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Preformulation

Following the identification of a new chemical entity that is suitable for development, the formulator will be called upon to produce dosage forms. Initially, this may involve the production of an injectable form suitable for early efficacy and toxicity testing and subsequently there will be a need to develop the final dosage form, which generally will not be an injection. The challenge for the formulator is to develop the initial and final dosage forms to the highest quality in the shortest time. This process is best achieved when certain physicochemical properties of the drug substance are investigated, understood, and effectively utilised: this is preformulation.

Preformulation studies include investigations of chemical form (for example, salts), crystal form (for example, polymorphism and habit), solubility, dissociation (pK_a), partitioning, mechanical properties, stability, and excipient compatibility. The number of experiments that could be performed is extremely large and it is necessary to balance the value of the results against the time taken to obtain them. There is also a need to obtain as much information as possible at the earliest stage. However, the quantities of drug available will be extremely limited until the synthesis has been scaled up, and also the changes in the chemical production process may result in changes in the physicochemical properties of the drug, for example, different crystal forms (which is discussed below). Thus, there must be careful thought about the experiments that will be performed and the stage at which they should be considered. The development scientist should, if possible, be involved at an early stage in the discussion on choice of synthetic route for the bulk production of drug substance, especially the final crystallisation step. Furthermore, the range of tests to be performed will vary depending upon the desired route of administration and dosage form selected. Thus, only for tableted products would one consider material compression properties. Such compression tests would usually be left to the later stages, simply on the basis of balancing material supply with the requirements of the test.

As preformulation covers such a large range of subject areas, the scope of this chapter has been restricted to an introduction to the concepts of preformulation, with the aim being to highlight the tests that are available and to draw attention to relevant texts for further reading.

The order of the sections below does not represent any chronological order in which the experiments are performed. For example, solubility experiments have a higher priority than investigations of some aspects of crystal form; however, it is easier to describe the solubility of polymorphs after introducing the concepts of polymorphism and that is the basis on which the chapter is arranged.

ORGANOLEPTIC PROPERTIES

With the Control of Substances Hazardous to Health (COSHH) safety regulations it would be unusual for preformulation scientists to routinely taste new chemical entities. In the following section, the need for accurate analysis is discussed; however, there are occasions when organoleptic aspects provide useful information. When an oxidation reaction produces a coloured degradation product it will often be detected by the human eye before the breakdown product has reached a sufficiently high concentration to be detected by chemical analysis. Equally, problematic crystal transitions can often be detected by simple light microscopy, where even qualitative observations on particle shape and approximate size distribution can also be a valuable guide to potential problems (for example, a wide size distribution would alert the worker to the possibility of Ostwald ripening in suspensions; acicular shaped crystals to potential problems with flow). Smell can be an efficient method by which chemical and microbiological instabilities can be detected. With the wide range of erudite techniques available to the scientist it is easy to forget that careful organoleptic observations and thorough note taking can be valuable tools by which to monitor changes in a drug and to make decisions about subsequent preformulation tests, as well as formulation and processing factors.

ANALYSIS

An essential part of preformulation is to be able to assay the drug. Analysis is a subject that is too large to be adequately addressed here; however, assays

are commonly undertaken by high performance liquid chromatography (HPLC), thin layer chromatography (TLC), or gas chromatography (GC), which can allow the drug and degradation products or related substances to be monitored (a stability-indicating assay). It is also useful to have a simple assay (based on an ultraviolet (UV)-absorbing chromaphore that obeys a Beer-Lambert plot) to allow easy and rapid quantification of the preformulation experiments. Users should be aware of the limitations of an assay, for example, whether it is stability-indicating or whether the breakdown product absorbs at the same wavelength, or if other ingredients in the formulation (for example, excipients) interfere with the assay by absorbing at the same wavelength.

CRYSTAL PROPERTIES

The majority of drug substances are regarded as crystalline materials; the molecules are packed in an ordered and reproducible manner. Excipients vary from crystalline materials to amorphous polymers. However, few samples will be entirely homogeneous, polymers will be partially crystalline and drugs at least partially amorphous. The extent of crystallinity of compounds will greatly affect their physical properties.

Polymorphism

Changes in the crystallisation process can affect not only the degree of crystallinity, but also the way in which the molecules are packed. When a particular solid has been shown to exist in more than one packing arrangement, it is said to exhibit polymorphism. There are two types of polymorphism. Monotropic polymorphs are those for which only one form is stable (irrespective of temperature and pressure) and the metastable form will revert to the stable form with time. Enantiotropic polymorphs are those for which different forms are stable under different experimental conditions, such that a change in pressure or temperature may alter the form that is stable.

Different monotropic polymorphs often have different melting points, with the most stable form generally having the highest melting point (see Thermal Methods below). They also exhibit different X-ray diffraction patterns and infrared (IR) spectra. At any one particular temperature and pressure, there will be only one stable polymorph, all other forms that exist for any detectable period of time (and there may be several) are termed metastable. Metastable polymorphs will have a faster dissolution rate than the stable form, and apparently have a greater equilibrium solubility, thus the bioavailability from a metastable form can be considerably greater than from the stable form of that drug. This type of behaviour is due to the fact that the melting point is an indication of the lattice energy of the crystal, so the most stable crystals will have the largest lattice energy, the highest melting point, and the lowest rate of solution, and *vice versa*. However, by definition, the metastable form is not stable and will tend to revert to the stable polymorph. Transitions in polymorphic form can occur gradually as a function of time, and can be accelerated by changes in storage conditions (such as increases in temperature and humidity) or energetic treatment (processing) of the powder. Thus, unit processing such as mixing, milling, and tableting can cause changes in crystal type and consequently change the physical, and potentially the biopharmaceutical, properties of a drug. It follows that great care must be taken to determine which polymorph is present, and under what conditions and for how long it will be stable. A useful stress test for a drug substance is to ball mill it for a defined time and then to check for any change in polymorphic form, perhaps by use of differential scanning calorimetry (see Thermal Methods below).

