CHAPTER - 1

Pilot Plant Design

Introduction, Basic Requirements for Design, Facility, Equipment Selection for Tablets, Equipment Selection for Capsules, Equipment Selection for Liquid Orals, Equipment Selection for Parenterals, Equipment Selection for Semisolid Preparation

INTRODUCTION

Pilot plant is *a place where the 5 M's like money, material; man, method and machine are utilized to perform the manufacturing of the products.* A pilot plant is a pre-commercial production system. It employs new production technology and/or produces small volumes of new technology-based products, mainly for the purpose of learning about the new technology. The technology obtained is then used for design of full-scale production systems and commercial products, as well as for identification of further research objectives and support of investment decisions. Other purposes include gaining public support for new technologies and questioning government regulations. Pilot plant studies must include a close examination of formula to determine its ability to with stand batch scale and process modifications; it must include a review of range of relevant processing equipment, also availability of raw materials meeting the specification of product. During the scale up efforts in the pilot plant production and process control are evaluated, validated and finalized.

The necessity of pilot plants development in pharmaceuticals has been felt extensively. The dispute comes out primarily on the need for piloting the processes is the production of organic chemicals. Baekeland's[1] famous comment, *Commit your blunders on a small scale and make your profit on a large scale*, can be applied to this situation where the pilot plant represents an intermediate stage between the laboratory studies and the industrial/ commercial plant. The necessity of the pilot plant will depend on the complexity of the formulation and the experience available. The pilot plant must be understood just not as a scale-up of laboratory equipment[2], but as a small scale simulation of the future industrial operations. Results of the laboratory studies will be used to choose the most suitable process and will lead to the selection of the equipment for each stage of the flow sheet. If the laboratory studies are positive and the pilot plant studies are necessary. The pilot plant will be designed to simulate the industrial operations. It is not

always necessary that the pilot plant include all of the flow sheets, but it must include at least those which

a) Require equipment not frequently used;
b) Fair and markedly different from conventional practice
c) Have caused some problems at the laboratory scale; and
d) Have some elements, even trace elements, that might build up in some streams, for example in solvent extraction.

In pilot plants for new chemical processes it is usually desirable to use the same materials of construction that will be used in the industrial plant.

Pilot plant is defined as a *part of the pharmaceutical industry where a laboratory formula is transformed into a viable product by the development of liable practical procedure for manufacture.*

As per the definition given above, a pilot plant is a pre-commercial production system that uses new production technology and/or produces small volumes of new technology-based products, mainly for the purpose of learning about the new technology. The knowledge obtained is then used for design of full-scale production systems of commercial products, as well as for identification of further research objectives and support of investment decisions. The schematic development of final of drug product from R & D to commercial production has been shown in Fig,1.1 below.

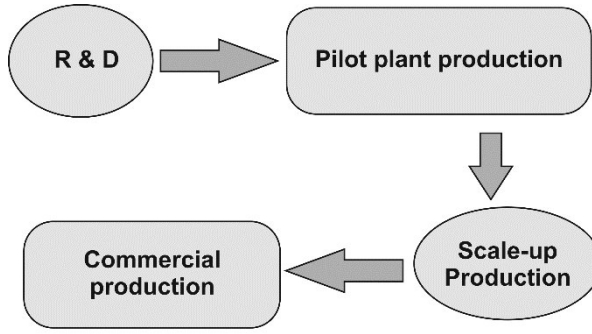

Fig.1.1 Schematic diagram of processes involved in design of pilot plant.

During the scale up experiments in the pilot plant production and process control are evaluated, validated and finalized[3].

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

Therefore, pilot plant can be designed for

- Evaluation of the results of laboratory studies and making the product and process corrections and improvements.
- Production of small quantities of the product for sensory, chemical, microbiological evaluations. Limited market testing or furnishing samples to potential customers, shelf-life and storage stability studies.
- Generating data that can be used in making a decision on whether or not to proceed to a full-scale production process. In case of a positive decision, designing and constructing a full-size plant or modifying an existing plant.
- Type and size of a pilot plant depends on the goals, evaluation of product and process; producing samples of product for evaluation.
- Close liaison between R&D and pilot plant is essential.
- Labour requirements and costs of staff, skilled operators and maintenance staff-pilot plant costs may exceed those of usual plant production costs.
- The pilot plant may be used for training of personnel for a full- scale plant.

To attempt a process on a model of proposed plant before committing large sum of money on a production unit[4].

The significance of a pilot plant is[3] to

- Standardize a formulae.
- Review the range of relevant processing equipment.
- Optimize and control of production rate.
- Inform about the infrastructure of equipment during the scale up batches and about the physical space required.
- Identify the critical features to maintain quality of a product.
- Maintain the appropriate records and reports to support GMP.

