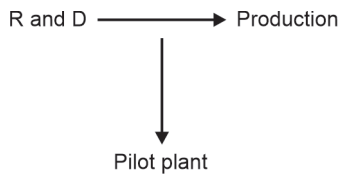
Chapter

1

Pilot Plant and Scale-up Techniques

1.1 INTRODUCTION



A pilot plant is a pharmaceutical industrial sector in which a lab-scale formulation is developed into a commercially viable product by developing a consistent production procedure.

A pilot plant is a pre-commercial production system that employs new manufacturing technology and produces small quantities of new technology products, mostly to learn about the new technologies. The knowledge gained is then used to design full-scale manufacturing systems and commercial goods, as well as to identify new research aims and to support investment choices. Other (non-technological) objectives comprise increasing public acceptance of new technology and challenging government regulations.

1.1.1 Scale-up Process

The process of raising batch size is referred to as scaling up. A process scale-up is also a way to adapt the same process to different output quantities. Increased batch size does not always imply increased processing output. In mixing applications, scale-up refers to raising the linear dimensions from the laboratory to the plant size. On the other hand, there are some processes (such as tableting) where "scale-up" simply indicates increasing output by increasing speed.

In modern pharmaceutical development, the scale-up process is closely aligned with quality-by-design (QbD) principles and the establishment of a design space for critical process parameters (CPPs). Under ICH Q8(R2), a design space is defined as the multidimensional combination and interaction of input variables (e.g. temperature, mixing speed, humidity) that have been demonstrated to assure quality.

During scale-up, one objective is to ensure that the manufacturing at pilot and commercial scale remains within the design space, such that deviations within that space are not considered regulatory changes. This gives operational flexibility. To support this, a control strategy is defined, specifying how CPPs are monitored, controlled, and linked to critical quality attributes (CQAs).

A practical way is to use statistical design of experiments (DoE) at a small scale, derive process models (e.g. regression, mechanistic), then validate the model predictions

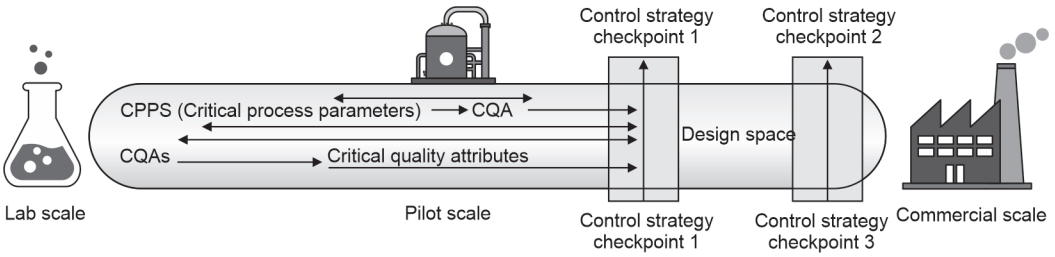


Fig. 1.1: Process scale-up with design space and control strategy

at a pilot scale. Any deviations observed should be mapped back to the design space bounds or lead to model refinement as shown in **Fig. 1.1**.

As a more recent method, an optimizer-based search for design spaces (e.g. linear combinations of parameter ranges) has been proposed in biopharmaceuticals to allow more effective definition of design regions.

1.1.2 Significance of Pilot Plant Studies

- Pilot plant studies must involve a comprehensive analysis of the formula to determine its ability to withstand batch-scale and process changes.
- An assessment of the available processing equipment.
- The supply of raw materials that fulfill the criteria of the product.
- Adjustment of production rates based on marketing requirements.
- Give a basic concept of the physical space needed and the functions that will be performed.
- To promote good manufacturing procedures, appropriate records and reports are issued.
- A methodology can be developed and validated.

1.1.3 Steps Involved in the Scale-up Process

The process of scale-up is not merely a mechanical enlargement of laboratory operations but a systematic and carefully planned transition towards commercial manufacturing. It involves a series of well-defined steps that begin with an evaluation of product economics and extend to the design and operation of a pilot plant. Each step ensures that the product can be manufactured consistently, economically, and in compliance with regulatory requirements. As illustrated in **Fig. 1.2**, the scale-up pathway starts with defining market feasibility and acceptable manufacturing costs, followed by laboratory investigations and the identification of critical rate-controlling steps. This is further supported by preliminary larger-than-laboratory studies to aid in plant design. The process culminates in the construction of a regulatory-compliant pilot plant and the evaluation of its performance to determine the suitability for full-scale production.

1.1.4 Pilot Plant Layout Design

An ideal pilot plant is organized to provide a logical flow of materials, personnel, and processes while minimizing cross-contamination risks and maintaining efficiency. As shown in **Fig. 1.3**, the facility layout typically includes controlled access entrances, receiving and shipping areas, and designated zones for raw material storage and quarantine.

