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A Review on "Pilot Plant Scale - Up Techniques for Tablet"

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Abstract: ***Pilot plant scale up techniques it is the part of pharmaceutical industry where a lab scale formula is transformed in to large scale by development of liable and practical procedure of manufacturing. Pilot plant scale up techniques for solid dosage form will provide guideline for manufacturing to large scale process and these will play crucial role in large scale manufacturing. General requirement for scale up such as reporting responsibility, personnel requirement, space requirement, review of formula, raw material, processing equipments, production rate, gmp consideration and the parameters such as blending, granulation, drying, compression will provide critical role in development of solid dosaseform. Pilot plants are relatively smaller than full scale production plant. Also a pilot plant intended for learning, the preparation of several clinical batches in the pilot plants provides its personnel with the opportunity to perfect and validate the process.***

Keywords: Pilot Plant, scale Up Techniques, Solid Dosage Form, Tablet, Drying, Blending, Compression

1. Introduction

1.1 Definitions

Plant
It is place where the 5's like money, material, man, machine and method are brought together for the manufacturing of the product.

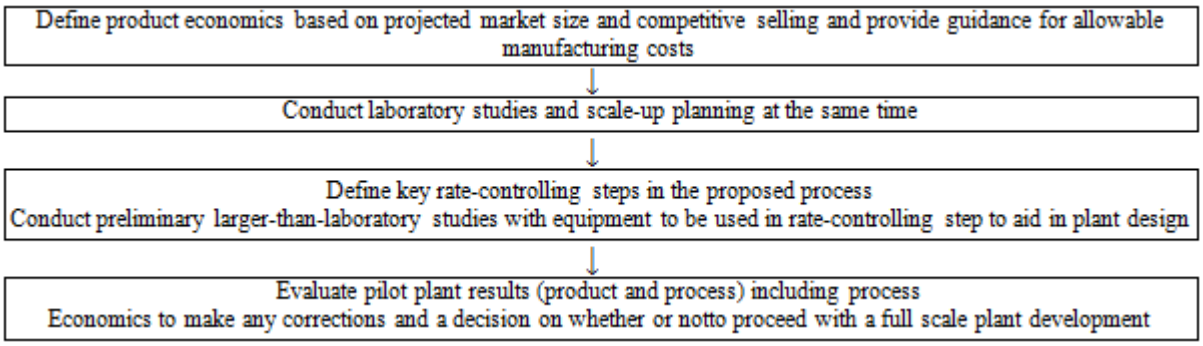
Pilot
It is the part of pharmaceutical industry where a lab scale formula is transformed in to viable product by development of liable and practical procedure of manufacture.

Scale up
The art for designing of prototype using the data obtained from the pilot plant model

1.2 Objectives

- To try the process on a model of proposed plant before committing large sum of money on a production unit.
- To identify the critical feature of the process.
- Guidelines for production and process control.
- To provide master manufacturing formula with instructions for manufacturing procedure.
- To avoid the scale - up problems.
- Evolution and validation of process and equipments.

1.3 Steps in scale up



1.4 General Requirements

Reporting Responsibilities
Pilot plant functions can be part of a research and development group with separate staffing. This arrangement is designed to provide a hierarchy of responsibility to scale up formulations that have been developed by other formulator within research and development, thereby providing a opportunity for critique a formula/process that is independent of the initial formulation function. Alternatively, the formulators who developed the product can take into production has been completed.

Personnel Requirements
The qualifications required for a position in a pilot plant organization are blend of good theoretic knowledge of pharmaceutics and sme practical experience in the pharmaceutical industry. The personnel should have the ability of communicate well, both in speaking and in

writing, and ability to develop good relationships with other peoples are important.

Space Requirements

Administration and information processing Documentation is important. Adequate office and desk space must be provided for both the scientist and technicians. These should be adjacent to the work area but sufficiently isolated to permit people to work without undue distractions.

Figure 1: Administration area

Physical Testing Area These area provide permanent bench - top space for routinely used physical testing equipment (e. g. balance, pH meter, and viscometer).

Standard Pilot Plant Equipment Floor Space Third area is descent plant space where equipment needed for manufacturing all types of pharmaceutical dosage form is located.

The equipment should be available in a variety of sizes known to be representative of production capability.

Storage Area separate provision should be made for the storage of the active ingredients and excipients. These should be further segregated in to approved and unapproved areas according to GMPs.

