25
Granulation

Malcolm Summers, Michael Aulton

CHAPTER CONTENTS

INTRODUCTION TO GRANULATION

Granulation is the process in which **primary powder particles** are made to adhere to form larger, multiparticle entities called **granules**. Pharmaceutical granules typically have a size range between 0.2 and 4.0 mm, depending on their subsequent use. In the majority of cases this will be in the production of tablets or capsules, when granules will be made as an intermediate product and have a typical size range between 0.2 and 0.5 mm, but larger granules are used as a dosage form in their own right (see Chapter 24).

Granulation normally commences after initial dry mixing of the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. After granulation the granules will either be packed (when used as a dosage form), or they may be mixed with other excipients prior to tablet compaction or capsule filling.

Reasons for granulation

The reasons why granulation is often necessary are as follows.

To prevent segregation of the constituents of the powder mix

Segregation (or demixing, see Chapter 13) is due primarily to differences in the size or density of the components of the mix, the smaller and/or denser particles concentrating at the base of a container with the larger and/or less dense ones above them. An ideal granulation will contain all the constituents of the mix in the correct proportion in each granule, and segregation of the ingredients will not occur (Fig. 25.1).

It is also important to control the particle size distribution of the granules because, although the individual components may not segregate, if there is a wide size distribution the granules themselves may segregate. If this occurs in the hoppers of sachet-filling machines, capsule-filling machines or tablet machines, products with large weight variations will result. This is because these machines fill by volume rather than weight, and if different regions in the hopper contain granules of different sizes (and hence bulk density), a given volume in each region will contain a different weight of granules. This will lead to an unacceptable distribution of the drug content within the batch of finished product, even though the drug is evenly distributed, weight per weight, through the granules.

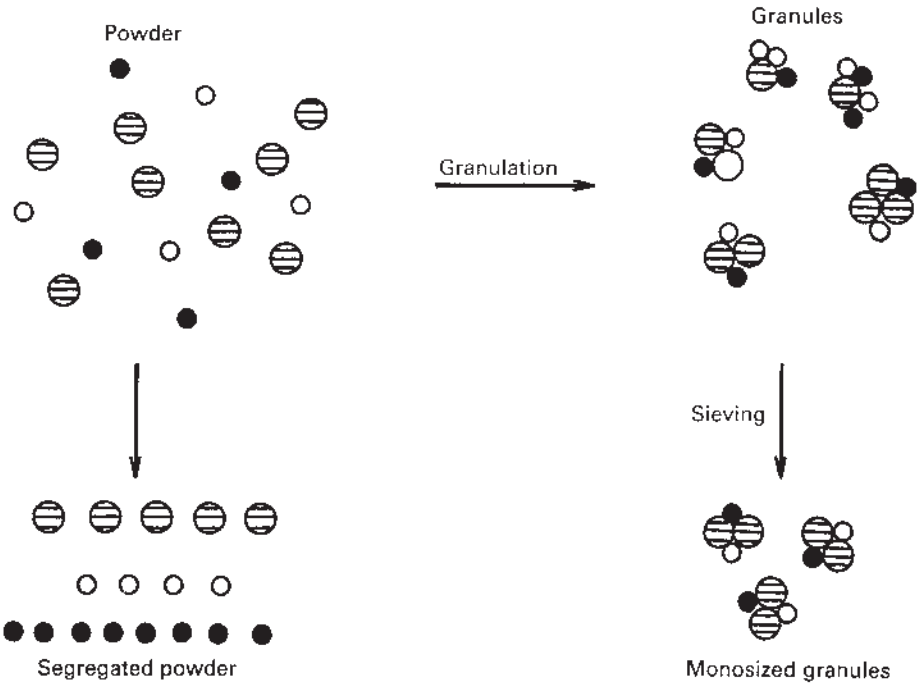

Fig. 25.1 Granulation to prevent powder segregation.

To improve the flow properties of the mix

Many powders, because of their small size, irregular shape or surface characteristics, are cohesive and do not flow well. Poor flow will often result in a wide weight variation within the final product owing to variable fill of tablet dies etc. Granules produced from such a cohesive system will be larger and more isodiametric, both factors contributing to improved flow properties.

To improve the compaction characteristics of the mix

Some powders are difficult to compact even if a readily compactable adhesive is included in the mix, but granules of the same formulation are often more easily compacted and produce stronger tablets. This is associated with the distribution of the adhesive within the granule and is a function of the method employed to produce the granule. Often solute migration (see Chapter 26) occurring during the postgranulation drying stage results in a binder-rich outer layer to the granules. This in turn leads to direct binder–binder bonding, which assists the consolidation of weakly bonding materials.

Other reasons

The above are the primary reasons for the granulation of pharmaceutical products, but there are other reasons that may necessitate the granulation of powdered material:

1. The granulation of toxic materials will reduce the hazard associated with the generation of toxic dust that may arise when handling powders. Suitable precautions must be taken to ensure that such dust is not a hazard during the granulation process. Thus granules should be non-friable and have a suitable mechanical strength.
2. Materials which are slightly hygroscopic may adhere and form a cake if stored as a powder. Granulation may reduce this hazard, as the granules will be able to absorb some moisture and yet retain their flowability because of their size.
3. Granules, being denser than the parent powder mix, occupy less volume per unit weight. They are therefore more convenient for storage or shipment.

Methods of granulation

Granulation methods can be divided into two types: **wet** methods, which use a liquid in the process, and ***dry*** methods in which no liquid is used.

In a suitable formulation a number of different excipients will be needed in addition to the drug. The common types used are diluents, to produce a unit dose weight of suitable size, and disintegrating agents, which are added to aid the break-up of the granule when it reaches a liquid medium, e.g. on ingestion by the patient. Adhesives in the form of a dry powder may also be added, particularly if dry granulation is employed. These ingredients will be mixed before granulation.

Dry granulation

In the dry methods of granulation the primary powder particles are aggregated under high pressure. There are two main processes. Either a large tablet (known as a '***slug***') is produced in a heavy-duty tabletting press (a process known as '***slugging***') or the powder is squeezed between two rollers to produce a sheet of material ('***roller compaction***'). In both cases these intermediate products are broken using a suitable milling technique to produce granular material, which is usually sieved to separate the desired size fraction. The unused fine material may be reworked to avoid waste. This dry method may be used for drugs that do not compress well after wet granulation, or those which are sensitive to moisture.

Wet granulation (involving wet massing)

Wet granulation involves the massing of a mix of dry ***primary powder particles*** using a ***granulating fluid***. The fluid contains a solvent which must be volatile so that it can be removed by drying, and be non-toxic. Typical liquids include water, ethanol and isopropanol, either alone or in combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved ***adhesive*** (also referred to as a ***binder*** or ***binding agent***) which is used to ensure particle adhesion once the granule is dry.