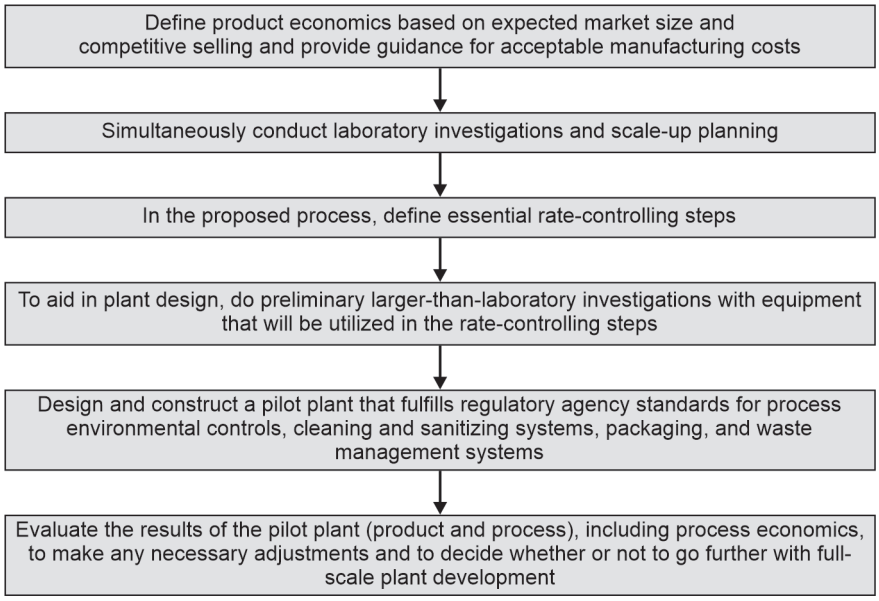


Fig. 1.2: Steps involved in scale-up process

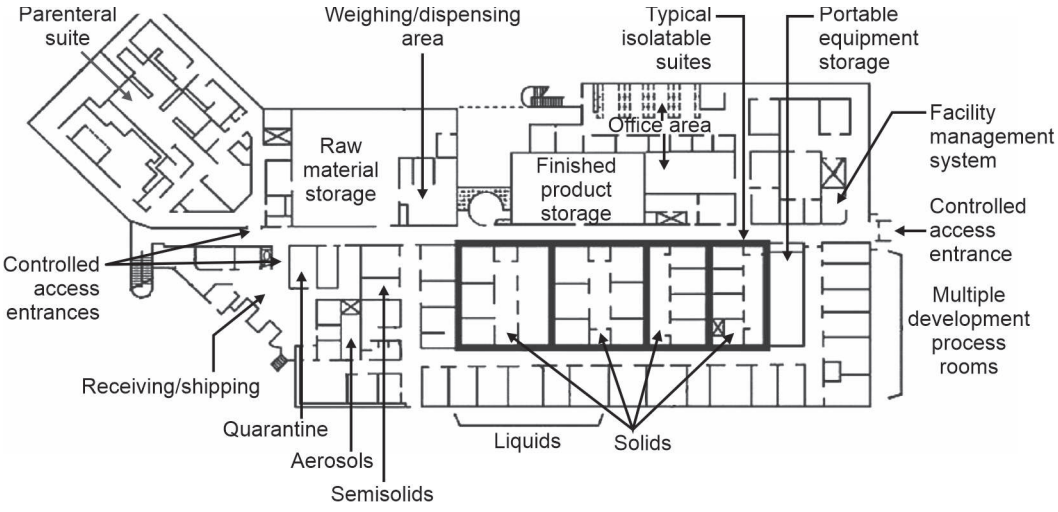


Fig. 1.3: Layout design of pilot plant

Critical functions such as weighing and dispensing, preparation of different dosage forms (solids, liquids, semisolids, and aerosols), and parenteral processing are accommodated in separate, well-defined areas. Finished product storage, office spaces, portable equipment storage, and facility management systems are also incorporated to support day-to-day operations. The inclusion of isolatable suites and multiple development process rooms ensures flexibility and compliance with regulatory expectations. A well-structured pilot plant layout thus establishes the foundation for reliable scale-up and smooth transition to commercial manufacturing.

1.1.5 General Considerations of Pilot Plant

In designing and operating a pilot plant, several general considerations must be considered to ensure smooth functioning and effective scale-up. These include reporting responsibility, personnel requirements, and space requirements, which define the organizational and infrastructural framework. Equally important is the review of the formula, along with the careful selection and management of raw materials and relevant processing equipment. From a production perspective, factors such as production rates, process evaluation, and the preparation of master manufacturing procedures are critical for consistency and compliance. In addition, the transfer of analytical methods to quality assurance ensures the reliability of testing, while thorough assessment of product stability and uniformity supports regulatory expectations and product performance.

Reporting responsibility	Production rates
Personnel requirements	Process evaluation
Space requirements	Master manufacturing procedures
Review of the formula	Transfer of analytical medical to quality assurance
Raw materials	Product stability and uniformity
Relevant processing equipment	

Reporting Responsibility

Pilot plant functions could be attributed to a different research and development team. This arrangement is intended to provide a level of responsibility for scaling-up formulations produced by other formulators within research and development, so offering a platform for independent evaluation of the formulation procedure. Alternatively, the product's formulators can put it into production and continue to support it even after the transfer is complete.

A pilot plant's purpose is to make it easier to transfer a product from the lab to production. The ease with which new materials or processes are implemented into regular production defines the pilot plant's performance. This is more effective if the pilot plant group and the other groups with which it interacts, such as research and development, processing, packaging, engineering, quality assurance, quality control, regulatory, and marketing, have a good working relationship.

Personnel Requirements

A position in a pilot plant organization requires a combination of theoretical understanding of pharmaceutics and practical experience in the pharmaceutical sector. Prior involvement in both pilot plant operations and actual production is desirable. They must clarify the formulator's purpose as well as the production staff's point of view. Pharmaceutically trained scientists provide core strength to the function by being able to recognize the extensive interaction between pharmaceutical processes and their potential influence on the chemical, physical, biochemical, and medicinal qualities of dosage forms.

It is important to evaluate the educational profile and degree of the group. However, the group must have some technical knowledge because the scaling-up of many of the

methods involves engineering ideas that are often not adequately taught in traditional pharmaceutical training. Furthermore, having members who are well-versed in both electronics and computers is becoming increasingly important for the organization. The size of a pilot plant group is defined by the number of products supported and the degree of help needed. Personnel working in pharmaceutical sector are shown in **Fig. 1.4**.

Space Requirements

Proper space allocation is a key factor in the design of a pilot plant, as it ensures efficiency, safety, and smooth workflow. The requirements are broadly classified into four types, each addressing specific functions such as material handling, processing, equipment placement, and storage. There are four different types of space requirements for a pilot plant as classified in **Fig. 1.5**.

Administration and information process: Documentation is essential for both scientists and technicians; adequate office and workstation space is required. This should be close to the work area yet far enough away so people may work without getting distracted.

