UNIT –I PILOT PLANT SCALE UP TECHNIQUES

POINTS TO BE COVERED IN THIS TOPIC

- INTRODUCTION
- GENERAL CONSIDERATIONS
- PILOT PLANT SCALE UP CONSIDERATIONS FOR SOLIDS
- LIQUID
- SEMI SOLIDS AND RELEVANT DOCUMENTATION
- SUPAC GUIDELINES
- INTRODUCTION TO PLATFORM TECHNOLOPGY

INTRODUCTION

- **PLANT** :- It is place were the **5 M' s like money** , material man, method and machine are brought together for the **manufacturing** of the products.
- **PILOT PLANT**:- It is the part of the **pharmaceutical industry** where a lab scale formula is transformed into a 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.

OBJECTIVE

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

GENERAL CONSIDERATIONS

1. Reporting responsibility

R and 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.

2. Personnel requirements

- **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 involves **engineering principles.**

3. Space Requirements

- **Administration and information** processing
- **Physical testing** area
- **Standard equipment** floor space
- **Storage area**

✓ **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.**

✓ **Standard pilot-plant equipment floor space**

- **Intermediate** – sized and full scale production equipment is essential in **evaluating** the effects of scale-up of **research formulations** and processes. Equipments used should be made portable where ever possible.
- So that after use it can be stored in the **small store room.**
- Space for **cleaning of the equipment** should be also provided.

✓ **Storage Area**

- **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.

4. Review of the formula

- 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.

5. Raw materials

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

6. 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.

8. Process Evaluation

- Order of mixing of components
- Mixing speed
- Mixing time
- Rate of addition of granulating agents
- Solvents, solutions of drug etc.
- Heating and cooling Rates

- Filters size (liquids)
- Screen size (solids)
- Drying temp and drying time

9. Master Manufacturing Procedures

- The three important aspects
  1. Weight sheet
  2. Processing directions
  3. Manufacturing procedure
- The weight sheet should clearly identify the chemicals required in a batch.
- 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.

10. 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.

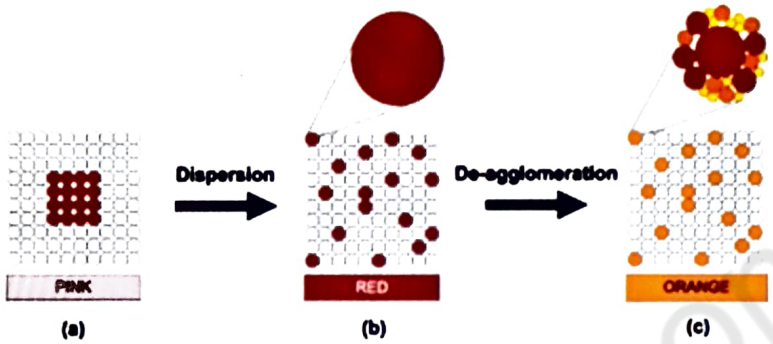
PILOT PLANT SCALE UP CONSIDERATIONS FOR SOLIDS

1. MATERIAL HANDLING SYSTEM

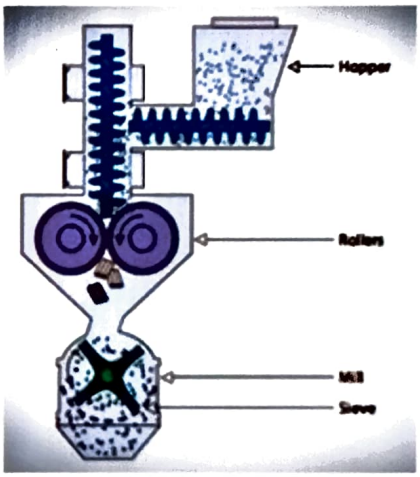
- In large-scale production, proper handling of materials is necessary.
- Accurate quantity of the ingredient should be delivered to the destination.
- Selection of the type of system depends on the characteristics of the materials.
- Different material handling systems are vacuum loading systems, devices to lift and tilt drums, meeting pumps, screw feed systems.

2. DRY BLENDING

- **Powders** should be used for **encapsulation** or to be granulated prior to **tableting** must be well blend to ensure **good drug distribution.**
- **Inadequate blending** could result in drug content uniformity variation, especially when the tablet or capsule is small & the **drug concentration** is relatively low.
- **Ingredients** should be **lumps free**, otherwise it could cause flow problems.