Water is commonly used for economical and ecological reasons. Its disadvantages as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products, and it needs a longer drying time than do organic solvents. This increases the length of the process and again may affect stability because of the extended exposure to heat. The primary advantage of water is that it is non-flammable, which means that expensive safety precautions such as the use of flameproof equipment need not be taken. Organic solvents are used when

water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required.

In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules which are then dried. A subsequent screening stage breaks agglomerates of granules and removes the fine material, which can than be recycled. Variations of this traditional method depend on the equipment used, but the general principle of initial particle aggregation using a liquid remains in all of the processes.

Effect of granulation method on granule structure

The type and capacity of granulating mixers significantly influences the work input and time necessary to produce a cohesive mass, adequate liquid distribution and intragranular porosity of the granular mass. The method and conditions of granulation affect intergranular and intragranular pore structure by changing the degree of packing within the granules. It has been shown that precompressed granules, consisting of compressed drug and binder particles, are held together by simple bonding during compaction. Granules prepared by wet massing consist of intact drug particles held together in a sponge-like matrix of binder. Fluidized-bed granules are similar to those prepared by the wet massing process, but possess greater porosity and the granule surface is covered by a film of binding agent. With spray-dried systems the granules consist of spherical particles composed of an outer shell and an inner core of particles. Thus the properties of the granule are influenced by the manufacturing process.

GRANULATION MECHANISMS

Particle-bonding mechanisms

To form granules, bonds must be formed between powder particles so that they adhere and these bonds must be sufficiently strong to prevent breakdown of the granule to powder in subsequent handling operations.

There are five primary bonding mechanisms between particles:

1. Adhesion and cohesion forces in the immobile liquid films between individual primary powder particles;
2. Interfacial forces in mobile liquid films within the granules;
3. The formation of solid bridges after solvent evaporation;
4. Attractive forces between solid particles;
5. Mechanical interlocking.

Different types of mechanism were identified in each group and the ones discussed below are those that are relevant to pharmaceutical granulations.

Adhesion and cohesion forces in immobile films

If sufficient liquid is present in a powder to form a very thin, immobile layer, there will be an effective decrease in interparticulate distance and an increase in contact area between the particles. The bond strength between the particles will be increased because of this, as the van der Waals forces of attraction are proportional to the particle diameter and inversely proportional to the square of the distance of separation.

This situation will arise with adsorbed moisture and accounts for the cohesion of slightly damp powders. Although such films may be present as residual liquid after granules prepared by wet granulation have been dried, it is unlikely that they contribute significantly to the final granule strength. In dry granulation, however, the pressures used will increase the contact area between the adsorption layers and decrease the interparticulate distance, and this will contribute to the final granule strength.

Thin, immobile layers may also be formed by highly viscous solutions of adhesives, and so the bond strength will be greater than that produced by the mobile films discussed below. The use of starch mucilage in pharmaceutical granulations may produce this type of film.

Interfacial forces in mobile liquid films

During wet granulation liquid is added to the powder mix and will be distributed as films around and between the particles. Sufficient liquid is usually added to exceed that necessary for an immobile layer and to produce a mobile film. There are three states of water distribution between particles, which are illustrated in Figure 25.2.

At low moisture levels, termed the ***pendular state***, the particles are held together by lens-shaped rings of liquid. These cause adhesion because of the surface tension forces of the liquid/air interface and the hydrostatic suction pressure in the liquid bridge. When all the air has been displaced from between

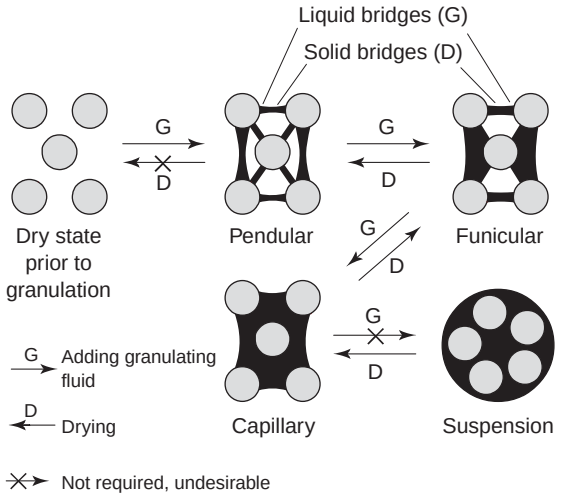

Fig. 25.2 Water distribution between particles of a granule during formation and drying.

the particles the ***capillary state*** is reached, and the particles are held by capillary suction at the liquid/air interface, which is now only at the granule surface. The ***funicular state*** represents an intermediate stage between the pendular and capillary states. Moist granule tensile strength increases about three times between the pendular and the capillary state.

It may appear that the state of the powder bed is dependent upon the total moisture content of the wetted powders, but the capillary state may also be reached by decreasing the separation of the particles. In the massing process during wet granulation, continued kneading/mixing of material originally in the pendular state will densify the wet mass, decreasing the pore volume occupied by air and eventually producing the funicular or capillary state without further liquid addition.

In addition to these three states, a further state, the droplet, is illustrated in Figure 25.2. This will be important in the process of granulation by spray-drying of a suspension. In this state, the strength of the droplet is dependent upon the surface tension of the liquid used.

These wet bridges are only temporary structures in wet granulation because the moist granules will be dried. They are, however, a prerequisite for the formation of solid bridges formed by adhesives present in the liquid, or by materials that dissolve in the granulating liquid.

Solid bridges

These can be formed by:

1. partial melting
2. hardening binders
3. crystallization of dissolved substances.

Partial melting Although not considered to be a predominant mechanism in pharmaceutical materials, it is possible that the pressures used in dry granulation methods may cause melting of low melting-point materials where the particles touch and high pressures are developed. When the pressure is relieved, crystallization will take place and bind the particles together.

Hardening binders This is the common mechanism in pharmaceutical wet granulations when an adhesive is included in the granulating solvent. The liquid will form liquid bridges, as discussed above, and the adhesive will harden or crystallize on drying to form solid bridges to bind the particles. Adhesives such as polyvinylpyrrolidone, the cellulose derivatives (such as carboxymethylcellulose) and pregelatinized starch function in this way.

Crystallization of dissolved substances The solvent used to mass the powder during wet granulation may partially dissolve one of the powdered ingredients. When the granules are dried, crystallization of this material will take place and the dissolved substance then acts as a hardening binder. Any material soluble in the granulating liquid will function in this manner, e.g. lactose incorporated into dry powders granulated with water.

The size of the crystals produced in the bridge will be influenced by the rate of drying of the granules: the slower the drying time, the larger the particle size. It is therefore important that the drug does not dissolve in the granulating liquid and recrystallize, because it may adversely affect the dissolution rate of the drug if crystals larger than that of the starting material are produced.

Attractive forces between solid particles

In the absence of liquids and solid bridges formed by binding agents, there are two types of attractive force that can operate between particles in pharmaceutical systems.