There should be generous storages areas for in - process materials, finished bulk products from the pilot plant, and material, and experimental scale up batches made in production.

2. Review of the Formula

A thorough review of each aspect of the formulation is important and should be carried out early in the scale up process. The purpose of each ingredient and its contribution to final product manufactured on small - scale laboratory equipment should be understood. Then, the effect of the scale up using equipment that may subject the product to stresses of different types of degrees can be more rapidly predicted, or recognized when they actually occur.

Raw Material

One responsibility of the pilot plant function is the approval and validation of the active and excipients raw materials use in pharmaceutical product. These is necessary because the raw material used during small scale formulations trial may not be representative of large volume of materials used in large scale production. Even though all analytic specification met, these larger lots of active ingredients may change in particle size, shape or morphology, resulting in different handling properties or differences in bulk density static charges, rate of solubility, flow properties, color etc.

Relevant Processing Equipments

During subsequent scale up, alternative manufacturing equipment should be considered. Based on the known processing characteristics of the product the equipment that premises to be the most economical, the simplest, the most efficient, and the most capable of consistently producing product within proposed specifications should be evaluated.

Figure 2: Continuous processing equipment

Production Rates
The immediate and future market requirement must be considered when determining the production equipment needed.

The size of the equipment should be such it is properly utilized.

Process Evolution

The previous sections have developed the product scale up program to the point at which the manufacturing process has been proposed and the equipment for production has been evaluated, selected, installed, and debugged. The next step is to evaluate the process critically and to optimize its performance based on that evaluation.

The following items should be examined;

- Mixing speed
- Mixing speed
- Heating and cooling rates
- Filter sizes (liquids)
- Screen size (solid)
- Drying temperature
- Drying time

Knowledge of the effect of these important process parameters on in - process and finished product quality is the basis for process optimization and validation.

Preparation of master manufacturing procedure

It includes

- The chemical weigh sheet. It should clearly identify the chemicals required in a batch and present the quantities and the order in which they will be used.
- The sampling directions.
- In process and finished product specification.
- Manufacturing directions should be in a language understandable by the operator termed as SOP's.
- Batch record directions should include specifications for addition rates, mixing times, mixing speed, heating and cooling rates, temperature.
- Proper documentation should be carried out.

GMP Consideration
GMP items that should be part of scale up are;

- Equipment qualification
- Process validation
- Regularly schedule preventative maintenance
- Regularly process review and revalidation
- Relevant written standard operating procedure
- The use of competent technically qualified personnel
- Adequate provisions for training of personnel
- A well defined technology transfer system
- Validated cleaning procedure.

Transfer of Analytic Method to Quality Assurance
Analytical methods developed in research must be transferred to QA department.

Transfer process include
- Review the process to make sure that proper analytical instrument is available.
- Personnel should be trained to perform the test.
- Reliability of the test should be checked.

- At last assay procedure should b reviewed before transfer.

Pilot plant design for tablet:
In scaling up the manufacturing of tablet from experimental laboratory batch sizes to intermediate and large scale production, each stage of the operation must be carefully considered. The following are the typical unit operations involved in production of solid dosage forms.

Material handling
in the laboratory materials are simply scooped, dumped, or poured by hand. These may also work in small sized production operations, but in intermediate and large scale operations, mechanical means of handling these materials often become necessary. If a system is used to transfer material for more than one product step must be taken for prevent cross contamination. Any material handling system must be delivered the accurate amount of the ingredient to the destination. Any type of system is selected also depend on the characteristics of the materials.

Dry blending
Powder to be used for encapsulation or to be granulated must be well blended to ensure good drug distribution. Inadequate blending at these stages could result in discrete portion of the batch being either high or low potency. Steps should also be take to ensure that all the ingredients are free of lumps and agglomerates.

The equipment used for blending are
- V - blender
- Double cone blender
- Slant cone blender

Scale up considerations
- Time of blending
- Blender loading
- Size of blender

Granulation
The most common reasons given to justify granulation are
- To import good flow properties to material
- To increase the apparent density of the powder
- To change the particle size distribution
- Uniform dispersion of active ingredient

Traditionally, wet granulation has been carried out using
- Signs blade mixer
- heavy - duty planetary mixer

Wet granulation can also be prepared using tumble blenders equipment with high speed chopper blades. More recently, use of multifunctional processors that are capable of performing all function required to prepare a finished granulation, such as dry blending wet granulation drying sizing and lubrication in a continuous process in a single equipment.

