# PILOT PLANT SCALE UP TECHNIQUES

B.Pharm VII sem
Industrial Pharmacy

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# PILOT PLANT

## OBJECTIVES

1. To try the process on a model of proposed plant before start of large procedure
2. To study or examine the formula that is used pilot plant or commercial scale
3. Evaluation replication of process and equipments

**NOTE—The pilot plant scale up technique basically identify the critical feature of the process evaluation parameters and there by control and assist /help for the preparation of master formula.**

# STEPS IN PILOT PLANT SCALE UP

1. **DEFINE PRODUCT- Economic basis, market size, competition selling.**
2. **Conduct lab study.**
3. **Define key rate controlling step.**
4. **Conduct preliminary study (pre -formulation study).**
5. **Design environment control, cleaning and sanitizing system, packaging, waste handling system and other regulatory requirements.**
6. **Evaluate pilot plant results (product , process , economy).**

# GENERAL CONSIDERATION of PILOT PLANT

- There must be separate staff that include RND group a formulator and supporting staff.

- Personal Requirement The qualification required for a position in a pilot plant organisation include a blend of good theoretical knowledge of pharmaceutics and some practical experience in the pharmaceutical industry.

- Space requirement:-----
  - 1. Administration and information processing,
  - 2.Physical testing area,
  - 3.Standard equipment floor space,
  - 4 Storage area

- **Review of the formula-** A throw review of each aspect of formulation must be conducted. (purpose of each ingredient, equipment configuration)

- **Raw material-** approved and validate active ingredient and excipient is required. All the raw material should be cost effective.

- **Equipment-** It must be economical and simple, must be efficient and working/ can produce desired product. The size of the equipment should be such that it can be used for large scale production. The selected equipment should not be too small or too large.

- **Production rate-** The immediate and the future market trends or requirement are considered while determining the production rate.

- **Process evaluation- several parameters should be monitored such as**
  - **1. Order of mixing of ingredients,**
  - **2. Mixing speed,**
  - **3. Mixing time,**
  - **4. Rate of addition of solvent in formulation,**
  - **5. Heating and cooling rate,**
  - **6. Filtration (filter size),**
  - **7. Prime temperature and time.**
- **Master manufacturing procedure.--**
  - **1. Weight sheet**
  - **2. Processing direction**
  - **3. Manufacturing procedure**
- **Product stability and uniformity-**

**1. Physical and chemical stability,**

**2. Process parameter that prepare uniform product,**

**3. Package stability**

# PILOT PLANT SCALE UP OF SOLID FORMULATIONS

## Pilot plant scale up technique

1. **There is a general consideration regarding for pilot plant staff members**
    - **i) They should have sufficient knowledge regarding new formulation**
    - **ii)They should scale large no of product in efficient way.**

2. **The design and construction of pilot plant for solid preparation should be**
    - **i) Feasible**
    - **ii)Cost effective**
    - **iii)Easy to maintain and clean**

**3. The design and construction unit should be installed on the ground floor that makes easy delivery and shipment.**

**4. All the preparation should be protected from any kind of microbial attack**

**i) Fluorescent lightning feature should be on ceiling**
**ii) There should be floor drain facility to make simplify cleaning.**
**iii) Construction area should be humidity control.**
**iv) High density concrete floor should be installed.**

**5. There should be enamel painting on the wall**

# PILOT PLANT SCALE UP FOR LIQUID PREPARATION

## QUALITY ASSURANCE FOR LIQUID ORALS

1. Dissolution of drugs in liquid
2. Content uniformity of drug
3. Effect of atmospheric conditions such as temp on uniformity of liquid preparation.