Members of the group should be able to meet with persons from other departments on a regular basis, and there should be a location where 3 to 4 people may come together to discuss subjects of mutual interest, since the group serves as a link between research, operations, and other disciplines. A computer terminal should be available for rapid

Fig. 1.4: Personnel in pharmaceutical sector

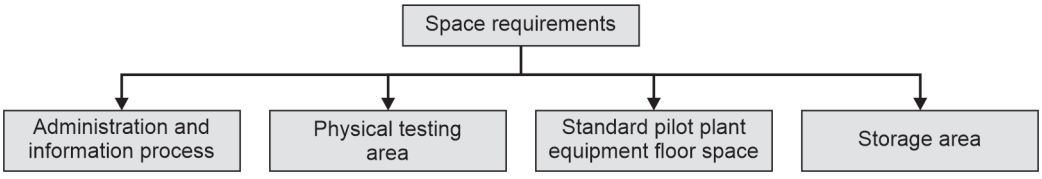


Fig. 1.5: Types of space requirements

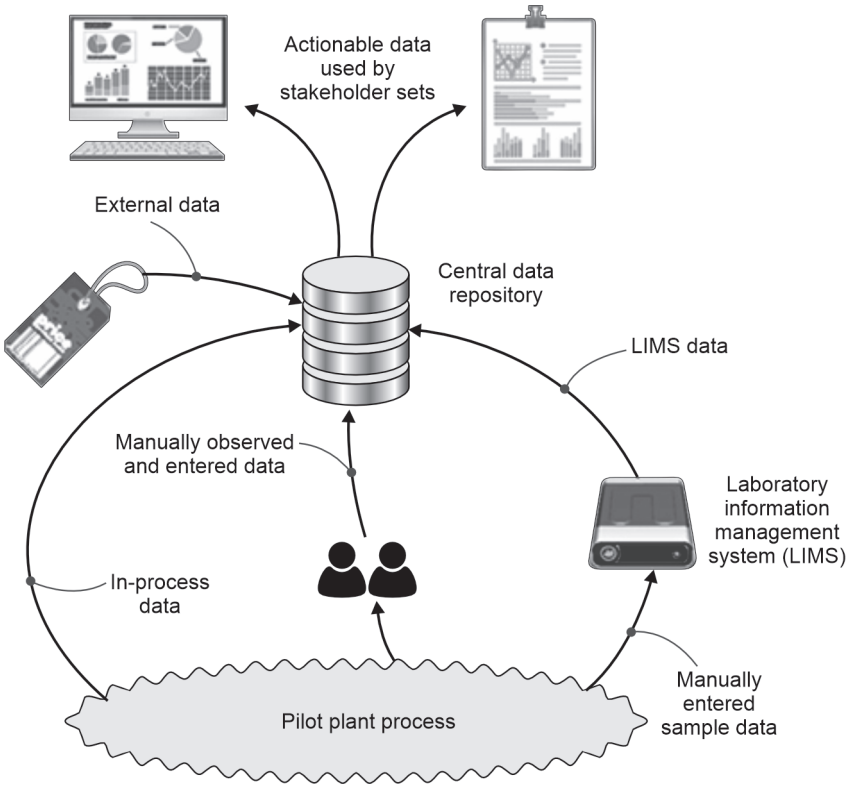


Fig. 1.6: Administration and information process

data entry and retrieval, as well as archives for stability, data techniques, and previous files. Schematic representation of the administration and information process is shown in **Fig. 1.6**.

Physical testing area: The second essential area is a suitable working environment, as shown in **Fig. 1.7**, in which samples may be put and analysed, as well as physical testing on these samples. Permanent desk space for routinely used physical testing equipment should be provided in this area (e.g. balance, pH meter, and viscometer).

Standard pilot plant equipment floor space: The third section is specialized plant space, which includes all of the equipment as shown in **Fig. 1.8** required to manufacture various pharmaceutical dosage forms. The equipment should be available in a range of sizes that indicate the manufacturer's capabilities. This layout improves the quality of the scale-up data collected while simultaneously conforming to the necessity to be cautious with higher-priced materials.

To investigate the impact of scaling up research formulations and methodologies, intermediate-sized and full-scale production equipment is required. When the space is divided into zones for solid dose, semisolid products, liquid preparations, and sterile supplies, it is most efficiently used. Further subdividing the areas should enable many activities to be carried out at the same time without causing GMP issues.

Fig. 1.7: Physical testing area

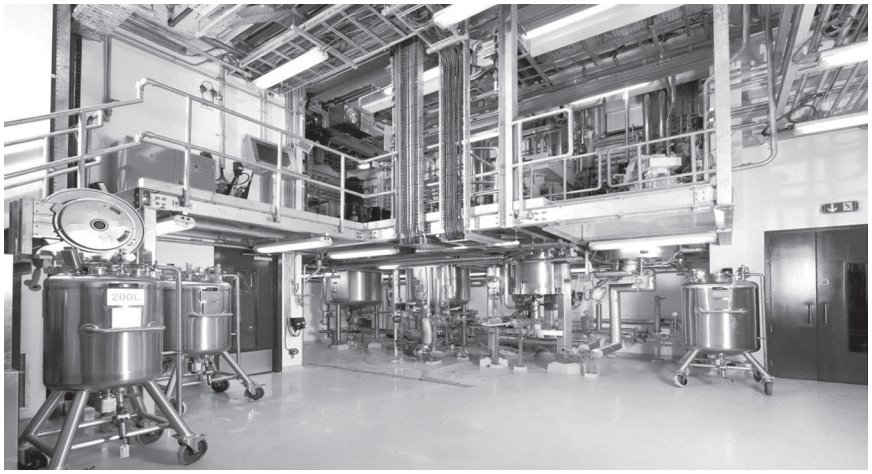


Fig. 1.8: Equipment section

The availability of an appropriate room for cleaning of inadequate plant equipment is a key necessity that is sometimes overlooked, yet is critical to all pilot plant operations. While some equipment may be cleaned in the site, the bulk of the equipment should be cleaned in a different section.

