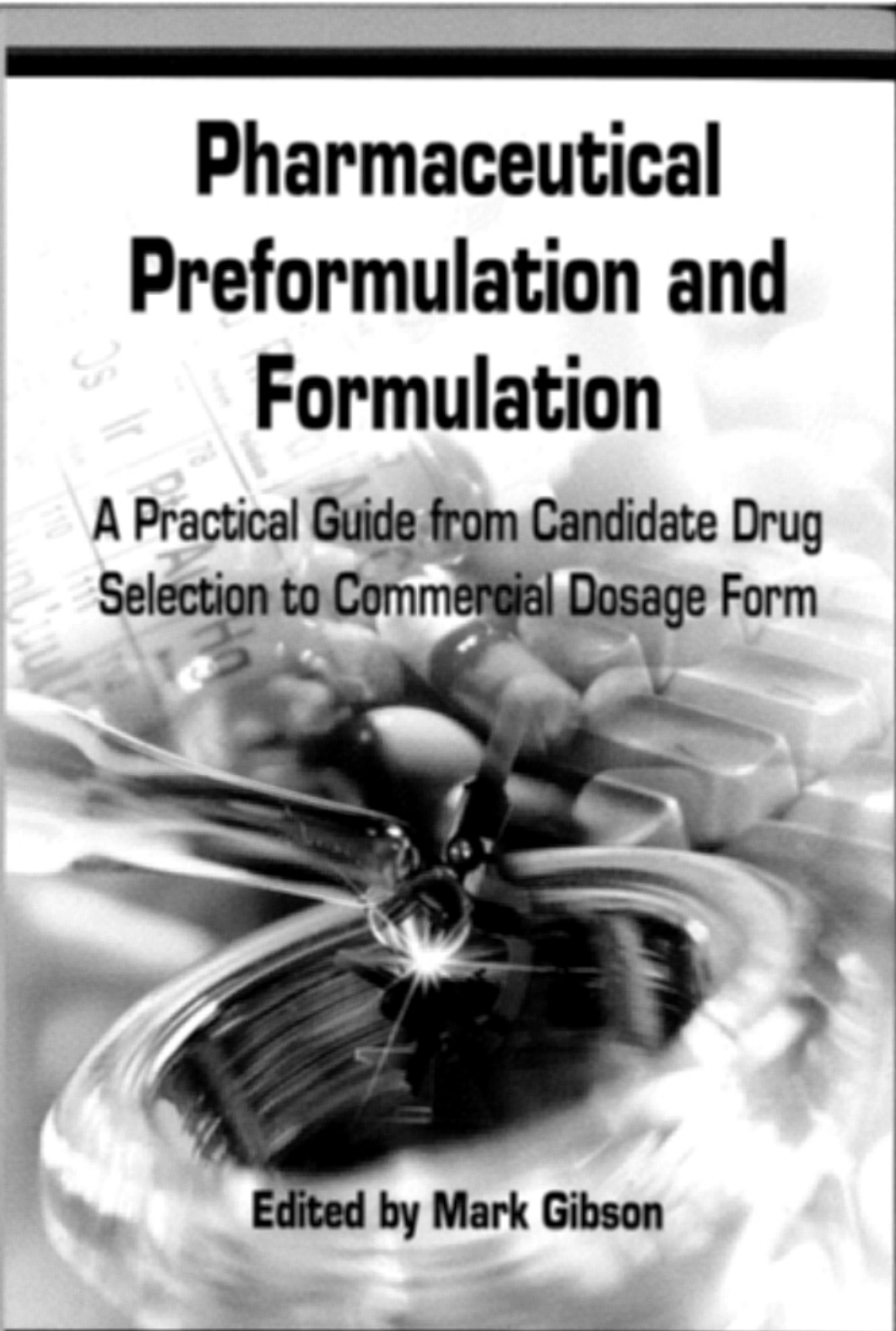




Pharmaceutical Preformulation and Formulation

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

Edited by Mark Gibson

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A Practical Guide from Candidate Drug
Selection to Commercial Dosage Form

Steptoe & Johnson LLP

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Edited by Mark Gibson



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Oral Solid Dosage Forms

Peter Davies

Roche Discovery
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In the last 15 to 20 years, there has been a huge resource in both academia and industry devoted to the development of drug delivery systems that target drugs more effectively to their therapeutic site. Much of this work has been successful and is reported within this text. In spite of this, oral solid dosage forms such as tablets and hard gelatin capsules, which have been in existence since the nineteenth century, remain the most frequently used dosage forms. This is not simply a reflection of the continued use of established products on the market, tablets and capsules still account for about half of all new medicines licensed (Table 11.1).

There are several reasons for the continued popularity of the oral solid dosage form. The oral route of delivery is perhaps the least invasive method of delivering drugs, it is a route that the patient understands and accepts. Patients are able to administer the medicine to themselves. For the manufacturer, solid oral dosage forms offer many advantages: they utilise cheap technology, are generally the most stable forms of drugs, are compact and their appearance can be modified to create brand identification.

Tablets and capsules are also very versatile. There are many different types of tablets which can be designed to fulfil specific therapeutic needs (Table 11.2). It is beyond the scope of this chapter to cover all these dosage forms, instead it will review the common principles, with more specific detail being given for those most commonly used.

For drugs that demonstrate good oral bioavailability and do not have adverse effects on the gastro-intestinal (GI) tract, there may be very little justification for attempting to design a specific drug delivery system. It is likely, therefore, that tablets and capsules will continue to remain one of the most used methods of delivering drugs to the patient in the future.

This chapter reviews the science behind the development of solid dosage forms, particularly tablets and hard gelatin capsules. Solid dosage forms are one of the most widely

Table 11.1
Number of FDA drug approvals for tablet and capsules from 1995 to 1999.

	No. of Tablets Approved	No. of Capsules Approved	No. of Other Dosage Forms Approved	Proportion of Tablets and Capsules (%)
1995	14	0	14	50
1996	69	17	101	46
1997	70	15	96	47
1998	48	9	66	46
1999	20	10	30	50

Source: Centrewatch.com, Clinical trials listing.

Table 11.2
Types of solid dosage forms.

Formulation Type	Description
Immediate release	The dosage form is designed to release the drug substance immediately after ingestion.
Delayed release	The drug substance is not released until a physical event has occurred, e.g., time elapsed, change in pH of intestinal fluids, change in gut flora.
Chewable tablets	Strong, hard tablets to give good mouth feel.
Lozenges	Strong, slowly dissolving tablets for local delivery to mouth or throat. Often prepared by a candy moulding process.
Buccal tablets	Tablets designed to be placed in buccal cavity of mouth for rapid action.
Effervescent tablets	Taken in water, the tablet forms an effervescent, often pleasant-tasting drink.
Dispersible tablets	Tablets taken in water, the tablet forms a suspension for ease of swallowing.
Soluble tablets	Tablets taken in water, the tablet forms a solution for ease of swallowing.
Hard gelatin capsules	Two-piece capsule shells which can be filled with powders, pellets, semi-solids or liquids.
Soft gelatin capsules	One-piece capsules containing a liquid or semi-solid fill.
Pastilles	Intended to dissolve in mouth slowly for the treatment of local infections. Usually composed of a base containing gelatin and glycerin.

researched areas of pharmaceuticals and, given the space allowed, this chapter can only cover the science at a very basic level. It is an area that is served by a number of excellent texts, and these will be referenced at the appropriate points.

POWDER TECHNOLOGY

Virtually all solid dosage forms are manufactured from powders, and an understanding of the unique properties of powder systems is necessary for their rational formulation and manufacture. Powders consist of solid particles surrounded by spaces filled with fluid (typically air) and uniquely possess some properties of solids, liquids and gases. Powders are not solids, even though they can resist some deformation, and they are not liquids, although they can be made to flow. Still further, they are not gases, even though they can be compressed. Powder technology is concerned with solid/fluid interactions, interparticle contact and cohesion between particles. These are strongly influenced by particle size and shape and by adsorption of the fluid or other contaminants onto the surface of the particles.

While tablets and capsules, the two most common solid dosage forms, have their own unique requirements, there are similarities between them. They both require the flow of the correct weight of material into a specific volume, the behaviour of the material under pressure is important; and the wetting of the powder is critical for both granulation and subsequent disintegration and dissolution of the dosage form.

While it is not possible to deal with all aspects of powder technology in a textbook covering such a diverse range of formulations, some basic principles of powder flow, mixing and compaction and compression properties will be described. For those interested in a more in-depth treatment of the topic, there are a number of excellent texts available (Rhodes 1990; Nyström 1995).

Particle Size and Shape

A knowledge of the particle shape and size distribution is essential to the understanding of the behaviour of powders, as it will contribute to knowledge of the secondary properties of a powder, such as flow and deformation, which influence the processability. This topic is dealt with in detail in Chapter 6.

Density

When a powder is poured into a container, the volume that it occupies depends on a number of factors, such as particle size, particle shape and surface properties. In normal circumstances, it will consist of solid particles and interparticulate air spaces (voids or pores). The particles themselves may also contain enclosed or intraparticulate pores. If the powder bed is subjected to vibration or pressure, the particles will move relative to one another to improve their packing arrangement. Ultimately, a condition is reached where further densification is not possible without particle deformation.

The density of a powder is, therefore, dependent on the handling conditions to which it has been subjected, and there are several definitions that can be applied either to the powder as a whole or to individual particles.

Particle Densities

British Standard 2955 (1958) defines three terms that apply to the particles themselves. Particle density is the mass of the particle divided by its volume. The different terms arise from the way in which the volume is defined.

1. True particle density is when the volume measured excludes both open and closed pores and is a fundamental property of a material.
2. Apparent particle density is when the volume measured includes intraparticle pores.
3. Effective particle density is the volume "seen" by a fluid moving past the particles. It is of importance in processes such as sedimentation or fluidisation but is rarely used in solid dosage forms.

Powder Densities

The density of a powder sample is usually referred to as the bulk density, and the volume includes both the particulate volume and the pore volume. The bulk density will vary depending on the packing of the powder, and several values can be quoted

- Minimum bulk density is when the volume of the powder is at a maximum, caused by aeration, just prior to complete breakup of the bulk.
- Poured bulk density is when the volume is measured after pouring powder into a cylinder, creating a relatively loose structure.
- Tapped bulk density is, in theory, the maximum bulk density that can be achieved without deformation of the particles. In practise, it is generally unrealistic to attain this theoretical tapped bulk density, and a lower value obtained after tapping the sample in a standard manner is used.

The porosity of a powder is defined as the proportion of a powder bed or compact that is occupied by pores and is a measure of the packing efficiency of a powder.

$$\text{porosity} = 1 - \left(\frac{\text{bulk density}}{\text{true density}} \right) \quad (1)$$

Relative density is the ratio of the measured bulk density divided by the true density.

$$\text{relative density} = \frac{\text{bulk density}}{\text{true density}} \quad (2)$$

POWDER FLOW

Good flow properties are a prerequisite for the successful manufacture of both tablets and powder-filled hard gelatin capsules. It is a property of all powders to resist the differential movement between particles when subjected to external stresses. This resistance is due to the cohesive forces between particles. Three principal types of interparticle force have been identified (Harnby et al. 1985): forces due to electrostatic charging, van der Waals forces and forces due to moisture.

Electrostatic forces are dependent on the nature of the particles, in particular, on their conductivity. For non-conducting particles, high cohesive stresses in the range of 10^4 to 10^7 N/m² have been reported.

Van der Waals forces are the most important forces for most pharmaceutical powders. The forces of attraction between two spherical particles is given by:

$$F = Ad \left(\frac{Ad}{12x^2} \right) \quad (3)$$

where A is the Hamaker constant ($L = 10^{-19}$ J), x is the distance of separation of the particles and d is the particle diameter. The forces are inversely proportional to the square of the distance between the two particles, and hence diminish rapidly as particle size and separation increases. Powders with particles below 50 μm will generally exhibit irregular or no flow due to van der Waals forces. Particle shape is also important; for example, the force between a sphere and plane surface is about twice that between two equal sized spheres.

At low relative humidities, moisture produces a layer of adsorbed vapour on the surface of particles. Above a critical humidity, typically in the range 65–80 percent, it will form liquid bridges between particles. The attractive force due to the adsorbed layer may be about 50 times the van der Waals force for smooth surfaces, but surface roughness will reduce the effect. Where a liquid bridge forms, it will give rise to an attractive force between the particles due to surface tension or capillary forces.

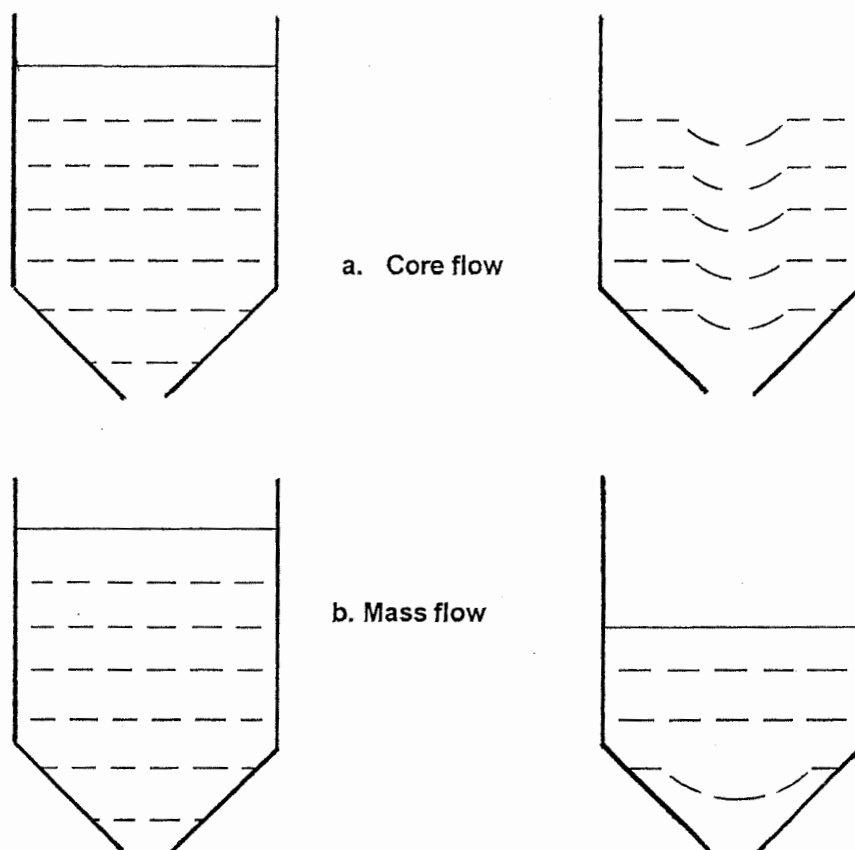
The role of the formulator is to ensure that the flow properties of the powder are sufficient to enable its use on modern pharmaceutical equipment. Two types of flow present the formulator with particular challenges: flow from powder hoppers and flow through orifices.

Powder Flow in Hoppers

Tablet machines and capsule filling machines store the powder to be processed in a hopper above the machine. It is important that the powder flows from the hopper to the filling station of the machine at an appropriate rate and without segregation occurring. There are two types of flow that can occur from a powder hopper: core flow and mass flow (Figure 11.1).

The flow pattern of a core flow is shown in Figure 11.1a. When a small amount of powder is allowed to leave the hopper, there is a defined region in which downward movement takes place and the top surface begins to fall in the centre. As more material leaves the hopper, the area which moves downward begins to widen, and the upper surface becomes conical. In the areas of the hopper outside the falling region, near the walls, the material has not moved. Even when the hopper has almost emptied, there will be regions where the powder is undisturbed. A core flow hopper is characterised by the existence of dead spaces during discharge. A mass flow hopper is one in which all the material is in motion during discharge, in particular the areas adjacent to the hopper wall (Figure 11.1b). As a small amount of powder is discharged, the whole bulk of the powder will move downwards.

Core flow hoppers have two significant disadvantages. First, flow from the hopper can stop for no apparent reason. The stoppage may be due to the formation of an arch between the walls of the hopper that is strong enough to support the weight of powder above it. Alternatively, it may be the result of piping or rat holing, in which the material directly above the outlet falls out, leaving an empty cylinder. The second disadvantage is that the flow pattern is likely to encourage segregation, and there may be a considerable loss of mixing quality.

Figure 11.1 Powder flow patterns in hoppers.

Whether core flow or mass flow is achieved is dependent on the design of the hopper (geometry and wall material) and the flow properties of the powder. For most pharmaceutical applications, the hopper design for a particular machine will be fixed; thus, it is incumbent on the formulator to ensure that mass flow is achieved by modification of the powder properties.

Powder Flow into Orifices

Flow into orifices is important when filling dies in tablet machines and in certain types of capsule filling machines. For a given material, the flow into or through an orifice is dependent on the particle size, and typically, a plot of flow rate versus particle size will display the trend

shown in Figure 11.2. At the lower end of the particle size range, cohesive forces will result in poor flow. As the particle size increases, the flow rate increases until a maximum is achieved, at an orifice diameter/particle diameter ratio of 20–30. As the particle size continues to increase, the rate decreases due to mechanical blocking or obstruction of the orifice. Flow will stop completely when the orifice/particle ratio falls below 6.

Measuring Powder Flow Properties

There are several different methods available for determining the flow properties of powders, and there are many literature examples demonstrating correlations between a test method and the manufacturing properties of a formulation. Listed below are some of the more commonly used tests, together with references, detailing their use in pharmaceutical applications.

Shear Cell Methods

Developed to aid silo and hopper design, shear cells provide an assessment of powder flow properties as a function of consolidation load and time. There are a number of types of shear cells available, the most common type being the Jenike shear cell (Figure 11.3).

The shear cell is filled in a standard manner to produce a powder bed with a constant bulk density. A vertical (normal) force is applied to the powder bed and a horizontal force applied to the moveable ring. As the powder bed moves due to the horizontal shear stress, it will change volume, either expanding or contracting depending on the magnitude of the vertical force. A series of tests are performed to determine the vertical load under which the bed remains at constant volume when sheared, referred to as the critical state. Once the critical state has been determined, a series of identical specimens are prepared, and each is sheared under a different vertical load, with all loads being less than the critical state.

Figure 11.2 Effect of particle size on the rate of powder flow through an orifice.

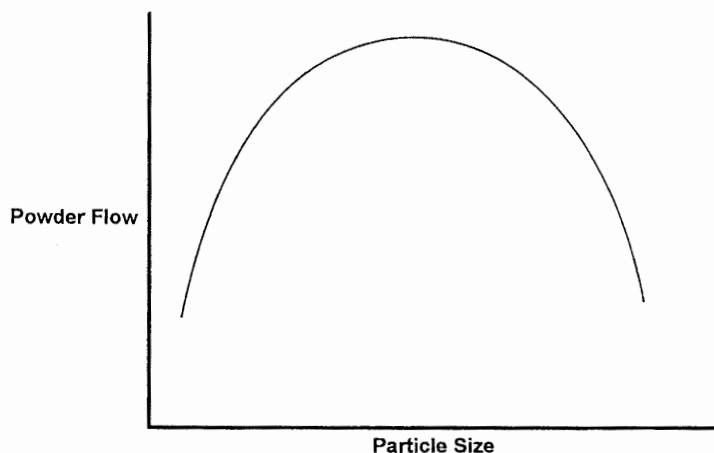
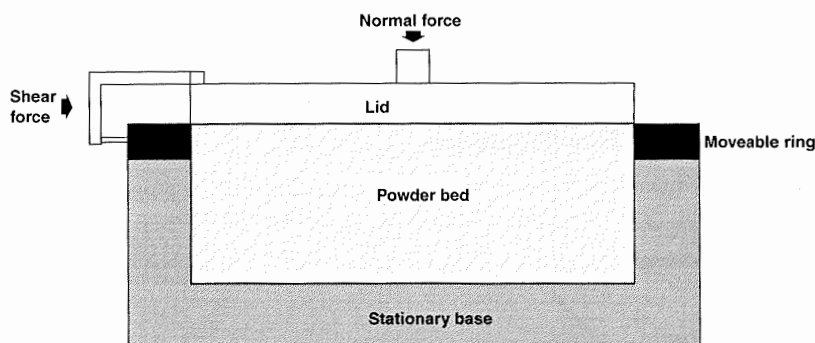


Figure 11.3 Jenike shear cell.

The test results are used to produce a graph referred to as a Jenike yield locus in which the shear stress required to initiate movement is plotted against the normal stress (Figure 11.4). The line gives the stress conditions needed to produce flow for the powder when compacted to a fixed bulk density. If the material is cohesive, the yield locus does not produce a straight line, and it does not pass through the origin. The intercept OT is the tensile strength of the consolidated specimen, and OC is the cohesion of the specimen, that is, the shear stress needed to initiate movement of the material when it is not subjected to normal force. The application of the yield loci to pharmaceuticals is well documented in the literature (Kocova and Pilpel 1972, 1973; Williams and Birks, 1967).

The limitations of the Jenike shear cell are that it is not very useful for measuring bulk solids with large shear deformations, e.g., plastic powders. The level of consolidation stresses required are inappropriate for pharmaceutical materials, and the quantity of material required is often beyond that available in the early stages of development. Alternative shear cells that have been used include annular shear cells (Nyquist and Brodin 1982; Irono and Pilpel 1982) and ring shear testers (Schulze 1996).

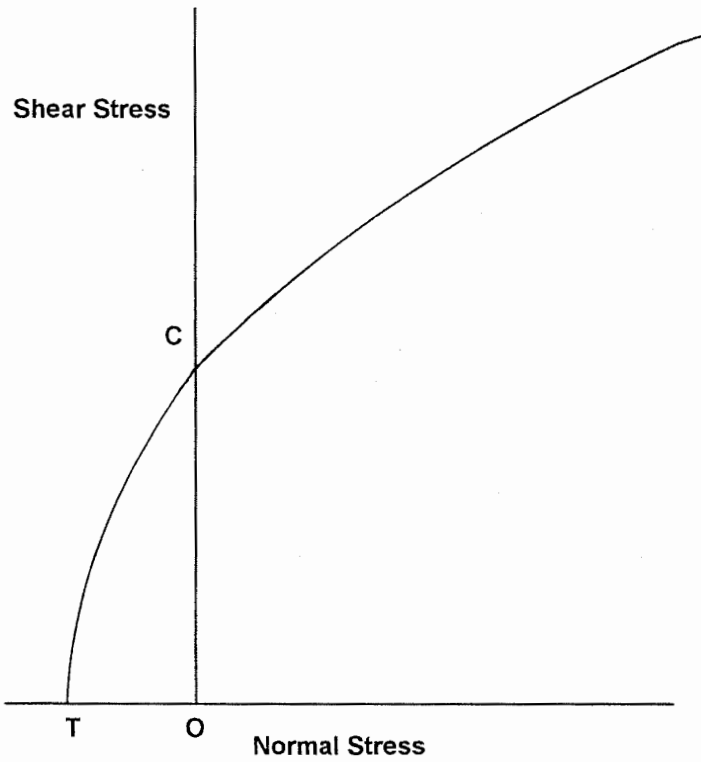
Changes in Bulk Density

The increase in bulk density of a powder is related to the cohesivity of a powder. Ratios of the poured to tapped bulk densities are expressed in two ways to give indices of flowability.

$$\text{Hausner Ratio} = \frac{\text{tapped bulk density}}{\text{poured bulk density}} \quad (4)$$

$$\text{Compressibility (Carr Index)} = \frac{100 \times (\text{tapped bulk density} - \text{poured bulk density})}{\text{poured bulk density}} \quad (5)$$

The Hausner Ratio varies from about 1.2 for a free-flowing powder to 1.6 for cohesive powders. The Carr Index classifications are listed in Table 11.3.

