Secondary pharmaceutical production

6

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6.1 Products and processes

6.1.1 Introduction

The selection of manufacturing methods for pharmaceuticals is directly related to the means by which the active substance is brought into contact with the agent responsible for the illness.

The obvious administration route for the delivery of drug therapy has long been via the mouth, perhaps on the basis that the ailment under treatment was probably caused by the assimilation of some hostile agent via the same route! More localized treatments involving the application of agents to the skin, or the insertion of medicament-containing substances into the various body cavities was a logical development of oral entry.

These methods, with enhancements and improvements, remain with us today and are still the most widely used, but they have been joined by injectable and other transcutaneous routes, inhalations and transdermals. A brief description of each of these, together with their associated manufacturing procedures, is outlined in the following sections.

6.1.2 Pills

One of the earliest forms of oral-dose treatment took the form of manually-rolled gum-based pills. Thomas Beecham, one of the pioneers of pharmaceutical formulation, sold his original 'Pills' in a market at Wigan. These wonders were originally produced by mixing the gums with herbal extracts known to have pain-killing or laxative properties, and were sufficiently popular that the initial production methods needed to be updated and mechanized quite soon in the products' life history. Thus, the pill-rolling machine was produced, followed by the introduction of quality control in the form of a device which ensured that the individual pills were as perfectly spherical and of equal size as the rolling machine could produce — rejects being recycled for further processing.

6.1.3 Tablets

Although a successful formulation, the pill suffered from production output restrictions and was overtaken by the modern tablet — produced by mechanically compressing suitable mixtures of drug substance and excipients held in a cylindrical cavity, or die, by the action of piston-type tools.

During the early development of the tablet, it was quickly realized that in most cases the active drug substance did not lend itself to the formation of a reliable compacted entity merely by the application of pressure. The addition of binding agents was found to be necessary, together with other excipients offering enhanced powder flow, and the following characteristics of well-made tablets were soon established as important:

- the ability to withstand mechanical treatment (packaging, shipping, dispensing);
- freedom from defects;
- reasonable chemical and physical stability;
- the ability to release medicaments in a reproducible and predictable manner;
- the drug and excipients are compressible.

6.1.4 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 scale-up, 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

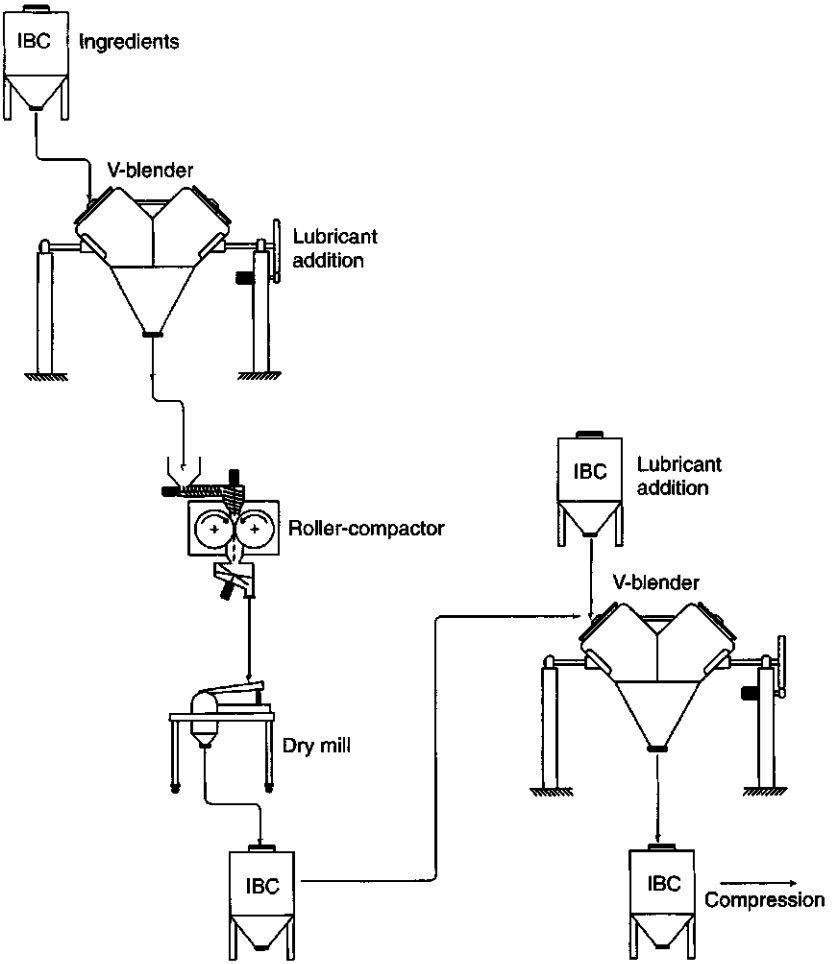


Figure 6.1 Typical dry granulation process

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 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 coarse-screen 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 (15 m s^{-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 m s^{-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:

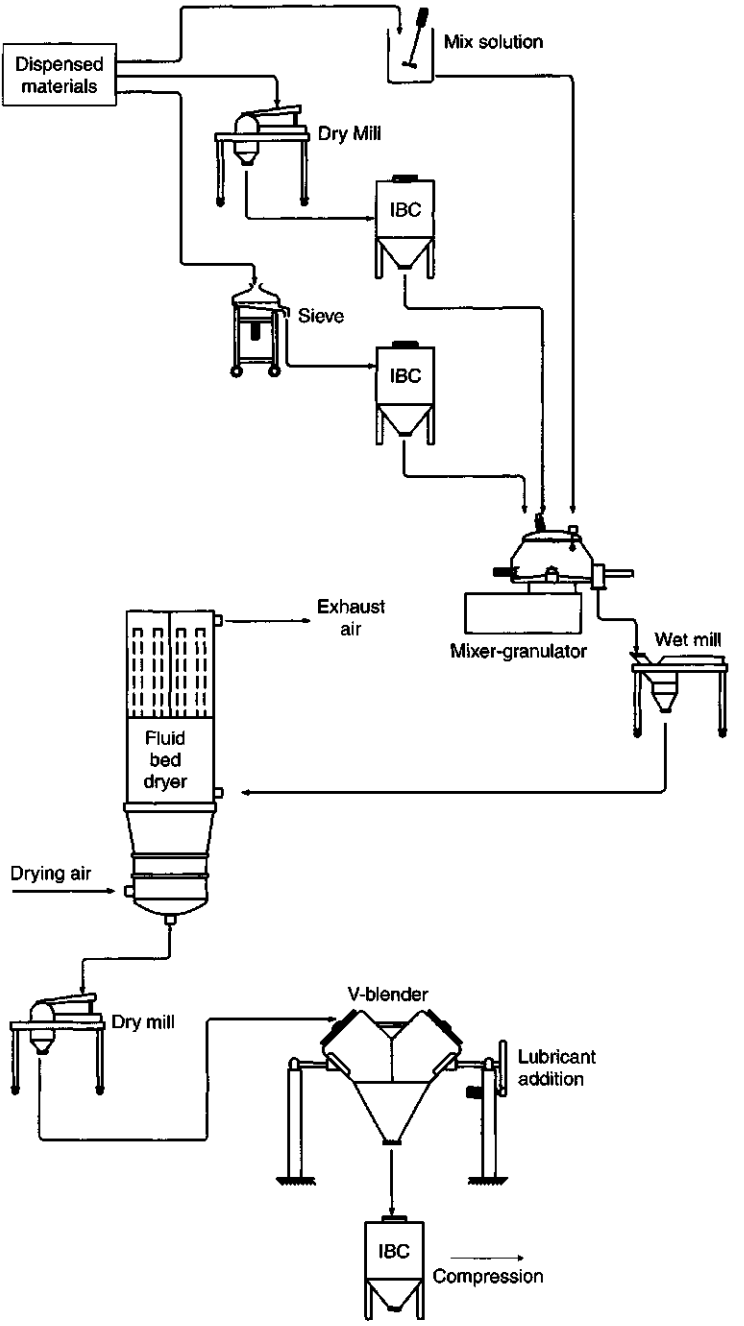


Figure 6.2 Typical wet granulation process

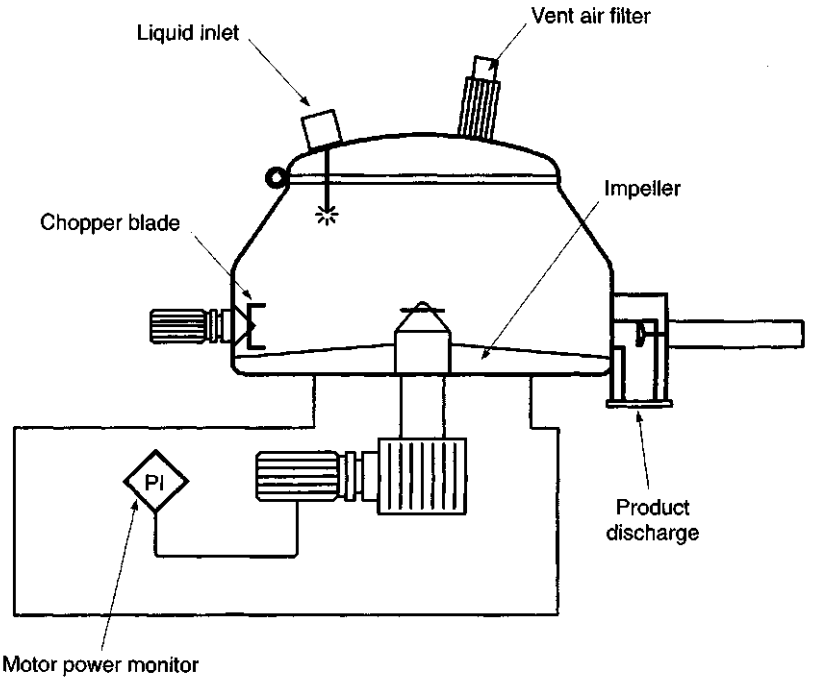


Figure 6.3 High shear mixer-granulator with opening lid

- 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.

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 heat-degradation. Finally, the absence of mechanical moving parts generally improves cleanability 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.

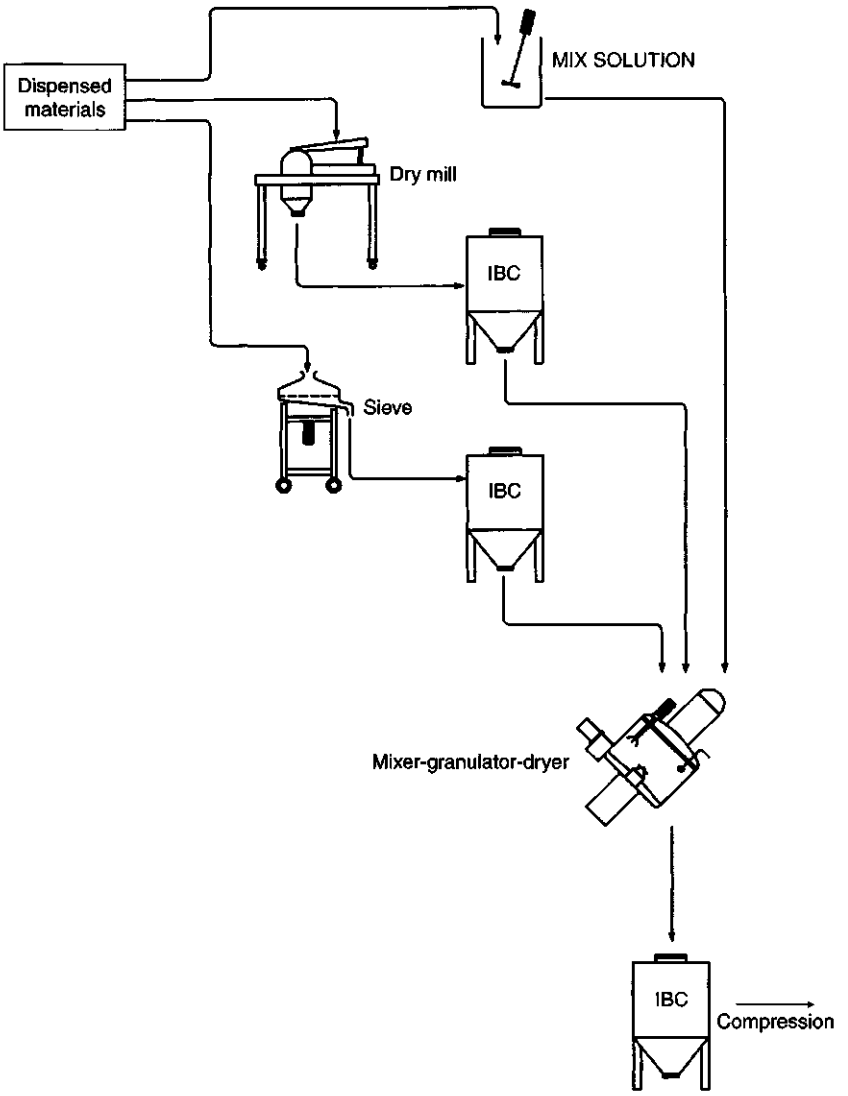


Figure 6.4 Typical combined granulation process

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.

6.1.5 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.

Figure 6.6 (see page 121) illustrates the principles of tablet machine operation.

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 shapes), and 'D' type which is suitable for tablets with a maximum diameter or

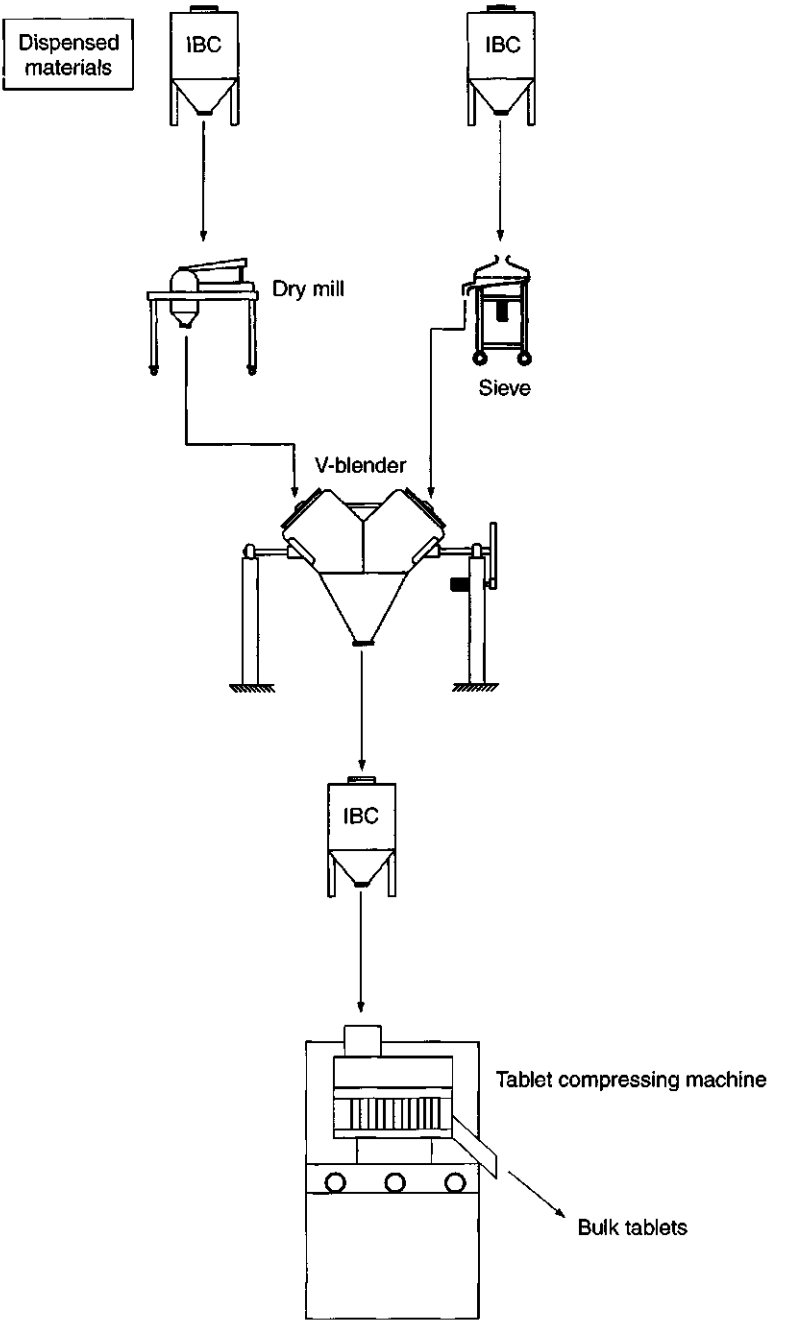
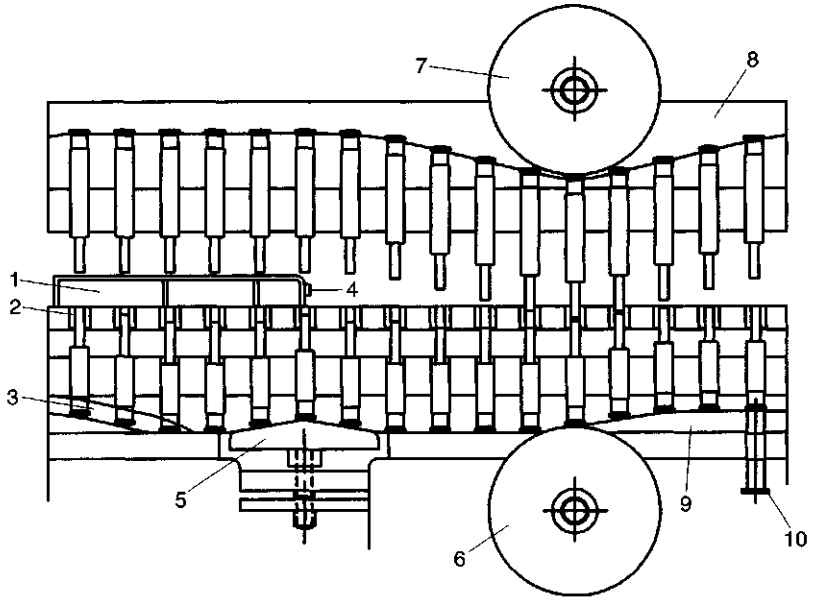


Figure 6.5 Typical flow diagram for direct compression



1 - Feed frame
2 - Die
3 - Pull down cam
4 - Wipe off blade
5 - Weight control cam
6 - Lower compression roll
7 - Upper compression roll
8 - Raising cam - upper punches
9 - Raising cam - lower punches
10 - Ejector cam

Figure 6.6 Rotary tablet compression machine operation

maximum length of 25.4 mm. The 'B' type punches can be used with two types 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 'B' 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.