Storage area: Storage space is the fourth section, as shown in **Fig. 1.9**. Storage of active substances and excipients should be handled separately. According to GMPs, they should be further separated into approved and unapproved areas for active ingredients and excipients. In-process materials, final bulk materials from the pilot plant, and material from experimental scale-up batches produced in production that can't be stored in operations storage areas should all have their own storage spaces. It is necessary to

Fig. 1.9: Storage section

provide storage space for the remaining samples from the pilot plant and experimental manufacturing batches. All of these requirements are in proportion to the area made aside in a controlled environment for stability sample storage.

Finally, packaging items must be stored. Because it is a typical necessity of the scale-up function to investigate alternative suppliers of packaging materials, it is essential to provide the necessary storage space for bottles, closures, tubes, vials, ampules, and other bulky components. It would be helpful if the material could also be classified as authorized or disapproved.

Review of the Formula

Early in the scale-up process, it is essential to initiate a detailed assessment of each component of the formulation. The function and contribution of each component to the finished product produced utilizing small-scale laboratory equipment should be known. The impacts of scale-up using equipment that may lead the product to various types and degrees of stress may thus be predicted or recognized more easily when they occur.

Raw Materials

The objective of the pilot plant is to approve and validate active and excipient raw materials used in pharmaceutical products. This is essential because raw materials used in small-scale formulation trials may not be representative of large volume shipments of materials used in large-scale production or because active ingredients manufactured on a laboratory scale are also being scaled up to meet the product's emerging requirements. These large quantities of active components fluctuate in particle size, shape or morphology despite meeting all analytic parameters, resulting in different handling parameters or variations in bulk density, static charges, rate of solubility, flow properties, color, etc.

Relevant Processing Equipment

The majority of formulation development work is likely undertaken on small, inexpensive laboratory equipment. Alternative production equipment should be considered while scaling up. The equipment that is intended to be the cheapest, simplest, most efficient, and capable of consistently producing product within the set criteria should be evaluated based on the product's known processing characteristics.

Cleaning should be examined, especially if the equipment will be used to make various products. It should be determined how much time it will take to disassemble the equipment in order to clean it and switch from one product to another. In some circumstances, this can be prolonged than the time required to manufacture a batch, and if frequent changeovers are expected, this becomes an essential factor to consider.

Trials should be conducted at the vendor's facilities to accurately evaluate these and other factors. Such experiences aid in determining the actual capability of the equipment as well as the quality of technical support provided by the proposed vendors.

Production Rates

When evaluating production rates and the type and quantity of manufacturing equipment required, immediate and future market demands must be considered. The size of the equipment should be sufficient so that it can be used efficiently. The equipment and procedure should be designed to account for product loss in the production equipment, the time required to clean the equipment among batches, and the number of batches that must be evaluated for release. Increased production capacity can be achieved at a lower cost by making maximum use of smaller equipment instead of acquiring larger equipment to meet future success.

Process Evaluation

The next step is to thoroughly evaluate the process and then optimize its performance based on that review. The information given here should be evaluated as shown in **Fig. 1.10**.

The impact of these major process parameters on in-process and finished product quality provides a framework for process improvement and validation. The purpose of process validation is to ensure that the manufacturing method used ensures product quality at various critical stages of the process in its finished form. This is accomplished

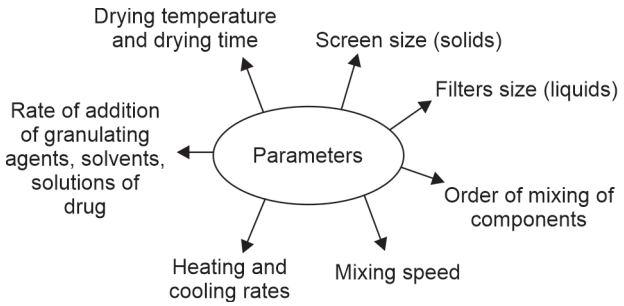


Fig. 1.10: Process parameters

by measuring the variation of observable characteristics within batches, such as content homogeneity, moisture content, and compressibility.

This information indicates where the process is working properly and where difficulties may develop. All procedures that produce observable changes in the condition of the material being processed, such as milling, mixing, heating, cooling, drying, sterilizing, compacting, and filling, must be assessed. This type of process data should be collected for a series of batches carried out using a certain equipment design and a well-documented procedure.

The process has been validated if the data shows that the process continuously works at the important stages to develop a product that meets release requirements. The process remains validated only if there are no changes in the formula, the quality of the ingredients or the equipment configuration.

Master Manufacturing Procedures

The three important aspects in pharmaceutical manufacturing are the weight sheet, processing and sampling directions, and the manufacturing procedure, which together ensure accuracy, consistency, and reliable batch production as shown in **Fig. 1.11**.

Weight sheet: The chemicals utilized in a batch should be clearly identified on the weight sheet. Furthermore, the worksheet should include the quantities as well as the sequence in which they will be used. To avoid confusion and unnecessary errors, names and identifying numbers for the ingredients should be included on batch records, and they should correspond to those on bulk raw material containers.

Processing and sampling directions: Specific and precise processing instructions are required. They should be written in a language and terminology that the operators are comfortable with. While writing the manufacturing processes, significant input should be collected from the existing operations or from someone with relevant knowledge and abilities in the processing areas. The batch records should contain an area for the weighing and inclusion of every substance, as well as valid counter signatures for each, in compliance with GMPs.

Manufacturing procedure: Problems arise when a multipage manufacturing process is used in place of adequate operator training and a collection of standard operating procedures (SOPs). Inconvenient instructions are those that are excessively complex or long, and too many sign-offs are just as problematic as too few. There are numerous instances in the industry of problems arising as a result of operators' failure to learn or follow very comprehensive procedures.

The batch record directions should include specifications for addition rates, mixing duration, mixing speeds, heating and cooling rates, and temperature, as well as

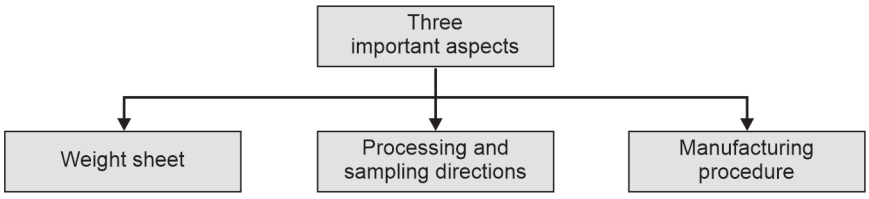


Fig. 1.11: Important aspects of master manufacturing procedures

reasonable ranges. Actual times, temperatures, and speeds should be documented. These are usually observed and measured by suitable controller recorders, which allow the operator to focus on the actual process and check that all equipment is operating correctly, and the process is behaving normally and acceptably.

