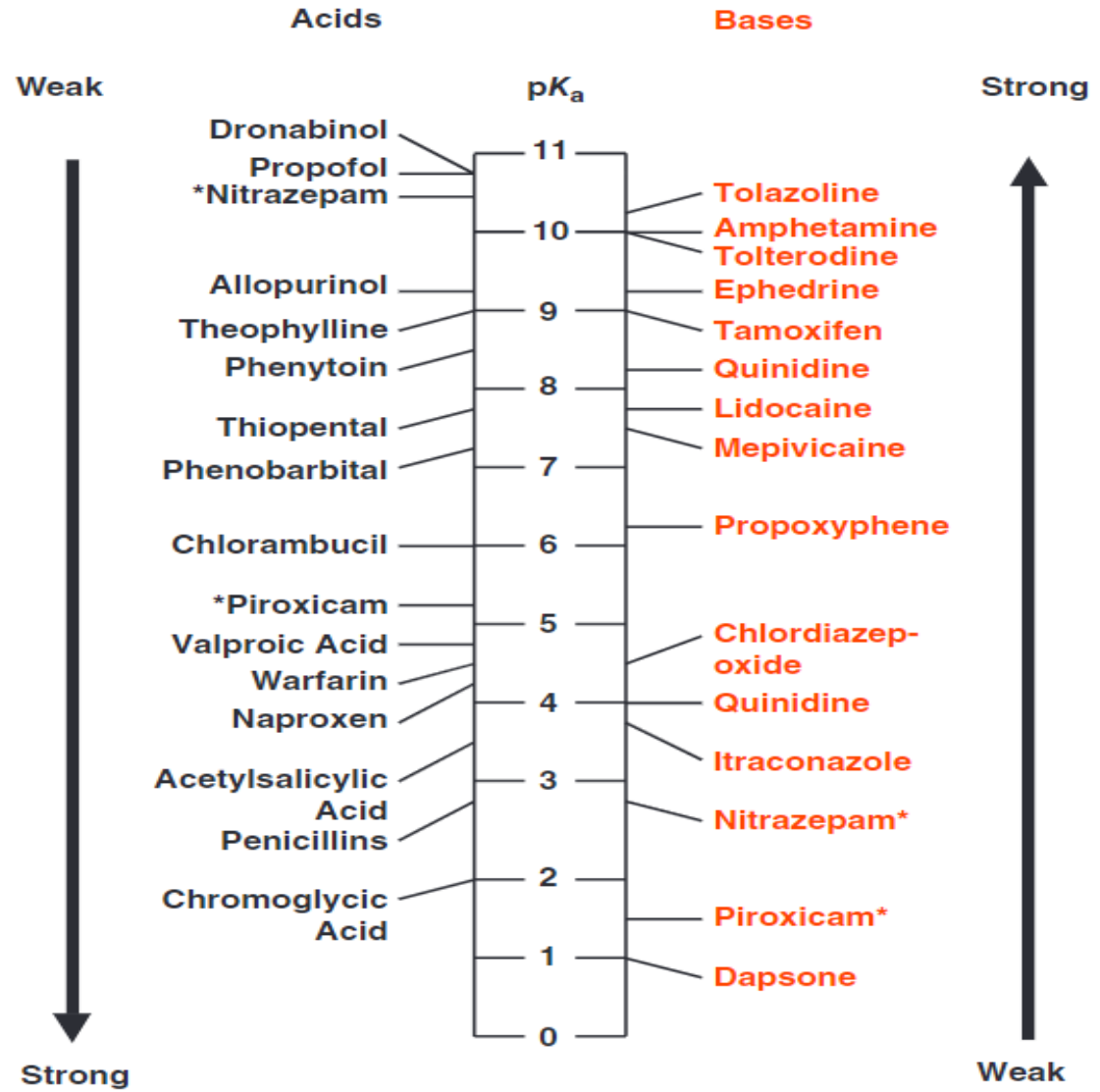


FIGURE C–1 The pK_a values of acidic and basic drugs vary widely. Drugs marked with an asterisk are amphoteric; they have both acidic and basic functional groups.

pH-partition hypothesis of drug absorption

- The extent to which a weakly acidic or basic drug ionizes in solution in the gastrointestinal fluid may be calculated using the appropriate form of the Henderson-Hasselbalch equation