Pseudopolymorphism

Changes in crystallisation processes can also result in inclusion of molecules of the solvent in the crystal, producing solvates (or in the unique case where water is included, hydrates). These crystals have different properties from the non-solvated sample, in a similar manner to different polymorphic forms, and are thus often termed 'pseudopolymorphs'. It has been shown that different solvates of the same drug can produce different blood concentrations following administration of a solid oral dosage form. However, whereas with polymorphs it is the form with the lowest melting point that will produce the highest blood concentrations, for solvates it can sometimes be the hydrate and for other drugs the anhydrous form that produces the highest concentrations.[1]

Crystal Habit

Habit is the term given to the outward appearance of a crystal. It is possible to change polymorphic form without altering habit and equally to change habit while maintaining the same polymorphic form; the two parameters are independent. Habit

can be described by variations on the theme of seven systems (cubic, tetragonal, orthorhombic, monoclinic, triclinic, trigonal, and hexagonal, see Table 1). The pharmaceutical significance of changes in habit can be an alteration in dissolution rate, powder flow, and compressibility; thus it can influence processing (for example, flow and compression during tableting[2]) and use of dosage forms. Dissolution rates are affected by the surface to volume ratio, while terms such as 'needle' (to describe the shape of acicular crystals) will indicate those that will have poor flow properties.

Table 1
Angles and lengths of axes that describe crystal habits

Crystal (synonym)	*Angles of axes*	*Length of axes*	*Example*
Cubic (regular)	$\alpha = \beta = \gamma = 90°$	$x = y = z$	sodium chloride
Tetragonal	$\alpha = \beta = \gamma = 90°$	$x = y \neq z$	nickel sulphate
Orthorhombic	$\alpha = \beta = \gamma = 90$	$x \neq y \neq z$	potassium permanganate
Monoclinic	$\alpha = \beta = 90 \neq \gamma$	$x \neq y \neq z$	sucrose
Triclinic (asymmetric)	$\alpha \neq \beta \neq \gamma \neq 90°$	$x \neq y \neq z$	copper sulphate
Trigonal (rhombohedral)	$\alpha = \beta = \gamma \neq 90$	$x = y = z$	sodium nitrate
Hexagonal	z at 90° to base	...	silver nitrate

Habit can be altered by changes in the crystallisation process. The habit is determined by the rate of growth of the different faces of the crystal. The fastest growing faces will tend to grow out of existence, and will, therefore, be the smallest faces on the final crystal, whereas the slow growing faces will dominate the final structure. As different faces can exhibit different proportions of the functional groups that make up the drug molecule, changes in the crystallising solvent may preferentially favour the interaction with different faces and consequently alter habit. The presence of impurities can result in adsorption at certain faces, which in turn can prevent (or slow) drug deposition to these faces, thus altering the growth rates of the exposed areas. Such adaptations can be accidental, due to impurities, breakdown products, or synthetic precursors in the crystallisation mixture, or deliberate due to the specific addition of impurities (such as surfactants). A well cited example of this is the modification of adipic acid crystals by Fairbrother and Grant.[3,4] The preformulation scientist should consider the optimum form of habit and, if possible, influence crystallisation procedures to ensure optimum properties are not due to serendipity, but rather a consequence of crystal engineering.

Crystal habit and morphology are best investigated by microscopy. Standard light microscopes fitted with polarising filters and phase contrast facilities can allow crystals to be visualised with ease, and habit and size to be quantified (for further detail on size, see Physicomechanical Properties below).

Crystal Defects

Bulk crystallisation of drug substances will be prone to produce imperfect crystals. The imperfections will be due to point defects and dislocations during the packing of the lattice. The addition (or accidental presence) of low concentrations of impurities will increase the disruption in the lattice. Disruptions in the crystal lattice can result in major changes in the ease of processing, chemical reactivity, and dissolution rate, and hence bioavailability.[5] York and Grant[5,6] have described a method by which it is possible to define a disruption index to quantify the disorder induced by additives and/or impurities in crystals. The disruption index can be calculated from differential scanning calorimetry measurements or from calorimetric measurements of the enthalpy of solution (see Thermal Methods for further details of these instruments).

Optical Isomers

Historically, attempts were not generally made to separate optical isomers for most compounds. However, drugs with one or more chiral centres are now given special consideration, as the preferred isomer must be identified and any other isomers regarded as impurities. It is important to identify the correct isomer and to eliminate all others. Considerable effort is being invested in the development of column-based systems for the separation of isomers.

Summary of Tests Relating to Crystal Properties

Standard tests should include melting point (to provide an indication of purity and crystal form) and thermal analysis (see separate section). It is usual to obtain a photomicrograph or for very small particles a scanning electron micrograph, from which comment about habit can be made. For the photomicrograph, image enhancement may be utilised (for example, polarised light). The tests described under Physicomechanical Properties are also relevant to crystal form. The aims are to identify the polymorph, solvate, habit, and optical isomer and to monitor the changes in properties against subsequent batches of drug.

Conclusions

The crystallisation process will influence the behaviour of the drug, in terms of its physical and

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