Figure 11.4 Jenike yield locus.**Table 11.3**
Carr indices.

Carr Index (%)	Flow
5-12	Free flowing
12-16	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Compressibility indices are a measure of the tendency for arch formation and the ease with which the arches will fail and, as such, is a useful measure of flow. A limitation of the bulk density indices is that they only measure the degree of consolidation; they do not describe how rapidly consolidation occurs.

Angle of Repose

If powder is poured from a funnel onto a horizontal surface, it will form a cone. The angle between the sides of the cone and the horizontal is referred to as the angle of repose. The angle is a measure of the cohesiveness of the powder, as it represents the point at which the interparticle attraction exceeds the gravitational pull on a particle. A free-flowing powder will form a cone with shallow sides, and hence a low angle of repose, while a cohesive powder will form a cone with steeper sides.

This method is simple in concept, but not particularly discerning. As a rough guide, angles less than 30° are usually indicative of good flow, while powders with angles greater than 40° are likely to be problematic.

Avalanching Behaviour

If a powder is rotated in a vertical disc, the cohesion between the particles and the adhesion of the powder to the surface of the disc will lead to the powder following the direction of rotation until it reaches an unstable situation where an avalanche will occur. After the avalanche, the powder will again follow the disc prior to a further avalanche. Measurement of the time between avalanches and the variability in time is a measure of the flow properties of the powder.

MIXING

The mixing of powders is a key step in the manufacture of virtually all solid dosage forms. A perfect mixture of two particles is one in which any group of particles taken from any position within a mix will contain the same proportions of each particle as the mixture as a whole (Figure 11.5). With powders, unlike liquids, this is virtually unattainable. All that is possible to achieve is a maximum degree of randomness, that is, a mixture in which the probability of finding a particle of a given component is the same at all positions in the mixture (Figure 11.6).

To determine the degree of mixing obtained in a pharmaceutical operation, it is necessary to sample the mixture and determine the variation within the mix statistically. In assessing the quality of a mixture, the method of sampling is more important than the statistical method used to describe it. Unless samples that accurately represent the system are taken, any statistical analysis is worthless. Furthermore, to provide meaningful information, the scale of scrutiny of the powder mix should be such that the weight of sample taken is similar to the weight that the powder mix contributes to the final dosage form.

A large number of statistical analyses have been applied to the mixing of powders. These tend to be indices where the variance of the actual mix is compared to the theoretical random mix. The statistics are beyond the scope of this text and can be found in a number of standard texts on powder technology (Rhodes 1990).

Figure 11.5 Perfect mix.

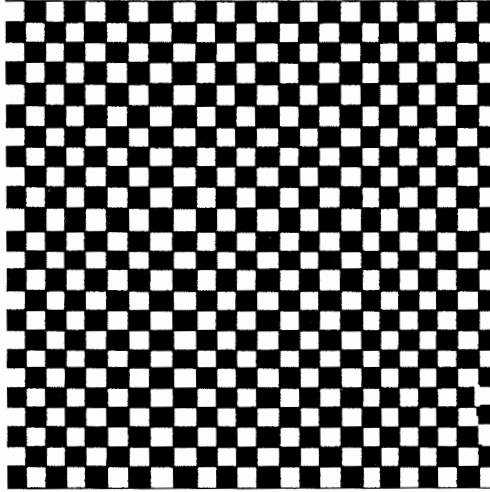
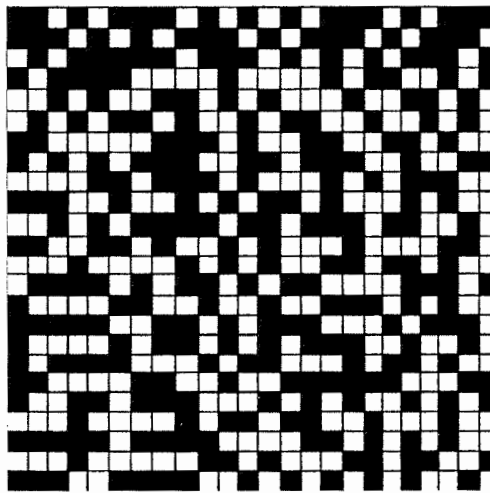


Figure 11.6 Random mix.



Segregation

If a powder consisting of two materials both having identical physical properties is mixed for sufficient time, random mixing will eventually be achieved. Unfortunately, most pharmaceutical powders consist of mixtures of materials with differing properties. This leads to segregation, where particles of similar properties tend to collect together in part of the powder. When segregating powders are mixed, as the mixing time is extended, the powders appear to unmix and equilibrium is reached between the action of the mixer introducing randomness and the resistance of the particles due to segregation.

While a number of factors can cause segregation, *differences in particle size* are far and away the most important in pharmaceutical powders. There are a number of mechanisms by which segregation of different sized particles can occur, and consideration should be given to these when designing pharmaceutical processes. *Trajectory segregation* occurs when a powder is projected horizontally in a fluid or gas; larger particles are able to travel greater horizontal distances than small particles before settling out. This could cause segregation at the end of conveyor belts or vacuum transfer lines. When a powder is discharged into a hopper or container, air is displaced upward. The upward velocity of this air may be sufficient to equal or exceed the terminal velocity of some of the smaller particles, and these will remain suspended as a cloud after the large particles have settled out. This process is known as *elutriation segregation*. The most common cause of segregation is due to *percolation* of fine particles. If a powder bed is handled in a manner that allows individual particles to move, a rearrangement in the packing of the particles will occur. As gaps between particles arise, particles from above will be able to drop into them. If the powder contains particles of different sizes there will be more opportunities for the smaller particles to drop, so there will be a tendency for these to move to the bottom of the powder, leading to segregation. This process can occur whenever movement of particles takes place, including vibration, shaking and pouring.

Ordered Mixing

As stated above, differences in particle size are the most common cause of segregation in pharmaceutical powders. One exception to this is when one component of a powder mix has a very small particle size (less than 5 μm) and the other is relatively large. In such circumstances, the fine powder may coat the surface of the larger particles, and the adhesive forces will prevent segregation. This is known as ordered mixing, and using this technique, it is possible to produce greater homogeneity than by random mixing.

COMPACTION

The manufacture of tablets, and to a lesser extent powder-filled hard gelatin capsules, involves the process of powder compaction, the purpose of which is to convert a loose incoherent mass of powder into a single solid object. Knowledge of the behaviour of powders under pressure, and the way in which bonds are formed between particles, is essential for the rational design of formulations.

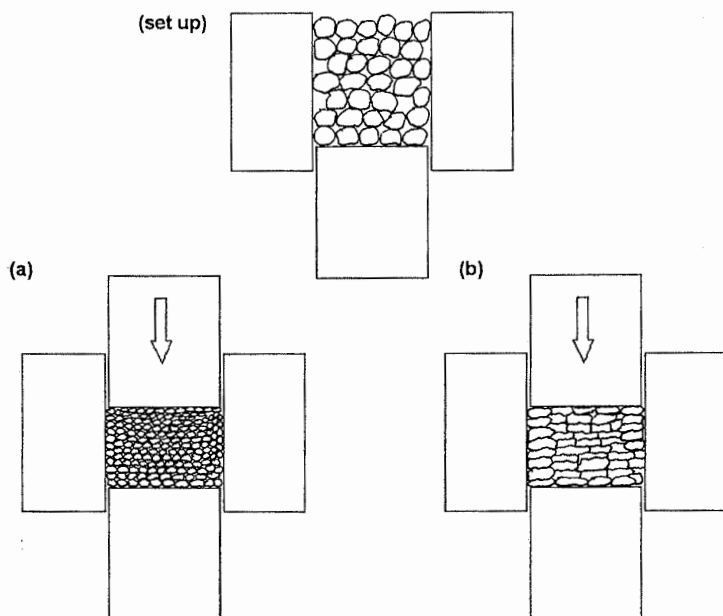
A powder in a container subjected to a low compressive force will undergo particle rearrangement until it attains its tapped bulk density. Ultimately, a condition is reached where further densification is not possible without particle deformation. If, at this point, the powder

bed is subjected to further compression, the particles will deform elastically to accommodate induced stresses, and the density of the bed will increase with increasing pressure at a characteristic rate. When the elastic limit is exceeded, there is a change in the rate of reduction in the bed volume as plastic deformation or brittle fracture of particles begins (Figure 11.7). Brittle materials will undergo fragmentation, and the fine particles formed will percolate through the bed to give secondary packing. Plastically deforming materials will distort to fill voids and may also exhibit void filling by percolation when the limit of plastic deformation is reached and fracture occurs. Either mechanism, therefore, consists of at least two submechanisms, and the processes could be repeated on the secondary particles produced by the fracture until the porosity is at a minimum and the internal crystalline structure supports the compressional stress.

Both processes will aid bonding to form a single compact, as plastic flow increases contact areas between particles irreversibly and fragmentation produces clean surfaces that bond strongly. The successful production of compacts depends on achieving high contact areas between uncontaminated surfaces.

To fully understand the compaction behaviour of a material, it is clear that it is necessary to be able to quantify its elasticity, plasticity and brittleness.

Figure 11.7 The behaviour of powders subjected to a compaction force: (a) brittle fracture and (b) plastic deformation.



Measurement of Compaction Properties

To characterise the compaction properties of a material or formulation, it must be possible to measure the relationship between the force applied to a powder bed and the volume of the powder bed. A typical instrumentation will consist of measurement of the forces on the upper and lower punches by means of strain gauges or load cells together with a measure of the punch movement, which is performed using displacement transducers, the most common type being linear variable-differential transducers (LVDTs). The positioning and installation of the load and displacement transducers are critical to obtain meaningful information. The topic of instrumentation is comprehensively covered by Ridgway Watt (1988). There are three approaches that have been used to generate compaction information, as discussed below.

Conventional Testing Machines

Testing machines are widely used in materials science and engineering laboratories for the measurement of physical properties of various materials. Many of the basic principles of compaction and the test methodologies currently employed in pharmaceutical formulation have been developed on testing machines by the metallurgy and ceramic industries. The drawback with testing machines is that the compression speeds that can be achieved are well below those encountered on tabletting machines, so while they are of value in fundamental studies, they are not necessarily useful for predicting the behaviour of a material or formulation in the factory.

Conventional Tablet Machines

The first tablet machines to be instrumented were single punch eccentric presses. While these provide useful information, the compression profiles differ from those of rotary tablet machines used for commercial production. The profile of a single punch involves the powder bed being compressed between a moving upper punch and a stationary lower punch, while on a rotary machine, both punches move together simultaneously. Consequently, rotary machines have been instrumented, even though this is technically more challenging than single punch machines. The instrumented rotary press provides information that is directly relevant to production conditions, although it should be borne in mind that profiles do vary between machines, and any results obtained may be peculiar to that machine. A major advantage of instrumented machines is that they provide information not only on the compaction properties but also on flow and lubrication. The disadvantage of using instrumented rotary machines is the quantity of material required to perform tests, making them unsuitable for preformulation activities, when material is in short supply.

Compaction Simulators

Compaction simulators are a development of testing machines. They consist of single punch machines in which the upper and lower punches are driven individually by hydraulic rams. The movement of the hydraulic rams is controlled by computer and can be programmed either to simulate the movement of any tablet machine or to follow a simple profile similar to a testing machine. The big advantage of the compaction simulator is that it can be used to prepare a single compact using a profile that might be encountered on a production machine, so only small quantities of material are required.

Quantitative Compaction Data

There are two principal types of compaction studies used to characterise material: pressure/volume relationships and pressure/strength relationships. While ultimately it is the strength of a tablet that is important, the pressure/volume relationships provide the information about the compaction properties of a material that allows an appropriate formulation to be developed.

Heckel Plots

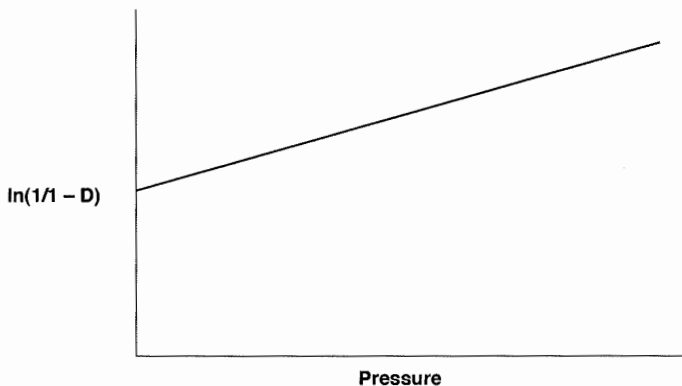
A large number of equations have been proposed to describe the relationship between pressure and volume reduction during the compaction process. Many of these have an empirical basis and may relate to a particular material or range of pressures, while others attempt to define the complete process of densification. The equation that has been most widely used to describe the compaction of pharmaceutical powders is the Heckel equation (Heckel 1961). This equation, originally used to describe the densification of ceramics, is essentially a curve-fitting equation that provides reasonable correlation with the observed facts over a wide range of pressures.

The equation is based on the premise that compaction is a first-order process where the rate at which pores within a powder can be eliminated is proportional to the number of pores present. As the compaction process continues, the number of pores will continue to drop, and consequently, the rate of volume reduction per unit increase in pressure will drop. This was expressed mathematically as :

$$\ln\left(\frac{1}{1-D_r}\right) = kP + A \quad (6)$$

In a system where there was no rearrangement of particles, and compaction was achieved solely by plastic deformation, a plot of $\ln(1/1 - D_r)$ versus P would yield a straight line (Figure 11.8).

Figure 11.8 Theoretical Heckel plot.



Pharmaceutical powders do not produce perfect straight lines, and the type of deviation provides information about the compaction behaviour of the material. A typical Heckel plot for a pharmaceutical powder is illustrated in Figure 11.9. A straight-line portion is obtained over a certain pressure range with a negative deviation at low pressures and a positive deviation at high pressures.

The curved portion at low pressures is due to particle rearrangement and possibly fragmentation, the deviation from a straight line (A–B) is a measure of its extent (Figure 11.9).

The gradient of the straight-line portion of the plot is related to the reciprocal of the yield pressure of the material, and as such is a measure of the plasticity of the material. While the absolute values obtained for the yield pressure will be dependent on the equipment and test conditions employed, the relative values obtained under given test conditions will provide information about the compaction properties of materials. Table 11.4 displays the values for yield pressure obtained for excipients, known to have differing compaction properties, tested using a compaction simulator.

The densification behaviour of powders has been categorised into types A, B and C (York and Pilpel 1973). Type A (plastic) exhibits parallel but distinct graphs for different size fractions, type B (fragmenting) exhibits particulate fragmentation at low pressures with graphs becoming coincident at higher pressures; and type C (extremely plastic) is characterised by a small initial curved section, a low value of mean yield pressure and a rapid approach to zero porosity at low pressure.

Figure 11.9 Heckel plots of pharmaceutical powders.

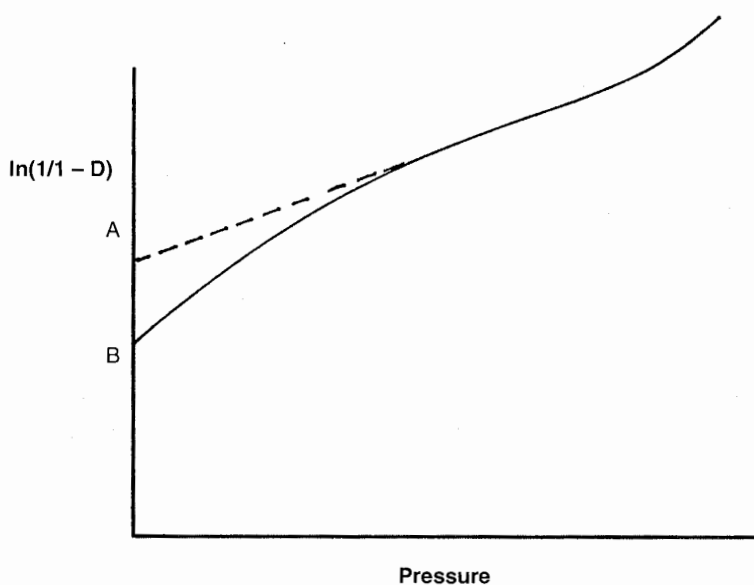


Table 11.4
Yield pressure for excipients.

Excipient	Yield Pressure (Mpa)	A-B	Deformation Mechanism
Microcrystalline cellulose	54	0.15	Plastic/deforming
Anhydrous lactose	174	0.5	
Calcium phosphate dihydrate	396	0.95	Brittle/fragmenting
Starch 1500	53	0.1	

The effect of compression speed on the yield pressure of a material has been suggested as a method of determining the time-dependent nature of materials compression properties (Roberts and Rowe 1985). Heckel plots are produced at two punch velocities, 0.03 and 300 mm/sec, and the yield pressures determined. The strain rate sensitivity (SRS) is calculated as:

$$\text{SRS} = \frac{P_{y2} - P_{y1}}{P_{y1}} \times 100 \quad (7)$$

where P_{y1} = the yield pressure at 0.03 mm/ms and P_{y2} = the yield pressure at 300 mm/ms. Materials that exhibit plastic deformation have larger SRS than values fragmenting materials.

Elasticity

While Heckel plots are able to distinguish between plastic and fragmenting mechanisms, they do not readily distinguish between plastic and elastic deformation. The data presented in Table 11.4 would suggest that microcrystalline cellulose and starch 1500 have very similar properties, yet the elastic nature of starch and its derivative products is well documented in the literature. Additional methods are, therefore, required to measure elasticity.

Elasticity can be determined either by monitoring the elastic energy during the decompression phase of a compact within the die or by comparing the dimensions of the ejected compact with the dimensions of the compact within the die at peak compaction pressure.

The elastic energy is determined by plotting a force-displacement curve. If punch force is plotted against punch tip displacement or punch tip separation, a curve with a progressively increasing slope is obtained, reaching a maximum force at the point of minimum separation. As the punch begins to retract, the compact will expand due to elastic recovery and will remain in contact with the punch. This recovery is apparent from the force-displacement curve. If the material being compressed was truly elastic, the curve for the decompression phase would overlay the compression phase. For a truly plastic material the force would fall to zero immediately the punch began to retract. Pharmaceutical materials tend to show a combination of elastic and plastic deformation.

Integrating the force-displacement curves gives a measure of the energy involved in the compaction process (Figure 11.10), it being possible to calculate both the elastic energy and the net energy of compaction.

An alternative measure of elasticity is the percentage elastic recovery ($ER_{\%}$) (Armstrong and Haines-Nutt 1972):

$$ER_{\%} = \frac{H - H_c}{H_c} \times 100 \quad (8)$$

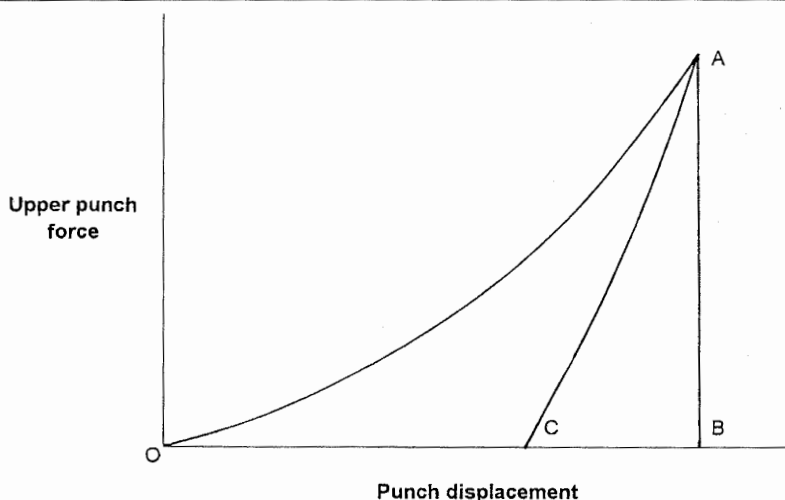
where H = thickness of compact after ejection and recovery and H_c = minimum thickness under load.

This measure differs from the elastic energy in that it includes the viscous contribution to elastic recovery as well as the purely elastic behaviour during the unloading period of compression. Whichever method is used to calculate the elasticity, it should be borne in mind that the punches will also display a degree of elasticity, and this must be allowed for when calculating punch separations at pressure.

Indentation Hardness

An alternative method of determining the plasticity and elasticity of a material is indentation hardness testing. The principle of indentation hardness testing is that a hard indenter of specified geometry, either a sphere or square-based pyramid, is pressed onto the surface of the test

Figure 11.10 Force displacement curve for a pharmaceutical powder. The total work of compaction is represented by the area defined by OAB; elasticwork by CAB. The net work of compaction is the area defined by OAC.



material with a measured load and the size of the indentation produced measured. The hardness of a material is the load divided by the area of the indentation, to give a measure of the contact pressure.

There are two types of hardness test: *static tests* that involve the formation of a permanent indentation on the surface of the test material and *dynamic tests* in which a pendulum is allowed to strike the test material from a known distance. Vickers and Brinell tests, two examples of static methods, are the most commonly used methods for determining the hardness of pharmaceutical materials. In the Brinell test, a steel ball of diameter D is pressed on to the surface of the material, and a load F is applied for 30 sec and then removed. The diameter d_I of the indentation produced is measured, and the Brinell Hardness Number (BHN) calculated by

$$\text{BHN} = \frac{2F}{\pi D_I \left(D_I - \sqrt{D_I^2 - d_I^2} \right)} \quad (9)$$

The Vickers Hardness test uses a square-based diamond pyramid as the indenter. The Vickers Hardness, H_v , is calculated by

$$H_v = \frac{2F \sin 68^\circ}{d^2} \quad (10)$$

where d is the length of the diagonals of the square impression.

Traditionally, it has been necessary to perform indentation testing on compacts due to the size of the indenters. The surface of compacts are not homogeneous, and this introduced variability. Recently, nanoindentation testers have been developed which are capable of performing indentation tests on single crystals. Such testers offer significant potential for characterising the mechanical properties of materials at an early stage of development.

Pressure/Strength Relationships

The strength of tablets has traditionally been determined in terms of the force required to fracture a specimen across its diameter, the *diametral compression test*. The fracture load obtained is usually reported as a hardness value, an unfortunate use of a term that has a specific meaning in materials science, associated with indentation. The use of the fracture load does not allow for compacts of different shapes, diameters or thicknesses to be directly compared. For flat-faced circular tablets, a complete analytical solution exists for the stress state induced during the test (Barcellos and Carneiro 1953), allowing the tensile strength to be determined from the fracture load:

$$\sigma_x = \frac{2P}{\pi Dt} \quad (11)$$

where P is the fracture load, D the tablet diameter and t the tablet thickness. The solution for tensile stresses can only be used for tablets that fail in tension, characterised by failure along the loaded diameter.

The stresses developed in convex tablets tested undergoing the diametral compression test have been examined by Pitt et al. (1989), who proposed the following equation for the calculation of the tensile strength:

$$\sigma_f = \frac{10P}{\pi D^2} \times \left(\frac{2.84t}{D} - \frac{0.126t}{C_L} + \frac{3.15C_L}{D} + 0.01 \right) \quad (12)$$

where P is the fracture load of the convex tablet, D the diameter, C_L the cylinder length and t the overall thickness of the tablet.