- For a weakly acidic drug having a single ionizable group (e.g. aspirin, phenylbutazone, salicylic acid) the equation takes the form of:

$$HA \rightleftarrows H^+ + A^-$$

$$pH - pK_a = \log \frac{[A^-]}{[HA]}$$

pH-partition hypothesis of drug absorption

- For a weakly basic drug possessing a single ionizable group (e.g. chlorpromazine) the analogous equation is:

$$B + H^+ \rightleftarrows BH^+$$

$$pH - pK_{a=} \log \frac{[B]}{[BH^+]}$$

pH-partition hypothesis of drug absorption

- For weak acids (with a pKa in the range 2.5–7.5), the unionized form of a weak acid predominates when the pH is lower than the pKa. Thus, weak acids will be predominantly unionized in the stomach, which favors their absorption in this region.
- In contrast, a very low percentage is unionized in the small intestine, which suggests unfavorable absorption for weak acids in this region.

pH-partition hypothesis of drug absorption

- For weak bases the reverse is true: when the pH is lower than the pKa, the ionized form predominates. Thus, weak bases are poorly absorbed, if at all, in the stomach since they are largely ionized at low pH, but they are well absorbed in the small intestine, where they are unionized.
- Strong acids (pKa<2.5), such as cromoglycate, as well as strong bases (pKa>11), such as mecamylamine, are ionized throughout the GI tract and are therefore poorly absorbed.
- Very weak acids and very weak bases are predominantly in the unionized form throughout the GIT.

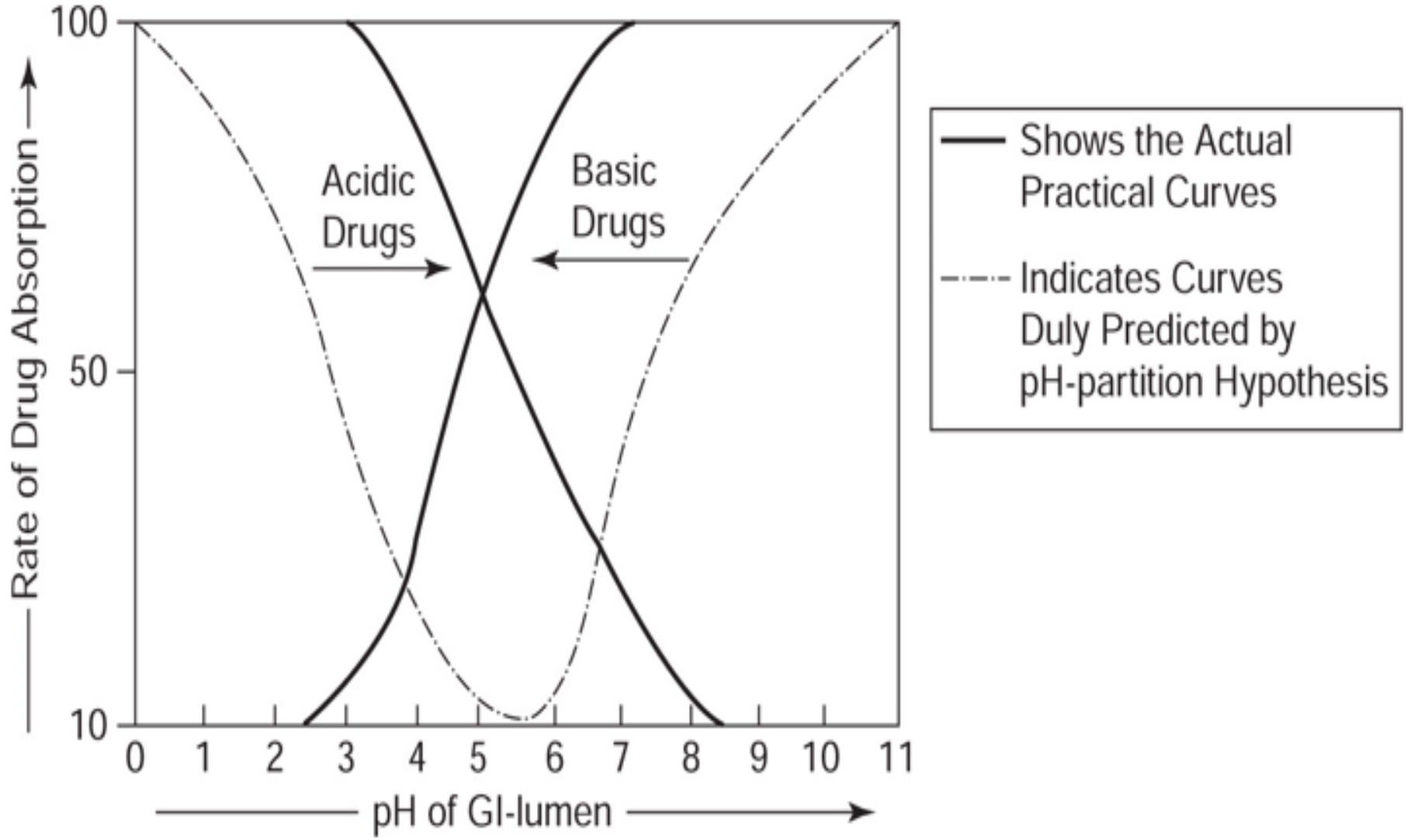
pH-partition hypothesis of drug absorption

