Deep Science Publishing
https://doi.org/10.70593/978-93-49307-31-5_1

Unit I

Techniques for scaling up from a pilot plant

Sachin S. Mali [1], Prajakta R. Patil [2], Dhanashree R. Davare [3]

[1] *Department of Pharmaceutics, Bharati Vidyapeeth college of Pharmacy, Kolhapur 416 013, India*
[2,3] *Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, 416 112, India*

[2] *prajaktapatil4601@gmail.com*

Abstract: General things to think about, like how important it is to have the right number of staff, the right amount of room, and the right raw materials. Pilot plant scaling up issues for solids, liquid orals, semisolids, and related paperwork. SUPAC guidelines. An introduction to platform technology.

Keywords: Automation, Optimization Process Control, Quality Assurance, Standardization, validation.

1.1 Introduction

Pilot plant scale-up methods involve making an experimental recipe on high-speed production equipment in a way that is both cost-effective and repeatable. In this part of the pharmaceutical business, the same steps are used for different output volumes, which are usually bigger than the ones used for dosage form research and development (R&D).

In the pharmaceutical industry, whether it's new or well-known, there always needs to be an intermediate batch size that shows processes and simulates those used for commercial production. This is done by checking how resistant the formula is to changes in batch size and method. Checking and validating the equipment is also needed to make sure that the medicine your company is making, which is its main goal, is still being made in large amounts. For a pilot scale-up to work, the product must be able to be processed on a big scale, often with tools that are only slightly similar to those used in the development laboratory. The idea is that you should know what makes these processes similar and find and fix a lot of scale-up problems before you spend a lot of money on a manufacturing machine.

The chemical makeup, quality, and effectiveness of the product should stay the same even if the production steps are changed because of new tools or larger samples.

Pilot Plant Scale-up must include:

1. The method needs to be carefully looked at to see how well it can handle big changes in procedure.
2. A look at the different relevant processing tools to see which ones would work best with the recipe and be the easiest, most cost-effective, and most reliable for making the final product.

During pilot plant scale-up ensure the:

1. Checking to see if the raw materials that are usually meeting the needs of the product can be found.
2. Figuring out how much space is needed and how to organize jobs that are related to make things run more smoothly in the short and long term.
3. Controls for production and processes are looked at, confirmed, and finished.
4. Giving a history of how the production formulation method, equipment train, and requirements have changed over time, along with enough records and reports to back up Good Manufacturing Practices (GMPs).
5. The development and testing of important methods for reprocessing products.
6. Identifying all the important parts of a scale-up process so that they can be watched closely enough to make sure the process is running smoothly and that each level of the scale-up keeps the qualities that were planned at the beginning.
7. How fast things are being made and what the market will need in the future.

1.2 General Considerations During Pilot Plant Scale-Up

Process engineers and production managers are interested in scaling up from a test plant. This is something that should be thought about from the start of a development project. We do this because a process that uses the same kind of equipment might not work at all the same when the size of the equipment and the amount of material used are greatly increased. The chemical makeup, quality, and effectiveness of the product should stay the same even if the production methods are changed because of new tools or a bigger sample size. Remember that expanding a pilot plant does not guarantee a smooth transfer on its own. A well-defined process might make a great product in the lab and on a small scale, but it might fail quality assurance tests when it is made on a large scale. Even if a well-

defined method makes a perfect product in the lab and the pilot plant, it might fail quality control tests when it is made on a large scale. (Introduction, not long ago).

Plant: Money, Material, Man, Method, and Machine are the 5Ms that are used to make things. The plant is where they all come together.

Pilot Plant: In the pharmaceutical industry, this is where a lab-scale success is turned into a marketable product by creating a safe and effective way to make it.

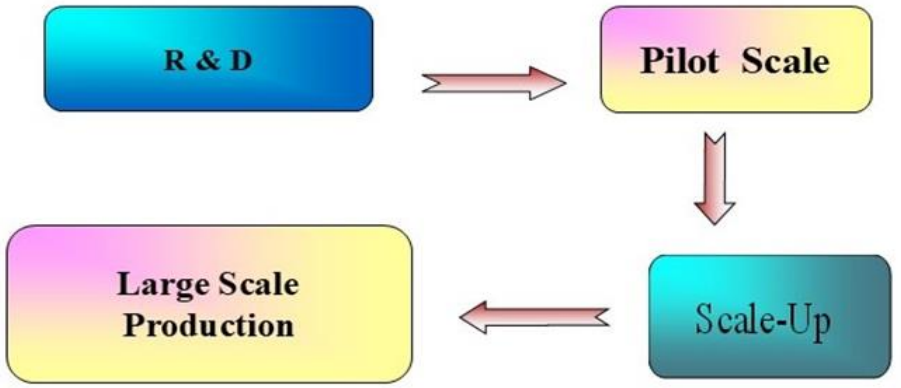

Fig. No.1.1: Pilot plant scale up process

Scale-up: Scale-up is the art of making a prototype using information from the test plant model.

Objectives of Scale-up:

1. Test the process on a model of the plant you want to build before you spend a lot of money on a product unit.
2. To look into the method that is used to figure out the batch scale capacity.
3. Review and approval of processes and tools.
4. To figure out what the process's most important parts are.
5. Make suggestions for how to control the output and process.
6. The goal is to give directions and a master method for making things.
7. To avoid problems with scaling up.