Typical plots of tensile strength versus compaction pressure are illustrated in Figure 11.11. Initially, most materials will demonstrate an increase in tensile strength proportional to the compaction pressure applied. As the compaction pressure increases, the tablet approaches zero porosity, and large increases in pressure are required to achieve small volume reductions, and consequently, small increases in bonding. Some materials will attain a maximum strength, and subsequent increases in pressure will produce weaker tablets.

Other materials will also display an initial increase in strength proportional to the applied pressure, but the strength reaches a maximum before falling off sharply. This is due to capping or lamination, that results in tablets failing in a characteristic manner (Figure 11.12). Capping is the partial or complete removal of the crown of a tablet from the main body, while lamination is the separation of a tablet into two or more distinct layers. The problem may be apparent on ejection of the tablet or may manifest itself when the tablet is subjected to further stress, e.g., mechanical strength testing or film coating.

Capping

Capping and lamination can affect both individual substances and formulations and constitute one of the most common problems facing the formulator. It occurs when a material is unable to relieve stresses present within a compact following compression by plastic deformation (Hiestand et al. 1984). When a material is compressed within a die by means of two opposing

Figure 11.11 Compaction pressure/tensile strength profile. Typical plot for a pharmaceutical material.

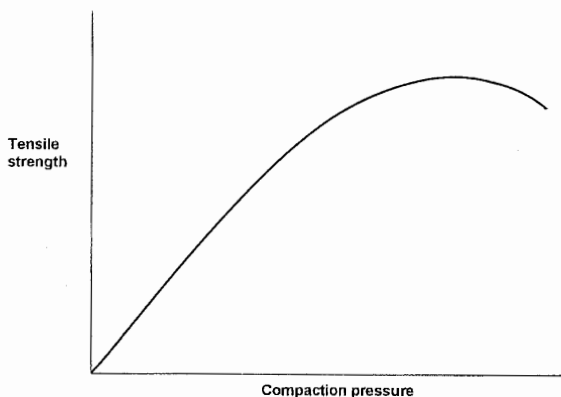
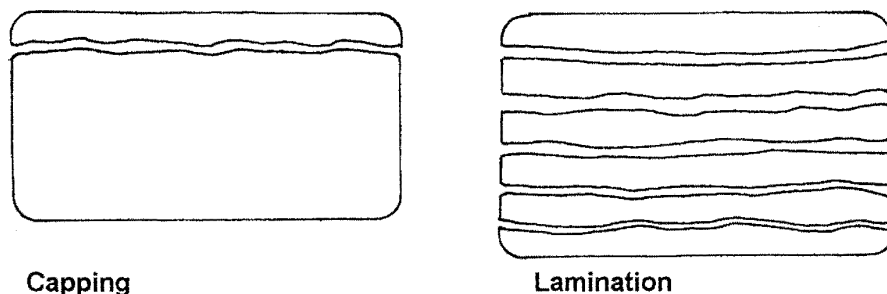
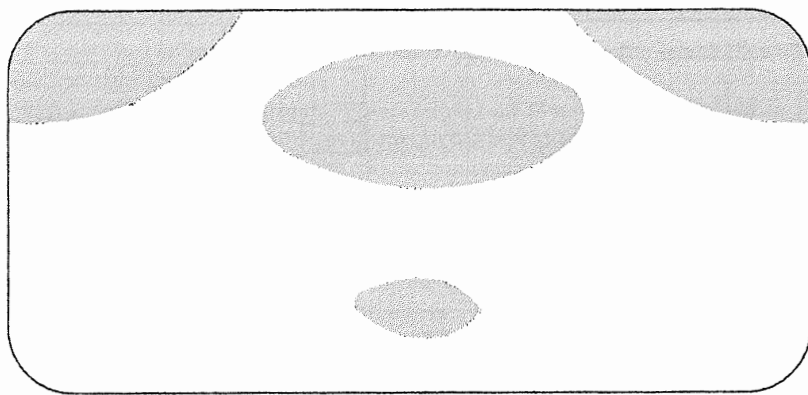


Figure 11.12 Tablet flaws: capping and lamination.

punches, the axial load that is applied through the upper punch is transmitted to the die as a shearing force. In addition, force is transmitted radially to the die wall. The nature of this radial force is determined by the elastic or plastic behaviour of the compact. When an axial force is applied to a column of powder in a die, the pressures developed within the powder vary with depth. This phenomenon is attributed to the development of friction between the powder and the die wall and leads to density variations within the final compact. The nature of such variations has been the subject of a number of investigations (Train 1957; Kamm et al. 1949; Charlton and Newton 1985). These studies have been performed on a number of materials that have been compressed in dies with one moving and one stationary flat-faced punch. The results obtained in each study indicated a similar density distribution within a compact, high-density region being present on the perimeter of the compact adjacent to the moving punch and low density regions near the stationary punch. In addition, there was a second high density region remote from the moving punch (Figure 11.13). An explanation for the density distribution has been proposed that is based on the development of high-density wedges of material at the die wall adjacent to the moving punch. Figure 11.14 represents the forces developed in the compact. At equilibrium, the axial force is supported by the punch in direction *a* and by the powder in direction *b*. The radial component is supported by the die wall in direction *c* and by the powder bed in direction *d*. The resultant force acting on the mass is denoted by *k*. The pressure front can be considered as a conical surface with its focal point *B*. The region around point *B* will be exposed to the greatest pressure and will have a greater density than the surrounding areas. The wedge-shaped areas bounded by the dotted lines adjacent to the moving punch will be highly densified due to the high shearing forces that they are exposed to. The central area, *A*, will be subject to negligible shearing forces and will be protected from normal axial pressures by the vaulting effect of the high density wedges resulting in an area of low density. The area *C*, adjacent to the stationary punch, will undergo no movement relative to the die wall, and thus will not be subject to shearing forces. Density in this region will be low, as consolidation will depend solely on transmitted axial forces.

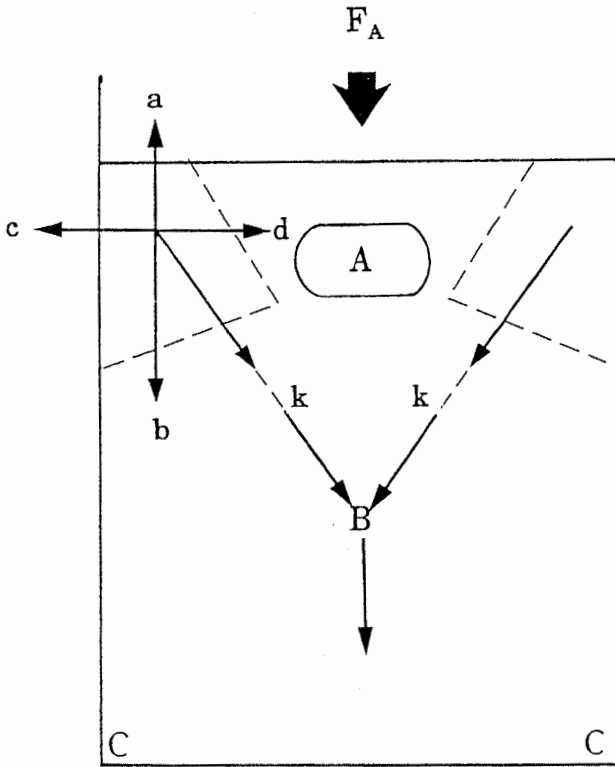
On removal of the upper punch, there will be a degree of axial elastic recovery resulting in expansion of the compact within the die. Following ejection, expansion may also occur in the radial direction. This elastic recovery is considered to be the most likely cause of capping. Train (1956) attributed capping to the strain imposed by elastic recovery of the areas of high

Figure 11.13 Regions of high density within a compact.

density within the compact on ejection (Figure 11.15). The elastic recovery of the dense peripheral ring would be larger than that of the adjacent, less dense, part of the tablet. The differential stress in this region is exacerbated by both axial and radial relaxation of that part of the tablet extruded from the die during the early stages of ejection.

Attempts have been made to predict the capping tendencies of materials. Malamataris et al. (1984) examined the plastoelasticity of mixtures of paracetamol and microcrystalline cellulose and showed that the tensile strengths of compacts were inversely proportional to the ratios of the samples' elastic recovery:plastic compression (as defined in Figure 11.10). Lamination and capping occurred when this ratio exceeded 9. Nystrom et al. (1978) measured the tensile strength of compacts in both the radial and axial directions and found that the values were not equal, the axial strength often decreasing at high compaction pressures. It was proposed that the ratio of axial to radial tensile strength should be close to unity for a good formulation. Krycer et al. (1982) examined the capping tendencies of three grades of paracetamol and proposed a capping index defined as the slope of the percentage elastic recovery versus residual die wall pressure (the pressure exerted on a die by a compact after removal of the upper punch). The higher the values of the capping index, the greater the tendency for capping. The residual die wall pressure relates to the irreversible deformation undergone during compaction. Low values for residual die wall pressure indicate that the compact had recovered axially and contracted radially, which would induce strain within the compact.

The methods of predicting capping discussed so far have been measures of the degree of elastic recovery occurring in the compact. For capping to occur, the stresses produced by the elastic recovery during decompression must be sufficient to disrupt the bonds that are formed during compression. Hiestand and Smith (1984) proposed a measure of the ability of a material to relieve localised stresses, called the brittle fracture index (BFI). This test involves comparing the tensile strength value obtained using the diametral compression test of a compact that contains a central, axial hole with one that does not. Under the conditions of the test, the hole acts as a stress concentrator; elasticity theory predicts that the stress concentration factor

Figure 11.14 Development of the pressure pattern within a compact (after Train 1957).

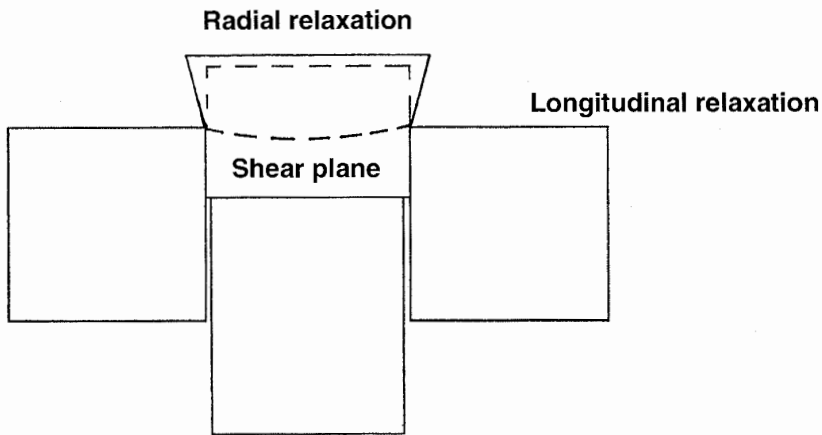
is approximately 3.2 for a hole in an isotropic solid. However, for most pharmaceutical materials, the ratio of tensile strengths obtained is less than 3 due to the relief of the highly localised stresses by plastic deformation. The BFI is defined as:

$$\text{BFI} = \frac{(\sigma_s - \sigma_0)}{2\sigma_0} \quad (13)$$

where σ_s is the tensile strength of the compact without the hole and σ_0 is the tensile strength of the tablet with the hole. A BFI of 1.0 would correspond to a purely brittle material; a value of zero would indicate that the stresses at the hole had been completely relieved by plastic deformation.

Hiestand and Smith (1984) proposed that a material with a high BFI would be less able to relieve the stresses occurring during decompression and ejection and would therefore be more susceptible to capping and lamination. Experiments showed that problems were likely

Figure 11.15 Elastic recovery of compact during ejection from die leading to capping (after Train 1956).



to occur with materials having a BFI of 0.8 or more. The BFI will be dependent on the relative density of a material; at low densities, pores may act as stress concentrators in the same way as the central hole, so the measurements should be made at fixed, high relative densities. Roberts and Rowe (1986) determined the BFI of compacts produced at a range of relative densities using a range of compaction speeds. Magnesium carbonate, a brittle material, displayed increasing BFI values with increases in compaction speed and relative density, while microcrystalline cellulose showed little change.

Summary

It is clear from the preceding discussions that there is not one single technique that can be used to fully characterise the compaction properties of a powder. A number of tests have been widely applied to pharmaceutical materials, but used in isolation, they will not provide the formulator with all the data required to fully understand their behaviour when tableted. Two sets of workers have tried to address this problem by suggesting a range of tests that, used in combination, will give a more complete picture of the materials properties.

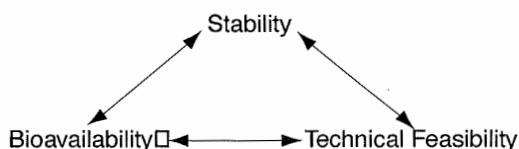
Hiestand and Smith (1984) proposed three indices referred to as Tableting Indices. The three indices are a strain index, bonding index and the BFI, which was described in the section on Capping. The strain index is a measure of the strain present in a material following compaction and is a measure of elastic recovery calculated by a dynamic indentation hardness test. The bonding index is a measure of the material's ability to deform plastically and form bonds and is the ratio of a compact's tensile strength and indentation hardness.

Roberts and Rowe (1987) have proposed a material classification based on a knowledge of Young's modulus of elasticity, yield stress, hardness and SRS.

Rational formulation relies on a thorough understanding of the physicochemical properties of the material. Ideally the mechanical properties should be determined at an early stage in the development process. It must, however, be borne in mind that the properties are sample dependent, and changes in particle size, morphology and so on during development will affect the compaction properties.

SOLID DOSAGE FORMS

When formulating any pharmaceutical dosage form, it is important to remember that there is an equilibrium between the bioavailability of the product, its chemical and physical stability and the technical feasibility of producing it.



Any changes made to a formulation in an attempt to optimise one of these properties is likely to have an effect on the other two parameters that must be considered. This is especially true of immediate-release solid dosage forms. Many of the properties required to optimise the bioavailability through rapid disintegration and dissolution of the active constituent, e.g., small particle size, must be balanced with the manufacturability, where the fluidity and compactibility of a powder will often be enhanced by an increase in particle size.

Tablets and hard gelatin capsules form the vast majority of solid dosage forms on the market. While the actual processes involved of filling capsules and compressing tablets differ, the preparation of the powders to be processed are, in many cases, very similar.

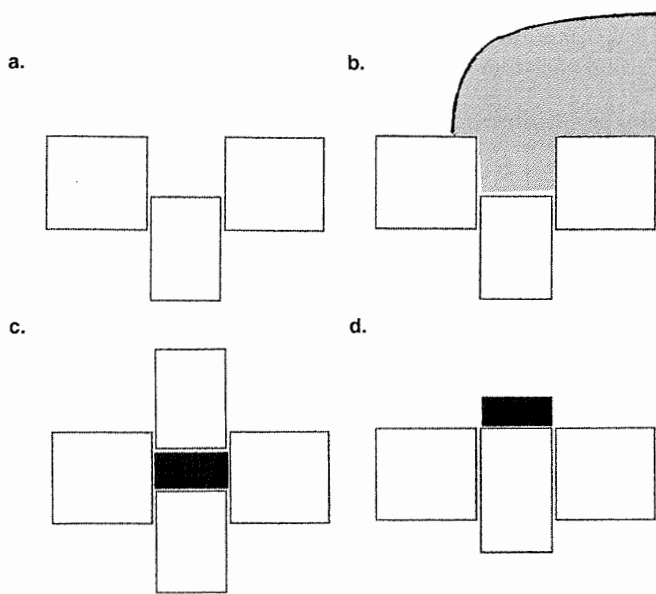
TABLETS

Tablet Machines

Tablets are produced using tablet presses. While these presses vary in their output, from approximately 3,000 tablets per hour to more than 1 million per hour for the fastest machines, the principle of manufacture remains the same. Powder is filled to a specified depth in a die and compressed between two punches. The compression force is ended by removal of the upper punch, and the lower punch then moves upward in the die to eject the tablet. Presses can be divided into two types, single punch (or eccentric) presses and rotary presses.

Single Punch Presses

Single punch presses are sometimes referred to as eccentric presses because the movement of the punches is controlled by an eccentric cam. The tableting cycle of a single punch machine is represented schematically in Figure 11.16. The powder hopper is attached to a feed shoe which oscillates horizontally.

Figure 11.16 Schematic representation of a single punch tablet machine.

- a. The upper punch is raised out of the die, and the lower punch drops to a set position.
- b. The feed shoe oscillates above the die, filling it with powder.
- c. The upper punch enters the die and compresses the powder.
- d. The upper punch is removed, and the lower punch rises in the die to eject the tablet.

The compression cycle starts with die filling. The lower punch descends in the die. The depth of the descent can be controlled, and this determines the tablet weight. The feed shoe then passes over the die a number of times allowing the die to be filled with powder. As the die shoe moves away, it removes all excess powder away from the die table leaving the die filled to an even level.

The upper punch then descends into the die, compressing the powder. The depth to which the punch descends into the die is adjustable, and this controls the compaction pressure applied. The lower punch remains stationary during the compression phase.

As the upper punch moves upward at the end of the compression phase, the lower punch will rise in the die until it is level with the die table. The feed shoe will then begin its oscillatory phase and knocks the tablet off the lower punch and down a collection chute. The lower punch then descends to its filling position as a second cycle commences.

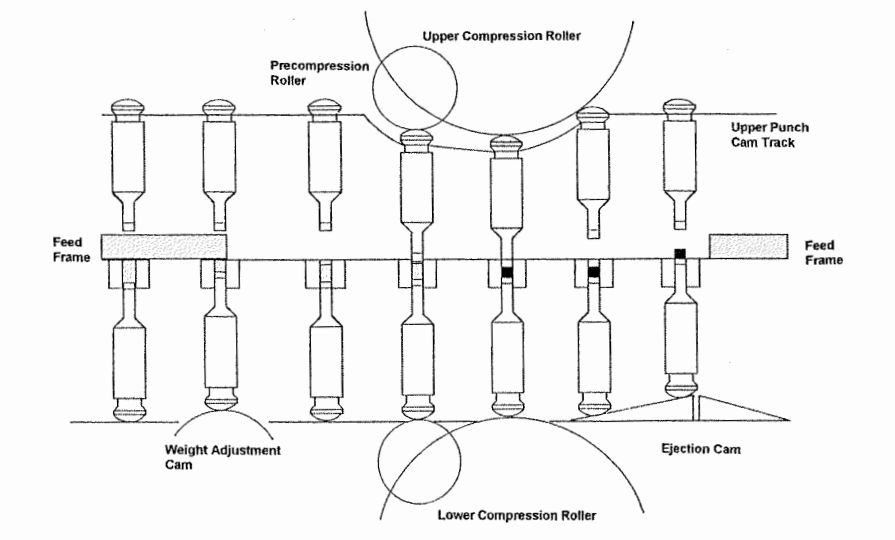
Single punch presses are rarely seen in production environments due to their relatively slow production rates, although there are still a number of old products that can only be successfully produced on this type of machine. They are still used in development laboratories because they require only relatively small amounts of material to produce tablets compared to most rotary machines.

Rotary Tablet Machines

Commercial manufacture of tablets is performed almost exclusively on rotary tablet machines due to their higher output. On a rotary machine, the punch and dies are positioned on a rotating turret, and output will depend on the number of stations positioned around the turret and the speed of rotation. Machines are available with anything from 4 stations for a development machine to 79 stations for the largest production machines. All such machines operate using virtually identical principles that are represented in Figure 11.17.

The powder hopper is positioned above a feed frame, a frame that retains a powder bed above the dies when the lower punch is in the filling position. As the lower punches pass below the feed frame, they descend within the die to their lowest possible position so the whole die cavity can be filled with powder. The powder is filled into the dies by the suction effect caused by their descent and gravity from the feed frame above. To optimise filling, the feed frame is designed so that the powder in contact with the die table and following the rotary action of the table is directed in a manner that makes it pass to and fro across the dies. Some machines

Figure 11.17 Schematic representation of a rotary tablet machine.



also have mechanical paddles in the feed frame. As the lower punches approach the end of the feed frame, they pass over a weight control cam, this causes the punch to rise, ejecting some of the powder which is scraped off by the edge of the feed frame. Adjusting the height of the cam controls the amount of material remaining in the die as the punch moves toward the compression stage.

Compression takes place when the upper and lower punches pass between compression rollers. During compression, the upper and lower punches move together, in contrast to the single punch machine, where only the upper punch moves. The compression force is controlled by moving the lower compression roller up or down, thus adjusting the distance between the punches at the point of maximum compaction. Some machines are fitted with two sets of rollers, a small roller being positioned between the feed frame, and the main compression roller allowing a small degree of compression to take place. This is termed *pre-compression*, and was introduced to minimise capping and lamination by removing air from the powder bed and effectively increasing the dwell time of the compression phase.

Following compression, the upper punches are removed by the upper punch cam track, and the lower punches pass over an ejection cam, a gentle ramp that moves the lower punches vertically within the die until the tablet is fully ejected. The tablets are removed from the punch tip by a scraper blade positioned on the edge of the feed frame, and the punch then descends to allow die filling to occur for the next cycle.

When developing formulations, it is usual for the early batches to be manufactured on either single punch machines or small rotary machines, due to the batch sizes being produced and the limited availability of new drug substances. It should be borne in mind that the formulations that are being developed may ultimately be required to run on larger rotary machines, and there are great differences in the rate of compression between the machines generally found in formulation laboratories and those found in production. These differences are summarised in Table 11.5.

The differences in punch speed at initial contact and dwell times, the period at which the compact is held at maximum compression, are likely to affect the nature of any tablets which have any viscoelastic components. Compaction simulators that are able to reproduce the punch speeds of production machines, yet only require small quantities of powder for testing, can have a valuable role to play in formulation development.

Tablet Formulation

A tablet formulation should possess the following properties to optimise the technical feasibility, stability and bioavailability of the formulation.

- Compatibility of drug substance with excipients
- Flowability
- Compactibility
- Lubricity
- Appearance
- Disintegration
- Dissolution

Table 11.5
Speed-related data for a number of commonly used tablet presses
operating at maximum output (adapted from Armstrong 1989).

Tablet Press	Production Rate per Die (tablets/min)	Time for Punch to Descend Last 5 mm (msec)	Punch Speed at First Contact with Powder (mm/sec)	Dwell Time (msec)
Manesty				
F3 (Single Punch)	85	68.6	139	0
B3B	44	61.4	163	10.84
Express	100	26.7	416	3.94
Unipress	121	19.1	485	3.16
Novapress	100	10.0	720	2.14
Kilian				
Tx	105	19.0	494	2.96
F1000	55	36.4	232	6.60
F1000	75	26.6	317	4.84
F2000	75	23.1	402	3.68
F2000	100	17.3	526	2.76
Korsch				
300	80	21.7	419	3.44
300	100	17.3	526	2.76

Compatibility

Compatibility studies have been discussed in detail in Chapter 6. The solid-state compatibility is of particular importance in tablets, due to the compaction process increasing the contact area between particles, and hence the potential for reactivity.

Flowability

The importance of powder flow was emphasised in the section on Powder Flow. The formulation should have sufficient flowability to ensure that the appropriate quantity of powder flows into the dies of the tablet machine on a consistent basis. While the tests described for powder flow are useful development tools, the ultimate test of a formulation is the uniformity of weight of tablets manufactured on a production tablet machine.