- So a weakly acidic drug, with pKa 3.0, will be predominantly unionized in gastric fluid at pH 1.2 (98.4%) and almost totally ionized in intestinal fluid at pH 6.8 (99.98%), whereas a weakly basic drug, pKa 5, will be almost entirely ionized (99.98%) at gastric pH of 1.2 and predominantly unionized at intestinal pH of 6.8 (98.4%).
- This means that, according to the pH-partition hypothesis, a weakly acidic drug is more likely to be absorbed from the stomach where it is unionized, and a weakly basic drug from the intestine where it is predominantly unionized. However, in practice, other factors need to be taken into consideration.

table 9.2 **Intestinal absorption of acids and bases in the rat at several pH values***

		Percentage absorption			
	pK_a	pH 4	pH 5	pH 7	pH 8
Acids					
Salicylic acid	3.0	64	35	30	10
Acetylsalicylic acid	3.5	41	27	–	–
Benzoic acid	4.2	62	36	35	5
Bases					
Amidopyrine	5.0	21	35	48	52
Quinine	8.4	9	11	41	54

*From B.B. Brodie. *Absorption and Distribution of Drugs*, (ed. T. Binns), Livingstone, Edinburgh, 1964


100
50
10
Rate of Drug Absorption
Acidic Drugs
Basic Drugs
0 1 2 3 4 5 6 7 8 9 10 11
pH of GI-lumen
Shows the Actual Practical Curves
Indicates Curves Duly Predicted by pH-partition Hypothesis

Limitations of the pH-partition hypothesis

- The extent to which a drug exists in its unionized form is not the only factor determining the rate and extent of absorption of a drug molecule from the gastrointestinal tract
- Despite their high degree of ionization, weak acids are still quite well absorbed from the small intestine. In fact, the rate of intestinal absorption of a weak acid is often higher than its rate of absorption in the stomach, even though the drug is unionized in the stomach.
- The significantly larger surface area that is available for absorption in the small intestine more than compensates for the high degree of ionization of weakly acidic drugs at intestinal pH values
- In addition, a longer small intestinal residence time and a microclimate pH, that exists at the surface of the intestinal mucosa and is lower than that of the luminal pH of the small intestine, are thought to aid the absorption of weak acids from the small intestine.

Limitations of the pH-partition hypothesis

- The mucosal unstirred layer is another recognized component of the gastrointestinal barrier to drug absorption that is not accounted for in the pH-partition hypothesis

- During absorption drug molecules must diffuse across this layer and then on through the lipid layer. Diffusion across this layer is liable to be a significant component of the total absorption process for those drugs that cross the lipid layer very quickly.

