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Pilot Plant Scale Up

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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, 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

I. INTRODUCTION

Pilot plant scale-up techniques involve reproducible manufacture of an experimental formulation on high-speed production equipment, in a cost-effective manner. It is a part of the pharmaceutical industry, where the same processes used during Research and Development (R & D) of dosage forms are applied to different output volumes; usually greater than that obtained during R &D.

In every emerging pharmaceutical industry or an already existing one, there is always a need to have an intermediate batch scale representing procedures and simulating that used for commercial manufacturing. It is achieved by determining the ability of formula to withstand batch scale and process modification.

There is equally a need for equipment evaluation and validation to ensure that the aim of your company which is the mass production of the drug in question is not defeated. For a pilot scale-up to be successful, a product must be capable of being processed in a large scale often with equipment that only remotely resembles that used in the development laboratory. The idea is that you understand what makes these processes are similar, identify and eliminate many scale-up problems before investing large sum of money on a production unit.

Maintain the chemical attributes of the product, its quality and efficacy even though the production processes are modified as a result of sample size increase and equipment changes.

Pilot Plant Scale-up must include:

1. A close examination of the formula to determine its ability to withstand large scale and process modification.
2. A review of a range of relevant processing equipment to determine which would be most compatible with the formulation as well as the most economical, simple and reliable in producing the product.

During pilot plant scale-up ensure the:

1. Determination of the availability of raw materials that consistently meet the specifications required to produce the product.
2. Determination of the physical space required and the layout of related functions to provide short-term and long-term efficiency.
3. Evaluation, validation and finalizing of production and process controls.
4. Issuing of adequate records and reports to support Good Manufacturing Practices (GMPs) and provision of the historical development of the production formulation process, equipment train and specifications.
5. Development and validation of meaningful product reprocessing procedures.
6. Identification of all critical, features of a scale up process, so that it can be adequately monitored to provide assurance that the process is under control and that the process at

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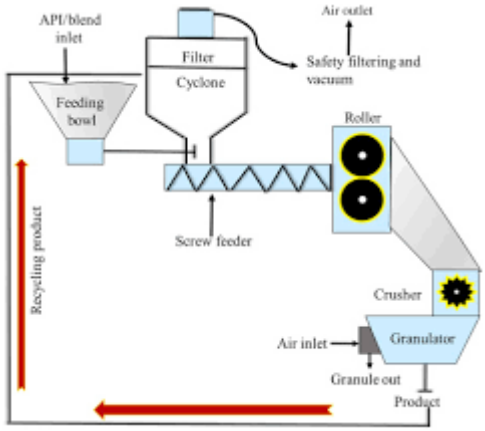
each level of the scale up maintains the specified attributes originally intended.

7. Production rate and future market requirements.

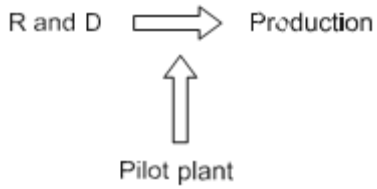
General Considerations During pilotPlant scale-Up

Pilot plant scale-up is of practical interest to formulation scientist/ production managers and should be considered from the inception of a development project. This is because a process using the same type of equipment can perform quite differently when the size of the equipment and the amount of material involved is
significantly increased. The chemical attributes of the product, its quality and efficacy should be maintained even though the production processes modified as a result of sample size increase and equipment changes. You should also bear in mind that pilot plant scale-up, in itself, does not guarantee a smooth transition. A well-defined process may fail quality assurance tests in full manufacturing scale even after generating a perfect product in both the laboratory and the pilot plant.



Plant: It is place were the 5M'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 fortune is transferred into a viable product by development of liable and practical procedure of manufacture.



Scale-up: It is the art for designing of prototype using the data obtained from the pilot plant model.

Objectives of Scale-up:

1. To try the process on a model of proposed plant before committing large sum of money on product unit.
2. To examine of the formula for determination of the ability to withstand batch scale.
3. Evaluation and validation for process andequipment's.
4. To identify the critical features of the process.
5. To provide guidelines for production and process controls.
6. To provide master manufacturing formula with instruction for manufacturing produces.