Electrostatic forces may be important in causing powder cohesion and the initial formation of agglomerates, e.g. during mixing. In general they do not contribute significantly to the final strength of the granule.

Van der Waals forces, however, are about four orders of magnitude greater than electrostatic forces and contribute significantly to the strength of granules produced by dry granulation. The magnitude of these forces will increase as the distance between

adjacent surfaces decreases, and in dry granulation this is achieved by using pressure to force the particles together.

Mechanisms of granule formation

In the dry methods, particle adhesion takes place because of applied pressure. A compact or sheet is produced which is larger than the granule size required, and therefore the required size can be attained by milling and sieving.

In wet granulation methods, liquid added to dry powders has to be distributed through the powder by the mechanical agitation created in the granulator. The particles adhere to each other because of liquid films, and further agitation and/or liquid addition causes more particles to adhere. The precise mechanism by which a dry powder is transformed into a bed of granules varies for each type of granulation equipment, but the mechanism discussed below serves as a useful broad generalization of the process.

The proposed granulation mechanism can be divided into three stages.

Nucleation

Granulation starts with particle–particle contact and adhesion due to liquid bridges. A number of particles will join to form the pendular state illustrated in Figure 25.2. Further agitation densifies the pendular bodies to form the capillary state, and these bodies act as nuclei for further granule growth.

Transition

Nuclei can grow in two possible ways: either single particles can be added to the nuclei by pendular bridges, or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed.

This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that this distribution is not excessively large, this is a suitable end-point for granules used in capsule and tablet manufacture, as relatively small granules will produce a uniform tablet die or capsule fill. Larger granules may give rise to problems in small-diameter dies owing to bridging across the die and uneven fill.

Ball growth

Further granule growth produces large, spherical granules and the mean particle size of the granulating system will increase with time. If agitation is continued, granule coalescence will continue and produce an unusable, overmassed system, although this is dependent upon the amount of liquid added and the properties of the material being granulated.

Although ball growth produces granules that may be too large for pharmaceutical purposes, some degree of ball growth will occur in planetary mixers and it is an essential feature of some spheronizing equipment.

The four possible mechanisms of ball growth are illustrated in Figure 25.3.

Coalescence Two or more granules join to form a larger granule.

Breakage Granules break into fragments which adhere to other granules, forming a layer of material over the surviving granule.

Abrasion transfer Agitation of the granule bed leads to the attrition of material from granules. This abraded material adheres to other granules, increasing their size.

Layering When a second batch of powder mix is added to a bed of granules the powder will adhere to the granules, forming a layer over the surface and increasing the granule size. This mechanism is only relevant to the production of layered granules using spheronizing equipment.

There will be some degree of overlap between these stages and it will be very difficult to identify a given stage by inspection of the granulating system. For end-product uniformity it is desirable to finish every batch of a formulation at the same stage, and this may be a major problem in pharmaceutical production.

Using the slower processes, such as the planetary mixer, there is usually sufficient time to stop the process before overmassing occurs. With faster granulation equipment the duration of granulation can only be used as a control parameter when the formulation is such that granule growth is slow and takes place at a fairly uniform rate. In many cases, however, the transition from a non-granulated to an overmassed system is very rapid, and monitoring equipment is necessary to stop the granulation at a predetermined point, known as granulation end-point control.

PHARMACEUTICAL GRANULATION EQUIPMENT

Wet granulators

There are three main types of granulator used in the pharmaceutical industry for wet granulation.

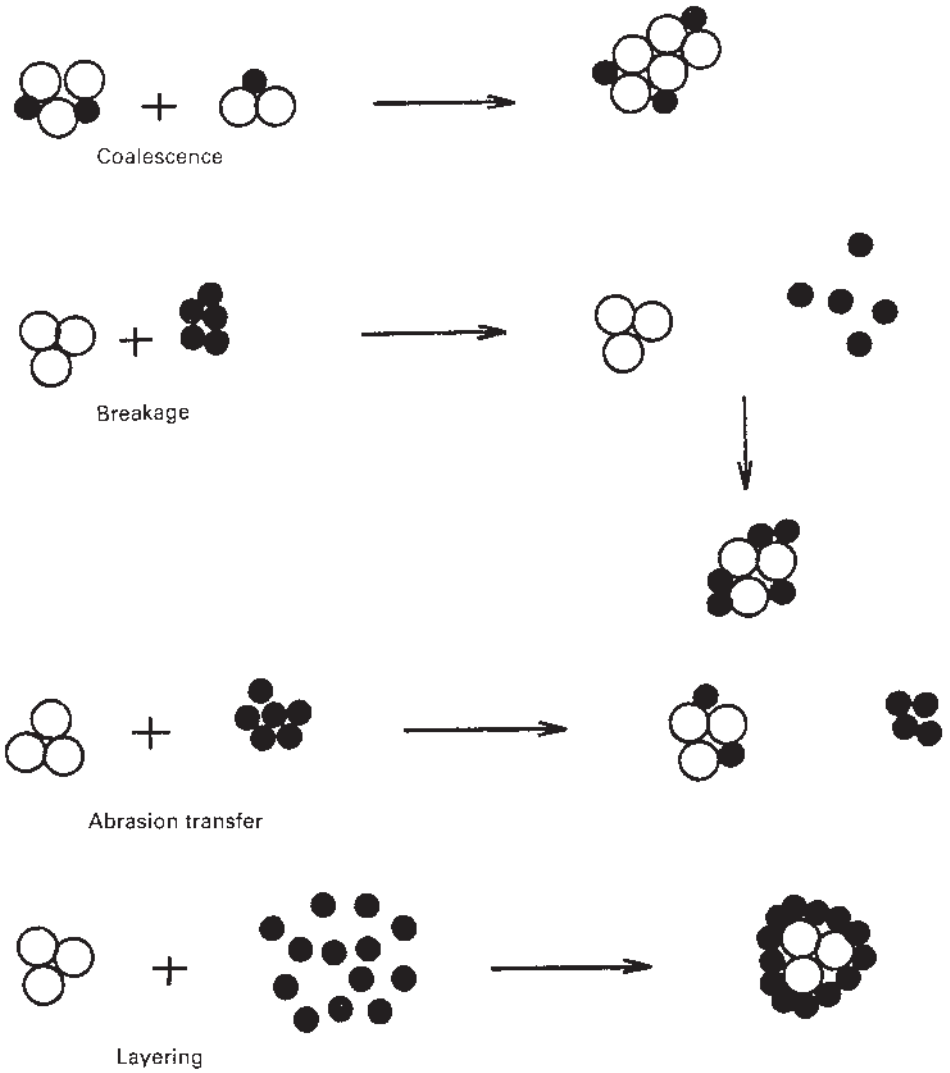

Fig. 25.3 Mechanisms of ball growth during granulation.