3. GRANULATIONS REASONS



- To **improve the flow properties.**
- To **increase the apparent density** of the powder.
- To change the **particle size distribution** so that the binding properties on **compaction can be improved.**

✓ **Types :-**

a) Wet Granulation

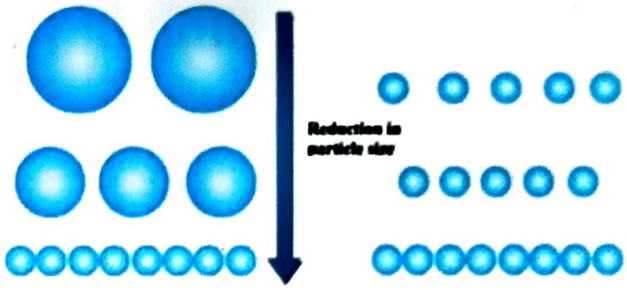
b) Dry Granulation

c) Direct Compression Method

4. 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**
- **Fluidized bed dryers** are an attractive alternative to the circulating **hot air ovens.**

5. REDUCTION IN PARTICLE SIZE



- **Particle size** to particle size distribution is important to the **compression characteristics** of a granulation.
- **Compression factors** that may affected by the **particle size distribution** are flow ability, compressibility, **uniformity of tablet weight,** content uniformity, **tablet hardness**, tablet color uniformity

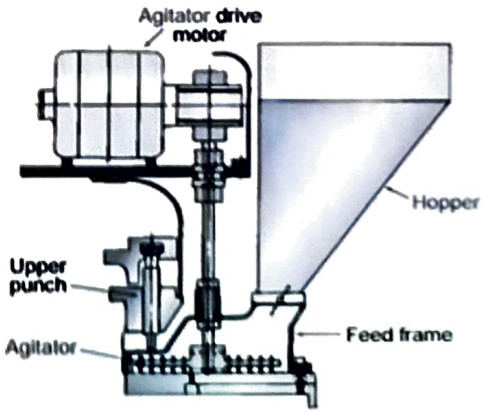
6. BLENDING

- **Consequent attention** should be paid to scale up of the **right design** is used and **blender loads, mixing speeds, mixing timing** are properly established.
- In any **blending operation segregation** and mixing occurs simultaneously, both processes are a function a **particle size, shape, hardness,** density and dynamics of the mixing action.
- **Low dose active ingredients** – directly compressed.

7. SLUGGING

- A **dry powder** blend that can not be **directly compressed** because of poor **flow properties** may in some instances be processed using a **slugging operation.**

8. COMPRESSION



- The **ultimate test** of the **tablet formulation** and granulation can be compressed on a **high-speed tablet press.**

9. QUALITY CONTROL AND STABILITY

- There are **also separate** areas for carrying out.
- **Stability studies**
- Accelerated light stability studies.
- **Forced degradation** studies in accordance with **ICH guidelines.**

PILOT PLANT SCALE UP CONSIDERATIONS FOR LIQUIDS

- The physical form of a drug product that can be incorporated demonstrates Newtonian or Pseudo-plastic flow behavior.
- It conforms to its container at room temperature.
- Liquid dosage forms may be dispersed systems or solutions.
- In dispersed systems there are two or more phases, where one phase is distributed in another.
- A solution refers to two or more substances mixed homogeneously.

❖ STEPS OF LIQUID MANUFACTURING PROCESS

- Planning of material requirements.
- Liquid preparation.
- Filling and Packing.
- Quality assurance.

❖ CRITICAL ASPECTS OF LIQUID MANUFACTURING

- Physical Plant.
- Heating, ventilation and air controlling system.

➢ SOLUTION

- The parameters to be considered are for scale up of solutions are
  - ✓ Impeller diameter.
  - ✓ Tank size (diameter).
  - ✓ Number of impellers.
  - ✓ Impeller type.
  - ✓ Mixing capability of impeller.
  - ✓ Rotational speed of the impeller.
  - ✓ Height of the filled volume in the tank.
  - ✓ Number of baffles.
  - ✓ Transfer system.

- ✓ Clearance between **Impeller Blades** and **wall of the mixing tank.**
- ✓ **Filtration equipment** (should remove desired materials but should not remove active or adjuvant ingredients).
- ✓ **Passivation of Stainless Steel** (Pre-reacting the SS with acetic acid or nitric acid solution to remove. the surface alkalinity of the Stainless Steel).

SUSPENSION

- The **parameters to be considered** are for scale up of suspension are;
- **Versator (To avoid air entrapment).**
- Wetting of **suspending agent.**
- **Addition and dispersion** of suspending agents.
- **Selection of the equipment** according to batch size.
- Time and **temperature required** for hydration of the suspending agent.
- **Mixing speeds** (High speed should not be used as it leads to air entrapment).
- **Mesh size** (Must be able to remove the foreign particulates and sieve selected based on production batch size trials).

