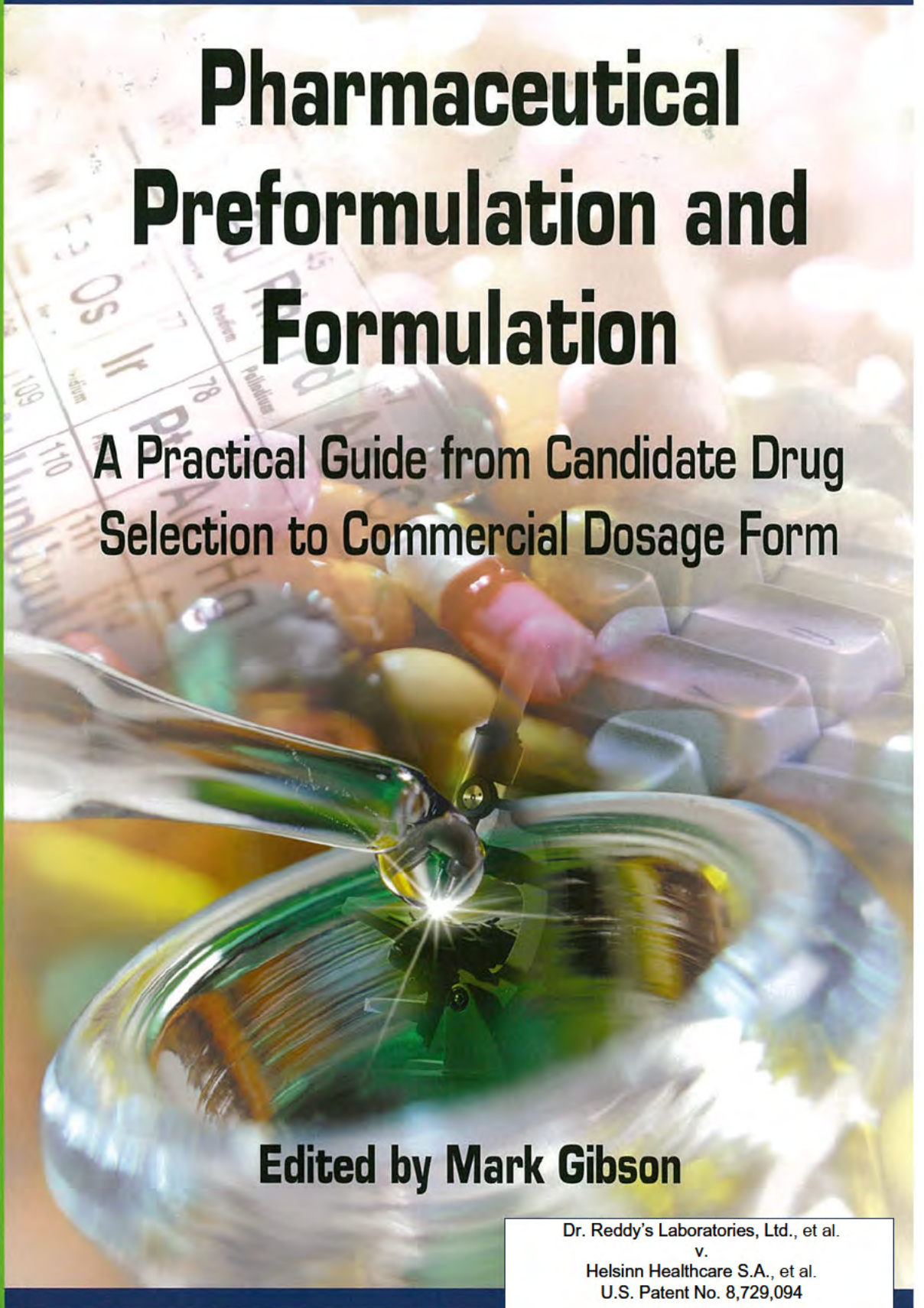
# Pharmaceutical Preformulation and Formulation

## A Practical Guide from Candidate Drug Selection to Commercial Dosage Form



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# Preformulation as an Aid to Product Design in Early Drug Development

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Preformulation is usually defined as the science of the physicochemical characterization of candidate drugs. However, any studies carried out to define the conditions under which the candidate drug should be formulated can also be termed preformulation. This is a broader definition than was used in Chapter 3, and, as such, it can include studies on preliminary formulations under a variety of conditions. These studies may influence the Product Design and should be conducted at the earliest opportunity at the start of development. In the interest of faster drug development and reduced drug usage, preformulation studies should not be undertaken on a "check-list" basis. Rather, they should be conducted on a need-to-know basis.

Whilst there are many traditional approaches to dosage form design, newer approaches based on expert systems are now becoming available. Expert systems are discussed further in Chapter 8 on Product Optimisation.

for example, the same chemical compound can have different crystal structures (polymorphs), external shapes (habits) and hence different flow and compression properties.

Cartensen et al. (1993) have usefully, although briefly, reviewed the physicochemical properties of particulate matter, dealing with the topics of cohesion, powder flow, micromeretics, crystallization, yield strengths and effects of moisture and hygroscopicity. Buckton (1995) has reviewed the surface characterization of pharmaceuticals with regard to understanding sources of variability. A general overview of the methods available for the physical characterization of pharmaceutical solids has been presented by Brittain et al. (1991). York (1994) has also dealt with these issues and produced a hierarchy of testing techniques for powdered raw materials. Finally, there is a book dealing with the physical characterization of pharmaceutical solids, edited by Brittain (1995).

A number of other studies can be performed on a candidate drug to determine other important solid-state properties, for example, particle size, powder flow and compression and polymorphism. Therefore, when a sample undergoes initial preformulation testing the following parameters should be noted: particle size, true, bulk and tapped density, surface area, compression properties and, powder flow properties. Some of these factors will be discussed in this chapter; others, however, are dealt with in more detail in Chapter 11 on Solid Oral Dosage Forms.

## Particle Size Reduction

The particle size of pharmaceuticals is important since it can affect the formulation characteristics and bioavailability of a compound (Chaumeil 1998). For example, sedimentation and flocculation rates in suspensions are, in part, governed by particle size, and inhalation therapy of pulmonary diseases demands that a small particle size (2–5 μm) is delivered to the lung for the best therapeutic effect. Particle size is also important in the tableting field, since it can be very important for good homogeneity in the final tablet. In this respect, Zhang and Johnson (1997) showed that a blended jet-milled compound exhibited a smaller range of potencies when compared to those blends where the compound had a larger particle size. It is therefore important that the particle size be consistent throughout the development studies of a product to satisfy formulation and regulatory demands (Turner 1987).

Thus, to reduce the risk of dissolution rate-limited bioavailability, and if there is sufficient compound, grinding in a mortar and pestle should be done to reduce the particle size of the compound. If larger quantities are available, then ball milling or micronization can be used to reduce the particle size. The main methods of particle size reduction have been reviewed by Spencer and Dalder (1997), who devised the mill selection matrix shown in Table 6.1.

### *Ball Milling*

In a review of milling, it was stated that ball milling was "the most commonly used type of tumbling mill in pharmacy" (Parrot 1974). Indeed, it is probably used most often at the preformulation stage to reduce the particle size of small amounts of a compound, especially for the



**Table 6.1**
**Mill selection matrix.**

| Slurry | Fluid Energy | Universal | Cone | Hammer |
|---|---|---|---|---|
| Less than average | Very favourable | Very favourable | Less than average | Average |
| Average | Very favourable | Very favourable | Favourable | Favourable |
| Less than average | Average | Average | Favourable | Less than average |
| Favourable | Unfavourable | Unfavourable | Very favourable | Favourable |
| Very favourable | Less than average | Less than average | Very favourable | Favourable |
| Very favourable | Favourable | Less than average | Very favourable | Favourable |
| Average | Average | Very favourable | Favourable | Favourable |

- B., Sizing up grinding mills, *Chemical Engineering*, Vol. 104, No. 4, pp. 84–87 (1997). With permission.

milling process and these include rotation speed, mill size, wet or dry milling and amount of material to be milled.

Although ball milling can effectively reduce the particle size of compounds, prolonged milling may be detrimental in terms of compound crystallinity and stability. This has been illustrated in a study that examined the effect of ball mill grinding on cefixime trihydrate (Kitamura et al. 1989). Using a variety of techniques, it was shown that the crystalline solid was converted to an amorphous solid after 4 h in a ball mill. The stability of the amorphous solid was found to be less than that of the crystalline solid, and the samples were discoloured due to grinding.

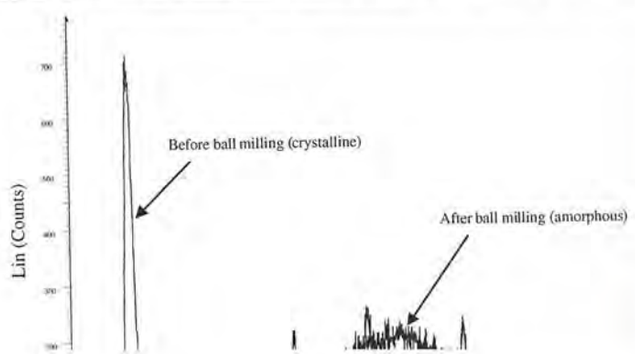
It is important to check this aspect of the milling process, since amorphous compounds can show increased bioavailability and possible pharmacological activity compared to the corresponding crystalline form. Ball milling may also change the polymorphic form of a compound, as shown by the work of Leung et al. (1999) with aspartame.

Figure 6.1, for example, shows the X-ray powder diffraction (XRPD) patterns of a sample of a compound "as received" and after ball milling. After ball milling for 1 h, the sample was rendered amorphous, and hence a shorter milling period was used.

### *Micronization*

If instrumentation and sufficient compound are available, then micronization can be undertaken. This technique is routinely used to reduce the particle size of active ingredients so that the maximum surface area is exposed to enhance the solubility and dissolution properties of poorly soluble compounds. Because of the enhanced surface area, the bioavailability of

**Figure 6.1** XRPD patterns showing the effect of ball milling on a compound.






compounds is often improved, e.g., micronization enhanced the bioavailability of felodipine when administered as an extended release tablet (Johansson and Abrahamsson 1997).

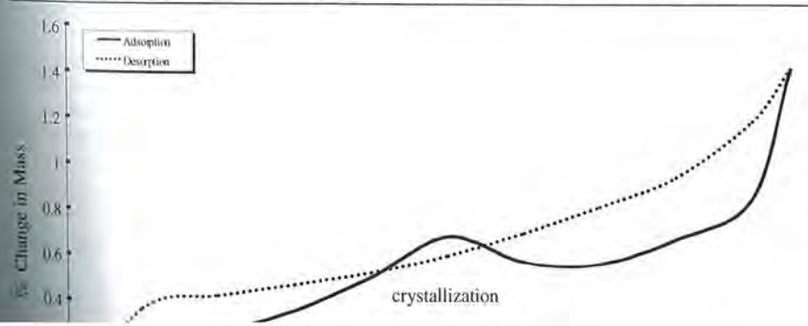
The process involves feeding the drug substance into a confined circular chamber where the powder is suspended in a high velocity stream of air. Interparticulate collisions result in a size reduction. Smaller particles are removed from the chamber by the escaping air stream towards the centre of the mill where they are discharged and collected. Larger particles recirculate until their particle size is reduced. Micronized particles are typically less than 10 μm in diameter (Midoux et al. 1999).

### *Effect of Milling and Micronization*

Although micronization of the drug offers the advantage of a small particle size and a larger surface area, it can result in processing problems due to high dust, low density and poor flow properties. Indeed, micronization may be counterproductive, since the micronized particles may aggregate, which may decrease the surface area. In addition, changes in crystallinity of the drug can also occur, which can be detected by techniques such as microcalorimetry (Briggner et al. 1994), dynamic vapour sorption (Ward and Schultz 1995) and inverse gas chromatography (Feeley et al. 1998).

Ward and Schultz (1995) reported subtle differences in the crystallinity of salbutamol sulphate after micronization by air jet milling. They found that amorphous to crystalline conversions occurred that were dependent on temperature and relative humidity (RH). It was suggested that particle size reduction of the powder produced defects on the surface that, if enough energy was imparted, led to amorphous regions on the surface. In turn, these regions were found to have a greater propensity to sorb water. On exposure to moisture, these regions crystallized and expelled excess moisture. This is illustrated in Figure 6.2, which shows the

**Figure 6.2** DVS isotherm showing crystallization effects due to moisture.



uptake of moisture, as measured by dynamic vapour sorption (DVS), of a micronized development compound. Note how the percent mass change increases and then decreases as the RH is increased between 40 and 60 percent during the sorption phase. This corresponds to crystallization of the compound and subsequent ejection of excess moisture. The compound also exhibits some hysteresis.

This effect can be important in some formulations, such as dry powder inhaler devices, since it can cause agglomeration of the powders and variable flow properties. In many cases, this low level of amorphous character cannot be detected by techniques such as XRPD. Since microcalorimetry can detect < 10 percent amorphous content (the limit of detection is 1 percent or less), it has the advantage over other techniques such as XRPD or DSC. Using the ampoule technique with an internal hygrostat, as described by Briggner et al. 1994, and shown in Figure 6.3, the amorphous content of a micronized drug can be determined by measuring the heat output caused by the water vapour inducing crystallization of the amorphous regions.

Figure 6.4 shows the calibration curve of heat output versus amorphous content of a development compound. In this case, the technique is used to crystallize, or condition, these amorphous regions by exposure to elevated RHs. Thus, if authentic 100 percent amorphous and crystalline phases exist, it is possible to construct a calibration graph of heat output versus percentage crystallinity, so that the amount of amorphous character introduced by the milling process can be quantified.

**Figure 6.3** Internal hygrostat and heat output due to crystallization of an amorphous phase measured by isothermal microcalorimetry.

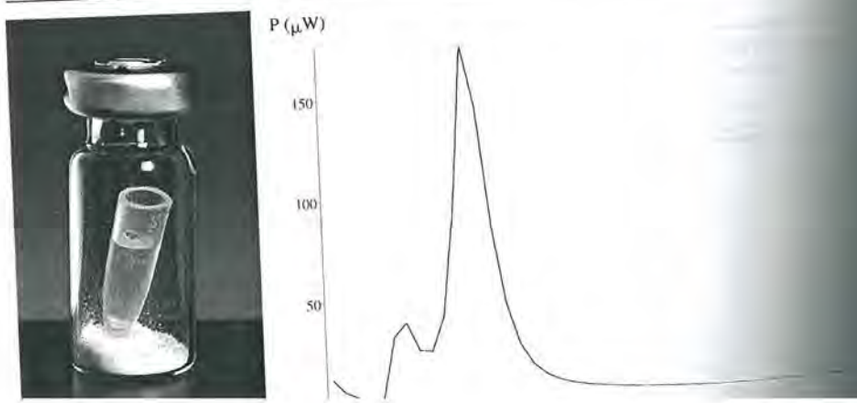
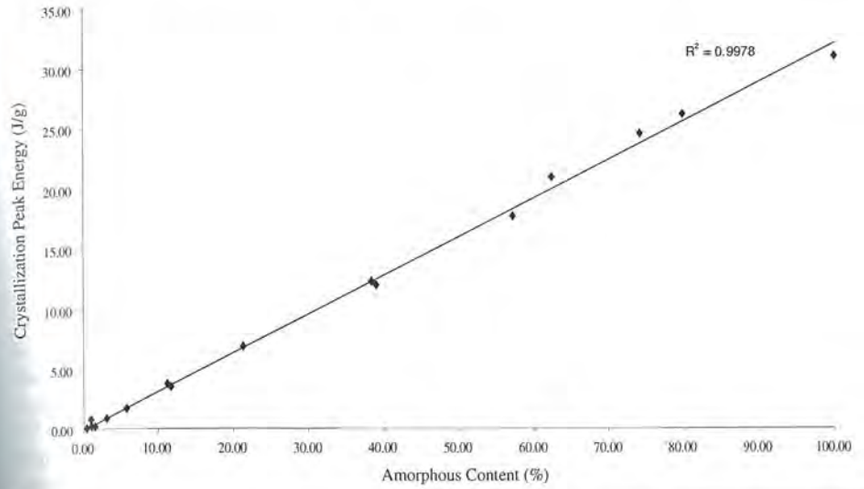





**Figure 6.4** Crystallization peak energy versus amorphous content using microcalorimetry.




### *Inverse Gas Chromatography*

In addition to the DVS and microcalorimetric techniques for characterizing the surface properties of powders, a recently introduced technique known as inverse gas chromatography (IGC) can also be used. This technique differs from traditional gas chromatography insofar as the stationary phase is the powder under investigation. In this type of study, a range of nonpolar and polar adsorbates (probes) are used, e.g., alkanes, from hexane to decane, acetone, diethyl ether or ethyl acetate. The retention volume, i.e., the net volume of carrier gas (nitrogen) required to elute the probe, is then measured. The surface partition coefficient ($K_s$) of the probes between carrier gas and surfaces of test powder particles can then be calculated. From this, a free energy can be calculated which can show that one batch may favourably adsorb the probes when compared to another, implying a difference in the surface energetics.

The experimental parameter measured in IGC experiments is the net retention volume, $V_n$. This parameter is related to the surface partition coefficient, $K_s$, which is the ratio between the concentration of the probe molecule in the stationary and mobile phases shown by

$$K_s = \frac{V_n}{m} \times A_{sp} \quad (1)$$

From $K_s$ the free energy of adsorption ($-\Delta G_A$) is defined by

$$-\Delta G_A = RT\ln\left(K_s \times \frac{P_{sg}}{P}\right) a\left(\gamma_L{}^D\right)^{1/2} \quad (2)$$

where $P_{sg}$ is the standard vapour state (101 KN/m$^2$) and $P$ is the standard surface pressure, which has a value of 0.338 mN/m.

IGC and molecular modelling have been used to assess the effect of micronization on dl-propranolol (York et al. 1998). The samples were jet milled (micronized) to various particle sizes and $\gamma_s{}^D$ was measured and plotted against their median particle size. This showed that as the particle size decreased due to the micronization process, the surface of the particles became more energetic. Interestingly, it was pointed out that the plateau region corresponded to the brittle-ductile region of this compound. This observation implied a change in the mechanism of milling from a fragmentation to an attrition process. The data for $-\Delta G_A{}^{SP}$ for the tetrahydrofuran (THF) and dichloromethane probes showed that the electron donation of the surface increased as the particle size decreased. Combining these data with molecular modelling, which was used to predict which surfaces would predominate, they showed that the electron-rich naphthyl group dominated the surface of the unmilled material. This led to the conclusion that as the particle size was reduced, this surface became more exposed, leading to a greater interaction with the THF and dichloromethane probes. However, as previously noted, as milling proceeded, the mechanism of size reduction changed, which might lead to exposure of the chloride and hydroxyl moieties.

Therefore, using moisture sorption, microcalorimetric, IGC, molecular modelling and other techniques, the consequences of the particle size reduction process can be assessed. Moreover, surface energetics can be measured directly and predictions made about the nature of the surface, which ultimately could affect properties such as the flow of powders or adhesion of particles (Podczeck et al. 1996b).

## Particle Size Distribution Measurement

Washington (1992) has discussed the concepts and techniques of particle size analysis and its role in pharmaceutical sciences and other industries. There are many different methods available for particle size analysis. The techniques most readily available include sieving, optical microscopy in conjunction with image analysis, electron microscopy, the Coulter Counter and laser diffractometers. Size characterization is simple for spherical particles, but not for irregular particles where the assigned size will depend on the method of characterization used. Table 6.2 lists particle size measurement methods commonly used and the corresponding approximate useful size range (Mullin 1993).

Figure 6.5 shows the particle size distribution of a micronized powder determined by scanning electron microscopy (SEM) and laser light scattering. The Malvern Mastersizer is an example of an instrument that measures particle size by laser diffraction. The use of this technique is based on light scattered through various angles, which is directly related to the diameter of the particle. Thus, by measuring the angles and intensity of scattered light from the particles, a particle size distribution can be deduced. It should be noted that the particle diameters reported are the same as those that spherical particles would produce under similar conditions. Table 6.3 shows the data obtained from the laser diffraction analysis shown in Figure 6.5.

Two theories dominate the theory of light scattering; the Fraunhofer and Mie. In the former, each particle is treated as spherical and essentially opaque to the impinging laser light. The



**Table 6.2**
**Particle size techniques and size range.**

| Method | Size Range (μm) |
|---|---|
| Sieving (woven wire) | 20–125,000 |
| Sieving (electroformed) | 5–120 |
| Sieving (perforated plate) | 1,000–125,000 |
| Microscopy (optical) | 0.5–150 |
| Microscopy (electron) | 0.001–5 |
| Sedimentation (gravity) | 1–50 |
| Sedimentation (centrifugal) | 0.01–5 |
| Electrical zone sensing (e.g., Coulter) | 1–200 |
| Laser light scattering (Fraunhofer) | 1–1,000 |
| Laser light scattering (quasi-elastic) | 0.001–1 |

From Mullin, J. W., *Anal. Proc.* 30:455–456 (1993). Reproduced by permission of The Royal Society of Chemistry.

Mie theory, on the other hand, takes into account the differences in refractive indices between the particles and the suspending medium. If the diameter of the particles is above 10 μm, then the size produced by utilizing each theory is essentially the same. However, discrepancies may occur when the diameter of the particles approaches that of the wavelength of the laser source.

The following are the values reported from diffraction experiments.

- $D\ (v, 0.1)$ is the size of particles for which 10 percent of the sample is below this size
- $D\ (v, 0.5)$ is the volume (v) median diameter of which 50 percent of the sample is below and above this size
- $D\ (v, 0.9)$ gives a size of particle for which 90 percent of the sample is below this size
- $D\ [4,3]$ is the equivalent volume mean diameter calculated using:

$$D\,[4,3] = \frac{\Sigma d^4}{\Sigma d^3} \quad (3)$$

- $D\ [3,2]$ is the surface area mean diameter; also known as the Sauter mean, where $d$ = diameter of each unit
- Log difference represents the difference between the observed light energy data and the calculated light energy data for the derived distribution
- *Span* is the measurement of the width of the distribution and is calculated using

$$Span = \frac{D\ (v,\ 0.9) - D\ (v,\ 0.1)}{D\ (v,\ 0.5)} \quad (4)$$

The dispersion of the powder is important in achieving reproducible results. Ideally, the dispersion medium should have the following characteristics:

- Have a suitable absorbancy
- Not swell the particles
- Disperse a wide range of particles
- Slow sedimentation of particles
- Allow homogeneous dispersion of the particles
- Be safe and easy to use

**Figure 6.5** SEM of a micronized powder and particle size measured by laser diffraction.

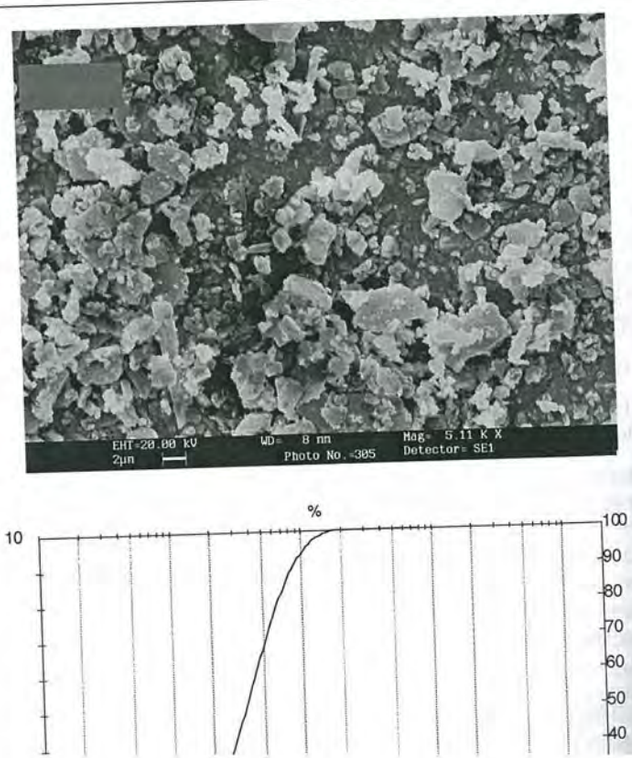





**Table 6.3**
**Particle size distribution of a micronized powder measured using laser diffraction.**

Beam: 2.40 mm Sampler: MS1 Obs': 15.8%
Analysis: Polydisperse Residual: 0.117%

Density = 1.427 g/cm$^3$ S.S.A. = 1.6133 m$^2$/g
*D* [4, 3] = 4.34 µm *D* [3, 2] = 2.61 µm
*D* (*v*, 0.5) = 3.50 µm *D* (*v*, 0.9) = 8.54 µm
Uniformity = 6.515E-01

| Volume under% | Size (µm) | Volume under% | Size (µm) | Volume under% | Size (µm) | Volume under% |
|---|---|---|---|---|---|---|
| 0.00 | 0.65 | 1.09 | 4.30 | 60.67 | 28.15 | 100.00 |
| 0.00 | 0.81 | 2.58 | 5.29 | 71.18 | 34.69 | 100.00 |
| 0.00 | 1.00 | 5.08 | 6.52 | 80.61 | 42.75 | 100.00 |
| 0.00 | 1.23 | 8.90 | 8.04 | 88.21 | 52.68 | 100.00 |
| 0.00 | 1.51 | 14.24 | 9.91 | 93.69 | 64.92 | 100.00 |
| 0.00 | 1.86 | 21.22 | 12.21 | 97.18 | 80.00 | 100.00 |
| 0.00 | 2.30 | 29.72 | 15.04 | 99.08 | | |
| 0.03 | 2.83 | 39.38 | 18.54 | 99.87 | | |
| 0.34 | 3.49 | 49.86 | 22.84 | 100.00 | | |

In terms of sample preparation, it is necessary to deaggregate the samples so that the primary particles are measured. To achieve this, the sample may be sonicated, although there is a potential problem of the sample being disrupted by the ultrasonic vibration. To check for this, it is recommended that the particle dispersion be examined by optical microscopy.

Although laser light diffraction is a rapid and highly repeatable method in determining the particle size distributions of pharmaceutical powders, the results obtained can be affected by particle shape. In this respect, Kanerva et al. (1993) examined narrow sieve fractions of spherical pellets, cubic sodium chloride and acicular anhydrous theophylline. Size distributions were made using laser light diffraction and compared to results using image analysis. The results showed that all determinations using the laser light scattering resulted in a broadened size distribution compared to image analysis. In addition, it has been pointed out that the refractive index of the particles can introduce an error of 10 percent under most circumstances if it is not taken into account (Zhang and Xu 1992).

Another laser-based instrument, relying on light scattering, is the Aerosizer. This instrument is for a particle sizing and is based on a time-of-flight principle as described by Niven (1993). The Aerosizer with aero-disperser is specifically designed to carry deaggregated particles in an air stream for particle sizing. This instrumentation has been evaluated using a salbutamol base, terbutaline sulphate and lactose (Hindle and Byron 1995).

For submicron materials, particularly colloidal particles, quasi-elastic light scattering is the preferred technique. This has been usefully reviewed by Phillies (1990). The particle size distribution of ofloxacin/prednisolone acetate for ophthalmic use has been investigated by image analysis photon correlation spectroscopy (PCS) and single particle optical sizing (SPOS) (Hacche et al. 1992). Using these techniques, it was shown that ball milling yielded a particle size of ~ 1 μm and that increasing the ball-milling time increased the reproducibility of diameter of particles. PCS was then used to show that extended ball milling reduced the particle size to a constant value.

## Surface Area Measurements

The surface areas of drug particles are important because dissolution is a function of this parameter (as predicted by the Noyes-Whitney equation). Surface area can also be quoted if the particle size is difficult to measure (Curzons et al. 1993).

Surface areas are usually determined by gas adsorption (nitrogen or krypton) and although there are a number of theories describing this phenomenon, the most widely used method is the Brunauer, Emmet and Teller, or BET, method. Adsorption methods for surface area determination have been reviewed in detail by Sing (1992). Two methods are used: the multipoint and single-point.

Without going into too much theoretical detail, the BET isotherm for Type II adsorption processes (typical for pharmaceutical powders) is given by:

$$\frac{P}{v(p_0 - p)} = \frac{1}{cV} + \left\{\frac{c-1}{cV}\right\}\left\{\frac{P}{P_0}\right\} \qquad (5)$$

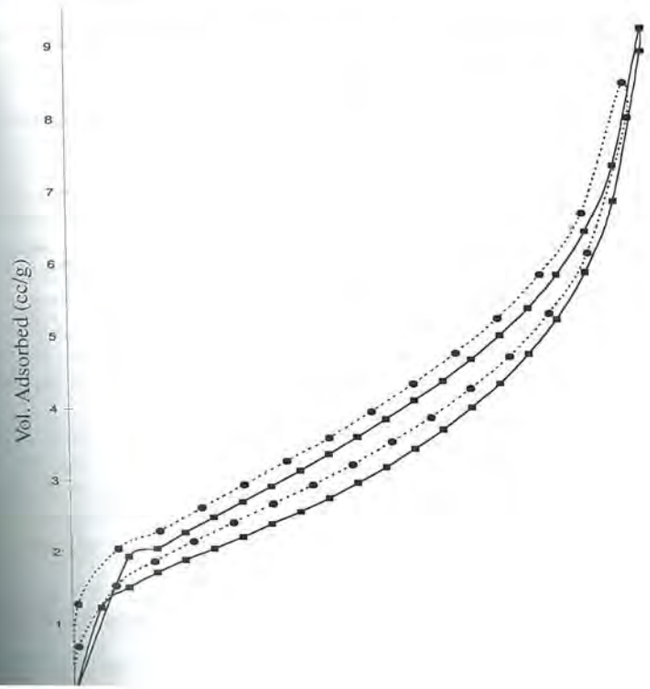


$$S_t = \frac{V_{mon} N A_{CS}}{M} \qquad (6)$$

where $N$ is the Arogadro's number, $A_{cs}$ is the cross-sectional area of the adsorbate and $M$ is the moleular weight of the adsorbate. It follows that the specific surface area is given by $S_t/m$, where $m$ is the mass of the sample. According to the U. S. Pharmacopeia (USP), the data are considered to be acceptable if, on linear regression, the correlation coefficient is not less than 0.9975, i.e., $r^2$ is not less than 0.995.

Figure 6.6 shows the full adsorption-desorption isotherm of two batches of the micronized powder shown earlier in Figure 6.4.

**Figure 6.6** Full Type IIb adsorption isotherm for two batches of a micronized powder.

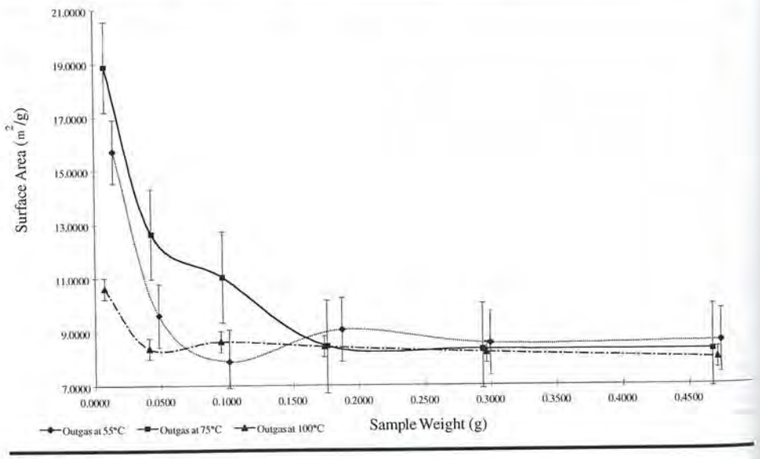


It should be noted that, experimentally, it is necessary to remove gases and vapours that may be present on the surface of the powder. This is usually achieved by drawing a vacuum or purging the sample in a flowing stream of nitrogen. Raising the temperature may not always be advantageous. For example, Phadke and Collier (1994) examined the effect of degassing temperature on the surface area of magnesium stearate obtained from two manufacturers. In this study, helium at a range of temperatures between 23 and 60°C was used in single and multipoint determinations. It was found that the specific surface area of the samples decreased with an increase in temperature. From other measurements using DSC and thermogravimetric analysis (TGA), it was found that raising the temperature changed the nature of the samples. Hence, it was recommended that magnesium stearate should not be degassed at elevated temperatures. Figure 6.7 shows the effect of sample weight and temperature of degassing on a sample of a micronized powder using a Micromeritics Gemini BET analyser. From this plot, it can be seen that the weight of the sample can have a marked effect on the measured surface area of the compound under investigation. Therefore, to avoid reporting erroneous surface areas, the sample weight should not be too low, and in this case, should be greater than 300 mg.