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Steps in Scale-up:

Define product economics based on projected market size and competitive selling and provide guidance for allowable manufacturing cost.

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Conduct Laboratory studies and scale up planning at the same time.

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Define key ratter controlling steps in the proposed process.

↓

Conduct Preliminary larger-than laboratory studies with equipment to be used in rate controlling step in aid in plant design.

↓

Design and contract a pilot plant including provisions for process and environment controls, cleaning and sanitizing systems, packaging and waste handling systems, and meeting regulatory agency requirements.

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Evaluate pilot plants result (Product and process) including process economics to make any corrections and a decision on whether to process or not with a full-scale plant development.

NEED OF PILOT PLANT STUDIES

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

A pilot plant can be used for:

1. Evaluating the results of laboratory studies and making product of process.
2. Monitoring of quality of Drugs and Cosmetics, manufactured by respective state units and those marketed in the state.
3. Investigation and prosecution in respect of contravention of large provisions.
4. Administrative actions.
5. Pre and post licensing inspection.
6. Recall of sub-standard drugs state drug control organization.

STATE DRUG CONTROL ORGANIZATION

CDSCO joined with state drug control board organization to regulate the import/export of drugs and medical device.

The State Drug Control Organization is responsible for:

- Providing license to drug testing laboratories.
- Approving drug formulation for manufacture.
- Carrying out pre and post licensing.
- Observing the drug manufacturing process by respective state unit and those marketed in the state.

Functions of State Licensing Authorities:

1. Licensing of manufacturing site for drugs including API and finished formulation.
2. Licensing of establishment for sale or distribution of drugs.
3. Approval of drug testing laboratories.
4. Monitoring of quality of drugs and cosmetics marketed in the country.
5. Investigation and prosecution of contravention of legal provision.
6. Recall of sub-standard drugs.

USES OF PILOT PLANT

1. To evaluate the results of laboratory studies.
2. To make process corrections and

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improvements.

3. To produce small quantities of product for sensory, chemical, microbiological evaluations, limited market testing or furnishing samples to potential customers, shelf-live and storage stability studies.
4. To provide 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.

GENERAL REQUIREMENTS FOR PILOT SCALE AND SCALE-UP

1. Reporting Responsibilities:

(i) R and D group with separate staffing.

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

2. Personal Requirements:

(i) 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.

(ii) The group should have some personnel with engineering knowledge as well as scale up also involves engineering principles.

3. Space Requirements:

(i) **Administration and information process:** Adequate office and desk space should be provided for both scientists and technicians. The space should be adjacent to the working area.

(ii) **Physical testing area:** This area should provide permanent bench top space for routinely used physical testing equipment.

(iii) **Standard pilot-plant equipment floor space:** Discrete pilot plant space, where the equipments are needed for manufacturing all types of dosage forms, is located.

(a) Intermediate sized and full-scale production equipment is essential in evaluating the effects of scale-up of research formulations and processes.

(b) Equipments used should be made portable. So that after use it can be stored in the small store room.

(c) Space for cleaning of the equipment should also be provided.

(iv) Storage area:

(a) It should have two areas divided as approved and unapproved area for active ingredients as well as excipients.

(b) Different areas should be provided for the storage of the in-process materials, finished bulk products from the pilot-plant and 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:

(i) A thorough review of each aspect of formulation is important.

(ii) The purpose of each ingredient and its contribution to the final product manufactured

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on the small-scale laboratory and equipment should be understood.

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

5. Raw Materials:

(i) One purpose/responsibility of the pilot plant is the approval and validation of the active ingredients and excipients raw materials.

(ii) Raw materials used in the small-scale production cannot necessarily be the representative for the large-scale production.

6. Equipments:

(i) The most economical and the simplest and efficient equipments, which are capable of producing product within the proposed specifications, aroused.

(ii) The size of the equipments should be such that the experimental trial's run should be relevant to the production sized batches.

(iii) If equipment is too small, the process developed will not scale up; whereas if equipment is too big, then there is 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 Parameters:

(i) Order of mixing of components.
(ii) Mixing speed.
(iii) Mixing time.
(iv) Rate of addition of granulating agents, solvents, solutions of drug,etc.
(v) Heating and cooling rates.
(vi) Filters size(liquids).
(vii) Screen size(solids).
(viii) Drying temperature and drying time.

