PRINCIPLES OF DRUG MANUFACTURE

Tablet compression

The basic principles of the tablet compression process have remained unchanged since their inception. The tablet press compresses the granular or powdered material in a die between two punches, each die/punch set being referred to as a station. Although many alternative methods have been tried, the principle of filling granules into a die and compressing them into a tablet between two punches is still the primary method of manufacture for all machines used in pharmaceutical manufacturing. Developments utilizing a slightly different configuration of punch and die are under current examination in Japan and Italy. The primary incentive of these developments is to produce an arrangement which can reliably be cleaned-in-place, rather than relying on the time-consuming process of dismantling the machine to remove product-contact parts for cleaning with its attendant risks of operator exposure to active products. Tablet machines can be divided into two distinct categories: those with a single set of tooling — single station or eccentric presses; those with several stations of tooling — multi-station or rotary presses.

The former are used primarily in the small-scale product development role, while the latter, having higher outputs, are used in production operations. Additionally the rotary machines can be classified in several ways, but one of the most important is the type of tooling with which they are to be used. There are basically two types of tooling — 'B' type which is suitable for tablets of up to 16 mm diameter or 18 mm length (for elliptical or similar hapes), and 'D' type which is suitable for tablets with a maximum diameter or of die; the small 'B' die is suitable for tablets up to 9 mm diameter or 11 mm maximum length, and the larger 'B' die is suitable for all tablet sizes up to the maximum for the 'B' punches. Machines can, therefore, be used with either 4B' or 'D' tooling, but not both. Machines accepting 'B' type tooling are designed to exert a maximum compression force of 6.5 tonnes, and machines accepting 'D' type tooling 10 tonnes. Special machines are available which are designed for higher compression forces. The maximum force that can be exerted on a particular size and shape of tablet is governed by the size of the punch tip or the maximum force for which the machine is designed — whichever is smaller.

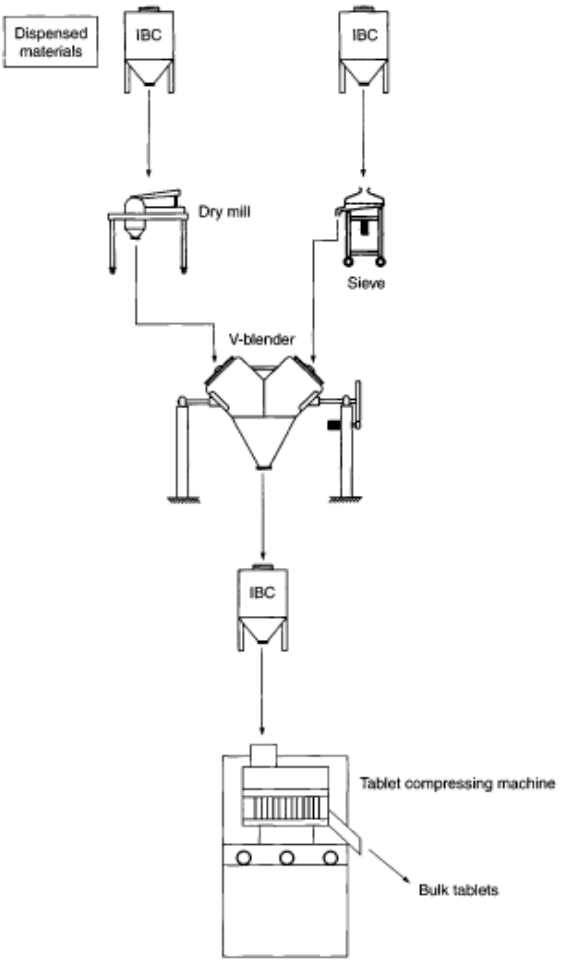

Figure 6.5 Typical flow diagram for direct compression

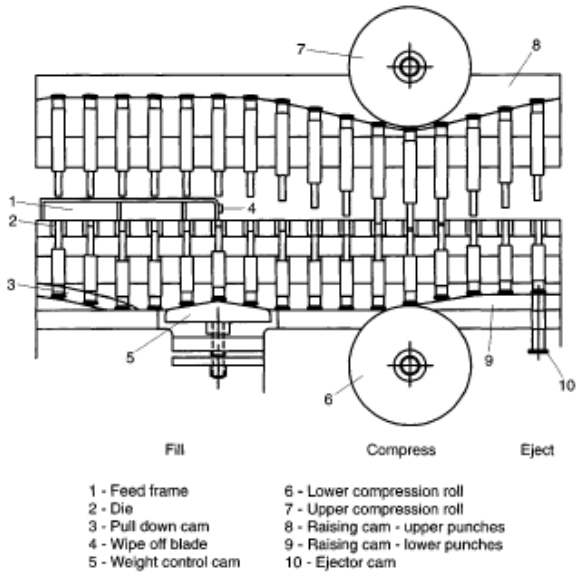

Figure 6.6 Rotary tablet compression machine operation

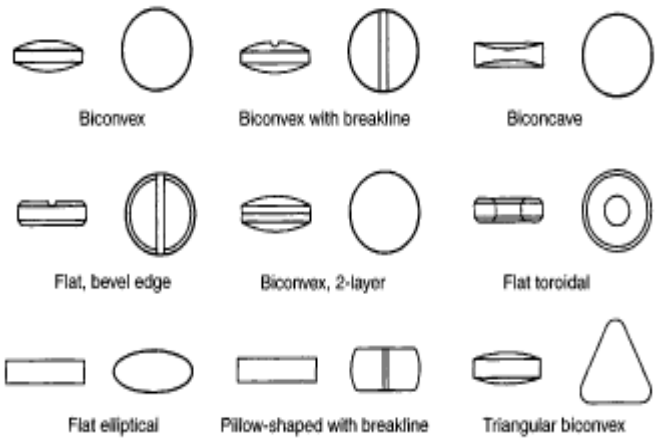

Figure 6.7 Some tablet shape possibilities

Tablets are now available in a range of diameters and thicknesses to suit the proportion, active dose and characteristics of the drug substance. Figure 6.7 shows some examples of tablet shape possibilities. Formulation has enabled the production of tablets with special characteristics such as:

- effervescent;
- chewable;
- multi-layer;
- delayed or sustained release;
- bolii for veterinary use.

These examples indicate the extent to which development of the tablet has continued since its original introduction. Much effort was expended during the first half of the 20th century in establishing the best particle size of the active drug and the range and rheology of excipients needed to produce a reliable tablet with acceptable dispersion and absorption characteristics. However, the technology of tablet compression did not advance significantly during this period; reliable and robust machinery was produced and its performance and output were considered suitable for the demands of the time. Subsequently, improved excipient development by the pharmaceutical industry, based on enhanced glidants and micro-crystalline cellulose binding agents, and the introduction of reliable sensors coupled with electronic control systems have allowed compression technology to advance.

Whereas the manufacture of a single tablet is simply a matter for formulation development, the production of such products at machine speeds in excess of 300,000 tablets per hour raises additional challenges. The critical stage here is the delivery of the granulation into a die on a high-speed rotating disc accurately, so that tablets of minimum weight variation can be produced. Very high-speed compression machines are now available with built-in tablet weight and thickness control and the ability to be self-monitoring from an output and quality standpoint. Hence, it has become possible for continuous, unmanned operation of the tabletting process to be carried out (the so-called 'lights out' working). More recently, the greater impetus to improve has come from regulatory pressures, under which the need for uniformity, consistency and reliability has become paramount. The principles of current Good Manufacturing Practice (cGMP) and validation have greatly influenced the development of the tablet manufacturing process and the materials and methods used therein.