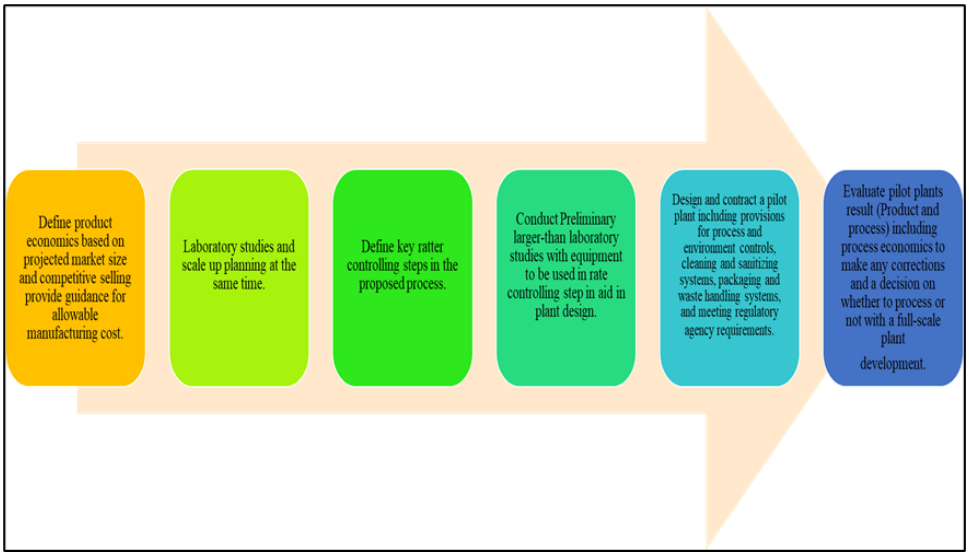

Fig. No.1.2: Steps in Scale-up

1.3 Need Of Pilot Plant Studies

1. In a pilot plant, a product and method can be tested on a smaller scale before a large amount of money is spent on full-scale production.
2. The effects of a many-fold growth in size are not always easy to predict.
3. Using only lab data is not a good way to build a large-scale processing facility.

❖ **A pilot plant can be used for:**

1. Checking the outcomes of lab experiments and creating the end product of the process.
2. Drugs and cosmetics made by different state agencies and sold in the state must be inspected for quality.
3. There will be an investigation and possible prosecution for breaking big provisions.
4. Taking administrative steps.
5. Before and after getting a license.
6. Drug control group in the state recalls drugs that aren't up to par.

State Drug Control Organization

CDSCO worked with the state drug control board group to set rules for the importing and exporting of drugs and medical devices.

The State Drug Control Organization is responsible for:

- Giving licenses to places that test for drugs.
- Giving the go-ahead for the drug mixture to be made.
- Getting licenses before and after the fact.
- Watching how drugs are made by each state's unit and how they are sold in that state.

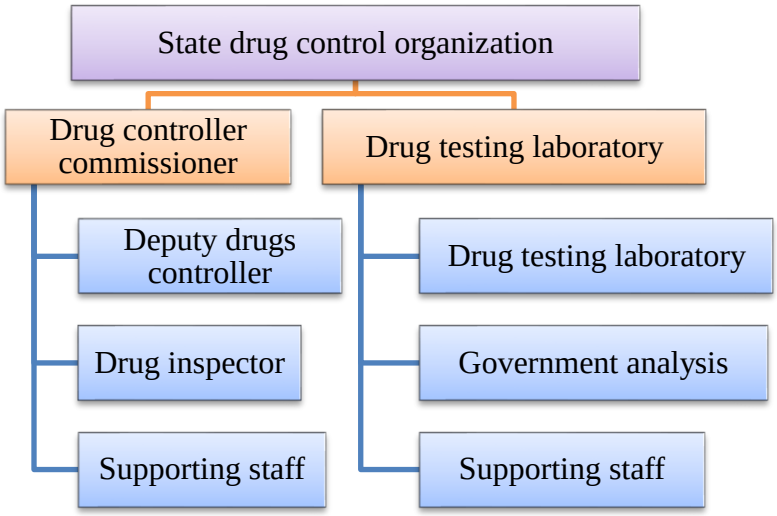

Fig. No.1.3: Drug Control Organization

Functions of State Licensing Authorities:

1. Licenses for the sites that make drugs, including the active ingredient (API) and the end product.
2. Getting a license for a business to sell or distribute drugs.
3. Authorization of labs that test for drugs.
4. Drugs and products sold in the country are checked for quality.
5. The violation of the law must be looked into and punished.
6. Recall of drugs that aren't up to par.

1.4 Ues Of Pilot Plant

1. To judge the outcomes of lab experiments.
2. To fix problems and make the process better.

3. To make small amounts of a product for testing its taste, smell, or microbiology, for limited market testing, or to give samples to possible customers, shelf-life and storage stability studies.
4. To gather information that can help decide if a full-scale production process should be started or not, and if it is decided to go ahead, to design and build a full-scale plant or make changes to an existing plant.

1. Reporting Responsibilities:

i. R&D group with separate people.
ii. The person who came up with the formula can take it into production and continue to help even after the changeover to production is over.

2. Personal Requirements:

i. Scientists who know how both the pilot plant and the real production area work are best because they need to understand both the mindset of the production staff and the formulator's goal.
ii. Some people on the team should know a lot about engineering, since growing up also involves technical ideas.