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

9. Master Manufacturing Procedures:

(i) The weight sheet should clearly identify the chemicals required in a batch. To prevent confusion the names and identifying numbers for the ingredients should be used on batch records.

(ii) The process directions should be precise and explicit.

(iii) 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, etc. should be mentioned in the batch record directions.

10. Product Stability and Uniformity:

(i) The primary objective of the pilot plant is the physical as well as chemical stability of the products.

(ii) Hence each pilot batch representing the final formulation and manufacturing procedure should be studied for stability.

(iii) Stability studies should be carried out in finished packages as well as raw material.

GMP CONSIDERATIONS

1. Equipment qualification.
2. Process validation.
3. Regularly schedule preventative maintenance.
4. Regularly process review and revalidation.
5. Relevant written standard operating procedures.
6. The use of competent technically qualified personnel.
7. Adequate provision for training of personnel.
8. A well-defined technology transfer system.
9. Validated cleaning procedures.
10. An orderly arrangement of equipment so as to ease material flow and prevent cross-contamination.

Advantages:

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

Disadvantages:

1. The frequency of direct interaction of the formulator with the production personnel in the manufacturing area willsbe reduced.
2. Any problem in manufacturing will be directed towards its own pilot-plant personnel.

PILOT PLANT SCALE UP FOR SOLID DOSAGE FORM

PILOT PLANT DESIGN FOR TABLETS

The primary responsibility of the pilot plant staff is to ensure that the newly formulated tablets developed by product development personnel will prove to be efficiently, economically and consistently reproducible on a production scale. The design and construction of the

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pharmaceutical pilot plant for tablet development should incorporate features necessary to facilitate maintenance and cleanliness. If possible, it should be located on the ground floor to expedite the delivery and shipment of supplies.

1. Formulation and process development.
2. Technology evaluation, scale-up and transfer.
3. Clinical supply manufacture.

Control Pilot Plant Studies:

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

Product Considerations:

1. MaterialHandling:

In the laboratory, materials are simply scooped or poured by hand, but in intermediate or large-scale operations, handling of these materials often become necessary. If a system is used to transfer materials for more than one product, steps must be taken to prevent cross contamination. Any material handling system must deliver the accurate amount of the ingredient to the destination. More sophisticated methods of handling materials are vacuum loading systems, metering pumps, screw feed system.

2. DryBlending:

Dry blend should take place in granulation vessel. Larger batch may be dry blended and then subdivided into multiple sections for granulation. All ingredients should be free of lumps, otherwise it causes flow problems. Screening and/or milling of the ingredients prior to blending usually makes the process more reliable and reproducible. The equipments used for blending are: V-blender, Double cone blender, Ribbon blender, Slant cone blender, Bin blender, Orbiting screw blenders, Vertical and horizontal high intensity mixers, etc.

Scale-up Considerations;

- Powders to 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 and the drug concentration is relatively low.
- Ingredients should be lumps free, otherwise it could cause flow problems.

3. Granulations:

The most common reasons given to justify granulating are: to impart good flow properties to the material, to increase the apparent density of the powders, to change the particle size distribution, uniform dispersion of active ingredient, etc. Traditionally, wet granulation has been carried out using, sigma blade mixer, heavy-duty planetary mixer:

- 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.

Direct compression method: A small amount of potent active ingredient can be dispersed most

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effectively in a carrier granulation, when the drug is dissolved in granulating solution and added during the granulating process.

Wet granulation has been carried out by using:

- Sigma blades.
- Heavy-duty planetary mixture.
- High speed chopper blades used in mixing of light powders.
- Multifunctional processors, dry blending, wet granulation, drying, sizing and lubricating.
- Effect of binding agent.

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. The important factor to consider as part of scale up of an oven drying operation are airflow, air temperature, and the depth of the granulation on the trays.

Fluidized Bed Dryer:

- Optimum loads - rate of airflow.
- Inlet air temperature.
- Humidity.
- Data used for small scale batches (1-5 kg) cannot be extrapolate processing conditions for intermediated scale (100 kg) or large batches.