Controller strip charts are used to verify that batch standards are followed. Maintaining consistent product quality necessitates frequent revalidation, appropriate manufacturing procedures, and control chart monitoring of final product test findings.

Transfer of Analytical Method to Quality Assurance

The analytical test procedures developed in research must be transferred to the quality assurance department during the scale-up of a new product. The quality assurance staff should assess the process early in the transfer process to ensure that the necessary analytical equipment is accessible and that staff are trained to perform the tests. To complete the transfer, researchers should check the assay procedure and the data produced from the validation studies to ensure that the analytical methods have not been altered in any way that could influence the test's reliability, precision or accuracy.

Product Stability and Uniformity

The pilot plant's primary purpose is to ensure the physical and chemical stability of the products.

As a result, the stability of each pilot batch, which represents the final formulation and production process, should be examined. Stability tests on finished packages should also be undertaken.

1.1.6 GMP Consideration

A listing of GMP components that should be included in scale-up or the introduction of a new product or procedure includes the following:

- Process validation
- Regular process review and revalidation
- Relevant written standard operating procedures
- The use of competent, technically qualified personnel
- A well-defined technology transfer system
- Validated cleaning procedures
- An organized arrangement of equipment to ease material flow
- Qualification of equipment

1.1.7 Product Considerations

Solid Dosage Form

Each stage of the process must be carefully reviewed when scaling up the manufacturing of tablets and capsules from the experimental laboratory batch to intermediate- and large-scale production. The following are the fundamental unit operations involved in the production of solid dosage forms:

Material handling: In the laboratory, materials can be simply picked, dumped or poured by hand. This may function well in certain small- or medium-sized industrial

processes, but in larger-scale operations, mechanical ways of managing these materials are frequently required. The type of system used is also determined by the properties of the materials, such as density or static charge.

Any material handling system should deliver the exact amount of the ingredients to the desired location. Long transfer processes may cause substantial loss, necessitating responsibility and compensation. Measures must be required to avoid cross-contamination if the system is utilized to transfer materials for more than one product. This can be accomplished by employing approved equipment cleaning techniques.

Dry blending: To achieve adequate drug distribution, powders that will be encapsulated or granulated before tableting or encapsulation must be well homogenized. Inadequate mixing at this step may cause discrete portions of the batch to be either very potent or too weak. This may result in differences in drug content homogeneity, particularly if the tablet or capsule is small and the drug concentration in the mixture is less.

The dry blend should ideally take place in the vessel where any following processing, such as granulation, will take place. However, not every production facility has the necessary equipment to enable such a procedure. As a consequence, a larger batch can be dry mixed and then divided into several parts for granulation. Check that all of the components (excipient and active) are free of lumps and agglomerates before beginning the dry mix. Failure to remove or break up all agglomerates may result in flow difficulties through the equipment, resulting in non-reproducible compression and encapsulation operations that have a significant influence on the consistency of the product. Because of these properties, screening and milling the components before blending improves the procedure's uniformity and reproducibility.

The equipment used for blending are V-blender, the double cone blender, ribbon blender, slant cone blender, vertical and horizontal high intensity mixers. Scale-up considerations include blending time, blender loading, and blender size.

Granulations: The most common reasons for granulating are:

1. Imparting good flow qualities to the material such that tablet presses and encapsulators can be appropriately loaded and a uniform tablet or capsule weight can be established,
2. Increasing the apparent density of the powders, and
3. Modifying the particle size distribution to improve compaction binding affinities.

When the drug is dissolved in the granulating solvent and absorbed into the batch during granulation, a very small amount of a potent active component can be disseminated most efficiently in a carrier granulation. The utilization of the granulation process to spread an active ingredient is another possible source of granulation.

Tumble blenders with high-speed chopper blades can also be used to prepare wet granulation. High-shear mixers are more successful in increasing the density of light powders, but they use a lot more energy and have a restricted load capacity. Some machines combine the advantages of high-speed choppers, which break up agglomerates and allow homogeneous distribution of the granulating fluid and more regulated granule size, with the high shear mixing action that is usually necessary for effectively increasing density.

The use of multifunctional "processors", as shown in **Fig. 1.12**, has become more popular in recent years. These are machines that can perform all of the operations

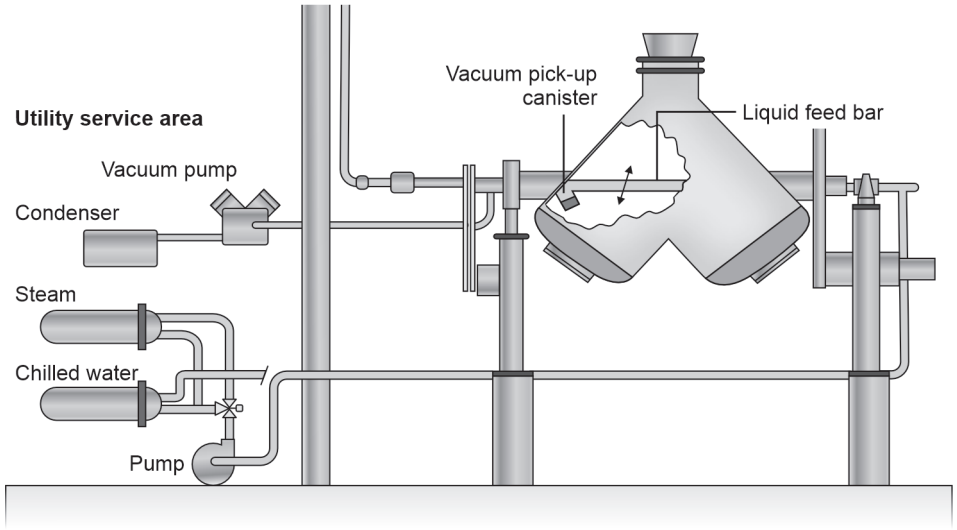


Fig. 1.12: Schematic diagram of multifunctional processor

necessary to prepare a finished granulation in a continuous process, such as dry blending, wet granulation, drying, sizing, and lubrication in a single piece of equipment. The advantages of implementing such equipment for scaling up a product might be significant in terms of space and human needs.

