CHAPTER 1

Pilot Plant Scale up Techniques

- General Considerations
- Significance of Personnel Requirements,
- Space Requirements,
- Raw Materials,
- Pilot Plant Scale up Considerations for Solids, Liquid Orals, Semi Solids
- Relevant Documentation,
- SUPAC Guidelines,
- Introduction to Platform Technology

General Considerations

Once a new drug molecule is discovered and it passes the pharmacological and toxicological tests, it goes to the formulation development department to create a suitable dosage form. The dosage form must be stable, able to release the drug at the right place and at the right time; so that the drug can exert its therapeutic effect. The dosage form should preserve the drug unchanged during its shelf life. To select and develop an appropriate dosage form, complete information about its absorption, distribution, metabolism and elimination of the drug is to be clearly understood by the formulators.

- *Absorption a drug depends on its solubility, partition coefficient, and permeability.* Knowledge of the site of absorption is also important in choosing the dosage form.
- *Distribution* of the drug within the body compartment depends on its solubility and lipophilicity. The biological half-life of a drug depends on its protein binding property. If the drug is highly bound, its half-life will be high because the bound drug cannot permeate to body tissues and thus, its metabolism and elimination will be delayed.
- *Metabolism* is the conversion of a drug from its lipid-soluble form to a mostly water-soluble form; so that it can be eliminated from the body. The liver is the main organ in which most of the drugs are metabolized. There are some enzymes, which can metabolize a drug by chemical means – oxidation, reduction, and hydrolysis. Cytochrome P450 plays an important role in the enzymatic metabolism of a drug.
- *Excretion* is the elimination of a drug either in metabolized form or as such from the body through urine, faces, sweat, etc. The kidney plays an important role in the excretion of a drug.

A formulation should be developed in such a way that it can be manufactured economically on a large scale repeatedly without any change in its characteristic property. The formulation is initially manufactured in laboratory scale using laboratory-sized commercial equipment's and machinery. This is done to avoid the variation in quality between the large scale/commercial production due to the changes in equipment's. The lot size of the laboratory scale is also less than that of the pilot scale production. This is done to reduce the expenditure and to increase the number of lots. In both cases, the cGMP must be followed.

Once the formulation manufactured in the laboratory is found to be of consistent quality as per expectation, the formula is tried in pilot scale. In pilot scale, the lot size is increased and the method of manufacture,

specifications of the raw materials used and those of the products are noted. The Fig. 1.1 expresses how the technology is transferred. All the processes are carried out as per the documented method and keenly observed. Any deviation in the method or characteristic properties of the intermediate or of the final product must be recorded. During the pilot plant scale production following points are to be documented.

- The availability and quality of each raw material
- Time required to complete each and all the processes
- Quality of intermediate at each step
- Processing parameters
- Environmental conditions for each process required
- Equipment's and machineries required and their specifications
- Space required
- Types of personnel required
- Processing loss
- Yield
- Methods of evaluation of intermediates and final product
- Specifications of the raw materials and finished products
- Type and quality of packaging material required
- Storage conditions for intermediates and final product
- Shelf life of the products

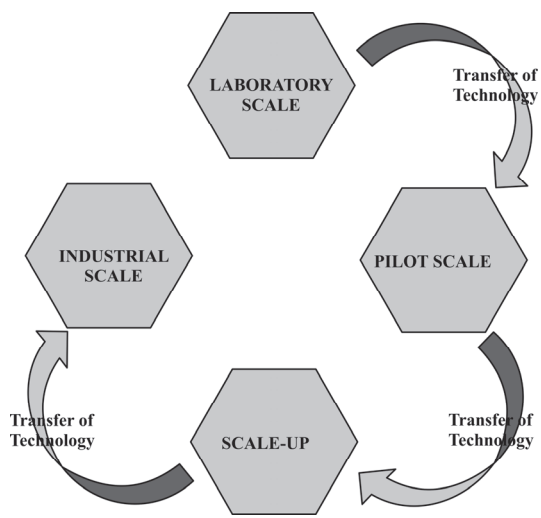

Fig. 1.1 Transfer of technology

Once the product produced complies strictly and consistently with the specifications, it may be considered that the pilot scale production is completed and the technology is ready to scale-up before transfer to commercial production. After successful completion of scale-up trials, the technology is transferred with all relevant documents to the production department for large-scale production. Thus, a pilot plant is a small industrial system, which is very similar to the large-scale production and is operated to generate information about the behavior of the system for use in the design of larger facilities. A pilot plant is an intermediate step in between the laboratory scale and industrial/large scale. These are usually smaller than full-scale production plants, but are built in a range of prototype sizes. (A pilot plant is a small-scale replica of the full-scale to provide design data for the ultimate large-scale production).

Usually, in the formulation development or research & development section, if the lot size is 1000 units, in the pilot scale, it becomes 10 000 and in the scale up, the lot size is increased to about 1 00 000, while in commercial production, the lot size becomes 5 – 10 lakhs. In other words, from R & D to the commercial scale, the lot size is increased as

$1X \rightarrow 10X \rightarrow 100X \rightarrow (500 – 1000)\ X.$

Objective of scale-up technique

- To develop a physically and chemically stable, therapeutically effective formulation, by optimizing various parameters.
- To create guidelines for production and process control.
- To develop specifications for raw materials handling and its requirements.
- To identify the critical steps and parameters involved in each process.
- To develop a master formula for manufacturing the dosage form.
- A pilot plant study was conducted to develop a formula identical to a commercial batch.
- Selection of infrastructural requirements to scale up the pilot plant.
- To evaluate, validate and finalize the production and processes.
- To evaluate and validate the developed product.
- To enlist the processing equipment.
- To establish the physical and mechanical compatibility of the equipment with the formulation.
- To determine the time and cost factor.

- To meet the needs of current market strategies.
- To transfer the technology from small scale to large scale production shown in Fig. 1.2.

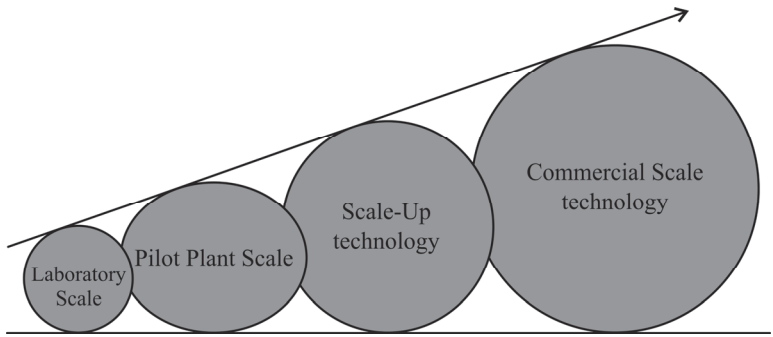

Fig. 1.2 Transfer of technology from a laboratory scale to commercial scale manufacturing

Steps involved in scaling-up of a technology

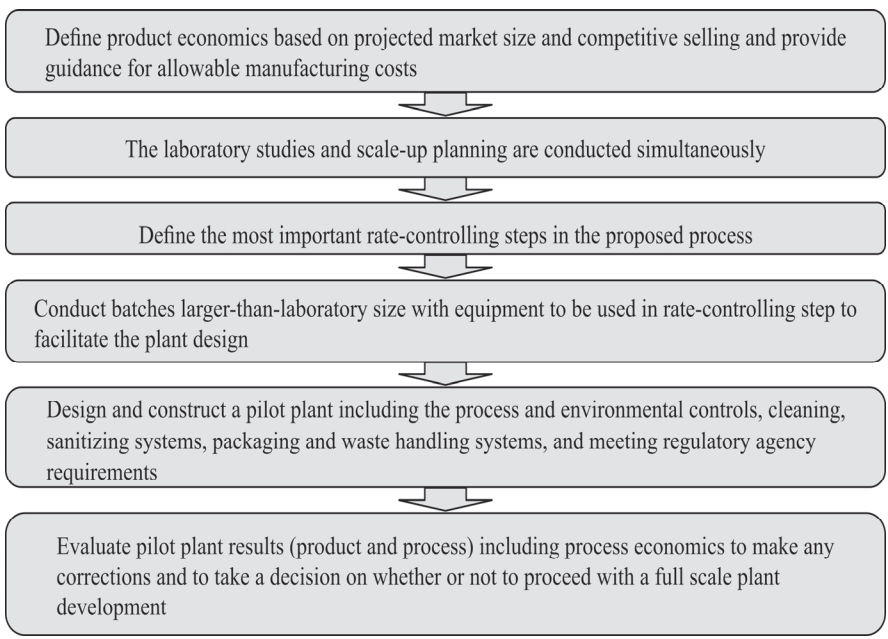

Fig. 1.3 Steps involved in scaling-up of a technology

During transfer of a technology from pilot scale and to large-scale manufacturing through scaling-up of technology following processes are followed as shown in Fig. 1.3.

Significance of Personnel Requirements

Most of the departments require people of different categories in terms of their level of education and work experience. Accordingly, they are assigned to different administrative levels. The activities in a pilot plant mostly require skill workmanship because a particular work needs to be completed within a minimum period. Persons lower than supervisor level working in a pharmaceutical pilot plant must understand why and how they are responsible and what may be the consequence of their failure. As such number of employees in a pilot plant department is limited, and depends on the number of products being developed. Usually 2–3 persons including product development scientist per product or two products are provided – an experienced scientist plus a knowledgeable and experienced operator, supported by an attendant. Therefore, the persons must have certain qualities, as listed below:

- Ability to read and understand the written directives/documents
- Intelligent analysis
- Ability to write the observations, requirements, etc.
- Possession of ethical values
- Possessing some hands-on experience of working in a pilot plant of a pharmaceutical industry
- Ability to communicate
- Ability to handle various equipment's and machineries
- Some sense of engineering.