## True Density

Density can be defined as ratio of the mass of an object to its volume; therefore, the density of a solid is a reflection of the arrangement of molecules in a solid. In pharmaceutical development terms, knowledge of the true density of powders has been used for the determination of

**Figure 6.7** Effect of sample weight and degassing temperature on the surface area of micronized powder.






the consolidation behaviour. For example, the well-known Heckel equation (7) requires knowledge of the true density of the compound:

$$\ln\left[\frac{1}{1-D}\right] = KP + A \tag{7}$$

where $D$ is the relative density, which is the ratio of the apparent density to the true density, $K$ is determined from the linear portion of the Heckel plot and $P$ is the pressure. The densities of molecular crystals can be increased by compression, for example, whilst investigating the compression properties of acetylsalicylic acid using a compaction simulator, increases in the true density were found (Pedersen and Kristensen 1994).

Information about the true density of a powder can be used to predict whether a compound will cream or sediment in a metered dose inhaler (MDI) formulation. The densities of the hydrofluoroalkane (HFA) propellants, 227 and 134a, which are replacing chlorofluorocarbons (CFCs) in MDI formulations, are 1.415 and 1.217 g/cm$^{-3}$, respectively. Therefore, suspensions of compounds that have a true density less than these figures will cream (rise to the surface), and those that are denser will sediment. Those that match the density of the propellant will stay in suspension for a longer period (Williams III et al. 1998). It should be noted, however, that the physical stability of a suspension is not merely a function of the true density of the material.

The true density is thus a property of the material and is independent of the method of determination. In this respect, the determination of the true density can be determined using three methods: displacement of a liquid, displacement of a gas (pycnometry) or floatation in a liquid. These methods of measuring true density have been evaluated by Duncan-Hewitt and Grant (1986). They concluded that, whereas liquid displacement was tedious and tended to underestimate the true density, displacement of a gas was accurate but needed relatively expensive instrumentation. As an alternative, the floatation method was found to be simple to use and inexpensive. Although more time consuming than gas pycnometry, it was accurate using relatively simple instrumentation.

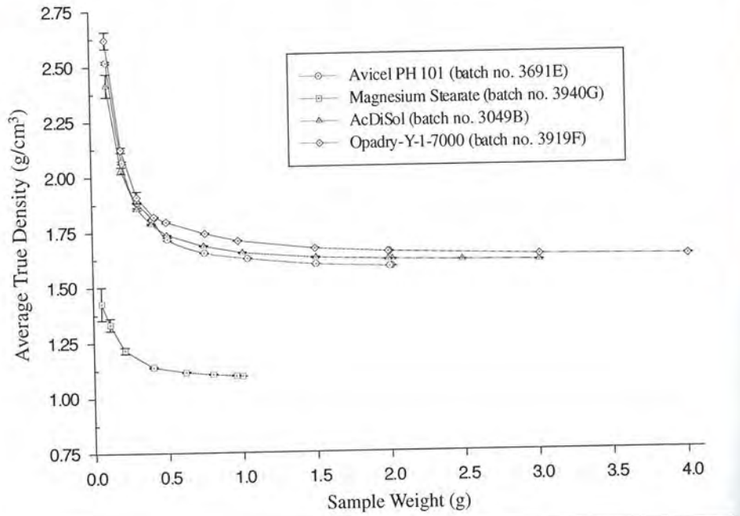
Gas pycnometry is probably the most commonly used method in the pharmaceutical industry for measuring true density. All gas pycnometers rely on the measurement of pressure changes, as a reference volume of gas, typically helium, is added to, or deleted from, the test cell.

Experimentally, measurements should be carried out in accordance with the manufacturers' instructions. However, it is worth noting that artefacts may occur. For example, Figure 6.8 shows the measured true density of a number of tableting excipients as a function of sample weight. As can be seen, at low sample weights, the measured true density increased, making the measurements less accurate.

## Flow and Compaction of Powders

Although at the preformulation stage only limited quantities of candidate drug are available, any data generated on flow and compaction properties can be of great use to the formulation scientist. The data provided can give guidance on the selection of the excipients to use, the formulation type and the manufacturing process to use, for example, direct compression or granulation. It is important that once the habit and size distribution of the test compound have been determined, the flow and compaction properties are evaluated, if the intended dosage form is a solid dosage form. York (1992) has reviewed the crystal engineering and particle

**Figure 6.8** True density as a function of sample mass for some excipients.




design for the powder compaction process, and Amidon (1999) has reviewed the powder flow methods.

The compression of flow powders is dealt with in more detail in Chapter 11, Oral Solid Dosage Forms. With respect to the preformulation screening of candidate drugs for solid dosage forms, a protocol to examine their compression properties devised by Aulton and Wells (1988) is recommended. Their scheme is shown in Table 6.4. Essentially, the compound is compressed using an infrared (IR) press and die under 10 tons of pressure, and the resulting tablets are tested with regard to their crushing strength.

The interpretation of crushing strengths was as follows. If the crushing strengths are of the order B > A > C, the material probably has plastic tendencies. Materials that are brittle are usually independent of the scheme, whilst elastic material can behave in a variety of ways. For example: (a) A will cap or laminate; (b) B will probably maintain integrity, but will be very weak; and (c) C will cap or laminate (Aulton and Wells 1988).

Figure 6.9 shows a scanning electron micrograph of a compound that had poor compression properties. Notice how the top of the compact has partially detached (capping) and how the compact has separated into layers (lamination).

As shown by Otsuka and Matsuda (1993), it is always worth checking the effect of compression on a powder if the compound is known to be polymorphic. Using the XRPD patterns of chlorpropamide forms A and C, they examined the effect of temperature and

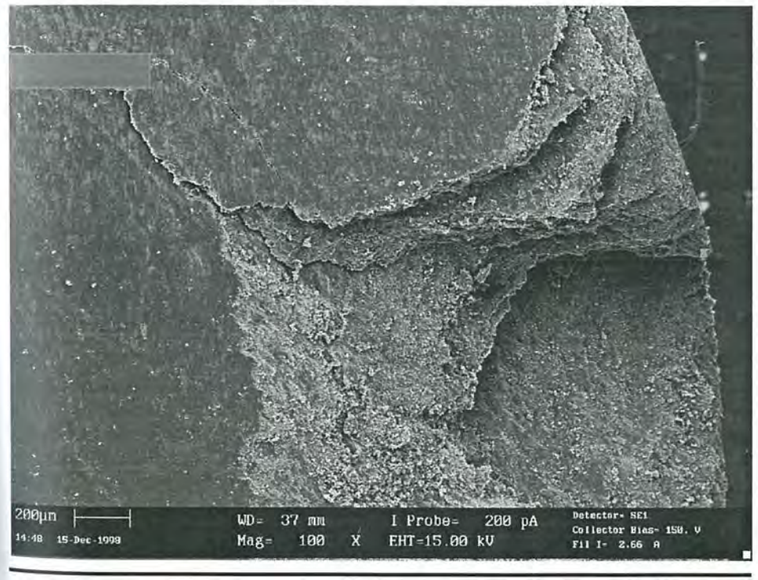


**Table 6.4**
**Compression protocol (Aulton and Wells 1988).**

| | 500 mg drug + 1% magnesium stearate | | |
|---|---|---|---|
| | **A** | **B** | **C** |
| Blend in a tumbler mixer for | 5 min | 5 min | 30 min |
| Compress 13 mm diameter compacts in a hydraulic press at | 75 MPa | 75 MPa | 75 MPa |
| Dwell time of | 2 sec | 30 sec | 2 sec |
| Store tablets in sealed container at room temperature to allow equilibration | 24 h | 24 h | 24 h |
| Perform crushing strength on tablets and record load | AN | BN | CN |

Aulton, M. A., and Wells, J. E. (1998), *Pharmaceutics: The Science of Dosage Form Design*, edited by M. E. Aulton. Reprinted with permission from Churchill Livingstone.

**Figure 6.9.** SEM of a compound that undergoes capping and lamination.



compression force on the deagglomerated powders and found that both forms were mutually transformed.

Computational methods of predicting the mechanical properties of a powder from the crystal structure are now being explored. There appears to be a relationship between indentation hardness and the molecular structure of organic materials. However, a prerequisite for predicting indentation hardness is knowledge of the crystal structure (Roberts et al. 1994). Payne et al. (1996) have used molecular modelling to predict the mechanical properties of aspirin and forms A and B of primodone. The predicted results of Young's modulus were found to be in good agreement with those determined experimentally, and thus compaction measurements might not always be necessary if they are difficult to perform.

## Colour

Colour can be useful when describing different batches of drug substance, since it can sometimes be used as an indicator of solvent presence or, more importantly, of degradation. In addition, subtle differences in colour may be due to variations in the particle size distribution. Usually colour is subjective and is based on individual perception; however, more quantitative measurements can be obtained by using, e.g., tristimulus colorimetry (Nyqvist et al. 1980; Vemuri et al. 1985; Nyqvist and Wadsten 1986; Stock 1993).

Stark et al. (1996) have observed colour changes during accelerated stability testing of captopril tablets, flucloxacillin sodium capsules, cefoxitin sodium powder for injection and theophylline CR tablets. Under ambient conditions, only the flucloxacillin sodium and cefoxitin were observed to show any significant colouring. However, under stress conditions of accelerated stability testing, a linear relationship between colour formation and the drug content of the formulations was found, except for the theophylline tablets, where discoloration occurred in the absence of any significant degradation. Interestingly, the rate of colouring was found to obey the Arrhenius equation. The authors proposed that the shelf life of the formulations could be specified using the Commission Internationale de'Ecalarage (CIE) system for colour.

## Electrostaticity

Powders can acquire an electrostatic charge during processing, the extent of which is related to the aggressiveness of the process. Table 6.5, from BS5958, gives the range of values that arise due to various processes. According to Kulvanich and Stewart (1987), static electrification of two dissimilar materials occurs by the making and breaking of surface contacts (triboelectrification). Thus, the extent of the electrostatic charge accumulation will increase as the surfaces collide and contact, e.g., by increasing the agitation time and intensity of a powder in a mixer. The net results will therefore increase the spot charge over the particle surfaces and adhesive characteristics. This technique has been used to prepare drug-carrier systems known as an interactive mixture. Kulvanich and Stewart (1987) have reported the effect of particle size and concentration on the adhesive characteristics of a model drug carrier (glass beads coated with hydroxypropyl methylcellulose [HPMC] plus a range of antibiotic sulpha drugs). From their results, they concluded that an increase in size and particle concentration decreased the adhesive tendencies of the drug.

The net charge on a powder may be either electropositive or electronegative. Although the process is not fully understood, it is generally accepted that charging occurs as a result of electron transfer between materials of different electrical properties.



**Table 6.5**
**Mass charge density arising from various operations (BS5958).**

| Operation | Mass Charge Density (μC/kg) |
|---|---|
| Sieving | $10^{-5}$ to $10^{-3}$ |
| Pouring | $10^{-3}$ to $10^{-1}$ |
| Scroll feed transfer | $10^{-2}$ to 1 |
| Grinding | $10^{-1}$ to 1 |
| Micronising | $10^{-1}$ to $10^{2}$ |



The electrostatic charges on the surface of a powder can affect the flow properties of powders. An electric detector can determine the electric field generated by the electrostatic charges on the surface of the powder. This acts as a voltmeter and allows the direct determination of both polarity and absolute value of the electrostatic field. As an example, the electrostaticity of the experimental compound ITF 296, when sieved at 200 μm, showed an electrostatic field of -60 V due to the charge on the powder surface (Dobetti et al. 1995). As a consequence, the powder formed stacked aggregates, which led to the unsieved powder being less wettable and difficult to handle. Führer (1996) has reviewed interparticulate attraction mechanisms.

Carter et al. (1992) designed and used an apparatus to investigate the triboelectrification process between α-lactose monohydrate and beclomethasone dipropionate and salbutamol sulphate. The results showed that particle size and the type and nature of contact surface resulted in differences in charging tendencies. Further work on this topic by this group (Carter et al. 1998) investigated the charging and its decay on compacts of lactose and salbutamol and polyvinyl chloride (PVC), which are commonly used dry powder inhaler devices. Results showed that PVC gained to the highest charge from a carona electrode. Whilst the PVC and the lactose lost their charge relatively quickly (within 30 min), salbutamol still had a measurable charge after 120 min.

## Caking

Caking can occur after storage and involves the formation of lumps or the complete agglomeration of the powder. A number of factors have been identified that predispose a powder to exhibit caking tendencies. These include static electricity, hygroscopicity, particle size, impurities of the powder and, in terms of the storage conditions, stress temperature, RH and storage time can also be important. The caking of 11-amino undeceonoic acid has been investigated, and it was concluded that the most important cause of the observed caking with this compound was its particle size (Provent et al. 1993). The mechanisms involved in caking are based on the formation of five types of **interparticle bonds:**

1. Bonding resulting from mechanical tangling
2. Bonding resulting from steric effects
3. Bonds via static electricity
4. Bonds due to free liquid
5. Bonds due to solid bridges

The caking tendency of a development compound was investigated when it was discovered to be lumpy after storage. An experiment was performed on the compound whereby it was stored at different RHs (from saturated salt solutions) for 4 weeks in a desiccator. Results revealed that caking was evident at 75 percent RH with the compound forming loosely massed porous cakes (Table 6.6). TGA of the samples showed that caked samples lost only a small amount of weight on heating (0.62 percent w/w), which indicated that only low levels of moisture were required to produce caking for this compound.

It is known that micronization of compounds can lead to the formation of regions with a degree of disorder which, because of their amorphous character, are more reactive compared to the pure crystalline substance. This is particularly true on exposure to moisture and can lead to problems with caking, which is detrimental to the performance of the product. It has been argued that these amorphous regions transform during moisture sorption, due to surface sintering and recrystallization at RHs well below the critical RH.

## Polymorphism Issues

Because polymorphism can have an effect on so many aspects of drug development, it is important to fix the polymorph (usually the stable form) as early as possible in the development cycle.

A U.S. Food and Drug Administration (FDA) reviewer's perspective of regulatory considerations in crystallization processes for bulk pharmaceutical chemicals has been presented by DeCamp (1996). In this paper, he stated that

**Table 6.6**
**Effect of moisture on the caking of a development compound.**

| %RH | Moisture Content | Appearance and Flow Properties |
|---|---|---|
| 0 | 0.31 | Free-flowing powder; passed easily through sieve |
| 11.3 | 0.24 | Ditto |
| 22.5 | 0.27 | Less free-flowing powder |
| 38.2 | 0.32 | Base of powder bed adhered to petri dish; however, material above this flowed |
| 57.6 | 0.34 | Less free flowing |
| 75.3 | 0.62 | Material caked |
| Ambient | 0.25 | Base of powder adhered to petri dish |



> process validation should include at least one, if not more, checks to verify that the process yields the desired polymorph. At the time of a New Drug Application (NDA) submission, it would be expected that occurrences of polymorphism would be established and whether these affect the dissolution rate or the bioavailibility.

He continued that

> It is not necessary to create additional solid state forms by techniques or conditions unrelated to the synthetic process for the purpose of clinical trials. However, submission of a thorough study of the effects of solvent, temperature and possibly pressure on the stability of the solid state forms should be considered. A conclusion that polymorphism does not occur with a compound must be substantiated by crystallization experiments from a range of solvents. This should also include solvents that may be involved in the manufacture of the drug product, e.g., during granulation.

Whilst it is hoped that the issue of polymorphism is resolved during prenomination and early development, it can remain a concern when the synthesis of the drug is scaled-up into a larger reactor or transferred to another production site. In extreme cases, and despite intensive research, work may have only produced a metastable form, and the first production batch produces the stable form. Dunitz and Bernstein (1995) have reviewed the appearance of, and subsequent disappearance of, polymorphs. Essentially, this describes the scenario whereby, after nucleation of a more stable form, the previously prepared metastable form could no longer be made.

The role of related substances in the case of the disappearing polymorphs of sulphathiazole has been explored (Blagden et al. 1998). These studies showed that a reaction by-product from the final hydrolysis stage could stabilize different polymorphic forms of the compound, depending on the concentration of the by-product. Using molecular modelling techniques, they were able to show that ethamidosulphthiazole, the by-product, influenced the hydrogen bond network, and hence form and crystal morphology.

In the development of a reliable commercial recrystallization process for dirithromycin, Wirth and Stephenson (1997) proposed that the following scheme should be followed in the production of candidate drugs:

1. Selection of solvent system
2. Characterization of the polymorphic forms
3. Optimisation of process times, temperature, solvent compositions, etc.
4. Examination of the chemical stability of the drug during processing
5. Manipulation of the polymorphic form, if necessary

Whilst examples of disappearing polymorphs exist, perhaps more common is the crystallization of mixtures of polymorphs. Many analytical techniques have been used to quantitate mixtures of polymorphs, e.g., XRPD has been used to quantitate the amount of cefepime · 2HCl dihydrate in cefepime · 2HCl monohydrate (Bugay et al. 1996). As noted by these workers, a crucial factor in developing an assay based on a solid-state technique is the production of pure calibration and validation samples. Moreover, whilst the production

of the forms may be straightforward, production of homogeneously mixed samples for calibration purposes may not. To overcome this problem, a slurry technique was employed, which satisfied the NDA requirements, to determine the amount of one form in the other. The criteria employed were as follows:

- A polymorphic transformation did not occur during preparation or analysis
- A limit of detection of 5 percent (w/w) of the dihydrate in monohydrate
- Ease of sample preparation, data acquisition and analysis
- Ease of transfer to a quality control (QC) environment

Calibration samples were limited to a working range of 1–15 percent w/w, and to prepare the mixes, samples of each form were slurried in acetone to produce a homogeneous mixture of the two.

With respect to solid dosage forms, there have been a few reports on how processing affects the polymorphic behaviour of compounds. For example, the effect of polymorphic transformations that occurred during the extrusion-granulation process of carbamazepine granules has been studied by Otsuka et al. (1997). Results showed that granulation using 50 percent ethanol transformed Form I into the dihydrate during the process. Wet granulation (using ethanol-water) of chlorpromazine hydrochloride was found to produce a phase change (Wong and Mitchell 1992). This was found to have some advantage, since Form II (the initial metastable form) was found to show severe capping and lamination compared to Form I, the (stable) form produced on granulation. As another example, Yamaoka et al. (1982) reported the cracking of tablets by one form of carbochromen.

Polymorphism is not an issue only with the compound under investigation; excipients also show variability in this respect. For example, it is well known that the tablet lubricant magnesium stearate can vary depending on the supplier. In one study, Wada and Matsubara (1992) examined the polymorphism with respect to 23 batches of magnesium stearate obtained from a variety of manufacturers. Using DSC, they classified the batches into six groups—interestingly, the polymorphism was not apparent by XRPD, IR or SEM observations. In another report, Barra and Somma (1996) examined 13 samples of magnesium stearate from 3 manufacturers. They found that there was variation not only between the manufacturers but also in the lots supplied by the same manufacturer.

## SOLUTION FORMULATIONS

Development of a solution formulation requires a number of key pieces of preformulation information. Of these, solubility (and any pH dependence) and stability are probably the most important. Since parenteral products probably represent the most common solution formulation type, these are discussed in more detail. The principles and practices governing the formulation development of parenteral products have been reviewed by Sweetana and Akers (1996) and are discussed in detail in Chapter 9 on Parenteral Dosage Forms. Rowe et al. (1995) have described an expert system for the development of parenteral products.



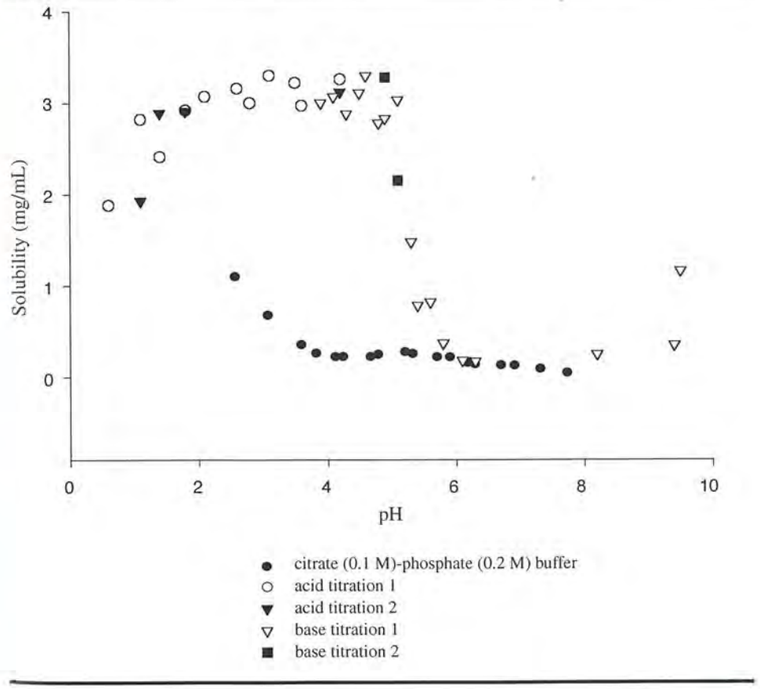
### Solubility Considerations

One of the main problems associated with developing a parenteral or any other solution formulation of a compound is its aqueous solubility. For poorly soluble drug candidates, there are several strategies for enhancing their solubility. These include pH manipulation, cosolvents, surfactants, emulsion formation and complexing agents. More sophisticated delivery systems, e.g., liposomes, can also be used in this way.

#### *pH Manipulation*

Since many compounds are weak acids or bases, their solubility will then be a function of pH. Figure 6.10 shows the pH-solubilty curve for a hydrochloride salt with p$K_a$s at 6.58 and 8.16. When the acid-base titration method (Serrajudden and Mufson 1985) was used, the solubility curve showed a minimum between pH 6 and 8. Below this pH region, the solubility

**Figure 6.10** pH-solubility curve of a development compound (amine hydrochloride).



increased as the $pK_a$ was passed, to reach a maximum between pH 2 and 4 and then decreased due to the common ion effect. As the second $pK_a$ was passed in the alkaline region, the solubility again increased.

When the solubility experiments were performed in 0.2 M citrate-phosphate buffer, the compound solubility decreased, and this illustrates the effect that ionic strength may have on drug solubility. Clearly, the region between pH 2 and 5 represents the area to achieve the best solubility. However, caution should be exercised if the solution needs to be buffered, since this can decrease the solubilty. Myrdal et al. (1995) found that a buffered formulation of a compound did not precipitate on dilution and did not cause phlebitis. In contrast, the unbuffered drug formulation showed the opposite effects. These results reinforce the importance of buffering parenteral formulations instead of simply adjusting the pH.

### *Co-solvents*

The use of co-solvents has been utilized quite effectively for some poorly soluble drug substances. It is probable that the mechanism of enhanced solubility is the result of the polarity of the co-solvent mixture being closer to the drug than it is in water. This was illustrated in a series of papers by Rubino and Yalkowsky (1984, 1985a, b, 1987a, b) who found that the solubilities of phenytoin, benzocaine and diazepam in co-solvent and water mixtures were approximated by the log-linear equation

$$\log S_m = f \log S_c + (1 - f) \log S_w \tag{8}$$

where $S_m$ = the solubility of the compound in the solvent mix, $S_w$ = solubility in water, $S_c$ is the solubility of the compound in pure cosolvent, $f$ = the volume fraction of co-solvent and $\sigma$ = the slope of the plot of log ($S_m/S_w$) versus $f$. Furthermore, they related s to indexes of co-solvent polarity such as the dielectric constant, solubility parameter, surface tension, interfacial tension and octanol-water partition coefficient.

It was found that the aprotic co-solvents gave a much higher degree of solubility than the amphiprotic co-solvents. This means that if a co-solvent can donate a hydrogen bond, it may be an important factor in determining whether it is a good co-solvent. Deviations from log-linear solubility were dealt with in a subsequent paper (Rubino and Yalkowsky 1987). Figure 6.11 shows how the solubility of a development drug increases in a number of water-solvent systems. Care must be taken when attempting to increase the solubility of a compound; a polar drug might actually show a decrease in solubility with increasing co-solvent composition (Gould et al. 1984).

It is often necessary to administer a drug parenterally at a concentration that exceeds its aqueous solubility. Co-solvents offer one way of increasing drug solubility, but the amount of co-solvent that can be used in a parenteral IV formulation is often constrained by toxicity considerations. The formulation may cause haemolysis (Fu et al. 1987), or the drug may precipitate when diluted or injected, causing phlebitis (e.g., Ward and Yalkowsky 1993). Yalkowsky and co-workers (1983) have developed a useful *in vitro* technique, based on ultraviolet (UV) spectrophotometry, for predicting the precipitation of parenteral formulations *in vivo* following injection. Figure 6.12 shows the effect of injection rate on the transmittance at 600 nm of a PEG 400 formulation of a compound being introduced into flowing saline. As shown, the faster the injection rate, the more precipitation was detected by the spectrophotometer. This simple technique can be used to assess whether preciptation of a compound might occur on dilution or injection.



**Figure 6.11** Solubility as a function of co-solvent volume for a development compound.

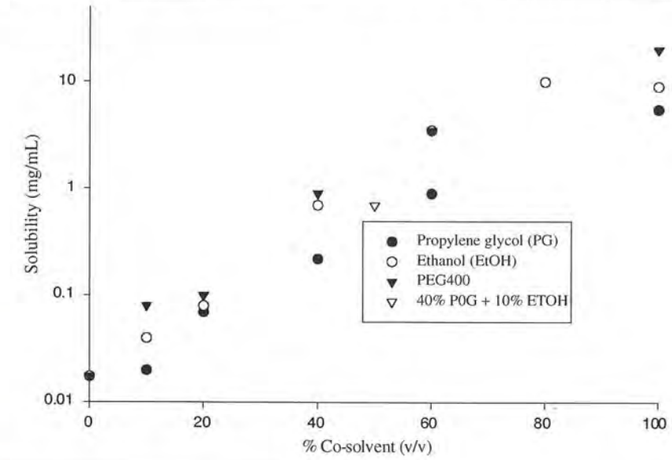
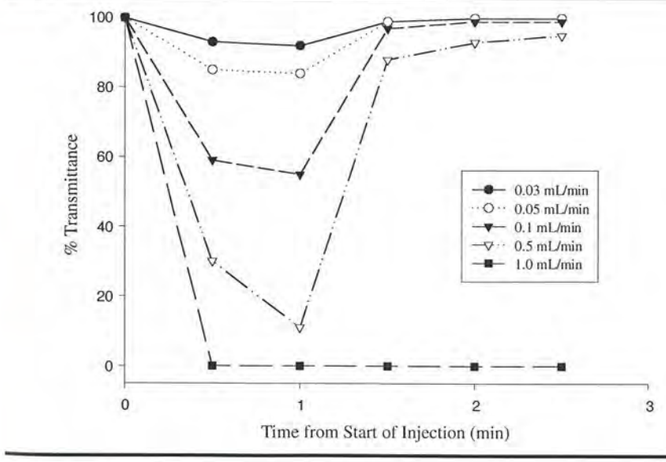



**Figure 6.12** Effect of flow rate on the precipitation of a PEG400 solution of a drug compound.



Whilst co-solvents can increase the solubility of compounds, on occasion they can have a detrimental effect on their stability. For example, a parenteral formulation of the novel anti-tumour agent carzelsin (U80,244), using a polyethylene glygol 400 (PEG 400)/absolute ethanol/polysorbate 80 (PET) formulation (ratio 6:3:1, v/v/v), has been reported (Jonkman-De Vries et al. 1995). Whilst this formulation effectively increased the solubility of the compound, this work showed that interbatch variation of PEG 400 could affect the stability of the drug through pH effects.

One point that is often overlooked when considering co-solvents is their influence on buffers or salts. Since these are conjugate acid-base systems, it is not surprising that by introducing solvents into the solution, a shift in the $pK_a$ of the buffer or salt can result. These effects are important in formulation terms, since many injectable formulations that contain co-solvents also contain a buffer to control the pH (Rubino 1987).

### *Emulsion Formulations*

Oil-in-water (o/w) emulsions have been successfully employed to deliver drugs with poor water solubility, e.g, diazepam (Collins-Gold et al. 1990). In preformulation terms, the solubility of the compound in the oil phase (often soybean oil) is the main consideration in using this approach. However, the particle size of the emulsion and its stability (physical and chemical) also need to be assessed. Ideally, the particle size of the emulsion droplets should be in the colloidal range to avoid problems with phlebitis. To achieve this size, a microfluidizer should be used, since other techniques may produce droplets of a larger size, as shown in Table 6.7 (Lidgate 1990). Emulsions are prepared by homogenizing the oil in water in the presence of emulsifiers, e.g., phospholipids, which stabilize the emulsion via a surface charge and a mechanical barrier.

The particle size of emulsions can be measured using PCS (e.g., Whateley et al. 1984), whilst the surface charge or zeta potential can be measured using electrophoretic mobility measurements (Levy and Benita 1989). Physical instability of emulsions can take a number of forms, e.g., creaming, flocculation, coalescence or breaking, whilst chemical instability can be due to hydrolysis of the stabilizing moieties. In order to assess the stability of the emulsion, heating and freezing cycles can be employed, as well as centrifugation (Yalabik-Kas 1985). Chansiri et al. (1999) have investigated the effect of steam sterilization (121°C for 15 min) on

**Table 6.7**
**Size of emulsion droplets produced by various methods.**

| Method of Manufacture | Particle Size (μm) |
|---|---|
| Vortex | 0.03–24 |
| Blade mixer | 0.01–9 |



the stability of o/w emulsions. They found that emulsions with a high negative zeta potential did not show any change in their particle size distribution after autoclaving. Emulsions with a lower negative value, on the other hand, were found to separate into two phases during autoclaving. Because the stability of phospholipid-stabilized emulsions is dependent on the surface charge, these emulsions are normally autoclaved at pH 8–9.

## Stability Considerations

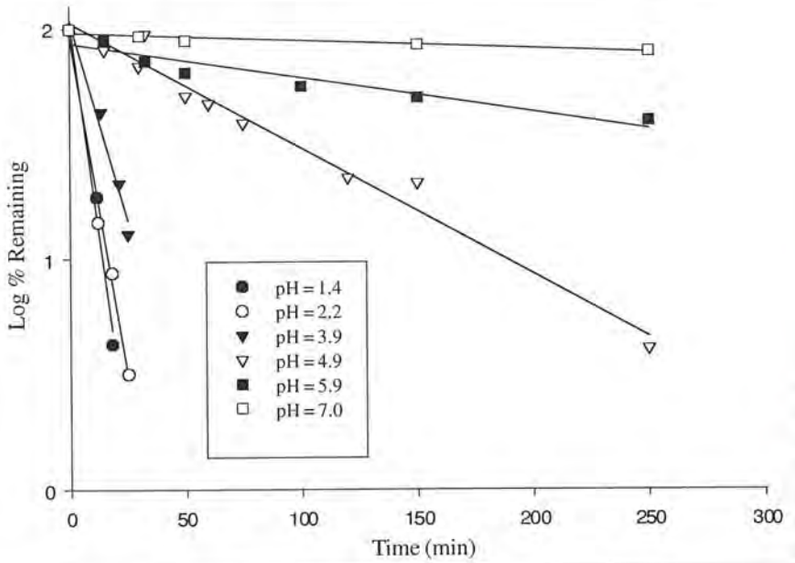
The second major consideration with respect to solution formulations is stability. Notari (1996) has presented some arguments regarding the merits of a complete kinetic stability study. He calculated that with reliable data and no buffer catalysis, 16 experiments were required to provide a complete kinetic stability study. If buffer ions contribute to the hydrolysis, then each species contributes to the pH-rate expression. Thus, for a single buffer, e.g., phosphate, a minimum of 6 experiments was required. A stock solution of the compound should be prepared in an appropriate solvent and a small aliquot (e.g., 50 μL) added to, e.g., a buffer solution at a set pH. This solution should be maintained at a constant temperature, and the ionic strength may be controlled by the addition of KCl (e.g., $I = 0.5$). After thorough mixing, the solution is then sampled at various time points and assayed for the compound of interest. If the reaction is very fast, it is recommended that the samples are diluted into a medium that will stop or substantially slow the reaction; for example, a compound that is unstable in acid may be stable in an alkaline medium. Cooling the solution may also be useful. Slow reactions, on the other hand, may require longer-term storage at elevated temperature. In this situation, solutions should be sealed in an ampoule to prevent loss of moisture. If sufficient compound is available, the effect of, e.g., buffer concentration, should be investigated.