Shear granulators

In the traditional granulation process a planetary mixer is often used for wet massing of the powders, e.g. Hobart, Collette, Beken (Fig. 25.4). Powder mixing usually has to be performed as a separate operation using suitable mixing equipment. With some formulations, such as those containing two or three ingredients in approximately equal quantities, however, it may be possible to achieve a suitable mix in the planetary mixer without a separate stage.

The mixed powders are fed into the bowl of the planetary mixer and granulating liquid is added as the paddle of the mixer agitates the powders. The planetary action of the blade when mixing is similar to that of a household mixer.

The moist mass has then to be transferred to a granulator, such as an oscillating granulator (Fig. 25.5). The rotor bars of the granulator oscillate and force the moist mass through the sieve screen, the size of which determines the granule size. The mass should be sufficiently moist to form discrete granules when sieved. If excess liquid is added, strings of material will be formed and if the mix is too dry the mass will be sieved to powder and granules will not be formed.

The granules can be collected on trays and transferred to a drying oven, although tray drying suffers from three major disadvantages:

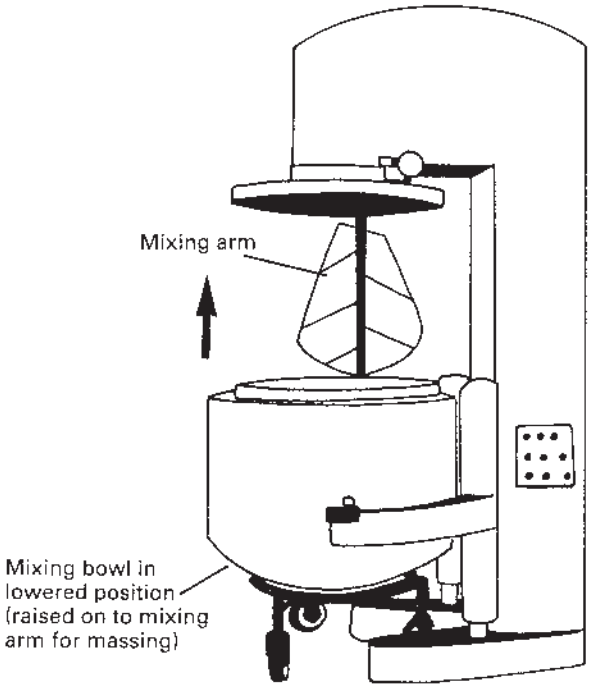

Fig. 25.4 Planetary mixer for wet massing.

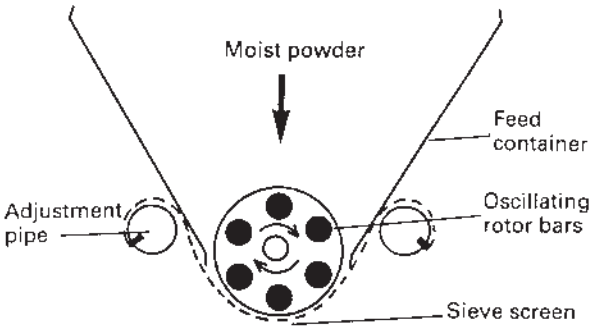

Fig. 25.5 Oscillating granulator.

1. The drying time is long.
2. Dissolved material can migrate to the upper surface of the bed of granules, as the solvent is only removed from the upper surface of the bed on the tray.
3. Granules may aggregate owing to bridge formation at the points of contact of the granules.

To deaggregate the granules and remix them, a sieving stage is necessary after drying.

An alternative method is to dry the granules using a fluidized-bed drier. This is quicker and, as it keeps the individual granules separated during drying, it reduces the problems of aggregation and intergranular solute migration, thereby reducing the need for a sieving stage after drying.

The disadvantages of this traditional granulation process are its long duration, the need for several pieces of equipment, and the high material losses that can be incurred because of the transfer stages. Advantages are that the process is not very sensitive to changes in the characteristics of the granule ingredients (e.g. surface area variations in different batches of an excipient), and the end-point of the massing process can often be determined by inspection.

High-speed mixer/granulators

This type of granulator (e.g. Diosna, Fielder) is used extensively in pharmaceutics. The machines have a stainless steel mixing bowl containing a three-bladed main impeller, which revolves in the horizontal plane, and a three-bladed auxiliary chopper (breaker blade) which revolves either in the vertical or the horizontal plane (Fig. 25.6).

The unmixed dry powders are placed in the bowl and mixed by the rotating impeller for a few minutes. Granulating liquid is then added via a port in the lid of the granulator while the impeller is turning. The granulating fluid is mixed into the powders by the impeller. The chopper is usually switched on when the moist mass is formed, as its function is to break up the wet mass to produce a bed of granular material. Once a satisfactory granule has been produced, the granular product is discharged, passing through a wire mesh which breaks up any large aggregates, into the bowl of a fluidized-bed drier.

The advantage of the process is that mixing, massing and granulation are all performed within a few minutes in the same piece of equipment. The process needs to be controlled with care as the granulation progresses so rapidly that a usable granule can be transformed very quickly into an unusable, overmassed system. Thus it is often necessary to use a suitable monitoring system to indicate the end of the granulation process, i.e. when a granule of the desired properties has been attained. The process is also sensitive to variations in raw materials, but this may be minimized by using a suitable end-point monitor.

A variation of the Diosna/Fielder type of design is the Collette–Gral mixer (Fig. 25.7). This is based on the bowl and overhead drive of the planetary mixer, but the single paddle is replaced by two mixing shafts. One of these carries three blades, which rotate in the horizontal plane at the base of the bowl, and the

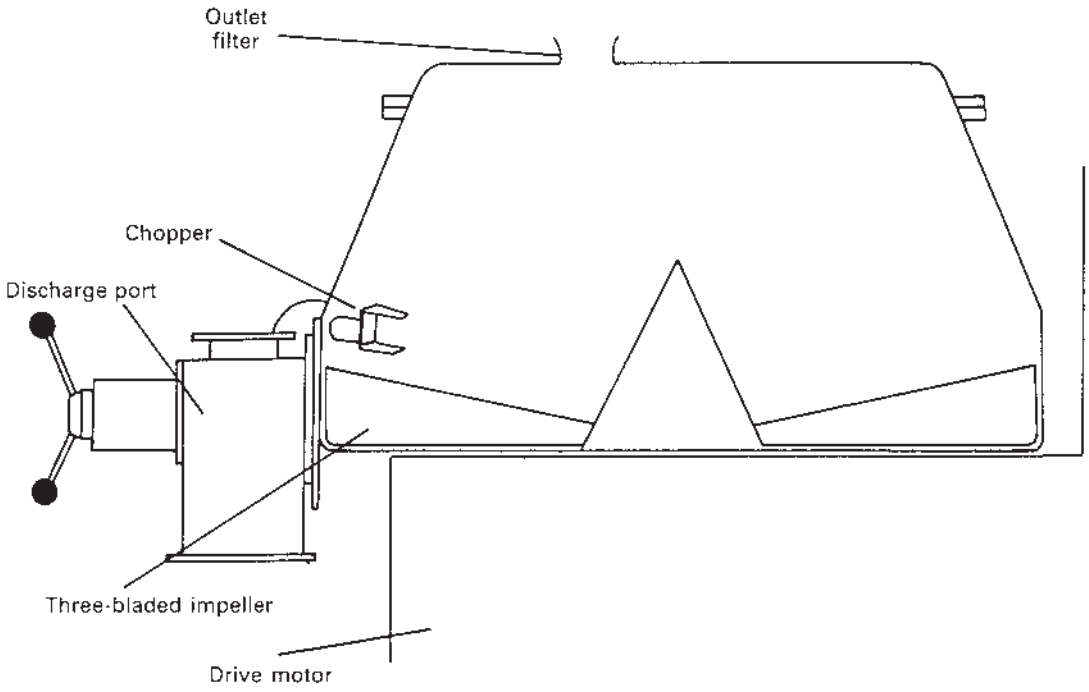

Fig. 25.6 High-speed mixer/granulator.