Space Requirements

In fact, there should be four sections of a pilot plant depending on the type of work to be carried out. Hence, there should four types of space requirements –

1. Administrative and information section
2. Physical testing section
3. Pilot plant Equipment section
4. Storage section

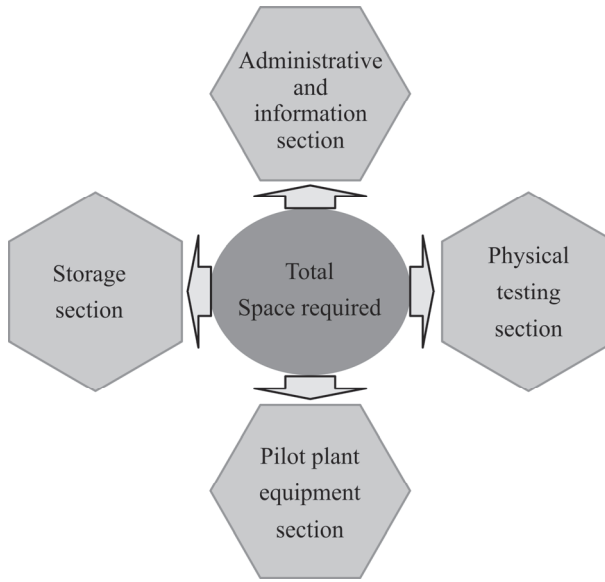

Fig. 1.4 Categorization of space required for pharmaceutical manufacturing

1. Administrative and information section

Documentation is a primary and essential activity in good manufacturing practices. Similarly, when some activities are going on information must be collected from various sources and needs to be communicated to some departments or some authorities. Thus, sufficient space should be provided to scientists and technicians working in a pilot plant to perform these activities. This space or section is called an administrative and information section. The location of this area should be adjacent to the work area but should be isolated from the work area so that the people can work without any disturbance.

The function of a pilot plant is to convert and transform the outcome of research and development activities into a feasible input of commercial production. People from the R&D department as well as those from the production department are expected to come to the pilot plant to discuss different issues. Thus, an adequate space is required so that at least five to six people can seat comfortably and discuss without disturbing other activities. At the time there should be an information centre attached to this section; where in a computer and printer must be available with internet facility to ensure that the information can be collected and documentation can be made conveniently.

2. Physical testing section

The next area or space must conduct experiments such as physical tests on the products prepared. This is a working area. There should be bench-top to keep the instruments required to perform mostly the physical tests and the samples. Commonly, the balance, pH meter, moisture balance, viscometer, desiccators, etc. Are to be placed on the bench-top. The space provided should be adequate to perform the tests comfortably.

3. Pilot plant equipment section

This is a standard pilot plant equipment floor area where the equipment required to manufacture different types of dosage forms is placed. Usually the equipment used in a pilot plant is similar to that used in an actual production department. These should be of different sizes. With the quality of scale up data collected can be assured, particularly when expensive materials are used. To evaluate the effect of the scale of research formulation and process, intermediate-sized and full-scale production equipment's would be required. In other words, to obtain the equivalence between the qualities of the products produced in a pilot plant and those produced in large scale, similar equipment's must be used in pilot scale production. This area should be used most efficiently; hence, it should be subdivided into different areas required as per the type of dosage form such as solid, semi solid, liquid, and aerosol manufactured.

Since, the dosage forms are irregularly manufactured in pilot plants as per requirement, use of pilot plant equipment's is also irregular; hence, the equipment in the pilot plant should be portable. The equipment is used only when a product is developed in the R&D department and needs to be scaled up. Thus, all the equipment is not used daily in the pilot plant department. These should be stored in a small area and be taken out before use. With this system, congestion can be removed, working space is increased and people can work comfortably. If sufficient space is there around each of the equipment's, the equipment can be cleaned easily and properly. There are equipment's which are used after cleaning in place and some are used when placed in clean area.

4. Storage section

This is the fourth area. Usually this space is found to be insufficient for storing of equipment's. Apart from equipment's, excipients, including actives (drug substances), packaging materials and finished products are to be stored orderly. All these materials should not be stored in a single area. Each category should be kept separately. Hence, the storage area should be subdivided into at least three areas – one for storing the equipment's, in

the second area excipients, and in the third area-finished products should be stored. The second and third areas need to be subdivided further to reject, under test, and approved materials as per GMP. According to GMP, the packaging materials are to be stored separately, not with raw materials. The raw materials and finished products should be stored at different conditions of temperature and humidity. For example, some materials require low temperatures and humidity. Some require a dry place.

The packaging materials are usually bulky in nature and require more space. Finished products are stored as retained samples to use as a reference till it is expired. The retained samples (finished products) should be stored as per the specifications provided in the label. These samples were tested to assess their stability under different environmental conditions. Therefore, the storage area should be provided according to the requirement with different environmental conditions. For example, capsule shells require low humidity and temperature. Bottles, vials and ampoules are stored under normal atmospheric conditions. Boxes of different categories are stored under normal atmospheric conditions.

Raw Materials

The responsibility of the pilot plant scale up department is to approve and validate the raw materials required for the product. Raw materials also include an active ingredient. Because the physical characteristics of raw materials used in small pilot batches may differ when these are used in large amounts. The analytical specifications of the materials including drug substance do not change, but their physical specifications such morphology, particle size, particle shape, colour, bulk density, static charge, flow properties, the rate of solubilization, etc. It is also necessary to verify the quality of the final product by using excipients including drug substance manufactured by other companies or supplied by different vendors; because to maintain an uninterrupted production schedule there should always be some alternative suppliers or manufacturers who can fulfill the requirement of materials in terms of quality and quantity.

Processing Equipments

The attributes of final products in most cases depend on the type of equipment used in processing. The equipment should be simple in operation, economical and should be easily cleaned and maintained. In the formulation development section, equipments of small capacity are generally used. Sometimes, the equipments used in formulation

development work does not match with what is actually used in large-scale production. Hence, the feasibility of the manufacturing processes is developed in formulation development and processing characteristics are determined. Once the process parameters and feasibility are established, pilot plant trials are conducted using large - scale production equipments with small capacities. If the desired equipment's is not available in house, the trial experiments of the pilot plant can be conducted at the equipment vendor's house to examine the feasibility and effect of equipment on the final quality of the product. Sometimes the quality of the intermediate product and time required to complete the process depends on the type of equipment used. For example, there are different types of mixers used in wet granulation, each has a different mixing efficiency. Hence, which mixer would be suitable for a particular product that needs to be decided? Similarly, for drying wet granules or even powders fluid bed dryer or hotair oven (tray dryer) can be used. But it may be necessary to decide the suitability of the dryer. If the capacity of the equipment is very small, it may be difficult to scale up the technology to a commercial scale. However, if the capacity of the equipment is large, the size of the experimental lots would be high and the cost of the equipment's would be high. Thus, overall expenses would be high. In fact, it would be very much difficult to run a trial experiment on an expensive drug.

When the process or technology developed is found to be realistic intermediate-sized batches are run before large-scale production.

Production Rate

In any industry, it is necessary to know how much and how long a product can be sold in the market. Depending on market requirements, the production rate should be fixed. To meet higher requirements, the rate of production should be increased and for this, equipment's of higher capacity would be required. This requires more capital investment. The following points should be considered before purchase of equipment;

- Cost of the equipment
- Whether the equipment can be used to manufacture other products or not?
- How frequently the equipment is used?
- Whether the operation and cleaning of the equipment are easy?
- Whether special training is required for the operation and maintenance of the equipment?
- What would be process-loss?

If the purchase of the equipment with a higher capacity is impossible, continuous operation of processes using equipment's of lower capacity and finally the intermediates are mixed and made a single batch. Accordingly, the production rate can be increased.

Process Evaluation

The knowledge of the effects of various process parameters as few mentioned above forms the basis for process optimization and validation. Any manufacturing process is necessary to be evaluated on the basis of certain critical parameters, as shown in Fig. 1.5.

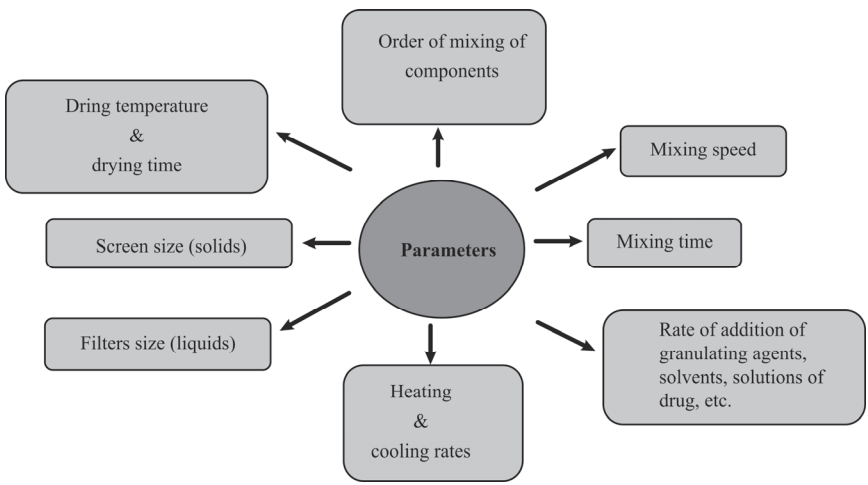

Fig. 1.5 Evaluation of the process

Pilot Plant Scale-up Considerations for Solids, Liquid Orals, Semi Solids

The primary responsibility of the pilot plant staff is to demonstrate that the product (dosage form) developed is therapeutically efficient, economical, and consistently reproducible on the production scale. The design and construction of the pharmaceutical pilot plant for every dosage form development should be such that the flow of materials, processes, and personnel are as per the norms of GMP and facilitates the maintenance and cleanliness of the area and equipment's. Irrespective of the type of dosage form, the processes are performed systematically. Each stage/step must be monitored very carefully and thoroughly starting from collection and storage of excipients to the manufacturing processes and quality of

product. At each step, the tests (IPQC tests) to be performed on the intermediates are enlisted to control and ensure the desired quality of the final product. It is to be established that the the same process, same equipment's of higher capacity when used with increased amounts of material does not change the quality of the product.