The first-order decomposition plot of an acid labile compound with respect to pH is shown in Figure 6.13. Clearly, this compound is very acid labile, and even at pH 7, some decomposition is observed. A stable solution formulation would, therefore, be difficult to achieve in this pH range.

A detailed paper on the mechanistic interpretation of pH-rate profiles is that by Loudon (1991). More recently, van der Houwen et al. (1997) have reviewed the systematic interpretation of pH-degradation profiles. The rate profiles obtained when pH is varied can take a number of forms. However, Loudon (1991) makes the point that they "usually consist of linear regions of integral slope connected by short curved segments". Indeed, the linear regions generally have slopes of –1, 0, or +1 and "any pH-rate profile can be regarded as a composite of fundamental curves".

It is also possible that compounds may be formulated in co-solvent systems for geriatric or paediatric use, where administration of a tablet would be difficult (Chang and Whitworth 1984). In addition, co-solvents are routinely employed in parenteral formulations to enhance the solubility of poorly soluble drugs; for example, Tu et al. (1989) have investigated the stability of a non-aqueous formulation for injection based on 52 percent N,N-dimethylacetamide and 48 percent propylene glycol. By stressing the preparation with regard to temperature, they found that, using Arrhenius kinetics, the time for 10 percent degradation at

**Figure 6.13** First-order hydrolysis decomposition of a compound (25°C).




### *Stability to Autoclaving*

For parenteral IV formulations, a sterile solution of the compound is required. A terminal sterilization method is preferred, rather than aseptic filtration, because there is a greater assurance of achieving sterility. As noted by Moldenhauer (1998), the FDA requires a written justification to explain why a product is not terminally sterilized. Therefore, it is mandatory to assess whether the candidate drug is stable to autoclaving as part of any preformulation selection process. Autoclaving (usually 15 min at 121°C) at various pHs is undertaken, after which the solutions should be evaluated for impurities, colour, pH and degradation products. Clearly, if one compound shows superior stability after autoclaving, then this will be the one to choose.

The effect of the autoclave cycle, i.e., fill, heat-up, peak dwell and cool down, on the theoretical chemical stability of compounds intended for IV injection has been investigated by Parasrampuria et al. (1993). Assuming first-order degradation kinetics, i.e., hydrolysis, the amount of degradation was calculated for any point during the above process. Although the



- Carbonate buffering loss
- Container closure problems
- Drug or excipient degradation

### *Effect of Metal Ions and Oxygen on Stability*

In formulation terms, the removal of oxygen and trace metal ions, and the exclusion of light, may be necessary to improve the stability of oxygen sensitive compounds. Formulation aids to this end include antioxidants and chelating agents and, of course, the exclusion of light where necessary. Antioxidants are substances that should preferentially react with oxygen and hence protect the compound of interest towards oxidation. A list of water and oil soluble antioxidants is given in Table 6.8 (Akers 1982).

Preformulation screening of the antioxidant efficiency in parenteral solutions containing epinephrine has been reported by Akers (1979), who concluded that screening was difficult on the basis of the redox potential, and was complicated by a complex formulation of many components. Indeed, the most recent study on the preformulation screening of antioxidants found that the ability of an antioxidant to consume the oxygen in the formulation was a superior indicator of suitability when compared to redox methods (Ugwu and Apte 1999).

To illustrate the effect of oxygen on a compound that was sensitive to its presence, and its effect on the antioxidant (sodium metabisulphite), we performed the following experi-

**Table 6.8**
**List of water and oil soluble antioxidants.**

| Water Soluble | Oil Soluble |
|---|---|
| Sodium bisulphite | Propyl gallate |
| Sodium sulphite | Butylated hydroxyanisole |
| Sodium metabisulphite | Butylated hydroxytoluene |
| Sodium thiosulphate | Ascorbyl palmitate |
| Sodium formaldehyde sulphoxylate | Nordihydroguaiaretic acid |
| l and d Ascorbic acid | α-Tocopherol |
| Acetylcysteine | |
| Cysteine | |
| Thioglycerol | |
| Thioglycollic acid | |
| Thiolactic acid | |
| Thiourea | |

ments. The formulation (which had been degassed by flushing with nitrogen) was dispensed into ampoules (using a modified Autopak machine) and the headspace was flushed with nitrogen or nitrogen-oxygen mixtures, which are normally used to calibrate gas-liquid chromatographs. The gases used to fill the headspace were oxygen free nitrogen, 1, 3.1 and 5.2 percent v/v oxygen in nitrogen; however, when analyzed by gas-liquid chromatography (GLC), the initial values were higher, giving 1, 1.7, 3.4 and 6.4 percent v/v oxygen in nitrogen, respectively. The amount of oxygen in the headspace was determined using GLC; decomposition of the compound was monitored by UV spectroscopy at 340 nm, because it gave a coloured decomposition product; and metabisulphite was assessed using Ellmans reagent 5,5 dethiobis-(2-nitrobenzoic acid). Figure 6.14 shows the increase in absorbance with time; Figure 6.15a shows the level of oxygen in the headspace; and Figure 6.15b shows the decrease in metabisulphite with time.

It is clear from these data that the metabisulphite consumed oxygen, reducing it in all cases to a constant low value. Nonetheless, only the two lowest oxygen headspace levels were deemed acceptable, illustrating the need to keep the presence of oxygen to an absolute minimum. It should be noted that, if the concentration of metabisulphite is greater than 0.01 M, it hydrolyses to give two molecules of bisulphite.

The reaction of bisulphite with dissolved oxygen is given by

$$2HSO^{-}_{3} + O_{2} \rightarrow 2SO^{-}_{4} + 2H^{+}$$

**Figure 6.14** Plot of absorbance versus time for a development undergoing degradation via oxidation.

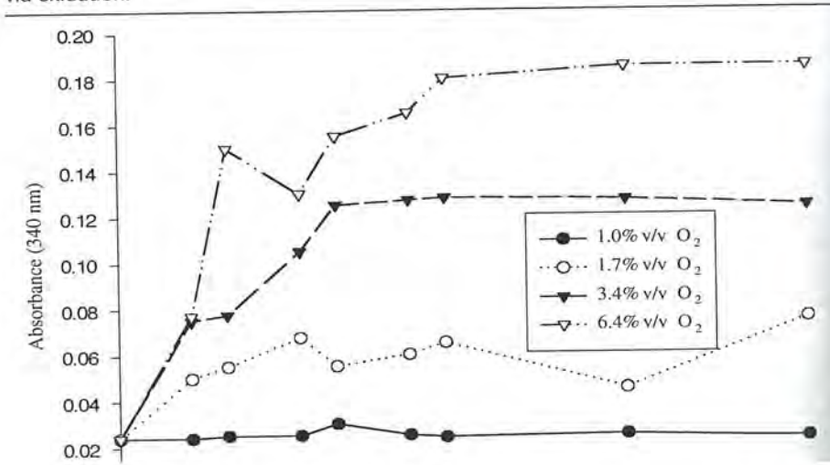
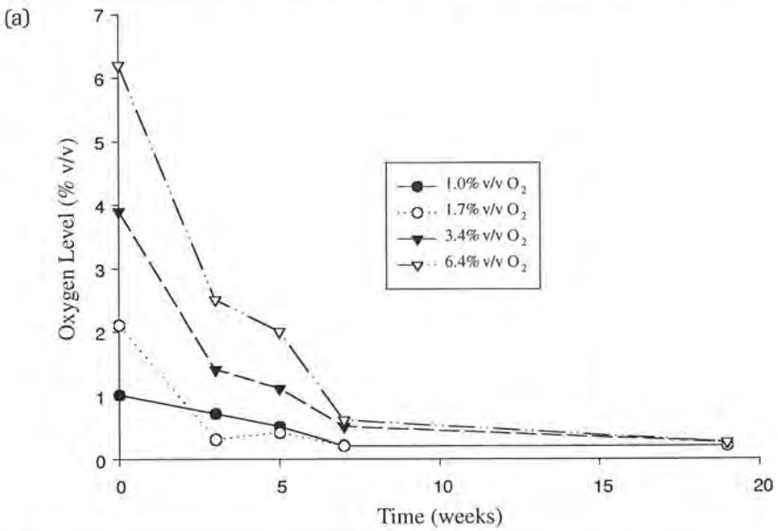
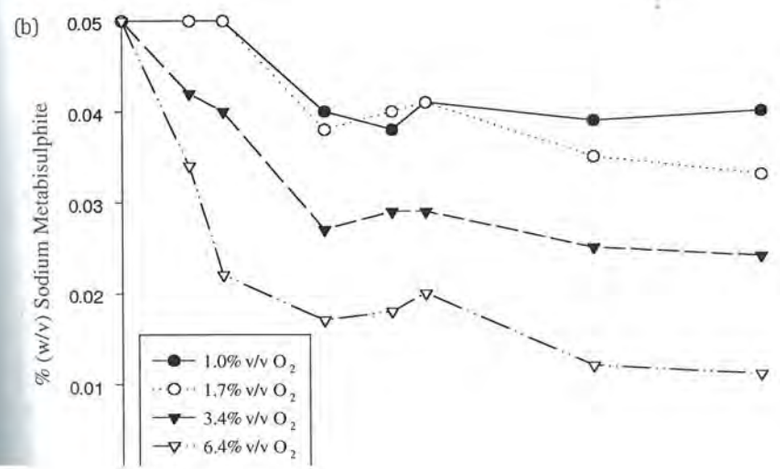





**Figure 6.15** (a) Decrease in headspace oxygen with time; (b) decrease in metabisulphite concentration with time for various headspace oxygen levels.



compounds (Asahara et al. 1990). Thus, oxygen-sensitive substances should be screened for their compatibility with a range of antioxidants. It should also be noted that bisulphite has also been known to catalyse hydrolysis reactions (e.g., Munson et al. 1977).

Trace metal ions can affect stability and can arise from the bulk drug, formulation excipients or glass containers. The effect of metal ions on the solution stability of fosinopril sodium has been reported (Thakur et al. 1993). In this case, the metal ions were able to provide, through complexation, a favourable reaction pathway.

Metal ions can also act as degradation catalysts by being involved in the production of highly reactive free radicals, especially in the presence of oxygen. The formation of these radicals can be initiated by the action of light or heat, and propagate the reaction until they are destroyed by inhibitors or by side reactions that break the chain (Scott 1988). Free radical oxygen species can be generated by transition metals in solution such that reactions can be initiated, illustrated by the potentiation of the auto-oxidation of dopamine by metal ions (Poirier et al. 1985).

### *Ethylenediaminetetraacetic Acid (EDTA) and Chelating Agents*

Because of the involvement of metal ions in degradation reactions, the inclusion of a chelating agent is often advocated. The most commonly used chelating agent are the various salts of EDTA. In addition, β-hydroxyethylenediaminetriacetic acid (HEDTA), diethylenetriaminepentaacetic acid (DTPA) and nitrilotriacetate (NTA) have been assessed for their efficiency in stabilizing, e.g., isoniazid solutions (Ammar et al. 1982).

EDTA has $pK_a$ values of $pK_1 = 2.0$, $pK_2 = 2.7$, $pK_3 = 6.2$ and $pK_4 = 10.4$ at 20°C. Generally, the reaction of EDTA with metal ions can be described by

$$M^{n+} + Y^{4-} \rightarrow MY^{(4-n)+} \tag{9}$$

In practice, however, the disodium salt is used because of its greater solubility, hence

$$M^{n+} + H_2Y \rightarrow MY^{(n-4)+} + 2H^+ \tag{10}$$

From equation 13, it is apparent that the dissociation (or equilibrium) will be sensitive to the pH of the solution, therefore, this will have implications for the formulation.

The stability of the complex formed by EDTA-metal ions is characterized by the stability or formation constant, $K$. This is derived from the reaction equation and is given by

$$K = \frac{\left[(MY)^{(n-4)^+}\right]}{\left[M^{n^+}\right]\left[Y^{4-}\right]} \tag{11}$$

Stability constants (expressed as log $K$) of some metal ion-EDTA complexes are shown in Table 6.9, and an example of a metal ion-EDTA complex is shown in Figure 6.16.

Equation 14 assumes that the fully ionized form of $EDTA^{4-}$ is present in solution, however at low pH other



**Table 6.9**
**Metal ion–EDTA stability constants.**

| Ion | log $K$ | Log $K_H$ | Ion | log $K$ | Log $K_H$ | Ion | log $K$ | Log $K_H$ |
|---|---|---|---|---|---|---|---|---|
| $Ag^+$ | 7.3 | -4.2 | $Co^{2+}$ | 16.3 | 4.3 | $Fe^{3+}$ | 25.1 | 13.1 |
| $Li^+$ | 2.8 | -9.2 | $Ni^{2+}$ | 18.6 | 6.6 | $Y^{3+}$ | 18.2 | 6.2 |
| $Na^+$ | 1.7 | -10.3 | $Cu^{2+}$ | 18.8 | 6.8 | $Cr^{3+}$ | 24.0 | 12.0 |
| $Mg^{2+}$ | 8.7 | -3.3 | $Zn^{2+}$ | 16.7 | 4.7 | $Ce^{3+}$ | 15.9 | 3.9 |
| $Ca^{2+}$ | 10.6 | -1.4 | $Cd^{2+}$ | 16.6 | 4.6 | $La^{3+}$ | 15.7 | 3.7 |
| $Sr^{2+}$ | 8.6 | -3.4 | $Hg^{2+}$ | 21.9 | 9.9 | $Sc^{3+}$ | 23.1 | 11.1 |
| $Ba^{2+}$ | 7.8 | -4.2 | $Pb^{2+}$ | 18.0 | 6.0 | $Ga^{3+}$ | 20.5 | 8.5 |
| $Mn^{2+}$ | 13.8 | 1.8 | $Al^{3+}$ | 16.3 | 4.3 | $In^{3+}$ | 24.9 | 12.9 |
| $Fe^{2+}$ | 14.3 | 2.3 | $Bi^{3+}$ | 27.0 | 15.0 | $Th^{4+}$ | 23.2 | 11.2 |

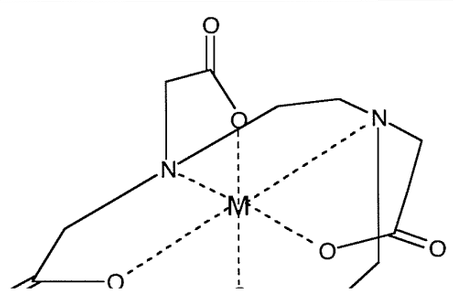
Note: Log $K_H$ values calculated for pH 2.5.

$$\alpha_L = \frac{[EDTA]_{allforms}}{[EDTA^{4-}]} \tag{12}$$

Thus

$$K_H = \frac{K}{\alpha_L} \text{ or } K_H = \log K - \alpha_L \tag{13}$$

**Figure 6.16** Structure of metal-EDTA complex.



where $\log K_H$ is known as the conditional stability constant. Fortunately, $\alpha_L$ can be calculated from the known dissociation constants of EDTA, and its value can be calculated from

$$\alpha_L = \left\{1 + \frac{[H^+]}{K_4} + \frac{[H^+]}{K_4 K_3} + \ldots\right\} = 1 + 10^{(pK_4 - pH)} + 10^{(pK_4 + pK_3 pH)} + \ldots \qquad (14)$$

Thus at pH = 4, the conditional stability constants of some metal-EDTA complexes are calculated as follows:

$\log K_H$ EDTA$Ba^{2+} = 0.6$

$\log K_H$ EDTA$Mg^{2+} = 1.5$

$\log K_H$ EDTA$Ca^{2+} = 3.4$

$\log K_H$ EDTA$Zn^{2+} = 9.5$

$\log K_H$ EDTA$Fe^{3+} = 17.9$

Thus at pH 4, the zinc and ferric complexes will exist; however, calcium, magnesium and barium will be only weakly complexed, if at all.

The inclusion of EDTA is occasionally not advantageous, since there are a number of reports of EDTA catalyzing the decomposition of drugs (Mendenhall 1984; Nayak et al. 1986). Citric acid, tartaric acid, glycerin and sorbitol can also be considered as complexing agents; however, these are often ineffective. Interestingly, some Japanese formulators often resort to amino acids or tryptophan because of a ban on EDTA in a particular country (Wang and Kowal 1980).

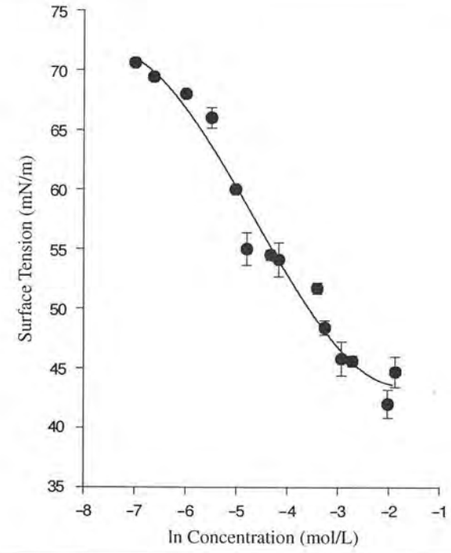
## Surface Activity

Many drugs show surface active behaviour because they have the correct mix of chemical groups that are typical of surfactants. The surface activity of drugs can be important if they show a tendency to, e.g, adhere to surfaces, or if solutions foam. The surface activity of compounds can be determined using a variety of techniques, such as surface tension measurements using a Du Nouy tensiometer, Whilhelmy plate and conductance measurements. Figure 6.17 shows the surface tension as a function of concentration (using a Du Nouy tensiometer) of a primary amine hydrochloride solution in water. The surface tension of water decreased due to the presence of the compound, however, there was no break, which would have been indicative of micelle formation. Even when the pH of the solution was adjusted to 7, where a solubility "spike" had been observed, the surface tension was not significantly different to that observed for water alone. Thus, although the compound was surface active, it did not appear to form micelles, probably due to steric effects.

The surface active properties of MDL-201,346, a hydrochloride salt, has been investigated by a number of techniques including conductivity measurements (Streng et al. 1996). It was found that it underwent significant aggregation in water at temperatures greater than 10°C. Moreover, a break in the molar conductivity versus square root of concentation was noted, which corresponded to the critical micelle concentration (CMC) of the compound and aggregation of 10–11 molecules. In addition to surface active behaviour, some drugs are known to form liquid crystalline phases with water, e.g., diclofenac diethylamine (Kriwet and Müller-



**Figure 6.17** Plot of surface tension versus the natural log of the concentration for a primary amine hydrochloride.




Goymann 1993). Self-association in water (vertical stacking) of the novel anticancer agent brequiner sodium (King et al. 1989) has been reported.

## Osmolality

Body fluids, such as blood, normally have an osmotic pressure which is often described as corresponding to that of a 0.9 percent w/v solution of sodium chloride and, indeed, a 0.9 percent w/v NaCl solution is said to be iso-osmotic with blood. Those solutions with an osmotic pressure lower than 0.9 percent w/v NaCl are known as hypotonic, and those greater than this value are said to be hypertonic. The unit commonly used unit to express osmolality is the osmol, and this is defined as the weight in grams per solute, existing in a solution as molecules, ions, macromolecules, etc., that is osmotically equivalent to the gram molecular weight of an ideally behaving non-electrolyte.

Pharmaceutically, osmotic effects are important in the parenterals and ophthalmic fields, and work is usually directed at formulating to avoid the side-effects or finding methods of administration to minimize them. The ophthalmic respose to various concentations of sodium chloride is shown in Table 6.10 (Flynn 1979).

**Table 6.10**
**Ophthalmic response to various concentrations of sodium chloride.**

| % NaCl | Ophthalmic Response |
|---|---|
| 0.0 | Very disagreeable |
| 0.6 | Perceptibly disagreeable after 1 min |
| 0.8 | Completely indifferent after long exposure |
| 1.2 | " |
| 1.3 | Perceptibly disagreeable after 1 min |
| 1.5 | Somewhat disagreeable after 1 min |
| 2.0 | Disagreeable after 1/2 min |

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Osmolality determinations are usually carried out using a cryoscopic osmometer, which is calibrated with deionized water and solutions of sodium chloride of known concentration. Using this technique, the sodium chloride equivalents and freezing point depressions for more than 500 substances have been determined and reported in a series of papers by Hammerlund and co-workers (e.g., see Hammerlund 1981). Figure 6.18 shows the osmolality of mannitol-water solutions.

## FREEZE-DRIED FORMULATIONS

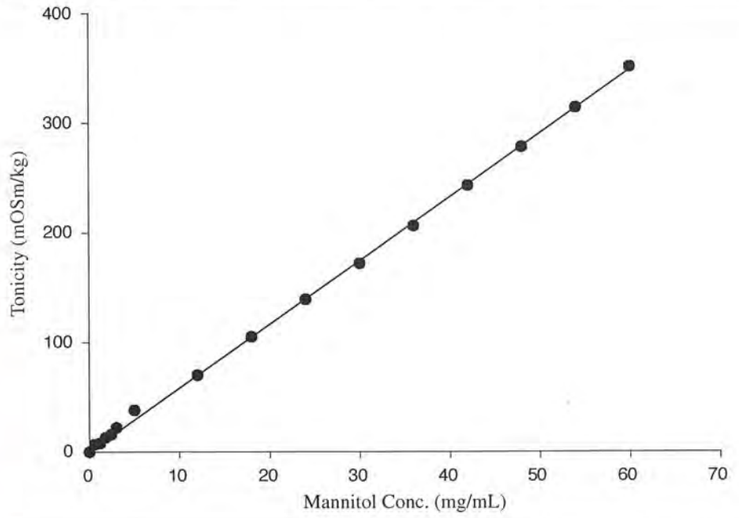
If a drug in solution proves to be unstable to autoclaving, then an alternative formulation approach will be required. Freeze-drying such solutions is often attempted to produce the requisite stability. Preformulation studies can be performed to evaluate this approach and to aid the development of the freeze-drying cycle. Briefly, freeze-drying consists of three main stages: (a) freezing of the solution, (b) primary drying and (c) secondary drying (Williams and Polli 1984). In many cases, the inclusion of excipients is necessary to act as bulking agents or stabilizing agents. Thus, production conditions should be evaluated to ensure that the process is efficient and that it produces a stable product. The first stage, therefore, is to characterize the freezing and heating behaviour of solutions containing the candidate drug. In this respect DSC can be used, as described by Hatley et al. (1996).

To understand the processes taking place during freezing a solution containing a solute, it is worth referring to the phase diagram described by Her and Nail (1994). If, on cooling a solution of a compound, crystallization does not take place, the solution becomes supercooled and thus becomes more concentrated and viscous. Eventually, the viscosity is increased to such an extent that a glass is formed. This point is known as the glass transition temperature ($T_g$).

Measurement of the glass transition of frozen solution formulation of the candidate drug is an important preformulation determination, since freeze-drying an amorphous system above this temperature can lead to a decrease in viscous flow of the solute (due to a decrease



**Figure 6.18** Plot of tonicity versus concentration for mannitol in water.

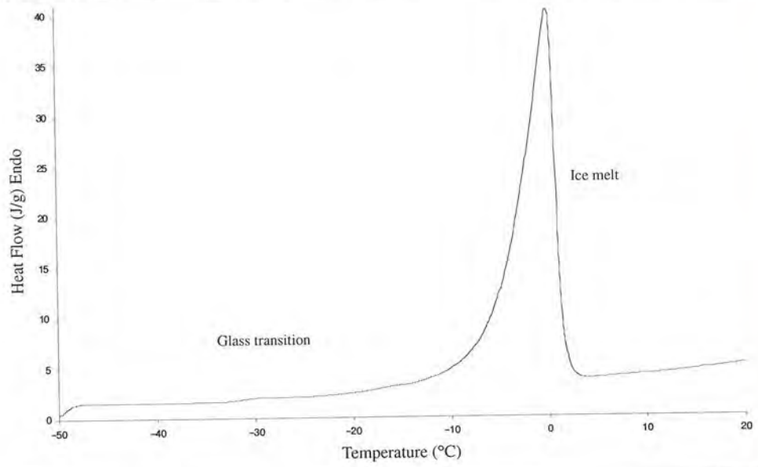



in viscosity) after the removal of the ice. This leads to what is commonly known as "collapse", and for successful freeze-drying, it should be performed below the $T_g$. Consequences of collapse include high residual water content in the product and prolonged reconstitution times. In addition, the increase in the mobility of molecules above the $T_g$ may lead to in-process degradation (Pikal and Shah 1990).

Figure 6.19 shows the glass transition, as determined by DSC, of a trial formulation of a candidate drug. The glass transition was measured by freezing a solution of the compound in a DSC pan and then heating the frozen solution. It should be noted that $T_g$ is usually a subtle event compared to the ice-melt endotherm, and so the thermogram should be examined very carefully. In some cases, an endotherm due to stress relaxation may be superimposed on the glass transition. It is possible to resolve these events using the related technique, modulated DSC (MDSC) or dynamic DSC (DDSC).

If during freezing the solutes crystallize, the first thermal event detected using DSC will be the endotherm that corresponds to melting of the eutectic formed between ice and the solute. This is usually followed by an endothermic event corresponding to the melting of ice. Figure 6.20 shows this behaviour for a 9% w/v saline solution. Normally, freeze-drying of these systems is carried out below the eutectic melting temperature (see e.g., Williams and Schwinke 1994). Another way of detecting whether a solute or formulation crystallizes on freezing is to conduct subambient X-ray diffractometry (Cavatur and Suryanarayanan 1998).

**Figure 6.19** DSC thermogram showing a glass transition of heated frozen drug solution.




If a lyophilized drug is amorphous, then knowledge of the glass transition temperature is important for stability reasons. Chemically, amorphous compounds are usually less stable than their crystalline counterparts. This is illustrated in Table 6.11, which shows some stability data for an amorphous compound (produced by lyophilization) and the crystalline hydrate form of the compound.

Although the moisture content of the amorphous form was increased, it did not crystallize. Other work showed that at RHs greater than 70 percent, the sample crystallized. It is important to note that moisture has the effect of lowering the glass temperature, which in turn increases the propensity for instability. This appears to be due to water acting as a plasticizer such that molecular mobility is increased, thus facilitating reactivity (Shalaev and Zografi 1996).

Duddu and Weller (1996) have studied the importance of the glass transition temperature of an amorphous lyophilized aspirin-cyclodextrin complex. Using DSC, the glass transition was found to be 36°C, and was followed by an exothermic peak, believed to be due to aspirin crystallization. The glass transition at this temperature was also observed using dielectric relaxation spectroscopy. When the aspirin/hydroxypropyl-β-cyclodextrin (HPCD) lyophile was exposed to higher humidities, the $T_g$ was reduced to a temperature below room temperature, and the product became a viscous gel. Craig et al. (1999) have reviewed the physicochemical properties of the amorphous state with respect to drugs and freeze-dried formulations.



**Figure 6.20** DSC thermogram of a frozen 9% w/v saline solution.

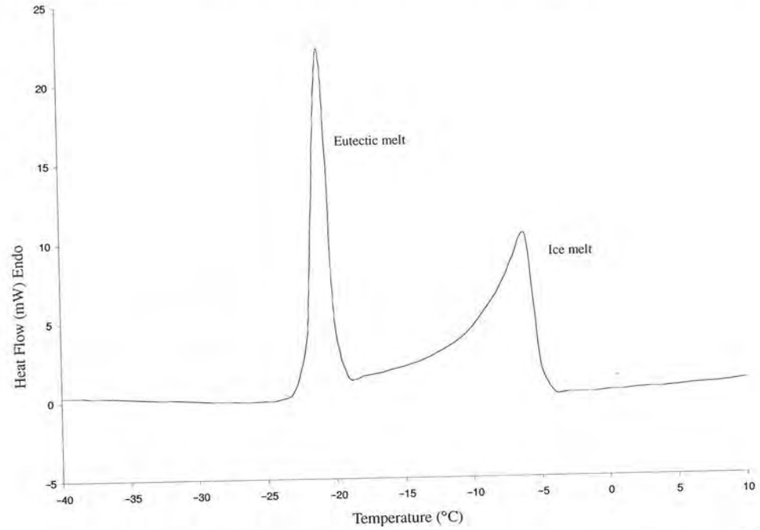



**Table 6.11**
**Stability data for an amorphous (lyophilized) and crystalline hydrate form of a compound.**

| | Storage Conditions (°C/%RH) | Time (month) | Moisture Content (%w/w) | Total Impurities (%w/w) |
|---|---|---|---|---|
| Crystalline | | Initial | 15.98 | 0.53 |
| | 25/16 | 1 | 15.78 | 0.54 |
| | 25/60 | 1 | 15.50 | 0.56 |
| | 40/75 | 1 | 15.76 | 0.59 |
| Amorphous | | Initial | 4.83 | 0.47 |
| | 25/16 | 1 | 8.31 | 0.57 |
| | 25/60 | 1 | 12.55 | 0.69 |
| | 40/75 | 1 | 12.72 | 1.44 |

## SUSPENSIONS

Data considered to be important for suspensions at the preformulation stage include solubility, particle size and propensity for crystal growth and chemical stability. Furthermore, during development, it will be important to have knowledge of the viscosity of the vehicle to obtain information with respect to settling of the suspended particles, syringibility and physical stability (Akers et al. 1987). In a report on the preformulation information required for suspensions, Morefield et al. (1987) investigated the relationship between the critical volume fraction as a function of pH. They noted that "it is usually desirable to maximize the volume fraction of solids in order to minimize the volume of the dose".

It should be obvious that for a successful suspension, insolubility of the candidate drug is required. Whilst for large hydrophobic drugs like steroids this may not a problem, weak acids or bases, however, may show appreciable solubility. In this instance, reducing the solubility by salt formation is a relatively common way to achieve this end. For example, a calcium salt of a weak acid may be sufficiently insoluble for a suspension formulation. However, difficulties may arise due to hydrate formation with concomitant crystal growth; e.g., Hoelgaard and Møller (1983) found that metronidazole formed a monohydrate on suspension in water. Another way crystals can grow in suspension, that is not due to a phase change, is by Ostwald ripening. This is the result of the difference in solubility between small and large crystals as predicted by

$$\frac{RT}{M}\ln\left(\frac{S_2}{S_1}\right)=\frac{2\sigma}{\rho}\left(\frac{1}{r_1}-\frac{1}{r_2}\right) \qquad (15)$$

where $R$ is the gas constant, $T$ is the absolute temperature, $S_1$ and $S_2$ are the solubilities of crystals of radii $r_1$ and $r_2$ respectively, $\sigma$ is the specific surface energy, $\rho$ is the density and $M$ is the molecular weight of the solute molecules. Ostwald ripening is promoted by temperature changes during storage, particularly if there is a strong temperature-solubility relationship. Therefore, as the temperature is increased, the small particles of the drug will dissolve, which is followed by crystal growth as the temperature is decreased. Ziller and Rupprecht (1988a) have reported the design of a control unit to monitor crystal growth; however, simple microscopic observation may be all that is necessary to monitor the growth of crystals. If a phase change occurs, then the usual techniques may be used to assess the solid-state form of the compound produced on storage such as DSC, hot stage microscopy (HSM) or XRPD. Polymeric additives may be employed to inhibit drug crystallization; Ziller and Rupprecht (1988b) found that polyvinylpyrollidone and bovine serum albumin inhibit crystal growth using a variety of compounds.

It is a pharmacopoeial requirement that suspensions should be redispersible if they settle on storage. However, the pharmacopoeias do not offer a suitable test that can be used to characterize this aspect of the formulation. In an attempt to remedy this situation, Deicke and Süverkrüp (1999) have devised a mechanical redispersibility tester, which closely simulates the action of human shaking. The crystal habit may also affect the physical stability of the for-



studies have shown that it only useful in some cases. For example, Biro and Racz (1998) found that the zeta potential of albendazole suspensions was a good indicator of stability, whereas Duro et al. (1998) showed that the electrical charge of pyrantel pamoate suspensions was not important for its stabilization.

