INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

RECENT ADVANCES IN PILOT PLANT SCALE UP TECHNIQUES - A Review

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ARTICLE INFO

Article history
Received 21/04/2018
Available online
12/05/2018

Keywords
Pilot Plant Technique,
Solid Dosage Form,
Tablets,
Compression.

ABSTRACT

Pilot scale up techniques for solid dosage form will provide guide line forthe manufacture of large scale process and this will play a pivotal role inlarge scale manufacturing. The parameters such as granulation feed rate,compression parameters, temperature and rate of drying will have acritical role in development of any solid dosage form.Pilot plant is a relative term in the sense that pilot plants are typically smaller than full-scale production plants, but are built in a range of sizes. Also, as pilot plants are intended for learning, they typically are more flexible, possibly at the expense of economy. Some pilot plants are built in laboratories using stock lab equipment, The past two decades particular have witnessed amazing inventions and innovations in pharmaceutical research, resulting in the ability to produce new drugs faster than even before. The new drug applications (NDAs) and abbreviated new drug applications (ANDA) are all-time high. The preparation of several clinical batches in the pilot plant provides its personnel with the opportunity to perfect and validate the process.

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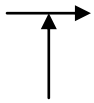
*Please cite this article in press as **AvinashV. Dhobale** et al. Recent Advances in Pilot Plant Scale up Techniques - A Review. Indo American Journal of Pharmaceutical Research.2018:8(04).*

INTRODUCTION

Pilot plant:

"Defined as a part of the pharmaceutical industry where a lab scale formula is transformed into a viable product by the development of liable practical procedure for manufacture."

R & D Production



Pilot Plant

A pilot plant is a pre-commercial production system that employs new production technology and/or produces small volumes of new technology-based products, mainly for the purpose of learning about the new technology. The knowledge obtained is then used for design of full-scale production systems and commercial products, as well as for identification of further research objectives and support of investment decisions. Other (non-technical) purposes include gaining public support for new technologies and questioning government regulations.Pilot plant studies must includes a close examination of formula to determine its ability to withstand batch-scale and process modifications; it must includes a review of range of relevant processing equipment also availability of raw materials meeting the specification of product and during the scale up efforts in the pilot plant production and process control are evaluated, validated and finalized.

Why conduct Pilot Plant Studies?

- A pilot plant allows investigation of a product and process on an intermediate scale before large y are committed to full-scale production.
- It is usually not possible to predict the effects of a many-fold increase in scale.
- It is not possible to design a large complex food processing plant from laboratory data alone with any degree of success.

A pilot plant can be used for

- Evaluating the results of laboratory studies and making product and process corrections and improvements.
- Producing small quantities of product for sensory, chemical, microbiological evaluations, limited market testing or furnishing samples to potential customers, shelf-live and storage stability studies.
- Determining possible salable by-products or waste stream requiring treatment before discharge.
- Providing data that can be used in making a decision on whether or not to proceed to a full-scale production process; and in the case of a positive decision, designing and constructing a full-size plant or modifying an existing plant.

Considerations in pilot plant development

- Kind and size – depends on goals; evaluating product and process; producing samples of product for evaluation; market testing or furnishing to potential customers.
- Location: near R&D facility? At an existing plant? Close liaison between R&D and pilot plant staff is essential.
- Labor requirements and costs: engineering staff, skilled operations and maintenance staff- pilot plant costs may exceed those of usual plant production costs. The pilot plant may be used for training personnel for a full- scale plant.

Objective

To try the process on a model of proposed plant before committing large sum of money on a production unit.

- Examination of the formula to determine it's ability to with stand Batch-scale and process modification.
- Evaluation and Validation for process and equipments
- To identify the critical features of the process
- Guidelines for production and process controls.
- To provide master manufacturing formula with instructions for manufacturing procedure.
- To avoid the scale-up problems.

Significance of Pilot Plant[3]

- Standardization of formulae.
- Review of range of relevant processing equipments.
- Optimization and control of production rate.
- Information on infrastructure of equipments during the scale up batches physical spacerequired.
- Identification of critical features to maintain quality of a product.
- Appropriate records and reports to support GMP.