Granulation

The process of tablet making using modern machinery involves the blending of the drug substance with binders, fillers, colouring materials, lubricants etc., followed by a series of operations designed to

increase the bulk density and uniformity of the mixture and prevent segregation of the drug. These operations are known as granulation, and are an important part of modern pharmaceutical product manufacture, notably for tablets but also for other products. The granulation process is a critical step in reliable drug manufacture, as it often involves the relative 'fixing' of several ingredients and must therefore be carefully designed and controlled. Regulatory pressures, demanding as they do a strict equivalence of product performance before and after development scaleup, ensure that during drug research and development the selection of granulation methods must be made carefully. This selection, including the choice of individual equipment types, can be difficult and costly to change, owing to the need for the validation of continued product performance. The desired increase in bulk density and uniformity can be achieved by compression methods followed by milling, a process known as dry granulation. The techniques used for compression include 'slugging', a process not unlike tablet making, and roller compaction, which involves the feeding of material between a set of closely spaced steel rollers. The former produces tablet-like structures, which can then be reduced to granules by milling, whereas the latter gives rise to a flake-like compact that is first broken into smaller pieces and then reduced by milling. In either case, the forces and friction involved are such that a lubricating material (such as magnesium stearate) is necessary. To ensure good material flow, a material such as Cab-o-Sil (silicon dioxide) is often used. Figure 6.1 shows a flow diagram for a dry granulation process. The dry granulation process is not very easy to contain in terms of dust emission and available equipment suitable for pharmaceutical applications is not common. This is mainly due to its greater use in heavy chemical, food and fertilizer manufacture. However, all formulation departments will attempt to formulate a dry process, as it is cheaper in capital equipment and a simpler process.

Therefore, the process most often used is wet granulation. This operation takes the blended materials, adds a suitable wetting agent, mixes the combined materials, passes the wet mass through a coarse screen, dries the resultant granules using a tray or fluid-bed dryer, and finally reduces the particle size of the dry material by passing it through a finer screen. Figure 6.2 (see page 115) shows a typical flow diagram for a conventional wet granulation process. The increasing potency of drug substances has encouraged manufacturers to seek granulation methods that are enclosed and free of dust emissions. Thus, a number of process equipment manufacturers have developed systems for enclosed processing which incorporate several of the granulation steps in a single unit.

The most common of these is the mixer-granulator, which combines the powder mixing, wetting, wet massing and cutting operations. These efficient machines can perform this set of processes within a matter of minutes, and discharge a wet granule which requires only drying, milling and final blending with

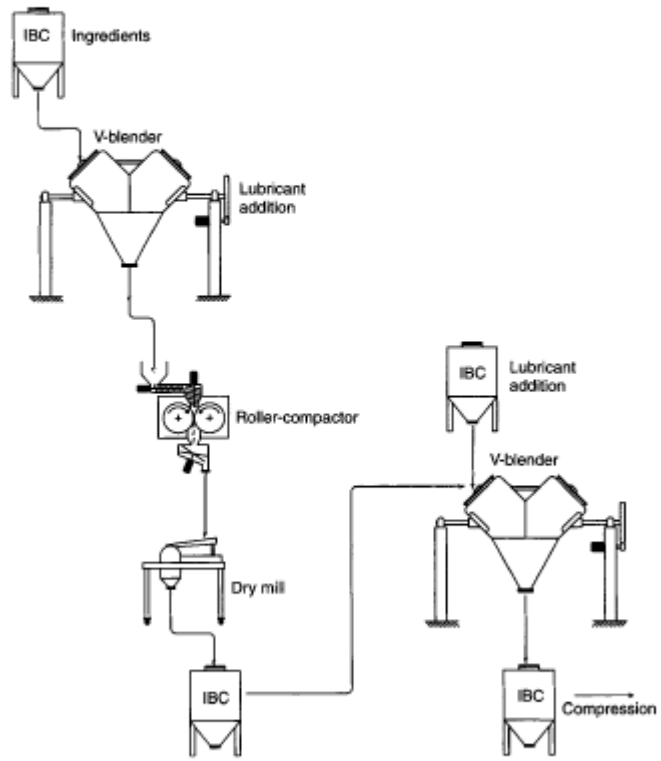

Figure 6.1 Typical dry granulation process

lubricants to produce a tablet compression mix. In most cases, however, the discharged wet granule will be further reduced in size by passage through a coarsescreen sieve prior to drying, in order to improve drying rates and consistency. The key to mixer-granulator operation is the combination of high-shear powder mixing with intense chopping of the wet granule. Figure 6.3 (see page 116) illustrates a typical mixer-granulator. The process steps employed in mixer-granulators are as follows:

- mixing of the dry ingredients with the main impeller and chopper rotating at high speed (15ms"1 impeller tip speed and 4000 rpm chopper speed) for, typically, 3 minutes;
- addition of a liquid binder solution by pumping, spraying or pouring it onto the dry material with the impeller and chopper running at low speed (5 ms"1 and 1500 rpm) for around 2 minutes;
- wet massing with impeller and cutter running at high speed (2 minutes);
- discharge of the granulated material through a coarse sieve or directly to a dryer.

The step times indicated will vary according to the product involved, and are generally critical in relation to granule consistency.

There are a number of advantages that combined-processor granulators have over conventional methods, as follows:

- the granulation steps are enclosed in a single unit that can integrate with subsequent-stage equipment, thus minimizing dust emissions;
- the process is rapid;
- binder liquid volumes can be reduced;
- granule characteristics can be adjusted easily by changing step times and binder addition rates;
- inter-batch cleaning can be performed easily, and can be achieved by use of automatic Clean In Place systems.