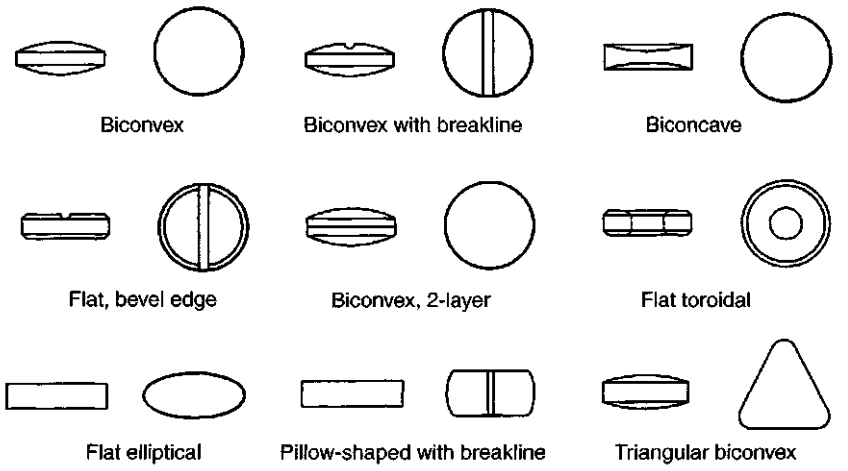


Figure 6.7 Some tablet shape possibilities

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.

6.1.6 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.

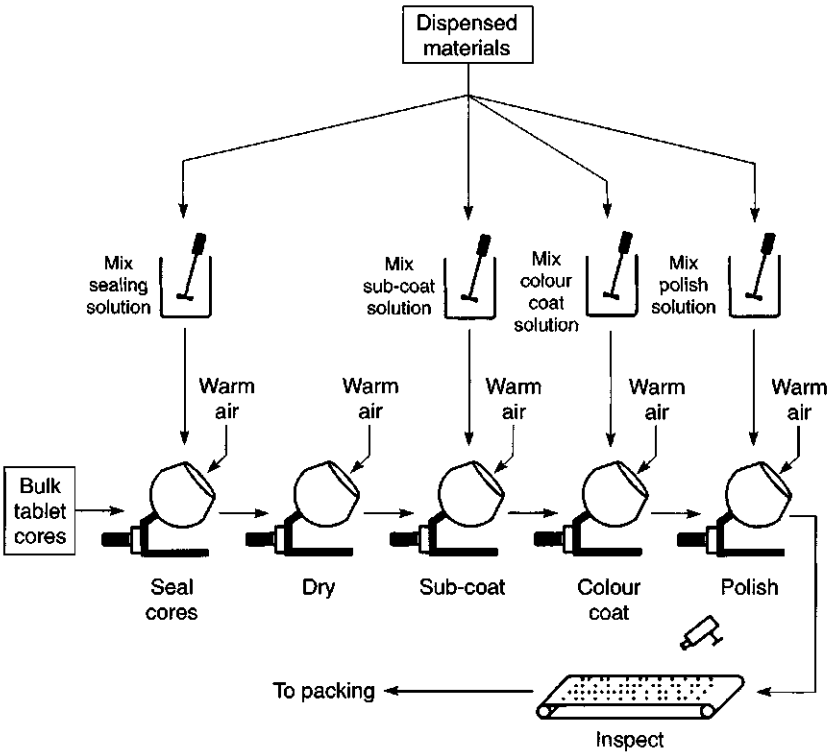


Figure 6.8 Tablet sugar coating

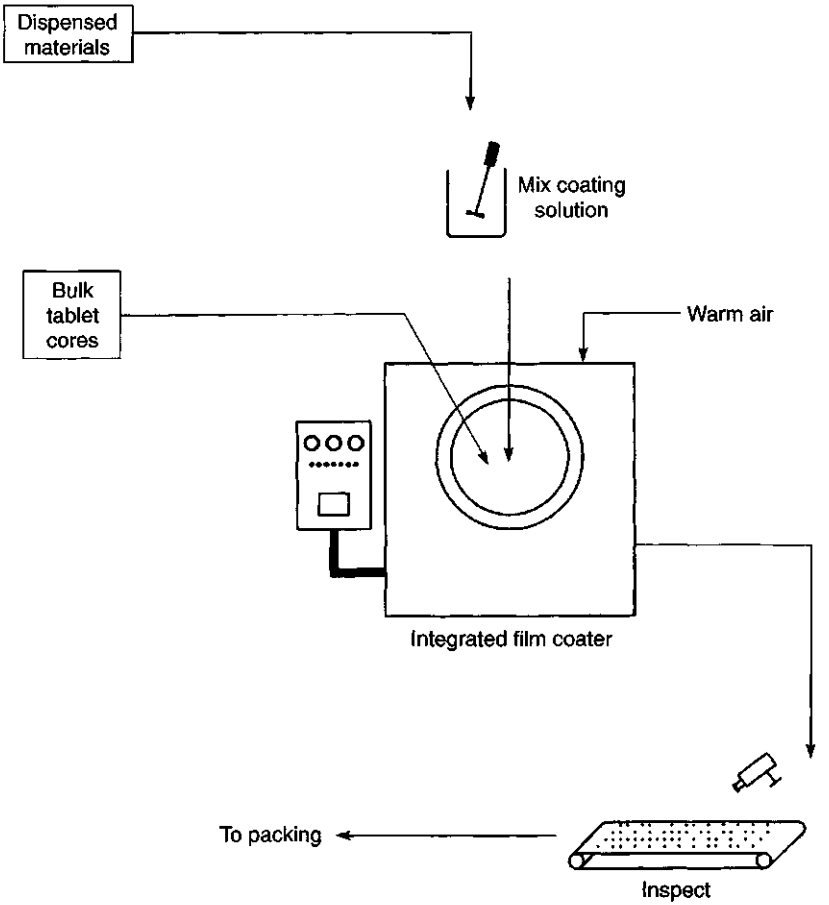


Figure 6.9 Tablet film coating

6.1.7 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 Höfliger 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.

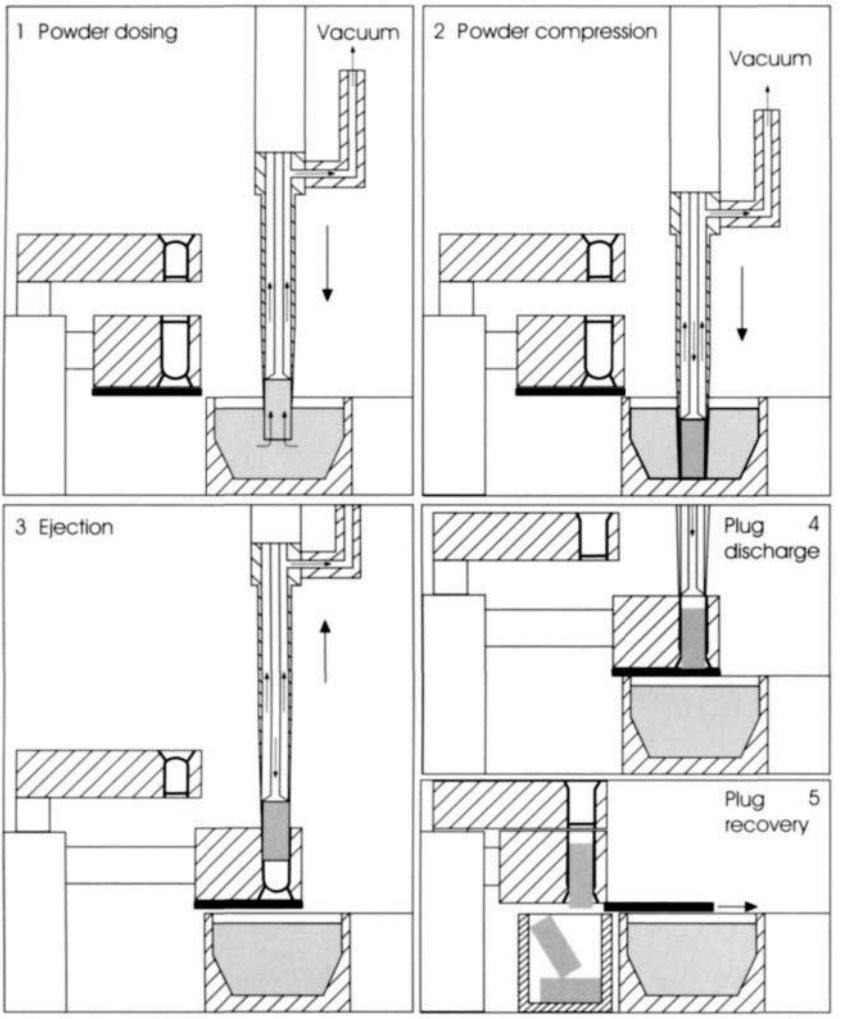


Figure 6.10 Details of powder filling on capsule filler

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, Höfliger 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 Höfliger 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.

6.1.8 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 cross-section, 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

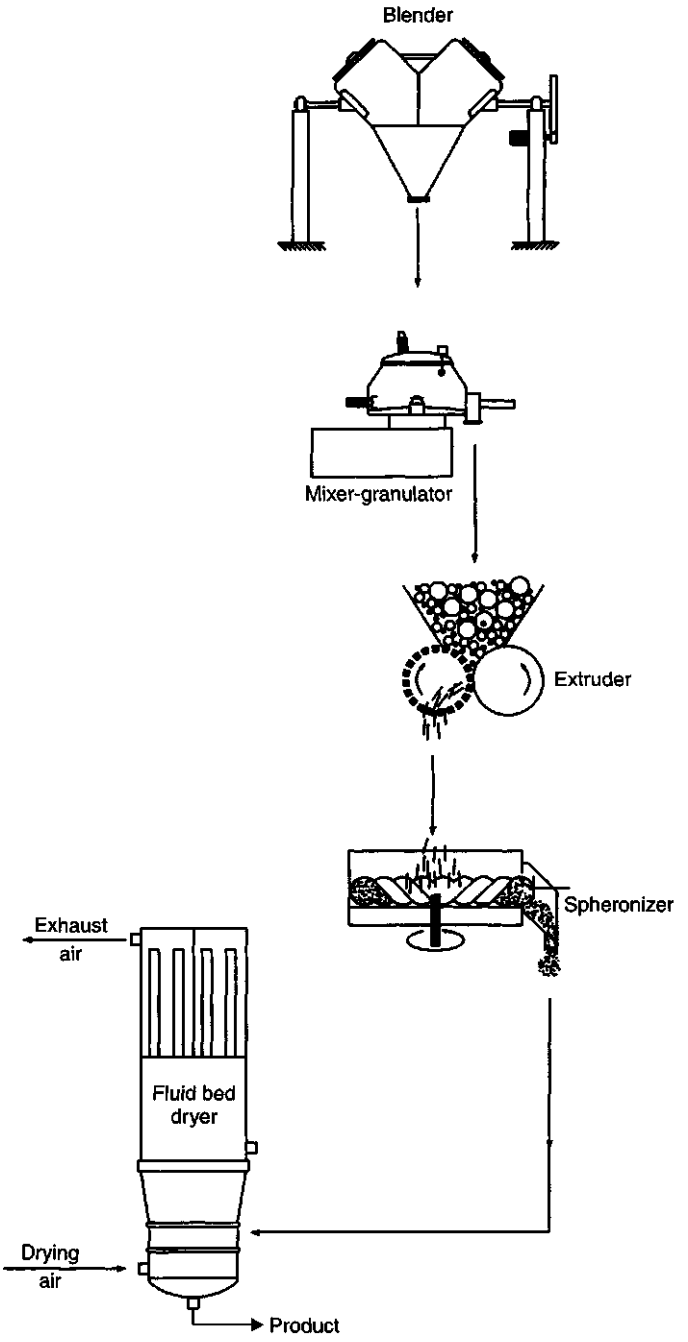


Figure 6.11 Typical spheronization process

thus possible to produce coated pellets of reasonably uniform size, which can exhibit dissolution or dispersion properties suited to the drug substance involved.

6.1.9 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).

6.1.10 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.

6.1.11 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).

6.1.12 Suppositories

The original suppositories were hand-formed pellets based upon white paraffin wax and containing active material and relevant excipients dissolved or dispersed in the melted matrix. Eventually the need for standardization resulted in the development of pre-formed moulds into which the cold product mass was forced by means of a piston and cylinder arrangement.

This slow process was later superseded for volume production by warming the mass to its melting point and pouring the liquefied material into split moulds, which were then solidified by cooling.

The early types were wrapped in greaseproof paper packaging and were successful except that any rise in ambient temperature would result in melting, with subsequent leakage and product spoilage; hence the introduction of plastic disposable mould materials which were closed with adhesive or heat-sealed cover strips. Initially the moulds were sold as pre-formed strips containing typically five moulds. Machinery was developed which filled these strips in rows, followed by cooling/solidification and the application of seal tapes.

These machines have relatively low output, but are suitable for the production rates often associated with this dosage form. Later form-fill-seal machines provide capacity for larger product sales, and involve the forming of moulds automatically on-line, followed by filling, cooling and heat sealing using a single packaging material. A feature of all fill-seal suppository machines is the need to allow for the shrinkage coincident with the cooling/solidification

process. This requires that the filled moulds are cooled to allow solidification of the contents prior to sealing, and the machines are often quite long in size to accommodate the length of the cooling section.

6.1.13 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.

6.1.14 Ophthalmic preparations

Two formulation types are generally used in ophthalmic treatment; ointments and liquid drops, which together provide for both water soluble and oil soluble active principals. They are produced in the same way as oral formulations in terms of the equipment and processes, although a higher level of cleanliness is required.

Products for the treatment of eye disorders have traditionally been manufactured under clean conditions, not least to avoid complications arising from the introduction of foreign particles to the eye (such as corneal ulcers or loss of eyesight). The need for medicines used topically on the eye surface to be aseptic was not originally thought necessary, owing to the fact that under normal conditions the eye's surface is in direct contact with the external environment, which contains many infective agents. Thus, like the alimentary system, the eye was thought able to cope with such challenges without additional protection. More recently however, it has become accepted that under many circumstances requiring medicinal treatment, the eye has an increased liability to infection by organisms such as *Staphylococci* or *Pseudomonas aeruginosa*, and should

therefore not be exposed to any substance likely to give rise to such infection. It is now an internationally recognized pharmacopoeial requirement that ophthalmic preparations be prepared aseptically.

6.1.15 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.

Although sometimes desirable for the terminal sterilization of heat-sensitive suspensions, it should be noted that irradiation is not without problems. Apart from the obvious safety considerations, the effect of gamma radiation on the type of glass used for ampoule and vial manufacture is to cause brown discolouration, thus adversely affecting subsequent inspection operations. The generation of free radicals within product solutions is also a possibility, with consequent chemical deterioration.

Where the active drug is unstable in solution (such as for certain antibiotics) the product is filled into vials, under sterile environmental conditions, as a dry powder. Such materials are often very moisture-sensitive, and special arrangements need to be made to ensure a low-humidity environment in areas of product exposure. A key consideration here is that the products are themselves required to be sterile before the filling operation, which implies preliminary processing under sterile conditions.