Scale Up Process[4]

Scale-up is defined as the process of increasing the batch size. Scale-up of a process can also be viewed as a procedure for applying the same process to different output volumes. Batchsize enlargement does not always translate into a size increase of the processing volume. Inmixing applications, scale-up is indeed concerned with increasing the linear dimensions fromthe laboratory to the plant size. On the other hand, processes exist (e.g., tableting) for which"scale-up" simply means enlarging the output by increasing the speed. In moving from R&Dto production scale, it is sometimes essential to have an intermediate batch scale. This scalealso makes possible the production of enough product for clinical testing and samples for marketing. However, inserting an intermediate step between R&D and production scales doesnot in itself guarantee a smooth transition.

Pilot plants: Destined for development

Pilot plants are on the verge of an unprecedented evolution. Read about the 10 factors that'll impact the design, construction and operation of these next-generation units.

I have seen many changes in pilot plants over the course of my career, but I predict that we are on the verge of an unprecedented evolution of these units.

My crystal ball sees 10 key factors influencing next-generation pilot plants:

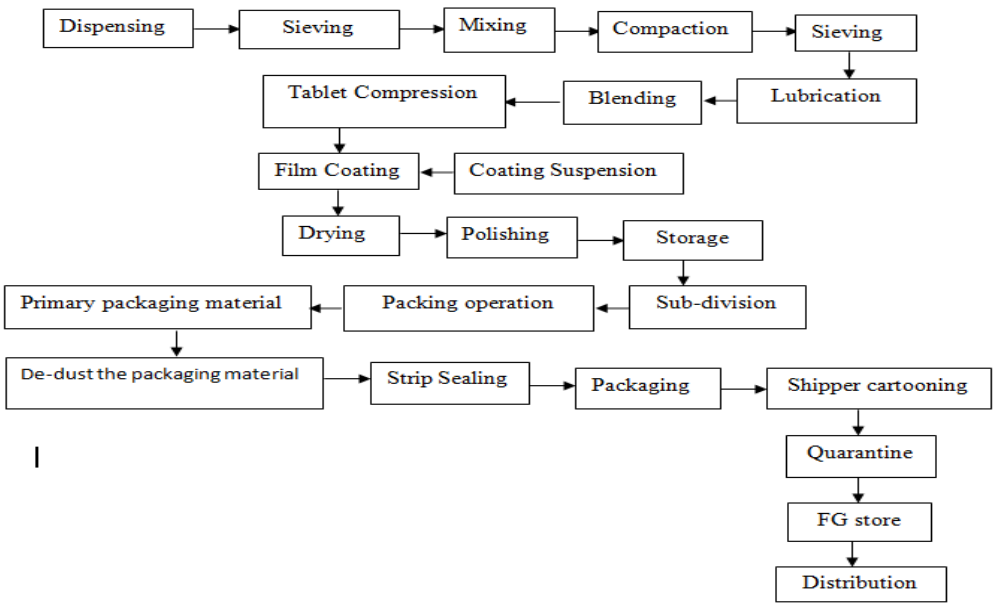
1. Outsourcing;
2. Automation;
3. Fugitive emissions,
4. Multiple trains; •
5. Online analytical capabilities;
6. Safety and control system interaction;
7. Wireless technology;
8. Instrument availability;
9. Instrument multi-functionality;

10 Unit size. Let's look at each of these and what they may spur

Pilot Plant Design for Tablets[1,2,5,6,7]

- The primary responsibility of the pilot plant staff is to ensure that the newly formulatedtablets developed by product development personnel will prove to be efficiently,economically, and consistently reproducible on a production scale.
- The design and construction of the pharmaceutical pilot plant for tablet developmentshould incorporate features necessary to facilitate maintenance and cleanliness.
- If possible, it should be located on the ground floor to expedite the delivery and shipmentof supplies.
- Each stage considered carefully from experimental lab batch size to intermediate andlarge scale production.
- Same process, same equipment but different performance when amount of materialincreased significantly.
- May involve a major process change that utilizes techniques and equipment that wereeither unavailable or unsuitable on a lab scale.

Layout ofpilot plant



Stages of Production of Tablets

- Material handling
- Dry blending
- Granulation
- Drying
- Reduction of particle size
- Blending
- Direct compression
- Slugging (dry granulation)

Material Handling System

`In the laboratory, materials are simply scooped or poured by hand, but in intermediate- orlarge-scale operations, handling of this materials often become necessary. If a system is usedto transfer materials for more than one product steps must be taken to prevent crosscontamination. Any material handling system must deliver the accurate amount of theingredient to the formulation. The More sophisticated methods of handling materials arevacuum loading systems, metering pumps, screw feed system. The types of the systemselected depend on the nature of the materials, e.g., density and static change.

