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 TECHNOLOGY**

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.

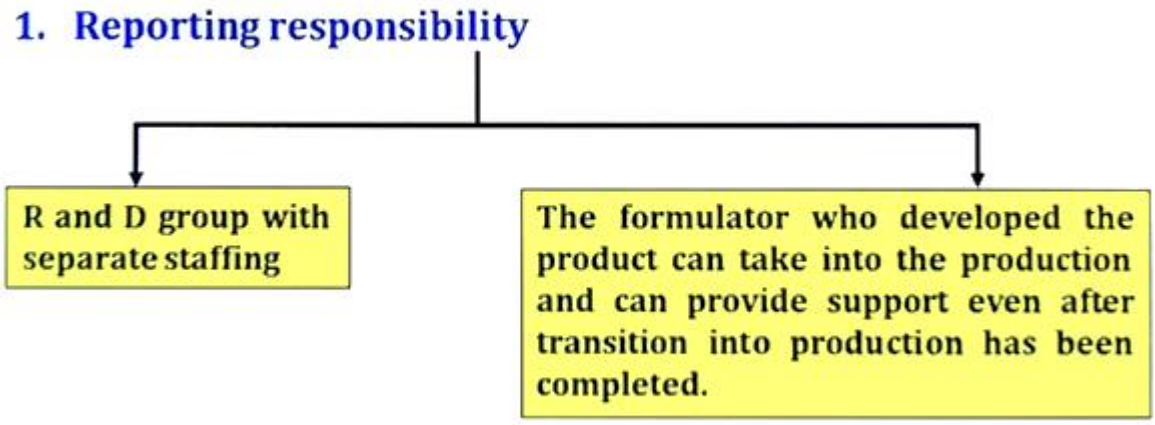
• To identify the **critical features** of the process.

• **Guidelines for production** and process controls.

• To provide **master manufacturing formula** with instructions for manufacturing procedure.

• To **avoid** the scale-up problems.

GENERAL CONSIDERATIONS



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** wherever 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 be 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 packing material should also be provided.

4. Review of the formula

• The purpose of **each ingredient** and its 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 representative for the **large scale production**.

6. Equipment

• The **most economical** and the **simplest & efficient equipment** 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 it is too big then the **wastage of the expensive active ingredients** occurs.

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**

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**.

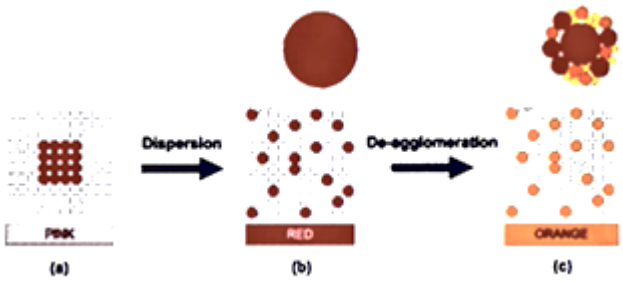
• Different material handling systems are vacuum loading systems, devices to **lift and tilt drums**, **meeting pumps**, screw feed systems.

2. DRY BLENDING

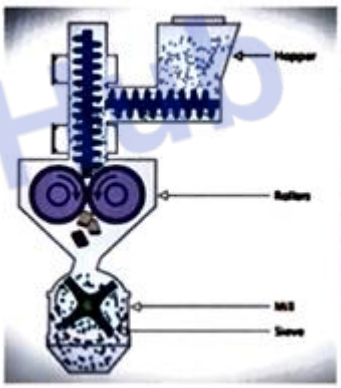
• **Powders** should be used for **encapsulation** or to be granulated prior to **tableting**; must be well blended to ensure **good drug distribution**.

• **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 binding properties on **compaction can be improved**.

✓ **Types :-**

a) **Wet Granulation**

b) **Dry Granulation**

c) **Direct Compression Method**

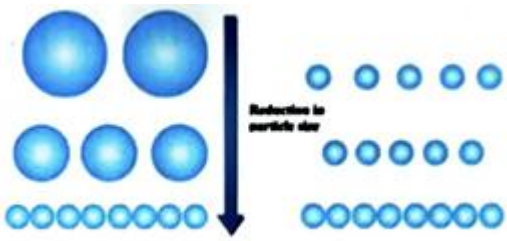
4. DRYING

• 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 be affected by 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**; blender loads, mixing speeds, mixing timing are properly established.

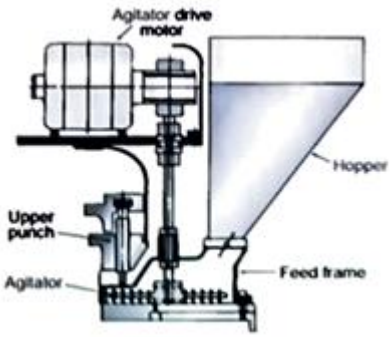
• In any blending operation **segregation** and mixing occur simultaneously; both processes are a function of **particle size,** shape, hardness, density and **dynamics of the mixing action**.

• **Low dose active ingredients** – directly compressed.

7. SLUGGING

• A **dry powder blend** that cannot 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 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**

• 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 TECHNOLOGY

➤ 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**.

• **Includes:**

- **Nanotechnology**
- **Microsphere**
- **Liposome**
- **Hot Melt Extrusion**
- **Sustained Release Formulations**
- **Orally Disintegrating Tablet**
- **Sprinkles**