The filling of powders into vials involves considerations not customary for liquid filling, such as the mechanism used for dosage weight control. Similar techniques to those used for capsule filling have been tried, but most suffer from excessive particulate contamination generation. Modern high-speed sterile powder filling machines utilize a vacuum/pressure technique which forms a temporary solid compact from the product powder prior to its ejection into the vial.

Although some powder products can be sterilized by gamma irradiation or heat sterilization, most cannot be treated this way. Methods adopted to manufacture bulk sterile products include spray drying, bulk freeze drying, and crystallization under sterile conditions.

An alternative technique for the manufacture of products exhibiting instability in solution is to prepare such solutions using non-sterile product material and sterilize them by filtration, fill them within a controlled time-span into vials in small batches, and freeze dry. This method ensures that a solution can be produced, sterile filtered and filled under aseptic conditions, then re-crystallized by sublimation within the vial.

Equipment for this process relies on the use of special vial seals or plugs which, when partially inserted into the vials, allow evaporation of the solvent

during the drying phase. The drying is followed by the automatic full insertion of the plugs within the dryer chamber, under aseptic conditions. In this way the finished filled vials can be demonstrated to be equivalent to vials filled with liquid under aseptic conditions.

6.1.16 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 range. 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 high-pressure 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.

It is common practice for autoclaves to be double-ended with access doors opening into a clean preparation area on the infeed side and an aseptic filling area on the outfeed, although single-door autoclaves are used in some applications.

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 200°C 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 100°C 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 small-space 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 1000 ppm in air and is regarded as product-safe due to its decomposition products being water and oxygen. It has a melting point of 0°C, and its commonly used 30% aqueous solution has a boiling point of 106°C.

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 validate 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.

There are two processes used for ethylene oxide sterilization, one at normal and the other at high pressure. The low-pressure process uses a 10% v/v concentration, a temperature of 20°C and a cycle time of around 16 hours. A suitable apparatus consists of a sterilizing chamber capable of withstanding the necessary changes of pressure, fitted with an efficient vacuum pump and with a control system to regulate the introduction of the gas mixture, maintain the desired gas pressure, adjust the humidity within the chamber to the desired level and, if required, a heating element with temperature controls.

The high-pressure process was developed to enhance output by reducing cycle times. It uses a more-substantial chamber design, suitable for the 10 barg operating pressure. The temperature is typically >50°C and the cycle time 3 hours.

As with any chemical sterilization process, the combination of time and sterilant concentration is the key factor. 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.

All these factors must be closely controlled for successful sterilization. The sensitivity of microorganisms to ethylene oxide is dependent on their state of hydration. Organisms that have been dried are not only resistant to the process but are also slow to rehydrate. Due to this, it is not sufficient to rely solely on humidification of the atmosphere within the chamber during the sterilizing cycle.

It has been found in practice that hydration and heating of the load can be more reliably achieved by conditioning it in a suitable atmosphere prior to commencing the sterilization.

Some materials absorb ethylene oxide and, because of its toxic nature, great care must be taken to remove all traces of it after the sterilization is finished; this is achieved by flushing the load with sterile air.

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 300 nm with a peak at 253.7 nm.

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.

High-intensity pulsed light

A recently developed method of sterilization uses very short pulses of broad-spectrum white light to sterilize packaging, medical devices, pharmaceuticals, parenterals, water and air. It has been demonstrated that this process kills high levels of all micro-organisms. Each light flash lasts for a few hundred millionths

of a second but is very intense, being around 20,000 times brighter than sunlight. The light is broad-spectrum, covering wavelengths from 200 to 1000 nm, with approximately 25% in the UV band. The latter component provides the sterilizing effect in short-duration high-power pulses, although the total energy required is quite low — an economic advantage.

High kill rates equivalent to 7–9 log reductions in spore counts have been demonstrated using a few pulses of light at an intensity of 4–6 joules cm^{-2}. Although the UV component provides the effectiveness of this method, it is considerably more rapid than conventional UV systems. Continuous in-line sterilization is, therefore, practical with this technology.

Pulsed light sterilization is applicable to situations and products where light can access all the important surfaces and also penetrate the volume. It will not penetrate opaque materials, but is efficiently transmitted through most plastics and may be used to sterilize many liquid products.

Filtration (liquids)

Liquids may be sterilized by passage through a bacteria-proof filter. This process has the advantage that the use of heat is avoided, but there is always a risk that there may be an undetected fault in the apparatus or technique used, and because of this each batch of liquid sterilized by filtration must be tested for sterility compliance.

Sterilizing filters can be made of cellulose derivatives or other suitable plastics, porous ceramics, or sintered glass. The maximum pore size consistent with effective filtration varies with the material of which the filter is made and ranges from about 2 μm for ceramic filters to about 0.2 μm for plastic membrane filters.

Particles to be removed in the sterilizing process range in size from 1 to 5 μm diameter, down to viruses of 0.01 μm. It appears at first sight that filters cannot remove particles smaller than the largest pore size of the filter. However, filtration occurs in a wide variety of mechanisms, including impaction, adsorption, adhesion and electrostatic effects, so that in practice particles much smaller than the interstitial channels may be effectively filtered out.

Filters for liquid sterilization have pore sizes of 0.2 μm, usually preceded by coarser pre-filters to remove larger particles. These filters are all fabricated as cartridges that are installed in leak-tight housings. For the filtration of liquids, hydrophilic forms of the filter material are used.

All standard filter types must comply with bacterial challenge tests performed by the manufacturer, which can be correlated with other integrity tests carried out routinely by the end-user.

Non-disposable filters must be tested periodically before use to ensure that their efficiency has not become impaired, using one or more of the following integrity test methods. Filters should be integrity tested after each sterilization and after each filtration. All integrity testing is performed on wetted filters. The tests depend on the principle that airflow through the wetted porous membrane is diffusive up to a certain pressure (the bubble point) and is a function of pore size and pressure. Above the bubble point, liquid is displaced from the membrane and bulk flow of gas occurs.

Bubble point test: In this test, air pressure upstream of a wetted filter is slowly increased. The pressure at which a stream of bubbles occurs downstream of the filter is the bubble point pressure. If a filter has a damaged membrane or an insecure housing seal, the test pressure will be below that specified by the manufacturer.

Forward flow test: A test pressure below the bubble point pressure is applied to a wetted filter. The diffusive airflow rate through the filter is measured. If it exceeds a specified value the filter is judged to be insecure.

Pressure hold test: A section of pipework upstream of the wetted filter is pressurized (below the bubble point). The rate of pressure decrease is measured. For a filter to be judged intact, this must occur below a specified rate.

Filtration is best carried out with the aid of positive pressure, as this reduces the possibility of airborne contamination of the sterile filtered solution through leaks in the system. If the filtration is likely to take a long time and the preparation is susceptible to oxidation, nitrogen or other inert gas under pressure should be used rather than compressed air.

Filtration (gases)

The uses of sterile air or inert gas in pharmaceutical sterile processing include the aseptic transfer of liquids using pressure, and blowing equipment dry after sterilization. In addition to these positive applications, air or gas also enters aseptic equipment during fluid transfers or cooling operations, and in all cases the air and gas must be completely free of micro-organisms. Air sterilization can be achieved by filtration with the required filter porosity being 0.2 μm as for liquids. Integrity testing also needs to be carried out in the same manner as with liquid filters.

6.1.17 Aerosols

The use of pressurized systems for the application of pharmaceuticals became common after World War II, when such methods were used for the topical administration of anti-infective agents, dermatological preparations and materials used for the treatment of burns. A logical development of spray

technology, the aerosol relies on the propulsive power of a compressed or liquefied gas. The latter type have been of greater benefit, based on gases boiling at below room temperature (20°C) and at pressures ranging from zero to 120 psi above ambient.

Initial applications utilized flammable hydrocarbon gases, which were then largely replaced for pharmaceutical use by chlorofluorocarbons, notably for use in inhalation products. Recent developments have worked towards the replacement of the suspected ozone-depleting chlorofluorocarbons with hydrofluoroalkanes for environmental reasons.

A further method of avoiding the oral route for internal administration is to introduce the drug substance by inhalation.

Aerosol products for inhalation use first appeared in the mid-1950s and were used for treatment of respiratory tract disorders, based on the establishment of several key benefits:

- rapid delivery to the affected region;
- avoidance of degradation due to oral or injectable administration;
- reduced dosage levels;
- ease of adjustment to patient-specific dosage levels;
- avoidance of possible interactions with concurrently-administered oral or parenteral drugs;
- ease of patient self-administration.

The typical modern pharmaceutical aerosol consists of an aluminium container, a product (in powder, solution or suspension form), a propellant and a cap/seal incorporating a metering valve. The propellant provides pressurization of the container at normal temperatures, and expels the product when the valve is opened. The dose is controlled by the valve orifice configuration, which allows the release of a single shot of product liquid together with sufficient propellant gas to ensure production of an aerosol.

Continuous aerosol sprays for topical application use slightly different valve types that do not limit the dose size. Such products also sometimes utilize compressed gases to provide propulsion, including carbon dioxide, nitrogen and nitrous oxide.

The manufacture of pharmaceutical aerosols is complicated by the need to maintain a pressurized environment for the propellants during storage, mixing and filling. This includes the systems used for transporting the propellants from the storage location to the point of use, and is made more complex where flammable materials are involved.

The relatively complex nature of gaseous aerosol manufacture has led to the consideration of other methods for the delivery of drug substances by inhala-

tion, including the creation of fine particles suspended in an air stream generated by the patient himself. Such powder inhalations utilize micronized powders delivered in unit-dose quantities, held in a device that simultaneously releases the fine material into air flowing through the device at the same time as that airflow is initialized by the user. By careful design using a multi-dose approach, a metered dose system providing relief of patient symptoms over a convenient time period is possible. Several such systems are currently available or under development.

6.1.18 Delayed and sustained release systems

The objective of any drug delivery system is to provide a specified quantity of the therapeutic agent to the appropriate location within the body, and to sustain the level of that agent so that a cure or symptom relief is achieved. In practice drugs are delivered in a broad-brush manner, which ensures arrival of sufficient drug to the body location needing it, but simultaneously provides the drug to parts not requiring treatment. This approach may ensure coverage but is somewhat wasteful and may engender unwanted reactions.

A targeted approach is therefore potentially valuable and there are a number of ways in which this can be achieved. The possible advantages of this approach are:

- improved patient compliance;
- reduced drug substance usage;
- reduced side effects;
- reduced drug accumulation;
- improved speed of treatment;
- improved bioavailability;
- specific delay effects possible;
- cost saving.

The objective stated above has two parts, namely the creation of a suitable drug level at the required site, and the maintenance of that ideal level for a period suited to the completion of treatment.

The first objective can be achieved by delayed release of the drug when taken orally, by localized application by injection, or by topical application local to the required site in the case of shallow-tissue disorders. Methods used for ensuring adequate levels of the therapeutic agent include sustained-release coatings for tablets and capsules, and formulations of injectable or topical drugs that allow controlled release of the active principal.

The combination of delayed and sustained release properties for orally dosed material can ensure, for example, that the drug is released, at a controlled rate, in the duodenum rather than the stomach. Such controlled-release is achieved

with oral dosage by the formulation or coating of tablets and capsules so that the excipients (either internally or as part of the coating material) have a physical action on the drug dispersion or dissolution rate.

Injectable drugs in a suitable formulation can offer delayed or sustained release when delivered intramuscularly, as a 'depot'. Dissolving or dispersing the drug in a liquid medium that is not readily miscible with body fluids can reduce the rate of absorption. Oil solutions or suspensions are often employed for this effect, while aqueous suspensions can be used with insoluble drugs.

An alternative injectable route is the use of solid material injected subcutaneously, the 'depot' thus being formulated to ensure suitable release rates. The surgical implantation of drugs can be even more targeted, albeit at increased patient risk.

Topical drug application has a number of benefits, especially the opportunity to remove the material from the skin by washing, so reducing and ultimately stopping the rate of application. The absorption of drugs via the skin e.g. transdermal products, including intra-ocular routes involves the formulation of the actives in such a way that they can be released from the carrier material at the rates required. Such formulation can involve the use of microporous materials to which or within which the drug is applied or mixed, applied directly or attached to a substrate (such as adhesive plasters).

6.1.19 Microencapsulation

The process of microencapsulation involves the deposition of very thin coatings onto small solid particles or liquid droplets and differs from the technique of, for example, tablet coating in that the particles involved are much smaller — typically 1 to 2000 μm in diameter.

The benefits to pharmaceutical product development relate to the very small and controlled size of the particles involved. The technique alters the physical characteristics of the materials concerned to the extent that:

- liquid droplets can exhibit solid particle characteristics;
- surface properties are changed;
- colloidal properties are changed;
- pharmacological effects are enhanced or reduced by changing release patterns;
- the surrounding environment is separated from the active drug substance.

Although some similar effects can be achieved by alternative methods, the microcapsule can, due to its small size, be used in many product applications which would not otherwise be technically practical.

Methods available for manufacturing microcapsules include spray drying, pan coating and air suspension coating. The former is of particular value in the production of very small microcapsules (typically 1 to 100 μm in diameter), and has been used in protein-based product manufacture in which a protein solution is sprayed into a co-current air stream to form microcapsules. The co-drying of such materials with pharmaceutically-active substances is capable of producing particles of such substances coated with a protective or carrier layer.

6.1.20 Ingredient dispensing

All pharmaceutical manufacturing operations involve the use of one or more chemical materials in pre-defined quantities on a batch or campaign basis. Such materials are most often held in a storage location, in containers providing sufficient quantities of the material to enable the manufacture of more than one batch. These containers will be of such design as to afford the required level of protection of the material during the storage period and facilitate allocation to the dispensary.

The activity involved in the weighing of materials on a batch-by-batch basis is known as dispensing, and may be considered as the first step in the manufacturing process.

The sub-division of a bulk material into smaller batch lots inevitably involves the removal of that material from its original container. The environment in which this process is conducted must, therefore, be of a quality suitable for the intended use of the manufactured pharmaceutical product. For example, the dispensing of ingredients for the manufacture of oral-dose products will usually be conducted under class 100,000 conditions (to US Federal Standard 209e). The same operation for handling sterile ingredients for injectable products will usually be conducted under class 10 or 100 conditions, possibly using a glove-box.

Another key feature of dispensing is the need for assurance that the operation has been carried out correctly. This need will often be met by the checking of each weight by a second operator. With modern computer-controlled dispensing systems, the latter situation is most common, as the reliability of the dispensing process itself is such that only the potential for errors in transit to the production area need to be checked.

Containers

As indicated above, the 'input' container will be of such design as to protect the integrity of the material, and so too must the container used for transferring the dispensed ingredient to the manufacturing location. Where high-potency

ingredients are involved, the latter must also ensure that subsequent handling can be performed without risk to operating personnel. Thus, a contained transfer system might be employed for this purpose (see Section 6.4 on page 176).

Incoming materials are likely to be contained in polyethylene-lined kegs (solids) or steel drums (liquids). These containers may hold as much as 200 kg of material and be transported on clean pallets. Space for the staging of such pallets adjacent to the dispensing zone is therefore required, together with handling devices suitable for positioning them conveniently for the removal of the required weights or volumes of ingredients.

Dispensed materials may be placed in similar containers to those used for incoming items. However, it is more usual for these aliquots to be transferred to manufacturing using dedicated sealable dispensed-material containers, often reserved for particular substances, and carrying provision for secure identification of the contents.

Weighing systems

As pharmaceutical ingredients are usually dispensed by weight (rather than volume), a suitable set of weighing scales is required. Scale sensitivity and accuracy usually diminish as capacity increases, so a two or three-scale arrangement is not uncommon. Thus, the active ingredients, which are likely to be of lower batch weights than the non-active or excipient materials, will usually be weighed-out on scales of higher accuracy. The three scales might, typically, have capacities of 1 kg, 10 kg and 100 kg respectively. The chosen scale capacities will depend on overall batch weights and on the weight of the active, or smallest, ingredient.

Electronic weighing scales are common in modern dispensaries, and these can be linked to computer-controlled dispensary management systems and to automatic identification and weight-label printers.

Operator protection and airflows

The protection of operating personnel from exposure to high-potency drug substances is as important during dispensing operations as it is in the subsequent processing. Hence, the arrangement of modern dispensing areas utilizes individual booths in which the ingredients for one product batch at a time are weighed and packaged. The operator must wear suitable protective clothing, which should include hair covering, long-sleeved gloves, dust mask, footwear and close-woven fabric overalls.

Modern pharmaceutical dispensing booths employ a ventilation scheme that seeks to separate the operator's breathing zone from the area in which product

or excipient powders or liquids are exposed during dispensing. The basic principle relies on a downward sweeping of the ventilation air, from the ceiling above and behind the operator, to the lower edge of the booth wall facing them. Thus, any dust generated during scooping of materials into receiving containers is entrained in the air stream and kept away from the operator's head. A typical dust entrainment velocity is $0.45\ m\ s^{-1}$, and proprietary dispensing booths are designed to provide an operating zone in which the air stream moves at or above this velocity.