There is bound to be some variability in tablet weight during manufacture due to variation in the particle size of the material being compacted, flow property variation and machine parameters (e.g., small differences in the lengths of the lower punches). To allow for such variability, Pharmacopoeias set tolerances to ensure adequate control without providing a specification that is impossible to achieve in production. The European Pharmacopoeia (EP) test

is to weigh 20 individual tablets and calculate the mean. The individual tablet weights are then compared to the mean. The sample is acceptable if no more than two tablets are outside the stated percentage limit and no tablet is outside twice the stated limit (Table 11.6). The pharmacopoeial limits are generous, and typically much more stringent limits will be applied as in-process controls. The in-process controls will also apply strict limits for the value of the mean tablet weight.

Uniformity of weight does not guarantee that there is uniformity of active ingredient throughout a batch of tablets. If there is segregation of the active ingredient occurring, the weights may remain uniform while the potency varies. For this reason, the U.S. Pharmacopeia (USP) only allows a uniformity of weight test for tablets containing 50 mg or more of an active ingredient comprising 50 percent or more, by weight, of the tablet. In all other instances, a content uniformity test must be performed.

Uniformity of weight is also important in achieving consistency of tablet strength, as there is a relationship between the quantity of powder in the die and the compaction pressure required to compress it to a given thickness, which is what the tablet machine is effectively doing. If the quantity of powder in the die is reduced to a lower compaction, pressure will be applied producing a weaker tablet. Variation in tablet strength may in turn lead to variability in the disintegration and dissolution properties of the product.

With low dose drugs, it may be possible to influence the flow properties by combining the drug substance with excipients possessing good flow properties. Where a formulation is prepared by simply dry mixing the drug with excipients prior to compaction, the process is referred to as direct compression. With high dose drugs, the quantity of such excipients that would be needed to achieve suitable flow and compaction properties may result in the final weight of the dosage form being unrealistically high. In such cases, the usual formulation approach is to granulate, a process that imparts two primary requisites to formulations: compactibility and flowability. Granulation is a process of size enlargement, whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified. The direct compression and granulation processes and their relative merits are discussed in greater detail in the section "Processing of Formulations".

The flow properties of a powder can be enhanced by the inclusion of a glidant. These are added to overcome powder cohesiveness by interposing between particles to reduce surface rugosity, thus preventing interlocking of particles and lowering the interparticulate friction. Commonly used glidants are listed in Table 11.7.

Table 11.6
European Pharmacopoeia uniformity of weight limits.

Average Tablet Weight (mg)	Percentage Deviation
80 mg or less	10
More than 80 mg and less than 250 mg	7.5
250 mg or more	5

Table 11.7
Commonly used glidants.

Glidant	Typical Percentage
Talc	1–5
Fumed silicon dioxide	0.1–0.5
Aerosil	
Cab-O-Sil	
Syloid	
Starch	1–10
Calcium silicate	0.5–2
Magnesium carbonate (heavy)	1–3
Magnesium oxide (heavy)	1–3
Magnesium lauryl sulphate	0.2–2
Sodium lauryl sulphate	0.2–2

Talc is traditionally one of the most commonly used glidants, having the additional benefit of being an excellent antiadherent. The level of talc that can be added to a formulation is restricted by its hydrophobic nature, too high levels resulting in decreased wetting of the tablet and a subsequent reduction in the rate of dissolution.

The *fumed silicon dioxides* are perhaps the most effective glidants. These are materials with very small (10 nm) spherical particles that may achieve their glidant properties by rolling over each other under shear stress. They are available in a number of grades with a range of hydrophobic and hydrophilic forms.

Starch has been used as a glidant, though relatively large amounts are required. The use of large amounts of starch has also aided the disintegration properties.

Compactibility

The aim of the formulator is to design a formulation that will reliably compact to form a strong tablet. The production manager wants a formulation that achieves the appropriate strength at a low compaction pressure, to reduce wear and tear on the tablet machine and increase the life of the punches.

The compaction properties of a formulation will largely be governed by its major components. For a high dose drug, the active ingredient will strongly influence the compaction, while for low dose drugs, it will be necessary for the tablet to be bulked out with an inactive material termed a diluent. High dose formulations may also use a diluent to overcome compaction problems experienced with an active substance. The selection of the diluent will depend to an extent on the type of processing to be used. A direct compression formulation will require a diluent with good flow and compaction properties. While a granulated formulation can be more forgiving, some degree of compactibility is desirable.

There are a number of general rules for selecting a diluent. The compaction properties of the active ingredient should be considered. If the material is extremely plastic, it is appropriate to add a diluent that compacts by brittle fracture; similarly, a brittle drug substance should be combined with a plastic filler. The solubility of the drug substance should also be considered. A soluble drug is normally formulated with an insoluble filler to optimise the disintegration process.

Apart from their flow and compaction properties, all diluents, and indeed other tablet excipients, should have the following properties:

- They should be inert and physically and chemically compatible with the active substance and the other excipients being used in the formulation.
- They should be physiologically inert.
- They should not have an unacceptable microbiological burden.
- They should not have a deleterious effect on the bioavailability.
- They should have regulatory acceptability in all countries where the product is to be marketed.

There will also be commercial factors in the selection of the diluent. There are hundreds of different brands and grades of diluents available, but it would be unrealistic for the formulator to expect to have a totally free choice. Most manufacturing companies wish to limit the inventory that they carry and will try to rationalise the excipients used in the factory. This inventory will have been selected on the basis of cost, availability and performance and will provide the formulator with a starting point.

Table 11.8 lists the more commonly used diluents. These have been listed in terms of their chemical nature. For each of the substances listed, there will be several suppliers offering branded goods that may or may not be equivalent. Most products will be available with a range of particle sizes.

As can be seen from the table, the excipients all have pharmacopoeial monographs, but it is important to understand that compliance with a monograph does not indicate equivalence between different grades or suppliers. The monographs confirm the chemical identity and purity of the excipients but do not measure the performance of the materials as diluents. To establish the equivalency of excipients obtained from different sources, it is necessary to perform some kind of functionality testing. The *Handbook of Pharmaceutical Excipients*, a joint publication between the Pharmaceutical Press and the American Pharmaceutical Association, contains some details of functional tests carried out on a wide range of excipients, but the onus on establishing equivalency of excipients still remains with the user.

Lubricity

The section on flowability discussed the role of glidants in tablet formulation. Glidants are one of three interrelated types of lubricant employed in solid dosage form manufacture. The two other classes of lubricant are antiadherent excipients, which reduce the friction between the tablet punch faces and tablet punches, and die-wall lubricant excipients, which reduce the friction between the tablet surface and the die wall during and after compaction to enable easy ejection of the tablet.

When two contacting solids are displaced relative to each other and parallel to the plane of contact, the resistance to the movement is termed friction. Contacting surfaces initially

Table 11.8
Common tablet diluents.

Diluent	Pharmacopoeia	Comments
Lactose	USP, Ph. Eur., JP	Available as anhydrous and monohydrate. Anhydrous material used for direct compression due to superior compressibility.
Microcrystalline cellulose	USP, Ph. Eur., JP	Originally a direct compression excipient, now often included in granulations due to its excellent compressibility.
Dextrose, glucose	USP, Ph. Eur., JP	Direct compression diluent, often used in chewable tablets.
Sucrose	USP, Ph. Eur., JP	Was widely used as a sweetener/filler in effervescent tablets and chewable tablets. Less popular nowadays due to cariogenicity.
Starch and derivatives	USP, Ph. Eur., JP	Versatile material, can be used as diluent binder and disintegrant.
Calcium carbonate	USP, Ph. Eur., JP	Brittle material
Dicalcium phosphate	USP, Ph. Eur., JP	Excellent flow properties. Brittle material.
Magnesium carbonate	USP, Ph. Eur., JP	Direct compression diluent.

touch at points on the asperities of the two surfaces. If a force is applied, these asperities will deform to form a contact area. For relative movement of the materials to occur parallel to the contact area, the materials must be sheared. The higher the shear strength of the materials in contact, the greater the force that will be required to produce movement. Die-wall lubricants work by reducing the shear force necessary to promote movement.

The level of a lubricant required in a tablet is formulation dependent and can be optimised using an instrumented tablet machine. On a single punch machine, strain gauges or load cells on the lower punch can directly measure the force required to eject the tablet. An alternative method of measuring lubrication is to measure the ratio of the maximum forces on the upper and lower punches during the compaction cycle (Hölzer and Sjögren 1978). On a single punch machine, the lower punch remains stationary during the compaction phase, and the compaction pressure is exerted by the movement of the upper punch. If there were no resistance to the movement of particles in the die, the force transmitted through the powder bed to the lower punch would be the same as the force applied by the upper punch. In practise, the interparticle friction and friction between the particles and the die wall result in a lower force being transmitted to the lower punch. The ratio of the upper to lower punch forces, termed the *R*-value, has been used as a measure of the lubricant efficacy. The *R*-value cannot be used on a rotary machine because the compaction pressure is applied from both the upper and lower punches simultaneously. The ejection force can be measured either by instrumenting the punch tips or by positioning load cells or strain gauges below the ejection cam. If an instrumented machine is not available, the signs of inadequate lubricity are the presence of scoring around the tablet circumference and screeching during ejection. While these problems can be overcome by increasing the level of lubricant added, the aim should be to use the minimum level of lubricant required to produce acceptable product, for reasons discussed later.

Die-wall lubricants can be divided into two classes, fluid and boundary lubricants. *Fluid lubricants* work by separating moving surfaces completely with a layer of lubricant. These are typically mineral oils or vegetable oils, and they may be either added to the mix or applied directly to the die wall by means of wicked punches. Tablets containing oily lubricants may have a mottled appearance due to uneven distribution. When added to the mix, they have an adverse effect on powder flow due to their tacky nature and have been reported to reduce tablet strength (Asker et al. 1973). Low melting point lipophilic solids can also act as fluid lubricants because the heat generated at the die wall is sufficient to cause them to melt, forming a fluid layer which solidifies on ejection. Fluid lubricants include stearic acid, mineral oils, hydrogenated vegetable oils, glyceryl behenate, paraffins and waxes. Low melting point lubricants should be used with caution in tablets that are to be film coated. Lubricants can melt on the tablet surface during the film coating process, resulting in tablets with a pitted appearance (Rowe and Forse, 1983). Their use tends to be restricted to applications where a suitable boundary lubricant cannot be identified.

Boundary lubricants work by forming a thin solid film at the interface of the die and the tablet. Metallic stearates are the most widely used boundary lubricants, and their activity has been attributed to adherence of polar molecular portions on their surface to the surfaces of one particle species and of non-polar surface components to the other species' surface. Such lubricants should have a low shear strength of their own and form interparticulate films that resist wear and reduce surface wear. A list of lubricants with typical ranges for their usage is given in Table 11.9.

Magnesium stearate is the most widely used lubricant; it forms dense, high melting point films between the powder and the die wall to reduce friction and has low shear strength between its own surfaces. Despite its popularity, which is a reflection of its excellent lubricant properties, the material is far from ideal and has had problems associated with product consistency, its effect on tablet strength and its hydrophobicity.

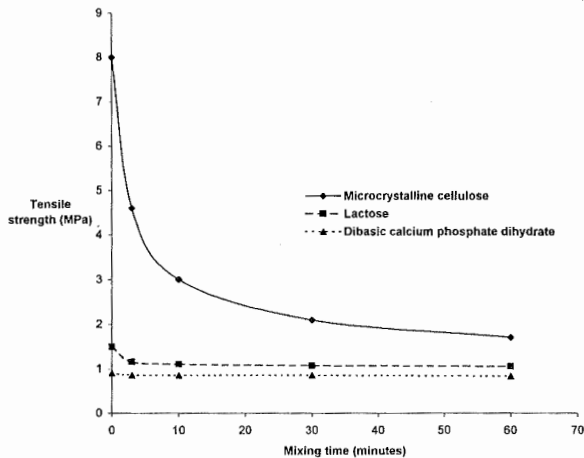
The magnesium stearate used in the pharmaceutical industry is not a pure substance but a mixture of magnesium salts of fatty acids though predominantly magnesium stearate and magnesium palmitate. The USP requires that the stearate content should account for not less than 40 percent of the fatty acid content of the material, and the stearate and palmitate combined should account for not less than 90 percent. Within this definition, there is clearly scope for a range of materials to be supplied as magnesium stearate. Furthermore, there is no pharmacopoeial particle size specification for the material. As the lubrication activity of the material is related to its surface area, substantial decreases in ejection force are noted when using sources of magnesium stearate with larger surface areas. For a given formulation, it is important that a single source of magnesium stearate is used for all batches. A new supplier should not be used until the effect on the compaction properties and dissolution rates have been assessed.

The lubricant activity of magnesium stearate is related to its readiness to form films on the die wall surface. When it is mixed in a tablet formulation, it will display the same film forming propensity on the surfaces of the drug and excipient particles, which can have two consequences: a reduction in the ability of the powder to form strong compacts and, due to its hydrophobicity, a deleterious effect on the dissolution rate of the tablets. Figure 11.18 illustrates the effect of mixing time on the mechanical strength of compacts produced using a range of excipients. While the strength decreases with increasing mixing time for all the materials tested, the effect is far more marked for materials that deform plastically. When plastic deforming materials are compressed, the film of magnesium stearate around the particles remains relatively intact, so the interparticulate bonds are primarily between

Table 11.9
Lubricants and their usage.

Lubricant	Level Required (%)	Comments
Boundary Lubricants		
Magnesium stearate	0.2-2.0	Hydrophobic, variable properties between suppliers.
Calcium stearate	0.5-4	Hydrophobic.
Sodium stearyl fumarate	0.5-2	Less hydrophobic than metallic stearates, partially soluble.
Polyethylene glycol 4000 and 6000	2-10	Soluble, poorer lubricant activity than fatty acid ester salts.
Sodium lauryl sulphate	1-3	Soluble, also acts as wetting agent.
Magnesium lauryl sulphate	1-3	Acts as wetting agent.
Sodium benzoate	2-5	Soluble.
Fluid Lubricants		
Light mineral oil	1-3	Hydrophobic, can be applied to either formulation or tooling.
Hydrogenated vegetable oils	1-5	Hydrophobic, used at higher concentrations as controlled release agents.
Stearic acid	0.25-2	Hydrophobic.
Glyceryl behenate	0.5%-4	Hydrophobic also used as controlled release agent.

Figure 11.18 Effect of magnesium stearate mixing time on the strength of compacts.



magnesium stearate particles which, by virtue of its lubricant properties, are inherently weak. Materials that compact by fragmentation are less sensitive to the lubricant because the fragmentation process produces a number of clean, uncontaminated surfaces that are able to form strong bonds.

The hydrophobic surfaces created by magnesium stearate have been shown to reduce the rate of dissolution and bioavailability of several tablet formulations. To minimise this effect, the manufacturing process should be designed to ensure that the lubricant is the last excipient to be added. When both lubricant and disintegrant are being added to a granulated formulation, the disintegrant should be blended with the granules prior to the addition of the lubricant to minimise the risk of forming a hydrophobic film around the disintegrant. The mixing time for the lubricant should be set as the minimum time required to produce the desired effect.

The third class of lubricant activity is the antiadherent. Some materials have adhesive properties and can adhere to the punch surfaces during compression. This will initially manifest itself as sticking, with a film forming on the surface of the tablets, leading to dull tablet surfaces. A more extreme version of sticking is picking, where solid particles from the tablet stick to the punch surface. This will often be evident in the intagliations on the tablet surface, resulting in poor definition of the surface markings.

Attempts have been made to assess picking tendencies using instrumented tablet machines. Load cells have been fitted to the edge of feed frames of rotary machines to monitor the force required to knock tablets off the lower punch following ejection. Shah et al. (1986) postulated that the magnitude of the residual force remaining on the lower punch of a single punch machine following removal of the upper punch was inversely related to the degree of adherence to the upper punch. In practise, sticking tends to be monitored during extended runs on tablet machines.

Most die-wall lubricants have antiadherent actions, and in many formulations, the addition of a specific antiadherent will not be required. Materials that can be added include talc, maize starch and microcrystalline cellulose.

Appearance

The appearance of a tablet is of great importance to the way that it is perceived by the patient. The macroscopic appearance of a tablet, its shape, size, colour and markings can all contribute to the patients' expectations of a medicine, while the microscopic appearance, such as surface roughness and colour homogeneity, are easily perceived as measures of quality. It is now the norm to be able to identify new products because of their unique appearance achieved by a combination of shape, size, colour and surface markings.

The size of a tablet is very often governed by the dose being administered. The compression weight of a high-dose drug will usually be determined by the level of filler required to impart the appropriate compactibility on the formulation, the aim being to produce the smallest possible tablet for ease of swallowing. For low-dose drugs, the quantity of filler added is determined by the minimum acceptable size for a tablet. The actual minimum acceptable size for a tablet will vary between pharmaceutical companies but is generally in the region of 6 or 7 mm diameter for a circular tablet, which would equate with a compression weight of 80 to 100 mg. Tablets below this range tend to be difficult for the patients to handle.

Early tablets were produced in cylindrical dies with flat-faced, flat bevel-edged or concave punches. While the majority of tablets are still circular, over the last 20 years, there has been an increasing shift away from circular to shaped tablets for new products. The tablet

identification section of the *Chemist and Druggist Directory* (2000) describes 274 non-circular tablet products that are on the market in Britain, while the *Physicians' Desk Reference* (PDR) (1998) contains illustrations of 502 non-circular tablets that are available in the United States. After round tablets, the most common presentation is the capsule-shaped tablet, sometimes referred to as a caplet. This shape is particularly popular for high dose products where the compression weight is necessarily high, as the elongated shape makes the tablet easier to swallow than round tablets of equal weight. A survey performed on the reaction of patients to the appearance of tablets has indicated that the tablet shape can influence patients' expectations of a medicine in terms of its potency, side-effects and suitability for a particular ailment (Anon. 1989). The studies found that tablets with highly angular appearances were universally disliked on the basis that they would be hard to swallow. Less predictable was the finding that other elements of tablet design, such as the number and depth of scorelines, the degree of rounding of corners and the hardness of the finish indicated by surface shine, appeared to play a role in determining how easy or hard to swallow a tablet might be. When designing a tablet shape, consideration should also be given to the processes following compression, such as coating and packaging. These processes depend on tablets being able to move relative to each other, and if the tablet shape allows tablets to form "structures" (e.g., due to straight sides), it may be problematic.

The colouring of tablets can be achieved either by incorporating a dye or pigment into the powder prior to compression or by applying a coloured coat to the tablet following compression. Coating methods, which are dealt with in the section "Tablet Coating", tend to provide a more uniform colour than inclusion of pigments in the compression mix but have the disadvantage of requiring an additional manufacturing process.

Colourants come in three forms: soluble dyes, insoluble pigments and lakes. Lakes are formed by adsorbing dyes onto the surface of an inert substrate, usually aluminium hydroxide. If the colourant is being added to a granulate, soluble dyes can be dissolved in the granulating fluid to ensure a uniform mix. When adding colourants as solids, the mixing process needs to be very efficient to achieve a uniform colour with no mottling. The usual method of inclusion is to form a premix with a portion of the powder mix and to mill this prior to incorporating the remaining ingredients. The problem can be reduced by the appropriate selection of colours, mottling being less evident with pastel shades. The insoluble pigments tend to be more light stable and less prone to fading than the soluble dyes.

The choice of colour is severely restricted by the number of regulatory acceptable dyes and pigments available to the formulator. This is particularly true when trying to achieve a globally acceptable formulation, due to the lack of international harmonisation of permitted colourants. Table 11.10 lists the commonly used pigments and dyes together with their international acceptability. It can be seen that for an international formulation the choice of colourants is restricted to the iron oxide pigments and indigo carmine, and as a result there are large numbers of tablets with varying shades of red, yellow, orange and brown being introduced onto the market.

The easiest way to give a tablet a unique identity is to mark the surface with a code or unique identifier. This can be achieved by applying a printed logo to the surface of the tablet or by compressing the powder with punches that are embossed with the code, producing tablets with intagliations. Printing is performed with ink jet printers applying approved inks to the surface of tablets. The advantage of printing is that it is possible to fit more information on to the surface than is possible with embossed punches, but it is an additional process and not all tablet surfaces are suitable for printing. The use of embossed punches does not increase the manufacturing time, but it does stress a formulation. The embossing of the punches

Table 11.10
Pharmaceutical colourants and their regulatory acceptability.

Colour	Other Names	Regulatory Acceptability		
		UK	USA	Japan
Azorubine	Carmoisine	+	-	-
FD&C Red 40	Allura Red	-	+ ^a	-
FD&C Red 2	Amaranth Bordeaux S	+	-	+ ^b
Ponceau 4R	Cochineal Red A Brilliant Scarlet 4R	+	-	+ ^b
FD&C Red 33	Acid Fuchsin D Naphthalone Red B	-	+ ADI 0-0.75 mg	-
Canthaxanthin	Food Orange 8	+	+	-
Red 2G	Food Red 10	-	-	-
FD&C Red 22	Eosin Y	-	+ ^a	-
FD&C Red 28	Phloxine B	-	+ ^a	+ AL-lake only
FD&C Red 3	Erythrosine	+	+ ^a lakes are prohibited	+
Cochineal Extract	Natural Red 4 Carmine	+	+	+
Iron Oxide-Red		+	+ ADI 0-0.5 mg elemental iron	+
Anthocyanin		+	-	-
Beetroot Red	Betanin	+	-	-
Fast Yellow	Acid Yellow G	-	-	-
FD&C Yellow 6	Sunset Yellow FCF Yellow Orange S	+	+	+
Yellow 2G		-	-	-
FD&C Yellow 5	Tartrazine	+ ^c	+ ^{a,c}	+
FD&C Yellow 10	Quinoline Yellow WS	+	+ ^a	-
β-Carotene		+	+	+
Turmeric	Curcumin Natural Yellow 3 Indian Saffron	+	-	-
Iron Oxide- Yellow		+	+ ADI 0-0.5 mg elemental iron	+
Riboflavin	Lactoflavin Vitamin B ₂	+	-	+

Table 11.10 continued on next page

Table 11.10 continued from previous page

Colour	Other Names	Regulatory Acceptability		
		UK	USA	Japan
Patent Blue V		+	–	–
FD&C Blue 1	Brilliant Blue FCF	–	+ ^a	+
FD&C Blue 2	Indigotine Indigo Carmine	+	+	+
FD&C Green 3	Fast Green FCF	–	+ ^a	+
Acid Brilliant Green BS	Green S Lissamine Green	+	–	–
Chlorophyllin		+	–	+
Brilliant Black BN	Food Black 1	+	–	–
Carbon Black	Medicinal Vegetable Charcoal	+	–	+
Iron Oxide–Black		+	+ ADI 0–0.5 mg elemental iron	–
Caramel	Burnt Sugar	+	+	+
Titanium dioxide		+	+	+

+ Permitted

– Not permitted

^aRequires FDA certification on each lot of dye.^bManufacturers have imposed a voluntary ban on this colour.^cRequires label declaration.

