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A comprehensive review on pilot plant scale up and platform technology

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Abstract

The pharmaceutical business uses pilot plant scale-up strategies to create reliable manufacturing procedures and turn lab-scale formulas into commercial products. The place called Pilot is where the five elements Material, Man, Method, and Machine are combined to manufacture things. A tiny, basic lab scale formula will be tested on a replica of the intended plant in the pilot plant before spending a significant amount of money on a production unit. Scaling up a pilot plant provides information on formula examination, reviewing the range of pertinent processing equipment, understanding raw material specifications, production rate, and physical space requirements. It can hold accurate documentation and reports for analysis in support of the GMP procedure. This review research discusses the factors for solids, liquids, and semisolids for scaling up pilot plants. The primary goal of a pilot plant is to "identify errors on a small scale and generate revenue on a large scale."

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INTRODUCTION

Pilot plant: This sector of the pharmaceutical industry is defined as the process of developing a reliable, feasible manufacturing process from a lab scale formula to a marketable product.

Scale up: Using the information gathered from the pilot plant model, it is the art of creating a prototype.

In the process of finding novel drugs and developing new medical products, pilot plant and scale-up approaches are both crucial and restrictive.

The pace of medication development and discovery has accelerated dramatically [1].

What is pilot scale and scale up:

Pilot scale: it is an intermediate batch scale where manufactures drug product by a procedure fully representative of and affect to that manufacturing scale.

Scale up: It is next to pilot scale and the process of increasing the batch size and the sample process to different output volumes.

Objectives of pilot plant scale up:

1. To try the process on a pattern of proposed plant before perform to large amount of money on a production unit.
2. Investigation of the formula to determine its ability to tolerate batch scale and process modification.
3. Process and equipment validation as well as assessment
4. To identify essential characteristic of the process.
5. Production and process control guidelines.
6. To give manufacturing technique guidance to master manufacturing.
7. To prevent issues with scaling up [2].

Significance of pilot plant studies:

1. These studies are effective in standardizing formulations.
2. These studies are helpful in analyzing different important manufacturing equipment.
3. These studies helpful in improving and regulating production rate.
4. These studies give information about equipment construction used during the scale up batches.
5. These studies recognize the specific features of a product required to maintain its quality.

These studies are helpful in maintaining suitable records and reports to support good manufacturing practice [3].

General considerations for pilot plant scale up:

Pilot plant studies should involve a close investigation of formula to find its ability to resist batch scale and process modifications.

1. Personal requirements:

- It is strongly advised that scientists have both real production area and pilot plant operations experience.
- As they have to understand the purpose of the formulated as well as understand the aspect of the production personnel.
- The group must have some person with engineering knowledge as well as scale up also involves engineering principles.

2. Space requirements [4]:

The four areas that make up the needed space in the pilot plant are as follows:

a. Information and administrative procedures

b. Area for physical examination

c. Floor space for standard equipment

d. Area for storage

a) The information and administration procedure:

Both scientists and technicians should be provided with adequate office and workstation space. The working area should be close to the space.

b) Physical testing area:

The area should provide permanent batch top space for regularly used physical testing equipment.

c) Standard equipment floor space:

The portion of the pilot plant containing the machinery needed to manufacture every kind of dosage form. In order to assess the consequences of scaling up research formulations and processes, wide-ranging, intermediate-sized manufacturing equipment is required. If at all possible, the equipment should be transferable so that it can be kept in the tiny store room after usage. Room for washing the equipment that should be supplied.

d) Storage area:

It supposed to have two areas divided as approved and unapproved area for active ingredients as well as excipients.

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

Storage area for the packaging materials should also be provided.

3. Review of the formula [5]:

It's critical to go over each part of the formulation. Understanding an ingredient's function and how it affects the finished product produced using small-scale laboratory equipment is important. Consequently, it will be easier to forecast or identify the impact of scaling up employing machinery that might expose the product to emphasis of various kinds and degrees.