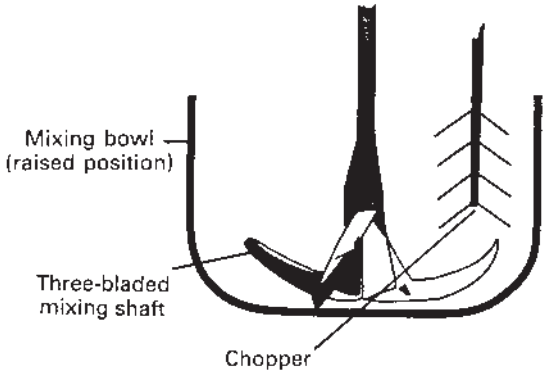

Fig. 25.7 Collette–Gral granulator: mixing shafts and bowl.

second carries smaller blades which act as the chopper and rotate in the horizontal plane in the upper regions of the granulating mass. Thus the operation principle is similar.

Fluidized-bed granulators

Fluidized-bed granulators (e.g. Aeromatic, Glatt) have a similar design and operation to fluidized-bed driers, i.e. the powder particles are fluidized in a stream of air, but in addition granulation fluid is sprayed from a nozzle on to the bed of powders (Fig. 25.8).

Heated and filtered air is blown or sucked through the bed of unmixed powders to fluidize the particles and mix the powders; fluidization is actually a very efficient mixing process. Granulating fluid is pumped from a reservoir through a spray nozzle positioned over the bed of particles. The fluid causes the primary powder particles to adhere when the droplets and powders collide. Escape of material from the granulation chamber is prevented by exhaust filters, which are periodically agitated to reintroduce the collected material into the fluidized bed. Sufficient liquid is sprayed to produce granules of the required size, at which point the spray is turned off but the fluidizing air continued. The wet granules are then dried in the heated fluidizing airstream.

Advantages of fluidized-bed granulation Fluidized-bed granulation has many advantages over conventional wet massing. All the granulation processes, which require separate equipment in the conventional method, are performed in one unit, saving labour costs, transfer losses and time. Another advantage is that the process can be automated once the conditions affecting the granulation have been optimized.

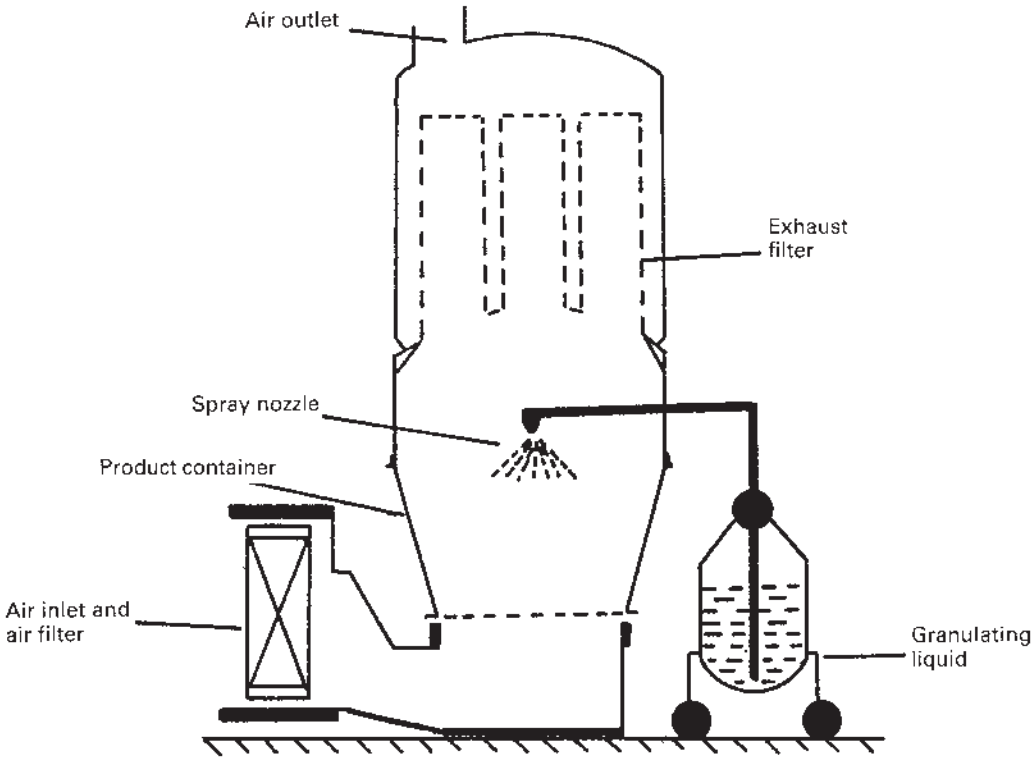

Fig. 25.8 Fluidized-bed granulator.

Disadvantages of fluidized-bed granulation On the downside, the equipment is initially expensive and optimization of process (and product) parameters affecting granulation needs extensive development work, not only during initial formulation work but also during scale-up from development to production. Similar development work for the traditional process and that using high-speed granulators is not as extensive.

This long and very product-specific development process has proved to be a serious problem with fluidized-bed granulation in the pharmaceutical industry. There are numerous apparatus, process and product parameters that affect the quality of the final granule. These are listed in Table 25.1. The extent of this list, coupled with the fact that each formulation presents its own individual development problems,

Table 25.1 Apparatus, process and product variables influencing fluidized-bed granulation

Apparatus parameters	Process parameters	Product parameters
Air distribution plate	Bed load	Type of binder
Shape of granulator body	Fluidizing air flow rate	Quantity of binder
Nozzle height	Fluidizing air temperature	Binder solvent
Positive or negative pressure operation	Fluidizing air humidity	Concentration of granulating solution
Scale-up	Atomization Nozzle type Spray angle Spraying regime Liquid flow rate Atomizing air flow rate Atomizing air pressure Droplet size	Temperature of granulation solution Starting Materials Fluidization Powder hydrophobicity

has led to fluidized-bed granulation not reaching its full potential in pharmaceutical production. This is exacerbated by the reality that most pharmaceutical companies have a wide range of products made at relatively small batch sizes, unlike other industries (fertilizers, herbicides, foodstuffs) where fluidized-bed granulation is used successfully and extensively.