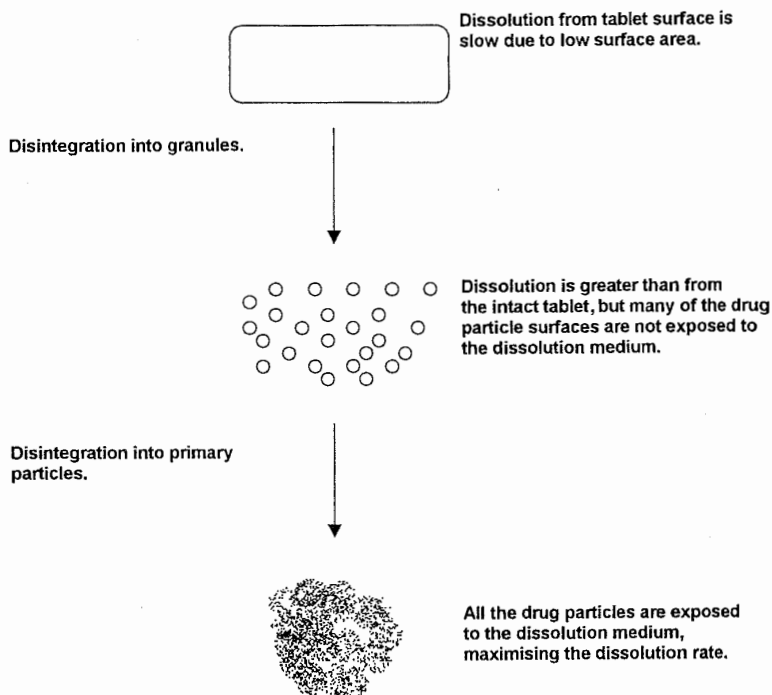
will exacerbate any tendency for punch adherence, and this should be considered when selecting the levels of lubricant and antiadherent in the tablet. The intagliations will also highlight the presence of any abrasion on the crown of the tablet, and care must be taken to ensure that the surfaces are sufficiently robust, particularly if they are to be subsequently film coated.

Disintegration

The chapter to date has concentrated on ensuring that it is possible to produce a tablet of sufficient strength that it can withstand the stresses of subsequent manufacturing operations, such as coating and packaging, and will reach the patient in an acceptable condition. However, once an immediate-release tablet is taken by the patient, it is important that it breaks up rapidly to ensure rapid dissolution of the active ingredient.

To maximise the dissolution rate of a drug substance from a tablet, it is necessary to overcome the cohesive strength produced by the compression process and break the tablet into the primary particles as rapidly as possible (Figure 11.19). This is achieved by adding disintegrants which will induce this process.

Starch was the first disintegrant used in tablet manufacture and is still used, although it has largely been superseded by the so-called super disintegrants, croscarmellose sodium,

Figure 11.19 Dissolution of drugs from tablets.

sodium starch glycolate and croscopovidone, which display excellent disintegrant activity at low concentrations and possess better compression properties than starches.

Traditionally, swelling and rate of swelling have been regarded as the most important characteristics of disintegrants. Rudnic et al. (1982) quantified the rate of swelling and force generated by the swelling of disintegrants and found no simple relationship between the maximum disintegrating force and disintegration time. It was the ability to develop a significant swelling force rapidly that appeared to be more important. The other important factor in a formulation is that as the swelling develops, it should not be accommodated within the tablet, which prevents a significant disruptive force from being generated. If the tablet displays elasticity to the swelling, the force will be expended on the system, and disintegration will not take place. Similarly, if the tablet is composed entirely of soluble components, their dissolution will deprive the disintegrant of a matrix to push against. As a general rule, soluble drugs are formulated with insoluble fillers to maximise the effect of disintegrants.

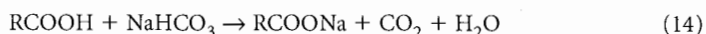
The positioning of disintegrants within the intragranular and extragranular portions of granulated formulations can affect their efficacy. Placing the disintegrant in the extragranular portion results in rapid disintegration to granular particles, while the disintegrant present in the granule will promote further disintegration to the primary particles thus aiding dissolution. Studies performed to determine the optimum location of disintegrant (Shotton and

Leonard 1972; Rubenstein and Bodey 1974) suggest that dividing it between the two portions, with between 20 and 50 percent being in the extragranular portion, produces the best results.

Optimising the level of disintegrant in a formulation is a good example of a situation where there are a number of opposing factors to consider, and the final formulation needs to be a compromise. To optimise the biopharmaceutical properties of the formulation, the tablet should disintegrate rapidly, which can be achieved by increasing the level of disintegrant. The particle size of most disintegrants is small to maximise the surface area, and thus increase the rate of water uptake. The addition of large quantities of such materials could have an adverse effect on the flow properties of the formulation. The compaction properties of many disintegrants, including starch, are less than ideal, and high concentrations could also reduce the strength of tablets produced. By their nature, disintegrants are hygroscopic materials and will absorb moisture from the atmosphere, which could negatively affect the stability of water sensitive drugs. The super disintegrants, if used at excessive concentrations, can actually absorb sufficient moisture from the atmosphere to initiate disintegration on storage, if the packaging does not provide adequate protection from the environment. Disintegrant activity can be affected by mixing with hydrophobic lubricants, so care needs to be taken to optimise the manufacturing process as well as the formulation. The commonly used disintegrants are listed in Table 11.11.

For a disintegrant to be able to function properly, the tablet surface must be amenable to wetting. If the tablet contains a high proportion of a hydrophobic drug that has a high contact angle, it may be wise to include a wetting agent or surfactant in the formulation, which will aid not only the disintegration time of the tablet but also the subsequent dissolution of the drug substance. The most commonly used wetting agents are sodium lauryl sulphate and the polysorbates.

An alternative mechanism of disintegration is used in effervescent tablets, which utilises a gas-liberating chemical reaction to effect rapid disintegration. These tablets contain an organic acid and an alkali metal carbonate which, when added to water prior to administration, react to produce carbon dioxide, e.g.,



Most pharmacopoeias include a disintegration test which can be applied to tablets and capsules. The USP test consists of six glass tubes, 3 in. long and open at the top, with a 10-mesh screen at the bottom and immersed in a beaker of disintegration fluid that is maintained at 37°C. The tubes are raised and lowered 5–6 cm at 30 cycles per minute such that the bottom of the tubes remain 2–5 cm below the liquid surface at the top of the stroke and are no closer than 2–5 cm from the base of the beaker at the lowest point. One tablet is placed in each tube, and the disintegration time is the time taken for all six tablets to break up sufficiently for all material to pass through the mesh at the bottom of the tube. If the dosage form floats, it is permitted to place perforated plastic discs in the tubes to ensure that they remain submerged during the test. Pharmacopoeial tests use water as the disintegration fluid for non-enteric coated tablets, but during development, it is prudent to test the tablets over a range of pH values.

Disintegration testing is an important part of in-process control testing during production to ensure batch-to-batch uniformity, but its role in end-product testing has largely been superseded by dissolution testing.

Table 11.11
Commonly used disintegrants.

Disintegrant	Normal Usage Concentration (%)	Comments
Starch	5–10	Probably work by wicking; swelling is minimal at body temperature.
Microcrystalline cellulose		Strong wicking action. Loses disintegrant action when highly compressed.
Insoluble ion exchange resins		Strong wicking tendencies with some swelling action.
Sodium starch glycolate	2–8	Free-flowing powder that swells rapidly on contact with water.
Croscarmellose sodium	1–5	Swells on contact with water.
Gums—agar, guar, xanthan	< 5	Swell on contact with water; form viscous gels that can retard dissolution, thus limiting concentration that can be used.
Alginic acid, sodium alginate	4–6	Swell like the gums but form less viscous gels.
Crospovidone	1–5	High wicking activity.

Dissolution

Drug materials administered orally are required to dissolve in the GI fluids before absorption can take place. Dissolution occurs most rapidly from the primary particles of the drug substance, hence the importance of rapid disintegration to this state. However, disintegration studies only demonstrate that a tablet will break up when immersed in fluid; there are many other factors that can influence the dissolution of a material. A carefully designed dissolution test will, therefore, be a better indication of the performance of a dosage form. The design of dissolution tests and the correlation between *in vitro* dissolution and *in vivo* performance is discussed in Chapter 7, “Biopharmaceutical Support in Formulation Development”. The optimisation of the dissolution of a substance is discussed in Chapter 8.

Processing of Formulations

The performance requirements of a tablet were discussed in the previous section, and it is clear that most tablets will contain several ingredients. The drug substance, probably a filler, a disintegrant and a lubricant will be common to most formulations, while glidants, colourants and wetting agents may also be included. The quality of the final product will be as dependent on the way in which the components are combined as it is on the components selected. Traditionally, tablet formulations have been prepared by one of two methods: direct compression or granulation.

Direct compression is the term used to define the process where powder blends of the drug substance and excipients are compressed on a tablet machine. There is no mechanical treatment of the powder apart from a mixing process. Granulation is a generic term for particle enlargement, whereby powders are formed into permanent aggregates. The purpose of

granulating tablet formulations is to improve the flow and compaction properties prior to compression. There are a number of different methods that can be used to granulate a powder blend but the most common one for pharmaceuticals is wet granulation, where a liquid is added to aid agglomeration and then removed by drying prior to compression. Even from this short description, it is obvious that direct compression is a much simpler process; yet it is not universally adopted. This section will review the advantages and disadvantages of the two techniques in an attempt to explain why granulation still plays an important role in tablet manufacture.

Direct Compression

The term *direct compression* was initially applied to the formation of compacts from materials that required no pretreatment and the addition of no additives or excipients. As such, it was only used for inorganic materials such as potassium bromide. Today, within the pharmaceutical industry, the term is used for tablet manufacture that does not involve the pretreatment of the drug substance apart from blending with excipients.

Advantages of Direct Compression. The most obvious advantage of direct compression is its simplicity and subsequent economy. The manufacture requires fewer operations, and the omission of a drying step results in lower energy consumption. If a new production line is being built for a product, there will be considerable savings in the plant required, equipment such as granulators and dryers being unnecessary. The reduced processing times will produce savings in labour costs, and the simplicity of the process should make process validation simpler. Some of these savings will, however, be offset by the need to use specialised, more expensive, excipients.

Direct compression can provide technical, as well as economic, benefits. Stability of certain drugs can be improved, and the elimination of a wetting and drying process can be beneficial when formulating drugs that are thermolabile or moisture sensitive.

For certain drugs, the dissolution rate can be improved by utilising direct compression. In the section on Disintegration, it was stated that for optimal dissolution, the tablet must disintegrate into its primary particles as quickly as possible. With no agglomeration stage involved in direct compression, the tablets will disintegrate directly to the primary particles.

Disadvantages of Direct Compression. The main limitation of direct compression is that it cannot be used for all drug substances; the technique depends on the major components of the formulation having appropriate flow and compaction properties. While it is possible to modify the properties of drug substances by particle engineering, this is usually outside the scope of the formulator, and the formulation must be designed to accommodate the limitations imposed by the drug substance. For low dose drugs, it is usually possible to overcome such limitations through careful selection of excipients, but there will be a dose level at which it becomes impractical to produce a tablet of acceptable size.

The challenges facing the formulator of low dose drugs by direct compression are related to achieving and maintaining a homogeneous mix. Very low dose drugs can be formulated to form ordered mixes that reduce the risk of segregation. Consideration must be given to the entire manufacturing process to minimise the possibility of segregation.

Direct compression places greater demands on the excipients, particularly the fillers. This has resulted in the introduction of a number of excipients that have been designed specifically for use in direct compression formulations, although they tend to be expensive.

Armstrong (1998) described the following requirements for direct compression fillers:

- Have good flow properties
- Possess good compaction properties
- Have high capacity (defined as the ability to retain their compaction properties when mixed with drugs substances)
- Have appropriate particle size distribution to minimize the segregation potential
- Have high bulk density
- Be capable of being manufactured reproducibly to minimise batch-to-batch variation

Jivraj et al. (2000) have classified the direct compression fillers in terms of their disintegration and flow properties (Table 11.12).

In addition to these excipients, there are also a number of proprietary preparations that combine two or more materials to optimise the flow and compaction properties. Examples of such excipients include the following:

- Ludipress—a combination of α -lactose monohydrate, polyvinylpyrrolidone and crospovidone
- Cellactose—microcrystalline cellulose and lactose
- Cel-O-Cal—co-processed microcrystalline cellulose and calcium sulphate
- Silicified microcrystalline cellulose—co-processed microcrystalline cellulose that has been silicified with colloidal silicon dioxide

A number of active drug substances are also available in co-processed forms for use in direct compression formulations. While such materials might not be considered direct compression in its purest form, they do pass on the advantages of direct compression technology to the tablet manufacturers.

Granulation

Granulation is the most widely used technique to prepare powders for compaction. The term *granulation* is a generic description for a process of particle enlargement in which particles are agglomerated while retaining the integrity of the original particles. A number of methods can be used to achieve the agglomeration; these are normally classified as either wet granulation, where a liquid is used to aid the agglomeration process, or dry granulation, where no liquid is used.

The purpose of granulating is to transform the powdered starting materials, which would otherwise be unsuitable for tableting, into a form that will run smoothly on a tablet machine. This is achieved in a number of ways. The most obvious benefit of granulation is the improved flow properties resulting from the increase in particle size.

In forming granules, individual particles of the starting ingredients are agglomerated together. If a homogeneous powder mix is achieved before commencing agglomeration, the granules will consist of a homogeneous mix of those ingredients. More importantly, the

Table 11.12
Direct compression fillers.

Classification	Examples	Comments
Materials that act as disintegration agents with poor flow characteristics	Microcrystalline cellulose	Probably the most widely used direct compression excipients. Excellent compactibility at low pressures, high dilution capacity.
	Directly compressible starch	
Free-flowing materials that do not disintegrate	Dibasic calcium phosphate dihydrate	Excellent flow properties. Very brittle material, and is best used in combination with microcrystalline cellulose or directly compressible starch.
Free-flowing powders that disintegrate by dissolution	Lactose	Anhydrous β -lactose possesses excellent compaction properties. Picks up moisture at elevated humidities and may be less compatible with moisture-sensitive compounds than the monohydrate form (Jain et al. 1998).
	Sorbitol	Good compactibility. Popular in chewable tablets due to its cool mouth feel.
	Mannitol	Hygroscopic.

particles of drug substance will be bound to the particles of the excipients, thus reducing the potential for segregation and improving the chances of content uniformity.

The granulation process usually involves the addition of a polymeric binder that sticks the individual particles together. It has been demonstrated with paracetamol (Armstrong and Morton 1977) that this process can reduce the elasticity of starting materials, thus improving the compactibility.

The polymers used as binders are usually hydrophilic in nature. This can have a beneficial effect on the dissolution of hydrophobic drugs. During the granulation process, a film of hydrophilic polymer will form over the surface of hydrophobic drug particles, which will aid wetting.

One of the advantages of granulation is that it results in the densification and subsequent volume reduction of the starting material. This is particularly useful in the case of voluminous starting materials. A further benefit is that the densified, coarse material will reduce the amount of air entrapment.

A number of methods are routinely used within the pharmaceutical industry to produce granulations. These are traditionally classified as dry granulation and wet granulation, depending on whether a liquid is used to aid the agglomeration.

Wet Granulation. Wet granulation methods are the most commonly used in tablet manufacture. These methods involve the addition of a liquid and, usually, a polymeric binder to the powdered starting materials, and a form of agitation to promote agglomeration followed by a drying process. In most cases, the liquid used is water, although in certain circumstances organic solvents such as ethanol or ethanol/water mixes are used. Non-aqueous granulation will be considered when the active substance is particularly unstable in the presence of water, when water will not wet the powder or, possibly, if the drug substance forms a significant portion of the granulate and demonstrates extreme solubility in aqueous media and control of the granulation process becomes difficult due to the occurrence of significant dissolution. While there are a number of approaches to wet granulation used in the pharmaceutical industry, they all share the following basic principles.

- Dry mixing—The starting materials are mixed together. Prior to mixing, the ingredients may be deagglomerated by a milling or sieving process. If the granulate has a low drug content, the active substance may be premixed with one of the ingredients prior to being added to the granulation vessel to ensure good content uniformity
- Addition of granulating liquid—The granulating fluid is added to the dry ingredients and mixed to form a wet mass. The mixing of the fluid with the dry ingredients leads to agglomeration of the powder. This agglomeration can be controlled by altering the amount of fluid added, the intensity of the mixing and the duration of the mixing. Depending on the state of agglomeration achieved, this stage may be followed by a wet sieving process to break up the larger agglomerates
- Drying—The fluid is removed by a drying process
- Milling—The dried granulate undergoes a sieving or milling operation to obtain the desired particle size distribution

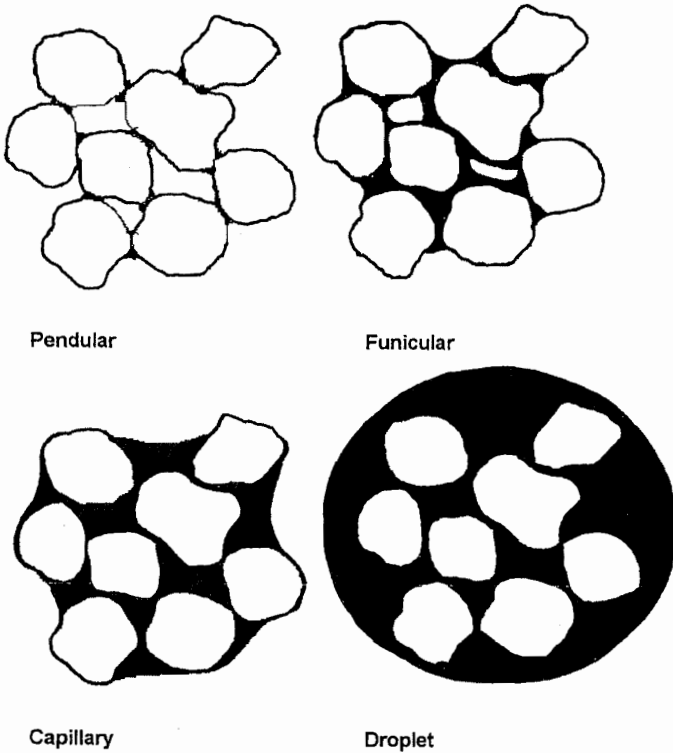
To understand the granulation process, it is necessary to consider what is occurring at the particulate level during the process. The aim of granulation is to increase the particle size of a powder mix, and this is achieved in wet granulation by the formation of liquid bridges between the powder particles. If a liquid that is able to wet the powder is added, the system will minimise its surface free energy by forming liquid bridges between the particles. The nature and extent of these bridges will be dependent on the amount of liquid added.

At low liquid levels, it is assumed that the liquid will distribute itself evenly through the bed, forming discrete liquid bridges at points of contact between particles (Figure 11.20). This is known as the pendular state. The strength of an individual pendular bond, σ , between two spherical particles can be calculated:

$$\sigma = \frac{2\pi rT}{1 + \tan \frac{1}{2}\phi} \quad (15)$$

where r is the radius of the spherical particle, T is the surface tension of the liquid and ϕ is the angle formed between the line joining the centre of the spheres and the edge of the pendular bond (Figure 11.21) (Eaves and Jones 1972). This equation predicts that the bond strength will increase as the surface tension of the liquid increases and as the liquid content decreases. In practise, the strength of agglomerates tends to zero at very low liquid contents, and this has

Figure 11.20 Stages involved in granulation.

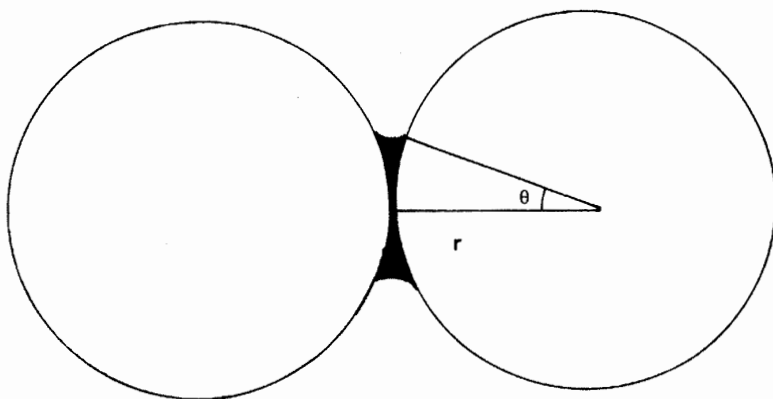


been attributed to the presence of dry joints occurring between particles, due to uneven distribution of the liquid throughout the powder bed.

As the liquid content is increased, the pendular state will remain until the pendular bonds start to coalesce and liquid bridges form between non-touching points. This is known as the funicular state (Figure 11.20). The state depends on the degree of liquid saturation or voidage saturation, which is defined as the ratio of the liquid volume to the total volume of pores in the powder bed. Typically, a powder bed will remain in the pendular state until the liquid saturation reaches around 25 percent, and in the funicular state between 25 and 80 percent.

As the liquid saturation rises above 80 percent, the powder reaches the capillary state, and the granule is held together by capillary suction as the liquid air interfaces on the granule surface. While the tensile strength of the granule is greater in the capillary state, the granulate is starting to assume a paste-like consistency which is unsuitable for wet sieving.

The theoretical tensile strength of agglomerates in the funicular and capillary states has been derived by Rumpf et al. (1974):

Figure 11.21 Calculation of the strength of a pendular liquid bridge.

$$\sigma = SC \left(\frac{1-\epsilon}{\epsilon} \right) \left(\frac{\gamma}{d} \right) \cos \theta \quad (16)$$

This equation applies to the strength of agglomerates formed from monosize spheres with diameter d that are packed to porosity ϵ . The degrees of liquid saturation is S , and the liquid has surface tension γ and a contact angle θ with the solid. C is a material constant. Note that in these states, the strength of agglomerates now increases with decreasing particle size. The porosity of the powder also affects the strength; if the material is densified, the agglomerate strength will increase. Addition of further liquid converts the capillary state into the droplet state where the particles are enclosed in a water droplet, and the mass takes on the properties of a slurry.

The gradual transition from pendular through funicular to capillary bonding assumes that there is always a uniform distribution of liquid throughout a powder bed. In practise, this is obviously not always the case because the dispersion of liquid through the powder is achieved by mechanical agitation which will take a finite time. What actually happens in a powder bed during a typical granulation process will be the creation of small areas of high saturation that will lead to the formation of agglomerates which, through mechanical agitation, are dispersed throughout the powder bed. The fate of the agglomerates will change as the degree of liquid saturation increases.

Three phases of agglomeration are recognised, and these will to an extent be occurring simultaneously within a powder bed as the liquid becomes distributed by agitation. The first stage of particle growth is nucleation, which occurs whenever a powder is wetted, particles being held together by liquid bridges. In practise, the liquid addition will lead to overwet agglomerates being formed, to which further powder adheres until the number of liquid bridges is saturated. At low saturation levels, interactions such as friction will also contribute to the strength of the agglomerates. The theoretical strength of the agglomerates is proportional to the degree of liquid saturation, so the initial agglomerates will tend to be weak, and in an

agitated environment, agglomerates will be constantly being formed and destroyed. The survival of the agglomerates will increase during the granulation process as the liquid saturation increases and as densification occurs, reducing the porosity of the powder bed.

The powder then undergoes a transition state as it takes up sufficient liquid for the effects of particle interactions to diminish, and the strength becomes controlled by the liquid bridges. The agglomerates become less brittle and more plastic in nature. At this stage, coalescence between colliding particles occurs, and particle growth takes place.

The final stage of granulation is ball growth, a period characterised by rapid growth in particle size. The large granules are formed by smaller granules being fractured, and the resulting fragments build up in layers on the surface of the larger agglomerates.

The above description of the granulation process illustrates that the formulator is dealing with a complex system and the quality of the final product will be influenced by a large number of factors, from the selection of the raw materials to the processing conditions employed.