4. Raw materials:

The pilot plant's approval and validation of the active components, excipients, and raw materials is one of its goals or duties. The raw materials utilised in small-scale production do not have to be the same as those utilised in large-scale production.

5. Equipment:

The equipment that can produce a product within the suggested criteria is the most practical, straightforward, and effective machinery.

The apparatus dimensions must align with the production-sized batches for the experimentation to be conducted.

The developed process won't scale up if the equipment isn't up to the task.

Conversely, expensive active substances may be wasted if the apparatus is too big.

6. Production rates [6]:

While determining the production rates, both the current and future market requirements are taken into account.

Process evaluation:

The product scale-up programme has reached the stage when a recommended manufacturing method and chosen, installed, and assessed production equipment are in place. The process will then be subjected to a critical examination, and its performance will be optimised accordingly. There are some requirements use in evaluation, they are [7]:

a. Heating and cooling rates

b. Filter sizes(liquids)

c. Screen sizes(solids)

d. Drying temperature

e. Drying time

7. Master Manufacturing Procedures (MPP):

There are three important forms in master manufacturing procedure they are:

a) Weight sheet
b) Processing directions
c) Manufacturing procedure

a. Weight sheet:

To avoid confusion, the important substances in a batch should be identified with clarity, and the ingredient numbers should be utilised on batch records.

b. Processing directions:

The processing guidelines supposed to be precise and explicit.

c. Manufacturing procedure:

The operator themselves ought to write it.

Tests, mixing duration, mixing speed, heating and cooling rates, and other variables.

8. Product stability:

The stability of the products' chemical and physical properties is the main goal of the pilot plant.

It is also necessary to examine the stability of each pilot batch that represents the final formulation and production process.

It is important to do stability studies on completed packages as well.

9. Reporting stability:

Research and development team with individual staffing.

The product's formulator can continue to develop and support the product even after the transition to manufacturing were completed.

Advantages of pilot plant:

Production and quality control personnel are accustomed to following scale-up runs with ease. Excipient and medication supplies verified by the quality control departments.

An equipment installation, maintenance, and repair procedure is started for engineering department personnel [8].

Disadvantages of pilot plant:

There will be less direct communication between the formulator and the manufacturing process on a regular basis.

Its own pilot plant will be used to identify any manufacturing issues.

Pilot plant design for solids (tablets)

Ensuring that the freshly compounded tablets generated by product development meet quality standards is the main duty of the pilot crew. Employees will prove to be productive and economical at a large scale.

Features that make cleaning and maintenance easier should be incorporated into the pharmaceutical pilot's design and construction.

To facilitate cleaning, the varied operating area (OA) should have floor drains. If at all feasible, the OA should be situated on the ground floor to expedite supply delivery and transportation.

Enamel cement coat over concrete is intended for the walls in the processing and packing facilities.

The pharmaceutical pilot plant's equipment needs to match what was used in production.

The various steps that are involved in the pilot plant for solid dosage form are [9-12]:

1) Material handling system
2) Dry blending
3) Granulations
4) binders
5) drying
6) reduction of particle size
7) blending

1. Material handling system:

In a laboratory, materials are simply poured by hand; nevertheless, managing these materials becomes necessary in intermediate and large-scale procedures.

To avoid class contamination, precautions must be made if a system is used to handling transfer materials for many products. Any materials handling system selected to must be deliver the proper amount of ingredients to the destination.

The type of system selected additionally depends upon the properties of the materials.

Screw feed systems and vacuum loading systems are examples of more advanced material handling techniques.

2. Dry blending:

To ensure optimal medication distribution, powders intended for granulation or encapsulation must also be thoroughly blended. A percentage of the batch that is either high or low in potency could arise from improper mixing at this point. It is also necessary to take precautions to ensure that there are no lumps or agglomerates in any of the ingredients.