Objectives of pilot plant

The main objective of the pilot plant is to check on a reduced scale, the process developed in laboratory studies. The decision to proceed with the full scale plant project should be based on a proven process, which gives a more reliable and economic estimate. Hence, to design correctly the full scale production, pilot plant and simulated full scale production using equipment of smaller capacity would be necessary. This is not only the purpose of a pilot plant. There are other objectives which should be fulfilled simultaneously and in some cases these objectives may provide the definitive considerations for the decision to build the pilot plant. Therefore, the objectives of a pilot plant, can differ depending on the specific circumstances of each project, and the decision for its conversion can include one or several of the following objectives:

- To optimize the operating parameters of the process,
- To study the effects of recirculating the process and accumulation of impurities over long periods.
- To obtain the process information necessary to specify and design the full scale plant,
- To test process control systems and procedures,
- To test materials of production,
- To optimize the requirement of the equipment.
- To obtain sufficient information to prepare a detailed and reliable estimates of capital and operating costs and to prepare a reliable economic evaluation of the project.
- To gain operating experience and to train the personnel that will operate the full scale plant,.
- To identify hazards in the process and ensure safety in design and operation, including the disposal of wastes[5-7]

In general, the products are prepared in the commercial scale after laboratory scale has been shown in Fig.1.2.

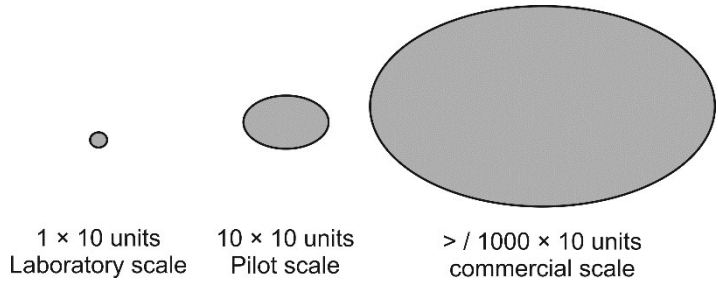

Fig.1.2 Progression of batches from laboratory to commercial scale.

BASIC REQUIREMENTS FOR DESIGN

Pilot plant can be viewed as a commercial manufacture of pharmaceuticals in miniature form. For preparation of any dosage form, the type and size of instruments/ equipment would not be same, for example, for making solution and blending for tablets[7], mixing is a common step but different type of mixers are required.

The design data required for each process can be classified under six heads:

- Data available from past experience.
- Data given in the laboratory report or which can be derived from the laboratory results.
- Data available in the literature.

- Data which can be approximated sufficiently and closely for design purpose by means of thermodynamic relations, the theorem of corresponding states, or some of the many empirical or semi empirical correlations that have appeared in recent year.
- Data which could be obtained by further research in the laboratory.
- Other practical felt to be necessary for design purpose.

Another important objective of a pilot plant is the training of personnel, especially in countries where similar processes do not exist. In this case, the personnel would be trained not only for operation of the different types of equipment, but only for control of the process.

FACILITY

Plant is a place where the 5's such as money, material, man, machine and method are brought together for the manufacturing of the product and pilot plant is a part of the pharmaceutical industry. A lab scale formula is transformed into viable product through the development of practical method of manufacture in a pilot plant.

The multi-functional facility will comprise a total area of about 50,000 sq. yard. It should be added substantial capacity to the current chemical development and API manufacturing capabilities of the company.

It will have facilities for testing of raw materials, intermediates and finished products. A separate quality assurance department will ensure that the output-quality meets established cGMP standards and manufacturing is carried out following the standard operating procedures.

Additional space should be made available for further expansions to support any increase in commercial manufacturing activities[8-10].

- Plant design should be made as per WHO-GMP norms.
- Uni-directional for Man and material flow should be provided.
- Separate and dedicated area for each activity based on respective formulation should be provided.
- In-house dedicated product testing facility should be there.
- The complete plant area should be centrally air-conditioned. The independent supply systems are fed with separated air handling units to avoid cross air contamination. Humidity, temperature and pressure gradients should also be maintained.
- For avoiding contamination in production area epoxy flooring is considered.
- Separate entry should be made for personnel and material in each critical production area to avoid cross contamination.