Solid Dosage Form (Tablet)

When a particular dosage form is developed by the R&D department and after that is sent for pilot plant scale up studies, the formula developed is standardized. The processing equipment's to be required for large-scale production are reviewed. The rate of is very much important for any manufacturing business; through a pilot plant study the rate of production is optimized and controlled. In fact, the infrastructural requirements for commercial manufacture are also known. While increasing the rate of production (scale up activity) the critical parameters are determined. Simultaneously, appropriate records to be maintained as per the GMP are known.

Steps involved in Tablet Production

The actual steps involved in the manufacture of tablets depend on the method used such as direct compression, dry granulation, and wet granulation. Irrespective of the method used, there are some common steps such as;

- Material handling
- Granulation
- Drying
- Reduction in particle size
- Blending
- Compression

In case of direct compression, the powders are mixed, lubricated and compressed. In case of dry granulation method, the blended powders are compressed to make slugs. The slugs are then crushed to make granules; the granules formed are blended with lubricant and diluent, if necessary and then compressed. When the tablets are prepared by wet granulation method, the powders are mixed first, then granulated with paste or solution of suitable binder, passed the wet mass through appropriate sieve, the wet granules are dried, crushed to form appropriate sized granules, the granules are then blended with lubricant; if necessary, and then compressed.

Material Handling System

In laboratory operations, the materials are handled simply by hand such as scooping, drawing or pouring. In intermediate- or large-scale operations, the materials are often handled by a suitable mechanical system such as vacuum loading systems, metering pumps, screw feed system. Note that when materials are transferred for the manufacture of more than one product, there is no cross contamination. The material handling system must deliver the accurate amount of the ingredient to the formulation. The Selection of the type of mechanical handling system depends on the materials such as density and static change.

Weighing of materials is an important activity in manufacturing either in small scale or large scale. The accuracy of the strength and quality of the product manufactured depends on the addition of all materials that are accurately weighed and processed properly. Weighing in a common processing area may cause problems such as

- Cross contamination, and
- Products may become misbranded due to the presence of incorrect amount of drug or due to the presence of minute amount of drug other than the declared one.

For this reason, some industries have weighing sections that are separated from other sections. This section means only weighing activity. After each weighing, it would be checked by another person and countersigned. According to product and its lot size, the amount of drug required is calculated and then weighed. This ensures that the correct quantity of drug is used in the manufacture of each lot. Each weighing balance is regularly maintained and calibrated by an authorized agency. This is a central department responsible for correct weighing. The sanitation, particulate matter in the circulating air are controlled in the area up to the highest degree.

A separate room or area is provided to weigh a highly potent drug such as steroid or alkaloid. The area is equipped with an efficient air filter, so that even minute contaminations do not occur. However, such an area can be used to weigh the dyes.

Dry Blending

The blending of powders should be done properly, otherwise uniform mixing would not be there. That is, samples of different portions of the mixture would show different potency. To ensure uniform mixing all the ingredients should be free from lumps and agglomerates. Hence, screening

and/or milling of the ingredients are done before mixing to make the mixture homogeneous and reproducible. The equipment used for blending are V- blender, double cone blender, Ribbon blender, slant cone blender Bin blender, orbiting screw blenders, Vertical and Horizontal high intensity mixers. The process of blending or mixing can be optimized by controlling the following parameters:

- Time of blending
- Blender loading
- Size of blender

It is well-known fact that the mixing of powders to make a homogeneous mixture is a challenging work. There are certain ways to achieve homogeneity. The order of addition of components should be monitored. The smallest amount is mixed with the small one; the mixture is then mixed gradually with portions of the powder of large quantity; like this. By this method, the drug can be uniformly distributed within the powder mix and variation in drug content can be reduced greatly, particularly when a small amount of drug is present in a unit dose such as per tablet or capsule. Mixing or blending of powders is generally done in a large container, which is then granulated in a mixer of similar capacity. If a manufacturer does not have such a large mixer for granulation, the powder mix (powder blend) is divided into portions and each portion is subjected to wet granulation. The dried lumps are converted into appropriate granules by milling or screening. The dried granules thus prepared are blended in a large container and the blended granules are then compressed. The process becomes more reliable and reproducible by milling or screening the lumps.

Granulation

As such homogeneous mixing of powders is a difficult task. Usually it is heterogeneous in nature and separation of particles according to their size is a common phenomenon, if particles of different size ranges are mixed. For this reason, the materials are passed through a particular sieve or mesh before mixing. The powder mixture is converted into granules of appropriate size range. Granulation is done either by dry or wet granulation method for the following reasons:

- After blending with suitable lubricant, the granules acquire good flow property, can flow uniformly from the hopper, can be easily compressed into tablet or encapsulated into capsules of suitable size, and uniformity of weight can be maintained.

- The bulk density of powders can be increased by granulating the powders; this helps encapsulating the granules in smaller size capsule shell.
- Granulation of the powders changes the particle size and hence, size distribution. Inter-particle binding properties during compaction or compression can be improved by changing the particle size distribution.
- Tablets of very small amounts of drug (mcg) contain higher amounts of excipient; in the granulation of a solution of drug when mixed with binder solution or paste and added to the powder, it results in a uniform distribution of the drug within the bulk powders.

Usually, Sigma blade mixer, Tumble blender, Heavy-duty planetary mixer is used for granulation. This equipment's can process 100 to 200-kg powders. Since this equipment is attached to a heavy duty motor, it can generate a high shear force. The high shear force generated by these equipment's and the weight of the material can granulate the powders within less time compared to that required during granulation in laboratory scale granulation. Such high shear mixer can increase the density of light powders.

Recently a multifunctional closed processor has been developed which can perform mixing of the powders, wet granulation, drying, sizing, and then lubrication in a continuous process. This type of equipment reduces the material handling and hence, reduces the processing loss and worker requirement considerably.

Binders are used in making tablets and it is added for granulation. In case of dry granulation, dry binders are used and for wet granulation either solution or paste of binder is used. The powders with adequate compressibility or compatibility can be compressed directly after lubrication. Otherwise, granulation must produce tablets. The properties of granules and the strength, friability, disintegration of tablets produced depend on the amount of binder used. Hence, it is necessary to optimize the amount of binder to be added per tablet or per lot of tablets. Moreover, different binders have different binding properties with respect to the concentration used; hence, the binder, its concentration and amount of solution or paste are to be optimized with respect to the properties of tablets. In some cases, the rate and time of mixing affect the characteristics of the granules. Thus, following parameters are to be standardized or optimized for effective granulation:

- Binder
- Concentration of binder

- Amount of binder solution or paste
- Duration of mixing
- Rate of mixing
- Type of mixer for granulation

In some cases, binding agent when is dissolved or dispersed in a granulating fluid or solvent, the consistency of the solution or dispersion becomes very high. Its addition to the powder mixture becomes difficult by pumping or pouring. In fact, during the pilot plant study such type of granulation is difficult to be standardized, particularly if a closed system is used. In such cases, by adding more of the solvent, the granulating solution/dispersion can be diluted; so that it can be handled easily.

If any component of the formulation, may be the drug or any excipient, whose quantity is very less, can be easily and uniformly distributed within the bulk by wet granulation. This is another advantage of this method. For example, the preservative or the drug must be uniformly present in the formulation and uniform mixing in the powder state is really difficult. By using either a solution or dispersion of these in granulating fluid, uniform mixing can be satisfactorily done. Sometimes, a mixture of water and water miscible volatile solvent such as alcohol is used as a granulating fluid.

Drying

The most common conventional method for drying a granulation continues to be the circulating hot air oven, which is heated by either steam or electricity. The important factor is to consider as part of scale-up of an oven drying operation are airflow, air temperature, and the depth of the granulation on the trays. If the granulation bed is too deep or too dense, the drying process will be inefficient, and if soluble dyes are involved, the migration of the dye to the surface of the granules. Drying times at specified temperatures and airflow rates must be established for each product, and for each oven load. Fluidized bed dryers are an attractive alternative to the circulating hot air ovens. The important factors considered as part of the scaled - up fluidized bed dryer are optimum loads, rate of airflow, inlet air temperature and humidity.

Reduction in Particle Size

The first step in this process is to determine the particle size distribution of granulation using a series of “stacked” sieves of decreasing mesh openings. The particle size reduction of the dried granulation of

production size batches can be carried out by passing all the material through an oscillating granulator, a hammer mill, a mechanical sieving device, or in some cases, a screening device. As part of the scale-up of a milling or sieving operation, the lubricants and glidants, in the laboratory are usually added directly to the final blend. This is done because some of these additives, especially magnesium stearate, tend to agglomerate when added in large quantities to the granulation in a blender.

Blending

The type of blending equipment often differs from that using in laboratory scale. In any blending operation, both segregation and mixing simultaneously occur simultaneously as a function of particle size, shape, hardness, and density, and of the dynamics of the mixing action. Particle abrasion is more likely to occur when high-shear mixers with spiral screws or blades are used. When a low dose active ingredient is to be blended, it may be sandwiched between two portions of directly compressible excipients to avoid loss to the surface of the blender.

Slugging

In the dry granulation method, the powder-mix is compacted in the form of slugs. Slugs range in diameter from 1 inch, for the more easily slugged material, to ¾ inch in diameter for materials that are more difficult to compress and require more pressure per unit area to yield satisfactory compacts. This is done on a tablet press designed for slugging, which operates at pressures of about 15 tons, compared with a normal tablet press, which operates at a pressure of 4 tons or less. If an excessive amount of fine powder is generated during the milling operation, the material must be screened and fines recycled through the slugging operation.