The equipment used for blending are:

i. v-blender
ii. double cone blender
iii. ribbon blender
iv. slant cone blender
v. bin blender.

Scale up considerations:

i. Time of blending
ii. Blender loading
iii. Size of blender.

3. Granulation:

Granulation in pilot plant of solid due to these reasons:

- To import good flow properties to the materials.
- To increase the unique density of the powders.
- To modify the particle size distribution.
- To achieve uniform dispersion of active substances.

Generally wet granulation has been carried out using:

- Sigma blade mixer
- Heavy duty planetary mixer

- Wet granulation may also be prepared by using tumble blenders with high chopper blades.

4. Binders:

Binders are used in tablet formulation to build tablets that are more compressible and less likely to break during handling. In other cases, the binding agent adds viscosity to the granulating solution, making fluid transmission problematic.

This issue can be avoided by including some or all binding agents into the dry powder prior to granulation. This could be performed by putting the wet through an oscillating type granulator with a sufficiently large screen or a hammer mill.

5. Drying:

The most common traditional way of drying granulation is to continuously circulate the hot air oven, which is heated either by steam or electricity.

Airflow, air temperature, and granulation depth on the trays are critical factors to consider while scaling up an oven drying operation.

If the granulation bed is too deep or too dense, the drying process will be inefficient, and if soluble dyes are used, the dye will migrate to the surface of the granules.

Drying times at defined temperatures and airflow rates are expected to be established for each product as well as specific oven load.

6. Reduction of particle size:

The particle size distribution may be implicated in compression parameters such as flowability, compressibility, uniformity of tablet weight, content uniformity, and tablet hardness.

The first step is to determine the particle size distribution of granulation using sieves with decreasing mesh apertures.

Particle size reduction of dry granulation of production size batches can be accomplished by putting the material through an oscillating granulator, hammer mill, or mechanical sieve device.

The lubricant and glidant, which are typically added to the final mix in the laboratory, are scaled up as part of a milling or sieving operation.

7. Blending:

Blending equipment is typically different from that used in laboratories.

Both segregation and mixing occur concurrently in each blending procedure, and are determined by particle size, form hardness, and the dynamics of the mixing motion.

To avoid damage to the surface of the blender, a low dose active component can be put between two pieces of immediately compressible excipient.

The following parameters should be considered when scaling up blending:

- Blender loads
- Blender size
- Mixing speeds
- Mixing times
- Bulk density of the raw material
- Characteristics of material.

Specialized granulation procedures [13-14]:

The other various specialized granulation procedures can be described by four methods.They are:

1) Slugging (dry granulation)
2) Dry compaction
3) Compression
4) Tablet coating

1) Slugging (dry granulation):

A mixture of dry powder with inadequate flow or compression characteristics, making it unable to compress it right away.

The tablet press used for this is made specifically for slugging, and it operates at a pressure of roughly 75 tonnes, as opposed to a standard tablet press that runs at 4 tonnes or less.

If the milling process produces an excessive amount of fine powder, the material needs to be screened, and the fines need to be recycled using the slugging process.

2) Dry compaction:

Powders can also be granulated by dry compaction, which involves moving the powder

between two rollers that compress the material at up to 10 tonnes per linear inch of pressure.

Roller compaction is necessary to provide a bulk density high enough for encapsulation or compression of materials with extremely low densities.

In order to create a granulation with the necessary quantity, pilot plant staff should determine whether the final medicine mix or active component could be processed more effectively in this way than through traditional processing.

3) Compression:

Is it possible to compress the granulation using a high-speed tablet press? This is the ultimate test of tablet formulation and granulation technique.

The tablet process carries out the following tasks during compression:

- filling the empty dye cavity with granulation
- precompressing the granules
- compressing the granules

Long trail runs at press speeds comparable to those used in regular production should be attempted when assessing the compression characteristics of a certain formulation. When issues with adhesion to the punch surface, tablet hardness, capping, and weight fluctuation are identified.