3. Space Requirements:

i. **Administration and information process**: Both scientists and technicians should have enough office and desk room. The area should be next to where you work.
ii. **Physical testing area**: This area should have permanent bench top room for physical testing equipment that is used often.
iii. **Standard floor space for pilot plant equipment**: The separate pilot plant space is where the equipment needed to make all different types of dose forms is kept.
   - It is important to use both intermediate-sized and full-scale manufacturing equipment when figuring out what happens when research formulas and processes are scaled up.
   - The tools must be easy to move around. so it can be put away in the small storage room when it's not in use.
   - There should also be a place to wash the tools.

iv. **Storage area**:

   a. It must have two parts for excipients and active substances: one for ingredients that are allowed and one for ingredients that are not allowed.

b. When making something, the materials from the trial scale-up batches and the finished bulk goods from the pilot plant should be kept in different rooms. Also, there needs to be a place to put the packing materials.

4. Review of the Formula

i. Formulation should be carefully looked at in every way.
ii. Understanding the purpose of each ingredient and how it fits into the final product made with small-scale lab tools is important.
iii. This makes it easier to predict or figure out what will happen when the process is scaled up with tools that could put the product under different types and levels of stress.

5. Raw Materials:

i. One of the pilot plant's jobs is to approve and test the raw materials for the active ingredients and excipients.
ii. The raw materials used in small-scale production don't always match those used in large-scale production**.**

6. Equipment:

i. The simplest, most cost-effective, and most effective gear is used to make the product according to the standards that have been suggested.
ii. The test tools should be big enough that the results can be used for large-scale production.
iii. The way that was made won't work on bigger machines, and if the machines are too big, the expensive active parts will be wasted.

7. Production Rates:

When setting production rates, both current and future market trends and needs are taken into account.

8. Process Evaluation Parameters:

i. The order in which the parts are mixed.
ii. Speed of mixing.
iii. Time to mix.
iv. The rate at which granulating agents, liquids, drug solutions, and other things are added.
v. Rates of heating and cooling.
vi. Size filters (for liquids).

vii. Size of the screen (solids).
viii. The temperature and length of time for drying.

Knowing how different process factors, like the ones listed above, affect the process is what makes process optimization and validation possible.

9. Master Manufacturing Procedures:

i. The weight sheet should make it clear which chemicals are needed for a batch. To keep things clear, batch records should list the names and identification numbers of the ingredients.
ii. The steps for the process should be easy to understand and follow. The real manager needs to write an output method.
iii. In the batch record directions, there should be a list of specifics, such as how much to add, how long to mix, how fast to mix, how to heat and cool, the temperature, and how to store samples of the finished product.

10. Product Stability and Uniformity:

i. The pilot plant's main goal is to make sure that the goods are stable in both their physical and chemical forms.
ii. So, it's important to check how stable each pilot batch is since it reflects the final recipe and production process.
iii. Stability tests should be done on both the raw materials and the finished package.

1.5 GMP Considerations

1. Getting along with the rules.
2. Designing and taking care of facilities.
3. System for managing quality (QMS).
4. Training for employees and cleanliness.
5. SOPs stand for standard operating procedures.
6. Maintenance and testing of equipment.
7. Control of raw materials.
8. Writing things down and keeping records.
9. Being valid and qualified.
10. Tests on the product and quality control (QC).

❖ **Advantages:**

1. Scale-up runs are easy for people in the production and quality control departments to see.
2. The more open places given to the production division can be used to get drugs and excipients that have been approved by the quality control division.
3. For installing, maintaining, and fixing tools, you can talk to people in the engineering department.

❖ **Disadvantages:**

1. There will be less direct contact between the formulator and the production staff in the manufacturing area.
2. Any problems with production will be directed at the people who work in the test plant.

1.6 Scale-Up

It's the art of making a prototype using information from the pilot plant model.

Objectives:

1. Make sure that the process can be repeated at higher rates.
2. Keep the quality and consistency of the goods.
3. Improve the cost-effectiveness and speed of production.
4. Find possible problems or risks and do what you can to fix them.
5. Check that the equipment is ready for large-scale output.
6. Make sure that legal standards are followed.
7. Get the best output with the least amount of waste.
8. Make it easy for technology to move from research and development to production.
9. Take safety and the surroundings into account.
10. Make sure that methods and controls are well documented.

Need of Scale-Up:

1. A clear-cut process.
2. A perfect result in the lab and the pilot plant.
3. But it might fail QA tests.
4. Because methods change depending on the size.
5. On a small scale and a big scale, processes work in different ways.
6. To find out how scaling up affects product quality, you have to grow up.

1.7 Pilot Plant Scale-Up Techniques for Tablets

The main job of the test plant crew is to make sure that the newly formed tablets made by product development workers can be made on a large scale in a way that is effective, cheap, and reliable. The pharmaceutical pilot plant for tablet development should be built and designed in a way that makes it easy to clean and maintain. If you want to speed up the supply and distribution of goods, it should be on the ground floor.

1. How to formulate and create a process.
2. Tech review, scaling up, and transfer.
3. Making clinical supplies.

Control Pilot Plant Studies:

1. It is possible to test a product and process on a small scale with a pilot plant before spending a lot of money on full-scale production.
2. Most of the time, you can't tell what will happen when you increase the scale by a lot.
3. It is not possible to successfully plan a large-scale processing plant based only on data from a lab.

Product Considerations:

1. Material Handling:

In the lab, it's easy to scoop or pour materials by hand, but in larger or more complex projects, it's often necessary to handle these materials. People who use the same method to move ingredients for more than one product must be careful not to cross-contaminate them. Any material handling method must get the exact amount of the part to where it needs to go. Screw feed systems, metering pumps, and vacuum loading systems are some of the more modern ways to handle materials.