EMULSION

- The **parameters** to be considered are for scale up of emulsion are;
- **Homogenizing equipment.**
- **Temperature.**
- **Mixing equipment.**
- **Phase densities.**
- In-process or **final product filters.**
- **Phase volumes.**
- **Screens, pumps and filling equipment.**
- **Phase viscosities.**

PILOT PLANT SCALE UP CONSIDERATIONS FOR SEMI SOLIDS

❖ **The following parameters are to be considered during the scale up of semisolid products;**

- **Mixing speed.**
- **Mixing equipment** (Could be able to move semisolid mass from outside walls to the center and from bottom to top of the kettle).
- **Motors** (Drive mixing system with appropriate handling system at its most viscous stage).
- **Heating and cooling process.**
- **Component homogenization.**
- **Product transfer.**
- Addition of **active ingredients.**
- Working **temperature range.**
- Shear during **handling and transfer** from manufacturing to holding tank to filling lines.
- **Transfer pumps** (Easily must move viscous material without applying excessive shear and free of entrapped air).

❖ **Following parameters must be consider during choosing the size and type of pump,**

- **Pumping rate.**
- **Pumping pressure** required should be considered.
- **Product compatibility** with the pump surface.
- Product **viscosity.**

SUPAC GUIDELINES

- The scale up and **changes whatever** made after taking approval from **governing body (FDA),** such as composition, **manufacturing process, manufacturing equipment,** site change, all comes under SUPAC.

- FDA has issued various guidance for SUPAC changes for

1. SUPAC-IR (Immediate release),
2. SUPAC- MR (modified release),
3. SUPAC-SS (non-sterile semi solid dosage form, cream, ointment, gel and lotions)

LEVEL OF CHANGE		
MINOR/ LEVEL 1	**MODERATE/ LEVEL 2**	**LEVEL 3**
Change of color flavor, expression of excipient in formulation level.	These changes could effect to the formulation, quality and assurance	The changes that are likely to have change total formulation quality and performance of formulation
	Change in technical grade in excipient, there percentage. Eg, avicel 102, avicel 100	Eg, any qualitative or quantitative excipient change in a potent drug formulation, the drugs that not need dissolution criteria when change in level 16

❖ SUPAC – IR

- The change in component and conjugation.
- The site of manufacture.
- The scale up of manufacture.
- The manufacturing process and equipment.

❖ SUPAC – MR

- Component and composition of non- release controlling excipient.
- Focus on changes on concentration of that excipient.
- Remove that excipient if possible.

➢ GENERAL CONSIDERATION FOR SUPAC CONSIDERATION

- All the **relevant data regarding** composition of formulation.
- **Stability data analysis.** – any trend of potency lost, - any degrading condition,
- All available **long term circumstances** data that **influence batches**
- Submission of **previous accelerated stability studies** for **better understanding** that must include – **expiration date**, - shelf life, - over ages, of **1st to 3 month study**. Details of production patches and any other report. **Clinical trial study/ time** and expense associated with these trials
- Variety of **physical and chemical test** commonly performed for **semisolid preparation** (solubility , particle size, viscosity, homogeneity) in vitro release study

INTRODUCTION TO PLATFORM TECHNOLOPGY

➢ PLATFORM TECHNOLOGY

- **Platform technologies** are considered a **valuable tool** to **improve efficiency** and quality in **drug product development.**
- The **basic idea** is that a platform, in combination with a **risk-based approach**, is the most systematic method to **leverage prior knowledge** for a given new molecule. Furthermore, such a **platform enables** a **continuous improvement** by adding data for every **new molecule** developed by this approach, **increasing the robustness** of the platform.

❖ DESIGNING OF PLATFORM TECHNOLOGY

- The **first step** is to identify **future market application** that the technology can address.
- Then determine the **core building blocks** that can be carried out over to the **new application.**
- **After identifying** the core **platform technologies**, determine what has to change beyond the platform to expand into **new application.**
- Where possible, **product platform** should be designed in a modular manner to take **full advantages of platform** benefits.
- **Specify and design** the platform performance such that it meets the known future **application needs.**

❖ APPLICATION OF PLATFORM TECHNOLOGY

✓ Medical devices

- **Medical device** companies face many of the **same challenges** of **new product development** as other industries however the **medical device industry** is for the challenged with **regulatory hurdles** as part of **new product development.**
- **Future product** line extensions benefit from **modular platform** that have **already gone** through **regulatory evaluation** such as product safety testing.

✓ Drug Delivery System

- Drug delivery system many companies like **CIPLA** has made a **strategic investment** in common **platform technologies** such as sustained release and combination product and in **key platform** to enhance **drug delivery system capabilities.**
  - **Nanotechnology**
  - **Microsphere**
  - **Liposome**
  - **Hot Melt Extrusion**
  - **Sustained Release Formulations**
  - **Orally Disintegrating Tablet**
  - **Sprinkles**