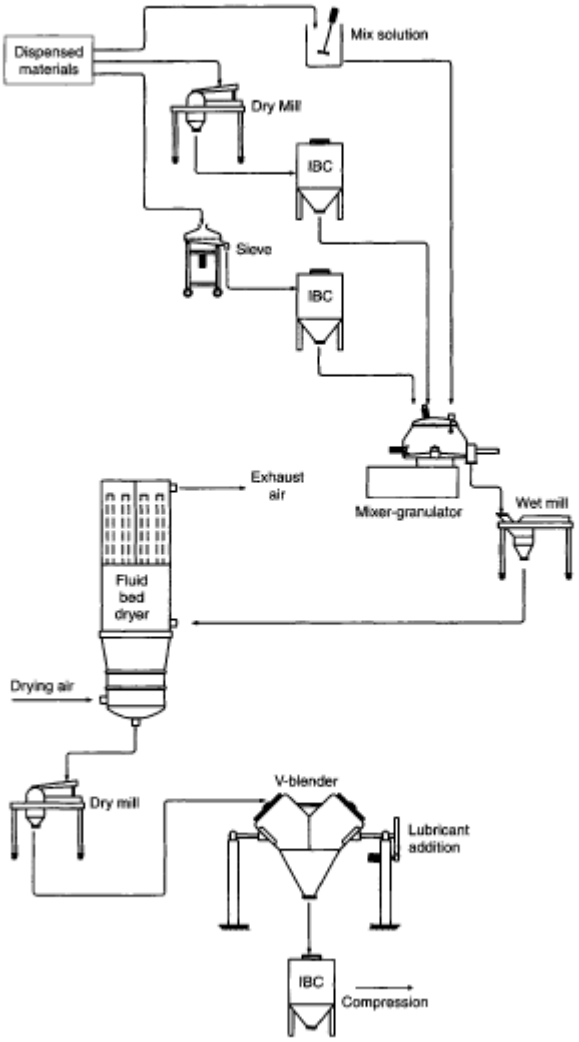

Figure 6.2 Typical wet granulation process

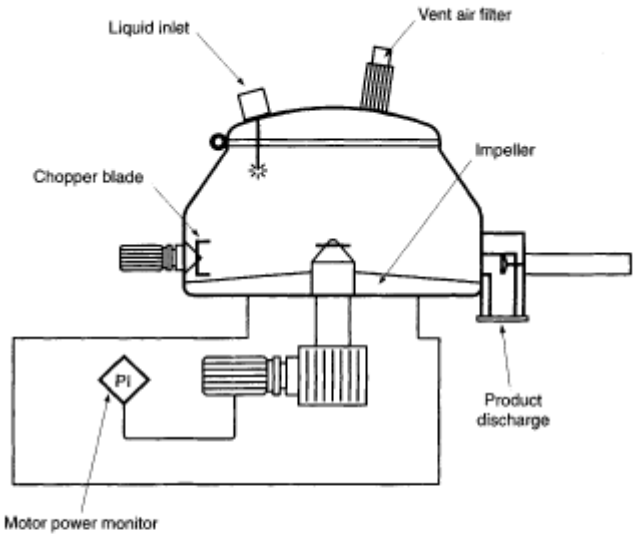

Figure 6.3 High shear mixer-granulator with opening lid

However, disadvantages do exist, mainly associated with the high speed and energy input provided by the agitators. This can give rise to mechanical breakdown of ingredient particles, over-wetting due to compaction producing over-sized granules, and chemical degradation of sensitive ingredients due to temperature rise. Developments of the mixer-granulator include jacketed and heated or cooled mixing bowls, which avoid over-heating of the granules or assist in their drying, and the use of vacuum to reduce drying times and temperatures. These 'single- pot' units aim to provide an efficient and contained operation covering as many granulation steps as possible in a single unit.

Single-pot mixer-granulators using vacuum and heated jackets, but employing slightly different configurations of impeller and chopper, include the Zanchetta Roto granulator/dryer, which uses a vertical-axis retractable chopper. This machine also operates slightly differently in that the bowl is pivoted so that the effective heat exchange surface can be maximized for reduced drying time. The planes of shear within the powder mass can also be altered at each stage of the process for optimum mixing and final size reduction.

The application of microwave energy for granule drying in-situ has been pioneered by Aeromatic-Fielder. The magnetron generators are situated on top of a mixer-granulator that operates under vacuum and are energized at the end of the wet massing/chopping cycle. Figure 6.4 (see page 118) shows a flow diagram for a combined granulation process.

Spray granulation

A different and somewhat unusual granulation technique is the use of the spray dryer. Spray granulation requires that all ingredients are soluble or dispersible in a common solvent and can be crystallized/combined from that solvent at a suitable temperature. The solution or suspension feed stream is

passed through a nozzle inside the spray dryer chamber, where it immediately comes into contact with a co-current or counter-current gas stream at controlled temperature. The solvent evaporates rapidly and the resulting solids are separated from the air stream by cyclone separators and filters. Spray granulation offers a number of advantages over mixer-granulation systems. The feed, being a homogeneous liquid, removes concerns over blending of liquid binders into dry solids. The resulting granules are homogeneous and, regardless of size, contain uniform proportions of the ingredients. Temperature control is also more consistent, thus eliminating problems of heatdegradation. Finally, the absence of mechanical moving parts generally improves clean ability and reduces contamination risks.

A recent example of this principle is the Spinning Disc Atomization system being developed in Switzerland by Prodima SA and EPFL. In this system a suspension of the product or a polymer melt is passed between rotating concentric conical discs and is released into the gas stream as fine uniform droplets, which dry or solidify to produce very spherical and similar granules.

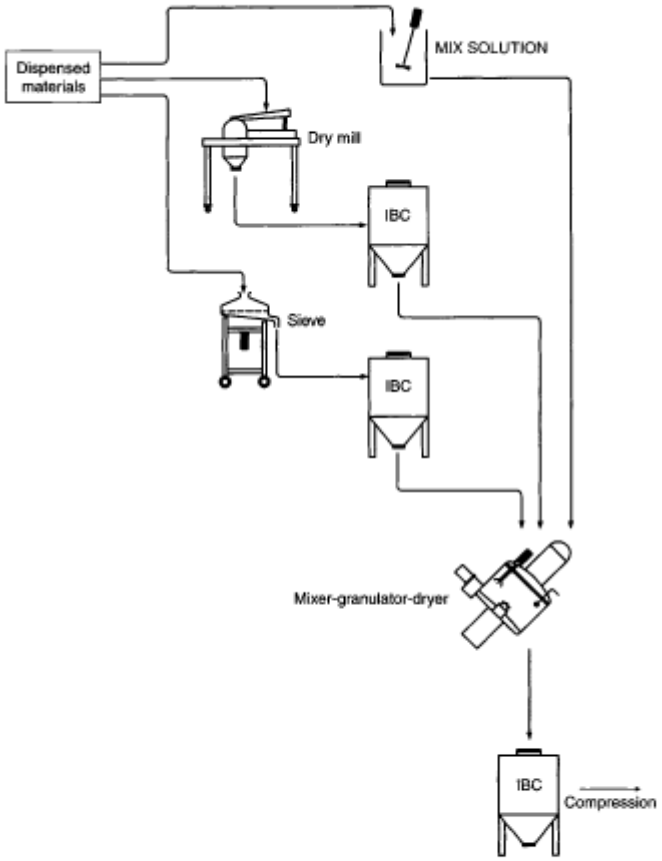

Figure 6.4 Typical combined granulation process

Fluid-bed granulation

A related process for achieving granulation by spray techniques utilizes the mixing action of a fluidized bed to mix powder ingredients in an otherwise conventional fluid-bed dryer. The mixture so

created is then subjected to a sprayed-on binder solution, the evaporation of whose solvent produces an intimately-mixed granulate which is then dried by the fluidizing air stream. Direct compression some drug substances have characteristics that allow them to be compressed without prior granulation, using a process known as 'direct compression'. This process avoids the cost and inconvenience of granulation, but often requires the use of special binding agents to avoid segregation during mass flow of the mix in the tablet compression process. Figure 6.5 (see page 120) shows a typical flow diagram for direct compression.

Coated tablets

Many tablet products contain active materials that require taste masking or a controlled release rate, and a variety of methods have been developed to achieve these objectives. A careful choice of excipients can mask the unpleasant taste of certain compounds, but a more reliable procedure is to coat the tablet with a barrier material. Such coating can be achieved by forming a compressed layer around the basic tablet, or core. There are compression machines that can accept a previously formed core and surround it with a layer of excipient material. An additional and similar use of compression can produce layered tablets. The traditional method of taste masking is to apply a sugar coating to the core, and although this method has largely been superseded by film-coating techniques, it is still used. Originally the sugar coating was applied by pouring a sugar syrup, usually coloured, onto a bed of pre-varnished tablet cores rotating in a steel or copper pan into which warm air was blown. The skill required to achieve a successful application of the sugar coat was such that the true art of tablet making/coating resided in the hands of a small and respected elite. A key feature of the sugar coating process was that the tablet weight increased significantly with the sugar coating accounting for typically 60% of total tablet weight.

Subsequently this skill has largely been replaced by a more-automated system using mechanized spray/jets of sugar syrup applied in a pre-determined and controlled manner to a bed of tablets rotating in a perforated drum and warmed with pre-heated air.

A logical development of automated sugar coating was the introduction of non-sugar coating materials, based on plastic film-forming solutions/ suspensions. This 'film coating' process has largely replaced the original sugar coating technique, although the method of application is basically similar. Advantages are the removal of food-type materials, a higher speed of throughput and a small increase in tablet size/weight, with consequent reductions in packaging cost.

Initially, most film-coating formulations included the use of flammable solvents for coating solution/suspension manufacture, and given the relative toxicity and safety risks associated with these materials it is not surprising that much effort has been expended in developing aqueous-based alternatives. The latter now make up the majority of film-coating formulations.

Figures 6.8 and 6.9 (see pages 124 and 125) are flow diagrams showing the stages of the film and sugar coating processes.