Spray-driers

These differ from the method discussed above in that a dry, granular product is made from a solution or a suspension rather than initially dry primary powder particles. The solution or suspension may be of drug alone, a single excipient or a complete formulation.

The process of spray-drying is discussed fully in Chapter 26. The resultant granules are free-flowing hollow spheres and the distribution of the binder in such granules (at the periphery following solute migration during drying) results in good compaction properties.

This process can be used to make tablet granules, although it is probably economically justified for this purpose only when suitable granules cannot be produced by the other methods. Spray-drying can convert hard elastic materials into more ductile ones. Spray-dried lactose is the classic example, and its advantages over α-lactose monohydrate crystals when compacted are discussed in Chapter 27.

The primary advantages of the process are the short drying time and the minimal exposure of the product to heat owing to the short residence time in the drying chamber. This means that little deterioration of heat-sensitive materials takes place, and it may be the only process suitable for this type of product.

Spheronizers/pelletizers

For some applications it may be desirable to have a dense, spherical pellet of the type difficult to produce with the equipment above. Such pellets are used for controlled drug release products following coating with a suitable polymer coat and filling into hard gelatin capsules. Capsule filling with a mixture of coated and non-coated drug-containing pellets would give some degree of programmed drug release after the capsule shell dissolves.

A commonly used process involves the separate processes of wet massing, followed by extrusion of this wet mass into rod-shaped granules and subsequent spheronization of these granules. Because this process is used so frequently to produce modified-release multiparticulates, it will be discussed in some detail.

Extrusion/spheronization

Extrusion/spheronization is a multistep process used to make uniformly sized spherical particles. It is used primarily to produce multiparticulates for controlled drug release applications. The major advantage over other methods of producing drug-loaded spheres or pellets is the ability to incorporate high levels of active ingredients without producing excessively large particles (i.e. minimal excipients are necessary).

The main steps of the process are:

1. ***Dry mixing of ingredients*** to achieve a homogenous powder dispersion;
2. ***Wet massing*** to produce a sufficiently plastic wet mass;
3. ***Extrusion*** to form rod-shaped particles of uniform diameter;
4. ***Spheronization*** to round off these rods into spherical particles;
5. ***Drying*** to achieve the desired final moisture content;
6. ***Screening*** (optional) to achieve the desired narrow size distribution.

Applications of extrusion/spheronization

Potential applications are many, but relate mainly to controlled drug release and improved processing.

Controlled drug release Both immediate-release and controlled-release pellets can be formed. In turn, these pellets can either be filled into hard gelatin capsule shells or compacted into tablets to form unit dosage forms. Pellets can contain two or more ingredients in the same individual unit, or incompatible ingredients can be manufactured in separate pellets.

Pellets can be coated in sub-batches to give, say, rapid-, intermediate- and slow-release pellets in the same capsule shell. Dense multiparticulates disperse evenly within the GI tract and have less variable gastric emptying and intestinal transit times than do single units, such as coated monolithic tablets.

Processing The process of extrusion/spheronization can be used to increase the bulk density, improve flow properties and reduce the problems of dust usually encountered with low-density, finely divided active and excipient powders.

Extrusion/spheronization is a more labour-intensive process than other forms of granulation and should therefore only be considered when other methods are either not satisfactory for that particular formulation or are inappropriate (i.e. when spheres are required).

Desirable properties of pellets

Uncoated pellets:

- Uniform spherical shape
- Uniform size
- Good flow properties
- Reproducible packing (into hard gelatin capsules)
- High strength
- Low friability
- Low dust
- Smooth surface
- Ease of coating.

Once coated:

- Maintain all of the above properties
- Have desired drug-release characteristics.

The process

Dry mixing of ingredients This uses normal powder-mixing equipment.

Wet massing This stage also employs normal equipment and processes as used in wet granulation. There are two major differences in the granulation step compared with granulation for compaction:

1. The amount of granulation fluid
2. The importance of achieving a uniform dispersion of fluid.

The amount of fluid needed to achieve spheres of uniform size and sphericity is likely to be greater than that for a similar tablet granulation. Poor liquid dispersion will produce a poor-quality product.

Extrusion Extrusion produces rod-shaped particles of uniform diameter from the wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter. The extrudate particles break at similar lengths under their own weight. Thus the extrudate must have enough plasticity to deform, but not so much that the extruded particles adhere to other particles when collected or rolled in the spheronizer.

There are many designs of extruder, but generally they can be divided into three classes, based on their feed mechanism:

- Screw-feed extruders (axial or end-plate, dome and radial)
- Gravity-feed extruders (cylinder roll, gear roll, radial)
- Piston-feed extruders (ram).

The first two categories (Fig. 25.9) are used for both development and production, but the latter is only used for experimental development work as it is easy to add instrumentation.

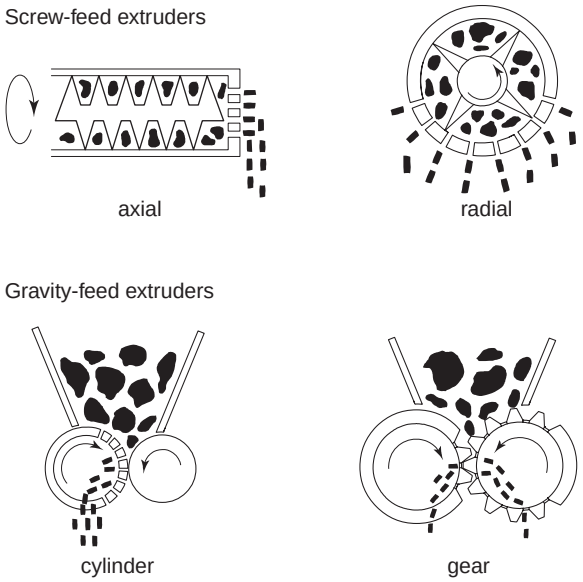

Fig. 25.9 Schematic representation of production extruders.

The primary extrusion process variables are:

- the feed rate of the wet mass
- the diameter of the die
- the length of the die
- the water content of the wet mass.

The properties of the extrudate, and hence the resulting spheres, are very dependent on the plasticity and cohesiveness of the wet mass. In general, an extrudable wet mass needs to be wetter than that appropriate for conventional granulation by wet massing.

Spheronization The function of the fourth step in the process (i.e. spheronization) is to round off the rods produced by extrusion into spherical particles.