Fluidized bed granulation
- Process inlet air temperature
- Atomization air pressure
- Air volume
- Liquid spray rate
- Nozzle position and number of spray heads
- Product and exhaust air temperature
- filter porosity
- cleaning frequency
- bowel frequency

Binders
Used in tablet formulation to make powder more compressible and produce tablet that are more resistant to breakage during handling. In some instances the binding agent impart viscosity to the granulating solution so that transfer of fluid become difficult. This problem can be overcome by adding some or all binding agent in the dry powder prior to granulation. Some granulation, when prepared in production sized equipment, take on dough like consistency and may have subdivided to a more granular and porous mass to facilitate drying. This can be accomplished by passing a wet mass through an oscillating type granulator with a suitably large screen or hammer mill with either a suitably large screen or no screen at all.

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

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

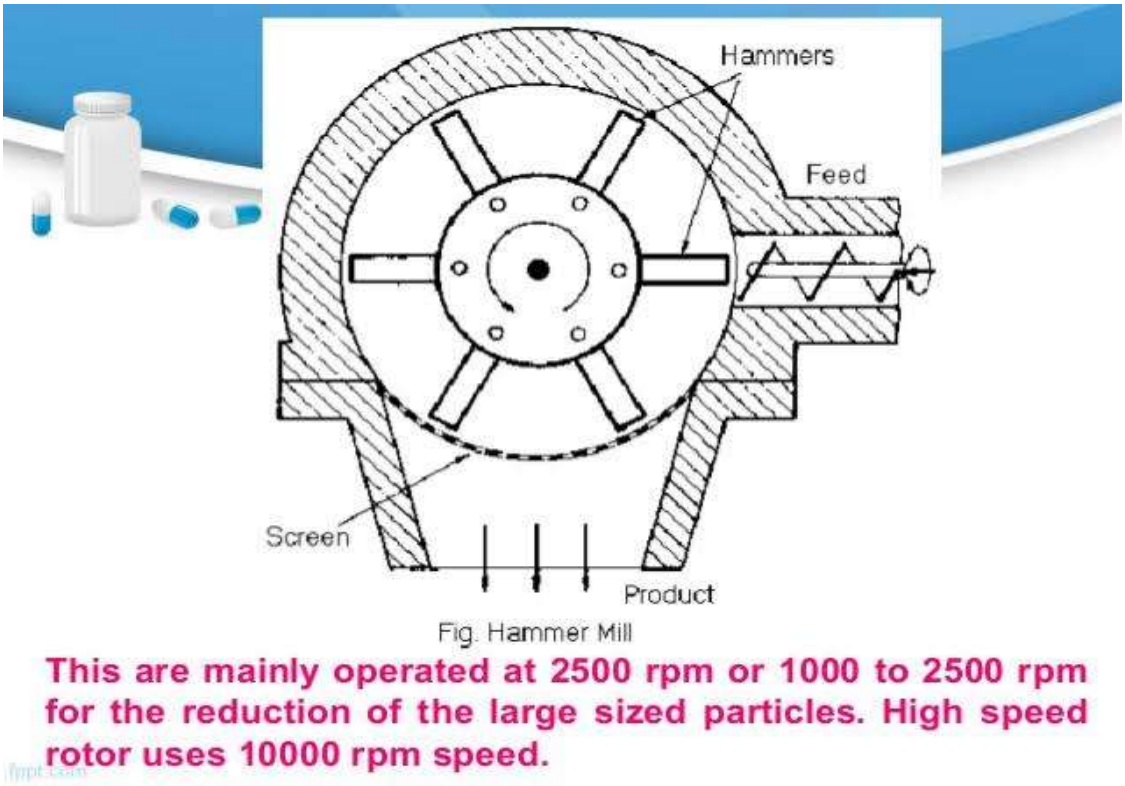


Figure 3: Hammer mill

Blending
Type of blending equipment often differs from that using in laboratory scale. In any blending operation, both segregation and mixing occur simultaneously are 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. In scale up of blending, following parameters should be considered;

- Blender loads
- Blender size
- Mixing speed
- Bulk density of bulk material
- Characteristics of material

Specialized granulation processors

Slugging (Dry granulation)
This is done on a tablet press designed for slugging, which operates at pressures of about 15tons, compared with a normal tablet press, which operates at pressure of 4 tons or less. 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. If an excessive amount of fine powder is generated during the milling operation the material must be screened & 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 in order to produce a granulation with the required tabulating 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 tobe 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. High speed 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.
- System should not cause segregation of coarse and fine particles, nor should it induce static charges.