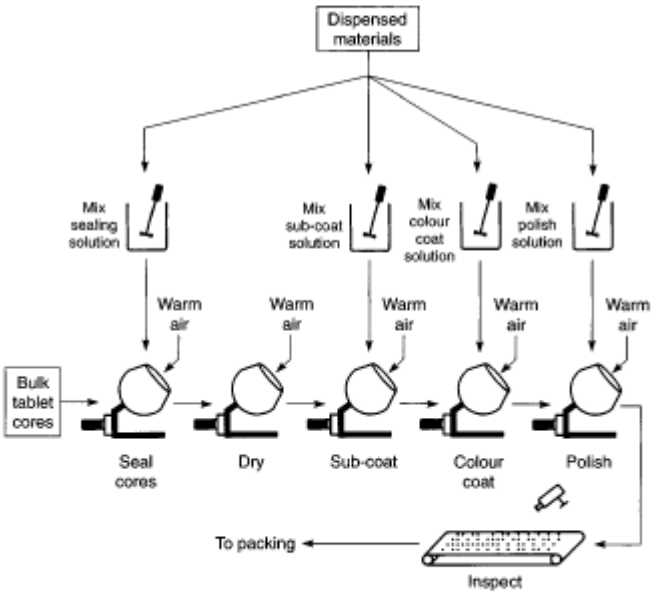

Figure 6.8 Tablet sugar coating

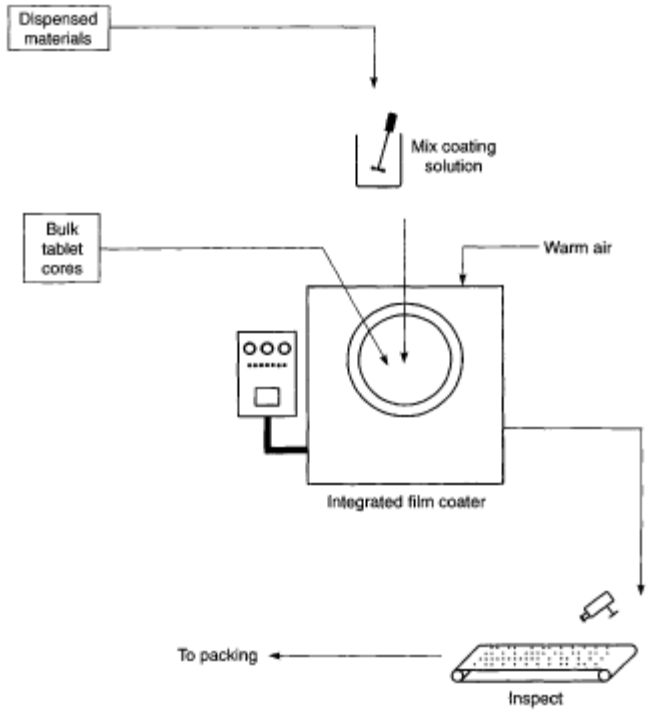

Figure 6.9 Tablet film coating

Capsules

The encapsulation process is an alternative to tablet compression, which also masks unpleasant tasting actives. It can also have advantages where compression could result in a compacted tablet with

unacceptably long or short dispersion time in the upper alimentary system. As with tablets, the gelatin barrier can be further coated with 'enteric' materials which ensure dissolution or dispersion only in that part of the system where optimum effect is produced. Capsules are generally of two types, made with either hard or soft gelatin.

Hard gelatin capsules

Hard capsules are manufactured from bone gelatin and are produced as empty two-part shells supplied to the pharmaceutical manufacturer for filling. The capsules are produced in a number of standard sizes designated 5 through 000, with larger sizes available for veterinary applications. Although originally filled by hand, and later by devices that allowed multiple cap/body separation, volumetric filling and reassembly, they are now filled on automatic machines. These separate the two parts, fill the body with powder, granules, pellets or semi-solids as required by the formulation to a controlled level, and reassemble the two parts prior to discharge. One disadvantage of the hard capsule is that a number of systems for dosage control have been developed by different filling machine manufacturers, so that (unlike tablets) the capsule has no standardized filling system. The original hard capsule type, which was conceived as long ago as the 1840s, consisted of two plain-sided cylinders with hemispherical ends, one of larger diameter, so that one formed the body and the other the cap. Tolerances during manufacture (by dipping pins in molten gelatin) ensured that the cap/body clearance was minimized to prevent the possibility of powder leakage. Originally designed to deliver powder products, improvements in formulations and capsule tolerances have allowed the use of this dosage form for delivering oils and pastes.

Where fine powder escape or simple separation of the two parts proved problematic, these capsules were sealed by the application of a band of molten gelatin at the cap/body joint. This was achieved using conveyor-type machines, which provided space and time for the gelatin band to set, and provided an opportunity for visual inspection of the capsules. The introduction in the late 1960s of the self-locking capsule, coupled with improved dimensional tolerances, largely removed the necessity for band sealing. After the initial establishment of hard-shell capsules as a dosage form, machines were developed to increase the production rates of filled shells. One of the first types, developed by Colton and by Parke-Davis, consisted of a two plate device that simply separated the two halves of the shells, filled the bodies volumetrically, and allowed recombination. One of the first commercially available machines to automate the process was developed by Hofliger and Karg of Germany, and filled at speeds of 150 capsules per minute. This machine used the differential diameter of the capsule cap and body to orientate and vacuum to separate the two parts, and an auger device to meter the product powders or granules and feed them into the

capsule bodies. The caps and bodies were then re-combined prior to ejection. Figure 6.10 (see page 127) illustrates a typical capsule filling process.

These techniques for capsule handling have basically been retained in later, higher-speed machines, but the dosing system has undergone a divergence in design. The original auger type filler is no longer used, mainly because it is not capable of high-speed operation without recourse to multiple stations, which would give rise to an unacceptably large machine. The system developed in the 1960s by the Zanasi brothers in Italy, and still used today, employs a plug-forming method to produce the required dose.

A tube is plunged into a container of product having uniform depth, and the column of product so contained is compressed in-situ by the downward motion of a piston inside the tube. On withdrawal of the tube a cylindrical compact is retained within it, and this is then discharged into a capsule body by further downward motion of the piston. The dose weight and degree of compression (and subsequent dispersion) of the product is capable of adjustment by altering the depth of powder/granule in the product container and the extent of downward motion of the piston. One advantage of this so-called 'dosator' system is that the tube is quite small, so that a number of them can be arranged in a dosing module of modest dimensions to give increased output. Original machines worked with an intermittent motion, but later versions were designed to operate continuously by arranging the capsule feed/handling groups and the dosing units on separate rotating turrets, emulating to some extent the conventional tablet press.

To meet the challenge of the higher-speed dosator machines, Hofliger and Karg introduced their GKF range of machines, which utilizes the natural capacity of the capsule body for controlling product dosing. The capsule bodies, having been separated from their caps and fed vertically into cylindrical machined holes in a rotating disc, are moved so as to pass under a container of product powder/granule (not unlike the feed frame of a tablet compression machine), so that the product mix flows into the empty bodies. Before leaving the product container, the contents of the capsule bodies are subjected to compression by the insertion of pistons to a pre-determined and adjustable depth. After compression, the bodies are removed from the dosing zone by the rotation of the disc and reunited with their caps. This system allowed for a significant speed increase compared with the auger type, but was disadvantaged in that the degree of dosage weight and compaction control was less than that allowed by the dosator system. A revised version was therefore introduced which included an intermediate dosing disc which allowed for the formation of a product 'plug', independently of the capsule body, which could then be transferred to the body after formation and compression. This development permitted the use of dosing discs of different thickness to control dose weight.

Again, the small dimensions of the Hofliger and Karg dosing arrangement made it possible to fill capsules at very high speeds of over 2500 filled capsules per minute. Apart from size considerations, the key to high-speed capsule filling is powder flow, which in turn relies on consistent particle size and shape distribution. The bulk density of the filling material is of parallel concern, and must be uniform if reliable dosage weights are to be achieved. As with tablet compression, the conditions and processes employed for preparation of the filling mix have critical impact on performance. A typical capsule filling mix for a high-dose product may contain only the active drug and a lubricant (for example, many antibiotic products are formulated in this way), so the options for formulation adjustment are limited. Products utilizing a lower active dose proportion may also contain a filler (such as lactose), flow-aid (for example, silicon dioxide) and surfactant (such as sodium lauryl sulphate) and may therefore have superior flow and output characteristics.