As noted above, the particle size of suspensions is another important parameter in suspension formulations. The particle size distribution can be measured using a variety of techniques, including laser diffraction. A point to note in laser diffraction is the careful selection of the suspending agent. This was illustrated by Atkinson and White (1992) who used a Malvern Mastersizer to determine the particle size of a 1 percent methylcellulose in the presence of seven surface active agents (Tween 80, Tween 20, Span 20, Pluronic L62, Pluronic F88, Cetomacrogol 1000 and sodium lauryl sulphate). The particle size of the suspensions was measured as a function of time and, surprisingly, Tween 80, which is widely used in this respect, was found to be unsuitable for the hydrophobic drug under investigation. Other surfactants also gave poor particle size data, e.g., Tween 20, Cetomacrogol 1000, Pluronic F88 and sodium lauryl sulphate. This arose from aggregation of the particles, and additionally, these suspensions showed slower drug dissolution in water. Span 20 and Pluronic L62 showed the best results, and therefore the authors cautioned the use of a standard surface active agent in preclinical studies.

Usually, suspensions are flocculated so that the particles form large aggregates that are easy to disperse—normally this is achieved using potassium or sodium chloride (Akers et al. 1987). However, for controlled flocculation suspensions, sonication may be required to determine the size of the primary particles (Bommireddi et al. 1998).

Although high performance liquid chromatography (HPLC) is the preferred technique for assessing the stability of formulations, spectrophotometry can also be used. Girona et al. (1988) used this technique for assessing the stability of an ampicillin-dicloxacillin suspension.

## TOPICAL/TRANSDERMAL FORMULATIONS

Samir (1997) has reviewed preformulation aspects of transdermal drug delivery. This route of delivery offers several potential advantages compared to the oral route, such as avoidance of fluctuating blood levels, no first-pass metabolism and no degradation due to stomach acid. However, the transdermal route is limited because of the very effective barrier function of the skin. Large, polar molecules do not penetrate the stratum corneum well. The physicochemical properties of candidate drugs that are important in transdermal drug delivery include molecular weight and volume, aqueous solubility, melting point and log $P$. Clearly, these are intrinsic properties of the molecule and, as such, will determine whether or not the compounds will penetrate the skin. Furthermore, since many compounds are weak acids or bases, pH will have an influence on their permeation.

One way in which the transport of zwitterionic drugs through skin has been enhanced is by salt formation. This was demonstrated by Mazzenga et al. (1992) who showed that the rank order of epidermal flux of the salts of phenylalanine across the epidermis was hydrobromide

the vehicle needs to be determined. Problems can arise from crystal growth if the system is supersaturated; for example, phenylbutazone creams were observed to have a gritty appearance due to crystal growth (Sallam et al. 1986). Indeed, in matrix patches, crystals of estradiol hemihydrate or gestodene up to 800 μm grew during 3 months of storage at room temperature (Lipp and Müller-Fahrnow 1999). As another example, needle-like crystals of the hydrate of betamethasone-17-valerate were found by Folger and Müller-Goymann (1994) when creams were placed on storage.

Chemical and physical stability also need to be considered. For example, Thoma and Holzmann (1998) showed that dithranol showed a distinct instability in the paraffin base due to light, but was stable when protected from light. In terms of kinetics, Kenley et al. (1987) found that the degradation in a topical cream and in ethanol-water solutions were very similar in the pH range 2–6. This suggested that the degradation of this compound occurred in an aqueous phase or compartment that was undisturbed by the oily cream excipients. If the compound decomposes due to oxidation, then an antioxidant may have to be incorporated. Table 6.8 lists the water soluble and oil soluble antioxidants that can be considered for incorporation into a topical formulation.

In an attempt to reduce the photodegradation of a development compound, Merrifield et al. (1996) compared the free acid of compound to a number of its salts, each of which they incorporated into a white soft paraffin base. Their results (Table 6.12) showed that after a 1 h exposure in a SOL2 light simulation cabinet, the disodium salt showed significant degradation.

Martens-Lobenhoffer et al. (1999) have studied the stability of 8-methoxypsoralen (8-MOP) in various ointments. They found that after 12 weeks storage, the drug was stable in Unguentum Cordes and Cold Cream Naturel; however, the Unguentum Cordes emulsion began to crack after 8 weeks. When formulated in a Carbopol gel, 8-MOP was unstable.

The physical structure of creams has been investigated by a variety of techniques, e.g., DSC, TGA, microscopy, reflectance measurement, rheology, Raman spectroscopy and dielectric analysis (see references in Peramal et al. 1997). Focussing on TGA and rheology, Peramal et al. (1997) found that when aqueous British Pharmacopoeia (BP) creams were analyzed by

**Table 6.12**
**Light stability of the salts of a candidate drug in a white soft parrafin base.**

| Salt/Form | % initial compound after 1 h exposure in SOL2 | | |
|---|---|---|---|
| | 0.1% conc. | 0.5% conc. | 2.0% conc. |
| Free acid (micronized) | 51.0 | 80.0 | 85.9 |
| Free acid (unmicronized) | 69.4 | nd | nd |
| Disodium (unmicronized) | 9.9 | 3.6 | nd |



TGA, there were two peaks in the derivative curve. It was concluded that these were due to the loss of free and lamellar water from the cream, and therefore TGA could be used as a QC tool. The lamellar structure of creams can also be confirmed using small angle X-ray measurements (Niemi and Laine 1991). For example, the lamellar spacings of sodium lauryl sulphate and cetostearyl alcohol liquid paraffin creams were found to increase in size (from 8.5 to 17.6 nm) as the water content of the cream increased until, at > 60 percent water, the lamellar structure broke down. This was correlated with earlier work that showed that at this point, the release of hydrocortisone was increased (Niemi et al. 1989).

Atkinson et al. (1992) have reported the use of a laser diffraction method to measure the particle size of drugs dispersed in ointments. In this study, they stressed the fact that a very small particle size was required to ensure efficacy of the drug. In addition, the size of the particles was especially important if the ointment was for ophthalmic use where particles must be less than 25 μm. Whilst the particle size of the suspended particles can be assessed microscopically, laser diffraction offers a more rapid analysis.

## INHALATION DOSAGE FORMS

### Metered Dose Inhalers

In pressurised metered dose inhaler (pMDI) technology, CFC propellants are being replaced with the ozone-friendly hydrofluoroalkanes (HFA)-134a and -227. In pMDI drug delivery systems, the drugs are formulated as a suspension or as a solution, depending on the solubility of

134a



227

the drug in the propellant. Although suspensions offer the advantage of superior chemical stability (Tiwari et al. 1998b), they may have problematic physical stability in terms of crystal growth or poor dispersion properties. In this respect, Tzou et al. (1997) examined whether the free base or the sulphate salt of albuterol (salbutamol) had the best chemical and physical stability for a pMDI formulation. In addition to the older CFC propellants, they examined the stability of the base and sulphate in HFA-134a. Results showed that all of the sulphate formulations were chemically stable for up to 12 months, however, the base was less stable. In terms of physical stability, the base formulations showed crystal growth and agglomeration, illustrating the need for undertaking a salt selection process.

One significant challenge in the transition from the CFCs to HFAs is that the surfactants and polymers used as suspension stabilizers in CFC formulations are not soluble enough in the HFAs to be effective. For example, sorbitan/trioleate (Span 85), commonly used in CFC formulations, is not soluble in HFA-134a or -227; however, other surfactants and polymers have been screened for their effectiveness in stabilizing propellant suspensions with some suc-

**Table 6.13**
**Apparent solubilities of some surfactants in HFA-134a and HFA-227.**

| Surfactant | HLB | Apparent Solubility (%w/w) HFA-134a | HFA-227 |
|---|---|---|---|
| Oleic acid | 1.0 | < 0.02 | < 0.02 |
| Sorbitan trioleate | 1.8 | < 0.02 | <0.01 |
| Propoxylated PEG | 4.0 | ≈ 3.6 | 1.5–15.3 |
| | | | 32.0–60.3 |
| Sorbitan monooleate | 4.3 | < 0.01 | < 0.01 |
| Lecithin | 7.0 | < 0.01 | < 0.01 |
| Brij 30 | 9.7 | ≈ 1.8 | 0.8–1.2 |
| Tween 80 | 15.0 | < 0.03 | 0–10.0 |
| | | | 25.0–89.8 |
| Tween 20 | 16.7 | ≈ 0.1 | 1.4–3.5 |
| PEG 300 | 20 | ≈ 4.0 | 1.5–4.3 |
| | | | 16.1–100 |
| PVP, PVA | | > 0.1 | |
| Oligolactic acids | | ≈ 2.7 | |

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isothermal microcalorimetry. The system investigated was the model CFC Arcton 113, salbutamol sulphate (crystalline and partially crystalline) and oleic acid or Span 85 as stabilizers. Using a perfusion-titration set-up, they titrated suspensions of the drug with solutions of the surfactant and followed heat output as a function of time. It was shown that the heat output and adsorption was different, depending on the crystallinity of the sample, i.e., there was less heat output for the more energetic, partially crystalline sample. From these data, it was hypothesized that the orientation of the surfactant molecule during adsorption was different, depending on the surface energy of the particles in suspension.

Drugs for inhalation therapy via a pMDI (and dry powder inhalers, DPIs) are reduced in size by micronization to particles of approximately 1 to 6 μm, which are capable of penetrating the deep airways and impact at the site of action. As noted earlier, micronization can cause problems due to the reduction in crystallinity and poor flow properties as a result of the milling process (see, e.g., Buckton 1997). The effect of micronization on samples can be assessed by a variety of techniques, e.g., DVS, microcalorimetry and IGC. IGC, for example, has



**Table 6.14**
**Heat of solution of triamcinolone acetonide recovered from pMDIs after storage.**

| | Heat of Solution (J/g) Raw Material | Recovered TAA (3 months, 25°C) | Recovered TAA (3 months, 40°C) |
|---|---|---|---|
| Unmicronized | 44.1 | 39.0 | 47.7 |
| Ball milled | 38.6 | 29.6 | 36.4 |
| Micronized | 43.7 | 36.0 | 35.2 |

Reprinted from Influence of micronization method on the performance of a suspension triamcinolone acetonide pressurized metered-dose inhaler formulation, by R. O. Williams et al., in *Pharm. Dev. Tech.*, Vol. 4, pp. 167–179. Courtesy of Marcel Dekker, Inc.

to condition the powder with moist air, which crystallizes the amorphous regions (Ahmed et al. 1996).

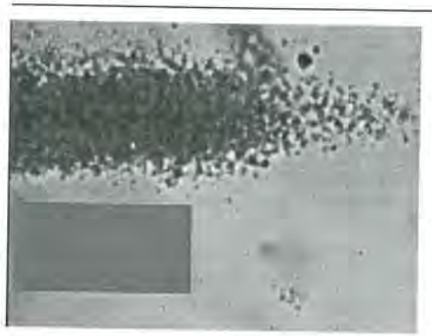
Williams III et al. (1999a) have reported the influence of ball milling and micronization on the formulation of triamcinolone acetonide (TAA) for MDIs. Both methods reduced the particle size of the powder; however, as shown by solution calorimetry measurements ball milling produced material with a greater amorphous content (Table 6.14). Although the ball-milled material was less crystalline, it was found have the smallest particles and the highest respirable fraction.

It is possible that a number of physical changes can occur due to suspension in the propellant. The first is due to Ostwald ripening, a phenomenon described earlier in this chapter. This arises when the compound shows some solubility in the propellant, resulting in particle growth and caking. In this process, the smallest micronized particles dissolve and then recrystallize on the larger particles. As shown by Phillips et al. (1993), optical microscopy can be used to assess the crystal growth of micronized salicylic acid in CFC pMDIs. In this study, the increase in the axial ratio (length/breadth) of the crystals was measured as a function of time. Although the crystals continued to grow after an initial increase in the axial ratio, after some time it did not change. It was therefore concluded that axial ratios of crystals should always by determined by microscopy to detect any physical instability in the early stages of MDI formulation development. In another paper by this group, Phillips and Byron (1994) have investigated the surfactant promoted crystal growth of micronized methylprednisolone in trichloromonofluoromethane (CFC-11). The effect of drug concentration, surfactant type and composition on the solubility of methylprednisolone was determined and related to the observed crystal growth in suspension. In particular, high concentrations of Span 85 (sorbitan trioleate) were found to increase the solubility of the compound with the consequence of crystal growth. Oleic acid and lower concentrations of Span 85, on the other hand, showed little particle size change. In addition to an increase in particle size, the crystals may also solvate

the range between 40 and 100°C. This thermal event was also evident in the DSC, which showed an endotherm corresponding to solvent loss followed by an exotherm probably due to crystallization. HSM showed that, when heated in silicone oil, a gas was evolved as the temperature was raised. This is illustrated is Figure 6.21. Notice how the crystals broke apart as the gas was released as the temperature was raised.

To confirm that the crystals had solvated the propellant, IR spectroscopy provided a useful test. The main difference between the IR spectra before and after storage was the appearance of a medium-strong peak at 1289 $cm^{-1}$. By reference to standard tables of IR stretching frequencies, this new peak was assigned as a C-F stretch that, with the other information, led to the conclusion that the compound had solvated the propellant gas (134a).

**Figure 6.21** HSM photographs of an inhalation drug before and after suspension in HFA-134a.



Before suspension


After 6 months' suspension. 57.6°C



A method for determining the solubility of drugs in aerosol propellants has been described by Dalby et al. (1991). At room temperatures, the propellants are gases. Special procedures are therefore required in separating the excess solid from the solution in the aerosol can; in this case, it is a simple filtration from one can to another. The propellent from the can containing the filtrate is then allowed to evaporate, and the residue is assayed for the drug using, e.g., HPLC. Appreciable drug solubility may lead to particle growth; this may be overcome, however, by the appropriate choice of salt if the compound is a weak acid or base. Table 6.15 shows the data obtained by Williams et al. (1999b) of some steroids in HFA-134a (+ 7.9 percent w/w ethanol) at 5 and 25°C.

For pMDIs, the compatibility of the propellants with the valve elastomers also needs to be evaluated. For example, Tiawari et al. (1998a) investigated the effect of 134a on a number of valve elastomers and found that it adversely affected the performance of the valve. Inhalation dosage forms are discussed in more detail in Chapter 10.

## Dry Powder Inhalers

Timsina et al. (1994) have reviewed the use of DPIs for drug delivery to the lungs. Although pMDIs remain the most popular device for the delivery of drugs to the lungs, DPIs have certain advantages over them. For example, DPIs do not rely on the CFC or HFA propellant gases and hence are more "environmentally friendly" than MDIs.

There are number of devices which can deliver drugs to the lungs as dry powders, e.g., Turbuhaler™ or Diskhaler™. DPIs rely on a larger carrier particle, such as α-lactose monohydrate, to which the drug is attached. (The lactose is usually fractionated such that it lies in the size range 63–90 μm.) On delivery, the drug detaches from the lactose and, because the drug is micronized, it is delivered to the lung, whereas the lactose is eventually swallowed. Staniforth (1996) has reviewed the preformulation aspects of DPIs. In that article, he states that measurements of the micromeretic, RH and electrostatic properties of the powder should be the basis of the characterization carried out. It was also shown that the polymorphic form of the lactose used could affect the aerosolization properties of the formulation. The results showed that, as function of flow rate, the β-forms were easily entrained, but held onto the

**Table 6.15**
**Solubility of some steroids in HFA-propellant/ethanol mixtures. at 5 and 25°C.**

| | Solubility in HFA-134a/Ethanol (μg drug per g solvent) | | Solubility in HFA-227/Ethanol (μg drug per g solvent) | |
|---|---|---|---|---|
| Compound | 5°C | 25°C | 5°C | 25°C |
| Hydrocortisone | 134.4 | 190.1 | 147.2 | 175.2 |

drug particles most strongly. The anhydrous α-form showed the opposite behaviour, and the α-form (the monohydrate) showed intermediate behaviour.

Micronized particles form strong agglomerates, and the size of these agglomerates, among other things, depends on the surface free energy of the powder. Since micronization can change the surface free energy of a material, the adherence properties of the compound will also be changed. For example, Podczeck et al. (1994, 1995a,b) have performed adhesion and auto-adhesion measurements of salmeterol xinafoate particles of various sizes to compacted lactose monohydrate surfaces using a centrifuge technique. This work was followed by work investigating the adhesion force of micronized salmeterol xinafoate particles to pharmaceutically relevant surface materials (Podeczeck et al. 1996a). Results showed that long contact times with PVC, polyethylene or aluminium should be avoided because the adhesion force between the drug and these surfaces was much higher than between it and the lactose carrier. Thus, detachment and loss of drug in the formulation could occur. In another study, Podczeck et al. (1996b) investigated the adhesion strength of some salts of salmeterol to lactose and other substrates with varying surface roughness, surface free energy and Young's modulus. It was concluded that many of these factors play a part, as do chemical forces, and that only experimental assessment could indicate whether the material was suitable. Boerefijn et al. (1998) have reported the disintegration of weak lactose agglomerates using an agglomerate impact test with high-speed digital video recording. The experiments showed that dry agglomerates were broken apart as a function of the square of the impact velocity.

As noted by Jashnani and Byron (1996), in formulation terms, it is always worth optimising the salt form. In this study, the performance comparisons of dry powder aerosol generation in different environments were determined for the sulphate, adipate (diethanolate) and stearate salts of albuterol. Overall, the stearate emptied and aerosolized best from the inhaler and showed the least sensitivity to environmental factors such as temperature and humidity. Another use of low solubility salts is to mask the taste of those compounds with unpleasant taste when delivered by DPI (or pMDI for that matter). By lowering the solubility, and hence dissolution rate, the taste can often be effectively eliminated.

Because lactose is the most commonly used carrier excipient in DPIs, its compatibility with the candidate drug should be assessed—particularly if it is a primary amine (see section on compatibility, below). The physicochemical characteristics of some alternative carrier particles have been described by Byron et al. (1996). The effect of the surface morphology of lactose carriers on the inhalation properties of pranlukast hydrate has been reported (Kawashima et al. 1998). The lactose carriers investigated were pharmatose 325M, pharmatose 200M (sieved to ~ 60 μm) and fluidized bed granulated lactose. Results showed that with increasing specific surface area and roughness, the effective index of inhalation decreased due the drug being held more tightly in the inhaled airstream. Therefore, characterization of the carrier particles by, e.g., surface area measurements, SEM and other solid-state techniques are recommended preformulation activities for DPIs.

### Nebulizer Solutions

Nebulizer formulations are normally solutions, however, suspensions are also used, e.g., the insoluble steroid budesonide has been successfully formulated for delivery by nebulization (Dahlback 1994). Some important preformulation considerations for nebulizers are stability, solubility, viscosity and surface tension (McCallion et al. 1996; Nikander 1997). In terms of solubility, the common ion effect may be important where, e.g., a hydrochloride salt is to be dissolved in saline. In addition, the temperature dependence of the solubility of the drug may



be important. Taylor et al. (1992), for example, found that the temperature of a solution of a pentamidine isethionate decreased by up to 13°C, causing the drug to crystallize from solution. The osmolality of solutions has been found to increase during nebulization, although the pH does not appear to do so (Schoeni and Kraemer 1989).

Table 6.16 shows solubility data for an inhalation candidate drug (secondary amine hydrochloride), which was to be delivered by a pMDI and as a nebulizer solution.

These data show the increase in solubility of the compound with respect to temperature and how the presence of the chloride ion depressed its solubility.

If the drug is insoluble, it is important that for a suspension formulation the drug be micronized to a size of less than 2 μm (Dahlback 1994). The particle size distribution of nebulized droplets can be measured using, e.g, laser diffraction (Clark 1995). Validation experiments showed that laser diffraction was robust and reliable and that the diffraction data were a good measure of the particle size of the aerosolized droplets.

Nebulized inhalation drugs are often admixed with others; however, their physical and chemical compatibility should be assessed before proceeding. For a discussion of this aspect of nebulizer therapy, see the review by Jutta (1997).

## COMPATIBILITY

Although there has been some debate in the literature about the nature of compatibility testing and the value of results (e.g., see Monkhouse and Maderich 1989, and Monkhouse 1993), it is felt that it still has some relevance to pharmaceutical preformulation. Essentially, there are four major stages in drug-excipient compatibility studies, but before considering such studies, it is worth checking whether there are any known incompatibilities, as is shown in Table 6.17 (Monkhouse 1993).

Whilst the Maillard reaction between lactose and primary amines is well known, the same reaction between the secondary amine fluoxetine hydrochloride (Prozac®) and lactose has recently been reported (Wirth et al. 1998). In the solid-state water content, lubricant concentration and temperature were also found to influence the degradation. In addition to the chemical reactions noted above, the drug may also interact to form a molecular compound. For example, solid-state interactions between trimethoprim and antimicrobial paraben esters to form a 1:1 molecular compound has been reported (Pedersen et al. 1994).

When conducting compatibility studies, there are four steps to consider:

**Table 6.16**
**Solubility of an inhalation candidate drug in water and isotonic saline as a function of temperature.**

| | Solubility (μg/mL) | | |
|---|---|---|---|
| **Solvent** | **4°C** | **25°C** | **40°C** |
| Water | 1789 | 2397 | 6837 |
| Saline | < 30 | 61 | 157 |

**Table 6.17**
**Known reactivities of some functional groups.**

| Functional Group | Incompatibilities | Type of Reaction |
|---|---|---|
| Primary amine | Mono and disaccharides | Amine-aldehyde and amine-acetal |
| Ester, cyclic, lactone | Basic components | Ring opening ester-base hydrolysis |
| Carbonyl, hydroxyl | Silanol | Hydrogen bonding |
| Aldehyde | Amine carbohydrates | Aldehyde-amine Schiff base or glycosylamine |
| Carboxyl | Bases | Salt formation |
| Alcohol | Oxygen | Oxidation to aldehydes and ketones |
| Sulphfhydryl | Oxygen | Dimerization |
| Phenol | Metals | Complexation |
| Gelatin capsule shell | Cationic surfactant | Denaturation |

From Monkhouse, D. C., Excipient compatibility possibilities and limitations in stability prediction. In *Stability testing in the EC, Japan and the USA. Scientific and regulatory requirements*, edited by W. Crim and K. Krummen (1993). Reprinted with permission from Wissenschaftlidie Verlassgellschaft mbH.

1. Sample preparation
2. Statistical design
3. Storage conditions
4. Method of analysis

Traditionally, a binary mixture of drug with the excipient being investigated is intimately mixed, and the ratio of drug to excipient is often 1:1; however, other mixtures may also be investigated. Powder samples, one set of which is moistened, are then sealed into ampoules to prevent moisture loss. These are then stored at a suitable temperature and analyzed at various time points using HPLC, DSC and TGA, as appropriate. Alternatively, the drug in suspension with excipients may be investigated (Waltersson 1986). Table 6.18 shows data for 250 mg of a primary amine hydrochloride mixed with 250 mg of spray-dried lactose and dispensed into clear, neutral glass ampoules. Half of the ampoules were sealed without further treatment, and to the others, 25 μL of distilled water was added prior to sealing. The ampoules were then stored at 25°C for 1, 4 and 12 weeks.

As expected, there is clear evidence of incompatibility between the amine hydrochloride and the spray-dried lactose. However, the results also showed that moisture was the catalyst for decomposition, as no degradation was observed in the dry state even after 12 weeks storage at 90°C. At the time of this writing, Serrajuddin et al. (1999) have devised a protocol for compatibility testing (Table 6.19).

Ahlneck and Lundgren (1985) and Ahlneck and Waltersson (1986) have described methods for the evaluation of solid-state stability and compatibility between drugs and excipients. Three methods were studied and compared isothermally and non-isothermally: suspension, storage of powders and compacts at specified humidities and elevated temperatures.



**Table 6.18**
**Compatibility study between a primary amine hydrochloride and spray-dried lactose.**

| Water Added (μL) | Storage Temp. (°C) | Storage Time (weeks) | Colour | Moisture by TGA | % Drug Recovered |
|---|---|---|---|---|---|
| 0 | 25 | 1 | White | 2.6 | 101.2 |
| | | 4 | White | 2.6 | 99.4 |
| | | 12 | White | 2.6 | 102.8 |
| | 70 | 1 | White | 2.6 | 105.0 |
| | | 4 | White | 2.6 | 101.8 |
| | | 12 | Off-white | 2.5 | 100.3 |
| | 90 | 1 | White | 2.6 | 102.5 |
| | | 4 | White | 2.6 | 98.5 |
| | | 12 | Off-white | 2.2 | 100.2 |
| 25 | 25 | 1 | White | 2.6 | 93.6 |
| | | 4 | White | 6.8 | 102.6 |
| | | 12 | White | 5.0 | 88.4 |
| | 70 | 1 | Brown | 3.2 | 91.4 |
| | | 4 | Brown/Black | N/I* | 99.7 |
| | | 12 | Brown/Black | N/I | 74.4 |
| | 90 | 1 | Brown | 4.0 | 98.5 |
| | | 4 | Brown/Black | N/I | 90.0 |
| | | 12 | Black | 'N/I | 51.4 |

*N/I: Thermogram not interpretable due to extensive sample degradation.

It was concluded that the suspension technique was good for fast screening of chemical instability. The other solid state procedures were found to be better predictors of the solid dosage form.

Depending on the number of excipients to be investigated, compatibility tests can be speeded up by using factorial or reduced factorial design experiments. Preformulation compatibility experiments utilizing such designs have been reported by, e.g., Dürig and Fassihi (1993). However, it should be remembered that drug instability or incompatibility can be the result of multiple excipient interactions, which is more difficult to address in a practical manner. Furthermore, the processing method used to formulate the drug can affect results, again complicating the matter.

The storage conditions used to examine compatibility can vary widely in terms of temperature and humidity, but a temperature of 50°C for storage of compatibility samples is considered appropriate. Some compounds may require higher temperatures to make reactions proceed at a rate that can be measured over a convenient time period. Methods of analysis also

**Table 6.19**
**Compatibility protocol.**

| | Experiment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 |
| | 200 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| | | 175 | | | | 170 | | | | 170 | | | 170 | | | | |
| | | | 175 | | | | 170 | | | | 170 | | | 170 | | | |
| | | | | 175 | | | | 170 | | | | 170 | | | 170 | | |
| | | | | | 175 | | | | 170 | | | | 170 | | | 170 | |
| | | | | | | 5 | 5 | 5 | 5 | | | | | | | | |
| | | | | | | | | | | 5 | 5 | 5 | 5 | | | | |
| | | | | | | | | | | | | | | 5 | 5 | 5 | 5 |

d dosage form composition through drug-excipient compatibility testing. Serrajuddin, A. T. M., A. B. Thakur, R. Ghoshal, M. G. Fakes, S. A. Ranadive, K. R. Morris, and ( 88:696–704. Copyright 1999 John Wiley and Sons, Inc. Reprinted by permission of Wiley-Liss, Inc., Jossey-Bass, Inc., a subsidiary of John Wiley & Sons, Inc.



vary widely, ranging from thermal techniques (DSC) to chromatographic techniques (TLC, HPLC) to microcalorimetry.

DSC has been used extensively for compatibility studies (for example, see Holgado et al. 1995). Although only milligram quantities of drug are needed for a DSC experiment, the interpretation of the thermograms may be difficult, and conclusions may be misleading on the basis of DSC experiments alone (van Dooren 1983, Charznowski et al. 1986). Nonetheless, the technique remains popular, and the protocol that has been adopted is that proposed by van Dooren (1983), who suggested the following scheme:

1. Run the New Chemical Entity (NCE) and excipients individually.
2. Run mixtures of the NCE and excipients immediately after mixing.
3. Run the NCE and excipients individually after 3 weeks at 55°C.
4. Run the NCE-excipient mix after 3 weeks at 55°C.
5. Run the single components and mixtures after 3 weeks at 55°C only if the curves of the mixtures before and after storage at this temperature differ from each other.

An excipient that is particularly desired may be investigated further by examining different weight ratios with the drug. This method of compatibility testing has been criticized by Chrzanowski et al. (1986) who found that the DSC compatibility method was an unreliable compatibility predictor for fenretinide and three mefenidil salts with various direct compression excipients. They concluded that an isothermal stress (IS) method (which requires a specific, quantitative assay method, e.g., HPLC, for either test substance or its degradation products) was preferred for its accuracy over DSC in compatibility testing. In addition, the IS method gave quantitative information. Disadvantages of the IS system compared to DSC are that the tests tend to consume more compound than the DSC test and are conducted over longer storage times, 1–2 months at 60 to 80°C. However, the whole point of DSC is speed of prediction. So DSC may be of use if the amount of drug available is small and an idea of compatibility is required (Venkataram et al. 1995). On the other hand, although DSC may be used to predict that interactions may occur, it provides little insight into the nature of the interaction (Hartauer and Guillory 1991).

Microcalorimetry has also been used in excipient compatibility studies (Phipps et al. 1998). In their study, 1:1 mixtures were prepared using a ball mill and examined for incompatibility by sealing samples in glass crimped vials using a microcalorimeter at 50°C at a set RH. After an equilibration period of between 1 and 4 days, thermal data were collected over 15 h. Generally, the data from the thermal activity monitor (TAM) was comparable to the corresponding HPLC analysis. However, it was less successful in prediction when mixtures contained a hygroscopic component. Other work by Selzer et al. (1998) has shown that microcalorimetry can be used to detect incompatibility. Microcalorimetry only detects heat flow, however, and they made the point that physical events such as crystallinity changes would be superimposed on the heat output signal. They also found that experimental temperatures close to ambient could not be employed because the enthalpy change was not large enough.

In solid dose form technology, Monkhouse (1993) has argued that it may be a better idea

any formulations that do not contain lactose and magnesium stearate should be successful! Other investigators may have different experiences and may not have access to a compaction simulator.

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# 8

# PRODUCT OPTIMISATION

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## PRODUCT OPTIMISATION PURPOSE AND SCOPE

The major objective of the product optimisation stage is to ensure that the product selected for further development (the intended commercial product) is fully optimised and complies with the design specification and critical quality parameters described in the Product Design Report (refer to Chapter 5). The key outputs from this stage of development will be

- a quantitative formula defining the grades and quantities of each excipient and the quantity of candidate drug;
- defined pack;
- defined drug, excipient and component specifications; and
- defined product specifications.

The approach to product optimisation will depend on the nature of the product to be developed. It will always involve testing a range of options, for example: a variety of excipients from different sources, with different grades and concentrations, and in different combinations, or a range of pack sizes or different packaging materials. Additionally, it could involve testing a range of particle size distributions of the candidate drug or of the excipients. Particle size may be critical for drug delivery or formulation processing. For example, material with a mean particle size distribution of 2–5 μm will be required for effective pulmonary delivery of aerosol suspensions and dry powders, whereas an even smaller particle size range (nanoparticles) may be required for the dissolution of poorly water soluble drugs in parenteral formulations.

At the early stages of optimisation, preformulation studies are usually conducted to screen excipients or packaging materials and to select those compatible with the candidate drug, using accelerated stress testing procedures. More details about the preformulation techniques, which can be employed for compatibility studies, are discussed in Chapter 3. The importance of doing compatibility studies is for reducing the number of excipients and formulation options to test in further product optimisation studies.

The final stage of optimisation will normally involve generating sufficient stability data on one or more variants to select the best variant. The optimal product will usually be selected based on technical merit. However, there may be a need to consider other factors, such as the use of novel excipients and the associated safety/toxicological implications, supplier and sourcing issues or the ability to patent the formulation or not. Some of these issues are discussed further below.

The manufacturing process used during product optimisation should be designed with large-scale manufacture in mind. Ideally, the process should be as representative as possible to the eventual commercial-scale manufacture. This is because the manufacturing process may affect product performance characteristics, and could influence the results of clinical studies. Although product and process design and optimisation have been depicted as separate stages in the development framework, in practice, they are often combined or closely linked. For example, it is important in pack optimisation to select a pack which is suitable for use in production and will satisfy the demands of a high-speed automated filling line. Alternatively, the pack may have to be able to withstand stresses during processing which could involve extremes of temperature or pressure, during autoclaving or freeze-drying, for example. Process design and process optimisation considerations are discussed later in this chapter.