5. Reduction in Particle Size:

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

Equipments:

- Oscillating granulator
- A hammer mill.
- Screening device.

Too large particle size causes:

- Weight variation
- Mottling

Hammer Mill

Too fine particle size causes:

- Weight variation.
- Capping.
- Both oversized and undersized granulation can adversely affect tablet content uniformity.
- Lubricants and Giants are added at final blend.

6. Blending:

- The 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 function of a particle size, shape, hardness, density and dynamics of the mixing action.
- Low dose active ingredients are directly compressed.

Equipments:

- Planetary type mixer
- Twin shell mixture
- Cone type

Over loading in blender:

- Retards the free flow of granules
- Reduces the efficiency
- Causes content un-uniformity If the load is to small:
- Powder blends slides rather than roll in blender.
- It causes improper mixing.

7. Slugging:

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A dry powder blend cannot be directly compressed because of poor flow or compression properties. This is done on a tablet press designed for slugging, which operates atPressures of about 15 tons, compared with a normal tablet press, which operates at pressure of 4 tons or less. Slugs range in diameter from 1 inch, for the more easily slugged material, to ¾ inch in diameter for materials that are more difficult to compress and require more pressure per unit area to yield satisfactory compacts. If an excessive amount of fine powder is generated during the milling operation, the material must be screened and finely recycled through the slugging operation.

8. Compression:

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

Steps involved during compression:

(i) Filling empty die cavity with granulation.
(ii) Pre-compression of granules.
(iii) Compression of granules.
(iv) Ejection of tablet from the die cavity.

Compression characteristics can be evaluated by press speed equal to normal production speed.

Then detect the problems such as,

- Sticking to punch surface
- Tablet hardness
- Capping
- Weight variation

Granules must be delivered at adequate rate.

9. Tablet Coating:

Pan and fluidized coating:

- Optimum tablet load.
- Operating tablet bed temperature.
- Drying airflow rate and temperature.
- The solution application rate.
- The size and shape of the nozzle aperture (for airless sprayer).
- The atomizing air pressure and the liquid flow rate (for air atomized sprayers).

Pan coating:

- Fixed operating parameters.
- Variable operating parameters.
- Other parameters; Pan Loading (kg), Solid content of coating suspension (% w/w), Spray gun dynamics, Drying Air (cfm), Inlet air temperature (°C), Gun to tablet bed distance, Coating System Spray rate (g min^{-1}), Quantity of coating applied (% w/w), Atomizing air pressure (psi, bar), Air Pressure (psi, bar), Pan speed Number of spray guns.

Coating Pans

Fluidized bed coating:

- Batch size.
- Drying/fluidizing air volumes.
- Spray nozzle dynamics.
- Spray evaporation rate.

Fluidized Bed Coating

Equipments:

- Conventional coating pan.
- Perforated pans of fluidized-bed coating column.

Types:

- Sugarcoating.
- Film coating.

(i) Tablet must be sufficiently hard to withstand the tumbling to which they are subjected while coating.
(ii) Operation conditions to be established for pan or column operation are optimum tablet load, operating tablet, bed temperature, drying air flow rate, temperature,

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PILOT PLANT SCALE UP TECHNIQUE FORCAPSULE

Capsules are solid dosage forms in which the drug substance is enclosed in either a hard or soft soluble container or shell of a suitable form of gelatin.

Different Steps in capsule production:

1. Mixing of ingredients
2. Granulation and lubrication
3. Making of capsules
4. Filling of capsules
5. Uniformity testing
6. Packing and labeling

Both tablets and capsules are produced from ingredients that may be either dry blended or wet granulated to produce a dry powder or granule mix with uniformly dispersed active ingredients. To produce capsules on high speed equipment, the powder blend must have the uniform particle size distribution, bulk density and compressibility required to promote good flow properties and result in the formation of compact of the right size and sufficient cohesiveness to be filled into capsule shells.

Manufacturing of Hard Gelatin Capsules Shell Composition:

- **Gelatin:** It is prepared by the hydrolysis of collagen. There are two basic types of gelatin: Type-A and Type-B. The two types can be differentiated by their isoelectric points (7.0 - 9.0 for type-A and 4.8 - 5.0 for type-B) and by their viscosity and film forming characteristics.