Soft gelatin capsules

Soft gelatin capsules, where the gelatin contains a plasticizer to maintain flexibility, were originally developed in France in the 1830s, and are generally used where the active product material is liquid or semi-solid, or where the most appropriate formulation is in this form. They were originally made in leather moulds, which provided an elongated shape and a drawn-out end which could be cut off to allow for the insertion of the product liquid, after which the end could be sealed with molten gelatin. Although less popular than hard-shell capsules, their 'soft' counterparts satisfy a different set of product/market criteria, under which the total containment of the active principals is a key concern.

The manufacture of soft-gelatin capsule products is generally regarded as more specialized than that of other dosage forms and has been limited to a small number of producers. These companies have very much influenced the development of the technology employed in the production process. R P Scherer developed the modern technology for automated soft-gelatin capsule production in the 1930s by designing the Rotary Die Process. The basic technique employed in soft-shell filling involves the melting of a gelatin/ plasticizer mixture and the extrusion of this between the two halves of a mould formed by twin rotating cylinders, while the product liquid or solid is injected between the two half-shells thus produced. The continued rotation of the cylindrical moulds results in the closing and sealing of the resultant capsule and its subsequent ejection.

Pellets and other extrudates

A feature of capsules, which can have drug-release benefits, is that they can be filled with materials other than powder or granule mixtures. In addition to liquids and pastes, which are generally more suited to soft gelatin types, product in the form of large granules or pellets can be filled into hard-shell capsules Whereas 'large' granules can be prepared by the methods already described, pellets have their own

production technology, based upon extrusion and spheronization. The spherical granules, or spheroids, have several advantages over conventional granules due to their uniform shape — they have superior flow properties, are more easily coated and have more predictable active drug release profiles. Dried spheroids may be coated and then filled into hard gelatin capsules to provide a sustained release dosage form capable of gradually releasing its active constituents into the gastrointestinal tract over several hours.

The process of extrusion has been the subject of much scientific study in the polymer, catalyst and metal industries. It may best be described as the process of forcing a material from a large reservoir through a small hole, or 'die'. Pharmaceutical extrusion usually involves forcing a wet powder mass (somewhat wetter than a conventional granulation mix) containing a high concentration of the drug substance together with a suitable binder and solvent, through cylindrical holes in a die plate or screen. Provided the wet mass is sufficiently plastic this produces cylindrical extrudates of uniform crosssection, not unlike short strands of spaghetti. These extrudates are loaded onto the 'spheronizer', a rotating scored plate at the base of a stationary smooth-walled drum. The plate initially breaks the strands into short rods, and then propels them outwards and upwards along the smooth wall of the drum until their own mass causes them to fall back towards the centre of the plate.

Each individual granule thus describes a twisted coil pathway around the perimeter of the plate, giving the whole mass a doughnut-like shape. This movement of the granules over each other combines with the friction of the plate to form them into spheres.

A typical spheronizer arrangement is shown in Figure 6.11 (see page 131). The basic core granules for the preparation of controlled release pellets for filling into capsules can be prepared by several methods, such as spray coating, pan/drum granulation, melt granulation, as well as spheronization. Core granules are then coated with a suitable polymer or wax to confer on them their controlled-release properties, either by spraying wax-fat solutions onto granules tumbling in pans or by spray coating them with polymers or waxes in a standard film coating machine.

The melt-granulation pelletization process is a fairly recent technique, based on high-shear mixer-granulator technology. In this process the core material (drug substance) is mixed with a suitable low-melting solid excipient (such as high molecular weight polyethylene glycol) in a high-shear mixer. The agitation is continued until the heat generated melts the excipient, which forms a wax-like coating around the core material. Under controlled conditions it is thus possible to produce coated pellets of reasonably uniform size, which can exhibit dissolution or dispersion properties suited to the drug substance involved.

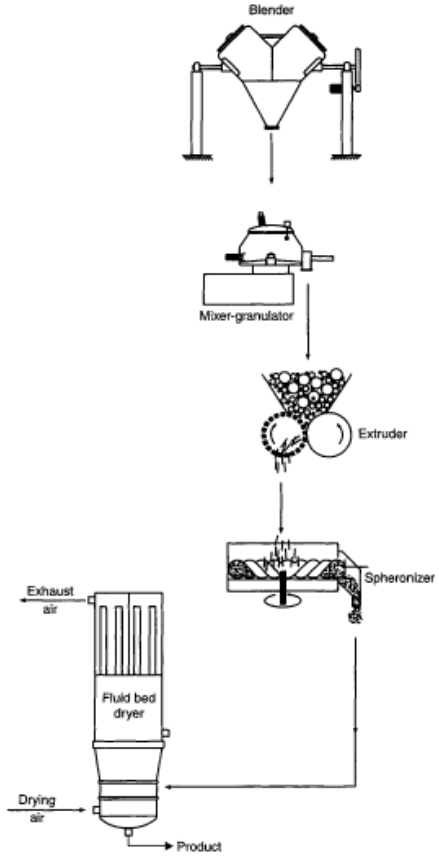

Figure 6.11 Typical spheronization process

Syrups, elixirs and suspensions

These dosage forms are basically produced by the dissolution or suspension of a drug substance in a suitable solvent/carrier (usually purified water), together with appropriate sweeteners, flavours, colours and stabilizing agents. The primary use of these products is in paediatric and geriatric treatment, where the patient may have difficulty in swallowing solid-dose medicines, although they are also valuable where the pre-dissolution or pre-suspension of the active drug can enhance therapeutic effect (for example, cough remedies). The production of solutions is a relatively straightforward procedure, typically using purified water heated to a minimum temperature suitable for dissolution of the materials, with the addition of the active and excipients followed by a filtration to remove possible haze prior to filling. The difficulties inherent in syrup manufacture are associated with product stability, for example dissolution and solubility, which may not be adequate at normal temperatures and taste masking, which is made more difficult when the drug is in solution.

Suspensions overcome some of these problems for suitable products, but other difficulties exist — notably maintaining the product in suspension. This latter challenge can only be met by the use of a high-shear dispersion system, or homogenizer, which utilizes wet-milling techniques to reduce particle size and enable reliable product suspension.

Elixirs are basically clear, flavoured solutions containing alcohols and intended for oral administration. Other ingredients may include glycerin, sorbitol, propylene glycol and preservatives. Quite high alcohol contents were common to ensure dissolution of certain drug substances, although products formulated in this way are becoming unusual. The distinction between medicated elixirs and solutions is not altogether straightforward, the latter often containing alcohol (for example, up to 4% is present in some ephedrine-containing syrups).

Emulsions

An emulsion is a two-phase liquid system where one liquid exists in very small droplet form (the internal phase), suspended in another (the external phase); the two liquids being otherwise insoluble in one another. An emulsifying agent contained within the mixture acts on the surface active properties of the two liquids such that the emulsion remains stable for a sufficiently long period to serve its purpose. If necessary, the liquids may be heated in order to enhance the stable formation of the emulsion, by reducing its viscosity. The active pharmaceutical material may be a solid, which is added to the liquid/liquid system, or may be soluble in one of the components. The product is prepared by high-shear mixing to reduce droplet sizes, using submerged-head agitation devices which draw the mixture through a high-speed rotating impeller contained within a close-fitting housing, not unlike a centrifugal pump. Most pharmaceutical or cosmetic emulsions contain water and oil as the two phases, and may be oil/water or water/oil, depending upon which is the internal and which is the external phase. It is possible for emulsions to 'invert'; a process in which is the internal and external phases change identity between the water and oil ingredients.