While one of the stated advantages of granulation over direct compression is that the technique is better able to cope with variations in raw material, the agglomeration process will be affected by significant changes in the raw materials used. The particle size of the starting materials will affect the strength of granules produced, as predicted in equation 16. The quantity of granulating fluid required to achieve granulation is dependent on the particle size and shape. This additional requirement is partly related to the increase in surface area but also relates to the material packing properties that affect the granule porosity and the degree of liquid saturation achieved. Granulation is essentially a wetting process and, as such, is dependent on the surface chemistry of the particles. It is well established that powder handling processes such as milling and drying can significantly affect the surface properties of powders. Small areas of amorphous material on the particle surface produced by particle attrition, too small to be detected by techniques such as X-ray powder diffraction, can have dramatic effects on the wetting characteristics.

Granulating Agents (Binders). It is possible to granulate a powder simply by adding water or an organic solvent to a powder. Provided that the liquid is able to wet the powder surface, it will form liquid bridges. When the granulate dries, the crystallisation of any solids that had dissolved in the liquid will form solid bonds between the particles. These bonds will usually be fairly weak, and friable granulates will be formed; often the granules will not be sufficiently robust to withstand the drying process. It is usual, therefore, to include granulating agents or binders to granulations to increase the granule strength. Granulating agents are usually hydrophillic polymers that have cohesive properties that both aid the granulation process and impart strength on the dried granulate.

For a granulating agent to be effective, it is vital that it is able to form a film on the particle surface. Rowe (1989) has suggested that binders should be selected on the basis of their spreading coefficients, where the spreading coefficient is defined as the difference between the "work of adhesion" of the binder and the substrate and the "work of cohesion" of the binder. The commonly used granulating agents are listed in Table 11.13.

The synthetic polymers such as polyvinyl pyrrolidone (PVP) and hydroxypropyl methylcellulose (HPMC) have almost totally superseded the use of natural products such as starch, acacia and tragacanth in modern formulations. The most common method of adding binders is as a solution in the granulating fluid. It is possible to add some of the synthetic polymers such as PVP and HPMC as powders and use water as the granulating agent. This approach, which has the advantage of not requiring a solution manufacturing step in production, is likely to result in incomplete hydration of the polymers during processing, which will affect the quality of the final granulate.

Table 11.13
Commonly used granulating agents.

Granulating agent	Normal Usage Concentration (%)	Comments
Starch	5-25	Was once the most commonly used binder. The starch has to be prepared as a paste, which is time consuming.
Pre-gelatinised starch	5-10	Cold water-soluble, so easier to prepare than starch.
Acacia	1-5	Requires preparation of paste prior to use. Can lead to prolonged disintegration times if used at too high a concentration.
Polyvinylpyrrolidone (PVP)	2-8	Available in range of molecular weights/viscosities. Can be added either dry or in solution. Soluble in water and ethanol.
Hydroxypropyl methylcellulose (HPMC)	2-8	Available in range of molecular weight/viscosities. Soluble in water and ethanol.
Methylcellulose (MC)	1-5	Low-viscosity grades most widely used.

The level of binder used needs to be a balance between the level required to produce a robust, compressible granulate and the biopharmaceutical properties. As the granule strength increases, there is often an adverse effect on disintegration and dissolution. The binders form hydrophilic films on the surface of the granules, which can aid the wetting of hydrophobic drugs; but if added in too great concentrations, the films can form viscous gels on the granule surface, which will retard dissolution. To optimise the dissolution of a drug from a granulated product, it is important that the granule should disintegrate into its primary particles as rapidly as possible, and it is usual to position at least a portion of any disintegrant inside the granules.

Wet Granulation Methods. A number of processing methods are commonly used within the pharmaceutical industry. Each method will impart particular characteristics and, as such, granulates produced by each method may not be equivalent in terms of either their physical properties (which will influence subsequent performance on tablet machines) or their biopharmaceutical properties. This latter point is well recognised by regulatory authorities who regard changes in the granulation method as potentially having a significant effect on the bioavailability of poorly soluble, poorly permeable compounds. The U.S. Food and Drug Administration (FDA) and industry representatives have outlined their expectations regarding the testing required when changing the method of granulation in *SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*. This document concludes that changing the type of granulation process used can, for some drug substances, result in the need to perform a bioequivalence study prior to the change being granted regulatory approval.

The three main methods of producing pharmaceutical granulates are low-shear granulation, high-shear granulation and fluid bed granulation. *Low-shear mixers* encompass machines such as Z-blade mixers and planetary mixers which, as their name suggests, impart relatively low shear stresses onto the granulate. Widely used in the past, this approach has largely been superseded by high-shear mixers. The low level of shear applied is often insufficient to ensure good powder mixing, so a premix is often required. The process is forgiving in terms of the amount of liquid added, although it does result in long granulation times. The degree of ball growth tends to be uncontrolled because there is insufficient shear to break up the plastic agglomerates, so a wet screening stage is almost always necessary prior to drying to reduce the larger agglomerates.

High-shear granulators are closed vessels that normally have two agitators; an impeller which normally covers the diameter of the mixing vessel and a small chopper positioned perpendicular to the impeller. The powders are dry mixed using the impeller, and then the granulating fluid is added. Wet massing takes place using the impeller and the chopper, and granulation is usually completed in a number of minutes. The granulation process can be controlled using an appropriate combination of impeller and chopper speeds and time. The ability of the chopper to limit the size of the agglomerates can negate the need for a wet screening stage for many granulates. High-shear mixers provide a greater degree of densification than the low-shear mixers. This, combined with the relatively short processing times, can lead to the process being very sensitive to the amount of granulating liquid added.

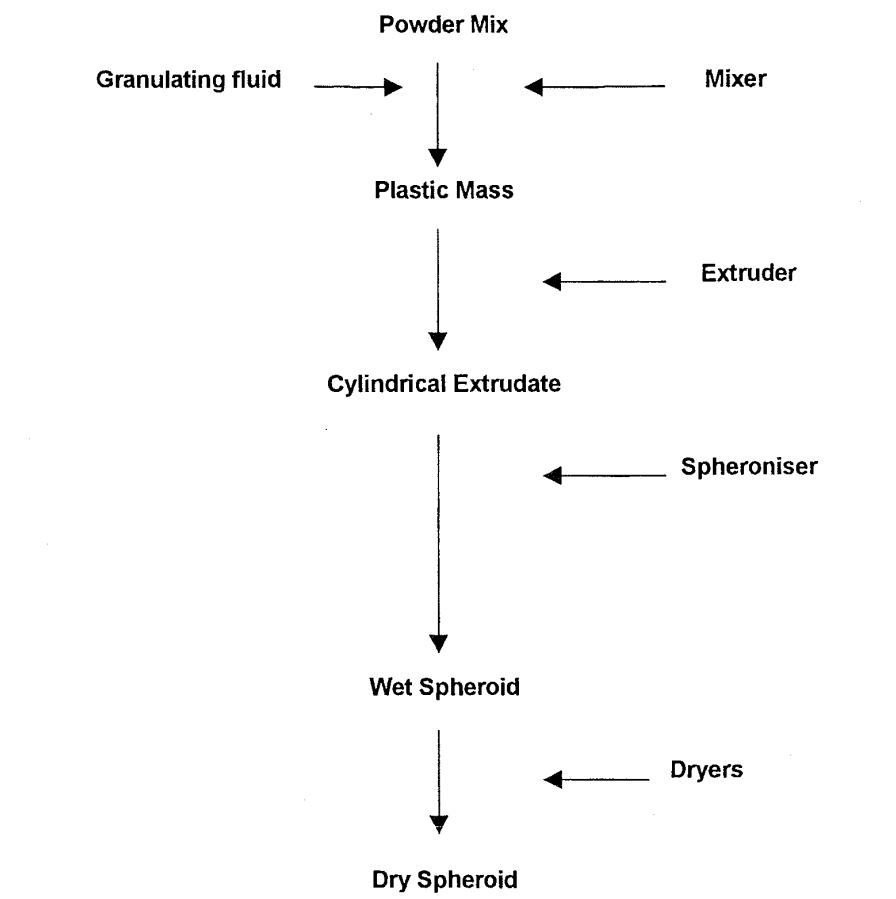
In both high-shear and low-shear mixers, the mode of liquid addition can affect the quality of the final product. The liquid can either be added in one go or slowly sprayed onto the powders. Slow spraying leads to the most uniform distribution of liquid but can increase the overall processing time. Pouring the liquid onto the powder will result initially in large over-wet granulates being formed. The mixer needs to impart sufficient energy to the system to break up the agglomerates to achieve uniform distribution of liquid.

Fluid bed granulation involves spraying the dry powder with a granulating fluid inside a fluid bed drier. The powder is fluidised in heated air and then sprayed with the granulating fluid. When all the granulating liquid has been added, the fluidisation of the powder continues until the granules are dry. Advantages of this technique are that the granulation and drying are performed in a continuous manner in the same vessel, and there is no need for a wet screening operation. Nucleation occurs by random collisions between the droplets of granulating fluid and particles until all the individual particles have been incorporated into agglomerates. Densification of materials is limited due to the lack of shear forces.

Seager et al. (1985) produced a detailed analysis on the influence of manufacturing method on the tableting performance of paracetamol granulated with hydrolysed gelatin. The main difference in the granules produced by different methods was their final density, high shear mixers producing denser granules than low shear granulators, which in turn produced denser granules than fluid bed granulations. Disintegration times were greater for tablets produced from the denser granulates.

Extrusion/Spheronisation

One specialised method of particle agglomeration is extrusion and spheronisation, to produce spherical or near-spherical particles. Such particles are suitable for coating with release modifying coats to produce controlled release formulations. The particles are usually filled into hard gelatin capsules for administration to patients. The process of extrusion/spheronisation is depicted in Figure 11.22.

Figure 11.22 Schematic description of extrusion/spheronisation.

The drug and filler are mixed with water to form a wet mass. This step will be performed using equipment similar to that of conventional wet granulation, though the quantity of water added will be greater, resulting in a plastic mass rather than granules. The mass is then extruded, that is, forced through a screen containing circular holes, to form a spaghetti-like extrudate. The extrudate is cut into lengths roughly twice the diameter of the holes and rolled by frictional and centrifugal forces on a rotating grooved plate known as a marumeriser or spheroniser. The rolling action compresses the cylinder along the length and rounds the ends, forming dumbbells which become further compressed along their length to form spheres. The spheroids are discharged from the spheroniser and dried, usually by fluid bed drying.

The basic ingredients of most spheroids are the drug substance, microcrystalline cellulose and water. Microcrystalline cellulose appears to be unique in its ability to form spheroids by

this method, due perhaps to its ability to hold onto the water during extrusion. The squeezing of the wet mass through a screen during extrusion forces most materials to lose water, and the resulting extrudates do not have the necessary plasticity to form spheroids.

The robustness of microcrystalline cellulose means that for most low dose drugs it is possible to make spheroids, certainly if the drug loading is below 10 percent. As the drug loading increases, the process becomes more difficult. Two factors appear to be required for success, the mass must retain the water during the extrusion process, and the extrudate must have the appropriate rheological properties.

There are many types of extruders available, with very different shear forces. The different shear forces will have an effect on the water distribution in the extrudates. As the water level is critical for optimising the spheronisation process, it is clear that the formulation development and process development need to be considered as one for this type of process.

Dry Granulation

It is possible to form granulates without the addition of a granulating fluid, by techniques generically referred to as dry granulation. These methods are useful for materials that are sensitive to heat and moisture but which may not be suitable for direct compression.

Dry granulation involves the aggregation of particles by high pressure to form bonds between particles by virtue of their close proximity. Two approaches to dry granulation are used in the pharmaceutical industry: slugging and roller compaction. In either method, the material can be compacted with a binder to improve the bonding strength.

Slugging. Granulation by slugging is, in effect, the manufacture of large compacts by direct compression. The slugs produced are larger than tablets and are often poorly formed tablets exhibiting cracking and lamination. As with tablets, it may be necessary to add a lubricant to prevent the compacts sticking to the punches and dies. The compressed material is broken up and sieved to form granules of the appropriate size. The granules are then blended with disintegrant and lubricant and compressed on a normal tablet machine.

Roller Compaction. In roller compaction, the powder is compacted by means of pressure rollers (Figure 11.23). The powder is fed between two cylindrical rollers, rotating in opposite directions. The rollers may be flat, which will produce sheets of compacted material, or they may be dimpled, in which case, briquettes in the shape of the dimples will be formed. If sheets are produced, they are milled and screened to the required size. Roller compaction requires less lubricant to be added than does slugging.

Selection of the Appropriate Process

The methods of formulating and manufacturing tablets have been described in the preceding sections. Each method has certain unique benefits and advantages as well as drawbacks, and these are summarised in Table 11.14.

For any given compound there will normally be more than one approach that is technically feasible, so how does one choose which approach to take? For most formulators, the choice is strongly influenced by the philosophy of the production department of the company in which they work. Different companies can have very different philosophies; some believe that the cost savings of direct compression are such that attempts should be made to

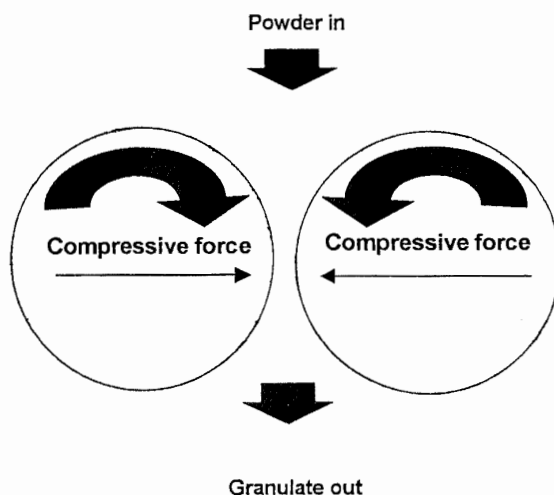
Figure 11.23 Principles of roller compaction.

Table 11.14
Manufacturing and formulating tablets—advantages and disadvantages.

Method	Advantages	Disadvantages
Direct compression	Simple, cheap process. No heat or moisture, so good for unstable compounds. Prime particle dissolution.	Not suitable for all drugs, generally limited to low dose compounds. Segregation potential. Expensive excipients.
Wet granulation (aqueous)	Robust process suitable for most compounds. Imparts flowability to a formulation. Can reduce elasticity problems. Coating surface with hydrophilic polymer can improve wettability. Binds drug with excipient, thus reducing segregation potential.	Expensive: time and energy consuming process. Specialised equipment required. Stability issues for moisture sensitive and thermolabile drugs with aqueous granulation.
Wet granulation (non-aqueous)	Suitable for moisture sensitive drugs. Vacuum drying techniques can remove/reduce need for heat.	Expensive equipment; explosion proof; solvent recovery.
Dry granulation (slugging)	Eliminates exposure to moisture and drying.	Dusty procedure. Not suitable for all compounds. Slow process.
Dry granulation (roller compaction)	Eliminates exposure to moisture and drying.	Slow process.

formulate all tablets by this route, other companies feel that wet granulation is a more robust process and should be used even when a compound looks amenable to the direct compression route.

Tablet Coating

For some tablets, compression marks the final stage of the production process, but many formulations involve coating the compressed tablet. There are several reasons for applying a coat:

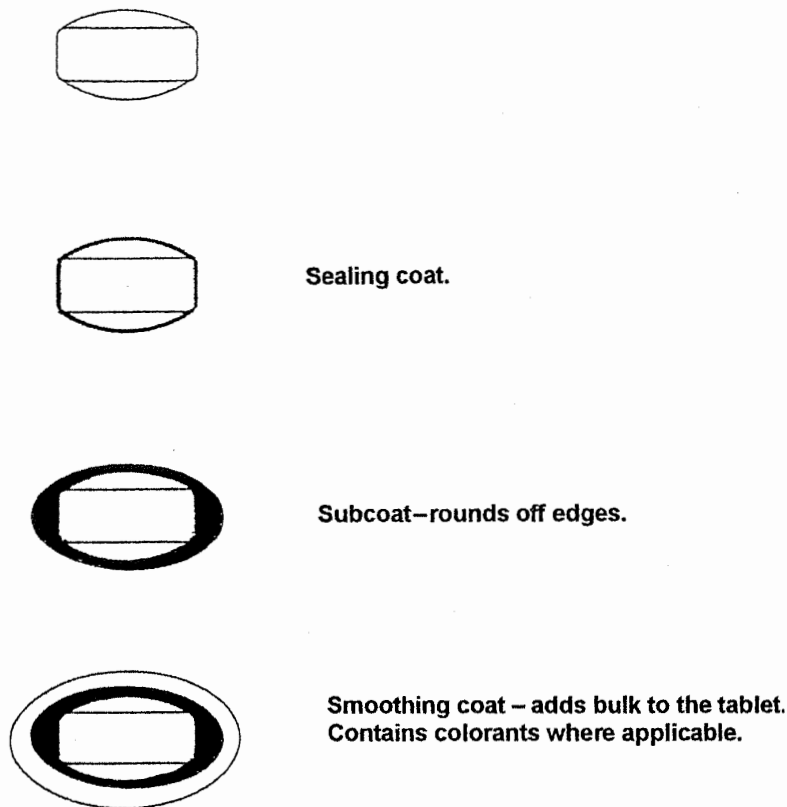
- Protection of the drug from the environment (moisture, air, light) for stability reasons
- Taste masking
- Minimising patient/operator contact with drug substance, particularly for skin sensitisers
- Improving product identity and appearance
- Improving ease of swallowing
- Improving mechanical resistance; reducing abrasion and attrition during handling
- Modifying release properties

There are three main methods used to coat pharmaceutical tablets: sugar coating, film coating and compression coating. Sugar coating was the most commonly used method until the 1970s, when it was largely superseded by film coating.

Sugar Coating

Sugar coating, as its name suggests, involves coating tablets with sucrose. This is a highly skilled, multistep process that is very labour intensive. The process involves applying a number of aqueous solutions of sucrose, together with additional components, which gradually build up into a smooth, aesthetically pleasing coat. The final coat can account for up to 50 per cent of the final tablet weight and will result in a significant increase in the tablet size. Traditionally, sugar coating has been performed in coating pans in which the tablets are tumbled. With the appropriate tablet load and rotation speed, the tablets are tumbled in a three-dimensional direction. The pan is supplied with a source of warm air for drying and an extraction system to remove moist air and dust.

The coating solution is ladled onto the tablet bed and is distributed around the tablets by their tumbling action. The tablets are then tumbled for a period of time to allow the coating to dry before a further quantity of solution is added. A dusting powder may be sprinkled onto the surface of the tablets during the drying phase to prevent the tablets sticking together. One of the skills of sugar coating is adding an appropriate quantity of solution. If too little is added, then not all tablets will pick up some of the coating and an uneven distribution will result. If too much solution is added, the tablets will stick together. The cycle of wetting and drying is continued until the desired amount of coating has been applied to the tablets. Typically, a sugar coating will consist of three types of coat: a sealing coat, a subcoat and a smoothing coat (Figure 11.24).

Figure 11.24 Stages of sugar coating.

One of the reasons for coating tablets is to protect the drug substance from environmental factors such as moisture, so it is important that the coating solution does not penetrate into the core. This is achieved by applying a sealing coat. Traditionally, a coating of shellac dissolved in ethanol was applied, but this has largely been replaced by the use of synthetic water-resistant polymers such as cellulose acetate phthalate or polyvinylacetate phthalate. The challenge for the formulator is to optimise the quantity of subcoat applied to ensure the core is protected while minimising the effect on drug release.

The subcoat is an adhesive coat on which the smoothing coat can be built. A second purpose of the subcoat is to round off the sharp corners of the tablet to produce a smooth surface. The subcoat is a mixture of a sucrose solution and an adhesive gum, such as acacia or gelatin, which rapidly distributes over the tablet surface. A dusting follows each application of solution with a subcoat powder containing materials such as calcium carbonate, calcium sulphate, acacia, talc and kaolin that help to produce a hard coat. The application of the subcoat continues until the tablets have a rounded appearance and the edges are well covered.

The smoothing coat consists of the majority of the tablet bulk and provides the tablet with a smooth finish. The coat consists of a sucrose syrup which may contain starch or calcium carbonate. Each application is dried, and layers are added until the required bulk has been achieved. The last few coatings will consist of sucrose solution and colourants, where required. The colourants may be either soluble dyes or lakes, lakes often being preferred because a uniform colour is easier to achieve with them.

The coated tablets are usually transferred to a polishing pan and coated with a beeswax-carnauba wax mixture to provide a glossy finish to the surface.

Film Coating

Film coating involves the application of a polymer film to the surface of the tablet and, in contrast to sugar coating, only adds up to 5 percent weight to the final tablet, with a negligible increase in tablet size. It is a technique which, while used mainly to coat tablets, can also be applied to hard gelatin capsules, soft gelatin capsules and multiparticulate systems such as spheroids.

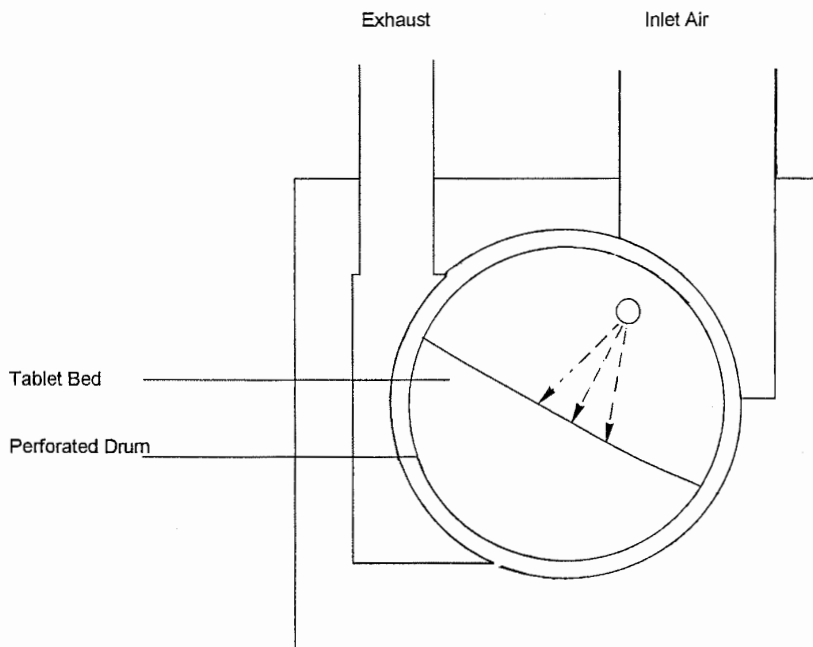
The method of application of the coat differs from sugar coating in that the coating suspension is sprayed directly onto the surface of the tablets, and drying occurs as soon as the coat hits the tablet surface. To achieve this, the tablet only receives a small quantity of coat at a time and the coat is built up in an intermittent manner. While the coating can be applied using a number of methods, all share the following properties: a method of atomising the coating suspension, the ability to heat large volumes of air (which heat the tablets and facilitate the rapid drying of the applied coat) and a method of moving the tablets that ensures all tablets are evenly sprayed. The main methods of coating are modified conventional coating pans, side-vented pans and fluid bed coating.

When the technique of film coating was first applied to tablets, the coatings were suspended in organic solvents, and conventional coating pans were used. Additional air handling was required to provide the volume of air necessary to dry the tablets and to extract the vapours from drying. The nature of the pans is such that the drying air is only present on the surface of the tablet bed; there is no mechanism for it to percolate through it. Providing the volume of air required for such drying was difficult, and a number of modifications have been made to the pans. The limitation in drying efficiency, however, remains a constraint, particularly as most coating now uses aqueous suspensions which impose even greater energy demands. A further limitation to the use of conventional coating pans is their poor mixing efficiency that results in dead spots in the tablet bed.

