Table 38.4 Common problems associated with poor nasal bioavailability and possible solutions

Problem	Challenge	Possible solutions
Low aqueous solubility of drug	Improve aqueous solubility of drug	Prodrugs Co-solvents Cyclodextrins Novel drug delivery systems
Enzymatic degradation of drug	Reduce affinity of drug for nasal enzymes Inhibit nasal enzymes Limit access of nasal enzymes to drug	Prodrugs Enzyme inhibitors Encapsulation, e.g. liposomes, microspheres, nanoparticles
Short contact time	Increase residence time of drug in turbinates	Increase viscosity of formulation Use mucoadhesive formulations
Low permeability across the nasal epithelium	Increase permeability Increase solubility Modify nasal epithelium	Prodrugs (with increased lipophilicity) Prodrugs (with increased hydrophilicity) Co-solvents Cyclodextrins Novel drug delivery systems Permeation enhancers

generally dictated by the stability of the drug but, within these constraints, a pH favouring more unionized molecules would be expected to enhance absorption. It is important to recognize that the formulation should be non-irritant to the nasal mucosa and formulating at a pH close to that of the nasal cavity (5.0–6.5) may also be desirable although, unexpectedly, it has been shown that pH values ranging from 3–10 can be tolerated by the nasal mucosa (Table 38.2).

Use of enzyme inhibitors

Should peptides be administered via the nasal cavity, they are clearly potentially prone to degradation by the enzymes of the nasal mucus and epithelium. Proteolytic enzyme inhibitors could prevent the hydrolysis of peptide and protein drugs in the nasal cavity improving their stability at the absorption site. As examples, the aminopeptidase and trypsin inhibitor, camostat mesilate, improved the nasal absorption of the peptide vasopressin and its analogue, desmopressin, and the absorption of calcitonin can also be enhanced by the use of trypsin inhibitors. However, proteolytic enzyme inhibitors do not improve the ability of peptide and protein drugs to cross the epithelium of the nasal cavity and therefore do not dramatically improve nasal bioavailability, as clearance mechanisms continue to operate to remove the drug from the absorption site.

Increasing nasal residence time

Unless a drug molecule possesses the ideal characteristics for rapid absorption, the percentage of the administered dose entering the systemic circulation is likely to be affected by the residence time of the nasal formulation in the turbinates. One way of increasing the time that the formulation is in contact with the absorptive mucosa is by the use of mucoadhesive polymers, such as cellulose derivatives, polyacrylates, starch and chitosan. Most of these polymers are 'Generally Regarded As Safe' (i.e. given GRAS status as categorized by the FDA) and if included as pharmaceutical excipients within the vehicle, have been shown to increase the absorption of hydrophilic macromolecules. The polymers themselves are not absorbed and therefore would not be expected to cause any systemic toxicity.

Adhesion of a polymeric material can occur to both the nasal epithelial surface (bioadhesion) and nasal mucus (mucoadhesion). Mucoadhesive formulations can be administered to the nasal cavity in the form of solid powders or particulates, gels or liquids. For good mucoadhesion, the formulation should spread well on the nasal mucosa (solid formulations should flow well