Dry Compaction

Granulation by dry compaction can also be achieved by passing powders between two rollers that compact the material at pressure of up to 10 tons per linear inch. Materials of very low density require roller compaction to achieve a bulk density sufficient to allow encapsulation or compression. One of the best examples of this process is the densification of aluminum hydroxide. Pilot plant personnel should determine whether the final drug blend or the active ingredient could be more efficiently processed in this manner than by conventional processing to produce a granulation with the required tableting or encapsulation properties.

Compression

The ultimate test of a tablet formulation and granulation process is whether the granulation can be compressed on a high-speed tablet press. When evaluating the compression characteristics of a particular formulation, prolonged trial runs at press speeds equal to that to be used in normal production should be tried, only then are potential problems such as sticking to the punch surface, tablet hardness, capping, and weight variation detected. Highspeed tablet compression depends on the ability of the press to interact with granulation. The following parameters are optimized during pilot plant techniques of granulation feed rate; delivery system should not change the particle size distribution. The system should not cause segregation of course and fine particles, nor should it induce static charges. The die feed system must be able to fill the die cavities adequately in a short period that the die is passing under the feed frame. The smaller the tablet, the more difficult it is to get a uniform fills a high press speed. For high-speed machines, induced die feed systems are necessary.

These are available with various feed paddles and with variable speed capabilities; so that the optimum feed for every granulation is obtained. Compression of the granules usually occurs as a single event as the heads of the punches pass over the lower and under the upper pressure rollers. This causes the punches to penetrate the die to a pre-set depth, compact the granules to the thickness of the gap set between the upper punch and lower punch. During compression, the granules are compacted to form tablet. Bonding among the compressible materials, due to cohesive force, must be formed, which results in the formation of tablet. Along with the cohesive force, adhesive force between granule and punch surface may be developed. If the strength of the adhesive force is more than the cohesive force, sticking may occur. This happens particularly when an embossed punch is used. To overcome sticking, the granules must be lubricated internally. If the granules contain a higher amount of lubricant or are lubricated for a longer time (over blending) soft tablets are produced, the wettability of the powder is decreased, and the dissolution time of the tablet can increase.

Binding to die walls can also be overcome by designing the die to be 0.001 to 0.005 inch wider at the upper portion than at the centre to relieve pressure during ejection. The machines used are high speed rotary machine, multirotary machine, double rotary machine, upper punch and lower punch machine and single rotary machine.

Whatever may be the tablet compression machine, during compression it performs at least three activities;

- Filling of empty die cavity with blended granules
- Compression of granules into tablets, and
- The ejection of tablets formed from the die cavity.

Sometimes a greater number of trials should be run during scale-up process. Safe operation, the number of tablets produced in unit time (productivity) and quality of tablets produced are to be optimized and for these, following points must be considered during pilot plant scale up technology.

- Characteristics of raw materials and/or formulation constraints are not suitable for high speed compression. The compression speed is reduced or tablet press of lower speed is used; so that the time required for filling the die cavities and compression can be optimized to achieve sufficient compaction process.
- Selection of suitable tablet press is necessary for a particular formulation; because the tablets compressed must be free from any defects and must be strong enough to withstand the shock of shipment and transportation. The tablet press with improved feed control mechanism, precompression and compression forces can solve many problems related to compression.
- Some granules have a tendency to cap when subjected to a single-step compression. This problem can be effectively solved using a tablet press with a series of pressure rollers that increase the compaction pressure stepwise; so that the air entrapped within the granules is escaped gradually and at the end capping problem would be over.
- High speed tablet press requires delivering the granules into the die cavities at a consistent and required rate. The rate of die filling should not change until the compression is completed.
- During die filling, theparticle size distribution in the granules must not change for any reason. This is because the uniformity of the drug content may change if the original particle size distribution is changed.
- The development of a static charge on the particles is another common problem that occurs frequently when segregation or separation of particles occurs particularly in case of small tablets. The die cavity must be filled uniformly with granules. Hence, particle size distribution

and particle flow property should be good enough and the mean particle size should be small to ensure uniform filling of the dies.

- If the die cavities are overfilled, the excess granules need to be removed by the feed frame to the centre of the die table. Otherwise, the granules shall be thrown from the table by the centrifugal force of the rotating die table. Hence, the scraper blade and die table should be adjusted to make necessary clearance for the removal of excess granules.
- Nowadays, high speed tablet press with induced die feed systems have been developed. These are also available with variable speed and different feed paddle. Such a system can feed every type of granule at an optimum level.
- During compression the materials present in granules are bonded, compacted, and finally the tablets are produced. A strong cohesive force within the material exists at the tablet interfaces. Along with the cohesive force adhesive force is also developed between tablet interfaces and die surface and punch. If the adhesive force is more than the cohesive force sticking of tablets will occur. Therefore, to avoid sticking adequate lubrication of the granules is required. Generally, metal stearates such as magnesium stearate are most widely used. The amount of lubricant to be used should be optimized; because poor lubrication may cause sticking, while excess lubrication and blending for a longer period may result in other problems such as softening of the tablets, poor wettability, and increase in dissolution time.
- The last step of the compression process is the ejection of tablets from the die cavity. In this step, the upper punch goes up leaving the tablet and the lower lunch push up the tablet to the die table. The take-off bar removes the tablet from the rotating die table. The tablet is collected through the chute fixed at a particular position adjacent to die table. The take-off bar and chute should be adjusted in such a way that the tablet once removed by bar falls into the chute; because the die table rotates.

The design and condition of the punch can cause sticking also. For example, embossing with punch can cause sticking. The punches and dies must be cleaned and kept carefully. The punch tips must remain sharp and smooth.

Tablet Coating

Since long the sugar coating has been used to coat the tablets using pan coating method. With development of technology, polymers and equipment film coating has replaced the sugar coating in many cases. The conventional pan has been replaced by perforated pan and fluidized bed coating column. Earlier polymers soluble in volatile inflammable organic solvents had been used. Due to safety problem and health hazards the earlier polymers have been replaced by newly developed water-soluble polymers.

As such, coating is a specialized activity. In manual system, the finish of coat depends on the expertise of the operator. Even after development in laboratory scale, it requires to be standardized or optimized during commercial production. Quality and finish of the coat depends mainly on;

- Design of the core tablet – the edge of tablet should not be sharp and surfaces should not be flat. Tablets with curve, shallow or deep, with bland edge are suitable for coating.
- Strength of the tablet – the tablets should be hard enough to withstand the shock produced during tumbling or rolling in the coating pan or in fluidized coating column.
- Embossing or engraving on tablet surface – the edge of the engraving should not be sharp and deep. The engravings should be shallow and the edges are bland or cuts should be angled.
- Nature of the core material –hydrophobicity of the core material is not suitable for aqueous coating solution. If the core components are originally hydrophobic, either the composition of the core or of the coating solution is be modified.
- Lot size of the core tablets – coating quality on small lot size may not match with that of higher lot size. This is due to increase in number of tablets (lot size), environmental conditions (temperature and humidity), rate of application of coating solution and drying cycles. Hence, further trials on larger batch size should be made to standardize the method.
- Friability or brittleness of the tablets –brittle tablets are not suitable for coating. The tablet should not break into fractions or should not produce powder due abrasion during rolling. If so happens, the surface of coated tablets would be rough and twin tablets would be produced.
- Design of the coating pan – chipping and loss due to abrasion can be appreciably reduced if the conventional coating pan is provided with baffles. Due to these baffles the tablets can roll uniformly; but not

slide. The tablet load would be redistributed and spread more uniformly over the entire tablet weight.

- Design of the coating column – by changing the length and diameter of the column of the fluidized bed coating column, the loss due to abrasion can be reduced appreciably. In this method the force of fluidizing air needs to be controlled.
- Design and type of the nozzle – for coating of tablets either the air-atomizing nozzle or airless atomizing nozzle can be used. If an airless sprayer is used the size and shape of nozzle is important. In case of air-atomized sprayer, the atomizing air pressure and the solution flow rate are important.

In traditional coating system the pan is attached to an exhaust duct to collect dust. As such the process creates a lot of dust and a single operator can handle four to five pans. The pan may be open or closed one. During coating lot of noise is also produced. Nowadays automated computerized method with microprocessor has been developed to coat the tablets.

Filling of Hard Gelatin Capsules

This has already been mentioned in the general method of manufacture of capsules that each size of capsule has a definite fill volume. Thus, the powder to be filled in a particular capsule shell must have definite bulk density, so that the required amount can be filled in a particular capsule. Depending on the amount of drug (unit dose of the drug) to be filled, its bulk density and capsule size, the drug can either be filled as such or first processed and then filled in the empty capsules. Hence, the drug is mixed with other excipients as is done to make tablets, mixed, and the dry powder blend is filled in capsules. The powder mix is wet granulated using a suitable binder; wet granules are dried, sieved and mixed with suitable lubricant. The lubricated granules are then filled in capsules. Thus, the manufacture of both capsule and tablet has got similarity.

For high speed machinery the powder/granules must have the required bulk density, particle size distribution, good flow property, and adequate compressibility for filling the capsules. The required number of particles should be compacted within the capsule shell to ensure filling of the correct amount of drug in each capsule. The excess lubricant present in the granules/powder or over-lubrication may increase the disintegration time and reduce the rate of dissolution. Environmental conditions are also to be considered; because definite temperature and humidity are required for the stability of the capsule shell. Hence, the factors to be considered during encapsulation of hard gelatin capsules are;

- Bulk density of powder/granules
- Particle size distribution
- Moisture content of the powder
- Powder/particle flow properties
- Compressibility of powder/granules
- Lubrication of powder/granules, and
- Environmental conditions.