The side-vented pan, which is now the most commonly used equipment for film coating, was designed to maximise the interaction between the tablet bed and the drying air. In such apparatus, the coating pan is made of perforated metal. The drying air is introduced into the centre of the pan but exhausted through the perforations in the pan beneath the tablet bed (Figure 11.25). Mixing efficiency is achieved by the use of appropriately designed baffles on the pan surface.

Fluid bed coating offers an alternative to pan coating and is particularly popular for coating multiparticulate systems. In fluid bed systems, the objects being coated are suspended in an upward stream of air, maximising the surface available for coating. The coating is applied by an atomiser, and this is dried by the fluidising air. There are three methods by which the coating can be applied (Figure 11.26):

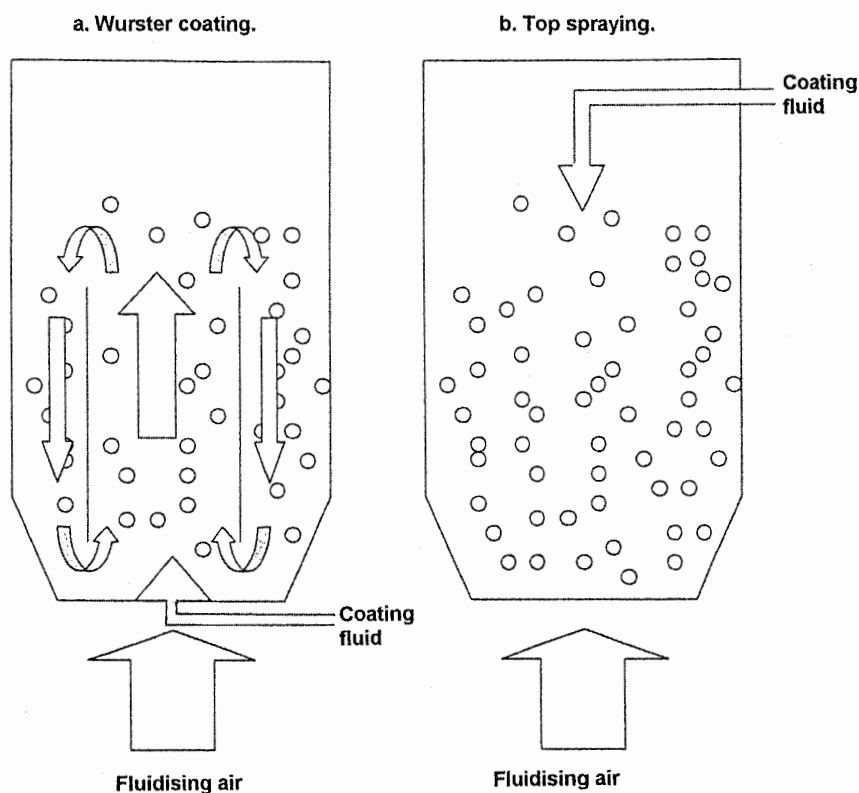
1. Top spraying involves the spray being applied from the top of the fluid bed chamber into the fluidising air using equipment similar to that used for spray granulation.

Figure 11.25 Schematic of the side-vented coating pan.

2. *Bottom spraying*, sometimes referred to as the Wurster process, involves the spraying of the tablets at the bottom of the fluid bed. In this setup, there is a column introduced into the fluid bed chamber, which ensures that tablets in the centre of the chamber are directed upward. At the top of the column, the tablets descend the chamber at the edge of the chamber from where they will be redirected to the spraying region.
3. The third method of coating is tangential coating which is restricted to the coating of spheroids.

A polymer for film coating will ideally meet the following criteria.

- Solubility in the solvent selected for application. These days, the solvent will usually be water, although certain types of film coat may require organic solvents to be used. Commonly used solvents include alcohols (methanol, ethanol and isopropanol), esters (ethyl acetate and ethyl lactate), ketones (acetone) and chlorinated hydrocarbons (dichloromethane and trichloroethane). The polymer should not only be soluble in the chosen solvent but should adopt a conformation in solution that yields the maximum polymer extension, which will result in films with the greatest cohesion strength. If mixed solvents are used, consideration should be given to the effect of the solvent ratios changing during the drying process. If the polymer is most soluble in

Figure 11.26 Fluid bed coating of tablets.

the most volatile component, it may precipitate out during the spraying before reaching the tablet surface.

- Solubility in GI fluids. Unless the coating is being applied for enteric coating or taste masking purposes, it should ideally be soluble across the range of pH values encountered in the GI tract.
- Capacity to produce an elegant film even in the presence of additives such as pigments and opacifiers
- Compatibility with film coating additives and the tablet being coated
- Stability in the environment under normal storage conditions
- Free from undesirable taste or odour
- Lack of toxicity

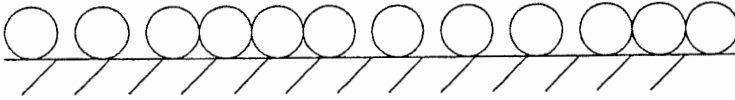
Table 11.15 lists the most commonly used polymers. With the exception of HPMC, the polymers are rarely used alone but are combined with other polymers to optimise the film-forming properties.

The actual film coating process is described schematically in Figure 11.27. There are two important stages: droplet formation and film formation. The film formation is itself a multi-stage process involving the wetting of the tablet surface followed by spreading of the film and eventually coalescence of the individual film particles into a continuous film. In order for such coalescence to be able to occur, it is necessary for the polymer to be in a plasticised state, that is, above its glass transition temperature, the point at which a polymer goes from being a rigid, brittle material to a flexible material. Most film forming polymers have glass transition temperatures in excess of the temperatures reached during the coating process (typically 40–50°C), so it is necessary to add plasticisers to the formulations, which act by reducing the glass transition temperature. The choice of plasticiser is dependent on the particular polymer(s) being used. The main factors to consider in selection are permanence and compatibility. Permanence is the duration of the plasticiser effect; the plasticiser should remain within the polymer film to retain its effect, so it should have a low vapour pressure and diffusion rate. Compatibility requires the plasticiser to be miscible with the polymer. Commonly used plasticisers include phthalate esters, citrate esters, triacetin, propylene glycol, polyethylene glycols and glycerol.

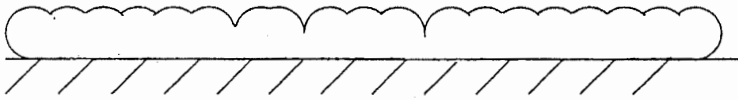
Film coating provides an opportunity to colour tablets, and most film coats will contain pigments or opacifiers. Insoluble pigments are normally preferred to soluble dyes for a number of reasons. Solid pigments produce a more opaque coat than dyes, protecting the tablet

Table 11.15
Commonly used polymers.

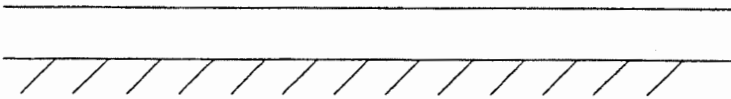
Polymer	Comments
Methylcellulose (MC)	Soluble in cold water, GI fluids and a range of organic solvents.
Ethylcellulose (EC)	Soluble in organic solvents, insoluble in water and GI fluids. Used alone in modified release formulations and in combination with water-soluble celluloses for immediate-release formulations.
Hydroxyethylcellulose (HEC)	Soluble in water and GI fluids.
Methyl hydroxyethylcellulose (MHEC)	Soluble in water and GI fluids. Has similar film forming properties to HPMC but is less soluble in organic solvents, which limited its popularity when solvent coating was the norm.
Hydroxypropyl cellulose (HPC)	Soluble in cold water, GI fluids and polar solvents. Becomes tacky when dried, so is unsuitable for use alone, often used in combination with other polymers to optimise adhesion of coat.
Hydroxypropyl methylcellulose (HPMC)	Soluble in cold water, GI fluids, alcohols and halogenated hydrocarbons. Excellent film former, and the most widely used polymer. Can be used with lactose to improve adhesiveness.
Sodium carboxymethylcellulose (NaCMC)	Soluble in water and polar solvents.

Figure 11.27 Mechanism of film formation on the tablet surface.

Droplets of the coating suspension wet the surface of the tablet.



The droplets spread, forming a continuous film over the surface.



Eventually the droplets completely coalesce to form a smooth film.

from light. The presence of insoluble particles in the suspension allows the rate of solid application to the tablet to be increased without having an adverse effect on the viscosity of the coating suspension, improving productivity. The pigments also tend to exhibit better colour stability than dyes.

Film coating of tablets requires both the process and the formulation to be optimised if a uniform intact coating is to be achieved. The most common flaws, their cause and possible remedies are described in Table 11.16.

It has been emphasised to this point that the coat should not delay the release of the drug substance from the tablet. It is possible to design a coat that will modify the release of a drug substance for a beneficial effect.

The most common type of modified release coating is the enteric coat that is designed to prevent release of the drug substance in the stomach because the drug is either irritant to the gastric mucosa or it is unstable in gastric juice. The most common method of achieving an enteric coating is to apply a polymer that contains acidic substitutions, thus giving it a pH-dependent solubility profile. Examples of such polymers are listed in Table 11.17.

Table 11.16
Film-coating defects.

Flaw	Cause	Remedy
<i>Wrinkling or blistering</i> Film detaches from tablet surface causing blister which can burst to form wrinkles.	Gases forming on tablet surface during coating; exacerbated by poor adhesion of film to tablet surface.	Reduce drying air temperature.
<i>Picking</i> Areas of tablet surface are not covered by film coat.	Overwet tablets stick together and pull film off surface as they move apart.	Decrease spraying rate. Increase drying temperature.
<i>Pitting</i> Holes appear on tablet surface.	Melting of lubricant on tablet surface. Most common with stearic acid.	Decrease coating temperature to below melting point of lubricant. Substitute lubricant.
<i>Blooming</i> Dulling of surface, normally after prolonged storage.	Migration of low molecular weight components of film to tablet surface.	Decrease temperature and length of drying process. Increase molecular weight of plasticiser.
<i>Mottling</i> Uneven colour distribution in film.	Inadequate pigment dispersion. Colour migration, a problem with dyes and lakes rather than pigments.	Alter suspension preparation to ensure pigment aggregates are dispersed. Replace dyes with pigments.
<i>Orange Peel</i> Film surface has a rough finish resembling orange peel.	Film coat droplets are too dry or too viscous to spread on tablet surface.	Reduce solids content of coating suspension. Reduce drying temperature. Reduce viscosity of polymer.
<i>Bridging</i> Film forms a bridge over intagliations, leaving them indistinct.	High internal stresses in film relieved by pulling the film off the surface of the intagliation.	Increase adhesion of coat to tablet by changing core formulation. Add plasticiser or increase plasticiser concentration. Alter geometry of intagliations.
<i>Cracking, splitting, peeling</i> The film cracks on the crown of the surface or splits on the tablet edge. Can be differentiated from picking by presence of loose film around the flaw.	High stresses in the film that cannot be relieved due to the strong adhesion of the film to the tablet surface.	Increase plasticiser concentration. Use stronger polymer.

Table 11.17
Commonly used enteric coating polymers.

Polymer	Solubility Profile	Comments
Shellac	Above pH 7	The original enteric coating material, originally used in sugar-coated tablets. The high pH required for dissolution may delay drug release. Natural product which exhibits batch-to-batch variability.
Cellulose acetate phthalate (CAP)	Above pH 6	The high pH required for dissolution is a disadvantage. Forms brittle films, so must be combined with other polymers.
Polyvinylacetate phthalate (PVAP)	Above pH 5	
Hydroxypropyl methylcellulose phthalate (HPMCP)	Above pH 4.5	Optimal dissolution profile for enteric coating.
Polymers of methacrylic acid and its esters	Various grades available with dissolution occurring above pH 6	

Film coating can also be used to delay the release of drugs. This is normally applied to multiparticulate systems where particles will be coated with differing thicknesses of water-insoluble polymers such as ethylcellulose

Compression Coating

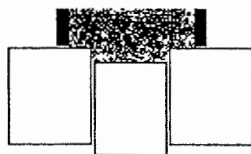
The third type of tablet coating used in pharmaceuticals is compression coating. This technique involves producing a relatively soft tablet core containing the drug substance and compressing a coating around it (Figure 11.28). This is achieved by placing the core in a large die that already contains some of the coating formulation. Further coating material is then added to the die and the contents compressed. The three types of coating have now been described, and the relative merits of each approach are summarised in Table 11.18.

HARD GELATIN CAPSULES

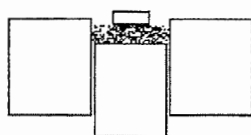
After tablets, hard gelatin capsules are the most common solid dosage form. Hard gelatin capsules are rigid two-piece capsules made from gelatin, water and colourants. The capsules are produced as empty shells consisting of a cap and body, which during the manufacture of the finished product are separated, filled with the formulation and then rejoined.

Hard gelatin capsules are generally considered to be more forgiving than tablets, from a formulator's perspective. While many of the challenges facing the formulator of tablets are still present, the need for a free-flowing material, powder homogeneity, lubricity and optimising the biopharmaceutical properties, the challenges of forming a robust compact have been

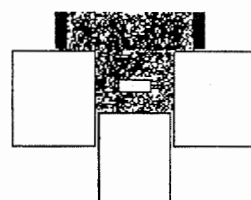
Figure 11.28 Schematic of the compression coating process.



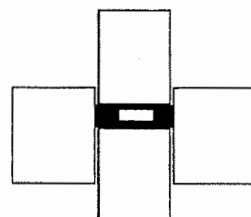
The die passes under the feed frame containing the compression coat material. A shallow fill takes place.



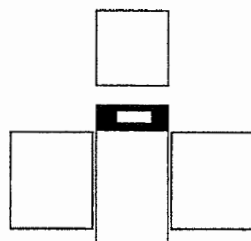
The tablet core that is to be coated is placed on the layer of coating material.



The lower punch moves down, and the die passes beneath a feed frame containing the coating material. The tablet core is now surrounded by the coating material.



The die contents are compressed between two punches to form a coherent compact.



The formed compression coated tablet is ejected from the die.

Table 11.18
Coating methods.

Coating Method	Advantages	Disadvantages
Sugar coating	Elegant final product. Tablets can be printed for identification purposes. Cheap, readily available starting materials. Simple equipment requirements. Excellent protection from environment.	Long process time. Traditional manufacture more an art than a science; high operator dependency. Significantly increases tablet size.
Film coating	Quick process, easy to automate. Negligible increase in tablet size. Tablets can be identified either by printing or through intagliations. Minimal effect on drug release. Enteric coating feasible.	Finish not as elegant as sugar coating. Coating process stresses tablet formulation, cores must be robust to resist abrasion and edge chipping during coating.
Compression coating	It is a dry process, so suitable for moisture-sensitive compounds. Can be used for combination products where the active substances are incompatible.	Significant increase in tablet weight. Possible to produce tablets with no inner core.

removed. Capsules have traditionally been filled with solid formulations such as powder mixes and granulations, but increasingly, multiparticulate formulations, liquid and semi-solid fills are being developed.

Hard gelatin capsules have some disadvantages compared with tablets. The filling speeds of capsule machines are lower than the speeds of the fastest tablet presses, and the cost of the capsule shells makes them a more expensive dosage form. Certain materials are unsuitable for inclusion in capsule shells due to incompatibility with gelatin or because of their affinity for water. One advantage sometimes claimed for capsules is ease of swallowing due to their elongated shape, but this may be countered by the fact that capsules are often larger than corresponding tablets due to the reduced compression of the powder and incomplete filling of the shells. Furthermore, there are concerns that capsules are more prone to sticking in the oesophagus than tablets following swallowing.

The manufacture and formulation of hard gelatin capsules has not been the subject of as much research as tableting, partly because encapsulation unlike compression is not a science shared by many other disciplines. Nevertheless, there has been important work performed on this dosage form, and much of it is captured in *Hard Capsules Development and Technology* (Ridgway 1987).

Manufacture of Empty Capsule Shells

Gelatin is a heterogeneous product prepared by the hydrolysis of collagen, the principal constituent of connective tissue. The suitability of gelatin for capsule manufacture is due to the following properties:

- It is commonly used in foods and has global regulatory acceptability. However, because it can be derived from a number of animal sources, not all gelatin is acceptable

in all markets, and capsule manufacturers will produce capsules from different animal sources to allow for local religious restrictions. All pharmaceutical capsule manufacturers now use gelatin produced in accordance with current requirements relating to bovine spongiform encephalopathy.

- It is a good film former, producing a strong flexible film.
- It is readily soluble in water and in GI fluids at body temperature, so will not retard the release of drugs.
- It changes state at low temperatures enabling a homogeneous film to be formed at ambient temperature.

The properties of a given batch of gelatin are determined by a number of factors: the source of the parent collagen, method of extraction, the pH of the hydrolytic process and its electrolyte content. The properties of most interest to capsule manufacturers are the bloom strength and the viscosity.

The bloom strength is a standard, but arbitrary, test of the rigidity of gel produced by a sample of gelatin. The test measures the force required to depress the surface of a 6.67 percent w/w gel, matured at 10°C for 16–18 h, by a distance of 4 mm using a flat-bottomed plunger 12.7 mm in diameter. The force is applied in the form of a stream of lead shot, and the weight, in grammes, is termed the bloom strength. Bloom strengths in the region of 230 to 275 are used for the manufacture of hard gelatin capsule shells. The standard viscosity is measured using a U-tube viscometer with a 6.67 percent w/w solution, and values in the range of 3.3 to 4.7 mPas being used for capsule shells.

Capsule shells are manufactured by dipping moulds into a gelatin solution, drying the gelatin to form a film, removing the dried film from the mould and trimming the film to the right size. The moulds are made of stainless steel and are referred to as pins. The cap and body of the capsule shells are made on separate pins with the body pins being longer than the cap. The external diameter of the body at its open end is slightly larger than the internal diameter of the cap at its closed end to ensure a snug fit when closed.

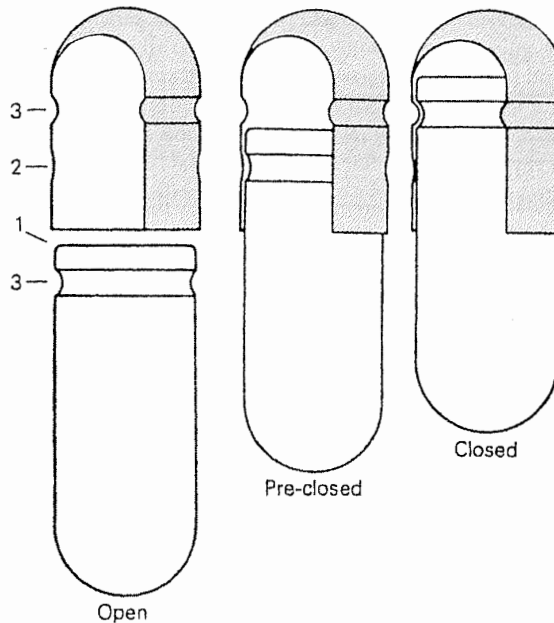
The empty capsule shells contain 13–15 percent water, a level that is important for optimum performance on capsule filling machines. If the level falls below 13 percent, the capsules become brittle, while if they take up too much water, the gelatin becomes soft and there are problems with capsule separation. The dimensions of the capsule shell will also change with variations in water content, typically increasing by 0.5 percent for every 1 percent increase in moisture content. It is important that capsule shells are both stored and filled in areas where the relative humidity is controlled between 30–50 percent.

It is also important that the capsule fill not adversely affect the moisture content of the shell. This is not a suitable dosage form either for deliquescent materials, which will dry the capsules making them brittle, causing cracking or splitting, or for efflorescent materials, which will soften the shells and may lead to capsules sticking together. Similarly, the presence of moisture in the capsule shells makes them an unsuitable delivery form for drugs that are highly moisture sensitive.

Any fill materials must be chemically compatible with gelatin. Cross-linking of gelatin can be catalysed by trace quantities of formaldehyde, rendering the gelatin insoluble in gastric fluids. Formaldehyde is sometimes present at trace levels in a number of excipients.

Capsules manufactured for use on automatic filling machines, which covers almost all pharmaceutical capsules, have locking devices moulded into the side of the capsule (Figure 11.29). There are two locking positions, a pre-lock to prevent premature opening prior to the

Figure 11.29 Locking mechanism of a hard gelatin capsule shell.



1. The tapered rim prevents faulty joins.
2. These indentations prevent the pre-closed capsules from opening too early.
3. These grooves lock the two halves together after filling.

filling process and a locked position which forms an interference seal to prevent the capsule coming apart after filling.

There are a number of companies manufacturing capsule shells for use in the pharmaceutical industry, and all produce capsules to standard sizes, which enables them to be filled on standard filling machines. There are eight sizes of capsules commercially available, listed in Table 11.19. The largest capsule size normally considered for oral administration is size 0, with the 00 and 000 capsules being difficult to swallow due to their size.

Capsule Filling

Before considering how to formulate products for filling into hard gelatin capsules, it is necessary to understand the capsule-filling mechanisms available. All capsule filling machines perform three basic operations: the orientation and separation of the empty capsule shell, the filling of the material into the shell and finally rejoining the cap and the body. From the formulator's perspective, the important stage is the filling, as this will determine the properties

Table 11.19
Capsule sizes.

Capsule Size	000	00	0	1	2	3	4	5
Fill Volume (mL)	1.37	0.95	0.68	0.50	0.37	0.30	0.21	0.13

required of the formulation. The requirements imposed by the filling mechanism will include factors such as powder flow, lubricity and compressibility, and as discussed in the section on tablets, the optimisation of these factors needs to take into consideration the effects on drug release from the formulation.

Drug release from capsules involves an additional step compared to tablets, the dissolution of the capsule shell. When placed in a dissolution medium at 37°C, the gelatin will begin to dissolve, initially retaining its integrity. Eventually, the capsule shell will rupture at its thinnest points, the shoulders of the cap and body, allowing the dissolution medium to penetrate into the capsule contents. The rate of penetration and, where appropriate, the disintegration of the capsule fill will be determined by a combination of the formulation and the processing method, including the filling mechanism.

Powder and Granulate Filling

The requirements of capsule formulations are very similar to those of tablets, and the general formulation principles described earlier apply equally to capsules. As with tablets, most capsules will contain a combination of ingredients including some or all of the following: the active drug substance, filler(s), disintegrant, binder, glidant and lubricant. The main difference in the requirements is the demands placed on the compressibility of the formulation. With tablets, it is necessary to produce a compact capable of withstanding the rigours of subsequent handling. For capsules, it is often necessary to form a plug for ejection into the capsule body, but it is not necessary for the plug to retain its integrity beyond the filling stage. While good flow is necessary for the successful manufacture of both tablets and capsules, the filling mechanisms on certain production capsule machines tend to be more forgiving than tablet machines.

Powder fills for capsules can be either simple blends of starting materials, analogous to direct compression formulations, or granulations. The reduced demands on compressibility and flow increase the options for powder mixes, making capsules a potential dosage form for active substances that do not possess the compression properties required for direct compression tablets and are not amenable to granulation.

Powders account for the majority of capsule fills and a number of quite disparate filling mechanisms have been developed unlike tableting, where the principle of manufacture, compression between two punches in a die, is the same for all machines. The mechanisms can be divided into two broad groups, those that rely on the volume of the capsule shell to control the dose, known as capsule dependent, and those methods where the quantity of powder to be filled is measured away from the capsule, known as capsule independent. The dependent mechanisms require the capsule shell to be well filled to achieve weight uniformity and are less flexible than the independent methods.