The air leaving the lower back wall of the booth may be filtered to remove entrained ingredient dust and recirculated, while supply air make-up and recirculated air will generally be filtered and conditioned to the environmental quality standard required by the product being dispensed, typically class 100,000 for oral-dose products. Figure 6.12 illustrates a typical airflow arrangement in a downflow dispensing booth.

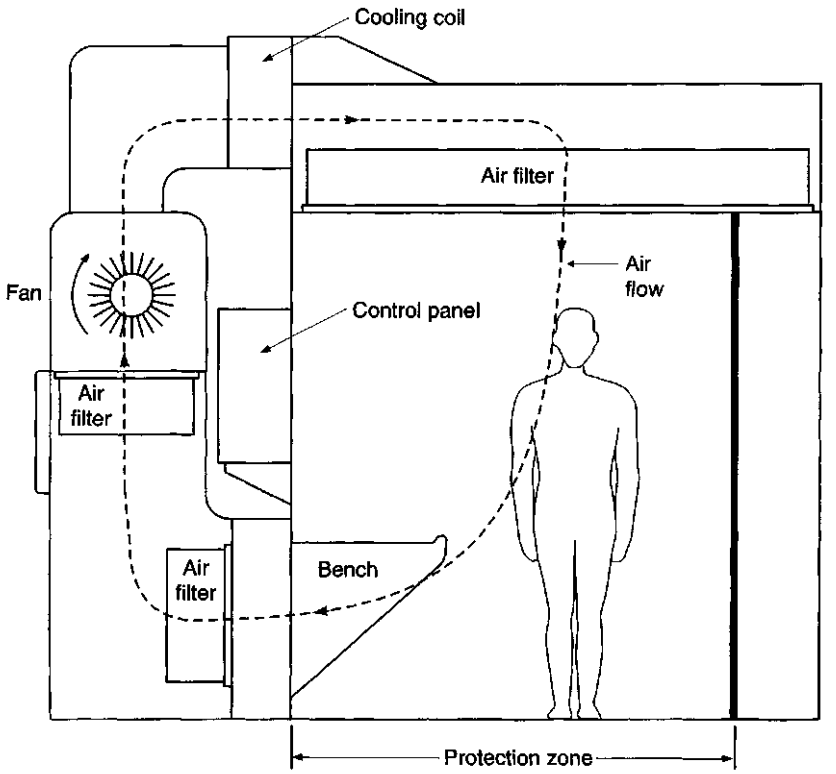


Figure 6.12 Sectional diagram of dispensing booth

Surplus materials

The disposal of surplus material remaining at the end of a product campaign in ingredient input containers generally poses a dilemma for dispensary managers. The options are to return the part-used container to the main raw material warehouse or to retain it as part of dispensing stock for later use. There is no universal 'best alternative', the decision being affected by such factors as the availability of space for storage within the dispensary area, the proximity of the main warehouse, the ownership of material stocks within the dispensary and warehouse, the sophistication of the materials management system, the level of security of the storage location etc. These all need to be considered when this issue is decided, but the overriding factor must be the security and integrity of the material itself.

Cross-contamination risks

In multi-product pharmaceutical manufacturing plants it is inevitable that the dispensary will be required to handle two or more products, probably at the same time. Thus, individual dispensing booths must operate in such a way as to ensure that there is no risk of materials from one product contaminating another. This is achieved by ventilation air pressure regimes that combine recirculatory air flow with slight positive pressure relative to adjacent access corridors and storage areas. By this means, dusts generated during the dispensing activity will be entrained and intercepted by the booth's extract filters, thus avoiding dispersion to the external environment. Meanwhile, any contaminant present in the adjacent spaces will be prevented from entering the booth by the positive pressurization.

Cleaning arrangements

One potential source of cross-contamination is the equipment and surfaces used during ingredient material handling. It is, therefore, important that all contaminated containers and utensils are removed from the dispensing booth for disposal or cleaning at the end of the operation, and that all working surfaces, including the fabric of the booth itself, are subjected to a validated cleaning procedure. Utensil and container washing is most effectively carried out in automatic washing machines, which should also incorporate a drying cycle. Open-sink washing of such items is unlikely to provide a validatable process, and should generally be avoided.

Operator clothing is a further source of contamination, and operators must change their outer garments when product changes are made, and in all cases should change their gloves between sequential batches.

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Labelling

It is essential that all dispensed ingredients are reliably identified — including the batch number and name of the product batch that is to contain the ingredient, the item weight and material name. It may also include the identity of the dispensing operator and the time and date of dispensing. Although the manual generation of labels can be acceptable (assuming suitable checking systems exist and are in use), it is now considered worthwhile to arrange for these to be produced automatically by the dispensary management system. Thus, at the end of each weighing operation, the acceptance by the operator of the correctness of the weight and identity will initiate a bar-coded or alpha-numeric label being printed by a printer located adjacent to his workstation. Such labels, usually of the self-adhesive variety, will then be applied to the dispensed material's container.

Materials management systems

Modern dispensary management systems are computer-driven, with fully-validated batch recipe information held electronically. They are most often linked to business management systems such as MRP2, warehouse management systems, and intermediate specialist control suites which organize the flow of material throughout the production process and seek to prevent errors in material usage. The latter, which usually incorporates the dispensary management element, must comply with the principles of cGMP and must, therefore, be driven by fully-validated software — this makes such systems very specialized and potentially costly.

Materials management systems automatically update stock levels at each stage in the material pathway, including transfers of ownership between different departments (between warehousing and production, for example). They ensure that only approved material can be allocated for use, or indeed used, and that materials are consumed in accordance with normal stock rotation principles (such as first in, first out).

The specific role of the dispensary management system is to ensure that ingredients are weighed out in accordance with pre-programmed recipe information and in the correct sequence. Instructions to dispensing operators may be provided via a printed batch sheet or visually by VDU screen.

The systems often also include provision for printing of ingredient labels that provide identity, weight and batch code information, in either bar-code or alphanumeric form. Various add-on facilities may also be incorporated, such as programmed weigh-scale calibration routines, and authorized-operator identification.

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6.2 Principles of layout and building design

6.2.1 Introduction

It has been said that the layout of a building can be designed in at least six different but equally acceptable ways. This may well be the case, although the degree of acceptability will vary depending upon the criteria applied by the accepting authority.

The criteria that give rise to the differences in pharmaceutical secondary production building layouts include, but are not limited to:

- safety/means of escape;
- complexity of the enclosed processes or activities;
- personnel level, type of occupancy and movement;
- ease of materials movement;
- specialized environmental classifications;
- type of partition construction;
- the structural design of the building.

6.2.2 Personnel safety

The primary safety consideration for all buildings is means of escape in the event of fire or other emergency. The issues are complex and covered by legislation and fire engineering principles, and will not be discussed here. However, the pharmaceutical engineer is well advised to take account of the basic considerations when planning the process-led layout of a building, and in doing so should seek the advice of a qualified architect at the earliest practicable point. Although failure to do so may not result in a potentially dangerous building, it will almost certainly involve time-consuming and costly reconsideration of the building layout during its architectural design phase.

Another important safety consideration relates to the product itself. In some cases the active materials involved in pharmaceutical manufacture are toxic in a high-exposure situation, and special precautions will then become necessary. These may involve modifications to the layout to accommodate specialist machines or environmental control equipment. The need for the use of flammable materials, although less common nowadays, may also arise and in such circumstances the design of the building may have to include the results of area zoning. This can be onerous, as construction materials may need different selections from those made elsewhere in the building, while the need for separate ventilation systems is also possible.

6.2.3 Process and activity complexity

Even simple pharmaceutical manufacturing and packaging processes must be carried out in areas with controlled environments. It is common practice to group final packaging operations, which usually involve the handling of products in a partially enclosed condition (such as filled and capped bottles, tablet blister packs) in a single room with limited spatial separation between linked groups of machinery, but with a common ventilation system. This is possible if the environment provides the required temperature (and sometimes humidity) to ensure product stability and that product cross-contamination is negated by the primary enclosure.

In the case of manufacturing operations, even where products require similar levels of product protection, separate environmental and spatial arrangements are usually necessary to prevent cross-contamination. It is, therefore, usual for manufacturing and primary packaging processes to be conducted in product-specific common environments and is essential for such processes where any degree of cross-contamination is hazardous to the product or patient to be separated physically, as a minimum.

It is possible for different products to share a common ventilation system, but only if that system allows for a single pass of the air supply, or if the recirculated air is passed through suitable filters. These filters must be of such porosity that it is possible to provide demonstrable evidence that any product dust passing through is of such low level as to ensure that products cannot become contaminated with one another at levels which pose measurable risk to patients.

Production processes involving specially clean conditions for product exposure (such as for parenteral, ophthalmic or inhalation products) add further complexity to the environmental and space planning activity. The transfer of materials between areas of differing cleanliness classification often involves a process such as sterilization by autoclaving or other means. Hence, the relative size, shape and position of the rooms on either side of the transfer process are important. In any event it is often considered necessary to separate such different areas by the insertion of air locks, in which decontamination of materials and equipment can be performed prior to transfer. This procedure will also be required during active product manufacture to prevent the possible spread of such material to adjacent areas.

In reality, the product mix in any production facility may be such that the above considerations demand dedicated spaces for different products. This demand inevitably impacts on the layout of the building, and it is for this reason that those responsible for facility space planning should understand the many and varying considerations.

6.2.4 Personnel occupancy level, type and movement

Although the use of machinery for manufacturing and packaging operations is widespread and increasing, pharmaceutical production requires the employment of people for the control of material selection, movement, processing and inspection, and it is unlikely that such employment will be eliminated in future.

A further consideration is that growing sexual equality coupled with a decreasing incidence of heavy lifting and movement means that both male and female production operators are equally likely to be employed on a process.

However, the numbers of personnel likely to be engaged on a given operation is relatively low by general industrial standards, so that this feature does not generally pose great difficulties in facility planning.

There is, nevertheless, a feature of pharmaceutical (and especially clean-room) operations that needs careful consideration. Just as air locks are a characteristic of material transfers, operator clothes-changing rooms are a common necessity in the protection of products from people. Clean areas generally need to avoid people-generated particles, while aseptic areas additionally need to be protected where possible from microbial contamination.

A careful selection of clean-room clothing, in terms of body coverage and particle-shedding ability, will significantly reduce both particle and microbial levels within the occupied clean room. Synthetic fibres generally shed lower particulate levels than cotton, and ceramic-coated synthetic materials are extensively used for clean-room clothing manufacture. However, fully covering synthetic-fibre clothing may enhance perspiration and thus microbial release, so high-specification clean areas should be operated at slightly lower temperatures to compensate.

The frequency of personnel movement within secondary production areas is not generally problematic, bearing in mind the relatively small numbers and the confined nature of the operations. However, the increased load on changing facilities at break times should not be overlooked, and neither should the ease of movement during any emergency condition. This is particularly important with clean areas, where many restrictions on movement occur such as the use of multiple doors, changing room step-over barriers etc., and where over-ambitious attempts to seal emergency doors to prevent dirt ingress have been known to result in blocked escape routes.

6.2.5 Materials movement

It is often the case that, along with personnel movement, material movement within pharmaceutical manufacturing facilities dominates the consideration of building layout. The separation of material and personnel pathways and the avoidance of cross-overs can consume a large amount of time during initial

planning. While such considerations are important, the extent of such importance must be first established by the performance of a movement review, which in turn requires a full understanding of the operation of the facility and the type, size and frequency of movements. It will often be found that the problems envisaged are imaginary, and bearing in mind the low-volume nature of most pharmaceutical products this should not be surprising.

The pharmaceutical engineer must, therefore, play a key role in establishing the realities of building layout design and ensure that he/she provides advice to those with whom he/she is working.

Once the understanding of material movement is established, consideration can be given to key factors such as corridor width, door width and type, and the adjacency of related operational areas.

One key item sometimes overlooked in preliminary planning is equipment, both fixed and mobile. Care must be taken in layout design and equipment selection to ensure that larger equipment can be moved through the facility to its final operational position, and that routinely-mobile items have transport routes which have been planned with their movement in mind.

6.2.6 Specialized environments

Where products demand special environmental conditions, the building structure and layout should include separate spaces for their manufacture and/or storage.

In general, these special environments either have increased cleanliness, unusual temperature or humidity, or provide extra levels of separation from surrounding areas by virtue of high potency or other risks. For example, aseptic conditions are required for the manufacture of injectable forms, demanding higher standards of surface cleanability and ventilation air filtration efficiency.

These features must be used in conjunction with stricter operator clothing regimes and closely defined operating/handling procedures. Layout considerations must include provision for separation from lower-grade areas by means of air locks. Positive pressurization of the processing areas is of course necessary to prevent ingress of dirt and microorganisms.

An important feature of aseptic processing areas is the selection of structure and finishes. It is not uncommon in modern facilities to employ modular partitioning systems with close-tolerance self-finished panels. These have the advantage of providing crevice-free stable walls and ceilings which do not move or crack, even when the main building structure surrounding the area is liable to move due to thermal expansion/contraction. In conjunction with heavy-duty clean-area grade welded vinyl flooring systems, these modular clean rooms provide reliable and easily maintained surfaces ideal for aseptic operations.

They are, however, relatively expensive, and a lower-cost alternative is the use of steel-frame and plasterboard systems for walls and ceilings, coupled with vinyl flooring. This approach also provides a good-quality environment, but requires higher levels of maintenance attention due to joint-cracking potential and less-durable surface finishes.

Where products are especially temperature or moisture-sensitive, the rooms in which they are exposed to the operating environment need to be supplied with ventilation air which has been conditioned to the required levels. This requirement may not affect the layout of the area concerned, although air locks coupled with positive room pressurization may be included to ensure greater control of the special environment. However, it will demand changes to the air handling system, and this is typically achieved by localized heating, cooling or dehumidification of the supply air.

Care must be taken when humidity levels are unusually low (below 20% RH), as operating staff may suffer dehydrating effects such as sore throats and cracked lips, which may be avoided by reduced individual working periods in the areas concerned.

Where product materials of an active nature are exposed in-process, operating personnel may be protected by personal protective equipment, provided the exposure is of short duration (for example, during maintenance or product transfers). Alternatively, isolation/barrier methods should be employed to prevent such exposure. However, under either scenario it is possible that product dust may be emitted, and the rooms involved should be designed to take account of this possibility by the use of negative pressurization and the inclusion of air locks. It also requires consideration of room exhaust air filtration to protect the external environment, preferably sited at the room wall or ceiling interface. Such filtration systems should include a method by which the exhaust filters can be changed from within the room in a safe manner, personnel involved being protected by temporary personal protective equipment.

An additional desirable feature of active product processing areas is easy-clean surfaces for walls, floors and ceilings. This is essential to ensure containment.

6.2.7 Internal structure

Certain products and processes demand special consideration of construction and finishes. However, it is a general requirement for pharmaceutical production and storage areas that they should be easily maintainable in a clean condition, and walls, floors and ceilings, together with pipework, ductwork and electrical features should be designed with this in mind.

It is first necessary to consider the degree of product exposure at each stage of the storage, dispensing or production process, and to consider the risks to the product from such exposure. This analysis will provide a framework for the selection of surface finishes in each area. Thus, the movement and storage of materials that are always enclosed in sealed containers requires a very different selection of surfaces from that needed where sterile materials are filled into ampoules under aseptic conditions.

Provided that the need for cleanability in all areas of pharmaceutical manufacturing plants is ensured, a variety of surface finishes are available for selection. These range from painted blockwork walls, sealed concrete floors and insulated and plastic-faced liners to ceilings in warehouses, to fully sealed and crevice-free clean-room systems with coved interface joints in sterile areas.

In production areas it is generally wise to avoid the use of painted blockwork, in favour of a plastered and painted finish. It is also best to avoid suspended ceilings with lay-in tiles, as these do not provide effective barriers between processing areas and the technical/services areas above and may allow dirt ingress. In such areas it is also preferable to provide access to services distribution and plantroom areas, which does not involve direct penetration of the walls or ceilings of the operating spaces themselves.

6.2.8 Building structure

The choice of structural materials can affect the internal environmental conditions. An example of this is the effect of external environmental conditions on natural expansion/contraction of the building's structural material. Steel framed buildings will naturally provide greater potential for such movement than those fabricated from concrete or similar materials. In any case, these natural movements must be taken into account in the structural design of the building, and the presence of expansion joints in walls, floors and ceilings may be the consequence. Wherever possible, such joints should be avoided in manufacturing areas, except in the case of aseptic processing rooms where they *must* be avoided.

6.3 The operating environment

6.3.1 Introduction

As a consequence of the increasing regulatory pressures being exerted on the industry, the environment in which secondary production is undertaken has

become progressively subject to greater inspection by the authorities. The 'environment' covers a number of issues, each of which is covered in the following sections:

- the avoidance of cross-contamination;
- product segregation;
- cleaning;
- environmental classification;
- ventilation systems;
- surface finishes;
- lighting selection.