Thus, during the pilot plant scale up process sufficient trials must standardize the filling operation. Usually the temperature should be maintained within 15 to 25°C and relative humidity within 35%-55%. If the humidity is high the capsule will swell because it absorbs moisture; if the humidity is too low the capsule shell will release moisture and will become brittle.

Liquid Dosage Forms

Liquid dosage forms commonly refer to nonsterile liquid dosage forms that include solution, suspension, and emulsion. These are either administered orally or topically. The scale - up of each product should be considered separately. Sterile liquids constitute a special class of preparations and require a separate consideration.

Solution

Solutions belong to a simple class of formulations and its scale up technique is also simple. Container/tank of suitable size and a mixer of required power and capacity are required for scaling up of the manufacturing process. For faster solubilization of solutes, heating facility should be attached to the tank. Generally, steam jacketed tank is used to prepare the solution or mixing. The solution requires filtration and transportation. Hence, suitable filtration equipment such as sparkler filter (filter press) is used for filtration of bulk solution. For transportation of solution of suitable capacity is used. All the equipment's used must be made of nonreactive material and should be cleaned easily. Stainless steel of type 308 or 316 is usually used to construct the equipment's, pipe, etc. Commonly stainless steel of type 316 is used because it is less reactive in nature. In fact, stainless steel is not nonreactive, it is less reactive. Some acidic preparations react with stainless steel. In such case, the steel should be treated with dilute acetic acid or nitric acid to neutralize the surface alkali of the steel. This process should be repeated on regular interval.

This process is called *passivation*. This must be out immediately after the preparation of an alkaline solution. Otherwise, the inner metallic surface should be coated with glass or polytetrafluoroethylene (Teflon). The metal surface becomes completely nonreactive, but it has disadvantage like cracking, flaking, peeling, or breaking.

Suspension

In case of disperse system the scale up ratio generally varies, from 10 to 100 from laboratory scale to pilot scale and from pilot scale to commercial scale varies from 10 to 200.

For scaling of a suspension formulation is not as simple as a solution. The disperse systems except microemulsion are in general thermodynamically unstable, multiphase system. Interfacial phenomena play an important role in making the system stable. The heterogeneity of the interphases is important, particularly due to the presence of solid particles. The solid state is the most complex state of matter and it confuses the process translation. The viscosity and flow properties of a suspension may vary considerably during the process translation. For example, in, the laboratory, the suspending agent is sprinkled over water and then stirred to prepare its dispersion. This is impossible in a large-scale production. In large-scale production, the dispersion medium is prepared using a vibrating feed system. Usually the steps in making a suspension are;

- Mixing
- Particle size reduction
- Material transfer
- Heat transfer

Mixing

This is the basic operation of suspension manufacturing. Sometimes the term agitation is used in place of mixing, which is wrong. When initially separated two or more phases are randomly distributed into and through one another, the process is called mixing or blending; while agitation causes movement or rotation of a material into a container. Agitation may not mix two or more separate components of a system into a uniform mixture.

Depending on the blades attached, a mixer may be propeller, turbine, paddle, helical ribbons, Z-blades, or screws. Moreover, the number of impellers, number of blades per impeller, the pitch of the impeller blades,

and the location of impeller can be changed to change the performance of the mixer. However, for effective mixing, a dispensator or rotor/stator mixer can be used in place of an impeller.

The manufacture of a suspension or emulsion mixing process may be a problematic operation due to the higher consistency and non-Newtonian flow characteristics of the system. Both laminar and turbulent flows occur simultaneously in different regions of the system. This does not happen in the case of low viscous liquids mixing. In high viscosity materials ($\eta > \sim 10^4$cps) mixing is relatively slow and is found not so effective. Generally, in such mixing, laminar flow occurs in place of turbulent flow; as a result, the inertial forces passed on during mixing disperse fast. Efficient mixing is required to provide convective flow. This is possible by high velocity gradient in the mixing zone. Hence, for highly viscous materials, mixing with specialized impellers, turbines, paddles, anchors, helical ribbons, and screws is suitable. Thus, during scaling up the proper mixing equipment should be selected.

Particle Size Reduction

Generally, the suspension is the dispersion of solid particles in a liquid vehicle. On storage, the dispersed particles may agglomerate, which is not desired. To produce homogeneous suspension and for prolonged dispersion, the dispersed solid particles should be very fine; hence, the size of the solid material should be reduced. With a decrease in the particle size, the number of particles increases. Thus, the interparticle and interfacial interactions increases. Particle size can be reduced by any of the four methods– (1) compression, (2) attrition, (3) impact, and (4) cutting or shear using particular equipment. Each method works with a particular mechanism.

- Crushing roll works involving a compression mechanism
- Grinder such as hammers mill, ball mills operate primarily with both the mechanism impact and attrition; however, compression is partially involved
- Ultrafine grinders such as fluid energy mills work primarily with attrition.

The grinding or crushing efficiency, $E_{C,\ is}$ the ratio of surface energy created by crushing or grinding to the energy absorbed by the solid and can be expressed as;

$$E_C = \frac{\sigma_s}{w_n}\left(A_{wp} - A_{wf}\right)$$

where, σ_s is the specific surface the area, A_{wp} is area per unit mass of product particles, A_{wf} is the area per unit mass of feed particles and W_n is the energy absorbed by the solid per unit mass. If W is the energy supplied to the mill; then $W - W_n$ is the energy spent for friction during crushing.

However, milling of the disperse phase using a ball mill, roller mill, and fluid energy mill has been found successful.

Usually the viscosity of dispersion is greater than that of its equation dispersion medium and according to the Einstein's equation, this can be expressed as;

$$\eta = \eta_o(1 + 2.5\varphi)$$

where, η is the viscosity of the dispersion, η_o is the viscosity of the dispersion medium, and φ is the volume fraction of the particular phase. The viscoelasticity of pharmaceutical suspensions indicates that these are non-Newtonian fluids – plastic, pseudoplastic. Their rheological behavior depends on φ; more precisely due to deformation of disperse phase and/or interparticulate interaction.

Material Transfer

The effect of the rate of mass transfer on the changes in the properties of a product is often neglected or ignored during scaling up of a manufacturing process. But it is an important activity and should be considered. During the manufacture of suspension, the material is transferred from the mixing or holding tank to processing equipment or to the filling line either by pumping or by gravity feed. This operation in most of the cases is found potential problematic. During pouring or transfer through the pump change in particle size distribution, physical or chemical instability may occur. Such changes occur due to the changes in the rate of transfer or in shear rate or shear stress. Hence at the time in scaling up of material transfer operation such changes in suspension and its time dependency should be considered and optimized because the product should be uniform at every point in time. Hence, during commercial production mass transfer time and its impact on product's quality must be scaled up.

Heat Transfer

In most of the cases heat is required to dissolve the materials while making a liquid formulation. Heat transfer is thus, an important parameter in the production of pharmaceutical formulations. The rate of heat transfer depends on the ratio of volume to surface area. This ratio is relatively

small in laboratory scale manufacturing; as a result, heat is transferred quickly and the product is cooled relatively faster. This is not true in the case of large-scale production. In large scale and even on pilot scale this ratio is large; hence, the time taken for cooling of the product is longer. As a result, the product is exposed to higher temperatures for a long time and may undergo thermal degradation. Thus, the mixing tank or solution preparation tank should be jacketed one through which cold water can be circulated to cool the product rapidly and if required, steam can be circulated in the jacket to increase the temperature of the contents in the tank.

The rate of heat transfer can be calculated as follows;

Say, $\frac{dQ}{dt}$ is the rate of heat transfer, A is the heated surface of jacketed tank, T_o is the temperature maintained within the jacket and T is the temperature of content in the tank, then $\frac{dQ}{dt}$ is proportional to heated surface area, A and the temperature gradient, $(T_o - T)$ at time t.

$$\frac{dQ}{dt} = C_p\left(\frac{dQ}{dt}\right)$$

where, C_p is the heat capacity of the jacketed vessel and its contents. If k is the heat transfer coefficient, then

$$\frac{dQ}{dt} = kA\,(T_o - T)$$

If $\frac{kA}{C_p} =$ a and T_i is the initial temperature of the tank, the above equation can be expressed as;

$$T_o - T = (T_o - T_i)\, e^{-at}$$

Thus, by using the above equation, the time, t required can be calculated to bring down the temperature, T_f, of the content in the tank.

Thus, on the basis of scale up performance the type of mixing tank, mixer, pump, mill, and the horse power of the motor should be carefully selected to prepare a commercial batch of pharmaceutical suspensions. The size of the equipment's should be selected as per commercial batch size. The type of mixer should be as per the maximum viscosity of the product.

According to Kline et al. The approaches to scale up of disperse systems can be classified into three categories;

- Modular scale up or limited scale-up
- Known scale up or limited scale-up, and
- Fundamental approach when scale-up ratio is high

Modular scale up refers to the scaling up of individual components or unit operations of a manufacturing process. The relationships among these individual operations result in a major scale-up problem. That is, if the process is used in large scale, the same quality of the product is not achieved. However, with the knowledge of the physicochemical properties of dispersion components, it may be possible to predict the scalability of some unit operations.

When laboratory or pilot scale experiments are less, known scale-up correlation can be applied using mathematical modeling of the manufacturing process and at various scale-up ratios experimental validation of the model can be done.

In fact, for scale-up of the dispersed system, no virtual guideline or model is available. The trial-and-error method has been commonly practiced and for success in the scalability of the process, practical experience plays a major role.

Emulsions

Emulsions belong to the disperse system, in which the globules of a liquid remain dispersed in a dispersion medium. The liquid dispersed phase may be a pure liquid or a solution. The emulsions may be O/W or W/O. In oil-in-water emulsions, oils or waxes are dispersed as globules in water while in water-in-oil emulsions aqueous solution remains dispersed globules in an oil medium. Emulsions may be in liquid form or in semisolid form, such as cream, ointment, etc. The manufacture of a liquid emulsion is a specialized process; hence, during scaling-up of the process selection of appropriate equipment and optimization of process parameters is very crucial. Extensive process development work and validation would be required.