At the completion of product optimisation, when the best product variant has been selected, it is a good idea to summarise the work conducted in a Product Optimisation Report. The report should reference the primary data from preformulation, product optimisation and stability studies, cross-referencing other investigational reports where necessary. It should clearly justify the recommendations for the quantitative formula and the excipient, component and product specifications. Such a document can be very useful to aid smooth technology transfer into production and for writing regulatory submissions.

## EXCIPIENT AND PACK OPTIMISATION CONSIDERATIONS

### Excipient Selection

Historically, pharmaceutical excipients have been regarded as inert additives, but this is no longer the case. Each additive must have a clear justification for inclusion in the formulation and must perform a defined function in the presence of the active and any other excipients included in the formulation. Excipients are included for all sorts of reasons. They may function, for example, as an antimicrobial preservative, a solubility enhancer, a stability enhancer or a taste masker, to name a few.

The International Pharmaceutical Excipients Council (IPEC) have defined a pharmaceutical excipient as

> any substance other than the active drug or prodrug which has been appropriately evaluated for safety and is included in a drug delivery system to either:





1. aid processing of the system during manufacture, or
2. protect, support or enhance stability, bioavailability or patient acceptability, or
3. assist in product identification, or
4. enhance any other attribute of the overall safety and effectiveness of the drug product during storage or use.

In the 1960s, excipients were commodity items and tended to be of natural origin, but today many are synthetic or have been physically modified. Performance testing was done by the user, not the supplier. This has now changed with the introduction of recognised quality and performance standards for raw materials, which are defined in various pharmacopoeias (Moreton 1999). The rationale for these changes is linked to the requirement to ensure that the patient is provided with the correct dose as safely and consistently as possible. This can only be achieved if the raw materials are of a consistent standard, together with the active and consistent processing.

Unfortunately, the standards for the same raw material can vary in different pharmacopoeias, and so the choice of pharmacopoeia will depend on the intended market for the product (see later comments about harmonisation of standards). Suppliers should provide materials that comply with the specified pharmacopoeial standards. Monographs for excipients provide minimum tests and specifications, which can save time and resource negotiating new specifications with the regulatory authorities. Even so, the user may have to do additional tests to show that the excipient is suitable for use in a particular product or drug delivery system.

The basic selection and acceptance criteria for excipients to be used in a product being developed should have been defined in the Product Design Report section on "Design Specifications and Critical Quality Parameters". In practice, each excipient must be shown to be compatible with the formulation and pack and effectively perform its desired function in the product. At the same time, the product design acceptance criteria should be complied with, such as the following: the excipient should be well established, and its intended route of administration should be safe and acceptable to the regulatory authorities; the excipient should comply with pharmacopoeial requirements, be globally acceptable and meet the proposed design specification.

The case for using well-established excipients (and packs) that have already been administered to humans by the intended route, and in similar dosage forms, has been emphasised previously in the section on "Safety Assessment Considerations" in Chapter 5. New chemical excipients (i.e., that have not been used in registered pharmaceutical products before) usually require a full development programme, including comprehensive toxicological testing, to gain "approval" by the regulatory authorities.

There are clearly cost and time savings of using well-established excipients that have already been approved for use in other registered products and that have an established safety profile. The regulatory status of excipients can easily be checked by consulting the FDA's (U.S. Food and Drug Administration) Inactive Ingredient Guide, the Japanese Pharmaceutical Excipients Directory or other similar sources of information (see Table 8.1). These sources should provide information about registered products already approved, which contain a particular excipient with quantities used, or a list of all products by dosage form that have contained a particular excipient.

Excipients are normally considered to be acceptable if they are listed in the major pharmacopoeias from the United States, Europe and Japan. There has been much progress in harmonising the monographs for key excipients in these pharmacopoeias. For products being

**Table 8.1**
**Sources of information for excipients and packaging materials.**

| Source | Information | Comments |
|---|---|---|
| Various pharmacopoeias, e.g., United States/National Formulary; British, European, Japanese, Pharmacopoeias; Martindale, The Extra Pharmacopoeia; The Merck Index; The British Pharmaceutical Codex | Include standards and monographs for drugs, excipients, containers/closures and medical devices | Updated regularly; many available in book format or CD-ROM; can be obtained through various publishers including Interpharm |
| FDA Inactive Ingredient Guide | Lists excipients used in FDA-approved drug products marketed for human use by route of administration and dosage form | Published by FDA, Division of Drug Resources (DDIR); available through FDA Web site; updated regularly |
| *Handbook of Pharmaceutical Excipients* | Excipient monographs containing data on uses, properties, safety, excipient interactions, standards; also a supplier's directory | A joint publication of the American Pharmaceutical Society and the Royal Pharmaceutical Society of Great Britain |
| *Handbook of Pharmaceutical Additives* | Excipients used in prescription and OTC products approved by the FDA or recommended by USP/NF, BP and Ph.Eur.; details manufacturers, composition, properties, function and applications, toxicology and regulatory status of additives | Compiled by M. and I. Ash; Published by Gower, Aldershot, UK, and Vermont, USA |
| Japanese Pharmaceutical Excipients Directory | Monographs on excipients used in pharmaceutical and cosmetic products | Edited by the Japan Pharmaceutical Excipients Council; available through Interpharm |
| Le Dictionnaire VIDAL | A codex of French approved medicines includes quantitative composition of many products | |
| ABPI Compendium of Data Sheets and Summaries of Product Characteristics | Data sheets prepared by pharmaceutical companies on prescription and OTC products, including quantitative details of formulation ingredients and packaging used | Published annually by Datapharm Publications Ltd., London |
| *Physicians' Desk Reference* | Compendium of FDA approved pharmaceutical products; details formulation, pack, administration and use; identification guide | Published by Medical Economics Co., N.J., USA, in participation with individual manufacturers; also PDRs for ophthalmology and non-prescription drugs; CD-ROM or hard copy |



developed for Japan, excipients must comply with the Japanese pharmacopoeia. If other pharmacopoeial grades are used, a detailed explanation of how these are equivalent or better quality is usually required. However, even if the excipient is listed in all the major pharmacopoeias, additional toxicological studies may still be required to qualify an excipient under certain circumstances, such as (1) excipients used previously in humans but not by the intended route or (2) increased concentration of an excipient above that previously used by the intended route. In either case, more extensive testing will be required so that the tests and specifications applied are shown to be capable of controlling the identity, strength, quality and purity of the excipient commensurate with its intended use. In Japan, excipients which have not been used previously in Japan will be treated as new excipients, even if they have been used in other countries.

Some assurance can be gained about the quality and safety of an excipient if a Drug Master File (DMF) is available and the DMF holder provides permission to reference it. This is a document submitted to the FDA by a vendor which provides detailed information, including toxicological data and specification tests, about a specific excipient (or packaging material, drug substance or manufacturing site). A DMF is never approved, but it will be reviewed by the FDA if it is associated with a product licence application. For more information about DMFs, refer to the FDA Guideline for Drug Master Files (September 1989).

Some food and colour additives may have (generally recognised as safe) (GRAS) status, which also gives some assurance that they could be used in pharmaceutical products with minimal additional safety testing. This is especially the case if the excipient is not likely to be absorbed systemically from the formulation.

However, there will always be situations where the introduction of a new excipient is inevitable. The candidate drug, for instance, may be incompatible with the current range of excipients. Another reason might be the phasing out of existing excipients for safety or environmental concerns, such as chlorofluorocarbons (CFCs) in metered dose aerosols. There may be a need to introduce a new excipient for a novel drug delivery system or to overcome disadvantages with the currently available materials.

A common factor which often influences the selection of excipients and excipient suppliers is a company's historical preference for certain excipients based on proven technical, commercial and quality criteria. Many pharmaceutical companies have a list of preferred suppliers that have already been audited and approved. There are significant advantages of selecting excipients that the company already uses, in terms of time and costs. Limiting the range of standard excipients on a company's inventory should minimise overhead because of the reduced auditing, analytical testing and development required. Also, a greater knowledge can be developed about the characteristics of excipients that have been extensively used. Technology transfer from research and development (R&D) to the final manufacturing site should be easier and faster if the excipients are already in the inventory, and the release specifications and analytical methods are already known to the quality control (QC) department. However, a downside to having a limited company inventory is the reduced options of excipient choice placed on the formulator when faced with a new formulation or drug delivery challenge.

For products intended for global marketing, selection of excipients that meet the regulatory requirements can often be more challenging than the technical issues. Obtaining marketing approval for a new product requires the regulatory acceptance of the new candidate drug and the excipients used in the formulation. The specifications for excipients must comply with the pharmacopoeial standard for the particular country. Unfortunately, there is a diversity of specification tests and limits for the same excipients in the different pharmacopoeias. This issue has long been recognised, and there is an ongoing programme to

harmonise or unify the different requirements for some excipients in the three major pharmacopoeias, Europe, Japan and the United States. This programme is referred to as ICH, or International Conference on Harmonisation of drugs. However, the process of establishing agreed international excipient specifications has proved to be extremely slow. Inevitably, some excipients for which pharmacopoeial standards are in conflict may be discounted from consideration, even though they perform well in terms of functionality.

Another issue for global marketing is the differences of opinion about the safety of some excipients in different countries. For example, ethylenediaminetetraacetic acid (EDTA) is permitted in most countries for use in intravenous (IV) injections as a metal ion sequestering agent, but not in Japan. Colours, artificial sweeteners and bovine-derived products are other examples where safety concerns vary significantly from country to country (Tovey 1995). All dyes available for food and drug use are banned in at least one country. However, it may be essential to add a colouring agent to a product to distinguish one product from another or to differentiate between a number of product strengths.

Colouring agents may also be required for developing placebos to match coloured products for blinding in clinical trials. Nedocromil sodium nasal, ophthalmic and respiratory products are examples which all required colour matching because of the inherent yellow colour of the drug substance. This can be especially challenging when a range of drug concentrations is required, with each concentration having a different colour intensity. For the above reasons, it is not always possible to develop a single formulation for the world-wide market.

The sourcing of excipients can be another important selection and optimisation criterion. It is generally desirable to have excipient sources available in the country where product manufacture is taking place, to avoid stockpiling material to compensate for possible transport and import delays. Even better is if there are multiple sources of the same type of excipient so that if one supplier fails to deliver or discontinues delivery, an alternative can be used. This might rule out the use of some suppliers or excipients. In order to cater to different manufacturing sites in different countries which might use slightly different equipment, it is important that the product and process developed are robust enough to cater to small differences in excipient characteristics and performance from different sources.

In conclusion, during product optimisation, excipients will be selected based on a variety of acceptance criteria. The quantities included in the formulation will be finalised, based on the performance characteristics of the excipient in the final product. At this stage it is important to fix the specifications of the excipients to ensure that the materials used, and hence the product, will be consistent throughout development. Setting specifications is discussed in a following section.

## Pack Selection and Optimisation Considerations

A logical approach to packaging optimisation is, first of all, to define the packaging function, followed by selection of the materials, then testing the performance of the packaging to ensure that it will meet all the product design and functional requirements that were identified in the Product Design Report.

Product optimisation of the pack should initially focus on defining the primary packaging (sometimes referred to as "primary container" or "immediate container"). This is most relevant to regulatory authorities because it is the primary packaging that is in direct contact with the drug product, including the closure, liner, and any other surface contacting the product.

The secondary packaging is that outside the primary pack, and by definition is not in direct contact with the drug product. Secondary packaging is often a carton or a blister, which may also function to protect the product from light or moisture. For example, it may be



preferable to use a carton and a clear ampoule or vial, rather than an amber container for a photosensitive parenteral product, to allow users to inspect the contents of the package for contamination or signs of instability. There may be a requirement to have sterile secondary packaging, for example, for a sterile product likely to be used in an operating theatre by a surgeon. The pharmaceutical company developing such a product should identify this requirement in the product design stage to ensure that the pack and sterilisation process are considered during development. In the majority of cases, the purpose of the secondary packaging is simply to be elegant in its appearance, provide clear labelling instructions and project a good marketing image.

Important selection and optimisation criteria for the primary packaging may include the following:

- Satisfies environmental and legislative requirements for world-wide markets
- Availability of a DMF
- Ability to source from more than one supplier/country
- Acceptable cost of goods (particularly if a sophisticated device)
- Consistency of dimensions
- Consistency of pack performance
- Ability to meet function/user tests, customer requirements and specifications

For some excipients, the global acceptability of some packaging materials varies from country to country. This can often stem from environmental concerns and the negative impact from the need to dispose of packaging waste. For example, polyvinyl chloride (PVC) is used widely to manufacture bottles and blisters for pharmaceutical products, but there is a growing concern about its safe use and disposal in some countries (Hansen 1999). Incineration is the preferred method of disposal for PVC, with the downside that it emits toxic gases. Materials that are readily biodegradable, or that can be recycled, are preferred. This is not always possible with some types of synthetic materials.

Multiple sourcing of some synthetic polymeric materials may not always be possible, or desirable, because each supplier may have its own range of additives for the basic packaging material. It is therefore important that, once the packaging material has been established for a product, there is an understanding between the pharmaceutical company and the supplier not to alter the polymer formula or processing conditions without consultation. Any changes should become apparent if the supplier has filed a DMF with the regulatory authorities. Some sophisticated drug delivery systems, such as valves for metering pumps used for nasal and pulmonary delivery, can contain a multitude of components made of different materials and grades. It is important that the pharmaceutical company is made aware of any changes during development so that the implications for product performance and stability can be considered.

The role of the pack will include the following:

- Containment and protection of the product: to ensure stability over shelf-life, protection to withstand the influences of climate, distribution, warehousing and storage during use, protection for child safety.
- Presentation to the user (e.g., doctors, patients, parents): provides relevant information, identification, visually attractive appearance and assurance against tampering.
- Administration of the product: provides convenient and consistent dose delivery.

### Protection of the Product

The formulation must be protected from the environmental elements of heat, light, moisture, gaseous and sometimes chemical or microbial attack, as well as physical protection during transport and handling. A product licence will not be granted unless the product quality, safety and stability of the formulation in the commercial pack of choice over the declared shelf-life has been demonstrated to the regulatory authorities. They will be looking for acceptable stability data when the product is stored under anticipated normal conditions, in addition to acceptable data from "accelerated" or stressed conditions. This might include, for example, storage of the product in different orientations or in adverse conditions of extremes of temperature and humidity. Appropriate stressed stability studies should demonstrate the integrity of the container and closure and any possible interaction between product and container. However, there is a possibility that components may be leached from packaging under accelerated/stressed conditions, which may not occur under normal conditions of use. Accelerated studies can be very useful for compatibility testing and screening materials, but they should be accompanied by long-term stability studies under normal conditions of use to confirm the suitability.

Other stress tests worth considering to establish the robustness of the product and pack include vibration and impact testing. Successful testing should instil confidence that the product can be transported and, to some extent, be physically abused (dropped) in the hands of users.

Two specific instances where the regulatory authorities will usually request extensive information are sorption of active(s) or excipient(s) from liquid and semi-solid formulations and leaching of pack components into liquid or finely divided solid preparations, over the proposed shelf-life of the product.

Plastics and rubber materials used in containers and closure systems can contain certain additives, for example, plasticisers, stabilisers, lubricants and mould-release agents. It is worth asking the material suppliers what polymer additives are involved so that these can be analysed when conducting compatibility studies. The regulatory authorities require that these additives should not be capable of extraction into the formulation or leach from the container/closure to contaminate the product. Mercaptobenzothiazole (MCBT) is a common additive to rubber compositions used in closures for multidose parenteral containers, which is extremely toxic. For synthetic polymeric materials, the leaching of additives can result in morphological changes to the packaging materials. These changes may in turn affect physical properties such as hardness, stiffness, tensile strength or viscoelasticity, which can be vital for pack performance. Leaking can be a problem because of the viscoelastic nature of some injection closure compositions. Other less obvious properties may also be affected, such as gas permeability and absorption. Permeation of gases or water vapour through the container material can affect formulation stability if the candidate drug is susceptible to hydrolysis or oxidation.

Drug and excipient interactions with the container may involve leaching, permeation, sorption, chemical reaction or modification of the physical characteristics of the polymer or the product. During product optimisation, formulation factors, such as the pH, concentration of ingredients, composition of the vehicle (solvents and surface active agents), area of contact and contact time, will need to be evaluated. Also, processing variables such as temperature might be important. There are cases where the drug may absorb into components of the pack. This can be a particular problem with protein/polypeptide drugs onto glass and plastic packaging components. The best known example of excipient adsorption or absorption is the loss of antimicrobial preservative from solutions to container/closure systems, most notably the



rubber bungs of multidose injection containers, or the rubber gaskets used in metered dose nasal pumps. The effective concentration in solution can be reduced to such an extent that the product is no longer protected from microbial growth.

There is also the possibility of constituents from label adhesives migrating through polyethylene or polypropylene containers. This is something to be aware of when carrying out stressed compatibility testing and long-term stability testing.

Packaging for sterile products must be effectively contained and sealed to prevent microbial contamination, and must be robust enough to withstand any sterilisation process required. The sterilisation process can affect the leaching of components from the container into the product or affect the physical properties of the container. For example, autoclaving can soften plastic containers, and gamma irradiation can cause certain polymers to cross link.

Other protective elements have also become important in recent years, namely those of child resistance and tamper evidence. Child-resistant packaging originated in the United States in the 1970s and was then introduced into Europe, adopted mainly in the United Kingdom and Germany. There has been an ongoing debate between pharmaceutical manufacturers, container suppliers and regulatory authorities on how to ensure that there is a practical balance between child safety and the pack being sufficiently user-friendly so that the elderly and arthritic can obtain their medication. Tamper-evident containers are closed containers fitted with a device that shows irreversibly whether the container has been opened. Tamper evidence is particularly important for sterile products, and has become increasingly desirable for other products, to demonstrate that the product has not been interfered with.

The FDA has published comprehensive information on container closure systems in a guidance for industry document, "Submitting Documentation for Packaging for Human Drugs and Biologics" (February 1987), shortly to be superseded by a new draft guidance for industry, "Submission of Documentation in Drug Applications for Container and Closure Systems used for the Packaging of Human Drugs and Biologics" (July 1999).

### Presentation to the User/Administration of the Product

For traditional dosage forms, such as tablets and capsules, the role of the pack is mainly for protection of the product during storage and presentation to the user. The design is not so critical for administration of the dose or performance of the product in the hands of the administrator (doctor or patient). For other dosage forms, such as inhalers for respiratory drugs and self-injection devices for parenteral products (e.g., insulin), the pack is an integral part of the drug product. These are often referred to as "drug delivery systems" because the packaging system or device in the hands of the administrator provides a means of ensuring that the correct amount of active drug product is delivered to the site of action as easily, reliably and conveniently as possible.

With metered dose inhalers (MDIs) for example, the FDA consider the drug product to be the canister, the valve, the actuator, the formulation, any associated accessories (e.g., spacers) and any protective secondary packaging. This is because the clinical efficacy of MDIs may be directly dependent on the design, reproducibility and performance characteristics of the packaging and closure system. For these types of products, and other more sophisticated drug delivery systems, it is important that these product performance aspects are addressed during the product optimisation stage. During development and before initiating critical clinical studies, the performance characteristics of the MDI (e.g., dosing and particle size distribution of the spray), in addition to the compatibility with the formulation, need to be thoroughly investigated.

When developing a product for Europe which uses both device and medicinal product components (such as metered-dose or powder-filled inhalers or prefilled syringes), the pharmaceutical company must establish whether the product will have to conform to the Essential Requirements of European legislation applied to medical devices (Medical Device Directive 93/42/EEC). If the medicinal product has a separate device element that could be refilled/reused, or the device and medicinal substance are presented separately, the device component will be subject to medical device controls, in addition to an application being made to the medicines authority (Tarabah and Taxacher 1999). To obtain a CE mark for a medical device registered in Europe, there will be implications for the pharmaceutical company (and its suppliers) to have suitable quality systems in place (e.g., EN46001). Obviously, this should be established early on in product design to enable the appropriate routes for authorisation to be obtained. Similar regulations apply for medicinal devices which will be marketed in the United States (cGMP, 21 CFR Part 820).

The packaging must also be convenient to use in order to promote good patient compliance, that is, to encourage patients to take their medication at the correct times. User acceptance of the pack and/or delivery device can lead to that product being preferred in the market place. Product optimisation studies may involve testing a range of pack options using a volunteer panel to establish the most user-friendly or patient-compliant packs that can be easily opened and closed. If a novel pack has been designed in-house by the pharmaceutical company, there is the possibility of filing a patent to gain market exclusivity for a number of years. Some examples of new innovations in pharmaceutical packaging development to improve drug delivery systems are described by Williams (1997).

## SOURCES OF INFORMATION

Knowing where to find information about excipients and packaging materials, as well as development and regulatory guidelines, is critical to the preformulation and formulation scientist during the product design and optimisation stages of development. Typical information that is often required for excipients and packaging materials include the chemical composition, function, chemical and physical properties, regulatory and safety status, manufacturers and suppliers, qualitative and quantitative composition of marketed products, stability data, known incompatibilities and so on. Having this information can save much valuable time in the laboratory generating the data from scratch.

There are also a lot of guidelines and regulations from various regulatory authorities and standard organisations to be aware of that affect product development. Some of the regulatory documents are legal requirements (regulations) such as the Code of Federal Regulations (FDA), and some are regulatory requirements which are stipulated within licence applications, such as pharmacopoeial monographs. Others are guidelines which must be followed or, if not, a very strong scientific argument must be provided for justification. For example, many of the documents published by the FDA as guidance are being held up by the assessors as a regulatory requirement. Companies have ignored these to their peril.

There is a host of reference sources available from literature, reference books, Web sites and publications from various regulatory authorities and standard organisations. This section is not meant to be exhaustive, but should provide some general guidance to those developing new formulations.

If the excipient or packaging material has been used previously in marketed products by your own pharmaceutical company, and the supplier has been audited, most of the information about these materials should already be available within the company. More often than not, excipients not listed in the company inventory will have to be considered. Some useful reference sources which may provide details of specific excipients and packaging materials are given in Table 8.1. These sources can be used to gain information about the choice and status of materials available. It should be possible to easily check whether the material of interest is well established, safe and meets regulatory authorities' requirements, or not. Some of the reference sources reveal quantitative compositions of products, giving an indication of acceptable levels that have been used previously in approved products.



Other leads can be found by browsing pharmaceutical and packaging technology journals or visiting trade shows and exhibitions.

Once a lead has been found on an excipient or packaging material of interest, the next useful step is often to contact the supplier for further information. It is usually in their interest to persuade pharmaceutical companies to use their materials because of the potential commercial return if the product is successful. Often, suppliers will assist customers with any enquiries and provide any missing information. They may provide small amounts of samples to try, in attempts to satisfy you that their materials should be used. However, if a new supplier or material is seriously anticipated, it is wise to arrange for an audit of the supplier to ensure that it meets your company's appropriate quality standards, before becoming too committed. Also, it is advisable that more than one batch be evaluated to ensure the material is consistent. Be aware that sample materials are not always representative of purchased materials. They may have a different impurity profile, for example, or might have slightly different physicochemical properties which might give misleading performance results.

The rapid development in information technology (IT) in recent years has revolutionised the availability and speed of retrieval of information. Many reference sources are now available on CD-ROM, which are generally much easier to store, access and search than books and journals. The introduction of the World Wide Web (WWW), with a user-friendly graphical interface based on hypertext links, provides easy access via the Internet to a wealth of information and databases which are kept continually updated (D'Emanuele 1996). Some of the useful Web sites for sources of information about pharmaceutical development and regulatory guidelines are listed in Table 8.2. The Web site addresses are correct at the time of this writing.

## EXPERT SYSTEMS

The development of a new medicinal product from a new chemical entity is a very time consuming and costly process. The formulator will usually start with a design specification. This could be very general, or it could be quite specific, perhaps expressed in terms of performance levels to be met in a number of predefined tests. In order to develop the formulation that will meet the product specification, the formulator will have to take into account several different technical issues such as the physicochemical properties of the candidate drug, the compatibility of the drug with pharmaceutical excipients and packaging and the manufacturing process to be used. The formulator might have to go through several formulation optimisation steps before the ideal product is achieved.

Pharmaceutical formulation development is thus a highly specialised and complex task that requires specific knowledge and often years of experience. This type of knowledge is very difficult to document and is therefore often passed on by word of mouth from experienced senior formulators to new personnel. The loss of senior formulators from a company through retirement or transfers to other companies can lead to the loss of irreplaceable knowledge. Formulation "expert systems" have been developed to provide a mechanism of capturing and utilising this knowledge and expertise.

**Table 8.2**
**Information technology (IT) sources of information and development guidelines.**

| Source | Information | Comments |
|---|---|---|
| Food and Drug Administration (FDA) | Guidance for industry notes on various aspects of pharmaceutical product development, registration in the USA and inspections | Web site: http://www.fda.gov/ |
| Committee for Proprietary Medicinal Products (CPMP) and European Medicines Evaluation Agency (EMEA) | Guidance for industry notes on various aspects of product development and registration in Europe, e.g., "Excipients in the dossier for application for marketing authorisation of a medicinal product (III/3196/91)" | Web sites: http://www.eudra.org/emea/cpmp and http://www.eudra.org/w3/emea.html |
| National Institute of Health Sciences, Japan | Guidance notes on registration of pharmaceutical products in Japan | Web site: http://www.nihs.go.jp/ |
| International Conference on Harmonisation (ICH) | Guidelines and information on harmonised requirements for product development and registration | Web sites: http://www.ifpma.org and http://www.chugai.co.uk |
| Web site for other regulatory authorities | Local regulatory guidance | http://www.pharmweb.net/ |
| UK Medical Devices Agency (MDA) | Medical device regulations and guidance notes for industry on European Directives for medical devices | Web site: http://www.medical-devices.gov.uk/ |
| *International Medical Device Registration* | A compilation of all the regulations affecting medical device registration world-wide | Book edited by M. E. Donawa. Published by Interpharm |
| Parenteral Drug Association (PDA) and British Parenteral Society (BPS) | Technical reports and guidelines prepared by industry on various parenteral topics, e.g., Sterile Pharmaceutical Packaging, compatibility and stability (PDA) | PDA Archive containing research papers, technical reports and conference proceedings available on CD-ROM; updated annually |
| International Federation of Pharmaceutical Manufacturers (IFPMA) | Information on pharmaceutical manufacturers | Web site: http://www.mcc.ac.uk/pharmweb/ifpma.html |



Several different definitions for an expert system have been used (Partridge and Hussain 1994; Turban 1995). They all state that an

> expert system is an advanced computer program that mimics the knowledge and reasoning capabilities of an expert in a particular discipline.

In essence, the programmer will build a system based on the expertise of one or more experts so that it can be used by the layperson to solve difficult or ambiguous problems. The intent of an expert system is not to replace the human expert but to aid or assist that person.

An expert system consists of three main components:

1. *The user interface*, which is necessary for the expert system to interact with the user and vice versa
2. *The inference engine*, the procedure which generates the consequences, conclusions, or decisions from the existing knowledge extracted from the knowledge base
3. *The knowledge base*, the set of production rules that is supplied by the human expert and encoded into rules so that the system can understand the information

Expert systems can be developed using a variety of techniques including conventional computer languages (PASCAL and C), artificial intelligence languages (PROLOG, LISP and SMALLTALK), and specialised tools known as shells or toolkits.

Expert systems shells are computer programs written in both conventional and specialised languages which are capable of forming an expert system when loaded with the relevant knowledge. The development time of an expert system using a shell is much faster than using conventional languages and has therefore proved to be the method of choice. Shells used in product formulation vary from the relatively small and simple systems, such as Insight 2+ and Knowledge Pro, to the large and flexible Product Formulation Expert System (PFES) from Logica (UK). PFES was developed from research work conducted by a consortium of Shell Research, Logica (UK) and Schering Agrochemicals under the UK Alvey programme, 1985–1987 (Turner 1991).

To build a pharmaceutical formulation expert system, the formulation process has to be broken down into a number of discrete elements in order to provide distinct problem-solving tasks, each of which can be reasoned about and manipulated. However, as the formulation process is so complex, none of these tasks can be treated independently. A means of representing interactions and communicating information between tasks is therefore required. For example, one task may result in certain preferences that must be taken into account by subsequent tasks. To achieve this level of communication between tasks, the information in an expert system has to be highly structured and is therefore often represented as a series of production rules. An example of a production rule is as follows:

> IF (condition)
>
> THEN (action)
>
> UNLESS (exception)
>
> BECAUSE (reason)

Using a pharmaceutical example, this production rule would read:

IF the drug is insoluble

THEN use a soluble filler

UNLESS the drug is incompatible with the filler

BECAUSE instability will occur

The knowledge used in the production rules can come from many sources, including human experts, textbooks, past formulations, company Standard Operating Procedures (SOPs) and development reports. The knowledge contained within these can be broken down into different types: facts which are the objects and concepts about which an expert reasons, and rules and heuristics, which are often referred to as the expert's rules of thumb. The differences between rules and heuristics is that rules are always true and valid, whereas heuristics are the expert's best judgement in a particular situation and therefore may not always be true (Rowe 1997). The knowledge will be input into the expert system shell by a knowledge engineer. The knowledge engineer is an information technology expert who, through a series of interviews with the formulation experts, will capture all the steps involved in the formulation process. The knowledge engineer will then encode these tasks into a series of production rules which he will build into the expert system. This process of knowledge acquisition can be very time consuming and therefore very expensive.

Reference to the use of expert systems in pharmaceutical product formulation first appeared on 27 April 1989 in the London *Financial Times* (Bradshaw 1989). This article was closely followed by one in the same year by Walko (1989). Both these authors were describing the work being undertaken by ICI (now Zeneca) Pharmaceuticals and Logica UK Ltd. to develop an expert system for formulating pharmaceuticals using PFES. Since these first publications, many companies and academic institutions have published on work being conducted in this area, as shown in Table 8.3.

**Table 8.3**
**Published work on pharmaceutical formulation expert systems.**

| Formulation | Company | System | Reference |
|---|---|---|---|
| Tablets | ICI (now Zeneca) | PFES | Rowe (1993a,b) |
| | Cadila Laboratories | PROLOG | Ramani et al. (1992) |
| | University of Heidelberg (GSH) | C/SMALLTALK | |
| Capsules | Sanofi Research Division | PFES | Bateman et al. (1996) |
| | Capsugel/University of London | C | Lai et al. (1995, 1996) |
| | University of Heidelberg (GSH) | C/SMALLTALK | |
| Parenterals | ICI (now Zeneca) | PFES | Rowe et al. (1995) |
| | University of Heidelberg (GSH) | C/SMALLTALK | |
| Aerosols | University of Heidelberg (GSH) | C/SMALLTALK | |



A flow diagram of the Zeneca tablet formulation expert system is shown in Figure 8.1. The formulator enters the physicochemical information known about the drug, the specification for the formulation and the formulation strategy (e.g., whether to use one or two fillers in the product). The system then goes through a series of steps from which the filler, the binder, the lubricant, the disintegrant, the glidant and the surfactant and their relative proportions will be chosen. A formulation will then be recommended to the formulator. A series of defined tests can be carried out on the formulation in order to ensure that it meets the original specification. If it fails to satisfy the necessary requirements, the formulation can be optimised by feeding back the results into the system. The system has been designed to give a report on the decision processes used, that is, the production rules that fired during the development of the formulation.

The following benefits have been seen from the development and use of formulation expert systems (Rowe and Upjohn 1993):

- Protection of commercial knowledge. The expert system acts as a knowledge archive for formulation information, thereby overcoming the problems of staff turnover.
- Harmonisation of formulation processes and excipient usage, giving a guarantee of a consistent approach to formulation within the same company.
- Training aid for novice formulators. Inexperienced formulators can quickly learn about a product or formulation area using an expert system. A spin-off from this is to release the time of more experienced formulators currently involved in the training process.
- Cost reduction. Based on the reduced time required for formulating and speed of development, Boots claim that they have saved 30 formulator days per year since the introduction of their sunscreen formulation expert system (Wood 1991).
- Improved communication. The formulator and decision-making process is transparent to everyone in the company.