Although more usual in cosmetic topical formulations, pharmaceutical emulsions are prepared for topical, oral and parenteral use. Owing to their difficulty in preparation, pharmaceutical emulsions are used infrequently and only where they exhibit particularly useful characteristics such as drug solubility or specific absorption capability.

Creams, ointments and other semi-solids

Creams are basically similar to emulsions in that they are two-phase liquid systems; however, they exhibit greater physical stability at normal temperatures than emulsions and can thus be more useful for topical applications. The external phase is often water, while the internal phase is usually a high-viscosity oil or semi-solid oleic material. Manufacturing involves the heating and stirring together of the two phases in the presence of emulsifying agents and other excipients (colour, stabilizers, perfume etc.) with the assistance of a high-shear mixing device (colloid mill, homogenizer or ultrasonic mixer). The operation is most often carried out at slightly elevated temperatures to enhance dispersion. If the active substance is a solid, it will normally be added to the stabilized mixture, followed by further agitation and homogenization. Ointments

are solutions of high melting point and lower melting point hydrocarbons, usually mineral oil and petroleum jelly. The active drug and other excipients are incorporated in much the same way as with creams with the semi-solid matrix being heated to assist dispersion of these additives. An advantage of ointments over creams is that, when used as a base for sterile products such as ophthalmics, being solutions they can be sterilized by filtration after the addition of a soluble active or prior to the final addition of an insoluble sterile active ingredient. Cream bases would break down under microfiltration conditions.

Modern ointments based on polyethylene glycols (PEGs), which are available in a range of viscosities, have the advantages of typical ointments but are water miscible. Pastes are similar to ointments except that they contain much higher insoluble solids content. They are prepared in a similar fashion, with the semi-solid base being added to the solids gradually with mixing until the required concentration is achieved and the dispersion is uniform. Pastes are used where a particularly high concentration of the medicinal compound is needed in contact with the patient's skin (such as for burns, prevention of sunburn or the treatment of nappy rash).

Gels are semisolid systems in which a liquid phase is held within a three dimensional polymeric matrix consisting of natural or synthetic gums, with which a high degree of physical or chemical cross-linking has been introduced. Polymers used to prepare pharmaceutical gels include natural gums such as tragacanth, pectin, carrageen, agar and alginic acid and synthetic materials such as methylcellulose, hydroxyethylcellulose, carboxymethylcellulose and the carbopols (synthetic vinyl polymers with ionizable carboxyl groups).

Oral, nasal, aural drops and sprays

Oral medicines applied in drop form are usually neonatal versions of paediatric syrups and suspensions. They are filled into small bottles, often of a flexible plastic that allows the container to be squeezed so that the requisite number of drops of liquid can be exuded through the plastic dropper insert. Nasal solutions are similar except that the formulation will usually be isotonic with nasal secretions to preserve normal ciliary action. The drugs used in such formulations include ephedrine, for reducing nasal congestion, antibiotics, antihistamines and drugs for the control of asthma. Products formulated as aural drops, usually referred to as otic preparations, include analgesics, antibiotics and anti-inflammatory agents. They are usually based on glycerin and water, since glycerin allows the product to remain in the ear for long periods. In the anhydrous form, glycerin has the added benefit of reducing inflammation by removing water from adjacent tissue. Sprays used orally or nasally, are similar in formulation to their equivalent drops, being simple solutions and suspensions traditionally applied to the mouth, throat or nose by bulb type spray

devices. Modern formulations make use of plastic pump sprayers or simple flexible bottle/nozzle combinations to produce the required spray pattern.

Injections

A potentially unwanted feature of orally dosed medicines is their introduction to the body's system via the route designed for digestion, a process more effective in decomposition of chemical entities than in their intact delivery to the remotest regions of human or animal physiology! The mouth, throat, stomach and intestines contain a complex mixture of enzymes and acids, which will usually ensure that any orally-ingested medicine is, at the very least, altered before it can be absorbed into the bloodstream. It is the bloodstream that distributes the absorbed material and until the said material enters the bloodstream it is unable to create any effect beyond areas of immediate contact within the alimentary system. Hence, if a medicinal substance has poor stability in acid solution or is easily broken down by digestive enzymes, it is of very little use in disease control as it will probably not reach those parts of the body's systems requiring treatment. A method of avoiding this effect and delivering the substance closer to the site of the illness or infection is via a transcutaneous injection. Although some drugs are unstable in body fluids including blood, the injectable route very much enhances the possibilities for overcoming instability problems. The two most common forms of injection are intramuscular, where the substance is injected into tissue containing small blood vessels and therefore remains most effective local to the injection site; and intravenous, involving direct injection into a larger blood vessel, thus ensuring rapid transit around the body. A further procedure involves sub-cutaneous injection, used for the deposition of controlled-release formulations.

Whether for intramuscular or intravenous use, these products are liquids or suspensions, which are produced as a pre-sterilized material contained in ampoules or vials. The medicinal product may be based on aqueous or oil formulation depending on the relative solubility of the drug substance and/or the required release rate into the surrounding body tissue. Most injectable products are made as single-dose containers, although multi-dose systems are available for use in vaccination and in veterinary practice. Additionally, drugs requiring sustained application via intravenous infusion over long periods are produced as large volume systems (typically 500 or 1000 ml).

Liquid products in solution can be filled under sterile conditions within suitable clean areas, the solution being itself sterilized by filtration using 0.2 micron porosity filters. However, the preferred manufacturing procedure is to ensure sterility by terminal sterilization of the filled ampoules or vials, by autoclaving or gamma irradiation. Only where such terminal sterilization techniques are likely to cause decomposition of the drug substance is it considered acceptable to rely only upon manufacture under sterile

conditions to achieve the required standard. In such cases the extent of sampling for sterility testing of the final product will be increased.

Sterilization techniques

Products intended for parenteral administration must not contain viable microbial organisms and their manufacture will inevitably involve one or more sterilization stages. Such stages may be used for the drug substance, the filling container or the finished product itself. Even where materials are processed under conditions of strict asepsis, it is now required that the finished product should be subjected to a terminal sterilization process wherever possible. A number of possible methods exist for the sterilization of products and materials, and the most appropriate method will be selected after careful consideration of the effects that the various alternative systems might have on those materials. Each method has particular benefits when applied to specific requirements.

The commonly used systems for sterilization include moist heat (autoclaving), dry-heat, chemical treatment, irradiation, high-intensity light and solution filtration. With the exception of the last one, all the methods rely on a combination of intensity and time to achieve the required reduction in microbial content. Another factor to be considered is the possibility for pyrogens to be present in the sterilized material or component. Pyrogens are substances that cause a rise in the patient's body temperature following administration of the injectable pharmaceutical. They are in fact complex polysaccharides arising from the breakdown of bacterial cells, and are most likely to be present following moist heat sterilization or other lower-temperature sterilization techniques (such as irradiation).

Autoclaving

The most useful and longest-standing batch sterilization technique is autoclaving, which exposes the subject materials to saturated steam at a temperature/ time combination appropriate to the stability of those materials. Established effective sterilization conditions range from 30 minutes at 115°C, to 3 minutes at 134°C. Commercially available autoclaves are supplied with standard cycles that provide time/temperature combinations falling within this ange. These standard cycles include specific time/temperature combinations and also the facility for cooling large-volume product solutions in containers at the end of the sterilization phase, by means of deionized or purified water sprays. The latter process includes the simultaneous application of cooling water and sterile compressed air to the autoclave chamber, in order to prevent highpressure drops across the container walls and consequent breakages.