Combination of pork skin and bone gelatin is often used to optimize shell characteristics. The physicochemical properties of gelatin of most interest to shell manufactures are the bloom strength and viscosity.

- **Colorants:** Various soluble synthetic dyes (coal tar dyes) and insoluble pigments are used. Colorants not only play a role in identifying the product, but also play a role in improving patient compliance. For example, white - analgesia, lavender - hallucinogenic effects, orange or yellow - stimulants and antidepressants.
- **Opaquing agents:** Titanium dioxide may be included to render the shell opaque. Opaque capsules may be employed to provide protection against light or to conceal the contents.
- **Preservatives:** When preservatives are employed, parabens are often selected.

Shell Manufacturing:

- **Dipping:** Pairs of the stainless-steel pins are dipped into the dipping solution to simultaneously form the caps and bodies. The pins are at ambient temperature; whereas the dipping solution is maintained at a temperature of about 50^{O}C in a heated, jacketed dipping pan. The length of time to cast the film has been reported to be about 12sec.
- **Rotation:** After dipping, pins are elevated and rotated 2-1/2 times until they are facing upward. This rotation helps to distribute the gelatin over the pins uniformly and to avoid the formation of a bead at the capsule ends.
- **Drying:** The racks of gelatin coated pins are then passed into a series of four drying ovens. Drying is mainly done by dehumidification. A temperature elevation to only a less degrees is permissible to prevent film melting. Under drying will leave the films too sticky for subsequent operation.
- **Stripping:** A series of bronze jaws strip the cap and body portions of the capsules from the pins.
- **Trimming:** The stripped cap and body portions are delivered to collects in which they are firmly held. As the collects rotate, knives are brought against the shells to trim them to the required length.
- **Joining:** The cap and body portions are aligned concentrically in channels and the two portions are slowly pushed together.
- **Sorting:** The moisture content of the capsules as they are from the machine will be in the range of 15-18% w/w. During sorting, the capsules passing on a lighted moving conveyor are examined visually by inspectors. Defects are generally classified according to their nature and potential to cause problems in use.
- **Printing:** In general, capsules are printed before filling. Generally, printing is done on offset rotary presses having throughput capabilities as high as three-quarter million capsules per hour.
- **Sizes and Shapes:** For human use, empty gelatin capsules are manufactured in eight sizes, ranging from 000 to5.

The largest size normally acceptable to patient is a No. 0. Three larger sizes are available for veterinary use: 10, 11, and 12 having capacities of about 30, 15, and 7.5 gm, respectively. The standard shape of capsules is traditional, symmetrical bullet

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shape. Some manufactures have employed distinctive shapes. For example, Lilly's pulvule tapers to a bluntly pointed end, Smith Kline Beacham'sspansule capsules taper at both the cap and body ends.

- **Sealing:** Capsules are sealed and somewhat reshaped in the Etaseal process. This thermal welding process forms an indented ring around the waist of the capsule where the cap overlaps the body.
- **Storage:** Finished capsules normally contain an equilibrium moisture content of 13-16% to maintain a relative humidity of 40-60% when handling and storing capsules.

Filling of Hard Gelatin Capsules:

- Equipments used in capsule filling operations involve one often of two types of filling systems:

(i) **Zanasi or Martelliencapsulator:** Forms slugs in a dosatar which is a hollow tube with a plunger to eject capsule plug.

(ii) **Hofliger-Karg machine:** Forms compacts in a die plate using tamping pins to form a compact.

- In both these systems, the scale-up process involves bulk density, powder flow, compressibility and lubricant distribution. Overly lubricated granules are responsible for delaying capsule disintegration and dissolution.
- Osaka Model R-180 Semi-Automatic Capsule Filling Machine.

Manufacturing of Soft Gelatin Capsules

Composition of the shell:

- Similar to hard gelatin shells, the basic component of soft gelatin shell is gelatin; however, the shell has been plasticized.
- The ratio of dry plasticizer to dry gelatin determines the "hardness" of the shell and can vary from 0.3-1.0 for very hard shell to 1.0-1.8 for very softshell.
- Up to 5% sugar may be included to give a "chewable" quality to the shell.
- The residual shell moisture content of finished capsules will be in the range of 6- 10%.

