



Fig. 49.1 • Effect of pH on drug degradation rate
(a) Typical curve where acid catalysed (H_3O^+), base catalysed (OH^-) and uncatalysed (H_2O) hydrolysis occurs
(b) Typical curve with narrow region of maximal stability
(c) Typical curve where the drug molecule ionizes.

degradation reactions. This is known as general acid catalysis and general base catalysis respectively. Buffer ions are a common cause of this, so careful selection of buffer for use in a formulation is needed. Hydrolysis of the amide bond of the antimicrobial drug chloramphenicol is catalysed by several common buffers, including phosphate and acetate.

Borate buffer, however, does not catalyse degradation and is used, for example, to buffer eye drops.

Ionic strength

The ionic strength of a medium is related to the concentration of ionic species in it. Changing the ionic strength by adding electrolyte to a solution has some influence on the rate of many degradation reactions. This effect is not high enough to be of importance in the formulation of drug solutions. However, it can be important in laboratory experiments to investigate the influence of pH on degradation rate. In this case, care should be taken to ensure the ionic strength of the various buffer solutions used is kept the same in order to avoid interference with the results.

Light

Containers made from tinted glass protect the product from light to some extent because they allow less ultraviolet light to penetrate than those which are untinted (Chapter 47). Placing the product in an opaque outer container such as a cardboard box is also an option, but it must be borne in mind that the patient might not return the product to its secondary packaging following use.

Oxygen

Oxidation reactions are less influenced by temperature than most other degradation reactions, so low-temperature storage may be less successful as a stabilization option. Flushing containers with an inert gas such as nitrogen before they are sealed will reduce the amount of oxygen in the product. However this technique will not remove all oxygen and is best suited for single-use containers such as ampoules.

Oxidation reactions are generally promoted by high pH, so aqueous products which are susceptible to oxidation should be formulated at as low a pH as possible.

Heavy metal ions, such as Cu^{2+} and Fe^{3+} , catalyse oxidation reactions, acting at the initiation and propagation stages. These ions are present at trace levels in all formulations. A chelating agent such as ethylenediamine tetraacetic acid (EDTA) or citric acid has a stabilizing effect by binding to the heavy metal ions and preventing them from acting as catalysts.

Chelating agents are usually used in combination with an antioxidant. Antioxidants act in one of two ways. They may act as oxygen scavengers – oxygen is removed from the formulation by reacting