Effect of the Binding Agent in Granulation

It is used in tablet formulations to make powders more compressible and to manufacture tablets that are less prone to breaking when handled.

In other cases, the binding agent causes the granulating solution to become viscous, rendering fluid transfer difficult. This problem is easily overcome by including some or all of the binding agents in the dry powder. Before granulation, the powder is ground into a fine powder. Some granulations have a doughlike consistency when manufactured in production-sized equipment and may need to be fractured into a more granular and porous mass to facilitate drying. This is accomplished by passing the wet bulk through an oscillating device, a granulator with a large enough screen or a hammer mill with either a large enough screen or no screen at all.

Drying: The circulating hot air oven, which is heated by steam or electricity, is the most common dry granulation technique. Airflow, air temperature, and the depth of granulation on the trays are all key factors to consider while scaling up an oven drying operation. The drying process will be ineffective if the granulation bed is too large or dense, and if soluble dyes are used, the dye will run to the surface of the granules. For each product and oven load, the drying time at given temperatures and airflow rates must be computed.

Fluidized bed dryers are preferred over circulating hot air ovens. When scaling up a fluidized bed dryer, it is extremely important to consider the optimal loads, rate of airflow, input air temperature, and humidity.

Reduction of particle size: The compression characteristics of granulation are influenced by particle size, particularly particle size distribution. Flowability, compressibility, tablet weight uniformity, content uniformity, tablet hardness, and tablet color uniformity are all compression parameters that may be influenced by particle size distribution. When granulation with too big particle size and insufficient fines is compressed, it is impossible to uniformly fill the die cavities, resulting in significant weight variation in the tablets. The coarser the granulation in colored granulations, the more mottled the final tablet appears. Tablet weight variation arises because of flow issues when there are too many particles present.

Also, the tendency toward capping increases and is further exaggerated as the speed of the press is increased. The uniformity of tablet content can be harmed by both oversized and undersized granulations. Particle size reduction of production-scale batches of dry granulation can be accomplished by passing all of the material through an oscillating granulator, a hammer mill, a mechanical sieving device, or, in some situations, a screening device.

Lubricants and glidants, which are usually added directly to the final blend in the laboratory, are often added to the dry granulation as part of the scale-up of a milling or sieving process during the sizing procedure. This is done because some of these additives, particularly magnesium stearate, tend to agglomerate when substantial amounts are added to the granulation in a blender. A preliminary dispersion of these ingredients is often done during the sizing operation to ensure proper distribution of these dry additives. This component of the process must be carefully optimized to ensure that the lubricants are not over- or under-mixed during the screening and subsequent blending procedures.

Blending: The mixing equipment used in the product development laboratory varies markedly. As a result, throughout the scaling-up of this process, care should be taken to ensure that appropriate equipment is used and that blender loads, mixing speeds, and mixing duration are correctly set. In any blending procedure, segregation and mixing occur simultaneously.

Both processes are influenced by particle size, shape, hardness, and density, as well as the kinetics of the mixing action. As a result, the properties of the individual particles in the blend, as well as the source of segregation, must be determined to optimize the blending method and produce a uniform mix.

Schematic representation of the granulating room with milling, mixing, and granulating areas is shown in **Fig. 1.13**.

Specialized Granulation Procedures

Slugging and compression technique are two specialized granulation procedures.

Slugging: In some circumstances, a dry powder mix that cannot be compressed directly because of insufficient flow or compression characteristics may be handled via a slugging process. This is done using a slugging tablet press, which runs at pressures of around 15 tons, as opposed to a regular tablet press, which runs at pressures of 4 tons or less. To make compressed slugs of the powdered substance, extra-large tablet punches are commonly used. Because of the inherent poor compressibility of powders, slower press speeds are necessary to provide the longer compression residence time under pressure necessary to keep the compacted material together.

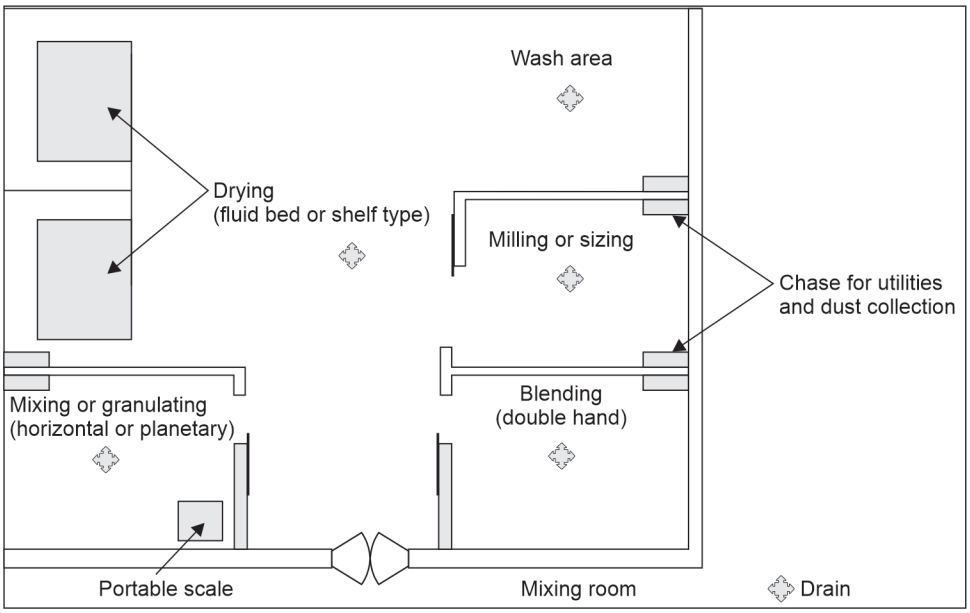


Fig. 1.13: Granulating room with milling, mixing and granulating areas

Slug diameters range from 1 inch for more readily slugged materials to inch for more difficult to compress materials that require intense force per unit area to achieve acceptable agglomerates. After compression, the slugs are segmented with a hammer mill or an oscillating granulator to yield granulation with an appropriate particle size distribution, as shown in **Figs 1.14 and 1.15**. If an excessive amount of fine powder is