Formulation:

- Formulation for soft gelatin capsules involves liquid, rather than powder technology. Materials are generally formulated to produce the smallest possible capsule consistent with maximum stability, therapeutic effectiveness and manufacture efficiency. The liquids are limited to those that do not have an adverseeffect on gelatin walls. The pH of the lipid can be between 2.5 and 7.5. Emulsion cannot be filled because water released from it will affect the shell.
- The types of vehicles used in soft gelatin capsules fall into two main groups:

(i) Water immiscible, volatile or more likely more volatile liquids such as vegetable oils, mineral oils, medium-chain triglycerides and acetylated glycerides.

(ii) Water miscible, non-volatile liquids such as low molecular weight PEG has come into use more recently because of their ability to mix with water readily and accelerate dissolution of dissolved or suspended drugs. All liquids used for filling must flow by gravity at a temperature of 35°C or less. The sealing temperature of gelatin films is 37°C - 40°C.

Manufacture Processes:

1. **Plate Process:** The process involves:

- Placing the upper half of a plasticized gelatin sheet over a die plate containing numerous die pockets,
- Application of vacuum to draw the sheet into the die pockets,
- Filling the pockets with liquor or paste,
- Folding the lower half of gelatin sheet back over the filled pockets, and
- Inserting the "sandwich" under a die press where the capsules are formed and cutout.

2. **Rotary DiePress:**

- In this process, the die cavities are machined into the outer surface of the two rollers.
- The die pockets on the left-hand roller form the left side of the capsule and the die pockets on the right-hand roller form the right side of the capsule.
- Two plasticized gelatin ribbons are continuously andsimultaneously fed with the liquid or paste fill between the rollers of the rotary die mechanism.
- As the die rolls rotate, the convergence of the matching die pockets seals and cuts out the filled capsules.

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3. AccogelProcess:

- In general, this is another rotary process involving a measuring roll, a die roll, and a sealing roll.
- As the measuring roll and die roll rotate, the measured doses are transferred to the gelatin-linked pockets of the die roll.
- The continued rotation of the filled die converges with the rotating sealing roll where a second gelatin sheet is applied to form the other half of the capsule. Pressure developed between the die roll and sealing roll seals and cuts out the capsules.

4. Bubble Method:

- The Globex Mark II capsulator produces truly seamless, one-piece soft gelatin capsules by a "bubble method". A concentric tube dispenser simultaneously discharges the molten gelatin from the outer annulus and the liquid content from the tube. By means of a pulsating pump mechanism, the liquids are discharged from the concentric tube orifice into a chilled-oil column as droplets that consist of a liquid medicament core within a molten gelatin envelop. The droplets assume a spherical shape under surface tension forces and the gelatin congeals on cooling. The finished capsules must be degreased and dried.

Soft/Liquid-filled Hard Gelatin Capsules

- Three formulation strategies based on having a high resting viscosity after filling have been described:

- Thixotropic formulations,
- Thermal-setting formulations,
- Mixed Thermal-Thixotropic systems.

The more the lipophilic contents, the slower is the release rate. Thus, by selecting excipients with varying HLB balance, varying release rate may be achieved.

- To produce capsules on high-speed equipment, the powder blend must have,

- Uniform particle size distribution.
- Bulk density.
- Formation of compact of the right size and of sufficient cohesiveness to be filled into capsule shells.

- **Equipments:**

- Zanasi or Mertalli – Dosator (hollow tube).
- Hoflinger-Karg – Tampingpins.

Weight variation problem can be encountered with these two methods. Overly lubricated granules – delaying disintegration.

- Humidity affects moisture content of:

– Granulation
– On empty gelatin capsules.

- **At high humidity:** Capsule swells make separation of the capsule parts difficult to interfere with the transport of the capsule through the process.
- **At low humidity:** Capsule brittle increased static charge interferes with the encapsulation operation.

Examination of the formula to determine:

1. Ability to withstand batch-scale.
2. Process modification.
3. Compatibility of the equipment with the formulation.
4. Cost factor.
5. Physical space required.
6. Market requirement.
7. Layout of the related functions.
8. Availability of the raw materials meeting the specifications.