The process parameters include the type of mixer, mixing speed, temperature, type of homogenizer, cooling process, screens, pumps used for material transfer, and filling equipment, etc. The physical properties such as appearance and viscosity, and physical stability of emulsion depend on how and to what extent the globule size of the dispersed phase has been reduced. The use of high-shear mixer generally causes air entrapment and therefore, physical appearance and chemical the stability of the product may greatly be affected. The use of a mixing container

operated under the controlled vacuum does not require aeration; as a result, above mentioned problems can be avoided. The presence of particulate matter in an emulsion affects the quality of the emulsion. Hence, the filtration of an emulsion is necessary to remove the foreign particles. It is better to filter the oil phase and water phase separately before emulsification, and sufficient care should be taken to ensure that no particulate matter is introduced into the product during preparation. It is wise to avoid filtering the final product.

To avoid, the problems of scaling-up and to answer the questions that may arise after the process has been operating smoothly for months or even years the pilot plant must be well designed. Thus, during pilot plant manufacture the same type of equipment's of smaller size must be used. In many cases scaling-up experiments are difficult to conduct with small volume and if done, it becomes very expensive. The equipment's should be capable of making a product of 20 to 100 lt. Even after scaling-up and successful production of few batches, it may be necessity to standardize the method of production. For example, any change in material supplier or change in personnel or change in the performance of a particular machine, there may be some deviation in the final quality of the product; hence, it becomes necessary to find out the reason responsible for such change in quality. It is expected that there will be no change in the production procedure.

Semisolid Dosage Form

Semisolids include paste, ointment, and cream. These also belong to dispersed system like suspension and emulsion; but their viscosity is very high. Thus, many Scale-up parameters related to these preparations are similar to suspension and emulsion. Because of high viscosity some parameters of these products are critical in nature. For example, mixer used to prepare suspension or emulsion would not be useful for ointments and creams. The turbulence created by the mixer during mixing of suspension shall entrap air which would be very difficult to remove. The mixing operation in making ointment should be such that the mass is removed effectively and continuously from side wall of the container to central zone and from bottom to top. The speed of impeller should be controlled to ensure uniform mixing without or minimum entrapment of air.

Processing steps such as during emulsification the mixing of aqueous and oil phases, homogenization, addition of active ingredient, and product transfer are usually performed at predetermined temperature. The

container or tank should be jacketed to circulate steam to heat the mass in the tank. After thorough mixing, the preparation needs to be cooled by circulating cold water. The temperature at which these operations are carried out is critical to the quality of the final product. For emulsification the temperatures of both aqueous and oil phases are raised to a temperature higher than the solidification point of the oil phase. This temperature is important for emulsification and the quality of the final product. The rate of heat transfer should be adjusted in such a way that the product is cooled slowly without affecting the texture of the product. Improper emulsification may result due to improper temperature control and viscosity differences in products. The particle size of poorly soluble drug can also be greatly affected by improper temperature control. If the drug is added when the temperature of the emulsion is too high, the solubility of the drug increases, a saturated solution of the drug is formed with the formation of a metastable product. After that, if the product is cooled recrystallization or crystal growth may take place, the crystals may be of different size or polymorphic form and particle size distribution can change. Finally, a gritty, less elegant, less stable product is formed. The product may be less therapeutically active.

Some gel and cream formulations are sensitive to shear. Such products should be manufactured carefully. These products should not be exposed to high shear during transportation from the manufacturing container to the holding container or filling lines. The viscosity of the product may change during such transportation or filtration, which is undesirable. Another problem occurs during the homogenization of an emulsion. For this purpose, various types of high shear mixer such as homogenizer, and colloid mill, are used. Among these, the colloid mill is the most commonly used. A colloid mill contains a fixed stator plate and a rotor platerotates at high speed. The gap between the stator and rotor is set to reduce the particle size of the product by the physical action and centrifugal force exerted by the rotor. The gap is adjusted within 0.005 to 0.01 inch. Recently supersonic homogenizer is used to reduce the particle size or aggregates and to micronize.

Highly viscous semisolid product is usually transferred using a positive displacement pump. This pump works without applying excessive shear or entrapment of air. The selection of pump should be based on the viscosity of the product, the rate of transfer, compatibility of the product with the pump surface, and the pumping pressure.

Thus, for scaling-up the manufacturing method of a semisolid product following processing parameters should be considered.

- Temperature at which emulsification to be done
- Viscosity of the product
- Temperatures of the aqueous and oil phases
- Rate of cooling the emulsion
- Homogenizer
- Selection of pump for transfer of product for filling

Relevant Documentation

During R&D processes before technology transfer of drug substances, information indicated below should be collected, and based on the information, technology transfer documentation should be prepared.

Information related to Raw Materials, Intermediates and Drug Substances

- Impurity profile and information on residual solvents (structure of impurities and route of synthesis)
- Information on descriptions of crystals of drug substances (crystallization, salt and properties of powders)
- Information on stability and description (raw materials, drug substances (including packaged drug substances), intermediates, solutions, crystal slurry, and humid crystals)
- Information on safety of drug substances, intermediates, and raw materials (Material Safety Data Sheet (MSDS))
- Information on animal origins of raw materials, etc.
- Information on packaging materials and storage methods (quality of packaging materials, storage temperature, and humidity)
- Information on reference standards and seed crystals (method of dispensing, specifications and test methods, and storage methods)

Information related to Manufacturing Methods

- Information on manufacturing methods (synthetic routes and purification methods)
- Information on operating conditions (control parameters and acceptable range)
- Information on important processes and parameters (identification of processes and

- Parameters, which will affect quality)
- Information on in-process control
- Information on reprocess and rework (places and methods)
- Basic data concerning manufacture (properties, heat release rate, reaction rate, and solubility, etc.)
- Data concerning environment and safety (environmental load and process safety)

Information related to Facilities and Equipments

- Information on equipment cleaning (cleaning methods, cleaning solvents, and sampling methods)
- Information on facilities (selection of materials, capacity, and equipment types, and necessity of special equipments)

Information related to Test Methods and Specifications

- Information on specifications and test methods of drug substances, intermediates, and raw materials (physical and chemical, microbiological, endotoxin and physicochemical properties, etc.)
- Validation for test methods of drug substances and intermediates

Items to be verified for Review of Scale-up

Sometimes manufacturing processes of drug substances use unstable chemical substances, and the unsteady processes accompany with chemical changes. Hence, handling period for each operational unit, stability of subject compounds during operation, and conditions of scale-up should be carefully established.

Since, the parameters related to equipments, operations can influence the quality of the product, they should be considered carefully.

Items to be verified for Reviewing Scale-Up of Reaction Processes

- Reproducibility of temperature pattern and its effects (effects of delay in temperature up and down on quality)
- Effects of churning in heterogeneous and semi-batch reactions (formations of concentration distribution and diffusion-controlled zone)
- Prediction and effect of operation period of consecutive reactions or exothermic reactions in semi-batch reactors (extension of operation

period due to insufficient capacity of facilities and its effects on quality)

- Balance between heat release rate and heat dissipation capacity (temperature pattern of exothermic reaction and its effects)
- Effects of facilities (validity of required capacity of utility, and effects from temperature distribution, dead volume, and overheating of laminar film)
- Confirmation of fluctuations due to scale-up (phenomenon, which did not appear at flask levels)

Items to be confirmed in Reviewing Scale-up of Crystallization Processes

- Effects of churning (effects on particle size and polymorphism, and selection of scale-up factors)
- Reproducibility of temperature pattern (reproducibility of established temperature pattern and effects on quality)
- Effects on facilities (temperature pattern, changes in flow pattern, effects of local concentration distribution and temperature distribution, super-cooling of laminar film, and scaling)
- Prediction of time for solid-liquid separation and its effects (stability of slurry waiting for filtration)
- Confirmation of ease of operation (problems at actual equipment levels such as slurryemission, transfer, and churn load)

Clarification of Quality Variability Factors

To elucidate quality variability factors, the following items should be reviewed during quality design through scale-up review.

Processes Affecting Quality

To identify processes, which may affect the quality of final drug substances, such as processes to generate final substances, structures with pharmacological activities, and impurities that cannot be eliminated in purification.

Establishment of Critical Parameters Affecting Quality

To search for parameters among those controlling the above processes, which may affect the quality of final drug substances, such as generation and elimination of impurities, and physicochemical properties of final drug substances, and establish a range of control.

Establishment of other Parameters

Parameters not affecting the quality of final drug substances are not subject to validation; however, they are subject to change control and change histories should be recorded.

Development Report on Synthetic Drug Substances

Information concerning the drug substances and intermediates to be described is as follows:

- Development history, including different synthetic methods used to manufacture investigational drugs
- Finally determined chemical synthetic route
- Change history of processes
- Quality profile of manufactured batches
- Specifications and test methods of intermediates and final drug substances
- Rationale for establishment of critical processes
- Critical parameters and control range
- References to existing reports and literature, etc.
- Master batch records of the manufacturing of investigational drugs or samples (format of manufacturing records)
- Manufacturing records of investigational drugs or samples (batches for establishment of specifications for application, validation batches, etc.)
- Plan and report of process validations
- Items of in-process control: IPC (test methods and specifications)
- Investigation report on causes of abnormalities (if occurred)

Information on Cleaning Procedures

- Master batch recording of cleaning
- Record of cleaning
- Plan and report of cleaning validation
- Test methods and specifications
- Validation report on analytical methods used for cleaning validation

Information on Analytical Methods

- Development report on analytical methods or those corresponding to the development report
- Test methods and specifications (raw materials, intermediates, final drug substances, and container/closure)

- Validation report on release test methods
- Stability test (validation report on analytical method, plan/report of stability test, container form, reference standard, and relevant reports)
- Investigation report on causes of OOS (out of specification)

Information on Methods of Storage/Transportation

- Container/closure system
- Date of retest/expiry date
- Conditions of transportation
- Information on sensitivity to temperature, humidity, light, and oxygen
- Instructions for temperature monitoring of drug substances which need cold storage

Information on Facilities

- Structural materials
- Category and type of main facility
- Critical facilities for final processing that may affect physicochemical properties (particlesize and surface conditions, etc.)