The following are the capacity of three common streams of the formulation and packaging plant:

Machine activity	Capacity
Capsule filling & sealing	500 caps./min (500 mg).
Semi-automatic capsule filling and sealing machine	60,000 caps/hr
Capsule Polishing Machine Empty capsule sorter	
Tablet compression	500 Tabs./min (500 mg)
Tablet compression Rapid Mixer Granulator (RMG)	 15/30 kg
Fluid bed drier (FBD)	30 kg
Roller compactor	20 Kg
Tablet compression machine	16 station
Auto coater	28" with 20" and 18" pan
Blister packing machine	100 blister/hr
Strip packing machine	100 strip/hr.
Liquid filling machine	40 bottles/min (100 ml)
Liquid online preparation tank	500ltr.
Bottle washing machine	3000-6000 Bottles/hr.
Bottle filling and sealing machine	40 bottles/hr.

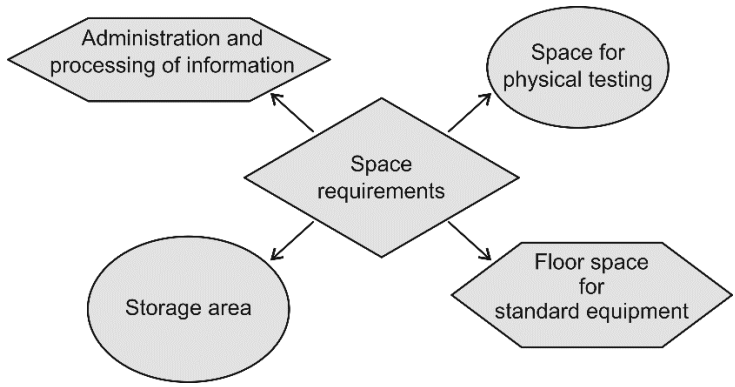

Fig.1.3 Schematic diagram for space required in pharmaceutical pilot plant.

In a large pharmaceutical organization, the development team may be made responsible for the transfer of new formulations to produce. A well-equipped space for conducting scale-up runs should also be provided. Such a developmental team may report administratively to the head of pharmaceutical research and development or the production head.

The various types of organizational structures that may exist in pharmaceutical pilot development, these are mentioned below.

- Research Pharmacist Responsible for Initial Scale-Up and Initial Production Runs
- Pharmaceutical Pilot Plant Controlled by Pharmaceutical Research
- Pharmaceutical Pilot Plant Controlled by the Production Division

Whatever may be the type of pharmaceutical pilot plant, the personnel working must be of very good educational background and must have some previous experience on pilot plant functioning. Let us discuss on a new tablet product.

A typical floor plan is shown in Figure 1.4; the floor plan reference is shown in Table 1.1. A typical floor plan for a small pilot plant is shown in Figure 1.5, and its reference is shown in Table 1.2. The variety of equipment installed must be narrow because of space limitations[11-13.] However, efficient use of such limited space can be made by borrowing from the production division, as required, portable tablet presses, mills, and coating pans.

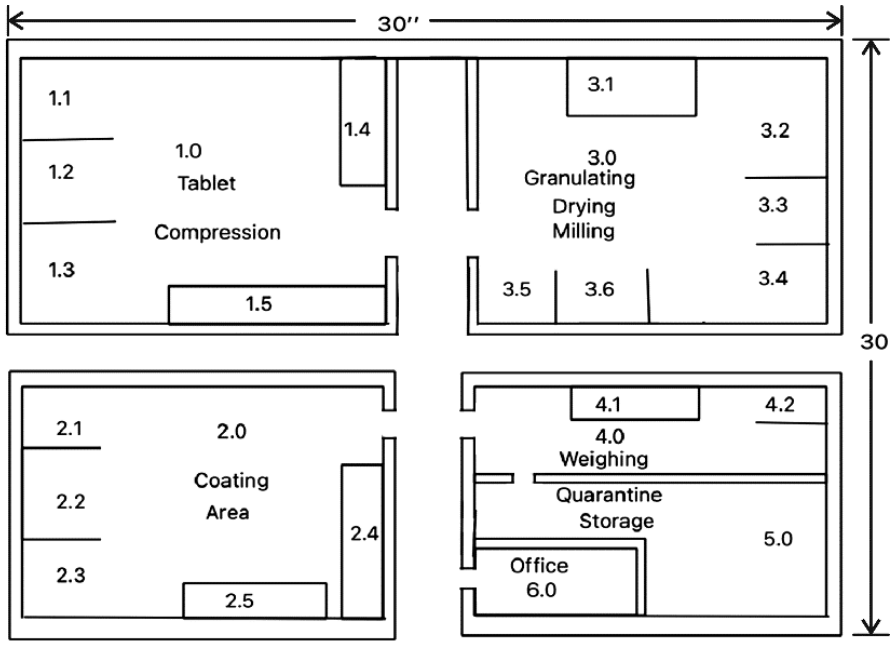

Fig.1.4 Floor plan for a small pilot plant for tablet development.