Suspension -- Low temp → high viscosity

High temp → low viscosity

Emulsion – As the temp. increases or decreases it will effct on efficacy of emulsion

Solution - solute solubility enhances as the temperature increases

**4. Microbiological control—suspending and emulsifying agent are prone for microbial attack, water is also good source of microbe growth.**

**5. Final volume –if solution is stored for long time – then sorption or permeation or leaching is possible in plastic container**

**6. Stability- (Accelerated stability studies) the preparation are kept in variable temp and humidity zones , then we check the potency and uniformity of preparation.**

# STAGE OF LIQUID PREPERATION

| |
|---|
| Raw material |
| Measuring and weighing |
| Mixing |
| Filling |
| Packing |
| Finished product storage |
| Quality assurance |

# INGREDIENTS OF LIQUID PREPARATIONS

**Solutions:**

| | |
|---|---|
| Protecting the API | Buffers, antioxidants, preservatives |
| Maintaining the appearance | Colorings, stabilizers, co-solvents, antimicrobial preservatives |
| Taste/smell masking | Sweetners, flavorings. |

**Suspensions:**

| Purpose | Agent |
|---|---|
| Facilitating the connection between API and vehicle | -wetting agents<br>Salt formation ingredients |
| Protecting the API | - Buffering-systems, polymers, antioxidants |
| Maintaining the suspension appearance | Colorings, suspending agent, flocculating agent. |
| Masking the unpleasant taste/smell | Sweeteners, flavorings |

**Emulsions:**

| Purpose | Agent |
|---|---|
| Particle Size | Solid particles, Droplet particles |
| Protecting the API | Buffering-systems, antioxidants, polymers |
| Maintaining the appearance | Colorings, Emulsifying agents, Penetration enhancers, gelling agents |
| Taste/smell masking | Sweetners, flavorings |

# PILOT PLANT SCALE UP OF SEMISOLID DOSAGE FORM

-Semisolids are complex formulation, consisting two phases- (external and internal)
eg cream, ointment, gels

-Partition coefficient plays important role to distribute active ingredient into other phase

-Physical properties factors- size, interfacial tension, partition coefficient, etc. they play a role in movement of API from one phase to another phase.

# PARAMETERS FOR SEMISOLID PREPARATION

1. Mixing equipment (should effectively move semisolid mass from outside walls to the center and from bottom to top of the kettle)
2. Motors (used to drive mixing system and must be sized to handle the product at its most viscous stage.)
3. Mixing speed
4. Component homogenization
5. Heating and cooling process
6. Addition of active ingredients
7. Product transfer
8. Working temperature range (critical to the quality of the final product)
9. Shear during handling and transfer from manufacturing to holding tank to filling lines
10. Transfer pumps (must be able to move viscous material without applying excessive shear and without incorporating air)
11. While choosing the size and type of pump ,
    a. Product viscosity
    b. Pumping rate
    c. Product compactibility with the pump surface
    d. Pumping pressure required should be considered.

# SUPAC – SCALE UP AND POST APPROVAL CHANGES

**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 2.** |

**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

1. All the relevant data regarding composition of formulation.

2. Stability data analysis. – any trend of potency lost, - any degrading condition,

3. All available long term circumstances data that influence batches

4. Submission of previous accelerated stability studies for better understanding that must include – expiration date, - shelf life, - over ages, of 1 st to 3 month study. Details of production patches and any other report. Clinical trial study/ time and expense associated with these trials

5. Variety of physical and chemical test commonly performed for semisolid preparation (solubility , particle size, viscosity, homogeneity) in vitro release study

# PLATEFORM TECHNOLOGY

**Plateform technologies are considered a valuable tool to improve efficiency and quality in drug product development. It is the risk based systematic approach that is based on prior knowledge. These technologies are designed to modify drug molecule and dosage for their better action**

# Key feature of platform technology

- It is robust and versatile.
- It improves chemical stability and solubility of the active molecule.
- Stable simply and solvent free technologies offer preparation of various formulations successfully.
- Reformulation of drug near patent expiration.
- Development of drugs that are not prepared and left over for preparation of formulation.
- New administration rules for a variety of molecules

**Example- Argos therapeutics is an immune oncology company that develops immunotherapies for the treatment of cancers. The company has developed ARCELIS® technology for mutation of various antigens through capturing complete genome, patient's dendritic cell cells of tumors etc., and applies suitable approach for the management of cancerous diseases. The technology reduces associated toxicity of those formulations by including suitable adjuvants**

# REFERENCES

Leon Lachman et al. The theory and practice of industrial pharmacy. Pilot Plant Scale-Up Techniques.

Scaling Up Manufacturing Processes : A Technology Primer : Supplement To Pharmaceutical Technology 2005 .