SUPAC Guidelines

In 1991, the American Association of Pharmaceutical Scientists, the Food & Drug Association (FDA), and the United States Pharmacopeia (USP) jointly organized two workshops to investigate the aspects of Scale-Up and Post-approval Change (SUPAC) in immediate-release of oral solid dosage forms and in 1992for oral extended-release dosage forms. The decisions taken in both workshops were published in 1993 and have been used as guidance to the industry and regulatory bodies.

Primarily four aspects discussed and defined in those proceedings are:

1. The impact of changes in formulation and composition on the finished quality parameters of these products.
2. The impact of changes in the process variables on the finished quality parameters of these products.
3. The impact of changes in process scales on the finished quality parameters of these products.
4. The impact of changes in process site on the finished quality parameters of these products.

To assess the significance and to record and report the post-approval changes, the FDA has issued the guidance for SUPAC changes designated as the following:

- Supac-IR (immediate release solid oral dosage form)
- Supac-MR (modified release solid oral dosage form)
- Supac-SS (non-sterile semi solid dosage form such as cream, ointment, gel and lotion)

These guidelines provide recommendations to the pharmaceutical industry producing new drug applications (NDAs), abbreviated new drug applications (ANDAs), and abbreviated antibiotic drug applications (AADAs). Sometimes, the manufacturers wish to change:

(a) The components or composition,

(b) The site of manufacture,

(c) The scale-up/scale-down of manufacture, and/or

(d) The manufacturing (process and equipment) of a modified releaseor immediate release solid oral dosage form during the postapproval period.

The guideline defines:

1. Levels of change such level 1 refers to minor changes, level 2 refers to moderate changes, and level 3 refers to major changes.
2. Recommended chemistry, manufacturing, and controls (CMC) tests for each level of change,
3. Recommended in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and
4. Documents supporting the change.

Level 1: when the changes are unlikely to have any measurable/detectable effect on quality and performance of the formulation. For example, (1) change in colon, flavor. (2) Changes in the amounts of excipients (expressed as the percentage (%w/w) of total of unit product weight) do not exceed5%.

Level 2: when the changes may have a significant effect on the quality and performance of the formulation. For example, (1) change in the technical grade of the excipient, such as use of Avicel PH102 in place of Avicel 200 or vice versa. (2) When changes in the number of excipients (expressed as the percentage (%w/w) of total of unit product weight), exceeds 5%, but not more than 10%.

The guidelines specify that an application should be given to the Centre for Drug Evaluation and Research (CDER). It should provide the information to ensure the product quality and performance characteristics of a modified release or immediate release solid oral dose formulation for specified postapproval changes.

Level 3: when the changes are likely to have a significant effect on the quality and performance of the formulation. For example, (1) qualitative or quantitative change of excipient mixed with a narrow therapeutic drug beyond the range of Level 1. (2) When the dissolution criteria of a drug do not meet the specification of Level 2.

Extended release solid oral dosage forms:

Level	Classification	Therapeutic range	Test Documentation	Filling Documentation
I	Complete or partial deletion of colour/flavour Change in inks, imprints Up to Supac-IR level 1 excipient ranges No other changes	All drugs	• Stability • Application/compendial requirements • No biostudies	Annual report
II	Change in technical grade and/or specifications Higher than Supac-IR Level1 but less than Level2 excipient ranges No other changes	All drugs	• Notification and updated batch records • Application/compendial requirements plus multi-point dissolution profile in three other media (water, 0.1N HCl, USP buffer media pH 4.5, 6.8) until ≥ 80% of drug is released or an asymptote is reached. • Apply some statistical test (F2 test) for comparing dissolution profiles • No Biostudy	Prior approval supplement

Contd….

Level	Classification	Therapeutic range	Test Documentation	Filling Documentation
III	Higher than Supac-IR Level2 excipient ranges	All drugs	• Updated batch record • Stability • Application/compendial (profile) requirements • Biostudy or IVIVC	Prior approval supplement

Introduction to Platform Technology

In the 1980s, the development of monoclonal antibodies (mAb) was started. Since then, it has become vastly successful as an effective and safe therapeutic for various diseases. The idea of establishing and applying Platform Technology for a process is still new and still there is no definition in ICH Q18 (R2). Now the platform technology has become one of the fastest growing areas in the pharmaceutical industry.

For each molecule development of antibodies was a tailored approach and this happened from discovery to development. Attempts have been made to establish a definite process and to assure quality by compliance. The knowledge about the quality of the product and technology started to increase the result development of new technology to achieve the safety and efficacy of biologics with the concept of Quality-by-Design (QbD). By adding data for every new molecule developed using this method, the platform can be improved continuously.

However, according to the principle of QbD, Platform Technology can be defined as; a systematic approach to influence the prior knowledge for standardized processes that has been revealed that the multidimensional combination and interaction of input variables and process parameters can be applied for a class of molecules with comparable characteristics to achieve assurance of quality.

According to this definition, it is necessary to establish the platform technology for the identification of a class of molecules possessing similar or comparable characteristics with respect to their physico-chemical properties and stability such as monoclonal antibodies. Any molecule having characteristics can be considered to belong to the same class.

Prerequisites to establish a Technology Platform for Early Development

To establish and justify the applicability of a Platform Technology, it is necessary to identify the molecules which can be considered next-in-class molecules.

A combined effort of multiple functions in late-stage discovery, involving candidate generation, screening and selection of the lead candidates is necessary to determine whether the selected lead molecule belongs to next-in-class molecule or not. This would be the systematic approach for this.

Target Molecule Profile

The characteristics of a drug molecule should be similar to those of a product. To develop a target drug product, thetarget product profile needs to be considered. Hence, the Target Product Profile must be defined first, and as per this definition a Target Molecule Profile (TMP) should be searched and the important or necessary characteristics of a molecule should be specified to ensure stability, safety and therapeutic efficacy. The figure 5 shows the screening process of potential target molecule profile, assessment of their drug like properties and to justify whether the platform process can be used on these molecules.

Screening and Selection

Such a screening process involves several functions and is carried out in different stages. The method can be used for a wide number of materials for screening at each stage. At the first stage assay is usually done to evaluate the primary amino acid sequence and to screen the methods to identify the sequence and structural configurations that might cause chemical or physical degradation, such as degradation, aggregation, colloidal instability or unwanted biological effects like immunogenicity.

The accuracy of this screening method cannot eliminate the candidates solely; subsequent testing is necessary to assign a development risk to each molecule. Based on prior knowledge, the molecules can be ranked according to predefined benchmark criteria. The molecules showing the overall best drug-like properties are selected as lead and backup candidates.

Finally, the result of the screening justifies whether the selected lead and backup candidate is a next-in-class molecule, and can be subjected to the platform process.

If none of the screened molecules match with the requirements of a next-in-class molecule, more extensive and customized formulation and process development efforts are made.

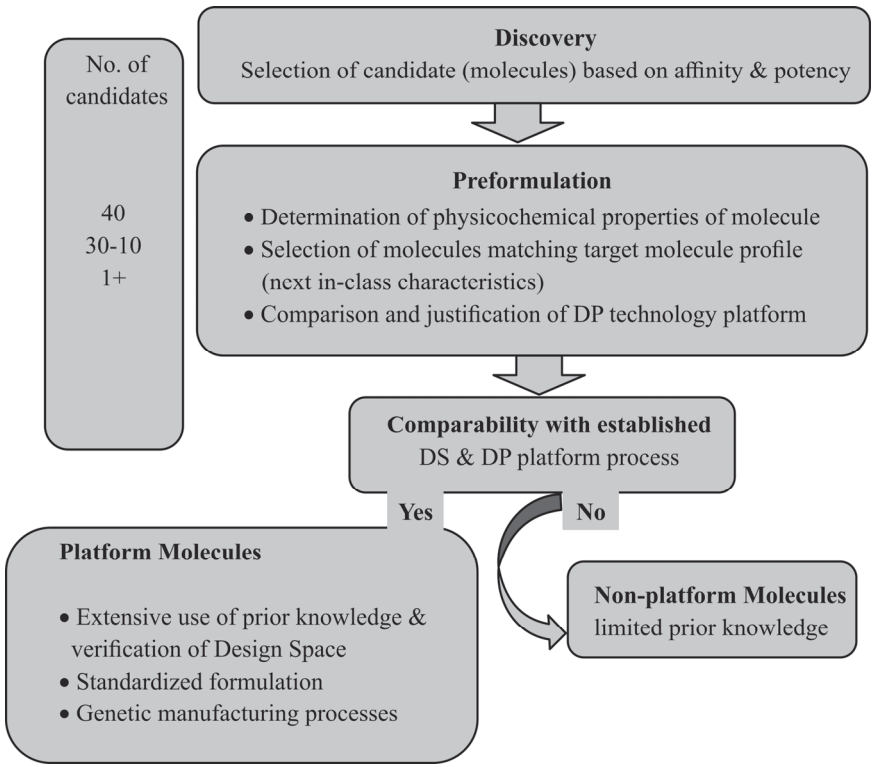

Fig. 1.6 Flow-chart of a standardized screening process to assess and identify next-in class molecules as defined by the Target Molecular Profile (TMP)

Establishing a Platform Process in Early Drug Product Development

The previously described activities are performed either after or during the late-stage discovery. This section provides an indication of the activities to be carried out in the development area.