PILOT PLANT CONSIDERATION FOR SEMI-SOLID DOSAGE FORMS

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 centre and from bottom to top of the kettle).

Motors (Drive mixing system with appropriate handling system at its most viscous stage).

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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.

PILOT PLANT OPERATION

Validation:

1. Design specification.
2. Installation qualification.
3. Operational qualification.
4. Performance qualification.
5. Compliance with cGMP and FDA standards.

Training:

1. Technical skills and knowledge.
2. Safety and environment responsibility.
3. Compliance withGMP.
4. Compliance withSOPs.

Engineering Support:

1. Design of facility.
2. Co-ordination scheduling.
3. Direction of ongoing operations.
4. Validation of facility.
5. Construction of facility.

Maintenance and Calibration:

1. To ensure the integrity and equipment reliability and research.
2. To meet cGMPnorms.

Computerized System:

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

Process and Manufacturing Activities:

1. Formulation and process development studies.
2. Technology evaluation scale up and transfer.
3. Clinical supply and manufacture.

Quality Assurance:

1. Auditing pilot plant.
2. Auditing and approval of component supplies.
3. Reviewing approval and mainframe batch records for clinical supplies.
4. Sampling and release of raw material.
5. Release of clinical supplies.
6. Maintaining and distributing facility and operating procedure(SOPS).
7. Review and approval of validation.
8. Engineering documentation.

Quality Control:

1. Release testing of finished product.
2. Physical, chemical and microbiological testing of finished clinical products, components required for supplies.
3. Testing for validation and revalidation.
4. QC in process testing during development scale-up and technology transfer.

SCALE-UP and POST APPROVAL CHANGES (SUPAC)

FDA and American association of pharmaceuticals scientist (AAPS) provided the scientific foundation for the scale-up and post approval changes required for immediate release product called SUPAC.

It provides guidelines for post approval changes in the following:

- Components
- Compositions
- Site of manufacturing
- Process and equipment

Significance of Pilot Plant:

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1. Examination of formulae.
2. Review of range of relevant processing equipments.
3. Production rate adjustment.
4. Idea about physical space required.
5. Appropriate records and reports to supportGMP.
6. Identification of critical features to maintain quality.

Advantages:

1. Members of the production and quality control divisions can readily observe scale- up runs.
2. Supplies of excipients and drugs, cleared by the quality control division, can be drawn from the more spacious areas provided to the production division.

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Disadvantages:

1. The frequency of direct interaction of the formulator with the production personnel in the manufacturing area will be reduced.
2. Any problem in manufacturing will be directed towards its own pilot-plant personnels.

General Stability Consideration:

The effect that SUPAC changes may have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, see the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics.

For SUPAC submissions, the following points should also be considered:

1. In most cases, except those involving scale-up, stability data from pilot scale batches will be acceptable to support the proposed change.
2. Where stability data show a trend towards more potency loss or degrading under accelerated conditions, it is recommended that historical accelerated stability data from a representative perchance batch be submitted for comparison.
3. It is also recommended that under these circumstances, all available long-term data on test batches from on going studies be provided in the supplement.
4. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.

INTRODUCTION TO PLATFORMTECHNOLOGY

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. The technology has distinct and differentiating competitive advantages. It can significantly improve the bioavailability of complex molecules due to its sub-micrometric size and adhesive systems for a higher time of contact to skin. It is also flexible, encapsulating a broad range of active principles and its systems can be adjusted to achieve desired properties.

In addition, the technology is robust and versatile, with key features such as:

- Chemical stability and solubility of the active molecule.
- High drug loadings can be achieved.
- High encapsulation efficiency.
- Developed industrial process and scalability.
- Stable, simple and solvent-free technologies.
- Reformulation of drugs near patent expiration.
- Development of drugs previously thought impossible.
- New administration routes for a variety of molecules.

II. CONCLUSION:

From the above finding it was concluded that the Pilot scale up techniques is one of the important tool for the optimization of large scale production. The parameters such as Granulation feed rate, compression and presence of lubricant and blending will play a important, role the development of pilot scale up techniques to large scale production solid dosage form. We all know that about the process in pilot plant design of solid dosage form.

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