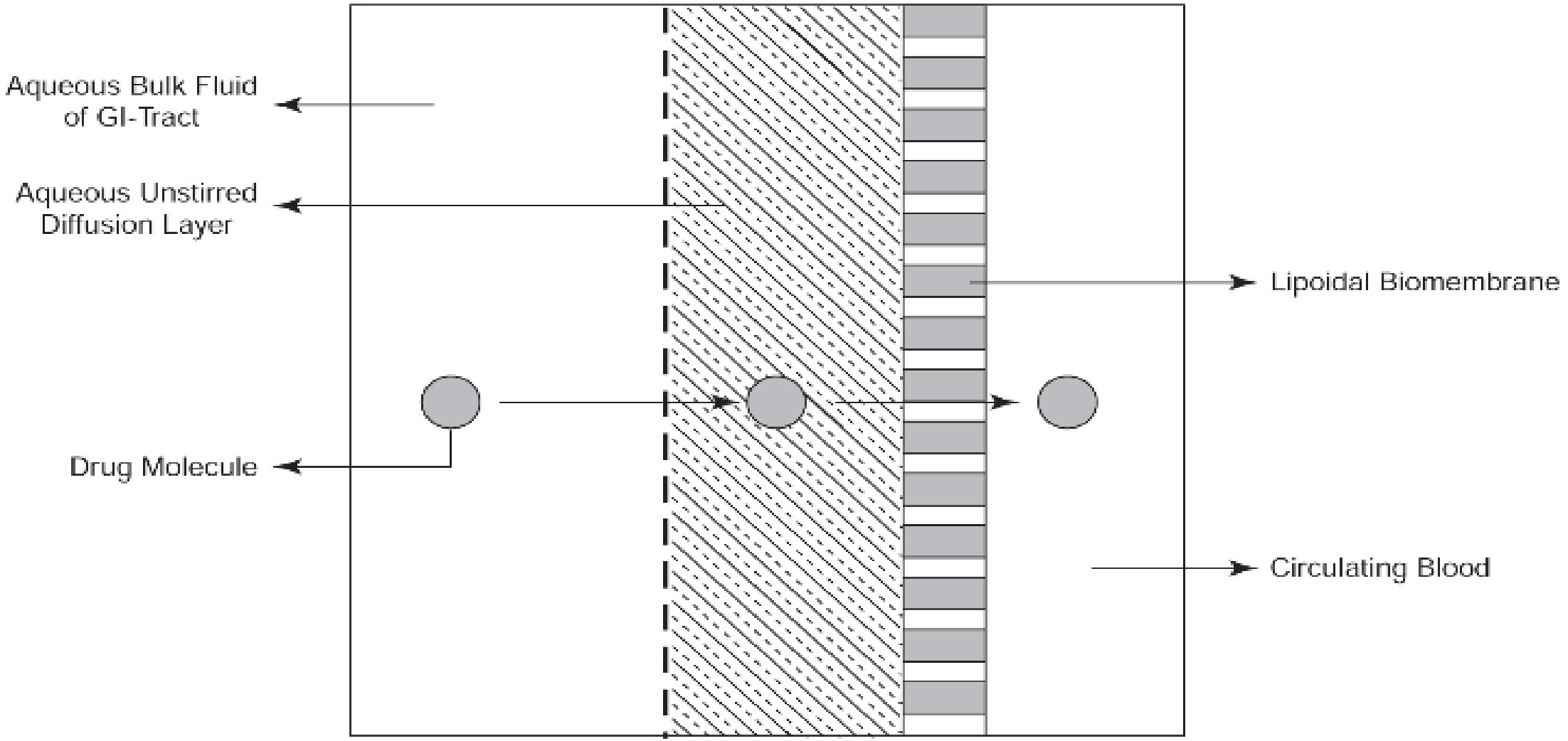


Figure 2.34 Diagrammatic representation of the critical presence of aqueous unstirred diffusion layer located upon the lipoidal biomembrane surface.

Limitations of the pH-partition hypothesis

- The pH-partition hypothesis cannot explain the fact that certain drugs (e.g. quaternary ammonium compounds and tetracyclines) are readily absorbed despite being ionized over the entire pH range of the gastrointestinal tract
- One suggestion for this is that the gastrointestinal barrier is not completely impermeable to ionized drugs. It is now generally accepted that ionized forms of drugs are absorbed in the small intestine but at a much slower rate than the unionized form
- Another possibility is that such drugs interact with endogenous organic ions of opposite charge to form an absorbable neutral species - an ion pair - which is capable of partitioning into the lipoidal gastrointestinal barrier and be absorbed via passive diffusion

Limitations of the pH-partition hypothesis

- Another, physiological, factor that causes deviations from the pH-partition hypothesis is convective flow or solvent drag. The movement of water molecules into and out of the gastrointestinal tract will affect the rate of passage of small water-soluble molecules across the gastrointestinal barrier
- Water movement occurs because of differences in osmotic pressure between blood and the luminal contents, and differences in hydrostatic pressure between the lumen and the perivascular tissue. The absorption of water-soluble drugs will be increased if water flows from the lumen to the blood, provided that the drug and water are using the same route of absorption; this will have greatest effect in the jejunum, where water movement is at its greatest

Limitations of the pH-partition hypothesis

- Water flow also effects the absorption of lipid-soluble drugs. It is thought that this is because the drug becomes more concentrated as water flows out of the intestine, thereby favoring a greater drug concentration gradient and increased absorption.