$$\text{Weak base: } B + H^+ \leftrightarrow BH^+ \qquad (24.2)$$

Depending on circumstances (discussed in Chapter 3) these equilibria will shift towards either the undissociated or dissociated forms.

Since ions are more soluble in water than neutral molecules, changing the pH of the medium to increase ionization of the drug is a common technique for increasing drug solubility in an aqueous medium. Weakly acidic drugs are ionized when the pH of the solvent is increased. Conversely, lowering pH favours ionization of weakly basic drugs. The pH required to achieve drug ionization can be calculated using the Henderson-Hasselbalch equations (see Chapter 3), and the pH can be adjusted using acids or alkali, or using buffers such as citrate, acetate, phosphate and carbonate buffers. Extremes of pH should be avoided however, so that the solution is physiologically acceptable; the pH ranges tolerated via the different routes are shown in Table 24.4.

In addition, the chosen pH should not adversely affect the stability of the drug and excipients. As mentioned above, the rate of chemical reactions which lead to degradation can be pH-dependent. The pH for optimal drug solubility may not be the same as that for optimal stability. pH can also be important for the optimal functioning of excipients. For example, the ionization, and subsequently the activity of a preservative may be influenced by the pH of the medium. Bioavailability of the drug should also not be compromised by a change in pH, union-ized drug molecules being absorbed to a greater extent through biological membranes than their ionized counterparts. The pH of a pharmaceutical solution is thus a compromise between drug solubility, stability and bioavailability, the function of excipients, and physiological acceptability of the product.

Co-solvents

Co-solvents are often used to increase the water solubility of drugs which do not contain ionizable group(s) and whose solubility can thus not be increased by pH adjustment. The principle ‘like dissolves like’ was mentioned in Chapter 2. That is, polar drugs generally dissolve in polar solvents and non-polar drugs generally dissolve in non-polar solvents. Thus, non-polar drugs are poorly soluble in water – a polar solvent. To increase the solubility of such drugs in water, the latter’s polarity should be lowered. This can be achieved by adding a third component such as a water-miscible organic liquid with a low polarity. Such a liquid, when used in this context, is called a co-solvent.

Most water-miscible organic liquids are however toxic, and only a few are used as cosolvents in pharmaceutical solutions. Examples include glycerol, propylene glycol, ethanol and the low molecular weight poly(ethylene glycol)s. The solubility of non-polar drugs in water can be increased by several orders of magnitude using co-solvents. Typically, a linear increase in co-solvent fraction results in logarithmic increases in drug solubility. The concentration of the co-solvent is however limited by its physiological acceptability. The co-solvent must be non-toxic at the concentrations used, and by the route of administration.

Complexation with cyclodextrins

Cyclodextrins (CDs) are non-reducing cyclic glucose-based oligosaccharides, comprising a variable number of D-glucose residues linked by α-(1,4) glycosidic linkages. The three most important CDs are alpha, beta and gamma cyclodextrins which consist of 6, 7 and 8 D-glucopyranosyl units, respectively, arranged in a ring. Three-dimensionally, CDs can be visualized as a hollow truncated cone (Fig. 24.1). The cavity in the cone has different diameters dependent on the number of glucose units in the ring; α-CD has a cavity diameter of about 0.55 nm, β-CD about 0.70 nm and γ-CD about 0.90 nm, with cavity volumes of 0.10, 0.14 and 0.20 mL/g, respectively. The side rim depth is the same for all three (about 0.8 nm).

The interior cavity of cyclodextrins is apolar, while their exterior is hydrophilic. The representation in Figure 24.1 needs careful interpretation as the –OH groups shown are actually attached to the top and bottom rims of the structure and not to either the inside or outside walls. The hydrophobic nature of the inside surface arises from the location of the –O– and C–H bonds of the glucose molecules being orientated there.

The hydrophilic exterior results in CDs being soluble in water. Concurrently, the less polar interior can accommodate non-polar drug molecules via non-covalent interactions, thereby allowing the non-polar drug to be ‘hidden’, enabling it to be molecularly dispersed in water. Thus, drug inclusion within CDs effectively increases their aqueous solubility.