Provided that the steam in the autoclave is saturated and free from air, the different cycle temperatures may be attained by developing various specified pressures in the autoclave. It is preferable however to control the process by the temperature attained rather than by the pressure, as the presence of air

in the autoclave results in a lower temperature than that expected under the correct conditions from the indicated pressure. In the case of porous materials, the air must be abstracted or displaced from the interstices in order to achieve sterilizing conditions, as the presence of residual pockets of air within the material may prevent contact between the steam and parts of the load. The period of heating must be sufficiently long to ensure that the whole of the material is maintained at the selected temperature for the appropriate recommended holding time. The time taken for the material to attain the sterilizing temperature or to cool at the end of the holding time can vary considerably and depends on a number of factors, including the size of the container or object and the thickness of its walls, and the design, loading, and operation of the autoclave. It is necessary, therefore, that adequate tests are conducted to ensure that the procedure adopted is capable of sterilizing the material and that the material can withstand the treatment. Chemical indicators can be included in the autoclave load, which change colour after the specified temperature has been maintained for a given time. Reliance should not be placed, however, on chemical indicators except when they suggest failure to attain sterilizing conditions.

The process can be monitored by temperature-sensitive elements (thermocouples) at different positions within the load. Some indication that the heat treatment has been adequate can be gained by placing indicators at positions within the load where the required conditions are least likely to be attained (such as the chamber drain). For the purposes of validating the sterilization conditions, the bactericidal efficiency of the process may be assessed by enclosing in different parts of the load small packets of material containing suitable heat-resistant spores, such as those of a suitable strain of Bacillus stearothermophilus. These are checked subsequently for the absence of viable test organisms.

Dry heat

Dry heat sterilization, often referred to as depyrogenation, uses high temperature conditions in the absence of moisture to destroy contaminating organisms and eliminate pyrogenic material. It is particularly useful for sterilizing glass containers (such as vials) or any other product-contacting material that will tolerate the required temperature. Typical conditions for this process are 2000C or more with a residence time at that temperature of 15 minutes, although sterilization alone is achievable at lower temperature/time combinations. The process can be operated on a batch basis using double-door machines (built into barrier walls in a similar manner to autoclaves), which accept clean containers on the non-sterile side and deliver them sterilized on the aseptic side. Modern high-output filling lines use continuous tunnel-type sterilizers, which include complex air-handling systems and deliver the cooled, sterilized containers into the aseptic filling machine located within the aseptic area. The validation of high-temperature sterilization techniques requires similar considerations to those applicable to autoclaving.

Heating with a bactericide

This process can be used for sterilizing aqueous solutions and suspensions of medicaments that are unstable at the higher temperatures attained in the autoclaving process. In this process, a bactericide is included in the preparation at the recommended concentration and the solution or suspension, in the final sealed container, is maintained at 98° to 1000C for 30 minutes to sterilize the product. The bactericide chosen must not interfere with the therapeutic efficacy of the medicament nor be the cause of any physical or chemical incompatibility in the preparation.

Ambient chemical methods

Formaldehyde was once used extensively as a means of sterilizing spaces such as aseptic production rooms and surgical operating theatres, but is now rarely used owing to its high toxicity and relative corrosiveness. It is only an effective sterilant in the presence of moisture; the process involves raising the ambient room humidity by water spraying, followed by the sublimation on an electric hot plate of paraformaldehyde pellets. Peracetic acid has been used as an alternative to formaldehyde for the sterilization of small spaces, such as filling machine enclosures, isolators, together with their contents. Like formaldehyde, it is corrosive and toxic and, therefore, is of limited application. It has been used in admixture with hydrogen peroxide for the sterilization of isolators. Peracetic acid has the advantage that the sterilizing effect is (as with all chemical sterilants) dependent on concentration, which can be easily measured with suitable detection equipment.

Hydrogen peroxide has now largely supplanted peracetic acid for smallspace sterilization, as this agent is far less likely to cause corrosion of equipment items. It is also used for sterilizing syringes, ampoules and other packaging materials. Hydrogen peroxide is used at concentrations of lOOOppm in air and is regarded as product-safe due to its decomposition products being water and oxygen. It has a melting point of 00C, and its commonly used 30% aqueous solution has a boiling point of 1060C.

It is, however, toxic, having a time-weighted exposure limit of 1 ppm and an acute toxicity limit of 75 ppm. Another disadvantage has been the difficulty in monitoring accurately the concentration of hydrogen peroxide vapour under sterilization conditions, although in recent times suitable sensors have been developed. These sensors have relatively slow response times, making real-time analysis of hydrogen peroxide difficult, but it is now possible to reliably alidate the sterilization process. Various alcohols (ethanol, iso-propanol) can be used to decontaminate the surfaces of containers or equipment items, usually by swabbing. However, this activity cannot be relied upon to provide sterility in its own right and must be preceded by a validated sterilization process.

Ethylene oxide sterilization

Certain materials cannot be sterilized by dry heat or autoclaving for reasons of instability, but they may be sterilized by exposure to gaseous ethylene oxide. This process can be carried out at ambient temperatures and is less likely to damage heat-sensitive materials. It does, however, present difficulties in control of the process and in safety, and is currently only considered where it offers the only solution to a problematic sterilization requirement. It must be performed under the supervision of experienced personnel and there must be adequate facilities for bacteriological testing available. The most frequent use of the technique in the pharmaceutical area is for the sterilization of medical devices (such as plastic syringes). Compared to other methods of sterilization, the bactericidal efficiency of ethylene oxide is low and consequently particular attention should be paid to keeping microbial contamination of subject materials to a minimum. Ethylene oxide is a gas at room temperature and pressure. It is highly flammable (at levels as low as 3% in air) and can polymerize, under which conditions it forms explosive mixtures with air. This disadvantage can be overcome by using mixtures containing 10% of ethylene oxide in carbon dioxide or halogenated hydrocarbons, removing at least 95% of the air from the apparatus before admitting either ethylene oxide or a mixture of 90% ethylene oxide in carbon dioxide. It is also very toxic to humans (time-weighted average exposure limit 1 ppm) and has been demonstrated to be carcinogenic. For these reasons ethylene oxide sterilization is no longer frequently used as an industrial process.

The sterilizing efficiency of the process depends upon:

- the partial pressure of ethylene oxide within the load;
- the temperature of the load;
- the state of hydration of the microorganisms on the surfaces to be sterilized;
- the time of exposure to the gas.

Irradiation

Sterilization may be effected by exposure to high-energy electrons from a particle accelerator or to gamma radiation from a source such as cobalt-60. These types of radiation in a dosage of 2.5 mega-rads have been shown to be satisfactory for sterilizing certain surgical materials and equipment, provided that precautions are taken to keep microbial contamination of the articles to a minimum. This method is not, however, widely regarded as a safe means of product sterilization, due to the possibility of chemical decomposition of many pharmacologically active substances.

This method can also be used for some materials that will not withstand the other sterilization methods. It has the advantage over other 'cold' methods of sterilization in that bacteriological testing is not an essential part of the routine control procedure, as the process may be accurately monitored by physical and chemical methods. It also allows the use of a wider range of packaging materials. Control of the process

depends upon exposure time and radiation level. It is important to ensure that all faces of the load are exposed to the required radiation dose.

Ultraviolet light

Ultraviolet light has long been known as a form of energy with bactericidal properties. It has particular uses in the maintenance of sterility in operating theatres and animal houses, and for the attenuation of microbial growth in water systems. Ultraviolet light exists over a broad wavelength spectrum (0.1 to 400 nm) with the bactericidal (UVC) component falling in the range 200 to 300nm with a peak at 253.7nm. It is particularly useful for maintaining sterility in pre-sterilized materials and is used widely in isolator pass-through chambers to protect the internal environment of the isolator. It can also be used for continuous production sterilization of pre-sterilized components feeding into such isolators. It can be used to sterilize clean materials in a continuous cycle provided that they are fully exposed to the radiation, but this is a relatively slow process requiring an exposure time of up to 60 seconds to achieve a 5-log reduction in viable organisms.

