product at realistic storage temperatures and humidities. However, the shelf-lives of commercial pharmaceutical products are typically of several years. Testing over such an extended period would be impractical early in product development in order to decide if a particular formulation was of sufficient stability. The Arrhenius equation (Chapter 7) allows the prediction of reaction rates at proposed storage temperatures, from data obtained at high temperatures. For example, if it is desired to formulate a new drug as a solution dosage form, simple buffered solutions of the drug are stored at a range of elevated temperatures for time periods ranging from minutes to days, depending on the relative stability of the drug (Chapter 48). In general, the rate of degradation will increase as the temperature of the test is increased (Chapter 7). Accelerated reaction rates are calculated at each temperature and the Arrhenius equation is used to predict the reaction rate at room temperature, which is then used to calculate the estimated shelf-life. Later in the development process, once the drug molecule's degradation characteristics have been assessed, prototype formulations must be subjected to the same process to allow optimization of the stability of the finished product.

There are a number of pitfalls in the use of this type of testing. The precision of the shelf-life estimate is poor, so studies typically yield estimates with a wide range of uncertainty. At high temperatures, other degradation reactions may take place that are not significant at normal storage temperatures. Alternatively, at high temperatures, the degradation products which are initially formed from the drug (the primary degradation products) may rapidly react to form further degradation products (the secondary degradation products) and so will not accumulate. Therefore, later in the development process, when the product undergoes stability testing at normal storage conditions, the primary degradation products may accumulate. If these degradation products are not foreseen, they could cause interference with chromatographic analysis of the product, or raise questions about the toxicity profile of the formulation.

The kinetics of drug degradation may also change at different temperatures. A reduction in the concentration of dissolved oxygen will also tend to occur at high temperatures, so use of the Arrhenius equation may not provide a reliable estimate of shelf-life in liquid products which degrade by oxidation. In the case of solid dosage forms, high temperatures often reduce moisture levels associated with drug or excipients, also leading to poor stability prediction. Semisolid dosage forms are often unsuitable for this type of stress testing due to melting of ingredients (particularly excipient bases) at elevated temperature.

Nevertheless, despite these drawbacks, the use of the Arrhenius equation to predict room temperature stability does allow the decision to be made concerning whether a particular formulation type is likely to be sufficiently stable to allow commercial production. It also allows the relative stability of formulations to be studied at an early stage of the development process.

There is however, no substitute for properly-conducted, long-term stability tests carried out under the normal storage conditions that are likely to be experienced by the product.

Temperature cycling

Temperature cycling studies involve storing the product at alternating high and low temperatures. These are often designed to subject liquid products to repeated freezing and thawing, for example. This may reveal stability problems because it potentially accelerates physical deterioration of the product. Temperature fluctuations encourage particle growth in suspensions (Chapter 26), the cracking of emulsions (Chapter 27) and precipitation of dissolved drug from solutions. Such studies also allow the effects of extreme temperature variations during distribution of the product to be evaluated (Helm et al 2003, Lucas et al 2004, Priston et al 2005).

Photostability testing

Photostability studies are carried out at various stages of the product development process and involve investigation of the effect of light on drugs and formulated products. Drug or product is exposed to light, provided by artificial-daylight fluorescent lamps that emit long-wavelength ultraviolet and visible light to simulate indirect, indoor sunlight. The study is performed within a cabinet which has a controlled temperature, typically of 25 °C. Initial photostability studies are carried out using pure drug, spread over the base of shallow containers and directly exposed to the light. After a period of storage, the material is chemically analysed to assess the degree of photodegradation. The drug's photosensitivity is shown by a reduction in assay of the drug molecule, the formation of photodegradation products or a colour change.