- many drugs are inherently unstable, and instability is increased when a drug is present in solution, i.e. as molecules. The solution formulation is therefore not feasible for certain drugs. For other drugs, stability can be enhanced by optimizing the formulation (see below)
- many drugs are poorly soluble in water. Their formulation as a solution is challenging (see below)
- liquids are bulky and less easy for the patient to carry, for example, the daily dose, compared to solid dosage forms. Liquids are also more expensive to transport, which increases the medicine's cost. The packaging of pharmaceutical solutions requires materials of higher quality (see Chapter 47).

Solution stability

A pharmaceutical solution must be stable for the duration of its shelf-life (period of storage and use). That is, it must retain the same physical, chemical, microbiological, therapeutic and toxicological properties that it possessed at the time of its manufacture. The product's physical properties (e.g. colour, clarity, viscosity, odour, taste) and efficacy must not change, and there should be no significant increase in toxicity. The product should remain sterile or resistant to microbial growth, and the drug's chemical nature and potency must not change.

However, many drug molecules undergo chemical reactions, such as, hydrolysis, oxidation, decarboxylation, epimerization, dehydration, with hydrolysis, oxidation and reduction being the most common. Chemical reactions occur more readily at high temperature, at certain pHs, in the presence of UV light and of substances which can act as a catalyst, and in solutions, where the drug is present as molecules. The resulting loss of drug molecules can reduce the efficacy of the formulation and increase the latter's toxicity if the products of the chemical changes are toxic. Pharmaceutical solutions are therefore formulated at the pH favouring drug stability, and often include excipients to enhance product stability. To reduce photo-oxidation, solutions are packaged in containers that do not allow light transmission. To reduce oxidation, antioxidants and/or metal chelators (as heavy metal ions catalyse oxidation) are used. Alternatively, oxygen can be excluded, by purging the solution with nitrogen and creating a nitrogen headspace within the container. To inhibit microbial growth during use, preservatives are used in multidose products. All the excipients used within a solution must be of suitable quality, non-toxic, compatible with the drug and with one another, and active at the solution pH. In addition, the excipient must remain in the solution throughout the shelf-life of the product. That is, the concentration of excipient must not decrease, which could happen, for example, if the excipient degraded or adsorbed onto the container walls.

Further detailed information about product stability can be found in Chapters 48, 49 and 50.

Enhancement of drug solubility

As mentioned above, water is the most commonly used vehicle in pharmaceutical solutions. Many drugs are water soluble, solubility being defined as the concentration of the drug in a solution when equilibrium exists between dissolved and undissolved drug. As described in Chapter 2, drug solubility in water depends on a number of factors such as the drug's molecular structure, crystal structure, particle size, pK_a and the pH of the medium (if the drug is a weak acid/base or a salt).

Unfortunately, many drugs are not sufficiently soluble in water and aqueous drug solubility must be increased by the inclusion of other solvents/chemicals. The nature of the solubility enhancer depends on the drug molecule and the route of administration, as well as the intended patient population. Certain enhancers may be safely administered via the oral route, but not parenterally due to their greater toxicity when administered parenterally. Others, e.g. ethanol, while widely used in medicines, should be avoided where possible in paediatric formulations. Different approaches to enhancing drug solubility in solutions are described below.

pH adjustment

Most existing drugs are either weak acids or weak bases. In solution, an equilibrium exists between the undissociated drug molecules and their ions. The equilibrium may be represented as:

$$\text{Weak acid: } HA \leftrightarrow H^+ + A^- \qquad (24.1)$$