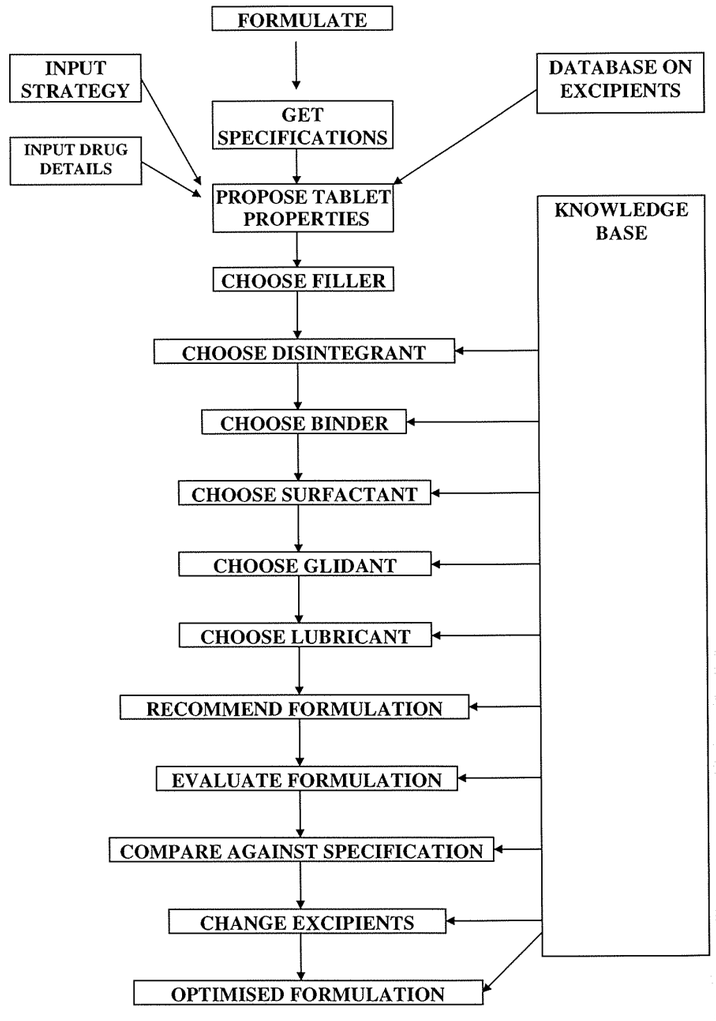
In spite of the many perceived benefits, the development of expert systems per se over recent years has been surprisingly slower than one would expect. One possible explanation for this is that when the systems were first introduced, their capabilities were overestimated and they were seen as the panacea to all formulation problems. This was obviously not the case, but as a result, the systems are viewed with some degree of scepticism. Several reviews on the issues and limitations with the development of an expert system have been published (Dewar 1989; Tinsley 1992; Rees 1996).

Further information on expert systems and the use of artificial intelligence software in pharmaceutical formulation can be found in the literature (Rowe and Roberts 1998).

## EXPERIMENTAL DESIGN

The concept of experimental design originated in the agricultural industry and was developed by Sir Ronald Fisher. His first article appeared in the *Journal of the Ministry of Agriculture* in 1926, followed by a book *The Design of Experiments* in 1935. The concept of experimental design gradually spread to other industries, with the first publication of pharmaceutical relevance appearing in 1952 (Hwang 1998). The popularity of experimental design techniques

**Figure 8.1** Flow diagram of the Zeneca tablet formulation.

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within the pharmaceutical sciences can perhaps be gauged by the number of relevant publications appearing in the pharmaceutical press; a search of International Pharmaceutical Abstracts elicited 41 publications since 1990 in which design of experiments (DOE) techniques were used for either formulation or process optimisation.

Pharmaceutical scientists are now almost universally aware of the disadvantages of traditional "one factor at a time" experimentation and recognise the advantages of a structured statistical approach to product development, as described below. Despite this, the routine use of experimental design in pharmaceutical development has only recently become widespread. The slow uptake of DOE techniques may have been a consequence of the lack of suitable user-friendly software packages. Until recently, scientists were forced to rely on SAS-literate statisticians, with the mechanics of data analysis being something of a "black box". This situation is changing with a number of easy to use software packages, such as Modde and Design Expert, being available. The impact of this development cannot be overstated; with relatively little statistical training, scientists are able to build their own experimental designs and analyse their data. Good statistical support remains of paramount importance, however, for all but the simplest of experimental designs, so that potential pitfalls are not overlooked. The key message from experience of using experimental design in pharmaceutical development is the importance of the pharmaceutical scientist and the statistician working side by side.

## Benefits of Experimental Design

The potential benefits of using a structured statistically valid experimental design rather than using traditional "one factor at a time" experimentation are summarised below and are illustrated by the examples given later in this section.

- *Savings in time, money and drug substance.* This is particularly important in early formulation development when both time and drug substance are usually at a premium. The use of a suitable screening design, such as a fractional factorial, can allow the main effects of a number of variables to be evaluated in a minimal number of experiments.
- *Identification of interaction effects.* One of the most important benefits of experimental design is that interaction effects between variables can be identified and quantified, as well as the main effects of the individual variables. This is vitally important in instances where the effect of one variable is dependent on the level of another.
- *Characterisation of response surface.* By defining how a response variable responds to changes in process variables, a process can be selected that is in a plateau region, thus avoiding carrying out a process close to an optimisation precipice. In addition, a knowledge of how a process responds to changes in one or more operating variables is invaluable in instances where process deviations occur.

## The Practical Use of DOE Techniques

A detailed discussion of the statistical principles underlying DOE techniques is beyond the scope of this book. Rather, some literature examples are presented which serve to illustrate the potential utility of DOE in all stages of pharmaceutical development.

### Screening Studies

Partial factorial designs are widely used in early preformulation and formulation development, since they allow a large number of variables to be evaluated using a relatively small number of experiments. Variables may be either quantitative or qualitative; for example, the presence or absence of a particular component at a fixed level could be an experimental variable. In full factorial experimental designs, every combination of variables is evaluated. This can lead to a large number of experiments, for example, a design which included four variables each at two levels would require 16 experiments. In a half factorial design this number would be reduced to eight. Clearly, there is a price to pay for this resource saving; some information on interaction effects will be lost by the process of confounding interaction effect terms with main effect terms. Nevertheless, the experiment can be structured such that those two-way interaction effects which are suspected to be most significant can be included in the model. Furthermore, fractional factorial experiments can be easily expanded by addition of the missing experimental runs. Hwang et al. (1998) described a tablet formulation optimisation study in which a fractional factorial design was used to identify the formulation factors which were critical to achieving a high-quality product. Nine experimental factors were evaluated with only 16 experiments. Only main effects could be detected using such a small number of experimental runs, but statistical analysis of the data showed that only one factor required further optimisation. This factor was then studied in detail in a subsequent optimisation study. Plackett-Burnham designs, which are based on the two-level factorial approach, are widely used for screening studies where the main effects of a larger number of variables require evaluation in a limited number of experiments.

### Optimisation Studies

The use of a full factorial experimental design can provide a detailed understanding of the experimental response surface. This type of design can be used when the number of variables to be investigated is small. Fransson and Hagman (1996) describe the use of a three-factor, two-level full factorial experimental design to evaluate the effects of light intensity, oxygen level and phosphate content on methionine oxidation of human insulin-like growth factor. Although the basic design required eight experiments, a further four experiments were carried out to provide an estimate of the inherent experimental variability. An interaction term was identified between the phosphate concentration and light intensity, with the effect of light being much greater when the phosphate concentration was high. The same technique was used by Bodea and Leucuta (1997) in the optimisation of a sustained-release pellet formulation. Again, significant interaction effects were detected.

One of the limitations of two-level factorial designs is the assumption of linearity of the effects. In reality, it is rather unlikely that the factor/response relationship will be linear. This relationship can be characterised more fully by the use of three-level factorial experiments, but this adds considerably to the number of experimental runs required. Various other experimental designs can be used if a detailed knowledge of the response surface is required. For example, Vojnovic et al. (1996) describe the use of a Doehlert experimental design in the optimisation of a high shear granulation process. In this case, the authors were using experimental design to identify an experimental region in which the quality of the product was relatively insensitive to small changes in processing variables, thus verifying the robustness of the process.

An alternative method of optimisation is the simplex search method. This is a model independent procedure in which the results of earlier experiments are used to define subsequent



experiments. This type of optimisation is based on a systematic "trial and error" search for the optimum rather than statistical principles but can nevertheless be a useful method for defining the experimental region of interest.

### Mixture Designs

Mixture designs are used in situations where the levels of individual components in a formulation require optimisation, but where the system is constrained by a maximum value for the overall formulation. This is most easily illustrated by considering the optimisation of a solution formulation containing a number of components each at a given percentage w/w. Clearly, the sum of all the components of the formulation, including water, must equal 100 percent. The experimental runs to be carried out depend on the model to be fitted. Marti-Mestres et al. (1997) describe the use of a simplex centroid design to optimise the relative proportions of three surfactants in a shampoo formulation. In this case, the total surfactant concentration was fixed at 18 percent, with the remainder being water and a number of minor components whose concentrations were also fixed and therefore not considered as experimental variables. Seven experimental runs were used to generate a quadratic model; a further three runs were carried out using other combinations of variables within the experimental region, in order to check the fit of the model. Three response factors were used to evaluate the quality of the formulations, and contour plots were developed illustrating acceptable formulations in terms of the individual responses. These contour plots were superimposed to yield a relatively small area of the experimental region in which all three response factors were satisfactory. Vojnovic and Chicco (1997) used a similar approach but used an axial design to evaluate the solubility of theophylline in a four-component solvent system.

It is evident that the use of suitably designed experiments can be an invaluable aid to the optimum use of resource at all stages of product development. In early development, screening studies enable the rapid assessment of the effect of several variables on the key characteristics of the product. More elaborate experimental designs can be used at the formulation, pack and process optimisation stages to ensure that the effect of all components and process variables are fully understood. Finally, prior to process validation, the use of experimental design techniques is invaluable in ensuring that the process is robust and that the operating region is not close to an "optimisation precipice". The software tools are now available to enable the pharmaceutical scientist to exploit the potential benefits of DOE, and the use of this approach should be considered in all experimental investigations.

## STABILITY TESTING

The purpose of stability testing is to provide evidence of how the quality of a drug substance or formulated product varies with time under the influence of a variety of environmental factors such as temperature, light and humidity. The ultimate goal of stability testing is the application of appropriate testing to allow the establishment of recommended storage conditions, retest periods and shelf lives.

It is necessary to establish the "fitness for purpose" of the product throughout a proposed shelf-life, that is, to establish that all those attributes affecting product performance in use are not unacceptably changed during the period of storage up to the proposed expiry date. Testing must include factors affecting drug potency, formation of degradation products and the microbiological and physical integrity of the product. It may also be required to measure other

quality parameters considered to be important, such as the organoleptic and aesthetic properties of the product.

Stability studies are carried out during all stages of development of new drug substances, formulated products, and where appropriate, novel formulation excipients. However, the stability design and type of testing will depend on the stage of the development process and the nature of the drug and product under test. The types of stability studies carried out during development will typically include the following:

- Accelerated stress stability testing
- Stability to support safety and clinical studies
- Stability to support product licence applications

## Accelerated Stress Stability Testing

These are studies in which samples are stored under conditions designed to stress the drug substance or product. Techniques that can be used, and test conditions, are further discussed in Chapter 6, "Preformulation Studies as an aid to Product Design in Early Drug Development". Generally, samples are exposed to extremes of temperature or humidity. Also, exposure to intense light, metal ions and oxygen may be investigated. The aim of these studies is to provide information about the possible routes of degradation of the drug substance and what chemical and physical factors will affect degradation. For the drug product, the compatibility of the candidate drug with potential formulation excipients and packaging, routes of degradation in potential formulations and the identity of the major degradation products can be established. This information will provide important guidance to the formulator on the formulation factors that will affect product stability. Stability data from accelerated studies can also be used to predict shelf-lives at ambient conditions as discussed below.

## Stability to Support Safety and Clinical Studies

Although real-time data provide the ultimate test of the defined shelf-life, the prediction of stability by the use of accelerated stress stability studies is vital in reducing the time to establish shelf-lives for products used in safety and clinical studies. By applying the principles of chemical kinetics to data from accelerated storage tests, predictions can be made of the rate of decomposition at ambient temperatures. The Arrhenius relationship is often assumed for this modelling. However, this approach can sometimes fail to give good predictions when applied, because more complex decomposition is occurring, involving both chemical and physical factors. In these cases, more complex predictive models can be applied, but it may be that only real-time data can be used.

The regulatory authorities recognise that modifications are likely to be made to the method of preparation of the new drug substance and formulation, and changes to the formulation itself, during the early stages of development (Phases I and II). The emphasis should generally be placed on providing information to develop a stable formulation, and to support a shelf-life suitable for the duration of the initial clinical studies.

During Phases I and II, stability testing is required to evaluate the stability of formulations used in these clinical studies. The duration of the stability study will depend on the length of the clinical studies, usually 1–2 years. Data generated should be of the appropriate



quality for submission to regulatory authorities, to support a Clinical Trials Application (CTA) or Investigational New Drug (IND) submission, for example. The information may also be used to provide supporting data for a Product Licence Application. These stability studies will monitor changes in product performance characteristics and identify formulation degradants produced under actual conditions of storage. Stability data should be sufficient to obtain the additional information needed to develop the final formulation, and to select the most appropriate primary container and closure.

## Stability to Support Product Licence Applications

In stability testing to support a product licence application (usually conducted during Phase III), the emphasis should be on testing the proposed commercial formulation stored in the proposed market packaging, and using the final manufacturing process at the proposed commercial production site. Alternatively, the process must be representative of the final manufacturing process at a scale which should be at least 10 percent of that proposed for full commercial scale manufacture. Ideally, drug substance used should be synthesised using the final process. Stability data will be required on at least three batches of drug substance, and for product batches made from three different batches of drug substance and different batches of excipients and packaging materials. If packaging components in contact with the product are obtained from more than one supplier, and they are not considered to be equivalent, then product packed in components from both suppliers should be tested.

Detailed regulatory guidelines are available to provide assistance to companies making regulatory submissions, including recommendations regarding the design, conduct and use of stability studies. These guidelines include, for example, the FDA guidance "Submitting Documentation for the Human Drugs and Biologics" (February 1987), shortly to be superseded by the FDA draft guidance for industry "Stability Testing of Drug Substances and Drug Products" (June 1998) and the Committee for Proprietary Medicinal Products (CPMP) notes for guidance on "Stability Testing: Testing of New Drug Substances and Products" (CPMP/ICH/380/95). Information is readily available from the Internet Web sites of various national and international regulatory authorities and manufacturers' associations:

- FDA (http://www.fda.gov/cder/guidance/index.html)
- CPMP (http://www.fda.gov/cder/guidance/index.html)
- ICH (http://www.ifpma.org)

Much progress has been achieved by ICH in harmonising the requirements for stability testing in the three areas of Europe, Japan and the United States. Thus, information generated in any one of these three areas should be mutually acceptable in both of the other two areas, thereby avoiding unnecessary duplication of effort. The FDA has incorporated many of the ICH recommendations into its own guidance for industry document "Stability Testing of Drug Substances and Drug Products". Examples are included where bracketing or matrixing could be acceptable—for different strengths of the same product, different pack sizes and different batch sizes, for example. A bracketing design can be usefully adopted to reduce the number of product strengths to be tested, but still cover the range of commercial product strengths. Similarly, a carefully designed matrix of testing can be used to reduce the number of product variants and time points tested, saving a lot of time and resource.

## DEVELOPING SPECIFICATIONS

A specification is defined by ICH as

> a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

Specifications will be required for the pharmaceutical active ingredient, any excipients used in the formulation, packaging components, and for the finished product (at time of manufacture and over the shelf-life). In all cases, the specifications tests and limits will evolve during development, as illustrated in Table 8.4. It is clearly beneficial to have full specifications in place for the start of the Phase III pivotal clinical studies, when the product and process should have been optimised, to ensure that there is equivalence between the product used in Phase III and the commercial product.

### Raw Material Specifications

The requirements for developing, testing and setting of specifications for raw materials, whether they are New Chemical Entities (NCEs), pharmacopoeial active materials, excipients or packaging materials, are essentially the same. Most emphasis is placed on establishing excipient and packaging specifications here because this usually involves an external supplier and the pharmaceutical company working together.

**Table 8.4**
**Development of specifications.**

| | Phase I | Phase II | Phase III | Commercial Product |
|---|---|---|---|---|
| **Active** | Batch analysis; certificate of analysis; test methods developing | Draft specification; test methods developed and validated | Full specification; test methods developed and validated | Full specification; test methods developed and validated |
| **Excipient** | Certificate of analysis and methods developing on functional properties | Draft specification; test methods developed and being validated | Full specification; test methods developed and validated | Full specification; test methods developed and validated |
| **Packaging** | Certificate of analysis and limited testing depending on functional properties | Draft specification; test methods developing and being validated | Full specification; test methods developed and validated | Full specification; test methods developed and validated |
| **Finished Product** | Batch analysis; draft specification; test methods being developed | Refined draft specification; test methods developed (provisional) and partially validated | Full specification; test methods developed and validated | Full specification; test methods developed and validated |



The initial concept and basic requirements for both excipient and packaging specifications should have been identified at the product design stage. For example, the design requirements for an antioxidant to be used in an IV injection may be of parenteral grade, GRAS status or previously approved for use by regulatory authorities but must be compatible with the active pharmaceutical ingredient under development. Similarly, the primary pack should meet the basic product design requirements and be acceptable to regulatory authorities, available from multiple sources and reputable suppliers, a suitable volume for use and sealed to maintain sterility; the container-closure system should be compatible with the formulation.

If compatibility testing of the pharmaceutically active ingredient, excipients and primary packaging components are satisfactory, development specifications are prepared for excipients and packaging materials to be used. These will contain essential information about the materials to be used, including the grade, proposed use, specific physical properties and any testing required for investigational purposes. The quality of the raw materials used is vital to the effectiveness and quality of the finished product.

At the early stages of development, for example, to support Phase I studies, pharmaceutical companies often accept excipient and packaging raw materials based on a certificate of analysis (CofA) or Certificate of Conformance provided by the supplier. This is especially the case if it is a reputable supplier of an established material used by the industry. This reduces the pressure on the pharmaceutical company's Analytical Department to develop methods to test the materials at this early stage. The supplier may also provide useful information such as details of the critical dimensions and drawings for packaging materials.

With a new supply source or a new material, a pharmaceutical company will usually want to audit the supplier, prior to accepting the material on a CofA. They may even want to repeat some of the tests on the CofA until there is confidence on compliance with the specification. The pharmaceutical company will want to seek assurance from the supplier that they are quality conscious at every stage of their process, and have the facilities and internal systems and procedures in place to be able to support this.

As product development progresses, the critical qualities of the raw materials will be identified which affect final product quality, and results of investigational studies will be obtained, to enable the specifications to be developed and refined.

Typical tests performed on raw materials, including the active pharmaceutical ingredient, excipients and packaging components, are as follows:

- Appearance, e.g., visual inspection, free from visible contamination
- Identity tests, e.g., comparison with a standard or by direct analysis, conformance with supplier's drawing
- Chemical tests where appropriate, e.g., for active, related substances, impurities
- Microbiological tests where appropriate, e.g., bioburden, absence of specific microorganisms
- Relevant physical properties, e.g., leak test, tensile strength, moisture vapour transmission, closure removal torque
- Dimensional analysis, e.g., for filling tolerances
- Investigational tests, e.g., reproducibility of dosing devices, particle size distribution of excipients

Official compendia may provide tests and standards for listed excipients and for glass and plastic containers.

Packaging and excipient specification functional tests are developed based on the functional requirements of these in the product. For example, the pack may have to prevent liquid loss, prevent moisture ingress, maintain sterility or deliver a defined dose. An excipient such as an antimicrobial preservative must be able to preserve the formulation in the presence of the active and other formulation ingredients and in the intended pack. Excipient and packaging optimisation must satisfy performance criteria, ensuring that packaging dimensional specifications and performance specifications can be consistently met at the extremes of the limits, and during processing, handling and transport. The evaluation of the sterilisation process is particularly important for sterile products. Robustness to the sterilisation process should be assessed, because it is possible that the thermal, electromagnetic or chemical energy could adversely affect the properties of the materials in question. For example, there may be an irreversible loss in product viscosity, the embrittlement of polypropylene or the loss in thermoplastic quality of polyethylene.

Once several batches of raw materials have been reviewed and tested to demonstrate that they will conform with the functional and quality requirements, the full excipient and packaging specifications can be finalised. Excipient and pack performance should be evaluated from a stability evaluation of the product and feedback from experience in clinical trials. Ideally, the specifications should be finalised for the start of Phase III clinical trials. If for some reason, the excipient or packaging material has to be changed for Phase III supplies, then some or all of the steps involved in the selection of materials, compatibility and stability studies may have to be repeated.

### Product Specifications

Product specifications will also evolve during development (see Table 8.4). In the early stages, testing is typically performed on only a small number of samples due to the small scale of manufacture available. There may only be one or two product batches made to support Phase I and early Phase II studies. The specification limits also tend to be wide, due to the limited data available. The specification limits are tightened as more information is gained from testing more batches, and the scale of manufacture is increased.

The product release specification contains tests and limits that apply after manufacture to release the product for use, whereas the product specification contains tests and limits with which the product must comply throughout its shelf-life. The limits may differ from the product release limits to allow for changes during storage, for example, to allow for some drug degradation. Both product release and shelf-life specifications are required for European regulatory submissions, but in Japan and the United States, they are currently only interested in shelf-life specifications. Some companies have internal or in-house specifications which are different (usually tighter) than regulatory specifications. However, this can lead to confusion about which specification the product must comply with. Since the FDA only accepts the existence of the regulatory specifications, it is better to have "action limits" corresponding to the internal specification, rather than two sets of specifications.

When developing product specifications, test methods and limits, the critical parameters must be identified and controlled which affect the quality, safety, performance and stability of the drug product. Several issues have to be considered, such as appropriate regulatory requirements and guidelines, e.g., ICH, relevant compendial monographs and standards and the capability of the manufacturing process and analytical methods used. Appropriate limits will also be influenced by safety/toxicology considerations. For example, impurities, degradation products, extractables and leachables and preservatives should be qualified in safety studies.



Regulatory authorities such as the FDA publish specification guidelines with the expectation that pharmaceutical companies will comply with them. If there are difficulties in achieving the guideline requirements, or in the interpretation of them, it is advisable to discuss those points with the FDA. The internal regulatory group is usually the point of contact with external regulatory bodies. There are helpful ICH guidelines available on specifications, test procedures and acceptance criteria which describe the attributes that should usually be included for a variety of dosage forms. Other ICH guidelines are available, describing impurities and residual solvents.

There are various general compendial monographs available on dosage forms, such as tablets and inhalation dosage forms, as well as compendial test methods and limits listed in the various pharmacopoeias. In spite of the progress made with harmonisation, there are still some significant differences in the test procedures and limits recommended in the major pharmacopoeias. Often, the testing applied is aimed to cover the most stringent requirements.

During process optimisation, the capability and robustness of the manufacturing process is assessed (as described later in this chapter on process robustness), to confirm that the specifications can be met at the extremes of the limits. The capability of the test method, accuracy, precision and reproducibility will also affect the limits that can be achieved.

With all test methods and limits there must be a sound technical justification to support them based on data generated for product and process optimisation, clinical batches and stability studies. A specification set too wide is likely to be challenged by regulatory authorities. However, a tight specification may result in some batches failing, and, once registered, it is very difficult to gain approval to widen again. It is considered best practice to freeze the specifications as late as possible so that as much confirmatory data are available from all batches made to justify the limits. It is also very important to document the justifications for the specifications, and any changes during development, so that the complete specification development can be accounted for. This information will be required for the development report to support FDA Pre-approval Inspection (PAI) and regulatory submissions.

## PROCESS DESIGN, PROCESS OPTIMISATION AND SCALE-UP

The primary objective of the process design and optimisation stages of product development is to ensure that manufacturing operations supporting Phase III studies, and ultimately commercial manufacture, are carried out under optimal conditions. The product should consistently comply with specifications.

Process design is the initial stage of process development where an outline of the clinical trial and commercial manufacturing processes are identified on paper, including the intended scale(s) of manufacture. This should be documented in a Process Design Report.

The Process Design Report should include all the factors that need to be considered for the design of the process, including the facilities and environment, equipment, manufacturing variables and any material handling requirements. A list of factors to consider is given in Table 8.5.

It is important to involve Production during the product design stage in the selection of equipment and the process. The eventual technology transfer is likely to be smoother if the same type of equipment employed by R&D is also available in Production on a larger scale. If a completely novel approach to manufacture is being considered, it is important that Production is made aware of this and can plan ahead to deal with the new process. This might involve the purchase of new equipment which will have to be validated.

**Table 8.5**
**Process design considerations.**

| Factor | Requirement | Purpose |
|---|---|---|
| Facility | • Organisation and layout | GMP |
| | • Space | Health and safety |
| | • Environmental control | Product sensitivity to: |
| | • Temperature | • Temperature |
| | • Humidity | • Moisture |
| | • Air quality | • Particulates/micro-organisms |
| | • Electrical zoned (flame proof) | Allow solvents for cleaning |
| | • Barrier protection | Operator protection |
| Equipment | • Type and design, e.g., bottom- or top-mounted mixing elements, baffles, heating/cooling jacket, etc. | Suitability for process<br>Mixing efficiency |
| | • Materials of construction | Compatibility, extractives |
| | • Range of sizes | Ease of scale-up |
| | • Access to internal parts | Ability to clean/maintenance |
| Material Transfer | • Product protection | Clean/sterile product |
| Transfer | •Operator protection | Hazardous materials |
| Manufacturing variables | • Order of addition of active and excipients | Mixing effectiveness |
| | • Temperature | Stability/dissolution |
| | • Speed | Mixing effectiveness |
| | • Time | Mixing effectiveness |
| | • Differences in excipient batches | Robustness of process |

Other process design factors to consider are the need for any in-process controls during manufacture, with details of the tests and proposed limits. For example, the thickness, hardness, friability and weight of tablets might be measured during the filling of a tablet product. The tests and limits applied will be based on experience gained from product development, optimisation and stability studies. Depending on the product being developed and type of process, it may be necessary to conduct preliminary feasibility studies before the Process Design Report can be written.

## Process Optimisation

Process optimisation will define and investigate critical process parameters, varying these within practical constraints to establish limits for the process parameters, within which acceptable product can be manufactured. Depending on the product being developed and type of process, it may be necessary to conduct preliminary feasibility studies before proceeding to process optimisation.



A useful approach to process optimisation is to identify all the critical process parameters that could potentially affect product quality or performance and prepare a Process Optimisation Protocol. Typically, data used to identify critical process parameters will be derived from laboratory or pilot-scale batches, and do not need to be confirmed on full-scale batches unless the control of the particular parameter can only be evaluated on a production scale. There is good incentive to use the production facilities at the earliest opportunity, drug availability permitting, to iron out any transfer difficulties. Manufacture of the stability batches to support Phase III studies, and also the Phase III clinical batches, at the final commercial site should minimise any questions from the FDA during PAI about possible differences between R&D and Production process used.

The Process Optimisation Protocol should outline the programme of work required to evaluate the effect of changes in the critical variables on product quality. This is in order to establish the working limits within which the process consistently produces product which meets specification. Critical parameters may include

- defining the order of addition of the active and excipients;
- defining the optimum equipment settings, e.g., mixing speed;
- optimising time-dependent process parameters;
- defining the optimum temperature range;
- evaluating the effects of different excipient/active batches (within specification);
- setting in-process targets and controls; and
- development of cleaning procedures for the process.

On completion of the work programme, a Process Optimisation Report should be written. This will summarise the results of the activities specified in the protocol and provide a rationale to define the operating limits for the process and the critical parameters affecting product quality or performance. The report should also conclude that the specifications for the raw active, excipients, components, in-process and product can be met.

### *Process Capability and Robustness*

Several pitfalls that are sometimes encountered with process development can hinder successful technology transfer to production, i.e., if the process has not been designed or optimised with production in mind or a representative scale of production has not been used for the optimisation studies. For example, the sterilisation of a viscous ophthalmic gel by autoclaving at R&D on a 2 kg scale did not require any mixing of the bulk product for efficient heating and cooling. However, when transferred to production at a 100 kg scale, the heating and cooling times were found to be extensive and the bulk contained hot spots because no stirring mechanism had been specified in the vessel.

Another pitfall is to design a process where the operating limits for one or more critical parameters are too narrow and cannot be consistently achieved. It is not acceptable if the process can be performed only by "experts" in R&D. Many pharmaceutical companies apply some measurement of process and equipment capability to demonstrate the reproducibility and consistency of the process in meeting specification limits. The Process Capability Index (CpK) is often used to measure the reproducibility as a function of the specification limits. It is normally, calculated from either of the two equations below, whichever gives the lowest number:

$$\text{CpK} = \frac{\text{upper limit of specification} - \text{mean}}{3 \times \text{standard deviation}}$$

or

$$\text{CpK} = \frac{\text{mean} - \text{lower limit of specification}}{3 \times \text{standard deviation}}$$

Some generally accepted rules, determined from experimental data, relate the CpK value with robustness. For example, a CpK of less than 0.8 is an indication that the process is not capable, as the acceptance criteria cannot be met routinely. Further work will need to be done to develop a more robust process. CpK values between 0.9 to 1.0 indicate a marginal process, between 1.0 and 1.25 are satisfactory, between 1.25 to 1.5 are good, and values greater than 1.5 are excellent. Using these measurements, it is possible to evaluate process variables and identify which variable has the least or most effect. However, a possible pitfall is to obtain excellent CpK values, but not to have an acceptable process because the mean value is not on target. The process developed needs to be reliable and consistently meet product specifications, to demonstrate it is manufacturable. Another pitfall is to aim for a CpK value much higher than 1.5, which is probably a waste of effort. The process does not have to be "bombproof".

### Scale-Up

In reality, product and process development and scale-up will be progressing concurrently in order to meet the demands of Phase I and II clinical and long-term safety supplies. The process used for initial clinical supply manufacture will probably be relatively small scale (laboratory scale). As more drug substance becomes available, and the clinical requirements increase, the product batch size will increase to pilot scale, and the process may have to be modified during scale-up. If drug substance is available and very large Phase III studies are anticipated, it may be essential to scale-up to production scale and transfer the process to the commercial production site.

The objective of scale up is to ensure that the process is scaled up to provide product which will comply with specification. Scale-up may encompass changes in process equipment and operation, with an associated increase in output, for example, in the following situations:

- An increase in batch size of 10-fold or greater on identical equipment
- Use of larger or high-speed versions of identical types of equipment
- Increase in output rate by more than 50 percent for identical equipment
- Changes in equipment type for a given process step

Whenever scale-up is to be undertaken, it is strongly recommended that an experimental batch is manufactured to demonstrate that the process is still acceptable and the product is manufacturable on the increased scale. It must meet all the appropriate in-process and product specification acceptance criteria.



### Technology Transfer

The actual transfer of the manufacturing process from R&D to Production, along with the necessary knowledge and skills to be able to make the product, is referred to as "technology transfer". The ultimate objective for successful technology transfer is to have documented proof that the process is robust and effective in producing product complying with the registered specifications and Good Manufacturing Practice (GMP) requirements.

The approach taken by different pharmaceutical companies to technology transfer varies widely from a "hand over the wall" to a more structured team approach. Clearly, the latter approach is more likely to result in successful technology transfer. In some companies, a third party is involved in the process, a specialised Technology Transfer group, who liaise between R&D and Production to ensure a smooth transfer. Companies vary in the way they divide responsibilities for Technology Transfer and the point of handover of responsibility, but there do not appear to be any clear advantages, provided the guidelines below are followed:

- Responsibilities are clear and well defined.
- Representation from Production and the Technology Transfer group are involved early, e.g., during product and process design/optimisation.
- Good communications are maintained with good R&D/Production interface. Time is spent face to face in factory and laboratory.
- There is good scientific basis for product/process design.
- Equipment used at laboratory/pilot scale is similar to production equipment.
- There is good documentation of product/process development and technology transfer.

