of formulation and as regards stability and biological activity. As might be expected, higher dissolution rates are obtained for metastable polymorphic forms; for example, the alternative polymorphic forms of rifaximin exhibit different in vitro dissolution rates and bioavailability. In some cases, amorphous forms are more active than crystalline forms.

The polypeptide hormone insulin, widely used in the regulation of carbohydrate, fat and protein metabolism, also demonstrates how differing degrees of activity can result from the use of different crystalline forms of the same agent. In the presence of acetate buffer, zinc combines with insulin to form an extremely insoluble complex of the proteinaceous hormone. This complex is an amorphous precipitate or crystalline product depending on environmental pH. The amorphous form, containing particles of no uniform shape and smaller than 2 μm, is absorbed following intramuscular or subcutaneous injection and has a short duration of action, whilst the crystalline product, consisting of 10–40 μm sized rhombohedral crystals, is more slowly absorbed and has a longer duration of action. Insulin preparations which are intermediate in duration of action are prepared by taking physical mixtures of these two products.

Polymorphic transitions can also occur during milling, granulating, drying and compacting operations (e.g. transitions during milling for digoxin and spironolactone). Granulation can result in solvate formation or, during drying a solvent or water molecule(s) may be lost to form an anhydrous material. Consequently, the formulator must be aware of these potential transformations which can result in undesirable modified product performance, even though routine chemical analyses may not reveal any changes. Reversion from metastable forms, if used, to the stable form may also occur during the lifetime of the product. In suspensions, this may be accompanied by changes in the consistency of the preparation which affects its shelf-life and stability. Such changes can often be prevented by additives, such as hydrocolloids and surface-active agents.

Stability

The chemical aspects of formulation generally centre on the chemical stability of the drug and its compatibility with the other formulation ingredients. In addition, it should be emphasized that the packaging of the dosage form is an important factor contributing to product stability and must be an integral part of stability testing programmes. It has been mentioned previously that one of the principles of dosage form design is to ensure that the chemical integrity of drug substances is maintained during the usable life of the product. At the same time, chemical changes involving additives and any physical modifications to the product must be carefully monitored to optimize formulation stability.

In general, drug substances decompose as a result of the effects of heat, oxygen, light and moisture. For example, esters such as aspirin and procaine are susceptible to solvolytic breakdown, whilst oxidative decomposition occurs for substances such as ascorbic acid. Drugs can be classified according to their sensitivity to breakdown:

1. stable in all conditions (e.g. kaolin)
2. stable if handled correctly (e.g. aspirin)
3. only moderately stable even with special handling (e.g. vitamins)
4. very unstable (e.g. certain antibiotics in solution form).

Whilst the mechanisms of solid-state degradation are complex and often difficult to analyse, a full understanding is not a prerequisite in the design of a suitable formulation containing solids. For example, in cases where drug substances are sensitive to hydrolysis, steps such as minimum exposure to moisture during preparation, low moisture content specifications in the final product and moisture-resistant packaging can be used. For oxygen-sensitive drugs, antioxidants can be included in the formulation and, as with light-sensitive materials, suitable packaging can reduce or eliminate the problem. For drugs administered in liquid form, the stability in solution as well as the effects of pH over the physiological range of 1–8 should be understood. Buffers may be required to control the pH of the preparation to improve stability; where liquid dosage forms are sensitive to microbial attack, preservatives are required.

In these formulations, and indeed in all dosage forms incorporating additives, it is also important to ensure that the components, which may include additional drug substances as in multivitamin preparations, do not produce chemical interactions themselves. Interactions between drug(s) and added excipients such as antioxidants, preservatives, suspending agents, colourants, tablet lubricants and packaging materials do occur and must be checked for during the design of formulations. Over recent