Following parameters to be considered during compression:

- The granulation feed rate, delivery mechanism, and particle size distribution should not be altered.
- Neither the system's induction of static charge nor the separation of fine and coarse particles should occur.

4) Tablet coating:

Sugar coating, which is done in traditional coating pans, has changed significantly due to recent advancements in coating technology, including the use of aqueous film coating.

A unique formulation of the tablet core and coating solution may be required for tablet cores made of naturally hydrophobic materials when film coating with an aqueous system.

In a small lab coating pan, a film coating solution might have been discovered to function well with a specific tablet, but it might be completely inappropriate for use on a large production scale.

Pilot plant design for liquid orals

At room temperature, the pourable medication product's physical form conforms to its container and displays Newtonian or pseudoplastic flow action.

Solutions or dispersion systems may be used for liquid dosage forms. Two or more phases, with one spread in another, are present in a dispersed system [15–17].

Steps of liquid manufacturing process:

i. Planning of material requirements

ii. Liquid preparation

iii. Filling and packing

iv. Quality assurance

Crucial elements of liquid manufacturing:

Heating, ventilation, and air control systems are essential components of the physical plant used in liquid manufacturing.

It is necessary to take into account the impact of processing durations at suboptimal temperatures on the physical or chemical stability of inputs and products.

Pilot plant design for solution:

Parameters to be considered as:

- Tank size
- Impeller type
- Rational speed of the impeller
- Number of impellers
- Mixing capacity of impeller
- Clearence among impeller blades and side of tank
- Height of the packed volume in the tank
- Filtration equipment
- Transfer system.

Pilot plant design for suspensions:

- Parameters to be considered as:

Table 1 Formulation aspects in Solutions

S.No	Purpose	Agent
1	Protecting API	Buffers, antioxidants, preservatives
2	Sustaining the appearance	colorings, stabilizers, co- solvents antimicrobial preservatives
3	Taste/smell mask	Sweeteners and flavoring agents

Table 2 Formulation aspects in Suspensions

S.No	Purpose	Agent
1	Facilitating the vehicle's and API's connection	Wetting agents and salt forming agents
2	Protecting the API	Buffers, polymers, antioxidants
3	Sustaining the suspension appearance	Colorings, suspending agents, flocculating agents
4	Reducing the unpleasant flavour	Sweeteners as well as flavoring agents

Table 3 Formulation aspects in Emulsions

S.No	Purpose	Agent
1	Particle size	Solid particles, droplet particles
2	Protecting the API	Buffers, antioxidants, polymers
3	Maintaining the appearance	Colorings, emulsifying agent, gelling agent
4	Taste/smell masking	Sweeteners and flavoring agents

- The distribution and addition of substances that suspend
- Hydration or wetting agent
- The temperature and duration required for suspending agents to hydrate
- Mixing speeds
- Selection of equipment according to batch size
- Variable for entrapment
- Mesh size.

Pilot plant design for emulsions:

Parameters to be considered as:

- Temperature
- Mixing equipment
- Phase viscosities
- Phase densities
- Homogenizing equipment
- In process of final product filters
- Screens, pumps and filling equipment phase volumes

Equipment used [18]:

I. Mixer
II. Homogenizer
III. Filtration assembly
IV. Botting assembly

Quality assurance:

- Dissolution of drugs in solution
- Potency of drugs in suspension
- Temperature uniformity in emulsions
- Microbiological control
- Product uniformity
- Final volume
- Stability

Pilot plant design to semi solid dosage form

Semisolid dosage forms typically have complex structural components and intricate formulas. They are often formed of two phases, water and oil, one of which is allocated as a scattered (internal) phase and the other as a continuous (external).

The active component disintegrates in one phase most of the time, but occasionally the medication is not completely soluble in the system and disperses in one or both phases, resulting in the development of a three-phase system.