## VALIDATION AND LAUNCH

### Clinical Trials Process Validation

At early clinical stages (Phases I and II), where only limited GMP batches of product will have been produced, and where product and process changes make batch replication difficult, only limited process validation may be possible. In such cases, the regulatory authorities will expect to see data from extensive in-process and end-product testing to demonstrate that the batch is adequately qualified, yielding a finished product which meets specification and quality characteristics.

For critical processes such as sterilisation or aseptic manufacture, even for the earliest human studies, the regulatory authorities will expect the process to be qualified, to attain a high degree of assurance that the end-product will be sterile. If drug availability is an issue, the aseptic processing of sterile products may be validated using media fills to simulate the process.

At later development stages, when process optimisation has been completed and clinical batches are being manufactured under replicated conditions, the regulatory authorities will expect more process validation. The actual process used and results obtained must be documented so that it can be duplicated. Normally, the product must meet predetermined product specifications and acceptance criteria on three occasions. The benefit of validating the process successfully is to reduce the amount of product testing.

## Validation of Commercial Process

Process validation is a requirement of the FDA Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals, 21 CFR Parts 210 and 211, and of the Good Manufacturing Practice Regulations for Medical Devices, 21 CFR Part 820, and therefore, is applicable to the manufacture of pharmaceuticals and medical devices intended for the United States.

In response to several enquiries from pharmaceutical companies, the FDA has published a useful document entitled "Guideline on General Principles of Process Validation". The guideline has recently been updated (Draft, January 1999). The document includes the principles and practices that are acceptable to the FDA and has a section that describes the types of activities that should be considered when conducting process validation. It is strongly recommended that the procedures in this guideline are reviewed and followed. Otherwise, alternative procedures should be discussed with the FDA in advance to avoid disappointment (and a waste of time and expenditure) if they are later found not to be acceptable. Likewise, in Europe in 1999, the European Agency for the Evaluation of Medicinal Products (EMEA) and the Committee for Proprietary Medicinal Products (CPMP) issued a draft guidance on process validation with the aim of drawing together and presenting more clearly the requirements for effectively validating pharmaceutical manufacturing processes.

The FDA definition of process validation is

> to establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

Documented evidence is achieved by preparing written validation protocols prior to doing the work, and writing final reports at the completion of the work. Information must be in writing, otherwise it does not exist, according to the FDA. The process equipment used should undergo installation qualification (IQ) and operational qualification (OQ) to establish confidence that the equipment was installed to specification and purpose and is capable of operating within established limits required by the process. Performance characteristics which may be measured could be uniformity of speed for a mixer or the temperature and pressure of an autoclave, for example.

Performance qualification (PQ) is to provide rigorous testing to demonstrate the effectiveness and reproducibility of the process. PQ should not be initiated until the IQ/OQ has been completed and the process specifications have been essentially proven through laboratory, pilot and scale-up batch manufacture. The PQ protocol should specify the approved procedures and tests to be conducted and the data to be collected. Acceptance criteria should be defined prior to starting the work. To gain a high degree of assurance that the process is reproducible, at least three successive replicated process runs are required to ensure statistical significance. It is expected that the conditions for the different runs will encompass upper and lower processing limits, widely known as "worst-case" conditions, to pose the greatest chance of product failure. This will demonstrate whether the process limits are adequate to assure that the product specifications are met. PQ should ideally be undertaken at the scale at which commercial production will take place, although it may be acceptable to use different batch sizes for the three replicated batches if scale has been shown not to be an issue.

Approval of the process for use in routine manufacturing should be based upon a review of all the validation documentation outlined in a Validation Master Plan, including data from IQ/OQ/PQ and product/package testing.



## Pre-approval Inspection

Once the clinical and safety evaluation studies for a new medicinal product have shown it to be safe, effective and of acceptable quality, the pharmaceutical company will usually want to submit a Marketing Authorisation Application (MAA) or New Drug Application (NDA) to the regulatory authorities. The chemistry, manufacturing and controls (CMC) section will form a major part of the application. For an MAA in Europe, a development pharmaceutics section is required to describe how the product was developed, and to explain the rationale for the selection of the formulation, pack, manufacturing process and specifications. Also required for Europe are expert reports for each of the pharmaceutical, safety and clinical parts of the application. These have to be written by experienced scientists nominated by the pharmaceutical company who have to critically appraise the development programme for the product. The pharmaceutical expert must acknowledge the acceptability of the CMC part of the application.

A current prerequisite to NDA approval in the United States is to have successfully passed a FDA PAI. In the future, the Mutual Recognition Agreement (MRA), if agreed on, may eliminate the need for FDA inspections in Europe and Japan.

The PAI will essentially be targeted at the commercial manufacturing facility to gain assurance that the facilities, equipment, procedures and controls to manufacture the product are in place and conform with the NDA submission. The FDA will also want to check for compliance with current Good Manufacturing Practice (cGMP).

The FDA may also want to audit R&D to gain assurance that the product development has been done satisfactorily. In particular, the FDA may wish to see data that support the manufacturing process and controls from preformulation, product/process optimisation, clinical trials process validation and stability studies.

It will check for equivalence, for both the drug substance and pharmaceutical product, between that used in the pivotal clinical studies, the pivotal stability studies and commercial production. This is usually achieved by inspecting product and control data such as clinical trial batch records, in-process and end-product test results and raw material, component and product specifications. During an R&D PAI the FDA will also check for general compliance with cGMP, will inspect the facilities and equipment used and check the appropriateness of control systems and procedures.

It is in the interest of pharmaceutical companies to be in a state of readiness for a PAI. Staff should be aware of all procedures, policies and regulations and have current training records. A good documentation storage and retrieval system is essential to be able to locate and retrieve records and reports efficiently. It is now considered essential to have prepared a Development Report for the FDA to aid the PAI. The purpose of the report is to summarise all the product development and to demonstrate the equivalence of the manufacturing process and controls used for the pivotal clinical and stability batches and the commercial product. The typical contents of the Development Report requested by the FDA are as follows:

- Active and key excipients: physicochemical characteristics, particle size, purity, batch analysis
- History of formulation and pack development: design rationale with critical characteristics affecting manufacture
- History of process development: design rationale with critical process parameters
- Specifications: rationale and supporting data for in-process and product

- Product stability summary: equivalence of controls with commercial
- Technology transfer batch history: list all batches made for development, safety, clinical and transfer
- Evaluate cause of failures and remedies

The Development Report should be concise and structured. Clearly, it cannot be finalised until development is complete, but the preparation is much easier if summary reports have been compiled during development, such as the product and process optimisation reports. The Development Report needs to be available to the FDA prior to the inspection, ideally, to give the FDA inspection team confidence that the product has been developed satisfactorily, perhaps resulting in a shorter inspection.

A successful PAI and regulatory approval of the NDA is usually followed by product launch. Launch activities need to be planned carefully and well in advance to ensure that no time is wasted after approval to sell the product on the market. Some companies plan to sell the PQ lots, especially if the product is very expensive. The product insert and label claim will also have to be approved by the regulatory authorities. It may be better to wait for confirmation of approval before printing the labels and pack inserts; everything else can be prepared in advance. The launch stock is then packaged and labelled, QC released and then distributed for sale. Leading pharmaceutical companies can achieve this in 1–2 weeks post-approval, with good preparation and planning.

## Post-approval Changes

It is inevitable that pharmaceutical companies will want to acknowledge changes after regulatory submissions have been submitted. Requests for post-approval changes could be for reasons outside the company's control, for example, because the source of raw materials changed, compendial specifications were revised or because suppliers of processing equipment made modifications. Alternatively, the change could be because the company wants to transfer a product to another manufacturing site. Sometimes changes are forced because the manufacturing process has not been properly evaluated and it is found not to be robust enough until a few production runs have been made. Such a situation may be a consequence of the company striving for the earliest submission date, with an attitude of "we'll fix it later"!

However, all of these changes require regulatory approval and this can take significant time and result in lost sales, it is therefore important that the company understands the consequences of post-approval changes prior to making a submission. The regulatory authorities, notably the FDA, have issued guidelines on the process for making changes in an initiative known as SUPAC or "Scale-Up and Post-approval Changes". SUPAC is designed to enable changes to be made to manufacturing processes with reduced regulatory input by providing guidance on what additional testing is required for specific changes.

There are a number of SUPACs, some approved (e.g., Immediate-Release Dosage Forms, Modified-Release Dosage Forms and Semi-Solid Dosage Forms) and some still being developed (e.g., Sterile Products). SUPAC establishes the regulatory requirements for making changes to the composition or components of the dosage form, the batch size, the manufacturing process or equipment or the site of manufacture. Different levels of change are defined and require different actions, for example:



- Level I—unlikely to have a detectable impact on product quality, e.g., a change in the mixing time within the validated range; action: notify FDA in the annual report
- Level II—could have a significant impact, e.g., a change of mixing time outside the validated limits; action: submit updated batch records, generate and submit long-term stability in annual report, generate dissolution profile data and notify the FDA of changes for approval
- Level III—likely to have a significant impact, e.g., a change from direct compression to wet granulation; action: (1) submit updated batch records, 3 months accelerated stability data, dissolution data, *in-vivo* bioequivalence study (unless *in-vitro/in-vivo* correlation verified), long-term stability data; and (2) notify the FDA of all changes for approval

In Europe, there are different arrangements from country to country when changes to MAAs are to be made. It is a legal requirement in the European Community (EC) that all marketed products comply with the details of the MAA. Changes may or may not require prior approval, depending on the type of change. For example, a Type I variation or minor change, such as a change in batch size, may not require prior approval. Details are submitted to all member states where the product is sold and are deemed approved if there are no objections within 30 days. Type II variations, or quite major changes, have to be submitted to all member states where the product is marketed, and the change must be approved or rejected within 90 days. A significant change such as a change of strength or indication would probably require a new application. Companies can make an early submission and avoiding regulatory delays by knowing in advance what changes are allowed without pre-approval.

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# 9

# Parenteral Dosage Forms

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The dictionary definition of parenteral is non-enteral or non-oral and, therefore, strictly speaking, the term *parenteral* includes all products administered other than by the oral route. The pharmaceutical convention, however, is to use the term parenteral to describe medicines administered by means of an injection. The most common routes of parenteral administration are intravenous (IV), subcutaneous and intramuscular, but there are a variety of lesser used routes, such as intra-arterial. In addition, products such as subcutaneous implants are usually classed as parenterals.

There are, arguably, a greater variety of formulations administered by the parenteral route than by any other. These include emulsions, suspensions, liposomes, particulate systems and solid implants as well as the ubiquitous simple solution. What sets parenteral products apart from most other dosage forms, (with the exception of ocular products), is the absolute requirement for sterility, regardless of the formulation type. This requirement must be uppermost in the pharmaceutical scientist's mind from the first stages of formulation conception, so that the formulation and manufacturing process can be developed in tandem to produce an optimised sterile product.

This chapter aims to provide a practical guide to the development of parenteral products, initially reviewing the basic principles of formulating a straightforward parenteral solution. Subsequent sections will examine the formulation options available when a more sophisticated formulation is warranted, for example when the candidate drug exhibits poor aqueous solubility, is a macromolecule or requires a more sophisticated delivery system. *In vitro* and *in vivo* testing methods for parenteral products will be touched on and the chapter concludes with a discussion of the manufacturing and regulatory issues unique to parenteral products. While, of necessity, the individual topics will be covered only briefly, the objective is to

provide the reader with the basic information necessary to evaluate the formulation options available and to provide appropriate references to sources of further and more detailed information.

## GUIDING PRINCIPLES FOR SIMPLE PARENTERAL SOLUTIONS

This section summarises the principles which should be followed when developing simple solution formulations; these, after all, comprise the majority of marketed parenteral products. The information presented has been gleaned from standard textbooks and references, but where appropriate an attempt has been made to summarise the industry "norms". For further detailed information on the concepts discussed in this section, the reader is referred to Avis et al. (1992).

### Selection of Injection Volume

Pharmacopoeias classify injectables into small-volume parenterals (SVPs) and large-volume parenterals (LVPs). The U.S. Pharmacopeia (USP) defines SVPs as containing less than 100 mL and LVPs as containing more than 100 mL. Many regulatory standards, for example, those for subvisible particulates, have first been developed for LVPs prior to their later application to all parenterals. SVPs can be given rapidly in a small volume; this type of injection is known as a bolus. They may also be added to LVPs, such as 5 percent dextrose and 0.9 percent sodium chloride infusion/injection, for administration by IV infusion. Some antibiotics are sold as LVPs, which eliminates the need for the extemporaneous addition of the drug to the infusion fluid prior to administration. The selection of bolus or infusion will depend on the pharmacokinetics of the drug and the distinction can be somewhat blurred. Infusions can be as brief as 15 minutes or may continue for several days. Generally speaking, if a medicament is to be administered by infusion, the simplest approach is to formulate it as a concentrate which will subsequently be diluted by the practitioner or pharmacist prior to administration.

Intramuscular or subcutaneous injections are almost always administered a bolus. Typically, the injection volume is less than 1–1.5 mL by the subcutaneous route and usually no more than 2 mL by the intramuscular route, although higher volumes (up to 4 mL) can be administered if essential (Ford 1988). Jorgensen et al. (1996) have shown a correlation between pain and the volume of a subcutaneous injection with volumes of 1–1.5 mL causing significantly more pain than volumes of 0.5 mL or less. Clearly, it is preferable to minimize injection volume wherever possible, particularly if chronic administration is anticipated. When the total volume to be administered cannot be reduced to an acceptable level, two or more injections at multiple sites may be required.

One of the first steps in the formulation of a solution product is, therefore, to select the administration volume and concentration. This may be dictated primarily by physiological considerations, such as maximum injection volume as discussed above, or by pharmaceutical considerations. For example, if solubility is low, a larger volume/lower concentration formulation may be required, whereas if stability is improved at higher concentrations, then the converse would be true.



### pH and Tonicity Requirements

#### *pH Considerations*

Clearly, a parenteral product should be formulated with a pH close to physiological, unless stability or solubility considerations preclude this. Often, the pH selected for the product is a compromise between the pH of maximum stability, solubility and physiological acceptability.

The first step in selecting a suitable formulation pH will be the generation of pH/stability and pH/solubility profiles. This type of information is often available in the preformulation data package. The target pH for maximum physiological acceptability is approximately pH 7.4. In practice, however, a reasonably wide pH range can be tolerated, particularly when dosing is via the IV route, and dilution with blood is rapid. In these circumstances pHs ranging from 2 to 12 can be tolerated (although formulations at the extremes of this range are not recommended). The dilution rate is slower when administration is via the intramuscular route and decreases further when the subcutaneous route is used. For this reason, pH ranges of 3 to 11 and 3 to 6, respectively, are recommended for these routes (Strickley 1999). Many products are formulated at a slightly acidic pH because of solubility or stability considerations, and the vast majority of licensed products have a pH between 3 and 9. A pH outside this range should be avoided if possible, since a pH of greater than 9 can cause tissue necrosis, whereas a pH of less than 3 may cause pain and phlebitis (DeLuc and Boylan 1992). Nevertheless, products with extreme pH values are encountered; Dilantin Injection (phenytoin sodium) is formulated at pH 12, whereas Robinul Injectable (glycopyrrolate) is formulated at pH 2–3. Both products are for intramuscular administration. When a pH at the extreme of the acceptable ranges is necessary, and administration is via the subcutaneous or intramuscular route, it is advisable to conduct *in vivo* studies to assess the level of pain on injection (see the section "Pain"). An important consideration in terms of the tolerability of a formulation is its buffering capacity of; this may be more important than the pH *per se*. The pH of commercially available 0.9 percent w/v Sodium Chloride Infusion, for example, can be as low as 4, but the lack of any buffering capacity means that it will have negligible effect on the pH of the blood into which it is infused, even when administration is rapid.

The use of buffers often can (and should) be avoided if the active ingredient is itself a salt which can be titrated with acid or base to a suitable pH for parenteral administration. Buffers may legitimately be required when the pH must be controlled at that of maximum stability or solubility. In the former case, the buffer concentration should be kept to a minimum so that after injection, the buffering capacity of physiological fluids will outweigh the buffering capacity of the formulation. Where buffers are used to improve solubility, the buffer concentration may need to be a little higher to prevent precipitation after injection. *In vitro* models have been developed which can be used to screen formulations for the potential to precipitate after injection. These are discussed further in the section "*In Vitro* and *In Vivo* Testing Methods".

The buffers most commonly encountered in parenteral products are phosphate, citrate or acetate. Phosphate is useful for buffering around physiological pH, whereas acetate and citrate are used when the required pH is lower. Table 9.1 summarises the buffers which are encountered in approved parenteral products. Typically, buffer concentrations are in the 10–100 millimolar range. In most cases, the sodium salts of acidic buffers are used, although potassium salts are occasionally encountered. Hydrochloride salts of basic buffers are usually used. It is preferable to avoid the combination of anionic drugs with cationic buffers (or vice versa) due to the risk of forming an insoluble precipitate.

**Table 9.1**
**Buffers used in approved parenteral products.**

| Buffer | pH Range |
|---|---|
| Acetate | 3.8–5.8 |
| Ammonium | 8.25–10.25 |
| Ascorbate | 3.0–5.0 |
| Benzoate | 6.0–7.0 |
| Bicarbonate | 4.0–11.0 |
| Citrate | 2.1–6.2 |
| Diethanolamine | 8.0–10.0 |
| Glycine | 8.8–10.8 |
| Lactate | 2.1–4.1 |
| Phosphate | 3.0–8.0 |
| Succinate | 3.2–6.6 |
| Tartrate | 2.0–5.3 |
| Tromethamine (TRIS, THAM) | 7.1–9.1 |

Data abstracted from Powell et al. (1998), Flynn (1980) and Strickley (1999).

### *Tonicity Considerations*

Wherever possible, parenteral products should be isotonic; typically, osmolarities between 280 and 290 mOsm/L are targeted during formulation. Isotonicity is essential for LVPs, but again, a wider range of osmolarities can be tolerated in SVPs, since either rapid dilution with blood will occur after injection, or the product itself will be diluted with an LVP prior to administration. Hypertonic solutions are preferable to hypotonic solutions because of the risk of haemolysis associated with the latter. Fortunately, hypotonic formulations can be easily avoided by the use of excipients, often sodium chloride, to raise osmolarity. Mannitol, dextrose or other inert excipients can also be used for this purpose and may be preferable if the addition of sodium chloride is likely to have an adverse effect on the formulation. Gupta et al. (1994a), for example, found that the presence of 0.9 percent w/w sodium chloride reduced the solubility of their candidate drug (Abbott-72517.HCl) by a factor of 3. Tonicity adjusters frequently have dual functionality; for example, mannitol often functions both to increase the osmolarity and to act as a bulking agent in lyophilized formulations.

## CHOICE OF EXCIPIENTS

As with all pharmaceutical products, the most important "rule" to bear in mind when formulating parenterals is the "keep it simple" principle. Wherever possible, formulations should be developed using excipients which have an established use in parenteral products administered by the same route as the product under development. Both the excipient concentration, rate



of administration and total daily dose should fall within the boundaries established by precedent in existing marketed products. The (U.S. Food and Drug Administration) FDA Inactive Ingredient Guide is a good place to start a search for information about a potential excipient, as it consists of an alphabetical list of all excipients in approved or conditionally approved drug products, and includes the route of administration of the products containing them. The *Physicians' Desk Reference* (PDR) provides an essential source of detailed information on products available on the U.S. market and includes the quantitative formulation of each product. This enables both the rate of administration and total daily dose of excipients in existing products to be calculated. The PDR can be obtained in a CD-ROM format which has a word search facility, thus providing a convenient means of searching for products containing a specific excipient. The PDR is also available in a web-based format, but unfortunately, this version does not have the word search capability. In addition to these reference sources, two excellent recent publications have specifically examined excipient usage in parenteral products on the U.S. market. Powell et al. (1998) have developed a compendium which provides a comprehensive list of excipients present in commercial formulations, together with their concentrations and the routes of administration of products containing them. Nema et al. (1997) carried out a similar review; their article presents the data as summary tables, enabling the frequency of use and concentration range of a particular excipient to be obtained at a glance. As this book goes to press, the first part of a review article entitled "Parenteral Formulations of Small Molecule Therapeutics Marketed in the United States (1999)" has been published in the *PDA Journal of Pharmaceutical Science and Technology* (Strickley 1999). This article provides information similar to the publications of Powell et al. and Nema et al., but collates the information in terms of formulation type and includes the structure of the active ingredients. It also lists the concentration of excipients administered following dilution as well as the concentration in the supplied preparation, thus saving formulators the trouble of performing these calculations themselves! Subsequent parts of this article are awaited with interest.

The information sources described above thus provide an invaluable resource to the parenteral formulator. The publications of Nema et al., (1997), Powell et al. (1998) and Strickley (1999) provide an instant, comprehensive and up-to-date reference source on U.S. licensed formulations, which can save the formulator many hours of trawling through the *Physicians' Desk Reference*! It is unfortunate that the same level of detail is not available for products outside the United States where manufacturers are not obliged to disclose the quantitative details of their formulations.

When considering the use of unusual excipients, or exceptionally high concentrations of "standard" excipients, it is important to bear in mind the indication for which the product is intended. An excipient which may be acceptable as a last resort in a treatment for a life-threatening condition should not be considered for a product to be administered chronically or for a less serious condition. A good example of this is the use of the solvent Cremophor EL in parenteral formulations of cyclosporin. This surfactant is associated with a range of toxic effects, and its use would not be envisaged unless all other more acceptable formulation strategies had been exhausted and the potential benefit of the treatment is such that the risk associated with the excipient is outweighed.

Another important consideration for excipients to be used in parenteral products is their quality, particularly in microbiological terms. Commonly used parenteral excipients can often be obtained in an injectable grade which will meet strict bioburden and endotoxin limits. Pharmacopoeial grades of other excipients may be acceptable, but it is prudent to apply in-house microbiological specification limits, where none are present in the pharmacopoeias. For non-pharmacopoeial excipients, the best approach is always to purchase the highest grade available and apply internal microbiological specification limits.

## STERILITY CONSIDERATIONS

The requirement for sterility in parenteral products is absolute and must be borne in mind at all stages of formulation and process development. The regulatory environment now requires that parenteral products be terminally sterilized unless this is precluded, usually by reason of instability (see the section "Manufacturing of Parenteral Products").

For a solution product, one of the earliest investigations carried out during formulation development will be a study of the stability to moist heat sterilization. The results of this study may impact the formulation selection; for example, the stability to autoclaving may be affected by solution pH. Where stability is marginal, attempts should be made through the formulation process to stabilize the product such that it can withstand the stresses of moist heat sterilization. The regulatory authorities will expect to see good justification for new products that are *not* terminally sterilized. In many cases, however, the product will simply not withstand the stresses associated with autoclaving, and in this case, the usual alternative is filtration through sterilizing grade filters followed by aseptic processing. For the formulation scientist, it is important to select a suitable filter early on in development and ensure that the product is compatible with it.

Whilst the vast majority of parenteral products are rendered sterile either by moist heat sterilization or by filtration through sterilizing grade filters, other methods of sterilization should be considered, particularly in the development of non-aqueous formulations or novel drug delivery systems. For implants, for example, gamma irradiation is an option that should be explored early on in development.

Preservatives should not usually be included in parenteral formulations except where a multidose product is being developed. The Committee for Proprietary Medicinal Products (CPMP) "Notes for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products" states that the physical and chemical compatibility of the preservative (or antioxidant) with the other constituents of the formulation, the container and closure must be demonstrated during the development process. The minimum concentration of preservative should be used, which gives the required level of efficacy, as tested using pharmacopoeial methods. Certain preservatives should be avoided under certain circumstances, and preservatives should be avoided entirely for some specialised routes. The guidelines also require that both the concentration and efficacy of the preservative are monitored over the shelf life of the product. In multidose injectable products, the efficacy of the preservative must be established under simulated in-use conditions. Table 9.2 shows some of the most commonly encountered preservatives in licensed products and their typical concentrations.

## STRATEGIES FOR FORMULATING POORLY SOLUBLE DRUGS

Increasingly, formulation scientists are being asked to develop parenteral formulations of compounds with solubilities in the order of nanograms or micrograms per millilitre. This presents enormous challenges, particularly given the limited range of excipients which have been used historically in injectable products. This section briefly describes some of the strategies which can be considered and highlights some of the issues associated with each. For a more detailed review of this area, the reader is referred to the recent review by Sweetana and Akers (1996).



**Table 9.2**
**Preservatives used in approved parenteral products.**

| Preservative | Typical Concentration (%) |
|---|---|
| Benzyl alcohol | 1–2 |
| Chlorbutanol | 0.5 |
| Methylparaben | 0.1–0.18 |
| Propylparaben | 0.01–0.02 |
| Phenol | 0.2–0.5 |
| Thiomersal | ≤0.01 |

Data abstracted from Nema et al. (1999) and Powell et al. (1999).

### pH Manipulation

As discussed in the section "Guiding Principles for Simple Parenteral Solutions", the acceptable pH range for parenteral products is reasonably wide. Where the poorly soluble compound is a salt, pH manipulation may be all that is necessary to achieve adequate solubility. The potential for precipitation after administration should be considered when using this approach, however. When administration is via the intramuscular and subcutaneous routes, consideration must be given to the possibility of pain on injection, particularly when the product is intended for chronic use. This may preclude the use of pH extremes and favour alternative formulation strategies.

### Co-solvents

Co-solvents are reportedly used in 10 percent of FDA approved parenteral products although the range is limited to glycerin, ethanol, propylene glycol, polyethylene glycol and N,N-dimethylacetamide (Sweetana and Akers 1996). Some marketed formulations containing co-solvents are shown in Table 9.1. The use of co-solvents is often one of the earliest options considered by the formulator when solubility is an issue. Quite often, mixtures of co-solvents are used so that the dose or concentration of individual solvents can be minimized, and any synergistic effects can be maximised. The concentration of co-solvent(s) which is acceptable will vary depending on the route, rate of administration and whether the product is to be given chronically. Again, the formulator will do well to be guided by the established precedent in marketed products and is once again referred to the publications of Powell et al. (1998) and Strickley (1999).

### Non-aqueous Vehicles

Poorly soluble drugs for intramuscular administration can be formulated in a non-aqueous vehicle; this can have the additional benefit of providing a slow release of the active moiety. Oily vehicles have been used historically; the most commonly encountered is sesame oil, and

six products containing it are listed in the PDR (Nema et al. 1997). Federal regulations, however, now require the specific oil to be included in the product labelling, because of the risk of allergic reactions to certain vegetable oils. This and the irritancy of oily vehicles has led to their decreased use. Formulations consisting entirely, or almost entirely, of organic solvents have also been developed, and examples are included in Table 9.3.

## Surfactants

Surfactants, generally the polyscrbates, are frequently encountered in parenteral products but generally at very low levels (<0.05 percent) and most commonly to prevent aggregation in formulations of macromolecules (see the section "Strategies for the Formulation of Macromolecules"). Few IV products contain significant levels of surfactant; two notable exceptions are Cordarone IV and Etoposide IV which contain 10 and 8 percent respectively, of polysorbate (Tween) 80. Both products require dilution before administration, such that the maximum concentration of polysorbate 80 in the infusion solution is 1.2 and 0.16 percent, respectively. It

**Table 9.3**
**The formulations of some co-solvent containing marketed products.**

| Active Ingredient | Route | Vehicle Composition | Special Instructions |
|---|---|---|---|
| **Diazepam** | IM/IV | 40% Propylene glycol<br>10% Ethyl alcohol<br>5% Benzoate buffer<br>1.5% Benzyl alcohol | Inject slowly (at least 1 min/mL) if giving IV. Do not use small veins. |
| **Co-trimoxazole** | IV | 40% Propylene glycol<br>10% Ethyl alcohol<br>0.3% Diethanolamine<br>1% Benzyl alcohol<br>0.1% Sodium metabisulphite | Must be diluted with 5% dextrose infusion. Discard if cloudy or if there is evidence of crystallization. |
| **Etoposide** | IV | 65% w/v PEG 300<br>30.5% w/v Alcohol<br>8% w/v Polysorbate 80<br>3% w/v Benzyl alcohol<br>0.2% w/v Citric acid | Must be diluted. At concentrations >0.4 mg/mL, precipitation may occur. |
| **Loxapine** | IM | 70% Propylene glycol<br>5% Polysorbate 80 | |
| **Lorazepam** | IV/IM | 80% Propylene glycol<br>18% Ethanol<br>2% Benzyl alcohol | Dilute twofold for IV injection. |



is worth noting, however, that the polysorbate component of Cordarone IV has been implicated in a few cases of acute hepatitis which have developed within hours of the start of administration. Somewhat higher levels of surfactants can be tolerated in products intended for the subcutaneous or intramuscular route. Aquasol A (vitamin A palmitate as retinol) for intramuscular administration, for example, contains polysorbate 80 at a level of 12 percent.

## Complexing Agents

Complexing agents, in this context, are molecules that have the ability to form soluble complexes with insoluble drugs. The most well-known examples are the cyclodextrins which have been widely studied as agents for solubilization and stabilization. They are able to increase the aqueous solubility of some poorly soluble drug molecules by orders of magnitude, as a result of their ability to form inclusion complexes. Cyclodextrins are oligosaccharides obtained from the enzymatic conversion of starch. Depending on the number of glucopyranose units, they are named as α (six units), β (seven units) or γ (eight units). These parent molecules can then be further substituted at the hydroxyl groups to alter the properties of the molecule. The nature of the substituents and the degree of substitution will influence the aqueous solubility, complexing capacity and safety of the molecules. An excellent review of the characteristics of cyclodextrins has recently been published (Thompson 1997). In addition, Stella and Rajewski (1997) have reviewed the use of cyclodextrins in drug formulation and delivery, and this provides an excellent summary of the "status quo" in terms of their toxicology and use in pharmaceutical formulations.

Although the potential of cyclodextrins as solubilizing and stabilizing excipients has been the subject of numerous research papers over the last decade, the FDA has only recently approved the first commercial parenteral products containing them. Edex (alprostadil) for injection contains α-cyclodextrin at a concentration of approximately 1 mg/mL. This product is unusual, however, in that it contains an unsubstituted cyclodextrin. In general, the unsubstituted α- and β-cyclodextrins are not considered suitable for parenteral use because they can cause severe nephrotoxicity. This has led to the development of modified cyclodextrins. Hydroxypropyl-β-cyclodextrin is the most popular of the cyclodextrin family for use as a solubilizer in parenteral solutions because of its low toxicity and high inherent solubility. The first parenteral product containing this derivative (itraconazole) was approved in April 1999. This product contains 40 percent hydroxypropyl-β-cyclodextrin and is administered intravenously after a two-fold dilution with saline (Strickley 1999). Although IV grades of hydroxypropyl-β-cyclodextrin are now commercially available, its widespread use has been hampered not only because of the inherent difficulties associated with introducing a new excipient but also because it is the subject of a Janssen/National Institutes of Health (NIH) patent which does not expire in Europe for several years. Until this time, other companies wishing to incorporate this derivative into a commercial IV formulation will need to obtain a license from either NIH or Janssen. The sulphabutyl ether derivative is also suitable for parenteral use and is present in at least one formulation in clinical development, but here again, there are patent issues hampering its widespread application. Nevertheless, the use of cyclodextrin derivatives is often the only method of achieving sufficiently high aqueous concentrations of poorly soluble molecules, and they are now widely used within the pharmaceutical industry in preclinical formulations. One could speculate that the upcoming expiry of the Janssen/NIH patent, coupled with the recent approval of the itraconzole formulation, is likely to lead to their routine consideration as a first-line approach in the formulation of poorly soluble drugs.

### Emulsions

Parenteral emulsions were first introduced to provide an IV source of essential fatty acids and calories. This has developed into the extensive and routine use of products such as Intraplipid, Lipofundin and Liposyn in total parenteral nutrition. There are relatively few commercially available emulsions containing active compounds; the only example on the U.S. market is Diprivan® Injectable Emulsion, the formulation of which is shown in Table 9.4. Diazepam is also available as an injectable emulsion on the UK market (Diazemuls®). For a more detailed discussion of the issues involved in developing parenteral emulsions, the reader is referred to Collins-Gold et al. (1990).

All parenteral emulsions are oil-in-water formulations, with the oil as the internal phase dispersed as fine droplets in an aqueous continuous phase. An emulsifier, usually egg or soy lecithin, is needed to lower the interfacial tension and prevent flocculation and coalescence of the dispersed oil phase. Mechanical energy, usually in the form of homogenization, is required to disperse the oil phase into droplets of a suitable size. For IV administration, the droplet size should be below 1 μm to avoid the potential for emboli formation.