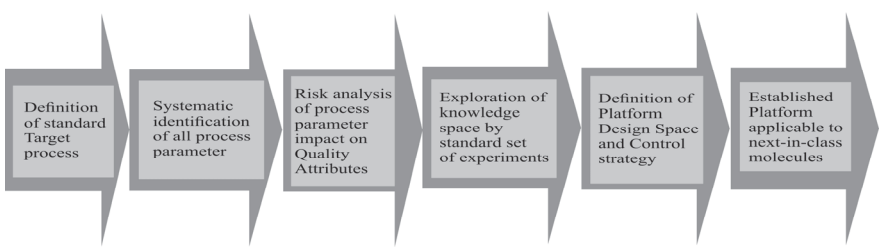

Fig. 1.7 Flow-chart of the various stages of implementing a technology platform

As shown in Figure 1.7, the method used to set up the platform closely follows the principle of QbD. However, the systematic approach begins with the definition of a standard target process. This method is subsequently used for all next-in-class molecules.

Thereafter, the identification of all process parameters starts and are analyzed using a risk-based approach on their impact on the Quality Attributes of the molecule.

During the implementation of the platform technologies, the knowledge space is explored depending on the available prior knowledge. Additional experiments are necessary to acquire an increased number of products and processes to define a Design and Control Space. For various molecules once the platform process is established and successfully demonstrated to be successful, no additional formulation or process development work is required. Whether the lead molecule can be considered a next-in-class molecule could be justified by the information achieved in late discovery and this will help know the Design and Control Space of the established platform.

Initial activities should focus on the basic characterization and formulation and process development of a given class of molecules about which prior knowledge is limited. Extensive studies during initial screening will provide information about suitable formulations. To simplify the process transfer activity a standardized manufacturing process is performed to assess the robustness rather than efficiency and a lead formulation is selected from the result of the above-mentioned stability assessment. The selected lead formulation can be used for subsequent clinical supply manufacturing. Additional backup formulations of any new molecule of the same class will be selected for the test.

In the next phase, the previously identified formulation can be used to confirm whether the molecules y- and z-mAb of the same class exhibit comparable characteristics (next-in-class molecules) or not.

These molecules are characterized in detail and their stability in the lead and in the backup formulations are analyzed. If the data for y- and z-mAb are found to be stableas x-mAb, the standardized formulation and manufacturing process can be used as a platform for this class of molecules. Because of extensive screening of preformulation candidates and the application of prior knowledge from x-, y- and z-mAb, any following next-in-class molecule such as next-mAb can be directly submitted for clinical supply manufacturing. Subsequent IND stability studies will ultimately verify the use of the platform process.

Recent advancements in protein engineering provide the tools to identify and create many potential antibody candidates toward a given target. A systematic screening method can assess whether the molecules possess drug-like properties and can identify the most promising molecules that match predefined stability criteria, as specified in the target molecule profile. In fact, the molecules matching with these criteria would show comparable characteristics and become next-in-class molecules and these can be subsequently developed using a technology platform using a standardized formulation such as composition, excipients, and packaging components, standardized process equipment and unit operations.

Use the prior knowledge can significantly reduce the development efforts required to start phase I clinical trials; while understanding of continuous improvement of the product and process with every molecule of the respective class becomes is very beneficial. Furthermore, the increased predictability and the accuracy of in-time development with synchronized multiple projects are the additional benefits.

A. Multiple Choice Questions

1. Which of the following statements is correct?
   a) Absorption of a drug depends only on the solubility of the drug
   b) Absorption of a drug depends only on the partition coefficient of the drug.
   c) Absorption of a drug depends only on the permeability of the drug
   d) Absorption of a drug depends only on the solubility, partition coefficient, and permeability of the drug
2. During the pilot plant scale production, which of the following information is not documented?
   a) The amount of drug and excipients purchased
   b) Type of personnel required for production
   c) Storage conditions for the intermediates and final product
   d) Shelf-life of the product
3. If 1000 units of a product are manufactured in the laboratory, the lot size on pilot scale would be
   a) 5000 b) 10000
   c) 100000 d) 1000000

4. The specifications for raw materials are developed finally in
   a) Laboratory manufacturing
   b) Pilot scale manufacturing
   c) Scale up manufacturing
   d) Commercial manufacturing
5. Which of the following is finalised during pilot scale manufacturing?
   a) Time required for completion of each and all the steps
   b) Master formula for manufacturing the dosage form
   c) Guidelines for manufacture and process control
   d) List of the equipment required for manufacturing
6. What is the objective of scale up technique?
   a) Environmental conditions required for each process
   b) Identification of the critical steps and parameters involved in each process
   c) Type and quality of packaging materials required
   d) To determine the processing loss.
7. What of the following points were not considered before the purchase of the equipment?
   a) Cost of the equipment
   b) How frequently the equipment is used?
   c) What would be processing loss?
   d) What is the resale value of the equipment?
8. Irrespective of the method used to manufacture of tablet, which of the following steps is common?
   a) Material handling
   b) Drying
   c) Wet granulation
   d) Crushing
9. Which of the following parameters is not optimized to optimize the process of blending?
   a) Time of blending
   b) Mechanism of blending
   c) Size of blender
   d) Blender loading
10. An effective granulation cannot optimize the following parameter?
    a) Composition of the mixture
    b) Concentration of binder
    c) Duration of mixing
    d) Type of mixer used for granulation

11. Which of the following statements is correct?
    a) Bulk density of the powder mix can be decreased
    b) True density of the powder is decreased
    c) Granule density of the blended powder is decreased
    d) Bulk density of the powder mix can be increased
12. Compression of granules performs which of the following activities?
    a) Mixing of the powders
    b) Selection of suitable tablet press
    c) Filling of empty die cavity with blended granules
    d) To determine the characteristics of the raw materials
13. The quality and finish of the coat does not depend on
    a) The expertise of the operator
    b) Strength of the tablets
    c) Design of the core tablets
    d) Size of the tablets compressed
14. Which of the following should not be considered a factor for the encapsulation of powders?
    a) True density of the drug
    b) Bulk density of the powder
    c) Filling volume of the capsule
    d) Lubrication of the powder/granules
15. The viscosity of a dispersion, η, can be expressed as
    a) $\eta = \eta_o + \varphi$ b) $\eta = \eta_o(1+ \varphi)$
    c) $\eta = \eta_o(1+2.5\ \varphi)$ d) $\eta = \eta_o \times \varphi$
    (Where, η is the viscosity of the dispersion, η_o is the viscosity of the dispersion medium, and φ is the volume fraction of the phase.)
16. Which of the following parameters does not belong to the processing of the semisolid dosage form?
    a) Temperature and humidity of the manufacturing area
    b) Temperature of the raw materials at which emulsification to be performed
    c) Rate of cooling of the product
    d) Temperature of the aqueous and oil phases

17. Which of the following information is not related to dosage form-manufacturing method?
    a) Information related to the synthetic routes and purification methods.
    b) Information related to crystallization, salt and properties of powders.
    c) Information related to operating conditions.
    d) Information related to environmental load and process safety.
18. Which of the following is related to the history of development of a drug product?
    a) Critical facilities for final processing that may affect the physicochemical properties
    b) Investigation report on causes of abnormalities
    c) Manufacturing records of investigational drugs or samples
    d) Specifications and test methods of intermediates and final drug product
19. Which of the following is not considered SUPAC guidelines?
    a) Information related to changes in the composition and formulation of the quality of finished products
    b) Information related to changes in process variables on the quality of finished products
    c) Information related to monitoring of temperature for drug substances, which require cold storage
    d) Information related to changes in the process site on the quality of the finished products.
20. To establish and justify the applicability of a Platform Technology, it is necessary
    a) To change the number of excipients of total of unit product weight
    b) To identify the molecules which can be considered the next-in-class molecule?
    c) To provide the information to ensure the product quality and performance characteristics of a modified release or immediate release solid oral dose formulation for specified post approval changes.
    d) None of the above

B. Short Questions

1. What is the information about a drug are to be known before selection and development of an appropriate dosage form?
2. During pilot plant scale production of a dosage form, what information is to be documented?
3. Write down the reasons for which the scale up technique is required in the pharmaceutical industry.
4. Briefly mention the reason why the knowledge on 'production rate' in the pharmaceutical industry is necessary.
5. What are the reasons for which granulation is done either by the dry or wet granulation method for making tablet?
6. Enlist the information related to raw materials, intermediates and drug substances required to be documented before the transfer of the technology in a pharmaceutical industry.
7. What are the areas or items required to be verified for reviewing scale-up of a reaction process?
8. Mention in short, the primary aspects to be discussed and defined in SUPAC guidelines.
9. In Platform technology, what is meant by 'Target Molecular Profile'?

C. Long Questions

1. Explain the significance of personnel requirement in pharmaceutical industries.
2. Write a brief note on the four types of spaces required in pilot plant of pharmaceutical industries.
3. Explain the importance of 'Material Handling System' in pharmaceutical industry with respect to pilot plant manufacturing.
4. Explain, why and how the granulation step is important in pilot plant manufacture in pharmaceutical industry?
5. Briefly discuss the most important scale-up parameters related to the manufacture of semisolid dosage forms.
6. Write down the information related to raw materials, intermediates, drug substances, and manufacturing methods are collected during R&D processes before the transfer of technology.

7. Write a brief note on SUPAC guidelines with respect to pharmaceutical product manufacturing.
8. Explain in brief the prerequisites to establish a technology platform for early development.
9. Discuss in brief how the standardized screening process be used to assess and identify next-in-class molecules as defined by the Target Molecular Profile (TMP).
10. Explain, how a platform process can be established in the early stage of development of a drug product?

MCQs Answers

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
D	A	B	C	A	B	D	C	B	A	D	C	D	A	C	A	B	D	C	B