2. Dry Blending:

The granulation jar is the right place for the dry mix. It is possible to dry mix a bigger batch before breaking it up into many pieces to make granules. The flow will be slowed down if any of the parts have lumps in them. To make the process more reliable and consistent, the materials are often screened and/or ground before they are mixed. To blend things, people use V-blenders, double cone blenders, ribbon blenders, slant cone blenders, bin blenders, rotating screw blenders, vertical and horizontal high intensity mixers, and other tools.

Scale-up Considerations:

- Powders that will be encapsulated or crushed before being made into tablets need to be well mixed to make sure the drug gets to all the cells.
- Drug content uniformity could change if the blending isn't done right, especially if the pill or capsule is small and the drug concentration isn't very high.
- Ingredients shouldn't have any lumps in them; if they do, it could block the flow.

3. Granulations:

Most of the time, granulating is done to improve the flow properties of the material, make the powders seem denser, change the distribution of particle sizes, make sure the active ingredient is evenly spread, and so on. In the past, a heavy-duty planetary mixer and a Sigma blade mixer were used to do wet granulation:

- to improve how the flow works.
- to make the powder look like it has more mass.
- to change the distribution of particle sizes so that the binding and compaction features can be made better.

Direct compression method: The best way to spread a small amount of a strong active ingredient is through a carrier granulation. This is when the medicine is mixed with a granulating solution and added while the granulation is happening. The following tools were used to finish the wet grinding process:

- Blades from Sigma.
- Heavy-duty mix of planets.
- Chopper blades that move quickly and are used to mix light powders.
- Processors that can do more than one thing, like dry mixing, wet granulation, drying, sizing, and lubricating.
- What the binding agent does.

4. Drying:

Among the most common techniques for drying granulations the old-fashioned manner is still the revolving hot air oven, which may be powered by steam or electricity. The flow of air, the ambient temperature, and the quantity of granulation on the trays are all important considerations when expanding an oven drying operation.

Bed Dryer with Fluid:

- The best loads—the breathing rate.
- Air temperature coming in.
- Dew point.
- Data from small batches (1–5 kg) can't be used to figure out how to process intermediated batches (100 kg) or big batches.

5. Reduction in Particle Size:

How a granulation compresses depends mostly on the particle size and how the particle sizes are spread out in the granulation.

The particle size distribution can affect a number of factors, such as the ability to flow, the ability to compress, the weight uniformity, the content uniformity, the hardness of the tablets, and the colour uniformity of the tablets.

Equipments:

- Granulator that is oscillating
- A mill with hammers.
- A device for screening.

Too large particle size causes:

- Changes in weight
- Mottling

Too fine particle size causes:

- Changes in weight.
- Capping.
- Granulation that is too big or too small can both make tablet material less uniform.
- Giants and lubricants are put at the end of the blend.

Blending:

You should make sure that the blender loads, mixing speeds, and mixing times are all set correctly and at the right scale.

When you blend something, segregation and mixing happen at the same time. The two depend on the particle size, shape, hardness, density, and the dynamics of the mixing action. Low dose active ingredients are directly squeezed.

Equipment:

- Mixer of the planetary type
- Mixture of twin shells
- Shape of a cone

Over loading in blender:

- Slows down the flow of granules
- Makes things less efficient
- Makes the information uneven If the load is too small:
- Instead of rolling in a mixer, powder blend slides.
- It leads to bad mixing.

6. Slugging:

A dry powder mix can't be directly crushed because it doesn't have the right flow or compression properties. A normal tablet press works with less than four tonnes of pressure. The sluggers, on the other hand, work with about fifteen tonnes of pressure, which makes it easier to join them on the tablet press. It is easier to use ¾ inch slugs for materials that are less resistant to slugging, while 1 inch slugs are for materials that are harder to crush and need higher pressures per unit area to make good compacts. If the milling stage makes too much fine material, it has to be a part of the material, and the ground-up finer amount is put back into the slugging process.

7. Compression:

A high-speed tablet press can be used to put the tablet formulation and granulation to the final test.

Steps that are taken during compression:

i. Using granulation to fill an empty die hole.
ii. Granules are compressed first.
iii. Granules are pressed together.
iv. The tablet is pushed out of the die hole.

When the press speed is set to normal output speed, the compression characteristics can be judged.

Then find the issues, such as

- Getting stuck on the punch surface
- How hard a tablet is
- Putting on caps
- Changes in weight
- Granules need to be sent out at the right rate.

8. Tablet Coating:

Pan coating and fluidized coating:

- Best way to load a tablet.
- Setting the warmth of the tablet bed.
- The rate and temperature of wind for drying.
- The rate at which the solution is used.
- The size and shape of the nozzle opening (for airless sprayer).
- In air-atomized sprayers, these are the atomizing air pressure and the flow rate of the liquid.

Pan coating:

- Set settings for operation.
- Operating conditions that can change.
- Other factors include Pan Loading (kg), Number of spray guns, Drying Air (cfm), Inlet Air Temperature (°C), Gun to Tablet Bed Distance, Coating System Spray Rate (g min−1), Amount of Coating Applied (% w/w), Atomizing Air Pressure (psi, bar), Air Pressure (psi, bar), Pan Speed, and the amount of solids in the coating suspension.

Fluidized bed coating:

- Size of the batch.
- Moving large amounts of air around.
- How the spray tube works.
- Rate of spray evaporation.

Equipment:

- A normal finishing pan.
- Fluidized-bed covering column pans with holes in them.

Types:

- Covered in sugar.
- Coating with film.

Tablets need to be tough enough to handle being tipped over while they are being coated.