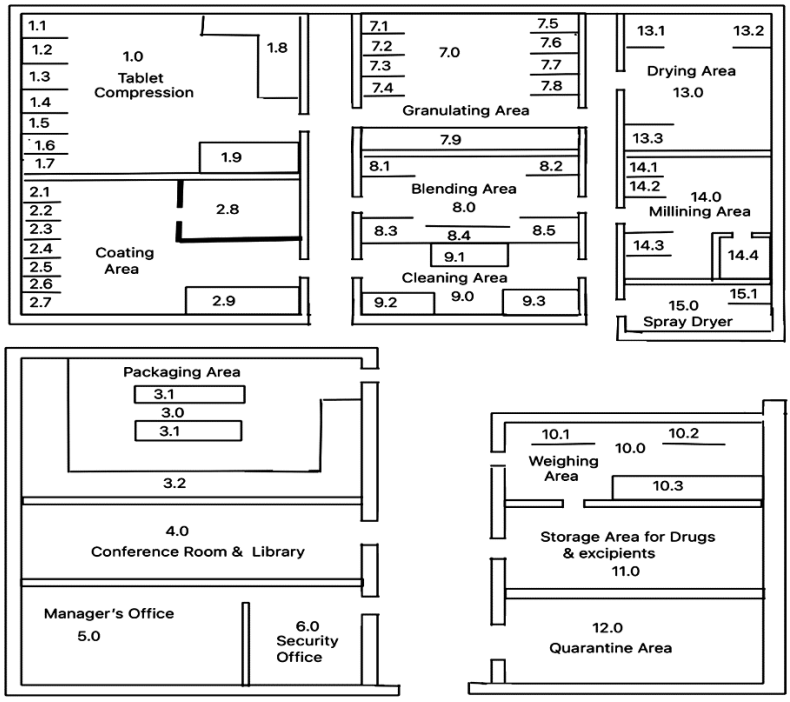

Fig.1.5 Floor plan of a pilot for development of a tablet.

Table 1.1 Floor plan for small pilot plant for Tablet manufacturing.

Sl. No.	Area specified for equipment	Sl. No	Area specified for equipment
1.0	Tablet compression room	3.0	Granulating, drying, and milling area
1.1	Tablet press, single-punch	3.1	Tray and truck dryer
1.2	Rotary tablet press 16 stations	3.2	Hobart mixer
1.3	Tablet deduster	3.3	Comminuting mill
1.4	Blench top with wall cabinets Ancillary equipment: Balances, Fibrilator, Dis-integration testing apparatus, Dissolution testing apparatus, Hardness tester	3.4	Hammer mill
1.5	Blench top with wall cabinets Ancillary supplies: Tools, Vacuum cleaner	3.5	Fluidized bed dryer

Table 1.1 ***contd…***

Sl. No.	Area specified for equipment	Sl. No	Area specified for equipment
2.0	Coating area	3.6	V-shaped blender with intensifier bar
2.1	Polishing pan, 36-in diameter	4.0	Weighing area
2.2	Coating pan, 36-in diameter	4.1	Bench top with wall cabinets
2.3	Airless spray equipment	4.2	Scale
2.4	Area for preparing syrups, Solutions, and suspensions for sugar or film coating	5.0	Quarantine and storage area
2.5	Sink	6.0	Office

Table 1.2 Floor plan (reference to Fig 1.5) of development of a tablet dosage form.

Sl. No	Area specified for equipment	Sl. No	Area specified for equipment
1.0	Tablet compression room	7.6	Comminuting equipment
1.1	Heavy-duty tablet press for dry granulation	7.7	Extractor
1.2	Rotary tablet press, 54 stations	7.8	Chilsonator
1.3	Rotary tablet press, 16 stations	7.9	Bench top with wall cabinets
1.4	Compression-coating tablet press	8.0	Blending area
1.5	Single-punch tablet press	7.6	Comminuting equipment
1.6	Tablet deduster	7.7	Extractor
1.7	Storage cabinet for the punches and dies	8.1	V-shaped blender with intensifier bar, 1 ft^3 capacity
1.8	Bench top with wall cabinets Ancillary equipment: balances, friabilator, disintegration-testing apparatus, dissolution-testing apparatus, hardness tester	8.2	V-shaped blender with intensifier bar, 5 ft^3 capacity
1.9	Bench top with wall cabinets Ancillary supplies: tools, vacuum cleaner	8.3	V-shaped blender with intensifier bar, 20 ft^3 capacity
2.0	Coating area	8.4	Ribbon blender
2.1	Coating pan. 36-in diameter	8.5	Lodige blender
2.2	Coating pan, 30-in diameter	9.0	Cleaning area
2.3	Coating pan, 20-in diameter	9.1	Sink
2.4	Perforated coating pan. 24-in diameter	9.2	Ultrasonic cleaner