Fig. 1.14: Hammer mill

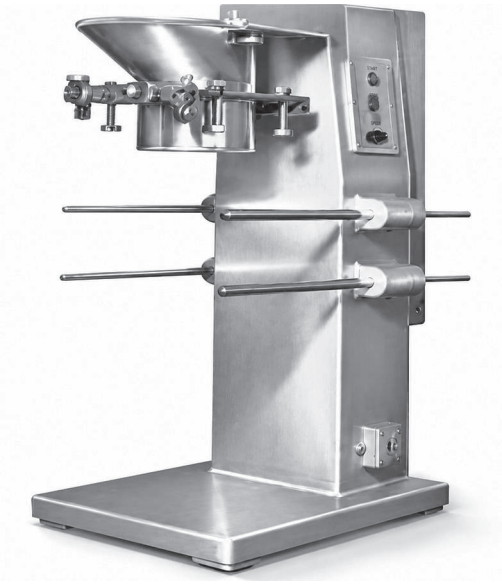


Fig. 1.15: Oscillating granulator

produced during the milling operation, the material should be screened and the "fines" recycled via the slugging operation. When scaling up such an activity, the pilot plant scientist should pay close attention to the slugging operation pressures, punch diameter, and the subsequent sizing and screening techniques.

Particle size and particle size distribution are affected by optimizing these parameters. Personnel at the pilot plant should establish if the final medicament mix or active ingredient can be processed more efficiently than in traditional processing to obtain granulation with the required tabletting or encapsulation qualities.

Compression technique: The ability of granulation to get compressed on a high-speed tablet press is the testing technique of a tablet formulation and granulation process. Compression steps are shown in **Fig. 1.16**.

The technique by which these functions are performed varies depending on the layout of the press. The design of the equipment also determines the possible range of compression forces at which it can work safely, as well as the press speed at which output may be maximised without compromising tablet quality. The compression process steps are as shown in **Fig. 1.17**.

When assessing the compression characteristics of a particular formulation, sustained trial runs at press speeds comparable to those used in the production process should be attempted; only then can potential problems such as sticking to the punch surface, tablet hardness, capping, and weight variation be identified. Such pilot plant initial production trials are essential for recognizing these issues early in the scale-up process, when modifications can be done more efficiently than later production runs, when shifting production schedules render modifying the formulation difficult.

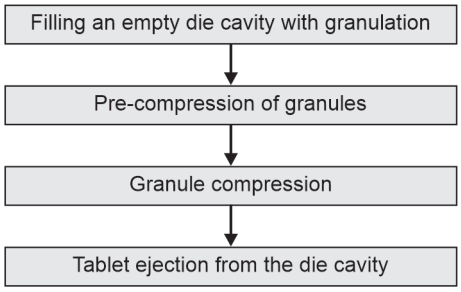


Fig. 1.16: Steps involved in the compression process

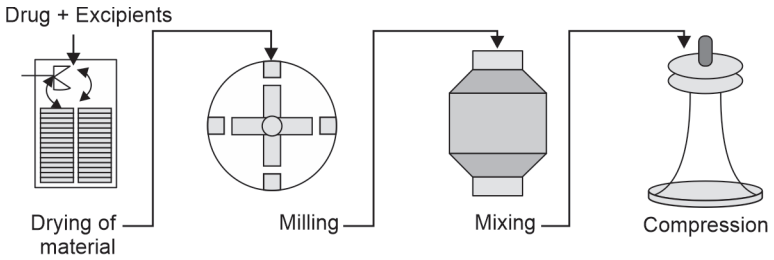


Fig. 1.17: Steps of the compression process

High-speed tablet compression is dependent on the press's ability to interact with granulation in order for a particular sequence of processes to be completed effectively. Granulation must be provided at a sufficient rate to the die feed system. The granulation delivery must not be interrupted, and the flow rate must not change. The particle size distribution must not be altered by the delivery method. The system must not produce fine and coarse aggregate particle segregation, nor should it develop static charges, which would hinder granulation flow and might cause the active component to segregate. The die feed system has the capability of adequately filling the die cavities in the limited time that the die is under the feed frame.

The smaller the tablet, the more challenging it is to maintain a consistent fill rate while pressing at high press rates. Induced die feed systems are required for high-speed machines. These are available with a number of feed paddles and variable speed options.

As a result, optimal feed for each granulation can be obtained. Granulation is often compressed in a single event as the heads of the punches pass over and below the lower and upper pressure rollers. When granulation is compressed to produce a tablet, bonding within the compressible material must be formed, resulting in sticking. A high degree of lubricant or over-blending can result in a soft tablet, a decrease in the powder's wettability, and an extension of the dissolution period.

Binding to the die walls can also be minimized by making the die 0.001 to 0.005 inches broader at the top than at the bottom in order to relieve pressure during ejection. High-speed rotary machines, multi-rotary machines, double-rotary machines, upper and lower punch machines, and single-rotary machines are all used as shown in **Figs 1.18 and 1.19**.

Tablet Coating

Sugar coating, which is performed in traditional coating pans, has experienced several changes as a result of advancements in coating technology as well as changes in safety and environmental requirements.

Fig. 1.18: Double-rotary press

Fig. 1.19: Single-rotary press

The standard sugar coating pan has been replaced with perforated pans and fluidized bed coating columns. The introduction of advanced polymeric materials has caused a change from aqueous sugar coating toward aqueous film coating and, more recently, aqueous film coating. The tablets should be strong enough to sustain tumbling in the coating pan or column. Because some tablet core materials are naturally hydrophobic, film coating using an aqueous system may necessitate a distinct tablet core and coating solution composition in these circumstances.