If the pan or column method is chosen, the following conditions must be met: the best tablet load, the working tablet, the bed temperature, the drying air flow rate, the temperature, and the rate at which the solution is applied.

1.8 Pilot Plant Scale-Up Techniques for Capsules

Drugs come in capsules, which are solid dose forms. The drug is inside a hard or soft, soluble shell or container made of the right kind of gelatine.

Different Steps in Making Capsules:

- Mixing of the parts
- Lubrication and swelling
- How tablets are made
- Putting pills inside
- Checking for uniformity
- Sticking labels on boxes

Tablets and capsules are both made from ingredients that are either dry-blended or wet-granulated to make a dry powder or granule mix that has the active ingredients spread out evenly. To use high-speed tools to make capsules, the powder mix needs to have a uniform distribution of particle sizes, a low bulk density, and the ability to be compressed. This will help it flow well and form the right-sized compact that sticks together enough to fill capsule shells.

Manufacturing of Hard Gelatin Capsules

Shell Composition:

- **Gelatin:** Collagen is broken down by water to make it. Gelatin comes in two main types: Type-A and Type-B. The isoelectric points of type A and type B are different. Type A's are between 7.0 and 9.0, and type B's are between 4.8 and 5.0. They can also be told apart by their viscosity and ability to make films.
- To improve the shell's properties, pork skin and bone gelatin are often mixed together. The bloom strength and viscosity of gelatin are the physicochemical qualities that shell makers are most interested in.
- **Colorants:** A number of synthetic colors that dissolve (coal tar dyes) and pigments that don't dissolve are used. Colorants help you tell what the product is, and they also help patients follow the directions better. For instance, white can ease pain, lavender can cause hallucinations, and orange or yellow can be used to treat depression and stimulate the mind.
- **Opaque agents:** Titanium dioxide can be added to make the shell opaque. For defence against light or to hide the contents, opaque capsules can be used.
- **Preservatives:** When stabilizers are used, parabens are often the ones that are chosen.

Shell Manufacturing:

- **Dipping:** Pairs of the stainless-steel pins are put into the dipping solution so that the caps and bodies can be made at the same time. The pins are at room temperature, but the dipping solution stays at about 50oC in a hot pan with a jacket. It was said that it took about 12 seconds to cast the picture.
- **Rotation:** The pins are raised and turned two and a half times so that they face upward after dipping. That way, the gelatin is spread out evenly over the pins, and a bead doesn't form at the ends of the capsules.
- **Drying:** The racks of pins covered in gelatin are then put into a set of four ovens to dry. Dehumidification is the main way that things dry out. To keep the film from melting, the temperature can only rise by a few degrees. If the films are dried too slowly, they will become too sticky to use again.
- **Stripping:** A set of metal jaws separate the capsules' caps and bodies from their pins.
- **Trimming:** The cap and body parts that have been stripped are sent to collects where they are securely stored. Knives are run along the shells to cut them to the right length as the collects turn.
- **Joining:** The cap and body parts are lined up in channels so that they are concentrically matched, and they are slowly pushed together.

- **Sorting:** The capsules will have between 15 and 18% water by weight when they come out of the machine. During sorting, inspectors look at the packages as they move along a lit conveyor belt. Most of the time, defects are put into groups based on what kind of trouble they might cause when used.
- **Printing:** Most of the time, packages are printed before they are filled. The most common type of printing machine is an offset rotating press, which can make up to 375 million capsules per hour.
- **Sizes and Shapes:** There are eight sizes and shapes of empty gelatin capsules made for human use, running from 000 to 5.A no. 0 is usually the biggest size that a patient will accept. For veterinary use, there are three bigger sizes: 10, 11, and 12, which can hold about 30, 15, and 7.5 grams, respectively. The standard form for capsules is a traditional bullet shape that is symmetrical. Different forms have been used by some manufacturers. Lilly's pulvule, for instance, ends in a sharp point, while Smith Kline Beacham's spansule capsules narrow at both the cap and body ends.
- **Sealing:** During the Etaseal process, capsules are sealed and changed in some ways. When this process is used, heat is used to make a ring with depressions around the capsule's waist, where the cap meets the body.
- **Storing:** When capsules are finished, they usually have an average moisture content of 13–16%. This keeps the relative humidity between 40 and 60% while they are being handled and stored.

Filling of Hard Gelatin Capsules:

- The equipment used to fill capsules usually has one of two types of filling systems:

i. **Zanasi or Martelli encapsulate:** This makes slugs in a dosa tar, which is a hollow tube with a pusher that pushes out the capsule plug.

ii. **Hofliger-Karg machine:** When tamping pins are used on a die plate, the Hofliger-Karg machine makes a compact.

- When these two systems are scaled up, the bulk density, powder flow, compressibility, and lubricant spread all play a role. Granules that are too lubricated are what slow down the breakdown and disintegration of capsules.
- The Semi-Automatic Osaka Model R-180 Capsule Filling Machine.

Manufacturing Soft Gelatin Capsules

Composition of the shell:

- Soft gelatine shells are mostly made up of gelatine, just like hard gelatine shells, but the shell has been shaped to be more flexible.

- How "hard" the shell is depending on the amount of dry plasticizer to dry gelatine. For a very hard shell, the ratio can be between 0.3 and 1.0, and for a very soft shell, it can be between 1.0 and 1.8.
- Up to 5 percent sugar can be added to make the shell "chewable."
- After the pills are finished, the amount of shell moisture that is left will be between 6 and 10 percent.