Dry Blending

Inadequate blending at this stage could result in discrete portion of the batch being either highor low in potency. Steps should be taken to ensure that all the ingredients are free from lumpsand agglomerates. For these reasons, screening and/or milling of the ingredients usuallymakes the process more reliable and reproducible. There are various equipment used inblending process they are V-blender, double cone blender, Ribbon blender, Slant coneblender Bin blender, Orbiting screw blenders vertical and horizontal high intensity mixers.

The blending will be optimized by following parameters.

1. Time of blending.
2. Blender loading.
3. Size of blender

Granulation

Sigma blade mixer, Heavy-duty planetary mixer. More recently, the use of multifunctional“processors” that are capable of performing all functions required to prepare a finishedgranulation, such as dry blending, wet granulation, drying, sizing and lubrication in acontinuous process in a single equipment.

Drying

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

Reduction of Particle Size

First step in this process is to determine the particle size distribution of granulation using aseries of “stacked” sieves of decreasing mesh openings. Particle size reduction of the driedgranulation of production size batches can be carried out by passing all the material throughan oscillating granulator, a hammer mill, a mechanical sieving device, or in some cases, ascreening device. As part of the scale-up of a milling or sieving operation, the lubricants andglidants, in the laboratory are usually added directly to the final blend. This is done becausesome of these additives, especially magnesium stearate, tend to agglomerate when added inlarge quantities to the granulation in a blender.

Blending

Type of blending equipment often differs from that using in laboratory scale. In any blendingoperation, 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 ismore likely to occur when high-shear mixers with spiral screws or blades are used. When alow dose active ingredient is to be blended it may be sandwiched between two portions ofdirectly compressible excipients to avoid loss to the surface of the blender.

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. Slugsrange in diameter from 1 inch, for the more easily slugged material, to ¾ inch in diameter formaterials that are more difficult to compress and require more pressure per unit area to yieldsatisfactory compacts. If an excessive amount of fine powder is generated during the millingoperation 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 rollersthat compact the material at pressure of up to 10 tons per linear inch. Materials of very lowdensity require roller compaction to achieve a bulk density sufficient to allow encapsulationor compression. One of the best examples of this process is the densification of aluminumhydroxide. Pilot plant personnel should determine whether the final drug blend or the activeingredient could be more efficiently processed in this manner than by conventionalprocessing in order to produce a granulation with the required tabletting or encapsulationproperties**.**

Compression

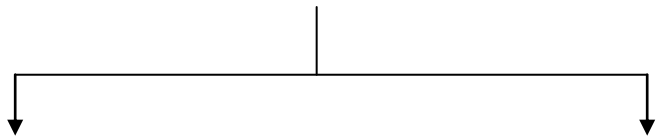
The ultimate test of a tablet formulation and granulation process is whether the granulationcan be compressed on a high-speed tablet press. When evaluating the compressioncharacteristics of a particular formulation, prolonged trial runs at press speeds equal to that tobe used in normal production should be tried, only then are potential problems such assticking to the punch surface, tablet hardness, capping, and weight variation detected. Highspeedtablet compression depends on the ability of the press to interact with granulation. Thefollowing parameters are optimized during pilot plant techniques of Granulation feed rate,Delivery system should not change the particle size distribution., System should not causesegregation of coarse and fine particles, nor it should induce static charges. The die feedsystem must be able to fill the die cavities adequately in the short period of time that the dieis passing under the feed frame. The smaller the tablet, the more difficult it is to get a uniformfill 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. Sothat optimum feed for every granulation can be obtained. Compression of the granulationusually occurs as a single event as the heads of the punches pass over the lower and under theupper pressure rollers. This cause the punches to thepenetrate the die to a preset depth,compacting the granulation to the thickness of the gap set between the punches. Duringcompression, the granulation is compacted to form tablet, bonds within compressible materialmust be formed which results in sticking. High level of lubricant or over blending can resultin 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 inchwider at the upper portion than at the center in order to relieve pressure during ejection. Themachine used are high speed rotary machine, multi rotary machine, double rotary machine,upper punch and lower punch machine ,and single rotary machined.

General considerations

Reporting Responsibility



R & D group with separate staffing

The formulator who developed the product can take into the production and can provide support even after transition into production has been completed

PERSONNEL REQUIREMENT

Scientists with experience in pilot plant operations as well as in actual production area are the most preferable. As they have to understand the intent of the formulator as well as understand the perspective of the production personnel.