Clearly, physical stability is of critical importance for emulsion formulations, and care must be taken to ensure not only that the product itself is physically stable but that any infusion solutions which may be prepared by dilution of the emulsion are also physically stable over the required period of time. In addition, parenteral emulsions should be able to withstand the stresses associated with moist heat sterilization. Alternatively, if this cannot be achieved, it may be possible to prepare an emulsion aseptically from sterile components, provided the process can be suitably validated. For a good introduction to the formulation and preparation of IV emulsions, the reader is referred to Hansrani et al. (1983).

## STRATEGIES FOR FORMULATING UNSTABLE MOLECULES

### Water Removal

The most common mechanism of instability in parenteral formulations is hydrolysis. Regardless of whether the formulation is a true solution, co-solvent solution, emulsion or contains a complexing agent, the largest component of the formulation is likely to be water. Frequently, the only formulation strategy which will result in adequate stability is water removal. This is usually (although not exclusively) achieved by means of lyophilization. Lyophilization has a number of advantages over other potential drying methods, such as the ability to obtain an elegant end-product with a very low moisture content, and significantly, the fact that it is amendable to being carried out in an aseptic environment.

Lyophilization is essentially a three-stage process. Following standard aseptic filling, partially stoppered vials are transferred to a steam sterilizable lyophilizer in which drying is carried out. Initially the product is frozen to a low temperature (typically, -30 to -40°C). During primary drying, a high vacuum is applied, and ice is removed via sublimation. In the secondary drying stage, the product is heated under vacuum to 20–40°C, and any remaining water is removed by desorption. Products with very low moisture contents (<2 percent) can easily be achieved. The process also allows vials to be backfilled with nitrogen, usually to slightly less than atmospheric pressure, prior to stoppering, thus creating an inert environment within the vials. At the end of the lyophilization cycle, the stoppers are fully inserted into the vials before removal of the product from the chamber.



**Table 9.4**
**Diprivan® injectable emulsion formulation.**

| Component | Concentration |
|---|---|
| Propofol | 10 mg/mL |
| Soybean oil | 100 mg/mL |
| Glycerol | 22.5 mg/mL |
| Egg lecithin | 12 mg/mL |
| Disodium edetate | 0.005% |
| Sodium hydroxide | qs |
| Water for Injection | to 100% |

The development of lyophilized products is a specialized area and requires a detailed understanding of the thermal properties of the formulation. Subambient differential scanning calorimetry studies are required to identify the eutectic melting temperature (Te) (in the case of a crystalline solute) or the glass transition temperature of the maximally concentrated solute (Tg′) (for an amorphous solute). The latter is closely related to the collapse temperature (Tc) which effectively represents the maximum allowable product temperature during the primary drying or sublimation phase of the process. Both Tc and Te can be estimated using freeze-drying microscopy, a technique in which the freeze-drying process is observed on a microscale, and the collapse or melting temperature visually determined. Lyophilized products usually contain excipients to act as bulking agents and/or improve the stability of the product. When the requirement is principally for a bulking agent, mannitol tends to be the favourite choice of formulators. Mannitol is a crystalline material with a Te of about -2°C and, as such, is easily freeze-dried to give a self-supporting cake with good aesthetic properties. On the other hand, where an increase in stability is desired, an amorphous excipient (such as sucrose) is preferred since, once dry, the unstable compound will be "dispersed" in an amorphous glass with often greatly improved stability. The downside of formulating with amorphous excipients is that their low Tg′ values (approximately -32°C for sucrose) result in long lyophilization cycles. The formulator must also ensure that the product reconstitutes rapidly and that reconstitution time as well as chemical integrity are not adversely affected by storage.

For a detailed discussion of lyophilization, the reader is referred to Jennings (1999). In addition, a thorough review of the manufacturing and regulatory aspects of lyophilization is provided in *Good Pharmaceutical Freeze-Drying Practice* (Cameron 1997).

### Use of Excipients

Excipients may be useful in preventing chemical and physical instability. Antioxidants are included in parenteral formulations, although their use is now in decline, and EU guidelines discourage their use unless no other alternative exists (see the section "Parenteral Products and the Regulatory Environment"). A preferred method of preventing oxidation is simply to exclude oxygen; this is usually achieved by purging the product with nitrogen and creating a

nitrogen headspace within the container. Where this is insufficient, a metal chelator, such as disodium edetate, or an antioxidant compound, such as ascorbic acid or sodium metabisulphite, may be considered. These are included in marketed products typically at levels of up to 0.05, 1 and 0.3 percent, respectively.

### Non-aqueous Vehicles and Emulsions

For the intramuscular and subcutaneous routes, the use of non-aqueous vehicles may be considered as a method of avoiding hydrolysis. For IV administration, the use of an oil-in-water emulsion is a possible, although little used, option. These approaches are discussed in the section "Strategies for Formulating Poorly Soluble Drugs".

## STRATEGIES FOR THE FORMULATION OF MACROMOLECULES

Macromolecules present unique challenges to both the formulator and the analyst. Their large size and complex structural nature make degradation difficult to detect and sometimes difficult to prevent.

Proteins are composed of an amino acid backbone which defines their primary structure. The amino acid side chains hydrogen-bond to each other, creating areas of local order such as α helices and β-pleated sheets. These types of arrangement are known as secondary structure. The overall folding of the molecule, which defines its three-dimensional shape, is known as the tertiary structure. Finally, some proteins, such as haemoglobin, are composed of more than one subunit; the spatial arrangement of these subunits is known as the quarternary structure.

The challenge to the formulator is ensuring the preservation of both the chemical integrity of the constituent amino acids and the overall three-dimensional folding or conformation of the molecule. Several amino acids are susceptible to degradation by oxidation (e.g., methionine, cysteine, histidine) and deamidation (e.g., glutamine and asparagine). Peptide bonds in the backbone can undergo hydrolysis, and disulphide bonds between amino chains can also be disrupted and refold incorrectly (disulphide interchange). Chemical modification may be detected by high performance liquid chromatography (HPLC) techniques, but it is often extremely difficult to pinpoint where in the molecule degradation is taking place. Protein molecules frequently undergo aggregation, both covalent (through disulphide bond formation) and non-covalent. Non-covalent aggregation cannot be detected by normal HPLC methods, and techniques such as sodium dodecyl sulpfate–polyacrylamide gel electrophoresis (SDS–PAGE) and size exclusion chromatography are required to detect this type of instability. In addition, protein molecules have a tendency to adsorb to surfaces such as filters.

It is clear that the formulation of a macromolecule is far from simple and requires a good understanding of protein chemistry in order that degradation pathways can be understood and degradation prevented. However, one faces the same limitation as formulators of small molecules, namely, a relatively small armoury of established excipients which can be safely used in parenteral products. Some of the excipients commonly encountered in formulations of macromolecules are listed in Table 9.5. For further guidance on the formulation of macromolecules, the reader is referred to Wang and Pearlman (1993). This text provides some excellent examples of strategies which have been used to develop commercial formulations of proteins and peptides, such as human growth hormone and alteplase.



**Table 9.5**
**Excipients encountered in formulations of macromolecules.**

| Excipient | Function |
|---|---|
| Polyhydric alcohols, e.g., mannitol | Stabilisation, bulking agent |
| Carbohydrates, e.g., sucrose | Stabilisation |
| Amino acids, e.g, glycine, arginine | Stabilisation, buffer, solubilisation |
| Serum albumin | Prevention of adsorption |
| Surfactants (e.g., Tween 80, Pluronic F68) | Prevention of adsorption and aggregation |
| Metal ions | Stabilisation |
| Antioxidants | Prevention of oxidation |
| Chelating agents (e.g., EDTA) | Prevention of oxidation |

## LIPOSOMAL DELIVERY SYSTEMS

Liposomes are single or multilayer phospholipid vesicles, typically less than 300 nm in size. They are capable of entrapping both water-soluble and lipid-soluble compounds. Their use in parenteral formulations has exploited their preferential distribution to the organs of the reticuloendothelial system (RES) and their ability to accumulate preferentially at the sites of inflammation and infection. Liposome encapsulated amphotericin B is considerably less toxic than the free drug because of the altered pattern of biodistribution (Betageri and Habib 1994). A sophisticated approach has been developed (commercialised as Stealth® liposomes), in which polyethylene glycol is grafted to the surface of the lipsome, resulting in prolonged circulation of the liposomes in the bloodstream. A doxorubicin product which uses this approach (DOXIL®) is now commercially available (Martin 1999).

## SUSTAINED-RELEASE PARENTERAL FORMULATIONS

The chronic administration of molecules, which have a short biological half-life and cannot be given orally, presents a difficult challenge to formulators. One strategy which might be considered is the development of a sustained-release intramuscular or subcutaneous injection. Other non-parenteral options could include the inhalation or intranasal route, both of which have their own unique challenges. Sustained-release parenteral formulations might also be required in circumstances where patient compliance is likely to be poor. This consideration has led to the development of some antipsychotics and contraceptives as sustained-release injections. Table 9.6 lists some of the sustained-release parenteral products which are available on the U.S. market and their respective formulations. The typical approaches used in the formulation of sustained-release parenterals are summarised in this section.

**Table 9.6**
**Examples of sustained-release parenteral formulations.**

| Compound | Route | Formulation |
|---|---|---|
| Penicillin-G benzathine | IM (aqueous suspension) | 0.5% Lecithin<br>0.6% Carboxymethylcellulose<br>0.6% Povidone<br>0.1% Methylparaben<br>0.01% Propylparaben<br>in sodium citrate buffer |
| Haloperidol | IM (oily vehicle) | 1.2% Benzyl alcohol<br>in sesame oil |
| Leuprolide acetate | IM (microsphere suspension) | After reconstitution:<br>0.13% Gelatin<br>6.6% dl-Lactic and glycolic acid copolymer<br>13% Mannitol<br>0.2% Polysorbate 80<br>1% Carboxymethylcellulose<br>in WFI |
| Dexamethasone acetate | IM/ soft tissue (aqueous suspension) | 0.67% Sodium chloride<br>0.5% Creatinine<br>0.05% Disodium edetate<br>0.5% Sodium carboxymethylcellulose<br>0.075% Polysorbate 80<br>0.9% Benzyl alcohol<br>0.1% Sodium sulphite<br>in WFI |

## Oily Vehicles

The use of oily vehicles as an approach for the formulation of poorly soluble molecules is discussed in the section "Non-aqueous Vehicles". For molecules which possess good oil solubility, a sustained-release profile may also be achievable. The nature of the sustained-release profile will depend to a large extent on the oil/water partition coefficient of the molecule in question. Molecules which are not oil miscible could also be formulated as oily suspensions. The latter will usually result in a longer duration of action, because the drug particles must dissolve in the oily phase prior to partitioning into the aqueous medium (Madan 1985). The use of oily vehicles would not normally be considered as a first-line approach for new formulations, however, because of concerns over allergic reactions to the oils.



## Aqueous Suspensions

This approach can be used to prolong the release of compounds with limited aqueous solubility. A suspension of a compound in its saturated solution can provide both immediate-release and sustained-release components of a dose (Madan 1985). A number of water-insoluble prodrugs are also formulated as suspensions, including hydrocortisone acetate and medroxyprogesterone acetate. As with any other type of suspension, excipients will usually be required to ensure the physical stability of the formulation. Strickley's (1999) article provides a table of parenteral suspension formulations; the most popular excipient combinations are clearly polyethylene glycol/Tween 80 and carboxymethylcellulose/Tween 80.

Perhaps the most well-known example of a parenteral suspension formulation is insulin. Many insulin formulations also take advantage of the different physical forms which can be produced when insulin is complexed with zinc. Suspensions of the amorphous form of insulin zinc have a faster onset of action and shorter duration of action compared to those of the crystalline form. In order to provide both a rapid onset and a long duration of action, many formulations are composed of a mixture of amorphous and crystalline zinc insulin.

## Emulsions

For a molecule with a high aqueous solubility, the use of a water-in-oil two-phase emulsion or a multiple phase water-in-oil-in-water emulsion may enable a measure of sustained-release to be achieved. In either case, the nature of the sustained-release delivery profile will be a function of the partition coefficient of the molecule between the two phases, which will define the rate at which the molecule is available for absorption.

## Microspheres

Polymeric micropsheres, particularly those prepared from the biodegradable polylactide/polyglycolide polymers, have been widely investigated as a means to achieve sustained parenteral drug delivery. The advantage of formulating the polymeric matrix as microspheres is the ability to administer them via a conventional needle and syringe as a suspension formulation, rather than as an implant (see below). Lupron® depot formulations are available which can provide therapeutic blood levels of leuprolide acetate for up to four months. These products are presented as lyophilized polylactic acid microspheres which are reconstituted to form a suspension prior to administration.

## Implantable Drug Delivery Systems

Implantable delivery systems extend the concept of sustained release beyond the capabilities of the strategies discussed so far in this section. Continual drug delivery lasting for months or even years has been achieved. Because these products must be administered as a solid rather than a liquid, they are usually supplied with a customised injection device.

The number of marketed implantable products is relatively limited, probably due in part to the limited market for this type of product. The most well-known example of an implantable delivery system is the Norplant® contraceptive device which can deliver levonorgestrel for up to five years. The device is composed of a number of capsules fabricated from Silastic® (dimethylsiloxane/methylvinylsiloxane copolymer)

The Norplant® device has been somewhat controversial, however, due to difficulties associated with its removal. A second example of an implantable drug delivery system is Zoladex®, which is an implantable biodegradable lactide/glycolide polymeric delivery system for the administration of goserelin acetate. It is available in one-month and three-month presentations and can be injected through a wide-bore needle.

## *IN VITRO* AND *IN VIVO* TESTING METHODS

When developing formulations for compounds with limited solubility or stability, where extremes of pH or co-solvents might be used, it is desirable to carry out screening studies to assess their potential to cause pain or other adverse events following injection. Haemolysis and phlebitis may occur as a consequence of IV therapy, whilst pain may occur on administration of any type of injection. Several *in vitro* and *in vivo* models have been developed to evaluate the potential for adverse effects following parenteral administration; these are discussed briefly below. For a more detailed discussion of this subject, the reader is referred to the excellent review by Yalkowsky et al. (1998).

### In Vitro Precipitation

Clearly, when a drug is formulated at a non-physiological pH, or using organic solvents because of low solubility, there is a real risk of precipitation immediately following injection into the bloodstream. Crude models have therefore been used in the past to assess formulations for their potential to result in *in vivo* precipitation. These have generally involved performing dilutions in a medium resembling blood and monitoring the formation of a precipitate by visual or other means. More recently, dynamic methods have been developed which more realistically simulate the *in vivo* situation. Typically, these involve a continuously circulating system of plasma or a medium representing plasma. After "injection" of the test formulation, the resulting solution passes through a flow-through cell within a spectrophotometer where light scattering associated with particle formation is monitored. Although it is obviously difficult to precisely mimic *in vivo* conditions, these models can prove useful in terms of discriminating between a number of potential formulations. In addition, they can be used to assess the effect of injection rate. Yalkowsky et al. (1983) have shown that, perhaps counterintuitively, the degree of precipitation of diazepam injection is in fact *inversely* proportional to injection rate.

### Haemolysis

Haemolysis occurs when the red blood cell membrane is disrupted, resulting in release of cell contents into the plasma. Severe adverse events can occur if high levels of haemoglobin are released into plasma. Clearly, hypotonic formulations have the potential to cause haemolysis, and as discussed earlier, the administration of such formulations should be avoided. Other excipients, such as surfactants and co-solvents, can cause haemolysis, as may the drug itself. *In vitro* models to evaluate haemolytic potential typically involve exposing the formulation to blood, either in a static or a dynamic configuration, and then assessing the quantity of free haemoglobin released. The contact time between blood and the formulation is critical, as an unrealistic contact time can result in a substantial overestimation of the haemolytic potential of a given formulation (Wakerley 1999). Haemolysis can also be measured *in vivo* by the measurement of free haemoglobin in blood or urine, and Krzyzaniak (1997) has reported agreement between a dynamic *in vitro* method and *in vivo* results.



### Phlebitis

Phlebitis refers to inflammation of the vein wall. It can result in clinical symptoms such as pain and oedema, and can cause thrombus formation which may have serious consequences. Particulate matter is the most widely implicated cause of phlebitis. It is not surprising, therefore, that a link has been proposed between precipitation and phlebitis. The *in vitro* precipitation models described above may therefore be a good indicator of the phlebitic potential of a formulation. Phlebitis can be tested *in vivo*, usually by means of a rabbit ear vein model in which the "test" ear is visually compared with the "control" ear.

### Pain

Pain on injection is usually of greatest concern with intramuscular injections because of the long residence time of the formulation at the injection site. Not surprisingly, there are no *in vitro* models to test the potential of a formulation to cause pain! It is therefore necessary to test for the potential to cause pain by means of an *in-vivo* model. Gupta et al. (1994b) describe the use of the rat "paw lick" model for the assessment of pain in response to formulation pH and co-solvent concentration. The potential for muscle damage should also be evaluated when developing an intramuscular formulation, and the industry standard is the rabbit lesion volume model (Sutton et al. 1996).

## PACKAGING OF PARENTERAL PRODUCTS

### Pack Selection

The packaging of parenteral products presents unique challenges in terms of the requirements for the packaging components to withstand sterilization prior to use and the requirement for the complete primary pack to maintain sterility throughout the shelf-life of the product. Traditionally, SVPs have been packaged in ampoules which are heat sealed after filling. Because of the inherent variability in the sealing process, products packaged in ampoules must be 100 percent integrity tested after sealing, usually by means of a dye immersion test. The use of ampoules for new products is now diminishing, partly because of the desire to avoid exposing medical personnel to injury on opening. This has led to an increase in the use of glass vials sealed with rubber stoppers for the packaging of SVPs. Regardless of whether an ampoule or a vial is used, the glass quality must be type I neutral. An increasing number of simple solutions are now being filled using blow-fill-seal technology, in which the (plastic) ampoule is moulded, aseptically filled and sealed in a continuous process. These manufacturing systems operate to high levels of asepsis and are validated by media fills in the same manner as conventional filling processes.

For products packaged in vials, a suitable rubber stopper must be selected. The surface of a rubber stopper is inherently less inert than the glass of an ampoule, and it is therefore important that the formulator ensures that the product and stopper are compatible by

conducting suitable testing. It is also necessary to ensure that the product does not extract an excessive quantity of leachables from the stopper. For lyophilized products, it is advisable to select a stopper with a low capacity to absorb moisture during the autoclaving process, since this can subsequently be transferred to the product during storage, which may lead to product deterioration. Various other specialized stoppers are available, such as Teflon-coated, which may be useful when a highly inert surface is required. Stoppers containing a desiccant are also under development. Stoppers cannot withstand the depyrogenation process and so are autoclaved prior to use, but the presterilization treatment should be designed to ensure a satisfactory level of endotoxin removal. Stoppers will almost always require some degree of siliconisation to allow them to be easily processed in automatic filling lines, and they can be purchased washed, presiliconised to an agreed level and packaged in ready-to-sterilize bags. Stoppers which are purchased in a ready-to-sterilize format should be tested by the supplier to a suitable endotoxin specification.

Increasingly parenteral products are being presented in more sophisticated packages, such as pre-filled syringes. These reduce the potential for needle-stick injuries by reducing the degree of manipulation required and facilitate administration in an emergency situation. A number of companies, such as Beckton-Dickinson and Vetter, specialize in this technology, and can supply purpose-designed filling equipment or can provide contract manufacturing services to fill product into their devices.

### Container/Closure Integrity

Considerable emphasis is now placed on providing an assurance of container closure integrity during the shelf-life of sterile products. Historically, this has been achieved by performing sterility tests as a component of stability testing, usually initially and at 12-month intervals, but this approach alone would not now be considered sufficient to validate the integrity of a new container/closure system. Most manufacturers usually perform media immersion tests in which media-filled vials are immersed in contaminated media and subjected to repeated vacuum/overpressure cycles. This provides an assurance of the integrity of specific pack configurations under highly challenging conditions. This test should also be conducted on stored media-filled vials to provide data on the integrity of "aged" packs. FDA guidelines now allow physical tests to replace microbiological tests in demonstrating container closure integrity, but only where those physical tests are suitably validated. This is by no means straightforward because of the difficulty in correlating leakage measured by a physical method with the potential for microbial ingress. Efforts are underway to develop physical methods, however and Kirsch et al. have recently published a series of articles in which they have been able to correlate helium leak rates measured by mass spectrometry and vacuum decay methods with a probability of microbial ingress (Kirsch et al. 1999, 1997a, b, c).

## MANUFACTURING OF PARENTERAL PRODUCTS

The manufacture of parenteral products is focussed at all times on the requirement for sterility of the finished product. Despite the fact that the regulators are clear in their preference for products to be terminally sterilized, the vast majority of parenterals are filtered through sterilizing grade filters and filled aseptically, primarily because stability considerations preclude the use of moist heat sterilization. The statistical limitations of sterility testing a sample



from a batch are well known, and attention is now well and truly focussed on process validation. The validation program must encompass facilities, instrumentation, sterilization of container and closures, clean room garments and gowning procedures as well as including regular media simulations of aseptic processes. Guidance on the frequency and numbers of units to be filled in media simulations can be found in the publications of the Parenteral Drug Association and the Parenteral Society (see the section "Parenteral Products and the Regulatory Environment"). In a production environment, a simulation of each aseptic process will typically be carried out at six-month intervals. It is important that media fills include planned interventions, such as filter changes, so that such interventions can be permitted during a manufacture if required. In addition, holding times after filtration should be validated. Where a product is lyophilized, the media simulation must include loading into and removal from the lyophilizer and should also include pulling and releasing partial vacuums. It is obviously essential to ensure that all personnel participating in aseptic processes are adequately trained and aseptic operators are required to participate in regular media fills. Another important element of aseptic process validation is environmental monitoring and particulate monitoring; manufacturers are expected to know the organisms which may be present in their facility and to establish acceptable limits.

With the majority of parenteral products sterilized by filtration, it is not surprising that the validation of filtration processes is receiving increasing regulatory interest. The 1998 PDA Technical Report No. 26 discusses this topic in detail (see the section "Parenteral Products and the Regulatory Environment"). There is now a regulatory expectation that the bacterial retention capability of sterilizing filters is demonstrated in the presence of product rather than simply water. Fortunately, the major pharmaceutical filter companies now have specialised validation laboratories which are able to provide filter validation services. All filters used in a process, including vent filters, must also be integrity tested before and after use. Organisms have recently been identified which are capable of passing through 0.22 μm filters, and the filter companies are now starting to launch 0.1 μm filters. One might imagine that the day will come when the use of 0.1 μm filters becomes the industry "norm", although a 1997 editorial in the *Journal of the Parenteral Drug Association* advised those in the industry to resist this development. Manufacturers are required to have a knowledge of the type of organisms which may be present in the solution to be filtered; provided that these do not have the ability to pass through a 0.22 μm filter, there is no compelling scientific argument for the use of a 0.1 μm filter.

For products which can withstand sterilization in their final container, the focus of the validation exercise will clearly be the sterilization process. A detailed discussion of sterilization is beyond the scope of this chapter (for this, the reader is referred to the recent text by Nordhauser and Olson [1998]) but the premise central to all methods of sterilization is the concept of a log-reduction in viable organisms. Pharmacopoeias now require an assurance that there is less than one chance in a million that viable microorganisms are present in a sterilized article or dosage form (Hall 1994). Achieving the required sterility assurance level of $10^{-6}$ is of course dependent on the initial microbiological loading of the material to be sterilized, and so it is vital to have knowledge of the initial bioburden and to set limits for this. For terminally sterilized products, the focus of the validation exercise will be in providing an assurance that sterilizing conditions have been reached in all units. Thus only loads and loading patterns which have been validated, usually by means of biological indicators, can be used. The concept of validated loading patterns also applies to the sterilization of equipment and packaging components to be used in an aseptic process.

The final stage in the manufacture of a sterile product is inspection. A 100 percent inspection for particulates, cracks and defects is a regulatory requirement. The inspection may

be carried out visually using suitable illumination, but in a production environment, a semi-automated or automated system is usually used.

Clearly, the manufacture of sterile products is a specialized area, and the above discussion simply serves to highlight some of the critical issues; it is by no means comprehensive. For a detailed discussion of the manufacture of sterile products, the reader is referred to Hall (1994) as well as the publications of the Parenteral Drug Association and the Parenteral Society, which are detailed in the section "Parenteral Products and the Regulatory Environment". In addition, the "Orange Guide" provides a very readable annex covering the manufacture of sterile medicinal products; this includes guidance on clean room classifications, gowning and sanitisation, as well as the manufacture and sterilization of medicinal products (MCA 1997).

## ADMINISTRATION OF PARENTERAL PRODUCTS

During product development, it is essential that the formulator keeps in mind the manner in which their product will ultimately be used. This is particularly true for products intended for IV infusion, since these will require dilution with IV infusion fluids prior to administration. The formulator must ensure that the active compound is compatible with all diluents which are to be included in the product labelling and must provide stability data to demonstrate that the resultant infusion solutions are stable for the period of time specified in the labelling. During clinical trials, compatibility and stability must be assured at the maximum and minimum concentrations to be administered during the study; this data will be expected by the regulatory authorities as part of an Investigational New Drug (IND) submission. It is also important to consider other drugs which may be co-administered with the product in question. The practice of mixing more than one drug in a single infusion is diminishing rapidly, and the labelling of new IV products usually specifies that this should be avoided. One must still consider, however, the potential for incompatibilities to occur when different infusion solutions mix in the infusion line or indeed the cannula. In general, mixing prior to the cannula can be avoided by the use of a different line for each infusion, but clearly, mixing in the cannula is inevitable where patients are receiving multiple IV infusions. The labelling of some medications, notably alteplase, specifically instructs that they should be administered in a completely separate infusion line to any other medications. The nature of alteplase may justify this statement, but in practice, such restrictions should be avoided, since they will clearly cause difficulties for medical practitioners.

When compatibility or stability issues do arise, there are limited options available to the formulator. The diluent cannot usually be controlled unless the manufacturer incurs the additional cost associated with supplying a custom diluent. Leachables from infusion bags can cause degradation, particularly oxidation. In addition, the low concentrations to which drugs may be diluted for continuous infusion can result in adsorptive losses. A number of products, therefore, specify a minimum concentration to which they can be diluted, presumably to address stability or adsorption issues. The infusion set itself can also contribute to instability and/or adsorption. Some product labelling, for example, that of glyceryl trinitrate infusion, specifies that PVC infusion lines should not be used. In extreme cases, it may be necessary to add an additional excipient to the product to prevent degradation on dilution, although this approach should only be considered as a last resort.



## PARENTERAL PRODUCTS AND THE REGULATORY ENVIRONMENT

The requirement for sterility in parenteral products means that their manufacture is scrutinised perhaps more closely than that of any other product type. A number of regulatory guidelines specifically pertain to parenteral products, and these are listed below. Included in these lists are also some more general guidelines where these contain sections specifically relevant to parenteral products. European Agency for the Evaluation of Medicinal Products (EMEA) publications provide useful guidance in formulation decision making and are essential reading early on in the formulation development process. The "Decision Trees for the Selection of Sterilisation Methods" document provides clear guidance on the selection of a sterilization strategy, this is discussed in detail in Chapter 12. Similarly, the "Notes for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products" is prescriptive in terms of defining the circumstances under which antioxidants and preservatives should be used. The former, for example, should be included only where their use cannot be avoided and where the manufacturing process has been optimised to minimize the potential for oxidation.

FDA guidelines are in general directed more towards the required components of a registration dossier and do not offer much in the way of guidance to the formulator. One exception to this is the "Guide to Inspection of Lyophilization of Parenterals"; this provides a useful indication of areas of specific interest to the FDA which the formulator would be well-advised to address during the development programme.

In addition to the regulatory guidelines, more detailed advice on specific issues relating to the development and manufacture of parenteral products can be obtained from the publications of the Parenteral Drug Association. This is an American organisation representing those involved in all aspects of parenteral product development and manufacture and is very active in lobbying the FDA. The PDA produces a bimonthly journal, the *PDA Journal of Pharmaceutical Science and Technology*, which is essential reading for all those involved in the development and manufacture of parenteral products. In addition, the PDA regularly publishes technical reports which provide a detailed discussion of pertinent issues within the parenteral field. Whilst these reports are not regulatory guidelines, they do provide a good indication of the direction in which the industry and indeed the regulators, are heading and those working in the field should take their recommendations seriously. Some of the recently published technical reports are listed below. In the United Kingdom, the Parenteral Society publishes a quarterly journal in conjunction with similar bodies in France, Germany, Scandinavia and Spain. This journal covers topics similar to those in the PDA journal. The Parenteral Society also publishes a number of monographs, some of which are listed below. These monographs provide a good indication of industry "norms" in the United Kingdom.

### FDA Guidelines

*Inspection Guidelines*

- Guide to Inspection of Lyophilization of Parenterals

*Guidance for Industry*

- Container Closure Systems for Packaging Human Drugs and Biologics
- Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products
- Container Closure Integrity Testing *in Lieu* of Sterility Testing as a Component of the Stability Protocol for Sterile Products
- Stability Testing of Drug Substances and Drug Products

### EMEA Guidelines

- Note for Guidance on Maximum Shelf-Life for Sterile Products for Human Use after First Opening or Following Reconstitution
- Notes for Guidance on Development Pharmaceutics
- Development Pharmaceutics for Biotechnological and Biological Products
- Decision Trees for the Selection of Sterilisation Methods
- Notes for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products

### PDA Technical Reports

- Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products, 50, S1, 1996
- Technical Report No. 23: Industry Survey on Current Sterile Filtration Practices, 51, S1, 1997
- Technical Report No. 24: Current Practices in the Validation of Aseptic Processing, 51, S2, 1997
- Technical Report No. 25: Blend Uniformity Analysis: Validation and In-Process Testing, 51, S3, 1997
- Technical Report No. 26: Sterilization Filtration of Liquids, 52, S1, 1998
- Technical Report No. 27: Pharmaceutical Package Integrity, 52, S2, 1998
- Technical Report No. 28: Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals, 52, S3, 1998
- Technical Report No. 29: Points to Consider for Cleaning Validation, 52, 6, 1998
- Technical Report No. 30: Parametric Release of Sterile Pharmaceuticals Terminally Sterilized by Moist Heat, 1999
- Technical Report No. 31: Validation and Qualification of Computerized Laboratory Data Acquisition Systems, 53, 4, 1999



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# 10

# Inhalation Dosage Forms

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Asthma and chronic obstructive pulmonary diseases (COPDs) such as bronchitis and emphysema are major and growing disease areas where the major route of administration is topically, at the site of action in the lung. Asthma is a common, chronic disease with a prevalence of more than 5 percent in adults and 15–20 percent in children, and is increasing in many parts of the world. The prevalence of COPD is even higher, and mortality rates are 10 times higher than those for asthma. At present, similar drugs are used for both diseases, with steroids and short- and long-acting β2s being the most common therapies. Anticholinergics and chromones are also employed. Inhalation allows the delivery of smaller doses directly to the lungs, with the advantage of reduced systemic side-effects. There are also other illnesses where pulmonary delivery is appropriate, such as cystic fibrosis, human immunodeficiency virus (HIV), lung cancer, pain and infections. In addition, the lung is being increasingly viewed as a route to the systemic circulation for the treatment of non-respiratory diseases, where normal oral administration is not technically possible. This is especially relevant to the delivery of peptides and proteins, of which insulin is a good example.

Unlike most other drug delivery systems, those in the respiratory area can have a major influence on physician/patient acceptance. A wide range of devices are available in the three main categories of dry powder inhalers (DPIs) and metered dose inhalers (MDIs), i.e., pressurised aerosols and nebulisers. The preferred type of inhaler varies considerably between countries (e.g., DPIs in Scandinavia and MDIs in the United States), and between patient groups (e.g., nebulisers for paediatrics).

Until the mid-1980s, the MDI was the dominant inhalation dosage form, but the Montreal Protocol lead to greatly increased activity in device development, for both existing drugs and new chemical entities. The propellants for the existing MDIs were chlorofluorocarbons