Dependent Methods

The simplest method of dependent capsule filling is levelling, in which the capsule bodies are held flush with a dosing table, and powder is filled into the bodies by gravity. The powder within the capsule bodies may be consolidated by vibration or tamping, and additional powder added to fill the space generated. The final fill weight will depend on the bulk density of the powder and the degree of tamping applied. This method is popular in hand filling devices such as the Tevopharm, Feton, Bonaface and Zuma, which are amenable to most powder mixes. Poor flowing powders will take longer to fill, but with skilled operators, should be feasible. The major formulation challenge is to prepare a blend that will provide an appropriate fill for a standard size capsule.

Osaka Automatic Machine Co. produce a fluidisation machine which is an automatic dependent filling machine. The capsule body in its holder passes below the powder hopper. The powder is fluidised by a vibrating plate to aid flow into the capsule body. The capsule body can be held below the hopper base so that it becomes overfilled, and the fill can be compressed into the capsule by raising the body against a flat surface prior to the capsule closing. This technique has not been the subject of published formulation studies, but appropriate flow properties and lubrication are likely to be required.

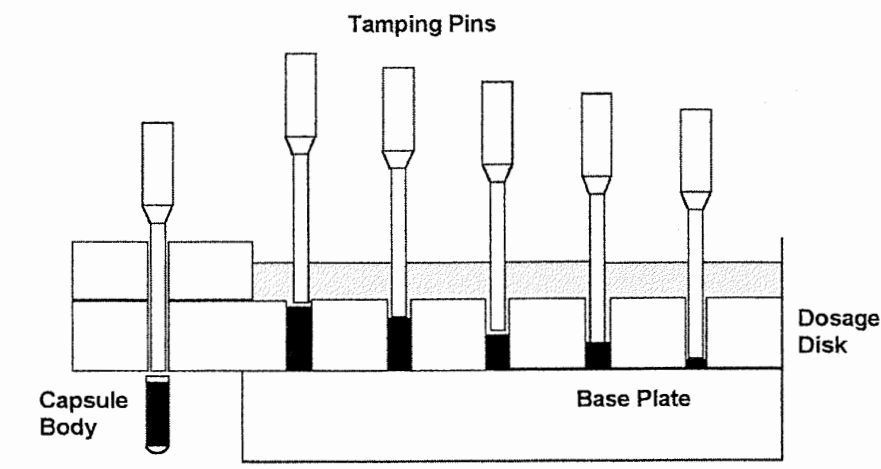
Independent Methods

Auger or Screw Method. This was the first mechanism used in industrial-scale machines, although the dosator and piston tamp mechanisms have now largely superseded it. The capsule body in its holder passes beneath the powder hopper on a turntable. The powder is fed into the capsule body by a revolving archimedean screw. The auger rotates at a constant rate so the fill weight is related to the duration of filling that is related to the speed of rotation of the turntable.

Formulation studies on auger machines have tended to concentrate on the optimisation of fill weight uniformity. Reier et al. (1968) demonstrated that the variation in the capsule fill weight was influenced by the machine speed, capsule size, powder density, powder flow and the presence of a glidant. Ito et al. (1969) determined that there was an optimum level of glidant for minimum weight variation. Powders still account for the majority of capsule fills, and a number of quite disparate filling mechanisms have been developed. Powders should be adequately lubricated to prevent build up of densified material on the auger.

Piston Tamp Method. In piston tamp machines, the powder passes over a dosing plate containing cavities slightly smaller than the internal diameter of the capsule. The powder falls into the holes by gravity and is then tamped by a pin to form a soft plug. This procedure is repeated several times until the cavity is full. Excess powder is removed from above the cavity by a deflector plate. The cavity is then positioned over the capsule body and the plug ejected (Figure 11.30). The dose is controlled by the thickness of the dosing plate, the degree of tamping applied and the height of the powder bed above the dosing plate.

The uniformity of fill weight for the piston tamp machines has been shown to correlate well with the angle of repose of the powders (Kurihara and Ichikawa 1978) and the angle of internal flow (Podczek et al. 1999). Lubrication of formulations is important to prevent build up of material on the tamping pins and to ensure smooth ejection of the plugs from the dosing plate. The ability of the material to compress into a plug, is important; if a formulation does not form a plug, the ejection will not be as clean and can lead to increased weight

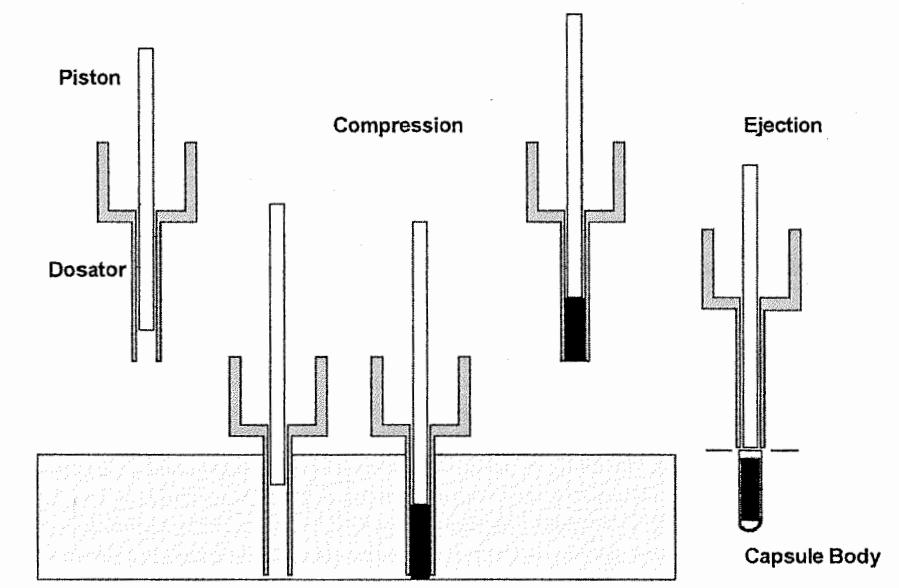
Figure 11.30 Schematic of a tamping pin type capsule filling machine.

variation. Studies have shown that for certain formulations, the tamping pressure applied by the pins can affect the dissolution rate of the final product (Shah et al. 1983). The minimum tamping force necessary to obtain a plug that will fit inside the body of the capsule shell should be aimed for.

Dosator Method. A dosator, consisting of a stainless steel cylinder containing a spring-loaded stainless steel piston, is lowered, open end first, into a flat powder bed. As the cylinder passes into the bed, powder is forced up into the cylinder until it reaches the piston, forming a plug. Additional compression of the plug can be obtained by applying a downward pressure on the piston. The dosator is lifted from the powder bed and, if a suitable plug has formed, the powder will remain within. The dosator is positioned above a capsule body and the plug ejected by lowering the piston. The dose is controlled by the dimensions of the dosator, the position of the piston within the dosator as it enters the powder bed and the height of the powder bed (Figure 11.31).

This mechanism is the most widely used mechanism and can be found on small pilot scale machines using an intermittent action similar to rotary machines capable of production rates in excess of 120,000 capsules per hour. As a result of its popularity, there have been considerable studies into the formulation of powder for filling on these types of machines and instrumentation of the dosators.

The fundamental requirements of a formulation to be filled on a dosator type machine are good flow properties, compressibility and lubricity. *Flow* is important in the powder bed: when the dosator dips into the powder, it leaves a void which must be closed with material of the same bulk density prior to the next dosator entering that area of the hopper. Irwin et al. (1970) investigated the effect of powder flow on the uniformity of weight achieved on a Zanasi filling machine and concluded that the better the rate of flow the better the uniformity of fill.

Figure 11.31 Schematic of a dosator type capsule filling machine.

Compressibility is necessary to form a plug of sufficient strength that powder does not escape from the dosator as it leaves the powder hopper and positions itself above the capsule body. Jolliffe and Newton (1982a,b) considered the theoretical aspects of powder retention using powder hopper design theory to calculate the forces required to hold a free powder surface in an open-end cylinder. The powder retention relies on the formation of a stable powder arch which is dependent on the shear developed at the dosator walls and the unconfined yield strength. It was demonstrated that the angle of wall friction between the powder and dosator could have an important influence on powder retention. This was explored experimentally (Jolliffe and Newton 1982a,b) by showing that the internal friction changed during manufacture as the powder fill coated the internal wall of the dosator. Furthermore, these authors proposed that the optimum design for a dosator would have two types of surface finish, a smooth finish with a low value of wall friction for the main body of the cylinder together with a higher value of wall friction at the outlet to promote arch formation. The dosator mechanism does permit high compressive forces to be applied to powder beds. The objective of a capsule formulation is not to make a mini tablet that can be filled into a capsule, the compression force should be restricted to the minimum level necessary to form a coherent plug. Whenever powders are compressed, there is the possibility of elastic recovery when the compressive stress is removed. The tolerance between the internal diameter of the dosators and the internal diameter of capsule shells is fairly tight, and any elasticity in capsule formulations can lead to the plugs not sitting properly in the capsule shells, resulting in powder loss as the cap

is reunited with the body. In such circumstances, the pragmatic approach is to use dosators designed for the next smallest capsule size.

The *lubricity* requirements of formulations being filled with dosators has been examined by Small and Augsburer (1978) using a Zanasi machine on which strain gauges had been attached to the dosator pistons. The magnitude of the force required to eject the powder plug from the piston was shown to be dependent on the identity and level of lubricant, the height of the initial powder bed, the piston height and the compression force applied.

Filling Capsules with Pellets

The use of multiparticulate systems to provide modified release formulations is ever increasing, and hard gelatin capsules provide an ideal way of delivering unit doses of such formulations. The two most common approaches to pellet formulation are extrusion/spheronisation (discussed in an earlier section) and the coating of non-pareil seeds. Non-pareil seeds are sucrose beads which can be film coated with a solution/suspension of the drug substance followed by layers of modified-release coatings to obtain the release profile required. The capsule filling method has to be gentle enough on the pellets to retain the integrity of the coating.

As with powder filling, the filling of pellets into capsules can be dependent or independent. A dependent method often performed uses a modified augur type machine, in which the pellets are simply poured by gravity into the capsule shells. The critical formulation aspect of this approach is ensuring that the required dosage of active substance is present in the volume of pellets taken to fill the capsule body.

An independent method uses a volumetric fill by a modified dosator method. The piston inside the dosator is narrower than those used for powder filling, and this allows air to flow between the piston and the dosator wall. The dosator is lowered into the pellet bed, but in this case, there is no compression applied. A vacuum source is applied from above the piston to retain the pellets as the dosator is moved above the capsule body. Once over the capsule body, the vacuum is removed, and the ejection of the pellets is aided by an air jet.

Tablets

Capsules can also be filled with tablets, which can be of use when preparing blinded clinical trial materials. Tablets are fed from a hopper into a chamber that simply releases one or more tablets into the capsule body as it passes underneath. The optimum formulation for capsule filling is a biconvex film-coated tablet, the film coating reducing abrasion and material loss.

Capsugel produce a range of specially sized opaque capsules specifically for the encapsulation of tablets for double blind clinical trial supplies. The capsules are wider than standard-sized capsules to allow larger diameter tablets to be filled but have shorter bodies to retain patient acceptability/tolerability.

Liquids and Semi-Solids

Two types of liquid formulations can be filled into hard gelatin capsules, those which are liquid at room temperature and those which are solid at room temperature. Such solid formulations can be liquefied either by heating to temperatures up to 70°C (the maximum temperature the gelatin shell can withstand) or by the application of shear stress. In the case of

liquids that are mobile at room temperature, the capsules need to be sealed after filling to prevent leakage of the contents.

The filling of such formulations requires machines fitted with hoppers that can provide a heating and stirring system. For most formulations, the capsules are filled using a volumetric pump, although certain viscous preparations may require an extrusion pump. The pump must be designed to be non-drip, and the capsule handling needs to be modified to control product spillage. A sensing system is required to detect the presence or absence of caps or bodies so that the pump can be stopped and the bushes not contaminated with fill material. With powder fills, contamination of the exterior of capsules can be removed by vacuum dedusting. With liquids, if one capsule is covered with liquid it can lead to major problems with capsules sticking together.

There are a number of applications for liquid/semi-solid filled capsules:

- Improvement of bioavailability
- Safety—minimising operator exposure to dusty processes
- Content uniformity—it is easier to achieve and maintain content uniformity in a solution system than a powder system
- Stability

These advantages are similar to those of soft gelatin capsules and are dealt with in greater depth in a following section.

With soft gelatin capsule technology being so well established, what advantages does liquid filling of hard gelatin capsules provide the formulator? The major advantage is that it is a technology that can be installed in-house relatively simply, unlike soft gelatin capsule manufacture which remains in the hands of a limited number of contract suppliers. This has been made possible by the development of techniques for sealing the capsules.

The approach taken to formulate a liquid-filled capsule will depend on the reason for selecting such a dosage form. The most important aspect of the formulation is to ensure that the fill is compatible with the gelatin shell. It is well known that the gelatin shell is sensitive to changes in moisture levels, and hence liquids that readily take up moisture such as the low-molecular-weight polyethylene glycols will be unsuitable. Capsugel, one of the main suppliers of capsule shells, performed extensive compatibility testing of liquid vehicles and has published a list of those deemed to be compatible (Stegemann 1999) (Table 11.20).

Capsule Sealing

The filling of liquids into hard gelatin capsules has been thought about for many years but was not commercially feasible until reliable methods for capsule sealing were available. The incidents involving the tampering of paracetamol capsules in the United States in the mid-1980s forced capsule manufacturers to develop a method of making capsules tamper evident. This, in turn, led to the development of the Quali-Seal capsule banding machine. This machine applies a narrow band of gelatin around the joint of the cap and body of filled capsules, which can be dried without the application of heat. Heat would cause air expansion within the capsule, disrupting the seal.

A recent development in sealing technology has been liquid encapsulation microspray sealing (LEMS) in which a sealing fluid of approximately 50 percent water and 50 percent

Table 11.20
Liquid excipients compatible with hard gelatin capsule shells.

Lipophilic Excipients	Hydrophilic Excipients	Amphiphilic Excipients
<i>Vegetable Oils</i>	Polyethylene glycol (PEG) 3000–6000 molecular weight	Poloxamers
Peanut oil		Lecithin
Castor oil		PEG Esters (e.g., Gelucir 44/14; 50/13; Labrafil)
Olive oil		
Fractionated coconut oil		
Corn oil		
Sesame oil		
Hydrogenated vegetable oils		
Soybean oil		
<i>Esters</i>		
Glycerol stearate		
Glycol stearate		
Isopropyl myristate		
Ethyl oleate		
<i>Fatty Acids</i>		
Stearic acid		
Lauric acid		
Palmitic acid		
Oleic acid		
<i>Fatty Alcohols</i>		
Cetyl alcohol		
Stearyl alcohol		

ethanol is sprayed onto the joint between the cap and body. This fluid penetrates the cap/body joint by capillary action and lowers the melting point of the gelatin; the capsule is then exposed to a short cycle of warm air which melts and fuses the gelatin at the joint. This technique is an elegant method of sealing, as the seal is not visible to the user.

Alternatives to Gelatin Capsules

There have been a number of attempts to make capsules from materials other than gelatin. Initially, the attempts were aimed at overcoming the original patents filed by Mothe in the nineteenth century and used materials such as starch, gluten and animal membranes. However, the only material with the correct film-forming properties was gelatin.

More recently, the attention has moved to synthetic polymers with the aim being to produce capsules that will overcome the shortcomings of gelatin, particularly its moisture content. Two alternative materials have been offered by capsule manufacturers, starch and hydroxypropyl methylcellulose (HPMC).

The starch capsules are produced by an injection moulding process using potato starch, and are produced in five sizes, all of the same diameter but with different lengths (Vilivalam et al. 2000). While the fill volumes are similar to gelatin capsules, the different dimensions necessitate specialised filling equipment. The capsule surface is less smooth than gelatin capsules, and the injection moulding allows a smooth join between cap and body to be obtained. These properties make the capsules amenable to film coating processes. The moisture content of the capsules is 14 percent.

HPMC capsules are made by the pin-dipping process used for gelatin capsules and are made to the same size specifications, allowing them to be filled on conventional capsule filling equipment. These capsules have a lower moisture content than gelatin capsules, and the moisture is tighter bound, making them more suitable for moisture sensitive drugs and hygroscopic excipients. The capsule surfaces have rougher finishes than gelatin capsules, and colouring the capsules is more difficult. The rough coat leads to better adhesion with coating materials, so they could have applications for enteric coating.

SOFT GELATIN CAPSULES

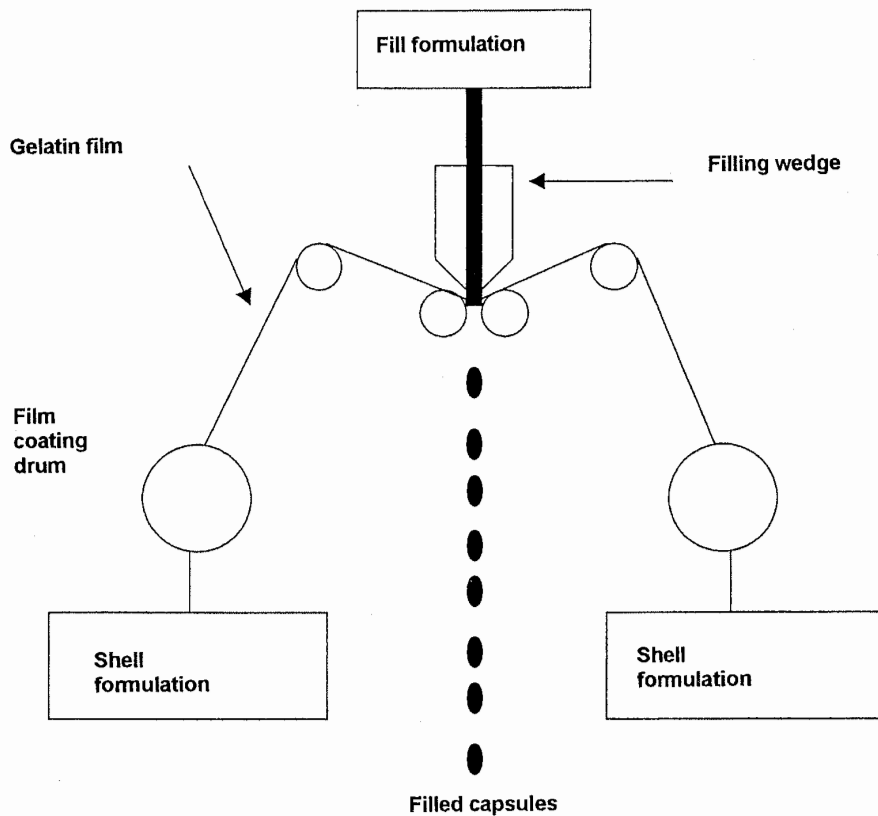
Soft gelatin capsules are included in this chapter on oral solid dosage forms, although there is debate as to whether or not they are solid or liquid dosage forms. The drug is presented in a liquid encapsulated in a solid thus combining advantages of liquid dosage forms with the unit dosage convenience of solid forms.

Manufacture

Unlike hard gelatin capsule shells which are manufactured empty and subsequently filled in a separate operation, soft gelatin capsules are manufactured and filled in one operation. This is a specialised process and tends to be performed by a limited number of companies. One consequence, therefore, of selecting a soft gelatin capsule formulation is that the product will probably be manufactured by a contract manufacturer. A desire to keep all manufacturing in-house is one of the reasons for companies considering the use of liquid-filled hard gelatin capsules as an alternative.

The shell ingredients of a soft gelatin capsule are gelatin, glycerol, which acts as a plasticiser, and potentially other ingredients which could include additional plasticisers such as sorbitol or propylene glycol, dyes or pigments, preservatives and flavours. The glycerol-gelatin mix is dissolved in water, then heated and pumped onto two cooling drums to form two gelatin ribbons which are fed into the filling machine. The liquid fill is pumped between the gelatin ribbons as they pass between the two die rolls of the filling machine, forcing the gelatin to adopt the shape of the die. The two ribbons are sealed together by heat and pressure and the capsules are cut from the ribbon (Figure 11.32). They then pass through a tumble dryer to remove the bulk of the water and conditioned at 20 percent relative humidity (RH).

The fill can be either a solution or a suspension, liquid or semi-solid. The main limitation is that the fill must be compatible with the shell. The main incompatibilities are: high

Figure 11.32 Schematic of the soft gelatin capsule manufacturing process.

concentrations of water or other solvents that will dissolve the shell, high pH (>7.5) solutions which will cause cross-linking of the gelatin which will retard dissolution of the shell, low pH solutions which may hydrolyse the gelatin and aldehydes which promote cross-linking. The types of vehicles that can be used in soft gelatin capsules are similar to those used for liquid-filled hard gelatin capsule shells listed in Table 11.20.

Benefits of Soft Gelatin Capsule Formulations

Soft gelatin capsules are a more expensive dosage form than either tablets or capsules, so they tend to be considered when they can offer a major benefit to the formulator. Justifications for their use include improved content uniformity, safety, improved stability and improved bioavailability.

Improved Content Uniformity

Because soft gelatin capsules are filled with liquids or suspensions, excellent content uniformity can be achieved with even the most potent of drugs. The accuracy of the filling mechanism enables the dose to be filled to a tolerance of ± 1 percent for solutions and ± 3 percent for pastes.

Safety

Dissolving potent drugs in a liquid vehicle reduces the risk of operator exposure to dusts that is present with tablet and hard gelatin capsule manufacturing operations.

Improved Stability

Varying the level of glycerol in the shell formulation will alter the permeability of the shell to oxygen. The filling process can be performed under nitrogen, so by appropriate selection of shell composition, this technology can provide excellent protection for oxygen sensitive drugs.

Improved Bioavailability

Presenting the drug to the GI tract in a solubilised form overcomes the processes of disintegration and dissolution that are required from hard gelatin capsules and tablets before the drug substance is available for absorption. This has been utilised to improve the bioavailability of drugs with a range of solubilities.

Acid soluble drugs can be dissolved or dispersed in water miscible vehicles that rapidly distribute the drug throughout the stomach following administration. Acid insoluble drugs can be dissolved in water miscible vehicles, which results in the drug precipitating as a fine suspension in the stomach. The surface area of the solid in suspension is high, resulting in rapid dissolution.

Formulation of compounds that have very low aqueous solubility in lipid vehicles is an area that has seen the most growth in recent years. Two approaches can be used, depending on the solubility characteristics of the drug substance. For compounds with log *P* values in the region of 2 to 4, the preferred approach is to form self-emulsifying systems. These formulations comprise a lipid vehicle, typically a medium-chain triglyceride together with a surfactant which, on contact with an aqueous environment, spontaneously form micelles. The drug remains solubilised in the micelles. Drugs with higher log *P* values can be dissolved in a digestible oil such as medium-chain monoglycerides that is immiscible with water. On release from the capsule the drug remains solubilised in the immiscible oil. The precise mechanism by which the drug is absorbed from the oil is not fully understood but there are a number of compounds on the market which have successfully demonstrated improved bioavailability by this route.

SUMMARY

This chapter has summarised some of the key aspects of powder technology that are important to the development of the principal solid dosage forms, tablets and capsules. Space restrictions have prevented this being a very detailed review, and there are many specific types

of tablets that have not been discussed at all. The area of solid dosage forms is very well served by the literature, and those interested in studying the subject area further are encouraged to consult the texts listed in the reference section.

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