Formulation:

- Liquid technology, not powder technology, is used to make soft gelatin pills. The materials are usually made to make the smallest capsules possible while still keeping the highest standards of stability, medicinal effectiveness, and manufacturing efficiency. The only solutions that can be used are those that don't hurt the gelatin walls. The lipid can have a pH of 2.5 to 7.5. Emulsion can't be filled because the water that comes out of it will damage the shell.
- There are two main types of cars that are used in soft gelatin capsules:

i. Liquids that don't mix with water, are volatile, or are likely to be more volatile, like mineral oils, veggie oils, medium-chain triglycerides, and acetylated glycerides.

ii. Liquids that don't evaporate easily and mix with water, like low molecular weight PEG, have recently become popular because they make it easier for drugs to dissolve or mix with water. Any liquid that is used for filling has to be less than 35°C and be able to flow by gravity. Gelatin films can be sealed at temperatures between 37°C and 40°C.

Manufacture Processes:

1.Plate method: This is what the method does:

- Putting the top half of a gelatin sheet that has been plasticized over a die plate that has many die holes,
- The use of vacuum to pull the paper into the die holes,
- Putting liquor or paste in the pockets,
- Folding the bottom half of the gelatin sheet back over the holes that have been filled
- Putting the "sandwich" under a die press, which makes the capsules and cuts them out.

2. Rotary Die Press:

- The die holes are machined into the outside of the two wheels in this process.

- The left side of the capsule is made up of the die pockets on the left roller. The right side of the capsule is made up of the die pockets on the right roller.
- The liquid or paste fill is constantly and simultaneously fed between the rollers of the rotating die mechanism onto two plasticized gelatin ribbons.
- As the die rolls turn, the matched die pockets press together to seal and cut out the capsules.

3. Accogel Process:

- In general, this is another rotating process with a die roll, a sealing roll, and a measuring roll.
- The amounts that have been measured are moved to the pockets of the die roll that are held together by gelatine as the measuring roll and die roll turn.
- The filled die keeps turning until it meets the spinning sealing roll. This is where a second gelatine sheet is put on to make the other half of the capsule. The capsules are sealed and cut out by the pressure that builds up between the die roll and the closing roll.

4.Bubble Method:

- The "bubble method" used by the Globex Mark II capsulate makes soft gelatine pills that are truly seamless and made of a single piece. A concentric tube dispenser lets the hot gelatine out from the outer ring and the liquid inside the tube out at the same time. The liquids are pushed out of the concentric tube opening into a chilled-oil column by a pulsating pump system. They come out as droplets with a liquid medicine core and a molten gelatine envelope. The surface tension forces make the drops round, and as the mixture cools, the gelatine hardens. Once the pills are done, they need to be cleaned and dried.

Soft/Liquid-filled Hard Gelatin Capsules

- Three formulation methods have been talked about that are based on having a high viscosity at rest after filling:
  - Formulations that thicken,
  - Formulated for thermal setting,
  - Mixed systems with heat and viscosity.

  It takes longer for things to release when they have more lipophilic contents. So, different release rates can be achieved by choosing excipients with different HLB balances.

- For high-speed tools to make capsules, the powder mix must have
  - Particles of the same size all over.
  - Dense chunks.
  - Making a compact that is the right size and sticks together well enough to be put inside capsule shells.
- **Equipment:**
  - Zanna or Mertalli: Dosator (tube with a hole in it).
  - Hoflinger-Karg: Pins for tamping.

With these two ways, you might run into problems with weight variation. Granules that are too lubricated, which slows down breakdown.

- Humidity changes the amount of water in:
- Bringing up
- On gelatine packages that are empty.
- **At high humidity:** When there is a lot of moisture in the air, the capsule swells up, making it hard to separate the parts and stop the capsule from moving through the process.
- **At low humidity:** When humidity is low, the capsule becomes brittle, and a rise in static electricity stops the encapsulation process.

Examination of the formula to determine:

1. Being able to handle batch-scale.
2. Changes to the process.
3. How well the tools work with the recipe.
4. The cost factor.
5. Needs physical space.
6. Needs of the market.
7. Layout of the tasks that are connected.
8. Getting the raw products that meet the requirements.

1.9 Scale-Up Liquid Orals

1. A drug product that can be poured has a shape that flows in a Newtonian or pseudoplastic way and fits into its container when it is at room temperature.It's possible for liquid dosage forms to be spread systems or solutions.
2. There are at least two stages in a dispersed system, and one phase is spread out in another.

3. A solution is a mixture of two or more elements that are all the same.

Steps in Liquid Manufacturing Process:

1. Planning what materials will be needed.
2. preparation of liquid.
3. Filling and putting away.
4. Making sure of quality.

Critical Aspects of Liquid Manufacturing:

Table No.1.1: Formulation Aspects of Suspensions

Sr. No.	Purpose	Agent
1.	Facilitating the connection between API and vehicle.	Wetting agents.
2.	Protecting the API.	Buffering-systems, polymers, antioxidants.
3.	Maintaining the suspension appearance.	Colorings, suspending agent, flocculating agent.
4.	Asking the unpleasant taste/smell.	Sweeteners, flavorings.

Table No.1.2: Formulation Aspects of Emulsions

Sr. No.	Purpose	Agent
1.	Particle size	Solid particles, droplet particles
2.	Protecting the API	Buffering-systems, antioxidants, polymers
3.	Maintaining the appearance	Colorings, emulsifying agents, penetration enhancers, gelling agents
4.	Taste/smell masking	Sweeteners, flavorings

Table No.1.3: Formulation Aspects of Solutions

Sr. No.	Purpose	Agent
1.	Protecting the API.	Buffers, antioxidants, preservatives.
2.	Maintaining the appearance.	Colourings, stabilizers, co-solvents.
3.	Antimicrobial.	Preservatives.
4.	Taste/smell masking.	Sweeteners, flavourings.