This is carried out in a relatively simple piece of apparatus (Fig. 25.10). The working part consists of a bowl with fixed side walls and a rapidly rotating bottom plate or disc. The rounding of the extrudate into spheres is dependent on frictional forces generated by particle–particle and particle–equipment collisions. The bottom disc has a grooved surface to increase these forces. Two geometric patterns are generally used:

- A cross-hatched pattern with grooves running at right-angles to one another
- A radial pattern with grooves running radially from the centre of the disc.

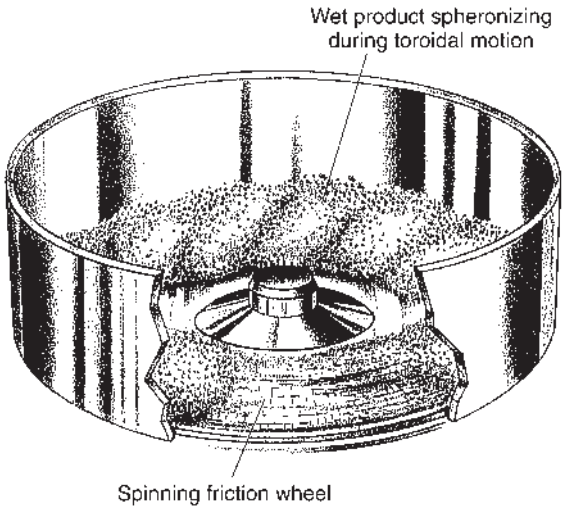

Fig. 25.10 A spheronizer showing the characteristic toroidal (rope-like) movement of the forming pellets in the spheronizer bowl during operation.

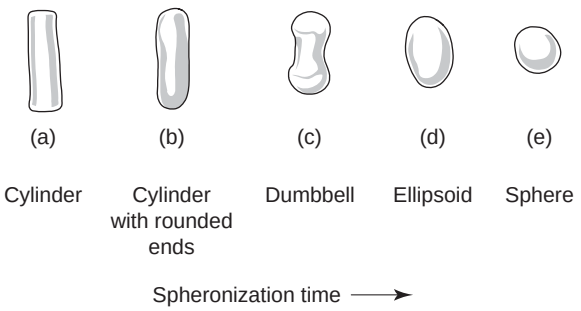

Fig. 25.11 Representation of a mechanism of spheronization. The diagram shows a transition from cylindrical particles (a) into cylindrical particles with rounded edges (b), then dumbbells (c), to ellipsoids (d) and finally spheres (e).

The transition from rods to spheres during spheronization occurs in various stages. These are best described by examining the following diagrams (Fig. 25.11).

If the mass is too dry spheres will not be formed: the rods will only transform as far as dumbbells.

Drying A drying stage is required in order to achieve the desired moisture content. This is often the final step in the process. The pellets can be dried in any drier that can be used for conventional wet granulations, including tray dryers and fluidized-bed driers. Both are used successfully for extrusion/spheronization. If solute migration (Chapter 26) occurs during drying of the wet spheres, this may result in:

- an increased initial rate of dissolution
- stronger pellets
- modified surfaces which might reduce the adhesion of any added film coats.

Screening Screening may be necessary to achieve the desired narrow size distribution. Normal sieves are used. If all the previous stages are performed efficiently and with careful development of process and formulation conditions, this step may not be necessary.

Formulation variables

The composition of the wet mass is critical in determining the properties of the particles produced. During the granulation step a wet mass is produced which must be plastic, deform when extruded, and break off to form uniformly sized cylindrical particles which are easily deformed into spherical particles. Thus the process has a complex set of requirements that are strongly influenced by the ingredients of the pellet formulation.

Summary

Extrusion/spheronization is a versatile process capable of producing spherical granules with very useful properties. Because it is more labour-intensive than more common wet massing techniques its use should be limited to those applications where a sphere is required and other granulation techniques are unsuitable.

The most common application of the process is to produce spherical pellets for controlled drug release.

Care must be taken to understand the required properties of the pellets and the manner in which the process and formulation influence the ability to achieve these aims.

Rotor granulation

This process allows the direct manufacture of spheres from dry powder. In the Freund granulator, the powder mix is added to the bowl and wetted with granulating liquid from a spray (Fig. 25.12). The baseplate rotates at high speed and centrifugal force keeps the moist mass at the edges of the rotor. Here, the velocity difference between the rotor and the static walls, combined with the upward flow of air around the rotor plate, causes the mass to move in a toroidal motion, resulting in the formation of discrete spherical pellets. These spheres (actually, of course, wet granules) are dried by the heated inlet air

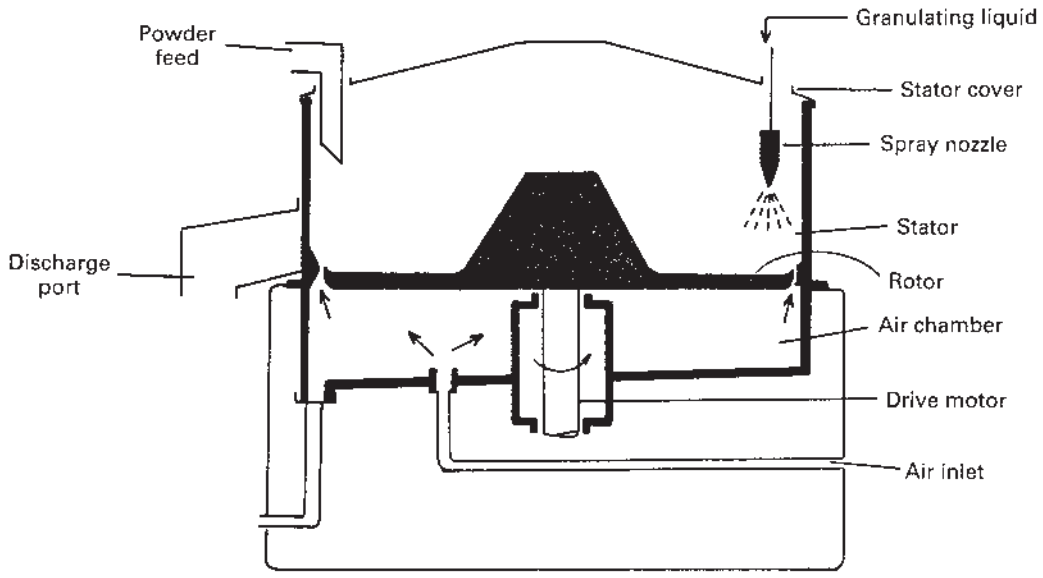

Fig. 25.12 Freund granulator.

from the air chamber, which also acts as a positive-pressure seal during granulation.

Using this technique it is possible to continue the process and coat the pellets by subsequently spraying coating solution on to the rotating dried pellets. In addition, layered pellets can be produced by using uncoated pellets as nuclei in a second granulation with a powder mix of a second ingredient or ingredients.