The art of providing the correct operating environment lies in the selection of the systems that provide, *as a minimum*, no greater risk of contamination of the end product than has been accepted by the authorities during the drug approval process. This requires the engineer to select systems that meet this standard and are:

- economically justified;
- operable;
- maintainable (to the 'as-new' conditions);
- to cGMP standards.

6.3.2 Avoiding cross-contamination

All customers wish to receive exactly what they have ordered (or been prescribed, in the case of patients). Failure to do so can have unacceptable, even fatal, results. However, even if the product is correctly delivered, without proper controls it can be contaminated with another material. This potentially can have severe side effects, particularly if the patient suffers from a reaction to the contaminating material. Clearly, if the potential contaminant is another pharmaceutically active material or a viable organism, cross-contamination must be rigorously controlled.

The most likely sources of cross-contamination are:

- the operator;
- the previous batch of material;
- other materials in the working environment (such as paint, dust, micro-organisms, implements).

Sources of contamination can be identified and the level of risk determined for each product. However the industry has established a number of standard practices to reduce the contamination risks at all times. These 'standards' are commonly described as part of 'current' Good Manufacturing

Practice (cGMP) and are not always available in written form, although many guides have been published. The following paragraphs identify the main sources of cross-contamination in secondary pharmaceutical manufacture.

The operator brings to work several sources of contamination. External contaminants, such as soil, clothing fibres, etc. can be removed by the use of personal hygiene techniques on arrival at work and the wearing of non particle shedding clothing for production duties. Personal contaminants, such as dead skin scales and living organisms on the skin surface or in exhaled air, cannot be eliminated but risks from them should be reduced when these are known to be hazardous to products.

It is normal practice for all operators to change into clothing suitable for their duties on arrival at the manufacturing plant. Except in the lowest classes of operating environment, operators will change all their external clothing for 'coverall' man-made fibre working clothes, wear dedicated shoes and cover their hair and ears with a fine mesh hair cover. Those with beards/moustaches may be required to use a beard 'snood'.

As the quality of the environment increases, the standard of clothing and other protective coverings will increase. It is becoming standard practice, therefore, for manufacturing plants to have a series of change requirements to match the operating conditions. In the extreme — aseptic production — areas, operators have only their eyes exposed to the environment. Operators with infections are not permitted to work in these aseptic conditions, as the risk to the product is too high, even when protected by further containment methods.

Training is the principle method by which operators can learn to avoid the risk of creating cross-contamination. It is essential that they fully understand the need for absolute adherence to the Standard Operating Procedures (SOP), which have been developed to reduce the risk to the product in manufacture. Strict compliance with the clothing disciplines is required to avoid bringing contamination from one product to another on their clothes/skin. Learning to work at a pace that does not create excessive particulate disturbance requires skill and practice, particularly over exposed product.

It should never be forgotten that the human body loses particles of skin throughout the working day (see Table 6.1). These particles can become the chief source of contamination in a clean working environment.

The previous batch of material will always be a source of cross-contamination. Only when the previous batch is made from exactly the same components does this create no risk.

Segregation of products and the cleaning procedures required to avoid contamination are discussed in Section 6.3.3 (see page 163).

Table 6.1 Release of human skin flakes to the environment

Activity	Flakes released per minute
Sitting still	100,000
Moving limbs gently	500,000
Moving limbs actively	1,000,000
Standing up/sitting down	2,500,000
Walking/climbing stairs	10,000,000

Unless a process is undertaken in a totally contained manner, it can be assumed that the materials utilized in the manufacture of a product will be in the manufacturing environment. This is caused by many sources, but normally from particulate escapes, aerosols of liquids and from operators' clothing.

Methods of handling these materials can significantly reduce their discharge to the environment and the training of the operator is essential in the reduction of contamination risk from these sources.

Cleaning of the equipment and the surrounding areas can clearly reduce the level of contamination risk, but the need for excessive cleaning regimes should be avoided. Careful planning of production batches can reduce, or even eliminate, the need for cleaning between batches. Excipients (non-active ingredients) may be used in many formulations and, therefore, cleaning between batches of different products using the same active ingredient may be reduced in scope.

In summary, the risk of cross-contamination from a previous batch must be understood and reduced to an acceptable level.

Other materials can be present in the environment and not be caused directly by the operator or the previous batch of materials. A main source of such contaminants is the poor design of the premises in which the operations are undertaken. Information is given on surface finishes later in this chapter, but the particle shedding properties of all surfaces can be a source of contamination when the process materials are exposed to the environment.

Of more importance is the elimination of any surface on which contaminants can collect and later fall into the process. Flat surfaces should be replaced by sloping faces of easily cleaned materials; fixed equipment should be enclosed and ideally sealed to the ceiling; doors and windows do not require architraves; controls should be built into the walls or equipment; lights should be sealed to their surrounds; service outlets should be designed with minimum exposed surfaces.

Two further important sources of contamination should be considered in the design of all facilities with risks reduced to a minimum:

- the movement of air;
- the movement of process materials.

Most modern pharmaceutical premises are provided with air handling plants that supply a controlled volume of air to each process area. Correct specification and installation of the air system is essential to ensure an acceptable level of contamination of the air supply into a process area. Additionally, air movements between process areas can carry contaminating particles. This risk has to be considered for each process area and solutions found, usually by air locks, to prevent particulate movement between areas.

All process materials have to come from outside the process area at some stage. Liquids can be piped directly to a process without external contact, but dry materials have to be transported. If this transport involves movement between areas, the facility design and process operations have to assume that other spilt materials can contaminate the materials. Cleaning regimes on entry to a process area will need to be agreed at an early stage in the process design.

6.3.3 Product segregation

Product segregation is needed to avoid contamination by another product. This would ideally be by installing separate facilities for each product, but this can rarely be achieved due to prohibitive capital costs. The industry has, therefore, adopted a number of universally applied segregation techniques:

- Do not produce high-risk products in the same facilities as low-risk products. Antibiotics are always manufactured in facilities designed to produce only this type of product, as historically, patients have suffered reactions from cross-contamination of low-risk products by antibiotics. Hormonal products are normally manufactured in dedicated facilities for this potentially highly active material. Segregation allows specific cleaning and materials handling technology to be used in a dedicated manner as well as specific operator protection and training.
- Manufacture products requiring the same environmental standards in one area. Products at high risk of contamination, such as sterile products, require far higher quality environments and the cleaning regimes are more stringent. These areas should be kept to a minimum. Operators need special purpose clothing (to protect the product) and training to work in these areas.

- Dedicate an area to the production of one product at a time and ensure that the area and equipment are thoroughly cleaned before commencing the manufacture of a new product in the same area.
- Contain the production process, ideally within the manufacturing equipment. Where this is not possible, use airflow (laminar airflow or local extract) and enclosures to retain product spillage within the smallest possible area.
- Establish fully validated cleaning regimes for each product in each area/equipment item. It is essential to know, and be able to demonstrate, that the production area and equipment is clean at the end of a production run. 'Clean', in this context, means that trace elements of the previous product left behind after the cleaning process are below acceptable limits.

Product segregation is therefore the practice of 'avoidance'. By avoiding the factors that cause cross-contamination between products, the risks are reduced to an acceptable level. For example:

- keep different products in separate locations;
- ensure that labelling clearly identifies the product and its components;
- never manufacture one product in the presence of another;
- prepare standard operating procedures that do not create a risk of cross product contamination;
- use clean equipment at the start of a new production run;
- identify the risks of cross product contamination (e.g. operator's clothing) and reduce these risks;
- train operators in the use of equipment and production processes;
- audit the production processes to ensure conformity.

6.3.4 Cleaning

Equipment

Emphasis has been placed on the need to avoid cross-contamination between products. The major source of such contamination, if not removed by cleaning, is the equipment in which the product is prepared, closely followed by sources outside the equipment.

It is not sufficient just to clean the equipment and assume that any risk of contamination has been removed. Every individual operator would use their own method of cleaning if they were not trained. Their individual methods will vary from time to time and there is no guarantee that any of the operators' methods will provide cleaning to the standards required to reduce the risk of contamination to an acceptable minimum.

It is critical to establish cleaning procedures that can be repeated consistently. Different procedures may have to be established for each product and all the cleaning procedures have to be validated for effectiveness.

Manual methods of cleaning cannot be guaranteed to be one hundred percent effective unless by 'overkill'. Mechanical means of cleaning, however, can be accurately reproduced on demand. For this reason, modern pharmaceutical plants are normally designed with 'in-built' Clean In Place (CIP) capability.

CIP technology, established in the brewing industry, is based on the combination of chemical/detergent action and mechanical action (from the effect of direct impact on, or flow of water over, surfaces). The sequence normally utilized consists of:

- initial hot or cold rinse to remove gross contamination;
- caustic detergent rinse to remove adhering materials;
- hot or cold water rinse;
- neutralizing acid rinse (if required);
- hot or cold water rinse;
- final water rinse of a quality equivalent to that used in the process.

Water quality is a critical factor in CIP systems and any possibility of contaminants being introduced by water from the cleaning process must be eliminated. For this reason, de-ionized water to USP23 or BP is normally used throughout the CIP sequence with a final rinse of Purified Water or Water for Injection quality if the process demands this standard of cleanliness.

CIP systems are normally controlled by automatic sequence rather than manual operation.

Large surfaces to be cleaned by CIP systems require the use of mechanical devices, such as spray heads, and an understanding of the 'shadow' effects created by internal fittings. Specialist companies supply both the equipment and 'know-how' for this technology.

Although cleaning by direct impact using spray heads can be designed into process equipment, the interconnecting pipework can only be cleaned by the flow of water and chemicals over the surfaces. Experience indicates that turbulent flow is required to provide maximum cleaning effect. This turbulent flow is normally created by flow rates at or above 1.5 ms^{-1} and the design of a CIP system should ensure that all process pipework is subject to this minimum flow rate.

The duration of flow of CIP fluids is determined by examination of the effects of the CIP process on the system. Access is, therefore, required to all cleaned surfaces during the validation of the cleaning process.

For this reason, most process pipework installations subject to a CIP system are designed to be taken apart on an agreed schedule to enable the cleaning procedures to be re-validated.

Materials of construction are frequently fabricated to a higher standard than is required by the process, to enable the cleaning procedure to be fully effective.

Contamination sources outside the equipment can be eliminated by the total containment of the process. For many reasons, the design of pharmaceutical processes cannot always permit this ideal arrangement and, in practice, many sources of contamination will exist that have to be controlled during production.

The following brief paragraphs aim to give an indication of some of the chief contamination sources that are created by normal operation of a process, and the techniques for avoiding these are outlined.

(a) Materials received into the facility from outside sources

These are expected to be contaminated by any material normally present during transport and materials handling operations. Normally all such materials are double wrapped (plastic linings inside outer containers) and are frequently over-wrapped by stretch film. Cleaning, other than gross contamination, will be left until the material is to be used.

(b) Sampling

This is undertaken of all incoming materials and requires the breach of the materials containment system. For this reason, sampling is undertaken within a sampling booth and the material containers will be cleaned externally before entry into the booth. The inner and outer containers will be resealed before return to storage.

(c) Storage and internal transport

These will not normally provide a severe risk of contamination, but all inner and outer containers must be kept sealed. Again, the outer containers will be cleaned before entry into the production area.

(d) Dispensing operations

This is naturally a dusty operation when dealing with dry materials. Contamination of other materials from this dust must be reduced to a minimum by cleaning the dispensary area. It should be noted, however, that cleaning between the dispensing of different materials for the same product is normally only on a limited housekeeping basis.

(e) Charging/discharging operations
Transfer into and from process equipment is normally dust free for operator safety reasons. Where, however, this operation is not dust free, the resultant dust spillage can be expected to contaminate all surfaces in the operating room as well as the operator. The operating area must be thoroughly cleaned on the completion of a production run, or at least once a week.

(f) The operator
The operator has freedom of choice in where to go and what to do. This freedom has to be strictly controlled, with high quality training provided and absolute discipline exercised to prevent the transfer of contaminating products between different process operations. Current practice indicates use of specific clothing for each production room and personal cleaning regimes on leaving the room. These cleaning regimes may be as limited as an external clothing change or as severe as air showers or water deluges, depending on the nature of the product and the company's policies.

(g) Processing equipment
This is normally selected to be non-particle shedding and, therefore, is not considered to provide a contamination risk. Care should be taken over new or maintained equipment that can be delivered with surface contamination invisible to the naked eye.

(h) Room fabric
This includes walls, floors, ceilings, doors, service entries, lights, etc. All have to be carefully chosen to avoid particle shedding characteristics and have easily cleaned surfaces. Ledges should be designed out of the room, but where unavoidable, should be sloped to prevent dust traps.

(i) Air handling systems
These bring a continuous source of replacement air to the operating environment. Care must be taken in the design of the air handling plant, equipment and, particularly, filters to prevent external contaminants being carried into the operations. The following sub-section provides information on the environments that have been found to be acceptable for pharmaceutical production.

6.3.5 Environmental classification

Pharmaceutical environments are classified by the number of particles of specific sizes contained in a measured volume of air, together with requirements for temperature and humidity. The information in this section is on European and United States requirements.

Table 6.2 United States Federal Standard 209D — air classifications

Class	Class limits in particles per cubic foot of size/ particle sizes shown (micrometers)				
	0.1 mm	**0.2 mm**	**0.3 mm**	**0.5 mm**	**5.0 mm**
1	35	7.5	3	1	NA
10	350	75	30	10	NA
100	NA	750	300	100	NA
1000	NA	NA	NA	1000	7
10,000	NA	NA	NA	10,000	70
100,000	NA	NA	NA	100,000	700

The most easily understood classification comes from US Federal Standard 209D (Table 6.2) and, although theoretically superseded, is still in extensive use. It is based on imperial measurements.

This Federal Standard has been updated to version 209E by conversion to SI units of measurement (see Table 6.3).

FS 209E permits the continuing use of 'English' terminology although SI units are preferred. Of particular importance in the Federal Standard is the need to specify and measure particle counts as either 'as-built' (no operators or equipment present), 'at rest' (equipment installed, but no operators present) or 'in operation' (equipment in use and operators present).

Table 6.3 United States Federal Standard 209E — air classifications

Class name		Class limits (volume units)									
SI	**English**	**0.1 mm**		**0.2 mm**		**0.3 mm**		**0.5 mm**		**5.0 mm**	
		(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)	(m^3)	(ft^3)
M1		350	9.91	75.7	2.14	30.9	0.875	10.0	0.283		
M1.5	1	1240	35.0	265	7.5	106	3.00	35.3	1.00		
M2		3500	99.1	757	21.4	309	8.75	100	2.83		
M2.5	10	12,400	350	2650	75	1060	30.0	353	10.0		
M3		35,000	991	7570	214	3090	87.5	1000	28.3		
M3.5	100			26,500	750	10,600	300	3530	100		
M4				75,700	2140	30,900	875	10,000	283		
M4.5	1000							35,300	1000	247	7.00
M5								100,000	2830	618	17.5
M5.5	10,000							353,000	10,000	2470	70.0
M6								1,000,000	28,300	6180	175
M6.5	100,000							3,530,000	100,000	24,700	700
M7								10,000,000	283,000	61,800	1750

In all cases, services must be functional.

There are a number of European Standards available based on national standards. The European Directives that created 'The Rules Governing Medicinal Products in the European Community' cover air classification systems for the manufacture of sterile products (see Table 6.4). These classifications are now considered as the established European standard and, for members of the EEC, are legal requirements.

In the 'Rules and Guidance for Pharmaceutical Manufacturers 1997' prepared by the MCA, a similar table is published for sterile production that gives further guidance between the 'at rest' and 'in operation' conditions (see Table 6.5).

For these airborne particulate classifications, the MCA also publish a table giving recommended limits for microbiological monitoring of clean areas 'in operation', (see Table 6.6, page 170).

Table 6.4 Air classification system for manufacture of sterile products

Grade	Max permitted number of particles per m^3 equal to or above		Max permitted number of viable micro-organisms per m^3
	0.5 mm	5.0 mm	
A Laminar air flow work station	3500	None	Less than 1
B	3500	None	5
C	350,000	2000	100
D	3,500,000	20,000	500

Extract from The Rules Governing Medicinal Products in The European Community. Note that class A refers to the air classification around the exposed product, whilst class B refers to the background environment.

Table 6.5 Airborne particulate classifications — MCA guidelines

Grade	Maximum permitted number of particles per m^3 equal to or above			
	At rest		In operation	
	0.5 mm	5.0 mm	0.5 mm	5.0 mm
A	3500	0	3500	0
B	3500	0	350,000	2000
C	350,000	2000	3,500,000	20,000
D	3,500,000	20,000	Not defined	Not defined

Table 6.6 Recommended limits for microbial contamination (average values) — MCA guidelines

Grade	Air sample cfu m^3	Settle plates (diam. 90 mm), cfu/4 hours	Contact plates (diam. 55 mm), cfu/plate	Glove print 5 fingers, cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

Note that all the above tables are published with comprehensive notes. It is important that these notes are fully understood before proceeding with the design of the environment.