Equipment Used:

1. Mixer
2. Mixing agent
3. Filtration set up
4. Assembly for bottling

General Flow Chart for Making Oral Liquids:

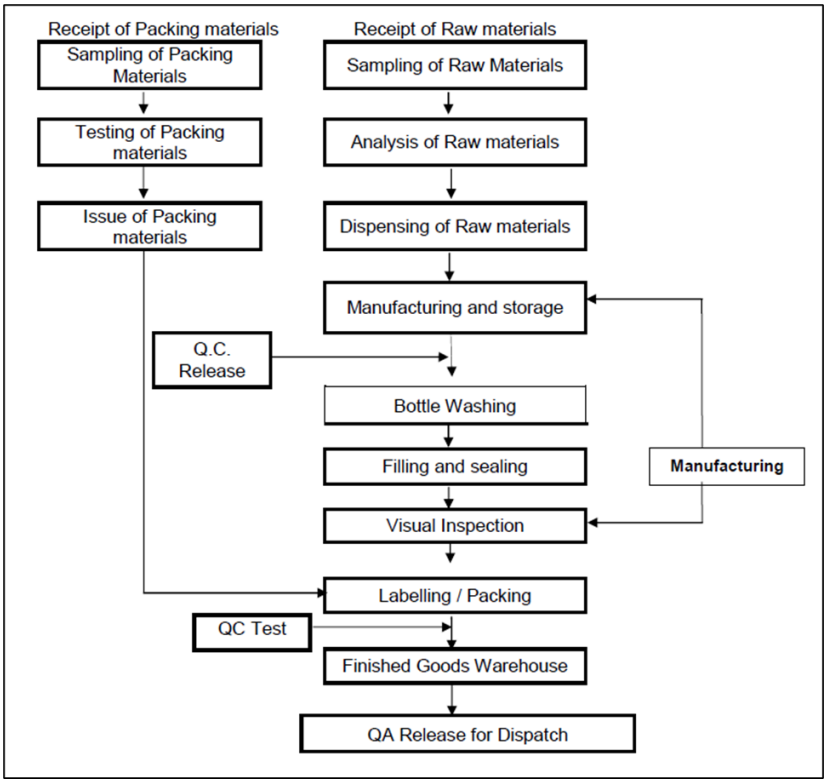

Fig. No.1.4: Chart for Making Oral Liquids

Quality Assurance:

- How drugs break down in solution
- The amount of drugs that can be suspended
- Even temperatures in emulsions
- Control with microbes
- Uniformity of the product
- The last book
- Being stable

1.10 Semi-Solid Dosage Forms

- In general, semisolid dose forms are complicated mixtures with complicated building blocks.
- They often have two parts: an oil and water phase that flows continuously (externally) and a water phase that spreads out (internally).
- The active ingredient usually dissolves in one phase. But sometimes the drug isn't fully soluble in the system and is spread out in one or both phases, making a three-phase system.

Parameters:

1. Most of the time, it doesn't matter what order the solutes are added to the solvent for a real solution.
2. Scattered formulations, on the other hand, can't be said to be the same because the way scattered matter spreads out depends on which phase it is added to.
3. The most important parts of a normal production process are when the active ingredient is added and when a one-phase system is first split into two phases.
4. In particular, this is important for solutes that are added to the mixture at a concentration that is close to or higher than the temperature at which the product will be used.
5. Any changes that happen in the manufacturing process after either of these events are likely to have a big effect on how the end product works.
6. This is especially true for any process, like homogenization, that aims to increase the degree of dispersion by making droplets or particles smaller.
7. It is very important that the finished bulk product is aged before it is packaged, and this should be specifically looked at in process validation studies.

1.11 Pilot Plant Operation

Validation:

1. Details of the design.
2. Qualifications for installation.
3. Qualification for operations.
4. Qualification based on performance.

Following the rules set by cGMP and the FDA.

Training:

1. Technical know-how and skills.
2. Safety and taking care of the surroundings.
3. Following GMP rules.
4. Following the SOPs**.**

Engineering Support:

1. Plan for the building.
2. coordinating the schedule.
3. How things are being run now.
4. Validation of the building.
5. Building of the building.

Maintenance and Calibration:

1. To make sure the study is honest and the equipment works well.
2. To follow cGMP rules.

Computerized System:

1. Control of materials
2. Labelling (GMP and GLP)
3. Stock List
4. Stocks (FIFO)

Process and Manufacturing Activities:

1. Studies on formulation and process improvement.
2. Evaluation of technology that can be scaled up and moved.
3. Supply and production for clinical use.

Quality Assurance:

1. Checking the test plant.
2. Checking and approving the quantities of parts.
3. Going over the approval and mainframe batch records for medical goods.
4. Taking samples and letting go of raw materials.
5. Giving out medical materials.
6. Cleaning and spreading safety and operating procedures (SOPS).
7. Validation is looked over and approved.
8. Documentation for engineers.

Quality Control:

1. Release testing of the complete product.
2. Testing finished medical goods physically, chemically, and microbiologically, as well as parts needed for supplies.
3. Checking to see if it's valid and checking again.
4. QC in process testing during creation, scaling up, and the transfer of technology.

Plant: This is the place where the 5Ms (money, materials, labor, method, and machine) come together to make the something.