A film coating solution that works effectively with one tablet in a small lab coating pan may be completely inappropriate on a larger scale.

It is used in tablet formulations to make powders more compact and to produce tablets that are less prone to breaking when handled.

Capsules

The processed powder mix must have the particle size distribution, bulk density, and compressibility needed to maintain acceptable flow properties and result in the development of compacts of the appropriate size and cohesiveness to fill into capsule shells on today's high-speed equipment. In capsule filling operations, one of two types of filling systems is used. Zanasi encapsulator, as shown in **Fig. 1.20**, produces slugs in a dosator (a hollow tube with a plunger to eject the capsule plug), whereas Höfliger–Karg machine, as shown in **Fig. 1.21**, uses tamping pins to manufacture compacts on a die plate. Bulk density, powder flow, compressibility, and lubricant dispersion are the most common scaling-up challenges with both systems.

Weight fluctuation is a typical issue that may be caused by poor granule flow characteristics, which can be produced by granule bulk density and particle size dispersion. Inadequate lubrication can also lead to plugs becoming attached to the dosator plunger surfaces or die walls, causing weight fluctuation. Too many lubricated capsule granules also prolong capsule breakdown and dissolution, which may lead to

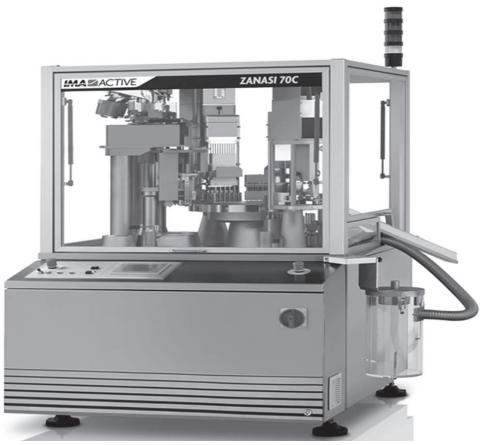


Fig. 1.20: Zanasi encapsulator

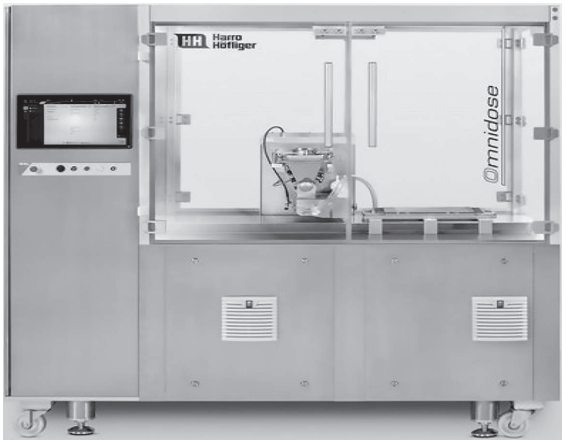


Fig. 1.21: Höfliger–Karg capsule filling machine

reduced bioavailability. Granulation moisture level can affect the chemical or physical stability of the final product, and excessive moisture causes flow and sticking issues during material transfer and filling.

Empty gelatin capsules should be kept at temperatures ranging from 15 to 18°C and relative humidity levels ranging from 35 to 65%. This condition is supposed to limit moisture absorption or loss during the encapsulation process, as well as the physical dimensions changes that result. Throughout encapsulation, the manufacturing room humidity should be kept between 45 and 55%. The capsules may enlarge owing to moisture absorption at higher humidity levels. This might make separating capsule components difficult and interfere with capsule administration during the encapsulation process. Low humidity causes the capsules to become brittle and their static charge to increase, causing the encapsulation process to be considerably hindered.

Liquid Dosage Form

Nonsterile solutions, suspensions, and emulsions are the three types of liquid pharmaceuticals encountered in the pilot plant, as shown in **Fig. 1.22**.

Solutions: Simple solutions are the most easily scalable, but they need huge tanks with mixing capabilities. To facilitate the quick breakdown of system components, the bulk of the equipment incorporates heating and cooling capabilities. Adequate transfer and filtering systems are required, but they must be assessed to ensure that they are capable of purifying the product without selectively eliminating active or adjuvant compounds.

All equipment must be constructed of appropriate, nonreactive, hygienic materials and be easily cleanable. Stainless steel is frequently used in the production of liquid pharmaceutical processing tanks, kettles, pipelines, mills, filter housing, and other components. Even with its less reactive nature, type 316 is the more often employed of the two stainless steel variants in the industry (type 308 and type 316). Although stainless steel is not inert, it does react with some acidic medicinal solutions. When this happens, the problem can be resolved by pre-treating the stainless steel with an acetic or nitric acid solution to remove the alkalinity on the surface. Liners made of glass or polytetrafluoroethylene (Teflon) may be used to avoid contact with metallic surfaces.

Suspensions: Because of the additional processing needs, suspensions require more monitoring in scale-up than simple solutions. When it comes to production-size batches, the introduction and dispersion of suspending agents, which may simply require sifting the material into the liquid vortex on a laboratory scale, may include the use of a vibrating feed system or some novel technique. The suspending agent is easy to wet in a concentrated slurry and can be more extensively disseminated using a high-shear mixer in a smaller volume of the vehicle. Such a slurry, when supplied in a high proportion of the vehicle, facilitates quick and thorough hydration of the suspending agent.

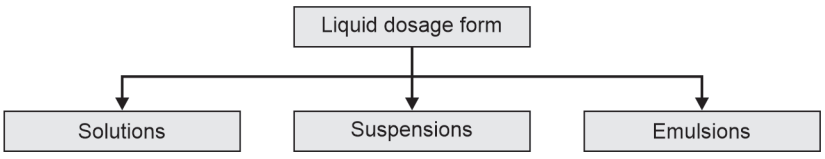


Fig. 1.22: Types of liquid dosage form