- The die feed system must be able to fill the die cavities adequately in the short period of time that the die is passing under the feed frame.
- The smaller the tablet, the more difficult it is to get a uniform fill a high press speeds.
- For high - speed machines, induced die feed systems is necessary.
- These are available with a variety of feed paddles and with variable speed capabilities. So that optimum feed for every granulation can be obtained.
- Compression of the granulation usually occurs as a single event as the heads of the punches pass over the lower and under the upper pressure rollers.
- This cause the punches to the penetrate the die to a preset depth, compacting the granulation to the thickness of the gap set between the punches.
- During compression, the granulation is compacted to form tablet, bonds within compressible material must be formed which results in sticking.
- High levels of lubricant or over blending can result in a soft tablet, decrease in wet ability of the powder and an extension of the dissolution time.
- 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 center in order to relieve pressure during ejection.

The machine used are high speed rotary machine, multi rotary machine, double rotary machine, upper punch and lower punch machine, and single rotary machine

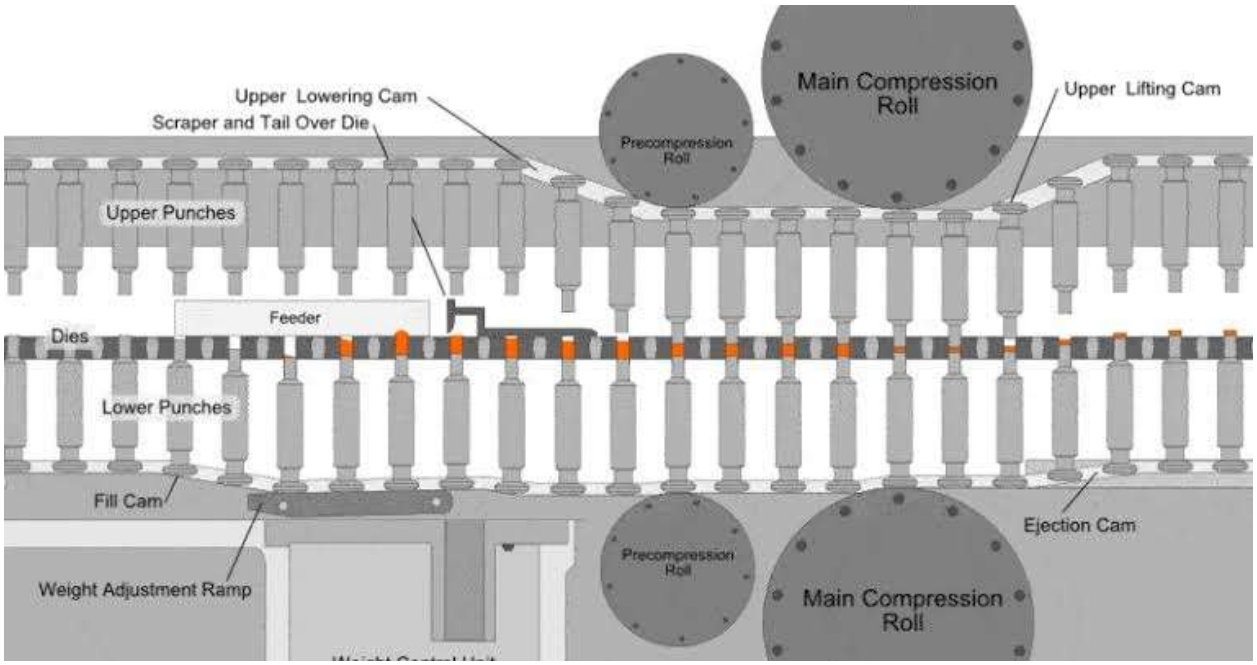


Figure 4: Compression process

3. Conclusion

From the above finding it was concluded that the Pilot scale up techniques is one of the important tool for the optimization of large scale production. The parameters such as Granulation feed rate, compression and presence of lubricant and blending will play a important, role the development of pilot scale up techniques to large scale production solid dosage form.

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