Packaging operations

Introduction

The early days of pharmaceutical product packaging saw predominantly manual systems involving, for example, the hand counting of pills or tablets which were dispensed to the patient in a suitable container, often merely a paper bag! As demand and availability increased, the risk of mistakes became greater due to the wider range of products available and the frequency of dispensing. The same factors applied to the production of medicines, where centralization of manufacture led to multiple pack despatches. Increasing standardization led to:

- automated counting;
- pre-printed standard labelling;
- specific tested containers;
- secure capping/sealing;
- pre-printed cartons.

Bottle packs

This packaging type utilizes containers with screw or press-on caps, containing either a single course of treatment, or larger types intended to be used for dispensing from, in order to produce such single courses. Methods of tablet/capsule counting range from photo-electronic sensing types to pre-formed discs or slats having a fixed number of cavities. All counting methods have potential inaccuracy due to the non-

symmetrical shape of tablets and capsules and the possibility of broken tablets giving false counts. Individual tablets or capsules have low weight in comparison with the container, so that container weight variation can be greater than the weight of an individual item. Thus, post-filling check weighing methods cannot be relied upon to detect missing tablets/capsules in a container.

Bottle packs have other disadvantages, namely:

- they offer no record of the dose having been taken;
- multiple-product treatment regimes mean the patient coping with several
- different containers;
- frequent pack opening may lead to product spoilage and risk of spillage;
- paper labels may become soiled, with risk of lost product identity.

Bottles

Early production systems for bottle filling were based upon manual dispensing from a bulk supply using a measuring container. As precision-moulded bottles became available and demand rose, methods of filling to a fixed level were established. Initially manual in operation, this approach was followed by a semi-automatic method in which the bottle was presented to a machine, which created a partial vacuum inside the bottle thereby encouraging the flow of liquid from a bulk tank or hopper. The liquid level rose in the bottle until it reached the height of the vacuum nozzle, when flow ceased. This vacuum method was developed for beverage production and is still used in some small companies. Manually presented level-fill systems led on to automated bottle movement and presentation, with consequent increases in output. Indeed, the basic technology is still used in high-speed beverage production. However, the fill-to-level method suffers from the disadvantage that the filled volume varies according to the accuracy of bottle moulding, making it relatively unsuitable for pharmaceutical product use.

Powders

The powder is not a common finished dosage form for Pharmaceuticals, but it is frequently used for granule or powder formulation products that have low stability in solution (such as antibiotic syrups/suspensions for paediatric use). Products manufactured are typically in bottle or sachet form, the latter used for single-dose applications. Powder filling systems can be either volumetric or gravimetric. The former is most often typified by auger filling machines, in which a carefully designed screw rotates in a funnel-shaped hopper containing the product powder. As the auger rotates, the number of rotations determines the volume of powder delivered at the bottom outlet of the funnel and into the container. Rotation sensors are used to control this number so that the volume and hence weight dose is also controlled.

A second volumetric system is the 'cup' type, in which a two-part telescopic cylindrical chamber is opened to the powder in a hopper and thus filled. The volume of this chamber is adjustable by varying its height telescopically. By rotating the position of the chamber between the powder hopper and a discharge chute, a controlled volume/weight of powder is discharged via the chute into the bottle or sachet. Automation of bottle or sachet feed allows relatively high output to be achieved. A key feature of all volumetric systems is the control of powder level in the hopper, as the height of product powder above the infeed to the dosage control system affects the bulk density of the powder and hence the weight dosed. A weight-dosing system can also be used for bottle filling. This method involves the automatic pre-weighing of the empty bottle followed by approximate dosing of typically 95% of the required fill weight (using an auger or cup filler). The partially filled bottle is then re-weighed and the weight compared with that of the empty bottle so as to allow calculation of the required top-up weight. The bottle finally passes under a top-up filler which delivers a calculated final amount to achieve the target weight. The advantage of this approach is that the overall dosage accuracy can be greater, due to the finer control capability of the lower weight second/top-up dose.

Creams and ointments

These products are mostly filled into collapsible tubes, but occasionally into jars. The latter are filled and packed in much the same way as liquids. These semi-solids are also applied to impregnated tulles, although they are generally for burns treatment, where aseptically-produced versions apply. Tubes used for pharmaceutical preparations are either of the fully collapsible aluminium or aluminium/plastic laminate type, or are non-collapsible plastic. They are filled with product from the seal end before closing — the aluminium types being closed after filling by flattening and folding, while the plastic types are sealed by heat/impulse methods. Filling machines are usually of the rotary plate type, with empty tubes inserted into holders fixed into this plate from a magazine by means of an automatic system. On low-output machines, tube insertion may be performed by hand.

The product is filled from a hopper via piston type dosing pumps through nozzles and into the tubes. These nozzles are often arranged so that they 'dive' into the empty tube and are withdrawn as the product is filled, a technique used to minimize air entrainment. The bulk product hopper is often stirred and heated, typically using a hot water filled jacket, in order to enhance product flow and uniformity.

Empty tubes are usually pre-printed with product information. This print includes a registration mark which allows the filling machine to sense the orientation of the tube, and rotate it prior to sealing so that the product name or details are conveniently positioned for user-reading. Modern machines can also be

equipped with code scanners that check a preprinted bar-code, comparing this code with microprocessor-held recipe information, and reject or produce an alarm on any false codes.

GOOD MANUFACTURING PRACTICES

Definition

A key part of the control of medicinal products and facilities relates to GMP. The EU Guide To Good Manufacturing Practice and Good Distribution Practice defines GMP as 'the part of Quality Assurance (QA) which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization or product specification.'

General GMP requirements

When first embarking on a new pharmaceutical facility, consideration will need to be made as to what cGMP requirements will apply to the project and how they will impact on the project life-cycle. These may vary. Although the words differ, there are common general requirements that run through virtually all the cGMPs worldwide. Common elements are:

- the establishment and maintenance of an effective quality assurance system;
- control of the process;
- personnel that are suitably qualified, trained and supervised;
- premises and equipment that have been located, designed, installed, operated and maintained to suit intended operations;
- maintenance of adequate records of all aspects of the process so that in the event of a problem being identified, an investigation can trace the complete
- history of the process, including how, when, and where it was produced,
- under what conditions and by whom (i.e. an audit trail);
- the prevention of contamination from any source, in particular from components, environment, premises and equipment by the use of suitable
- premises and equipment and through standard operating procedures.

GMP design requirements

Based on an assessment of the regulatory requirements (as described above) we can begin to define the GMP requirement for the project. Generally, issues and areas to be considered during the conceptual design phase will include:

process issues:

- closed or open (Is it to be completely contained with piping and equipment at all times or will it be exposed to the surrounding environment? In which case, what measures are to be taken to prevent/minimize contamination?);
- level of batch to batch integrity required (Is simultaneous filling and emptying of vessels with different batches in known proportions or limits to be permitted? Do systems need to be engineered to be self-emptying? Will process systems need to be subject to cleaning, drying or sterilization
- between batches?);
- level of segregation or containment required (Is it acceptable to manufacture product A in the same facilities as product B? Will processes be campaigned?);
- level of production required.

layout issues:

- site location and layout (including existing site, brown field, green field, overall site layout and its suitability in terms of space, general layout);
- facility layout (including cored versus linear layout; use of transfer corridors, segregation of areas, environment, containment strategy, modularization/ expansion, security and access control).

automation strategy issues:

- level of technology, use of design tools and models, number of layers — hierarchy;
- availability/redundancy/maintainability, modularization/expansion;
- instrumentation/cabling/field devices;
- paperless batch records, electronic signatures. flow issues:
- people (security, access, occupancy level, shift patterns);
- equipment (mobile or fixed, use of hard piping, flexible piping or

disposable transfer bags, cross-contamination/mix-ups);

- components/materials (materials handling systems, cross-contamination/ mix-ups).

regulatory issues:

- stage of product development, stage of production, category of the product and production processes employed, facility location, and location of the markets that the facility will serve.

validation strategy issues:

- validation required, validation team(s), validation plan(s).