The group should have some personnel with engineering knowledge as well as scale up also in volves engineering principles.

SPACE REQUIREMENTS

Administration and information process:

Adequate office and desk space should be provided for both scientist and technicians.

The space should be adjacent to the working area.

Physical testing area

This area should provide permanent bench top space for routinely used physical- testing equipment.

Storage Area

It should have two areas divided as approved and unapproved area for active ingredient as well as excipient.

Different areas should provided for the storage of the in-process materials, finished bulk products from the pilot-plant & materials from the experimental scale-up batches made in the production.

Storage area for the packing material should also be provided.

REVIEW OF THE FORMULA

A thorough review of the each aspect of formulation is important.The purpose of each ingredient and it's contribution to the final product manufactured on the small-scale laboratory equipment should be understood.

Then the effect of scale-up using equipment that may subject the product to stresses of different types and degrees can more readily be predicted, or recognized.

RAW MATERIALS

One purpose/responsibility of the pilot-plant is the approval & validation ofthe active ingredient &excipients raw materials. Raw materials used in the small scale production cannot necessarily be the representative for the large scale production

EQUIPMENT

The most economical and the simplest & efficient equipment which are capable of producing product within the proposed specifications are used. The size of the equipment should be such that the experimental trials run should be relevant to the production sized batches. If the equipment is too small the process developed will not scale up, Whereas if equipment is too big then the wastage of the expensive active ingredients.

7.PRODUCTION RATES

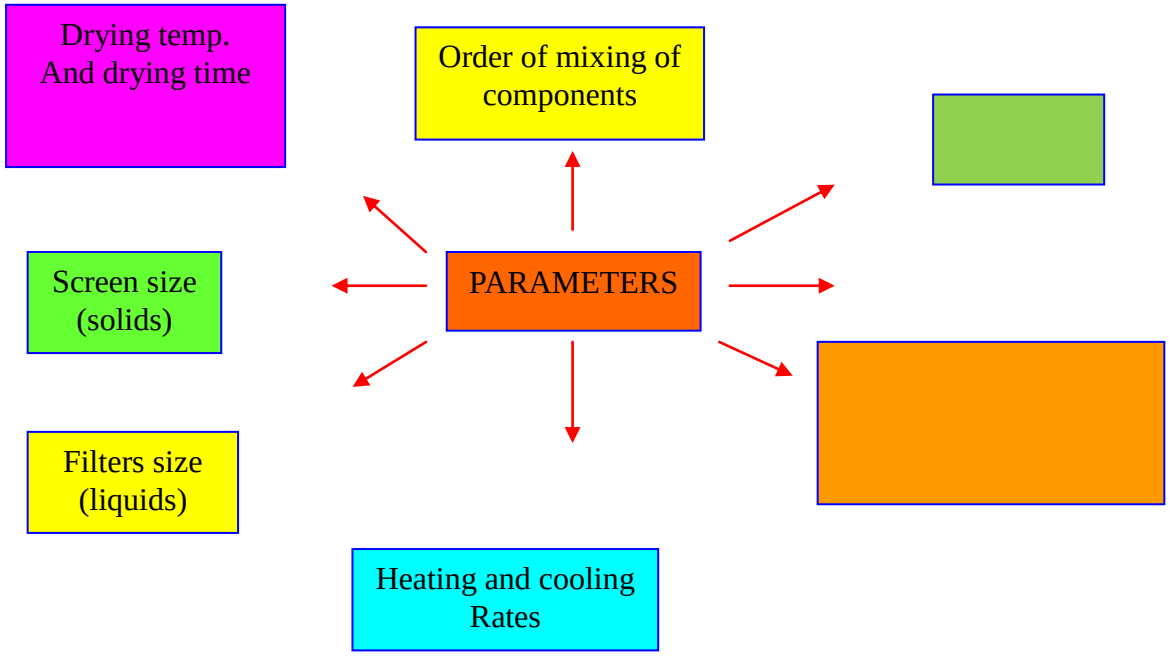
The immediate as well as the future market trends/requirements are considered while determining the production rates.

Why to carry out process evaluation?

The knowledge of the effects of various process parameters as few mentioned above form the basis for process optimization and validation

PROCESS EVALUATION

Parametrs Order of mixing of components Mixing speed Mixing time Rate of addition of granulating agents, solvents, solutions of drug etc. Heating and cooling Rates Screen size (solids) Drying temp. And drying time.



