

important degradation mechanisms and these are dealt with separately later in this chapter.

Temperature

The rate of degradation reactions is markedly influenced by temperature. Storage of the product in a refrigerator (at 2–8 °C) is an option if the product is unstable at room temperature.

Using a freezer (at less than –15 °C) to store unstable formulations is sometimes adopted, however, this makes storage and distribution of the product inconvenient. Also, because a liquid product needs to be thawed before administration, there is the risk of degradation occurring if heat is used to achieve this. Moreover, some drugs, for instance amoxicillin are less stable in solution when frozen than when stored at refrigerator temperature (McDonald et al 1989). Freezing can cause degradation of biopharmaceuticals (see Chapter 46) and live vaccines, though the inclusion of a cryoprotectant, such as trehalose, in the formulation may protect against this.

Finished products are most at risk of exposure to unacceptable temperatures during transportation or storage in vehicles, such as in ambulances (Helm et al 2003, Lucas et al 2004, Priston et al 2005).

Solvent

Replacing an aqueous solvent in a formulation with a non-aqueous one is a potential means of avoiding hydrolysis.

The dielectric constant of a solvent is related to its polarity, more polar solvents having higher values. The dielectric constant can influence the rate at which charged species react. However, the practical considerations of choosing a solvent for a formulation, such as its toxicity and compatibility with the drug, usually outweigh consideration of any effect due to the solvent's dielectric constant.

Solid dosage forms of a drug, such as tablets or capsules, are usually more stable than liquid ones. However, reactions can occur in water adsorbed onto the surface of a drug particle or other dosage form component. This is why poorly stored aspirin tablets may smell of acetic acid, formed by the hydrolysis of aspirin. Injection formulations of unstable drugs, such as penicillins, can be formulated as freeze-dried powders, which are reconstituted with water or saline (0.9% w/v sodium chloride solution) immediately before administration.

Suspension formulations are often more stable than a solution formulation of the same drug because much of the drug is protected within the insoluble particles.

Acid and base catalysis

A catalyst is a species that accelerates the rate of a reaction without itself being consumed in the reaction. Hydrolysis is often catalysed by hydrogen ions (which exist as H_3O^+ in solution) or hydroxyl ions. The pH of an aqueous formulation is therefore a critical factor which determines its stability. Specific acid catalysis is catalysis by hydrogen ions and specific base catalysis is catalysis by hydroxyl ions.

Investigation of the relationship between pH and the degradation rate of a drug is performed during the preformulation phase of drug development (Chapter 23). Plotting the logarithm to base 10 of the first-order reaction rate constant against pH may yield useful information about the degradation mechanism. A typical curve is shown in Figure 49.1a. The increase in degradation rate at low pH is due to specific acid catalysis. The increase in rate seen at high pH is due to specific base catalysis. Straight lines with gradients of –1 in the acidic region and +1 in the basic region are characteristic of specific acid and specific base catalysed hydrolysis. The flat region of the curve is largely due to uncatalysed hydrolysis. The product should be maintained at a pH within this region for optimal stability. Cefuroxime and other cephalosporin antibiotics typically show this shape of graph.

For some drugs, such as many penicillins, the uncatalysed reaction with water is relatively less important than that shown in Figure 49.1a, so there is no flat base to the curve and a V-shaped graph results (Fig. 49.1b). In this case, the pH needs to be more precisely controlled than in the previous example because there is a narrower region of optimal stability.

Many drug molecules undergo ionization, to an extent that often depends on the pH. These typically give a curve as shown in Figure 49.1c. The ionized and unionized forms of the drug degrade at different rates. Therefore, the rate of reaction changes as the pH influences the relative proportion of ionized drug present and this gives an inflection point on the graph. Aspirin is an example of a drug which shows this characteristic.

Other species in a formulation besides H_3O^+ or OH^- may act as acids and bases and thus catalyse