Table 1.2 ***contd…***

Sl. No	Area specified for equipment	Sl. No	Area specified for equipment
2.5	Polishing pan	9.3	Bench top with wall cabinets
2.6	Fluidized bed coating apparatus	10.0	Weighing area
2.7	Airless spray equipment	10.1	Scale
2.8	Area for preparing syrups, solutions, and suspensions for sugar or film coating	10.2	Scale
2.9	Bench top with wall cabinets	10.3	Bench top with wall cabinets Small scales and balances positioned on bench top
3.0	Packaging area	11.0	Storage area for drugs and excipients
3.1	Working tables	12.0	Quarantine area
3.2	Storage cabinets containing packaging supplies	13.0	Drying area
4.0	Conference room & library	13.1	Tray and truck dryer
5.0	Manager's Office	13.2	Fluidized bed dryer
6.0	Secretarial Office	13.3	Freeze dryer
7.0	Granulating area	14.0	Milling area
7.1	Comminuting mill	14.1	Hammer mill
7.2	Sigma blade mixer	14.2	Ball mill3
7.3	Planetary-type mixer	14.3	Muller
7.4	Tornado mill	14.4	Fluid energy mill (micronizsrs) 2 in diameter
7.5	Fluidized bed spray granulator	15.0	Spray-drying area
		15.1	Spray-dryer

Communication between pilot plant (Research) and Quality Control and Production Department

When a formulation say, a tablet formulation has been developed at the pilot scale, it becomes responsibility of the tablet formulator to issue clearly in written instructions for its manufacture' for example, the use of micronized drug may be specified. Moreover, the analytical specifications for the ingredients must be thoroughly described unambiguously. The in-process control steps describing the milling conditions to be followed must also be written down. Moreover, the particle size characterization of the micronized material must be included. In other cases, the characterization would be included as a responsibility of research team to inform the quality control or purchased micronized bulk drug. The tablet formulator should be well aware of the necessity to use micronized material on the basis of dissolution studies

conducted during the early stages of formulation development. When bulk drug specifications are being established, such information becomes related to the members of the quality control and production divisions[14,15]. A raw material (RM) number is designated for the micronized bulk drug along with any physical or chemical information considered significant. Melting point is not only an important indication of the purity of a compound, it serves as an additional checkpoint for the desired polymorphic form on a crystalline compound. A stringently low trace metal content may be specified in some cases, if improved drug stability desires it. A typical specification sheet for ascorbic acid has been shown in Table 1.3. There may be several grades of particle sizes of ascorbic acid within the company. It is important to remember to specify the desired grade (Table 1.4 - 1.6) demonstrate manufacturing instructions for tablets containing 50 mg of hydrochlorothiazide. The sheet, Table. 1.5 listed the ingredients with mention of the amounts per tablet, and the amounts of each ingredient required for the batch size. In the Table 1.4 and Table 1.5 there may be the words "product code number." Such designation will help to avoid confusion by the various departments involved in the manufacture and release of the finished tablets. There may be hydrochlorothiazide tablet potencies other than 50mg also being manufactured in the company. When a new drug is to be marketed in a tablet dosage form a new product code number is assigned and subsequently used. There are columns headed by the words "compounded by" and "checked by". When each ingredient is weighed, the individual who has weighed, puts his or her initials alongside the ingredient weight. The observer of this operation also puts his or her initial as a double check on the accuracy of the weighing operation. A similar procedure is followed for each step in the compounding operation. Such double checking is required by the Food and Drug Administration for all new drug application-type products. Such a double-checking procedure should be followed to ensure that there are no weighing or compounding errors.

In the list of ingredients, the lot number of each ingredient and the code number allotted to each ingredient, may be active ingredient or excipient, used must be recorded. Such recordings are of special importance when one attempts to trace the history of a particular batch of tablets. Troubleshooting can be simplified in some cases by tracing the source of a raw material. A typical problem that may arise can be due to a particular lot number of a substandard excipient that could have been unintentionally used.

On the sheet of the proposed manufacturing instructions (Table. 1.4) the stepwise procedure to be followed (instructions) is required to be described. The words selected and written should be readily understood by the individuals who will be reading these instructions. Thus, the personnel of quality control department can consider the establishment of in-process

controls, pilot, and production operators who are supposed to follow the procedure for the first time. One should not be confused by cryptic phrases containing technical words and can easily understand. The tablet formulator should consider that his or her manufacturing procedure may also be circulated to foreign manufacturing organizations. Manufacturing instructions that are clearly written are also advantageous because they avoid confusion which may cause errors. Table 1.6 represents a list of specifications for the finished tablets indicating the product code and lot number. There are three forms which become a part of the file for the lot number of the batch of tablets prepared[17-19]. These three sheets work as a historical record. Attachments that are included, for example, would be the clearance data from the quality control department and a record of the physicians receiving the material for clinical study.