Parameters:

1) The order in which the solutes and solvent are combined usually makes little difference for a satisfactory solution.
2) For dispersed formulations, it is impossible to say as the dispersed matter can spread differently depending on the phase in which a particulate material is added.
3) The beginning of a normal manufacturing process, the division of a one-phase system into two phases, and the addition of the active ingredient are often the most important points.
4) At any temperature that the product may be exposed to, it is especially crucial for solutes supplied to the formulation at a concentration that is either close to or greater than their solubility.
5) Changes in the manufacturing process can occur; both of these occurrences have a tendency to be crucial for the final product's qualities.
6) This is especially true for any procedure (like homogenization) that aims to promote dispersion by decreasing droplet or particle size.
7) Before packaging, the final bulk formulation must be developed; this should be especially covered in process validation studies [19].

Pilot plant operation:

Validation:

1. Design specification.
2. Installation qualification.
3. Compliance with cGMP and FDA standards.

Training:

1. Safety and environment responsibility.
2. Compliance with GMP.
3. Compliance with SOPs.

Engineering Support:

1. Design of facility.
2. Co-ordination scheduling.
3. Construction of facility.

Maintenance and Calibration:

1. To provide the purity and equipment stability and research.
2. To meet cGMP norms.

Computerized System:

1. Material control
2. Labelling (GMP-GLP)
3. Orders (FIFO)

Process and Manufacturing Activities:

1. Research on process development and simulation.
2. Technology assessing transfer and scale-up.
3. Medical supply and production.

Quality Assurance [20]:

1. Pilot plant auditing.
2. Confirmation and endorsement of component suppliers.
3. Examining batch records for clinical supplies, including approval and management.
4. Market research and raw material distribution.
5. Clinical supply release.
6. Disseminating standard operating procedures (SOPS) and maintaining the facility.
7. Evaluation and validation approval.
8. The paperwork for engineering.

Quality Control:

1. Release testing of the completed item.
2. Microbiological, chemical, and physical examination of completed clinical items, as well as ingredients needed for supplies.
3. Conducting validation and revalidation tests.
4. Process testing quality control through technology transfer and scale-up development.

1. Plant [21]: In order to manufacture goods, the five Ms—material, labour, machinery, and money—come together in this location.

1. For the past 25–30 years, pharmaceutical research has been conducted in an advanced way.
2. Last 25-30-year pharmaceutical researches functioning an advanced manner.
3. Have exhibited remarkable invention and innovation in pharmaceutical field.

4. New drug application (NDA) and abbreviated new drug application (ANDA) are all time high.
5. Researchers are influenced to approve new processes and technology.
6. Successful completion of the bioequivalency study and clinical testing depends on scale-up batches.
7. Scaling up pilot plants is one of the most important phases of developing a product.

Overview of the platform technologies

Platform technologies are an intended helpful instrument to improve the effectiveness and calibre of pharma product development.

The fundamental concept is that a platform in combination with a risk-based approach, is the most systematic method to affect previous information for a given new molecule.

The technology has recognizable and differentiating competitive advantages.

It can considerably improve the bioavailability of complex molecule due to its submicrometric size and adhesive systems.

It is also adaptable, incorporating a wide variety of active principles and it's systems can be modified to achieve desired properties.

Moreover, the technique is highly adaptable and breakthrough, containing crucial elements like [22–23]:

The active components' solubility and chemical consistency.

It is possible to attain high drug loadings.

Scalability and developed industrial process.

Solvent-free, straightforward, and stable technologies.

Reformulated medications close to their patent expiration. Premature drug development.

A new route of administration for a range of molecules.

The following are some advantages of platform technology:

- Reduction in process development expenses, time, and activities.
- Diminished rates of failure.
- One can carry out risk evaluations.
- Document simplicity.
- Product performance consistency.
- Explanation of technology transfer operations (from research and development to manufacturing facilities).
- Diminished workload for individual training.