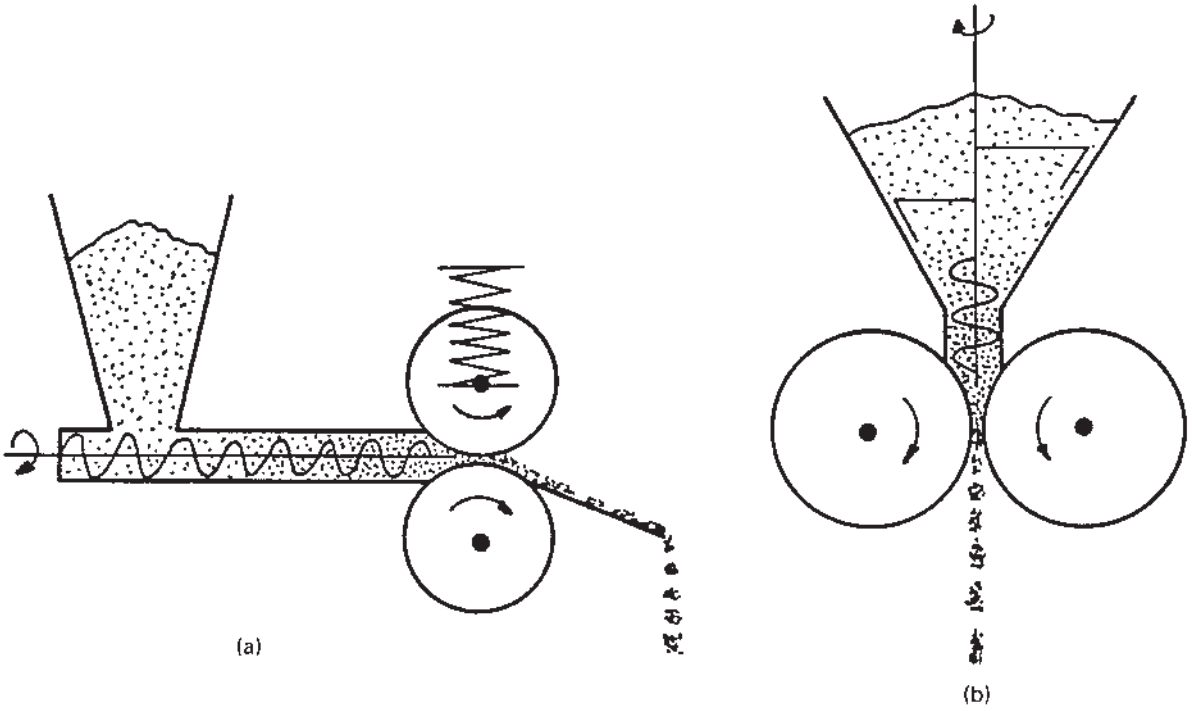

Fig. 25.13 Roller compaction: (a) Alexanderwerk and (b) Hutt types.

Dry granulators

Dry granulation converts primary powder particles into granules using the application of pressure without the intermediate use of a liquid. It therefore avoids heat–temperature combinations that might cause degradation of the product.

Two pieces of equipment are necessary for dry granulation: first, a machine for compressing the dry powders into compacts or flakes, and secondly a mill for breaking up these intermediate products into granules.

Sluggers

The dry powders can be compressed using a conventional tablet machine or, more usually, a large heavy-duty rotary press can be used. This process is often known as 'slugging', the compact made in the process (typically 25 mm diameter by about 10–15 mm thick) being termed a 'slug'. A hammer mill is suitable for breaking the compacts.

Roller compactors

Roller compaction is an alternative gentler method, the powder mix being squeezed between two rollers to form a compressed sheet (Fig. 25.13). The sheet normally is weak and brittle and breaks immediately into flakes. These flakes need gentler treatment to break them into granules, and this can usually be achieved by screening alone.

BIBLIOGRAPHY

There are a large number of published papers in the field of pharmaceutical granulation and only a limited number are listed below.

Baert, L. (1992) Correlation of extrusion forces, raw materials and sphere characteristics. *J. Pharm. Pharmacol.*, **44**, 676–678.

Das, S. and Jarowski, C.I. (1979) Effect of granulating method on particle size distribution of granules and disintegrated tablets. *Drug Dev. Ind. Pharm.*, **5**, 479.

Faure, A., Grimsey, I.M., Rowe, R.C. York, P. and Cliff, M.J. (1999) Applicability of a scale-up methodology for the wet granulation process in Collette Gral high shear mixer granulators. *Eur. J. Pharm. Sci.*, **8**, 85–93.

Gandhi, R., Kaul, C.L. and Panchagnula, R. (1999). Extrusion and spheronization in the development of oral controlled-release dosage forms. *Pharm. Sci. Tech. Today*, **2(4)**, 160–81.

Gergely, G. (1981) Granulation – a new approach. *Mfg Chem. Aerosol News*, **52**, 43.

Landin, M., York, P., Cliff, M.J. and Rowe, R.C. (1999) Scale up of a pharmaceutical granulation in planetary mixers. *Pharm. Dev. Tech.*, **4(2)**, 145–150.

Law, M.F.L. et al (1997). Comparison of two commercial brands of microcrystalline cellulose for extrusion–spheronization. *J. Microencap.*, **14(6)**, 713–723.

Lindberg, N.-O. and Leander, L. (1982) Instrumentation of a Kenwood major domestic-type mixer for studies of granulation. *Drug Dev. Ind. Pharm.*, **8**, 775.

Maejima, T. et al (1998) Application of tumbling melt granulation (TMG) method to prepare controlled-release fine granules. *Chem. Pharm. Bull*, **46(3)**, 534–536.

Nurnberg, E. and Wunderlich, J. (1998). Manufacturing pellets by extrusion and spheronization (Part I). *Pharm. Technol. Eur.*, **11(2)**, 41–47; Part II **11(3)**.

Ogawa, S. et al (1994) A new attempt to solve the scale-up problem for granulation using response surface methodology. *J. Pharm. Sci.*, **83(3)**, 439–443.

Parikh, D.M. (1997). *Handbook of Pharmaceutical Granulation Technology*, Marcel Dekker, New York.

Rubino, O.R. (1999) Fluid-bed technology; overview and criteria for process selection. *Pharm. Tech.*, **(6)**, 104–113.

Shah, R.D. et al (1995) Physico-mechanical characterization of the extrusion-spheronization process. *Pharm. Res.*, **12(4)**, 496–507.

Thoma, K. and Ziegler, I. (1998) Investigations on the influence of the type of extruder for pelletization by extrusion–spheronization I. Extrusion behavior of formulations. *Drug Dev. Ind. Pharm.*, **24(5)**, 401–411; II Sphere characteristics. *Drug Dev. Ind. Pharm.*, **24(5)**, 413–422.

Wørts, O. (1998) Wet granulation – fluidized bed and high shear techniques compared. *Pharm. Techn. Europe*, **10(11)**, 27–30.

Zhang, F. and McGinity, J.M. (1999). Properties of sustained-release tablets prepared by hot-melt etrusion. *Pharm. Dev. and Tech.*, **4(2)**, 241–250.