Table 1.3 Specification sheet for ascorbic acid.

Description	Specification
Ingredients	Ascorbic acid
Synonym	Vitamin C; L-Ascorbic acid, 3-Oxo-L--gulofuranolactone
Formula	$C_8H_8O_6$
Molecular weight	176.13
Product Code	SPVCOS
CAS No.	50-81-7
Properties	
Self-life	36 months
Description	White/ almost white crystals/ crystalline powder
Assay (GC)	99.0 - 100.5%
Melting point	190 - 192°C
Loss on drying	≧ 0.4%
Colour of solution	≧ BY_7
Clarity of solution	Clear
Optical rotation	+ 20.5 - +21.5°
Density at 20°C	1.65 g/ cm^3
pH (5% solution)	2.1 - 2.6
pH (2% solution)	2.4 - 2.8
Sulphated ash	≧0.1%

Table 1.4 A sample of manufacturing instructions to prepare hydrochlorothiazide Tablets.

Name of the Product: Hydro-chlorthiazide tablets Strength: 50 mg	**Product Code Number**	**Lot Number**	**Page 1**
Steps	Manufacturing Instructions	Compound by	Checked by
1.	Pass items 1, 2 and 3 through a #16 screen using a comminuting mill to break up any lumps		
2.	Blend the three Ingredients in a V shaped blender for 1 hour.		
3.	Add the magnesium stearate and continue blending for 15 mins.		
4.	Subdivide the blended material into polyethylene lined drums. Submit representative samples to the Quality Control division to determine the homogeneity of blend.		
5.	After receipt of clearance from Quality Control, tablet the blend with 5/16 standard, round concave puncres on the 54 station, rotary tablet machine.		
6.	Submit representative samples of the finished tablets to the Quality Control division for final release.		

Table 1.5 List of ingredients used in manufacturing hydrochlorothiazide tablets (50 mg).

Product and Strength Hydrochlorthiazide Tablets, 50 mg	Product Code Number		Lot Number			Page 2
	Batch Size 50,00,000			Starting Date		Completion Date
	Prepared By			Production Approval		Quality Control Approval	
Number Ingredient	Grade	Grams/ Tablet	Grams/ Batch	Compounded by	Checked by	RM	Lot
1. Hydrochlor-thiazide	U.S.P.	0.050	250.000				
2. Microcrystalline Cellulose (PH 101)	N.F.	0.050	250.00				
3. Dicalcium phosphate, dihydrate	N.F.	0.099	495.000				
4. Magnesium Stearate	N.F.	0.001	5,000				
Total		0.200	10,00,000				

Table 1.6 An example of tablet specifications of hydrochlorthiazide tablets.

Name of the Product: Hydrochlorthiazide Tabs. **Strength:** 50 mg	**Product Code Number**	**Lot Number**	**Page 3**
Tablet Specifications			
Each tablet weighs: 0.200 g Range of weight : 0.190 – 0.210 g Strength : 50 mg per Tablet Range of strength : 46.25 – 53.75 mg per Tab. Hardness of the tab : 7 – 9 (Strong-Cobb Units) Disintegration Time: Less than 5 mins. (USP method) Dissolution Rate : 60% of the labelled claim (potency) shall dissolve within 30 mins (USP method) Colour of the Tabs. : White			

EQUIPMENT SELECTION FOR TABLETS

With the development of pharmaceutical companies worldwide, pharmaceutical machinery manufacturers have also developed high tech machinery to meet the demands of pharmaceutical products. Tablets are one of the most convenient way to consume medicines. Hence, manufacturing machinery of tablet is one of the most important segment of pharmaceutical machinery. As a result of the technological evolution and growth of the pharmaceutical industry, a wide range of advanced machines is available for various applications in the tablet manufacturing process[20].

In the tablet manufacturing process, various types of machines are used for different applications at different stages from production to packaging. Applications of some of the major equipment used for pilot plant study for tablet are mentioned below:

Tablet Press Machine, Double Cone Blender and Rapid Mixer Granulator

Different models of tablet press machine, like Single Sided Rotary Tablet Press Machine, Double Sided Rotary Tablet Press Machine and High Speed Rotary Tablet Press Machine are used for the production of the tablets of different shapes and size. The production capacity and features of these machines may vary based on their type. For the mixing of dry powders and granules, companies mostly use Double Cone Blender. Similarly, Rapid Mixer Granulator is used for mixing of the ingredients and wet granulation.

