intestine) are thought to aid the absorption of weak acids from the small intestine.

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. Diffusion across this layer will also depend on the molecular weight of the drug.

A 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 because of 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. Water flow also affects 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 favouring a greater drug concentration gradient and increased absorption.

Lipid solubility. A number of drugs are poorly absorbed from the gastrointestinal tract despite the fact that their unionized forms predominate. For example, the barbiturates: barbitone and thiopentone have similar dissociation constants – pK_a of 7.8 and 7.6 respectively – and therefore similar degrees of ionization at intestinal pH. However, thiopentone is absorbed much better than barbitone. The reason for this difference is that the absorption of drugs is also affected by the lipid solubility of the drug. Thiopentone, being more lipid soluble than barbitone, exhibits a greater affinity for the gastrointestinal membrane and is thus far better absorbed.

An indication of the lipid solubility of a drug, and therefore whether that drug is liable to be transported across membranes, is given by its ability to partition between a lipid-like solvent and water or an aqueous buffer. This is known as the drug's *partition coefficient* and is a measure of its lipophilicity. The value of the partition coefficient P is determined by measuring the drug partitioning between water and a suitable non-water miscible solvent at constant temperature. As this ratio normally spans several orders of magnitude it is usually expressed as the logarithm, log$P$. The solvent that is usually selected to mimic the biological membrane, because of its many similar properties, is octanol.

$$\text{Partition coefficient} = \frac{\text{concentration of drug in organic phase}}{\text{concentration in aqueous phase}} \tag{20.7}$$

The effective partition coefficient, taking into account the degree of ionization of the drug, is known as the *distribution coefficient* and again is normally expressed as the logarithm (log$D$); it is given by the following equations for acids and bases:
For acids:

$$D = \frac{[HA]_{org}}{[HA]_{aq} + [A^-]_{aq}} \tag{20.8}$$

$$\log D = \log P - [1 + \text{antilog}(\text{pH} - \text{p}K_a)] \tag{20.9}$$

For bases:

$$D = \frac{[B]_{org}}{[B]_{aq} + [BH^+]_{aq}} \tag{20.10}$$

$$\log D = \log P - [1 + \text{antilog}(\text{p}K_a - \text{pH})] \tag{20.11}$$

The lipophilicity of a drug is critical in the drug discovery process. Polar molecules, i.e. those that are poorly lipid soluble (log$P < 0$) and relatively large, such as gentamicin, ceftriaxone, heparin and streptokinase, are poorly absorbed after oral administration and therefore have to be given by injection. Smaller molecules that are poorly lipid soluble and hydrophilic in nature, such as the β-blocker atenolol, can be absorbed via the paracellular route. Lipid-soluble drugs with favourable partition coefficients (i.e. log$P > 0$) are usually absorbed after oral administration. Drugs which are very lipid soluble (log$P > 3$) tend to be well absorbed but are also more likely to