Designing of platform technology:

The primary phase is to identify future market demand that the technology can handle.

Then set up the central building blocks that can be implemented over to the new application.

After identifying the central platform technologies, determine what has to change over the platform to extend into new application.

Where possible, product platform should be designed in a modular manner to take full advantage of platform benefits.

Determine and design the platform presentation such that it meets the recognized future application needs.

Application of platform technology [24-25]:

1. Medical devices:

Medical device platform development is highly applicable to medical devices.

Medical device companies facing many of the same difficulties of new product development as other industries but the medical device industry is for the contested with regulatory barriers as part of new product development.

Future product course increase benefit from interchangeable platform that have already gone through regulatory analysis such as product safety testing.

Platform provides next-generation product development acceleration and reduced development time risk and cost modular platform that are divided across multiple product lines may also benefit from economy of scale.

2. Drug delivery system:

Drug delivery system companies like CIPLA has made a planned investment in common platform technologies to improve the capabilities of the

medication delivery system, such as combination products and sustained release.

These technologies improve the targeted therapy method's efficacy and safety for drugs.

The goal of the master plan is to create unique products that outperform the main drawbacks of traditional drug delivery methods and enhance already existing products.

a) Nanotechnology:

The use of nanotechnology in the development of targeted treatments for diseases like cancer has gained acceptance. It involves utilizing nano-sized particle to deliver drug to specific type of cell such as cancer cell.

The particle is engineer so that they are attracted to diseased cell which allow direct treatment of those cells.

The purpose is to prevent undesirable toxicity due to while distribution improve patient compliance and does supply beneficial clinical outcomes.

b) Microsphere:

Microsphere technology is used to develop important formulations for targeted delivery.

This technology is used for a site is specific action to eliminate trouble of repeated injections and to decrease toxic side effects.

c) Liposomes:

Liposome technology is different method used to enhance the delivery of drugs.

Liposome offer excellent opportunity to selectively target drugs which is expected to improve the pharmacokinetic parameters to pharmacological effect and to reduce the toxicity of the drugs.

d) Hot melt extrusion:

Solid molecular dispersion can be produced using hot melt extrusion facilities, which have significant advantages over solvent-based processes like co-precipitation and spray.

This method is being used for targeted, customised, and sustained medication delivery.

This technique is being applied to tablet implants and topical delivery systems, which include transdermal patches and topical liposome formulations.

e) Sustained release formulations:

The once-daily tablet distribution method of the osmotic controlled release oral delivery system (OROS) has been modified.

By delivering the drug in several therapeutic locations using osmotic pressure, this cutting-edge technique can improve safety by achieving a uniform drug action, lowering dose frequency, and improving drug concentration safety.

f) Orally disintegrating tablet:

Orally disintegrating tablet disintegrates rapidly when placed upon the tongue and assure faster onset of action.

Utilising this technology, a variety of compounds are extended to improve patient compliance and convenience.

g) Sprinkles:

Sprinkles are original oral granule formulation.

These are specially for pediatric patient. They can be added to a child's meal preparation; the drug's appetising formulation takes care of the complaints.

A fundamental challenge in pediatric therapy, this technology was used to generate anti-HIV therapy for children.

CONCLUSION

The process of finding novel drugs and developing new pharmaceutical goods requires the use of both pilot plant and scale-up procedures. When large sums of money are invested in full-scale manufacturing, a product and process can be tested on a smaller scale using a pilot plant. The formula's resistance to batch scale and process modification is examined in the pilot plant. Additionally, it provides specifics regarding dose forms, including the varieties of solid, liquid, and semisolid dosages, the equipment needed to prepare them, and the architecture of the pilot plant. SUPAC guidelines play an essential role in maintaining the quality, safety and efficacy of a pharmaceutical product. It reduces the time of manufacturing, improve yield and reduce cost.

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