route provides a much smaller area for absorption than the transcellular route (the paracellular route comprises about 0.01% of the transcellular route in the gastrointestinal tract), the absorption of hydrophilic compounds is much slower than that of lipophilic drugs. For both lipophilic and hydrophilic molecules, absorption is relatively efficient for drugs with a molecular weight below 1 kDa but then declines. Nevertheless, calcitonin (salmon) is successfully used to reduce the risk of vertebral fractures in postmenopausal osteoporosis (Table 38.2) despite being a hydrophilic peptide with a molecular weight of 3432 Da and having a nasal bioavailability that is just 3% of its bioavailability when delivered intramuscularly. When considering dose reproducibility from the nasal cavity, dosing is relatively consistent for low molecular weight drugs when compared to the oral or parenteral routes, whereas for compounds with a high molecular weight, such as peptides and proteins, relatively high variability is exhibited compared to injections.

Degree of ionization

For drugs that are weak acids or bases, the pH of the nasal cavity will affect the degree of ionization of the drug. The pH at the surface of the nasal mucosa has been reported to be 7.4 while the pH of the mucus is in the range 5.5–6.5. In addition, the pH of the formulation itself can alter the local pH, particularly if buffered vehicles are employed. Studies have indicated that the non-ionized form of a drug, which has a higher partition oil/water partition coefficient than its ionized counterpart, is better absorbed than the ionized form (pH partition hypothesis) (Chapter 20). The ionized form of the drug also shows some permeability, the degree of which may be dependent upon the nature of the counter-ion.

Formulation factors affecting intranasal systemic delivery

The same general formulation considerations apply to drugs formulated for systemic action as for local action, as indicated by the case examples shown in Table 38.2. However, additional strategies can be employed to increase absorption across the nasal epithelium. In essence, the bioavailability of nasally administered drugs can be limited by:

- low aqueous solubility
- rapid and extensive enzymatic degradation of the drug in the nasal cavity
- short contact time between the drug and the absorptive epithelium of the turbinates due to mucociliary clearance
- poor permeability of the drug across the respiratory epithelium.

Approaches that have been used to overcome these limitations are summarized in Table 38.4 and include the use of prodrugs (see above), enzymatic inhibitors, mucoadhesive formulations and permeation enhancers which affect the epithelial barrier.

Increasing aqueous solubility

As discussed above, for a drug to be absorbed it should normally be in solution. Drug solubility can be increased by using a mixed solvent system or a co-solvent in the formulation. Solvents used with water for nasal delivery include glycerol, ethanol, propylene glycol and polyethylene glycol (PEG). It is important that any co-solvents do not irritate the nasal mucosa and it is likely that ethanol, used at high concentrations, would not be well-tolerated. However, PEG 300 has been used successfully to increase the solubility of buprenorphine hydrochloride and melatonin, and has enabled clinically relevant doses to be administered with low nasal irritation being observed in humans.

Cyclodextrins (Chapter 24) are cyclic compounds composed of α-D-glucopyranose units. They tend to be water-soluble due to their hydrophilic/polar outer surface, but have a hydrophobic/less polar centre. They are able to increase the aqueous solubility of lipophilic compounds by forming dynamic inclusion complexes where the lipophilic part of the drug molecule is incorporated into the lipophilic central cavity of the cyclodextrin ring. An intranasal formulation containing 17-β-estradiol solubilized in dimethyl-β-cyclodextrin (seven glucopyranose units) was available for the treatment of menopausal symptoms, until it was withdrawn in 2006. The formulation was well-tolerated and as effective as transdermal and oral formulations of estradiol. The dimethyl-β-cyclodextrin was reported to increase absorption of the drug by both enhancing its solubility and increasing the permeability of the nasal epithelium.

pH of the formulation

Many drugs are weak acids or bases and their degree of absorption will depend on their pK_a and the pH of the absorption site. The pH of a formulation is