1. In the last 25 to 30 years, study into pharmaceuticals has moved forward.
2. Have seen amazing inventions and new ideas in the pharmaceutical area.
3. The NDA and ANDA are at their highest points ever.
4. It is important for researchers to use new methods and tools.
5. For the clinical tests and bioequivalence study to go well, scale-up batches are a must.
6. A pilot plant scale-up is one of the most important steps in making a new product.

1.12 Scale-Up and Post Approval Changes (Supac)

The FDA and the American Association of Pharmaceutical Scientists (AAPS) gave the scientific basis for the changes that had to be made to the immediate release product called SUPAC after it was approved.

It provides guidelines for post approval changes in the following:

1. The Parts
2. Parts and pieces
3. Place where goods are made

4. The process and the tools

Significance of Pilot Plant:

1. Formulas are looked at.
2. Review of the range of processing tools that is needed.
3. Changes to the production rate. idea of how much space is needed.
4. The right records and papers to back up GMP.
5. Finding the most important traits to keep quality high.

Advantages:

- It's easy for people in the production and quality control departments to see scale-up runs.
- The production division has been given more space to store drugs and excipients that have been approved by the quality control division.
- People from the engineering area can be used to install, maintain, and fix equipment.

Disadvantages:

- There will be less direct contact between the formulator and the production staff in the industrial area. Any problems with production will be directed at the people who work in the test plant.

General Stability Consideration:

- It should be looked at what changes to SUPAC might mean for the safety of the drug product. See the FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics for basic information on how to do stability studies.

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

- Most of the time, stability data from pilot scale batches will be enough to back the proposed change. The only exceptions are cases involving scale-up.
- If stability data show that the substance loses its effectiveness or gets worse faster, it is suggested that historical rapid stability data from a batch that is representative of the whole batch be sent in for comparison.
- Due to these circumstances, it is also suggested that all long-term statistics on test batches from ongoing studies be included in the supplement.
- It would be easier to review and approve the supplement if past accelerated and available long-term data were sent in.

1.13 Introduction To Platform Technology

Platform technologies are seen as a useful way to make the process of making new drugs faster and better. The main idea is that using a platform and a risk-based technique together is the best way to make the most of what we already know about a new molecule. Moreover, this kind of platform can keep getting better by adding data for each new molecule created using this method, which makes the platform more reliable. The technology gives companies clear benefits over their competitors. It can greatly increase the solubility of complex molecules because it is submicrometric and has systems that stick to skin for a longer time. It's also adaptable, as it can hold a lot of different active principles and its systems can be changed to get the qualities that are wanted.

- The technology is also strong and flexible, with important features like
- How stable and soluble the active molecule is chemically.
- It is possible to get high drug loads.
- Very good at sealing.
- Created an industry process and made it possible to grow.
- Technologies that are stable, easy to use, and don't need solvents.
- Remaking drugs whose patents are about to run out.
- The creation of drugs that were thought to be impossible before.
- New ways to give different chemicals to people

Review Questions

Short Answer 02 marks

1. Describe the pilot plant and its importance. Describe the objectives for scaling up the pilot plant.
2. Explain the reasoning for the pilot plant research.
3. What is SUPAC? Describe the goal of the SUPAC recommendations.
4. Describe platform technology and its significance.
5. Describe the various degrees of change as determined by SUPAC.

Short Essay 05 marks

1. What cGMP factors need to be taken into account when scaling up the pilot plant?
2. Provide the infrastructure and design for the scale-up of the pilot plant.

3. Write a note on State Drug Control Organization
4. What facilities and circumstances are needed for the HGC/liquid orals pilot plant scale up?
5. Describe the SUPAC rules for site modifications, batch sizes, equipment, and procedures.
6. Describe SUPAC. Describe the various change levels in accordance with SUPAC.

Long Essay 10 marks

1. Describe the general factors to be taken into account when using pilot plant scale up approaches.
2. Describe the process for scaling up the tablet prototype facility.
3. Describe the process for scaling up the pilot plant for liquid orals.
4. Showcase and talk about the scale-up considerations for liquid orals in pilot plants.
5. Describe the infrastructure and state of the tablet pilot plant scale up.

References

General considerations:

1. Wood-Black, F. (2014). Considerations for scale-up–Moving from the bench to the pilot plant to full production. In *Academia and Industrial Pilot Plant Operations and Safety* (pp. 37-45). American Chemical Society.

Pilot plant for solid, liquid, semisolid:

2. Kiran, R. S., Pranitha, T., Shirisha, V., Meenakshi, V., & Rao, T. R. (2022). Review on Pilot Plant Scale up Techniques Used in Solid, Liquid and Semisolids. *Systematic Reviews in Pharmacy*, *13*(6).

SUPAC guidelines:

3. Pund, S., Dhande, M., Jayatpal, S., Tupe, A., Deore, S., & Tare, H. (2024). Scale-up and postapproval changes (SUPAC) guidelines for industry: A comprehensive review. *Multidisciplinary Reviews*, *7*(4), 2024071-2024071.
4. Yelvigi, M., Chambliss, W. G., & Sam, T. (2013). Scale-Up and Post Approval Changes (SUPAC). In *Encyclopedia of Pharmaceutical Science and Technology, Six Volume Set (Print)* (pp. 3052-3055).

Introduction to platform technology:

5. Levandowski, C. E., Corin-Stig, D., Bergsjö, D., Forslund, A., Högman, U., Söderberg, R., & Johannesson, H. (2013). An integrated approach to technology platform and product platform development. *Concurrent Engineering*, *21*(1), 65-83.