The particulate classifications in use are normally referenced by either the FS 209D system (100, 10,000, etc.) or by the EEC rules (A, B, etc.). These two classifications correspond approximately and both are accepted by the regulatory authorities. In summary, Table 6.7 provides a brief check for the user.

It is recommended that the designer specify the particulate levels in the 'at rest' condition. In addition to the particulate levels, room operating conditions of temperature, humidity and pressure must be specified.

Humidity creates contamination risk to the product from condensation, absorption and human perspiration. It is, therefore, normal practice to maintain the operating conditions at 45% to 55% relative humidity.

Where a product is expected to absorb water from the environment, such as effervescent tablets, hard gelatine capsules, etc., the humidity has to be reduced. The humidity has to be controlled at a level that is acceptable

Table 6.7 Approximate equivalent international standards

MCA guidelines	FS 209D	FS 209E	ECC rules	Germany VDI 2083	UK BS 5295	ISO 14644 Part 1
1997	1988	1992	1992	1990	1989	Draft
	1	M1.5		1	C	3
	10	M2.5		2	D	4
A	100	M3.5	A	3	E or F	5
B	100	M3.5	B	3	E or F	5
	1000	M4.5		4	G or H	6
C	10,000	M5.5	C	5	J	7
D	100,000	M6.5	D	6	K	8

to the operator as well as avoiding risk to the product. In extreme cases, it will be necessary to provide the operator with a breathing air supply.

Temperature should normally be maintained at a level that permits the operator to work in comfort. The air supply temperature should allow for heat gains from all sources within the operating area. Many alternative methods of temperature control are available and the designer should seek expert advice. It is essential, however, to maintain the room temperature within the specified — and validated — limits over the full range of operational conditions.

Where production has to be undertaken at temperatures normally unacceptable to the operator, e.g., cold rooms, then protective clothing should be provided.

Pressure differentials are an essential part of the design of a clean room facility. To protect a product from contamination from outside sources, it is normal practice to pressurize the rooms in which the product is exposed to the environment. Where a sequence of operating rooms is installed, pressure 'cascades' are frequently used so that the most sensitive areas are at the highest pressure and the least sensitive at, or just above, atmospheric pressure. This situation is most frequently present in aseptic operations.

Where the product concerned is of high potency, negative pressure is used to contain the hazard to within the operating area. The risk from external contamination is usually reduced by surrounding the negative pressure room with other areas (e.g. changing rooms) at positive pressure.

The most commonly used pressure differential is 15 Pa.

6.3.6 Ventilation systems

Ventilation systems designed into any secondary pharmaceutical facility need to be carefully designed, installed, controlled and operated. The designer should consult with experts in this field to achieve the desired conditions within the process areas, but the following paragraphs give some general guidance.

The environmental standards specified within any operating area must be maintained to those standards at all times when process operations are active. At no time should the product, or the surfaces with which the product comes into contact, be exposed to environmental conditions that may cause unacceptable contamination. In practice, this means that ventilation systems will be fully operational for the majority of the time and only revert to night/weekend operation when all risks of contamination have been contained.

Assuming that the ventilation system has been correctly designed and installed, the system should not provide any significant source of contamination. This is achieved by both filtration of the air supply and monitoring and control of the pressure, temperature and humidity in each operating area.

Each area will have been commissioned against a specification that meets the environmental classification for the product being made and the area will be monitored on a regular basis for maintenance of this classification. Any deviation has to be reported and action taken. Significant deviation from acceptable limits will result in cessation of production.

To prevent this extreme situation, ventilation systems are normally designed to meet the following criteria:

Class A: Laminar airflow through terminal HEPA (High Efficiency Particulate Air) filters at a velocity of $0.45\,m\,s^{-1} \pm 20\%$ at the working position (MCA guidance) with low-level extract. In all cases, operations at Class A should be contained within a purpose-designed workstation with no operator access other than gloved hands.

Class B: Downward airflow through terminal HEPA filters with low-level extract. The operator will be working and creating high particle counts in this area. Air volumes should be sized to ensure that particulate conditions for the 'at rest' state will be achieved in the unmanned state after a short 'clean-up' period of 15–20 minutes.

To ensure that the air movement is able to clean up the working area, current designs now utilize turbulent air movement delivered by purpose designed diffusers.

Class C: Airflow provided through (normally terminal) HEPA filters with air movement of sufficient volume to maintain the classification of the area. There is considerable debate on the use of low-level extract for Class C areas, but there is no specific requirement. Air volumes should be sized to ensure that particulate conditions for the 'at rest' state would be achieved in the unmanned state after a short 'clean-up' period of 15–20 minutes.

The higher cost of installing low-level extracts needs to be considered against the risks created by moving particles in the air stream over the entire working area when high-level extracts are used.

Class D: Airflow provided through filters (normally HEPA) with air movement of sufficient volume to maintain the classification of the area. High-level extract is the usual installation for this classification. Air volumes should be sized to ensure that particulate conditions for the 'at rest' state would be achieved in the unmanned state after a short 'clean-up' period of 15–20 minutes.

Where possible, air movement should be designed to flow downward over any exposed product to avoid particulate entrainment being carried over the product.

In areas where the majority of operations only require a minimal environmental classification, it is acceptable to provide higher local environmental

conditions by use of air curtains. A good example of this method of protection can be found in many packing halls, where the general area will be to Class D, but local conditions around the product at the filling head will be to Class C.

HEPA filters are normally used to achieve the stated environmental classifications. Within Europe, the grades of HEPA filter are distinguished by the use of EU classifications, each of which has a known retention efficiency at 0.3 mm (see Table 6.8).

In the USA, HEPA filters are required to have efficiencies of 99.97% (EU12 and greater).

Not only is it essential that the filter specifications meet the requirements of the environment, but also that the installation does not compromise the filter integrity. This can be caused through damage to the filter medium, or through passage of unfiltered air between the medium and its frame, or between the frame and the air supply system. Assurance of the integrity of an installed filter system must be subject to an 'in-situ' integrity test.

6.3.7 Surface finishes

Throughout this section, emphasis has been placed on the avoidance of possible contamination of the product. Consideration has been given to sources of contamination from outside the operating environment but it is equally important to appreciate that the fabric of the area and the equipment in which the product is produced, can itself contaminate the product.

All materials of construction should be non-particle shedding. Traditional building materials must, therefore, be sealed by the application of a surface coating. Current practice is to use a two part epoxy coating (or equivalent) that provides both an abrasion resistant surface and a sufficient degree of elasticity to avoid minor wall movements opening up hair line cracks, thus permitting particulate escape.

The use of partition systems has become widespread and several alternative systems are available. These systems, although more expensive, eliminate the

Table 6.8 Classification of retention efficiencies of HEPA filters

Eurovent classification	Efficiency at 0.3 mm (%)
EU10	≥95 – < 99.9
EU11	≥99.9 – < 99.97
EU12	≥99.97 – < 99.99
EU13	≥99.99 – < 99.999
EU14	≥99.999

wet building trades and provide an acceptable pharmaceutical finish with no further surface treatment.

Joints in wall and ceiling construction are normally filled with a silicone sealant that permits some building movement without any crevices forming. For ease of cleaning, joints between walls and floors are always coved in any area in which product is exposed. Current practice is to cove at wall to wall joints in Class C areas and also wall to ceiling joints in Class A/B areas.

Floors present a more difficult choice, as they have to accept movement of heavy loads, building settlement and movement as well as possible damage from containers, etc. Currently, epoxy floor coatings up to 6 mm thick are proving successful, but their expense limits their use to the more severely loaded areas. Vinyl floor, wall and ceiling coverings are an acceptable solution — reserved for lightly loaded areas and are the material of choice in Class A/B areas for many manufacturers.

In selecting materials of construction for the building elements, thought must also be given to the damage that may be caused by the normal daily operations, such as trucks and pallets hitting walls. Where such damage would expose particulates, wall protection is usually provided.

The cleaning regimes in the production environment normally involve wetting the surfaces of the area. In the controlled environment, these conditions provide excellent sources for microbial growth and it is, therefore, important to ensure that surface finishes do not support microbial growth.

Process equipment comes into intimate contact with the product and, therefore, the materials of construction are of most significance. Non-corroding materials are essential, not only to prevent contamination of the product, but also to stop any damage to the surface finish of the equipment.

A poor surface finish harbours crevices that can support microbial growth and traces of previous products and cleaning agents. For this reason, emphasis is placed on the specification of surface finishes and the methods by which they are prepared.

The great majority of pharmaceutical process equipment is fabricated from 316 or 316L stainless steel because of the non-corrosive nature of the material for most products and the ease with which it can be given a high quality surface finish. The surface finishes are normally specified (as Ra — average roughness) in either micro inches or microns. The polishing medium grit size should not be used as an indication of the surface finish.

Individual producers of stainless steel equipment will use both mechanical and electro polishing methods. Electro polishing gives a higher quality look to the surface and provides a more rounded edge to the microscopic grooves in the

polished steel. This more desirable finish is, however, more expensive than mechanical polishing.

The selection of the surface finish is determined by:

- existing standards within a facility;
- end user preference;
- the need for a reduction in crevice size to reduce microbial growth;
- cost.

Table 6.9 lists surface finishes specified for stainless steel equipment.

6.3.8 Lighting selection

Apart from the need to ensure a safe working environment, the regulatory authorities are interested in the lighting levels in a facility to ensure the manufacturing operations are undertaken without error.

Although many operations in the modern pharmaceutical production facility are now automatically controlled, the operator still needs to oversee these operations. Frequently his work requires him to read Standard Operating Procedures and the slightest risk of error caused by misreading the instructions, instrumentation and alarms is not acceptable.

Lighting selection must, therefore, ensure that the level of illumination is sufficient to read documentation, displays and instrumentation and that this does not cause operational difficulties from glare, reflection or too high an intensity.

Designers of pharmaceutical facilities are recommended to take expert advice in the illumination specifications to ensure that all working areas are well lit throughout.

Table 6.9 Polished finished on stainless steel sheet — Sillavan metal services

Description	BS1449 No	Approx. μm Ra value	Reflectivity %
Coarse grade 80 grit	3A	2.5	10
Coarse grade 180 grit	3B	1.0	10
Silk	3B	0.4	30
Supersilk	3B	0.35	30
Brush	3B	0.2	30
Bright buff	No 7	0.05	48/55
Bright polish	No 7	0.05	53/60
Mirror	No 7	0.05	58/63

6.4 Containment issues

6.4.1 Operator protection

Pharmaceutical manufacturing operations involve the handling of sophisticated chemical compounds, many of which can exhibit toxic effects on personnel handling them in concentrated quantities. Additionally, and often at the same time, pharmaceutical materials and products can suffer if exposed to the operating environment (for example, sterile products for injection).

Operator protection can be provided by means of personal equipment (gloves, overalls, masks), while the creation of suitable macro-environments can provide aseptic facilities for injectable manufacture. However, the validity of these methods is questionable, and the use of techniques which enclose the product materials in a smaller space and provide means of remote operator access have become commonplace. These techniques are known as isolator or containment technology. Although the application of these methods differs between operator and product protection requirements, there are similarities in the equipment involved.

6.4.2 Product protection

A second application of containment technology is its use for the protection of products from environmental contamination. This application applies particularly to the aseptic manufacture of injectable or infusion products, which has traditionally been performed in high-quality environments conforming to Class 100 or better (to US Federal Standard 209E). The accepted approach is for the equipment and operations involved to be sited in Class 100 clean rooms, with localized enhanced protection to Class 10 being provided by fixed or mobile air supply units. The latter are designed to provide airflow of minimum turbulence (effectively 'laminar' flow when the units are unoccupied) so as to minimize particulate pick-up by the air steam in areas where sterile product or product-contacting components are present.

This arrangement has been demonstrated over a period of twenty or more years to provide minimal validated risk of contamination, and this proven assurance has given rise to its use in the majority of modern pharmaceutical aseptic processing facilities.

However, two undesirable features remain:

- the construction and operation of facilities reaching Class 100 conditions is expensive;
- there remains the possibility of human operator contact with product materials, with consequent risk of contamination.

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Hence, recent developments of isolator technology have concentrated on the use of such equipment to provide a reliable localized barrier between the product and the operator, with the isolator forming a separate sealed environment of Class 100 or better, within which aseptic manipulations can be performed, either by hand using glove ports or automatically.

Apart from the increased potential for reliable sterility, the use of isolators having a sealed high-grade internal environment has meant that the surrounding room space need not be to the same high standard. Current opinions differ on the desirable room environment quality, the regulatory view being based on Class 10,000, while some authorities among users and equipment manufacturers claim reliable validated operation at Class 100,000. Clearly, the capital and operating cost of such environments is lower than that of a Class 100 suite.

The isolator equipment commonly used for aseptic processing is sophisticated and by no means low cost, but it does allow lower cost surroundings while supplanting the need for localized laminar flow units and often filling machine guards.

It is possible to link several machines for washing, sterilizing, filling, capping and sealing of injectable product containers within a set of linked barrier isolators or use a form-fill-seal technique

6.5 Packaging operations

6.5.1 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.

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

Much of this paralleled the growth of other consumer products, but the special security and safety requirements of medicines have extended pack features, which now include:

- tamper-evident closures;
- child-resistant closures;
- special protection against hostile shipping environments;
- security coding systems.

The early manual assembly of packaged products has given way to progressively more-automated methods. Machines for counting unit dose products (such as tablets) and discharging the correct number into manually-presented containers soon gave way to in-line counting, filling, capping, labelling and cartoning units linked by conveyors. These transport systems had gateing, accumulation and flow control elements built-in. Thus, the modern packaging line incorporates sophisticated handling and sensing equipment designed to minimize human intervention and eliminate human error.

As seen later in this chapter, the structure of healthcare management arrangements is leading to increasingly sophisticated and patient-dedicated packaging, which curiously is taking developments full-circle and returning the objective back to the days of direct patient-specific dispensing.

6.5.2 Tablets and capsules

The packaging of solid unit-dose items is generally carried out in one of two ways. These utilize multiple-item containers (typically glass or plastic bottles) and blister packs.

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.

As a result, modern counting machines are equipped with missing-item detection systems, utilizing infrared sensing or matrix camera technology.

Containers may be of either glass or plastic, but are increasingly of the latter as plastic materials with improved moisture-resistance have been developed.

Capping systems have been designed which prevent non-evident pilferage or which are resistant to the attentions of young children. These benefits do, however, become disadvantageous when used for arthritic patients, who may have difficulty in opening the packs.

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.

However, they have two significant advantages, being generally cheaper to produce and of smaller size than the equivalent blister pack.

Blister packs

These are produced by a form-fill-seal process using PVC or similar thermoplastic material in reel form as the blister material. For products having enhanced moisture sensitivity, plastics such as polyvinylidine chloride may be used. The blister cavities are formed from the thermoplastic film using heated die plates or drums, with plug or vacuum assistance.

Tempered aluminium lidding foil with laminated plastic or an adhesive coating allows the two parts of the pack to be heat-sealed together. An alternative to plastic films for blister pack formation is the use of cold-formed aluminium foil, which can offer improved product protection from moisture ingress.

Blister forming methods include the use of continuous-motion cylindrical formers with blister cavities machined into them, or flat-platen types which cycle in a manner which matches the horizontal speed of the blister web, giving higher potential outputs.

The sealing together of the filled blister and lidding foil is achieved by the concurrent flow of the two material streams followed by the application of heat and pressure using heated rollers or platens.

Modern machines can operate at speeds of typically 400 blisters per minute, giving an equivalent tablet/capsule output of 4000 per minute for a ten-item blister.

A critical factor influencing machine output is the mechanism used for feeding the tablets/capsules into the formed blister cavities. Similar methods for detecting missing items to those used for bottle packs are employed.

It is not uncommon for finished blister packs to contain more than one blister strip. This packaging method requires the blister form-fill-seal machine to incorporate a stacking/counting unit for the blisters, prior to carton insertion.

6.5.3 Liquids

Liquid pharmaceuticals are packaged using either bottles or sachets, the latter being used for unit-dose applications.

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.

In consequence, modern pharmaceutical liquid packaging systems utilize volumetric measurement, either by means of adjustable-stroke piston pumps, or by positive-displacement rotary lobe-type pumps controlled by rotation sensors.

High-speed dosing machines utilize 'diving nozzle' systems in order to reduce air entrainment and foaming problems (see Section 6.5.5 on page 182).

Sachets

Sachet packaging is mostly used for powders, which are then reconstituted with water or another suitable diluent by the end-user. However, a small number of examples exist of liquid-filled sachets. The pack is an ideal single-dose provision system. Sachets are formed from laminated foils, usually including

a plastic inner layer with aluminium foil centre laminate and an outer layer of paper that provides a printable surface.