Fluid Bed Dryer, Multi Mill, Octagonal Blender and V Cone Blender

Drying is one of the very important stages in the tablet manufacturing process and Fluid Bed Dryer is used for drying the product like wet powder at a desired temperature. Multi Mill is a versatile machine which is used for granulating, pulverizing, mixing, shredding and chopping of materials at high speed. For the blending of different types of materials, the pharmaceutical companies mostly use advanced machines like Octagonal Blender and V-Cone Blender. These machines are also widely used in the food and cosmetic industries for mixing the materials[21].

Vibro Sifter, Conventional Coating Pan and Automatic Tablet Coater

Vibro Sifter is a hightech machine mainly used for separating mass composition of solids, liquid from solid. Another important application of it is gradation of materials as per particle sizes. Masking the smell and taste of the drug is very important for the pharmaceutical companies and this process is effectively executed by Conventional Coating Pan. With constantly increasing demands of the pharmaceutical products, most of the companies use Automatic Tablet Coater for tablet coating.

Besides, machines such as Mass Mixer, Vacuum Tray Dryer, Starch Paste Kettle, Tablet De Duster, Ribbon Blender, and Tablet & Capsule Inspection Machine are also used in different stages of the tablet manufacturing process. Over the years, there has been good research and development in this area and today, an extensive range of tablet manufacturing machine is available for the pharmaceutical industry.

There are six things to think before selection of an equipment for tablet making.

1) Scalability

Scaling up a tableting process from R&D to production can be challenging, with formulation problems likely to arise in the form of tablet defects. Advanced R&D processes help to prevent issues by mimicking the tablet compression characteristics of high-speed production equipment. Compaction simulators, for example, can replicate the punch movement and speed of a rotary tablet press, mimicking compression time, dwell time, and strain rate.

"This allows formulation scientists to develop tablets as if they were using production equipment, so there is less surprise when they move to industrialisation.

2) Return on investment (ROI)

Price is important for pharmaceutical laboratories, but ROI is what matters most. The right tablet press should result in significant cost savings for your business. It is important to select a system with comprehensive data acquisition and analysis software. This can help to evaluate tablet quality and develop more robust formulations, meaning less defects and downtime during production.

With compaction simulation technology, companies can avoid performing experimental development work on their production equipment. Beyond the obvious benefit of freeing up the industrial press for commercial manufacturing, this can result in several cost savings.

A CDMO (Contract Development and Manufacturing Organization) specialising in oral solid dosage forms, notable reductions in costly product waste is an advantage. The CDMO can also calculate the significant time savings when using the compaction simulator. The reduced time in the assembly and cleaning phases, experiments that would have taken 168 hours on an industrial press, took just 24 hours on the compaction simulator.

A compaction simulator can also be beneficial during production. For example, if quality control is registering a high number of reject tablets, the technology can be used for troubleshooting formulation issues, thus helping the companies in reducing downtime while optimising output[22].

3) Versatility

A versatile R&D tablet press is key for flexible drug development. This is where compaction simulation really shines. With one compaction simulator, one can have access to several production processes in one place. One can simulate all the high-speed production presses or roller compactors on the market, this means versatility.

Versatility and flexibility is a way to secure the investment for the next 10 to 15 years. It is critical to find an R&D press that can not only answer the needs of current project but also those far into the future, whether they may be multi-layer tablets or tab-in-tab.

4) Ease of use

Tablet compression and powder characterisation technology is primarily complex, but it should not seem so to users. Most vendors will claim to offer intuitive software, so it is important to consider what actions are to be taken during development to ensure this.

The complexity of the equipment in the technical areas is hidden and can make it easy for a beginner in compression or an expert. This goes from set-up of the experiment to cleaning and dismantling, not forgetting analysis. The software is made flexible, whether it is desired to look at simple graphs or go deeper into the raw data.

5) Operator safety

Insufficient toxicology data during the early stages of drug development means new molecules should be treated as dangerous until more is known. With increasing use of highly potent active pharmaceutical ingredients (HPAPIs) by pharmaceutical companies, purchasing tablet presses with containment features is becoming more and more critical.

When selecting a system, it is essential to first evaluate the user safety level (i.e. OEB level) the products necessitate. After that, make sure to balance safety against ergonomics, as the introduction of large isolator boxes has the potential to turn a nifty tablet press into a huge, cumbersome machine.

6) Strong service network

Maintenance is necessary to keep the tablet press running smoothly throughout a long service life. This is usually a simple calibration or a quick change of wear parts. In the time-pressured environment of pharmaceutical R&D, slow service from the tablet press partner could set back in time and money.

The company now has tableting experts positioned across the world to service machines, and help the customers to get the most from their purchases. It is the quality of a vendor's service and the scientific expertise behind their machines that the buyers should value the most. The team should speak the same language as the scientists.