Master Manufacturing Procedures:-

The three important aspects:

1)Weight sheet

2)Processing directions

3)Manufacturing procedure

Master Manufacturing Procedures

- The weight sheet should clearly identify the chemicals required In a batch.
- To prevent confusion the names and identifying nos. for the ingredients should be used on batch records.
- The process directions should be precise and explicit.
- A manufacturing procedure should be written by the actual operator.

Various specifications like addition rates, mixing time, mixing speed, heating, and cooling rates, temperature, storing of the finished product samples should be mentioned in the batch record directions.

PRODUCT STABILITY AND UNIFORMITY

The primary objective of the pilot plant is the physical as well as chemical stability of the products.
Hence each pilot batch representing the final formulation and manufacturing procedure should be studied for stability.
Stability studies should be carried out in finished packages as well.

GMP Consideration

- Equipment qualification
- Process validation
- Regularly process review & revalidation
- Relevant written standard operating procedures
- The use of competent technically qualified personnel
- A well-defined technology transfer system
- Validated cleaning procedures.
- An orderly arrangement of equipment so as to ease material flow.
- Equipment qualification.

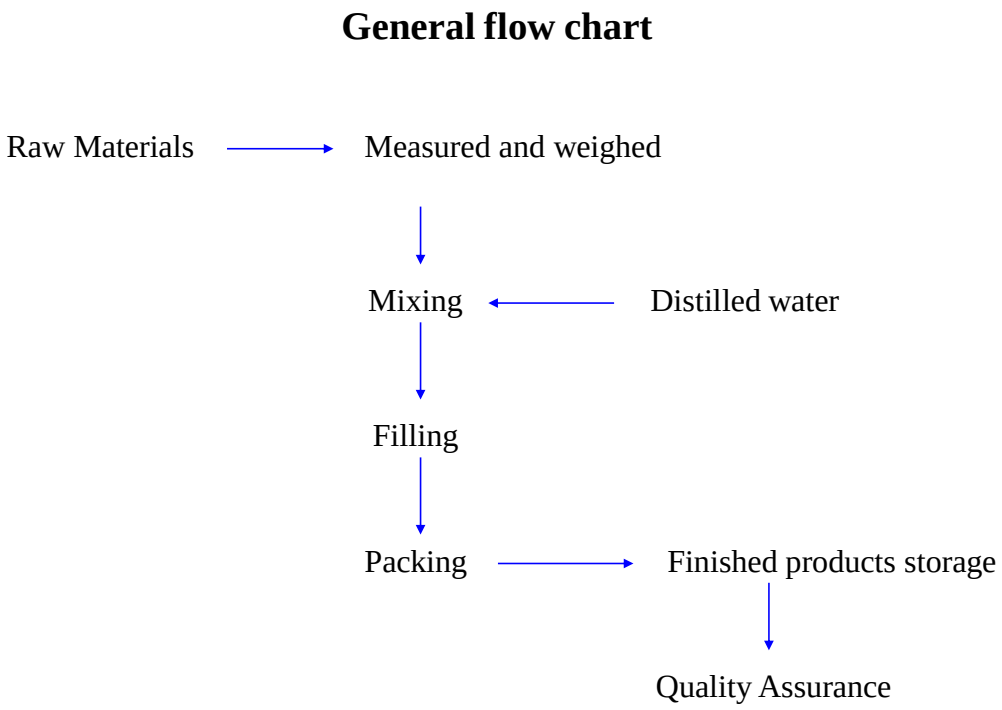
Advantages

- Members of the production and quality control divisions can readily observe scale up runs.
- Supplies of excipients & drugs, cleared by the quality control division, can be drawn from the more spacious areas provided to the production division.
- Access to engineering department personnel is provided for equipment installation, maintenance and repair.

Disadvantages

- The frequency of direct interaction of the formulator with the production personnel in the manufacturing area will be reduced.
- Anyproblemin manufacturing will be directed towards it'sown pilot-plant personnel's**.**

General flow chart



- General stabilityconsiderationfor general guidance on conducting stability studies, see the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.
- A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol.
- Production batches, and to report the results in subsequent annual reports.

CONCLUSION

From the above finding it was concluded that the Pilot scale up techniques is one of theimportant tool for the optimization of large scale production. The parameters such asGranulation feed rate, compression and presence of lubricant and blending will play aimportant, role the development of pilot scale up techniques to large scale production soliddosage form.

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