The sachets are formed as three-side sealed units prior to filling, and the final top seal is then applied, together with a batch/expiry date code.

Sachet packaging is more common for non-pharmaceutical products, where outputs can be as high as 100 sachets per minute.

The assembly/collation and cartoning methods of sachets are basically similar to those for tablet blister packs.

6.5.4 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.

6.5.5 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

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 pre-printed bar-code, comparing this code with microprocessor-held recipe information, and reject or produce an alarm on any false codes.

6.5.6 Sterile products

It can be assumed that products manufactured aseptically arrive at the packaging stage in sealed containers that assure the integrity of the product.

The exceptions to this are items manufactured using integrated form-fill-seal systems, and impregnated dressings, where specific handling arrangements apply.

Ampoules and vials

Although some unit sterile products (both liquid and powder) are filled into pre-printed ampoules or vials, it is not uncommon that these components are effectively unidentified prior to labelling. It is, therefore, essential that filling controls are such as to ensure that the containers are held in identifiable lots, and that these lots are labelled with minimum delay or handling. It is thus usual for ampoules and vials to be labelled immediately following aseptic filling or terminal sterilization. In the latter case, they will be held in sterilizer-compatible trays that are used as loading cassettes for the labelling machine.

Wherever possible, manufacturers will arrange for unlabelled injectable product containers to have a form of product-specific machine-readable code. In such cases, the first task of the labelling machine will be to read this code and compare it with recipe information held in its control system.

As with oral-dose products, modern labelling systems use self-adhesive pre-printed/coded labels in reel form. It is common for these labels to use a transparent substrate such as polyester film to facilitate product visual inspection after labelling.

Pre-printed code checking is also included in modern labelling machine technology, and is again linked to control-system recipe information.

Syringes

Similar procedures apply to syringe packaging as for ampoules and vials, but the inconvenient shape of pre-filled syringes means that specifically engineered handling systems are required.

Form-fill-seal

High-volume production of single-dose and large volume infusion solutions is frequently performed using integrated-system technology. This approach is based on the use of high-quality thermoplastic materials (such as polypropylene) in granule form being heat-moulded in an enclosed system within a controlled-environment machine enclosure, to produce sterile empty containers, which are immediately filled in-situ with the sterile-filtered product solution. The filled containers, which may be single or multiple-moulded units, are immediately heat-sealed prior to emerging from the controlled enclosure.

This form of production requires sophisticated and expensive machinery but has high throughput and the possibility of locating the forming-filling unit in an area of lesser environmental quality. It is also possible to emboss product and batch code information onto the containers at the point of manufacture, thus enhancing identification integrity.

Creams and ointments

Such products are often filled aseptically into collapsible tubes using techniques similar to those employed for non-sterile products. These procedures are most often used for the manufacture of ophthalmic ointments.

Another application for semi-solid products is in the preparation of impregnated dressings. Although it is not a common product type, it has particular importance in the manufacture of material for the treatment of severe skin conditions, including burns. The technology involves the dosing of the medicated product onto a suitable substrate (usually tulle) in reel form, in a continuous or semi-continuous automated process carried out under aseptic conditions. The impregnated tulle is then cut into unit-treatment sections, which are packed into sachets, using a form-seal process. The sachet-forming material would consist of paper/foil/plastic laminates in reel form, pre-sterilized by irradiation.

6.5.7 Container capping and sealing

Solid or liquid products packed in glass or plastic bottles, jars or tubs require some form of lid closure to protect the contents. A typical bottle closure would be a pre-moulded screw-on plastic cap with a composite paper wad to provide a seal.

Such caps were originally hand-applied and tightened, but this action gave rise to unreliable seals and leakage, so mechanized systems were developed which provided a constant application torque, although the bottles were still hand-presented. As outputs increased the arrangement was changed to one of automatic presentation, application and tightening.

A small number of incidents of product pilferage occurred, so the consequent requirement for tamper-evidence led to various attempts to provide a 'pilfer-proof' feature. One such, for jars, involved the application of a plastic/aluminium foil laminate, heat-sealed onto the jar by means of heat/impulse sealer (similar to the system used for instant coffee jars). This solution provided the added benefit of enhanced product protection from moisture ingress.

Alternative tamper evident methods included the use of roll-on aluminium type caps, where the bottle thread is followed by spinning rollers that form the cap thread. These have also been utilized without the tamper-evident feature.

Plastics have been used successfully for many years as a material for both container and cap manufacture. These include both screw and press-on flexible plastic caps, the latter also being employed for glass bottles. Such flexible materials have the added possibility of including a press-on tamper-evident cap, which combines adequate product protection with ease of application.

6.5.8 Container labelling and coding

Early labelling systems used vegetable or animal-derived semi-solid glues manually applied to paper labels, which were then applied to the container.

This approach had many failings, notably:

- there were no reliable checks on label identity or batch code;
- the position of the label on the container was not fixed;
- there was no automatic batch coding.

Later systems, still used in many non-pharmaceutical applications, retain the use of wet glues but employ machine-application. Early versions of such machines employed automatic batch code printing, although the resulting print quality was not good.

Most modern pharmaceutical labels are of the self-adhesive type, which allows cleaner operation and reliable appearance. Automatic machines usually include product bar-code scanning and automatic batch coding, with alarm systems for integrity failings.

A long-standing feature of pharmaceutical packaging has been the use of market-specific labelling. This requirement gives rise to a potentially wide range of label alternatives, with stock holding and cost consequences.

A modern system has been developed to overcome this problem, utilizing plain self-adhesive label stock onto which all product, batch and expiry details are automatically printed in multiple colours using microprocessor controls. Recipe information held by the microprocessor system is fully validated to ensure correct output.

6.5.9 Cartoning

The placement of filled containers of liquid or unit solid pharmaceutical products into cartons was initiated for a number of reasons, including the need to insert leaflets providing patient usage instructions and, in the case of liquid products, the addition of a standard dose-measuring spoon. Such placements were initially performed manually.

As demand and output increased, automatic machines were introduced. This automation created a number of challenges to consider, for example:

- the importance of detail design, accuracy of cutting and assembly of blank cartons to ensure efficient mechanical erection and closing;
- the importance of humidity control during carton storage due to the effect of moisture on carton board making it less pliable and increasing friction — very significant for higher speed machines;

- the engineering design of cartoning machinery to allow smooth and reliable high-speed operation.

Modern cartoners may be fitted with automatic leaflet insertion, using pre-printed plain sheets, folded prior to insertion, or reel-fed leaflet stock. They may also be fitted with automatic batch and date coding and code scanning to determine correctness of carton type and overprinted information.

Automatic and semi-automatic cartoners are generally of four alternative types, which are characterized by method of motion indexing (intermittent or continuous) and by direction of container insertion (horizontal or vertical). Intermittent motion vertical (IMV) machines are used frequently in pharmaceutical packaging, not least because they can be operated in a manner that permits manual insertion of bottles/leaflet spoons at one or more operator stations. For high throughput, however, continuous motion horizontal (CMH) machines are favoured.

6.5.10 Collation, over-sealing, case packing and palletizing

The automation of 'end of line' operations within the pharmaceutical industry is not a universal practice, although it is becoming more commonplace for higher-output packing lines. Owing to the fact that, at this late stage in the production cycle, the product is fully sealed, protected and identified, the equipment required for final packaging does not generally need to be specialized. It is, thus, acceptable for it to be of the same type and source as that used for consumer goods packaging.

Collation of filled cartons and over-sealing with cellulose or polymer film is common for many medium-selling products. On low-output packing lines the collation is performed by hand and the over-sealing is performed using a semi-automatic heat-sealing unit with manual operation.

For higher-speed lines, typically over 20 cartons per minute, the collation of cartons and feeding into a wrapper/sealer is often performed automatically.

Automatic case packing and palletizing is not universally used, due to the relatively low outputs typical of many pharmaceutical products. However, it is not unknown, and once again, consumer goods equipment is employed.

One advantage of automatic final packaging is that it facilitates the automatic application and checking of outer carton labels.

6.5.11 Inspection systems

Modern pharmaceutical packaging systems rely heavily on inspection systems to verify the correctness of critical product parameters, including:

- fill volumes or unit counts;

- absence of contamination;
- container seal integrity;
- container label identity;
- label position and orientation;
- carton identity;
- outer container label identity;
- batch number;
- manufacturing date;
- expiry date.

In common with other consumer product industries, the pharmaceutical industry originally relied on human visual inspection to detect contamination and pack faults. Examples included the use of visual checking for particulate contamination in ampoules and liquid vials, container, label, cartons identity checking, and the monitoring of fill levels.

These procedures were known to be of limited reliability due to operator fatigue and attention-span limitations, and also suffered from slow and variable output rates, especially if inspection speeds were operator-controlled.

Initial mechanized systems, in which the containers were automatically presented to the operator's line of sight in an ergonomically efficient manner, were introduced. These still relied on operator visual acuity and attention, with benefits to output and reliability, but these were not significantly faster than a competent human operator, and remained less than 100% reliable.

A considerable amount of survey work was carried out in the 1960s and 1970s, especially in connection with injectable product inspection, and the data generated was used to compare performance with mechanical methods.

Camera-based systems were introduced during the 1970s by a small number of European and Japanese companies, and these provided benefits in terms of improved output rates to match similarly improved filling machine performance. Detection rates were improved and became more consistent, but the machines were limited in capability to a set number of reject types, largely due to limitations in the camera technology. These rejects were based upon physically measurable parameters (including volumes, counts, contaminants).

The introduction of digital matrix camera technology during the 1980s gave rise to an expansion in automatic inspection capabilities. These microprocessor-driven systems can be programmed to recognize deviations from standard shapes, the presence of contaminants, and even the correctness of components codes and batch and expiry-date numbers.

As with many advances in production technology, the improvements in inspection systems have arisen from the quality and output-led demands of the pharmaceutical and other high-volume product industries. These challenges have been met by the machinery and equipment manufacturing industry and the reader is recommended to approach these manufacturers for information on the latest advances in this fast-moving area of technology.

6.6 Warehousing and materials handling

6.6.1 Introduction

The storage of materials for pharmaceutical manufacture and the products themselves utilizes systems and procedures much like those employed in any high-volume consumer products operation. However, there are some special considerations applicable to pharmaceuticals resulting from the critical need to ensure the integrity of raw materials and products, and these affect the selection of storage systems, materials management systems and material transportation arrangements. The ultimate choice of system available in each of these aspects will be influenced by many 'normal' considerations, but ultimate pharmaceutical product security and integrity are the overriding factors.

6.6.2 Conventional storage

The extent of raw materials and finished product holding typical of pharmaceutical industry operations is not normally considered large. Hence, automated high-capacity storage systems are not always required or cost-effective. In these situations, 'conventional' warehousing, consisting of racking systems having, typically, no more than five pallets in the vertical direction and aisle widths between rack faces of around 2.5 to 3 metres, are common, assuming standard 1.0×1.2 metre size pallets.

The advantage of this arrangement is that the racking can be fully free-standing with no top-end fixing, and regular ride-on counterbalance fork lift trucks (which can also be used in a variety of non-warehouse duties) are suitable for stacking and de-stacking movements.

Although such arrangements are relatively low-cost, they do have certain disadvantages, notably that the pallet density per unit floor area is low, so that the area utilization is poor where site space is limited. A further specific disadvantage for pharmaceutical warehousing is that, being basically flexible and operator-controlled, the extent of automatic cGMP compliance in relation to material segregation is effectively zero, and adherence to procedures

becomes the only method of avoiding mistakes in the selection of materials for production.

A solution to these deficiencies is the employment of automated systems (see Section 6.6.4).

6.6.3 High bay options

Where material volumes are high, in terms of total inventory and frequency of movements, conventional warehousing is inefficient, both in storage density and in speed of pallet insertion and removal. Where site space is limited, the storage density is especially significant.

High bay warehouses, having vertical pallet stacks of between 5 and 20 units, provide a solution to high-density storage requirements. They typically have narrower trucking aisles and special trucks which cannot be utilized for non-warehouse duties. The trucks can be of two alternative types — operator-controlled ride-on, or automatic crane. The former has many similarities with conventional systems, whereas the latter has no direct operator involvement and is controlled by a computerized materials management system. Many permutations are possible, and the selection will depend on material selection frequency, total capacity, number of alternative materials, etc.

Computer-controlled systems have considerable benefit in pharmaceutical warehousing duties, as quality assurance is enhanced by the automated nature of material selection and location (see Section 6.7).

These high racking configurations usually require structural bracing at the top in order to provide stability. Indeed, it is not unusual for very high warehouses to utilize the racking system as part of the building structure, with exterior cladding and roofing supported off the rack framework.

6.6.4 Automated warehousing

Some of the major international pharmaceutical companies have invested in automated production systems, including warehousing. The latter, based on high bay arrangements, utilize materials management systems for the control of material movement and usage, interfaced to warehouse control systems that handle the insertion, removal and security of raw materials and finished product. Such warehouses are typically un-manned and employ stacker cranes.

As there is no physical operator involvement in materials selection, it is possible for automated warehouses to be employed for the storage, in a single warehouse, of raw materials and finished products having 'quarantine' as well as 'approved' status. The selection of materials is controlled by the materials management system, which carries material status information and transmits simple location-only instructions to the warehouse crane.

This type of warehouse and management system may integrate with automatic production systems, where material movement within the manufacturing area is also mechanized, and where the production materials are always enclosed within the processing equipment or transfer containers.

'Islands of automation' arrangements are ideally suited for single-product manufacturing facilities, but have also been employed for multiple generic product manufacture. Their most significant challenges relate to the specification of control systems and their validation, and to the design of mechanisms for enclosed material transfer.

6.7 Automated production systems

6.7.1 Introduction

Earlier sections of this chapter refer to the application of automatic manufacture systems.

The adoption of automation in pharmaceutical manufacturing is driven by the need to minimize costs, and the desire to avoid the effects of human error. As labour costs increase, the reduction of direct manpower requirements makes economic sense. At the same time, the cost of pharmaceutical machinery is escalating as a result of enhanced technical sophistication and cost inflation, so that increased daily running times are necessary to meet return on investment criteria.

Although automated materials handling has been and continues to be utilized in pharmaceutical manufacture and warehousing, its application has generally been restricted to operations which basically involve a single-product type (such as tablets), or those where high-potency product containment has led to the development of enclosed systems.

The additional costs of fully automatic, or 'lights out' operation, are largely related to the inclusion of microprocessor-based monitoring and control systems, the hardware costs of which are steadily reducing in real terms. Hence the cost/benefit relationship is moving in favour of the adoption of automation.

In addition to these manpower and capital cost savings, automation can bring other advantages, including:

- improved product consistency and quality;
- enhanced adherence to validated systems;
- reduced services usage per unit output.

6.7.2 Process automation

Automatic semi-continuous operation of individual process units where bulk material input and product output systems are possible (including tablet presses, capsule fillers, inspection units) is achieving greater acceptance. Such units utilize automated sampling for off-line QC analysis, as well as automated measurement and feedback control of fill/compression weight, hardness and thickness. Self-diagnosis of electronic systems coupled with automatic switching of backup systems can also be expected to become common in the medium term.

Other less continuous processes can more easily be automated (such as granulation, drying, blending), as the number and range of control parameters are limited. However, automation of the product transfer arrangements linking these individual steps is perceived to be more difficult to achieve due to the greater separation distances involved and the need for connection and disconnection.

This perception can be answered by amalgamating unit operations within single areas, having 'permanent' connections between process steps, and using validated Clean In Place systems for inter-batch decontamination. This approach allows complete sets of linked operations to be run as 'continuous' processes. Applications of this nature are common in certain other industries and technology transfer is clearly a major opportunity.

Additionally, where scale of operation and product mix permit, Automated Guided Vehicle (AGV) systems for IBC movement with automatic docking facilities can be utilized. This is particularly attractive where bin movements and docking operations can take place within technical (non-GMP) areas.

6.7.3 Packaging automation

There is considerably wider scope for automation in pharmaceutical packaging operations, where higher unit volumes and repetitive tasks traditionally require the employment of large labour forces. Cost reduction and quality improvements have been achieved throughout the industry over the past 40 years by the use of automated operations and higher-speed machinery. There remains considerable scope for further automation of these activities, but factors determined by market and regulatory pressures are of great current interest (i.e., the movement towards original-pack dispensing and patient-specific production).

The following section of this chapter describes a pioneering approach to meeting these challenges, and provides useful information on the engineering aspects associated with packaging automation. The authors are grateful to Richard Archer of The Automation Partnership for agreeing to the inclusion of this section.

6.8 Advanced packaging technologies

6.8.1 Introduction

Compared to most other manufacturing sectors, the pharmaceutical industry occupies a unique position where the direct manufacturing cost of many of its products is a small proportion of the end user price. The major costs in pharmaceutical companies are the indirect ones in R&D, marketing and distribution, not manufacturing. In simplistic terms, it could be said that pharmaceutical manufacturing costs were not really important. If this statement seems contentious (which it deliberately is), consider the impact on respective company profitability of halving the production cost of a car compared with that of a tablet and how such a proposition would be viewed. For a car company, manufacturing costs are of paramount importance in achieving competitiveness, with the whole product design and development process geared to manufacturability and provision of maximum product features and choice at minimum cost. For the pharmaceutical companies, the primary emphasis is on discovering and launching increasingly effective molecules and therapies. Provided there is a method of manufacture that can be well controlled and monitored, the actual direct production cost is comparatively unimportant.

This unique situation has changed, however, as pharmaceutical prices have come under greater scrutiny from governments, healthcare providers, insurance companies and the challenge of changes in the selling and distribution of prescription drugs. Both the direct and indirect costs of production and distribution are under pressure, while the market is demanding greater choice, improved service, faster response and lower prices.

In many respects, therefore, the pharmaceutical industry is now having to face the same issues of cost and flexibility that most manufacturing sectors had to address decades ago. The industry is, however, unfamiliar with the key principles of truly flexible manufacturing and much of the available processing equipment is unsuited to rapid changeover and responsiveness. Too few pharmaceutical companies today recognize that the ultimate objectives of advanced flexible manufacturing are reducing indirect costs and generating new business opportunities, not direct cost reduction.

Packaging of solid dosage products is indicative of these aspects. The current equipment is comparatively high speed and is geared to long, efficient production runs in one pack format. Increasing pack variants and inventory reduction pressures have led to smaller batch sizes, but this then results in lines where changeover time often exceeds running time.

This section describes how a radically different approach to tablet packaging has been developed which seeks to address these new market issues. The objective, as with modern car manufacturing, is to reduce the viable batch quantity to a single product unit.

6.8.2 Conventional pharmaceutical packaging and distribution

Conventional drug packaging lines are geared to large batch quantities of single products, which are subsequently distributed through a complex internal and external chain of warehouses and distributors. (It has been suggested that it typically takes six months from packaging for a prescription drug to be received by the patient). It could be said that the inflexibility of the conventional packaging process is the cause of the current multi-stage distribution route rather than a consequence of it. Remember that the end user ultimately purchases one pack at a time; in other words, large batch quantities are a consequence of the existing packaging/distribution process not a customer requirement.

Traditional bottle filling systems are mechanically tooled and controlled, using tablet specific slats or pocketed disks to provide a pre-determined fill quantity. Tablet inspection, if used, is usually provided by eye. Changeover can take up to a shift to achieve and is primarily a mechanical technician task. Market data suggests that purchases of this type of filling system are declining markedly and that electronically controlled vibratory fillers are now selling in increasing numbers. These newer technology fillers, while theoretically slower, have fewer, if any, tablet specific components, use electronic counting methods and incorporate some basic automatic inspection of tablet area. Product changeover can be achieved in perhaps 1–2 hours. The trend to these new types of machine indicates that the industry is beginning to recognize that equipment flexibility is more important than absolute speed.

Aside from filling, the other areas of inflexibility in packing is the production and control of printed material, most particularly labels. Off-line printing techniques are used and the resulting materials are handled and released using control methods not dissimilar to those needed for producing banknotes. Nevertheless, labelling errors still cause around 50% of product recalls, with significant costs both financially and to product/company image.

While many pharmaceutical companies recognize the limitations imposed by their packaging equipment, it has been an area of relatively slow technology change. There are two related causes for this. Much of the pharmaceutical packaging equipment is produced by companies who, with few exceptions, are small relative to their customers. Not unreasonably, the equipment companies do not have the financial or technical resources to undertake major new product development programmes involving radically different technology and tend to

concentrate on enhancing their existing products. In contrast, the pharmaceutical companies have the size and financial resources to develop new equipment but traditionally have not sought to develop their own packaging equipment and have sat back awaiting new offerings, preferably from well known vendors. It is not difficult to see how these two effects can lead to technology stagnation.

A further restricting factor is the relationship in pharmaceutical companies between marketing and engineering. Again taking car manufacture as a comparison, the linkage between these two departments in pharmaceutical companies is relatively small. Marketing would not naturally look first to areas such as packaging engineering for significant new business opportunities. It is typical to find internal 'new production technology' groups with no formal marketing involvement or, indeed, 'new market development teams' with no engineering input. Innovative in-house process technology developments have, therefore, to be justified against relatively small efficiency gains in direct labour reduction and material usage, rather than the substantial returns associated with new business generation. The end result is that where internal process innovation is pursued, it is often under-funded, has a low commercial priority and lacks a clear business objective and focus.

6.8.3 What does the market want?

In the last ten years the distribution channels for pharmaceuticals in the United States have undergone some dramatic changes and continue to do so. Pressure from corporate health programmes, medical insurance providers and government to reduce healthcare costs has resulted in new purchasing and distribution routes emerging. A key example is the explosive growth of companies who manage the purchase of pharmaceuticals on behalf of health plan providers. These companies act on behalf of the healthcare provider and negotiate substantial volume discounts with the drug producers against a restricted list of recommended drugs. These companies handle patient prescriptions at centralized semi-automated facilities and the packaged drug is shipped direct by mail to the patient. The conventional manufacturer/wholesaler/pharmacy distribution route is completely bypassed. A substantial proportion of the US population now receives many of its prescription pharmaceuticals in this way. Other organizations, such as hospitals and nursing homes, are now pursuing similar methods to obtain price benefits through centralized pharmacies. Whilst these are primarily US phenomena today, it would be naïve to assume that similar developments will not appear in Europe in due course once the financial impact of these programmes become apparent to government-funded health services.

There are a number of other market-related issues, all of which mitigate against conventional drug packaging methods. These include:

- 'globalization' of production by companies such that a single site may now produce all country and pack variants of a drug, requiring multiple label/language formats in the same facility with frequent changeovers;
- the requirement of the large supermarket-based pharmacy chains to have product identification and expiry date incorporated in a label bar-code to allow automated stock control. Conventional label production methods do not handle this need easily. Many chains are seeking their own branding on the label in addition to, or instead of, the manufacturer's name;
- label and insert data change frequently in response to new drug indications and side effects. Obtaining pre-printed material can delay the launch of a new or revised product by several weeks;
- direct management of retail shelf space by the supplier.

In summary therefore the market is demanding:

- increasing pack complexity, variety and customization;
- order delivery in a day with no intermediate handling and inventory costs;
- frequent pack design changes;
- single pack unit batch quantities;
- lower end user pricing.

The implication is that a make to order strategy is needed rather than make to stock. It is apparent that better management of, or enhancements to, conventional drug packaging lines will not address these new market needs, and that radically different equipment will be needed whose technology origins may be from outside the pharmaceutical industry.

6.8.4 New technologies

Other industries had to address the responsiveness/flexibility issues many years ago in order to survive. These manufacturers have had to take the initiative in stimulating the development and implementation of new manufacturing process equipment. Many of the principles and technologies that have resulted from this are equally applicable to pharmaceutical packaging.

Technologies that are relevant to an advanced tablet packaging system include:

- **'robotic' equipment design:** Whilst not necessarily using anthropomorphic arms, the underlying technology of electronically controlled actuation can give rise to machines that can switch instantaneously, under computer control,

between different tasks and make intelligent decisions at high speed. That these machines may be both slower and more expensive than their less flexible predecessors should be neither surprising nor a problem, when the bigger commercial issues described earlier are taken into account.

- **image processing:** Machine vision is increasingly used for identification and inspection functions. The exponential growth in cheap computing power means that complex inspection and counting functions can be implemented in practical systems.
- **product identification:** A wide range of identification methods is available which allows product to be located and tracked by remote methods. Radio Frequency (RF) tags are extensively used in car manufacture to locate and route cars and components through variable process paths. These feature a short-range (50 mm) radio receiver/transmitter, memory electronics (typically a few Kbyte), and a battery in a compact, low cost format. All relevant product/process option data can be written to these tags and a complete process history recorded. On completion of the process these tags are reset and returned to the process start. These 'active' tracking methods have benefits over passive techniques, such as bar-codes, because they eliminate much of the need for large centralized tracking computers.
- **real-time computer control:** The use of smart machines depends on direct high-speed computer control. Whilst computer control of chemical processes is well understood in pharmaceuticals, it is comparatively uncommon to find computers used in this way in secondary processes. In general, computers are used only for scheduling, supervisory machine control and paperwork generation. The uncertainty of computer validation only leads to further caution over using direct computer control.
- **on-line printing:** Printing technology has been revolutionized in the last decade as sophisticated, low cost, high quality equipment has appeared, mostly for the office market. It is perhaps ironic that a packaging manager probably has more sophisticated computer power and printing technology on the department secretary's desk than on the packaging lines. Developments in ink jet, laser and thermal printing allow single, unique, high quality images to be produced rapidly and on demand. Technology developments for other industries will soon allow near photographic image quality to be achieved at line speed. Real time generation of unique single labels is already a practical proposition in both monochrome and colour.

Much of the necessary technology for an advanced, high flexibility, tablet packaging line already existed. The challenge was to select and configure it in an appropriate way.

6.8.5 Postscript technology

In 1991 The Automation Partnership ('TAP') began collaboration on a number of developments of novel manufacturing processes with Merck and Co. TAP offered a skill set in robotics, machine vision and computer control, while Merck recognized the need to take the initiative in developing radically different, advanced secondary process technologies. A number of these projects were aimed at line changeover time reduction, particularly the areas of tablet filling and on-line label printing. These early projects resulted in prototype production equipment which demonstrated that much higher levels of flexibility could be achieved for small batch, single product packaging, under GMP. These were still aimed at make for stock production.

These separate developments led subsequently to a concept, which became known as 'Postscript', for customer-specific packaging of tablets. With this, a customer order, down to a single bottle of tablets (such as a prescription), could be received electronically, counted, inspected, packed, uniquely labelled and despatched within a few minutes. Ideally, there would be little direct manual involvement in the process and a very high degree of integrity would be guaranteed by the system design. In principle, the line concept could receive, pack and directly despatch small end user orders within a day, eliminating all or most of the conventional distribution chain, large intermediate product inventories and the need for complex scheduling/forecasting systems. In other words, it would be closely aligned to the new market needs discussed earlier.

Not surprisingly, the concept was received with a mixture of technical concerns and business interest. It was decided that Merck would jointly develop, construct and demonstrate a near full-scale pilot line which would include all the essential novel elements and allow the feasibility and practicality of the new process to be assessed. The key functions and technology are described below; however, the concept's modularity allows a range of alternative configuration and capacities to be created for other specific needs.

6.8.6 Pilot plant configuration and equipment

The pilot plant line uses a U-shaped configuration with a conventional process flow involving empty bottles entering at the line start then progressing through filling, capping, labelling, collation and packing into shippers at the end.

For the purpose of demonstration, the pilot line was configured to receive small (hypothetical) electronic orders from customers, such as individual retail pharmacies, for a combination of differing product types. In this first case, up to four different tablet or capsule types were packed on the line simultaneously (although by adding a further four-channel filler modules this could be easily expanded to sixteen products or beyond). Orders comprised typically 20 bottles

for a single customer with unique labels on each bottle showing the product identification, manufacturer, tablet count and the retailer's address. The bottles were packed into an order shipper at the line end, together with a dispatch label and order manifest. The system was, however, equally capable of packing a single patient prescription.

The key elements of the line were as follows:

(a) 'Puck'

The line had about two hundred identical 'pucks', which were used to carry individual bottles through the system. The base of the puck contained a proprietary RF tag, which allowed all relevant details of the order to be carried through the process with the bottle. The fingers on the upper part of the puck located the bottle while still allowing it to rotate for labelling. Specific finger designs allowed differing bottle sizes to be processed.

(b) Puck Handling Station ('PHS')

Four PHS's were used on the line to provide tracking and routing. The data on the puck could be erased, written or read at the PHS and the puck plus bottle could then be sent in alternative directions or rejected if faulty.

(c) Flexible filler

The filler was a novel patented design that used a vibratory feed, conveyor belt, imaging system and diverter to feed, inspect, count and divert tablets to the bottle. The filler consisted of four separate identical channel modules, each of which processed one single tablet type. Each channel could process between 500 and 1000 tablets per minute (dependent on tablet/ capsule size) and every tablet was automatically inspected for size, shape and colour. Damaged or rogue tablets were automatically diverted out of the stream and eliminated from the count. Tablet count was verified by two independent systems and any count discrepancies resulted in bottle rejection. The tablet count in a given channel could be varied for each successive bottle.

(d) Labeller

The labelling station used a conventional labelling machine but with a customized high-speed thermal printer. A specific label was printed on blank feedstock, in response to the bottle's puck data, and then applied. The label could also be verified by on-line print quality and character verification systems. The label incorporated a unique bar-coded serial number, giving each bottle a unique identity.

(e) Collation system
The order collator used multiple tracks and gates to assemble complete order sets. The puck determined the order routing. On completion of the order, the set was released and the bottles transferred from the pucks to a tote and then to the shipper carton.

(f) Control system
The system used multiple networked PC's to provide machine control, system monitoring and order tracking. System set up and running was through a touch screen. The system software was developed and tested under a structured environment suitable for validation.

(g) Ancillary equipment
The line used a conventional capper, and standard equipment, such as cotton and desiccant inserters, could be easily added as additional stations. The pucks were transferred on normal slat conveyors. The neck of the bottle, irrespective of its size, was always in the same position relative to the puck base. An overhead conveyor returned the empty pucks back to the line start. The pucks were reloaded with empty bottles using conventional unscramble/centrifugal feeder mechanisms.

6.8.7 Packing flow

The process flow is as follows:

- pucks are loaded with empty bottles fed from bulk and then queued on the conveyor;
- the first PHS erases all previous data on the puck and verifies a bottle is present;
- the filler receives a common train of empty bottles/pucks which feed the four channels as required;
- the filler receives data on the next bottle's fill requirement from the controller and then inspects and counts the correct number of tablets into that bottle. The puck receives all the data specific to the bottle while filling is in progress. Any errors in filling (such as a count error) give rise to an error flag in the puck data;
- the second PHS verifies the data on the puck and rejects any misfilled bottles. If appropriate, routing to alternate parallel cappers could occur at this point (e.g., choice of regular or tamper proof formats);
- the capper applies the cap;
- the third PHS verifies cap placement and reads the relevant data from the puck for label printing;
- the on-line printer produces a correct sequential stream of labels, which are then applied by the labeller;

- the final PHS reads the unique bar-coded bottle serial number on the label and correlates this with the serial number held on the puck. This ensures that the label is always correctly assigned to the right bottle;
- the collator uses the puck data to assemble completed orders. Note that several orders are processed in parallel — consecutive bottles on the line do not necessarily belong to the same order;
- successful completion of an order is reported back to the line controller. Parallel new orders are continually being initiated automatically.

6.8.8 System features

Particular features are:

- each filling channel operates asynchronously, i.e. the tablet fill speed and bottle rate through each channel will be different and may be zero at times depending on the content of individual orders;
- depending on tablet count per bottle, the throughput limit for each channel is determined by either the 500–1000 tablet/minute rate or the 20 bottle/minute rate. For example, typical limits for a four channel filler module would be 80 bottles/minute at 30 tablets/bottle or 40 bottles/minutes at 100 tablets/bottle;
- capsules and tablets can be packed simultaneously using identical channel equipment;
- the channels are physically isolated from each other and contained, with vacuum extraction to reduce dust generation and prevent cross-contamination;
- the product contact parts in a channel can be replaced within about ten minutes without the use of tools. There are no tablet-specific parts;
- the system can 'learn' the size/shape/colour profile of a new tablet design in about two minutes;
- labels can be designed off-line using standard software and then electronically downloaded into the system;
- on completing a run, the line automatically empties itself of orders;
- the system generates a separate computer batch record for every bottle processed, giving unparalleled traceability;
- an order can be filled, labelled, packed and ready for despatch within five minutes of receipt.

Overall the pilot system has demonstrated all the specified functions and performance, and has shown that the concept is valid and achievable. It has been subjected to an extensive validation programme.

6.8.9 Future developments

TAP is exploiting the technology more widely and is currently evaluating various applications in pharmaceutical packaging and distribution that might use a rapid pack to order approach. These include:

- direct supply to retailers;
- mail order pharmacy;
- clinical trial packing;
- product repackaging;
- hospital supplies.

Each of these would use the same core technology but in different line configurations. TAP is also exploring the opportunities for a similar concept for blister pack products for the European market. On-line, on demand, printing of blister foil has already been demonstrated at a prototype level by TAP and similar systems are becoming available from other suppliers.

6.8.10 Conclusions

The Postscript system has demonstrated that the concept of automatically packing a batch quantity is both feasible and reliable for solid dosage forms in bottles. Changing to a true make to order strategy from make to stock methods is, therefore, becoming a viable proposition. Whilst the system has unique elements, many of the principles and technologies have been successfully transferred from related applications in other industries. Perhaps the most fundamental conclusion, however, is that pharmaceutical product packaging can change from what some perceive today as a non-value adding process, to being an important strategic manufacturing technique that generates significant new business opportunities.