In general, the equipment used in commercial manufacturing of tablets, are used in pilot plant but with lower capacity[23].

EQUIPMENT SELECTION FOR CAPSULES

Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which one or more active ingredient(s). Inert ingredients are enclosed in a small shell or container usually made of gelatine. There are two types of capsules, “hard” and “soft”. The hard capsule is also called “two pieces” as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the “cap” which fits over the open end of the longer piece, called the “body”. The soft gelatine capsule is also called as “one piece”. Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and odours can be masked by the tasteless gelatine shell. The administration of liquid and solid drugs enclosed in hard gelatine capsules is one of the most frequently utilized dosage forms.

Properties of empty capsule: Empty capsules contain a significant amount of water that acts as a plasticizer for the gelatine film and is essential for their function. The specification for standard moisture content for hard gelatine capsules is between 13 % w/w and 16 % w/w. This value can vary depending on the environmental conditions to which they are exposed, that is at low humidity they will lose moisture and become brittle, and at high humidity they will gain moisture and soften. The moisture content can be maintained within the correct specification by storing them in sealed containers at a specified temperature and humidity. Capsules are readily soluble in water at 37°C. When the temperature falls below this, their rate of solubility decreases. At below about 30°C they are insoluble and simply absorb water, swell and distort. This is an important factor to take into account during disintegration and dissolution testing. Because of this, most Pharmacopoeia have set a limit of 37°C ± 1°C for the media for carrying out these tests. Capsules made from have different solubility profile, being soluble at temperatures as low as 10°C.

Types of materials for filling into hard gelatine capsules:

- Dry solids – powders, pellets, granules or tablets
- Semisolids – suspensions or pastes
- Liquids – non-aqueous liquids

The standard sizes, volume, locked length and external diameter of two pieces capsules are given in Table 1.7.

Table 1.7 Standard sizes of two pieces capsule.

Size	Volume (ml)[A]	Locked length (mm)[A]	External diameter (mm)[A]
5	0.13	11.1	4.91
4	0.21	14.3	5.31
3	0.3	15.9	5.82
2	0.37	18	6.35
1	0.5	19.4	6.91
0	0.68	21.7	7.65
0E	0.7	23.1	7.65
00	0.95	23.3	8.53
000	1.37	26.14	9.91
13	3-2	30	15.3
12	5	40.5	15.3
12el	7.5	57	15.5
11	10	47.5	20.9
10	18	64	23.4
7	24	78	23.4
Su07	28	88.5	23.4

One-piece shell capsules are formed, filled, and sealed in a single process on the same machine and are available in a wide variety of sizes, shapes, and colours. The most common type of one-piece capsule is that produced by a rotary die process that results in a capsule with a seam. The soft gelatine shell is somewhat thicker than that of two-piece capsules and is plasticized by the addition of polyols such as glycerine, sorbitol, or other suitable material. Depending on the nature of the fill material, the ratio of the plasticizer to the gelatine can be varied to change the flexibility of the shell its intended usage, or environmental conditions. In most cases, one-piece capsules are filled with liquids. Typically, APIs are dissolved or suspended in a liquid vehicle. Classically, an oleaginous vehicle such as a vegetable oil has been used. However, the nonaqueous, water-miscible liquid vehicles such as the lower molecular weight polyethylene glycols now are more common. The physicochemical properties of the vehicle can be selected to ensure stability of the API and to influence the release profile from the capsule shell.

The equipment should be selected for plant activities according to the equipment to be used for commercial manufacture of capsules. Same equipment of less capacity are used for pilot scale manufacturing. The completely automatic machine most commonly used for capsule production consists of mechanisms for automatically dipping, spinning, drying, stripping, trimming, and joining the capsules.

- Stainless steel pins are used on which the capsule is formed and controls some of the final critical dimensions of the capsule.
- One hundred and fifty pairs of these pins are dipped in to gelatine sol of carefully controlled viscosity to form caps and bodies simultaneously. The pins are usually rotated to distribute the gelatine uniformly, during which time the gelatine may be set or gelled by a blast of cool air.
- The pins are moved through a series of controlled air drying kilns for the gradual and precisely controlled removal of water. The capsules are striped from the pins by bronze jaws and trimmed to length by stationary knives while the capsule halves are being spun in chucks or collets. After being trimmed to exact length, the cap and body sections are joined and ejected from the machine. The entire cycle of the machine lasts approximately 45 min.
- Thickness of the capsule wall is controlled by the viscosity of the gelatine solution and the speed and time of dipping. Mould pin dimensions, precise drying, and machine control relating to cut lengths are matters that are critical to the final dimensions. Precise control of drying conditions is essential to the ultimate quality of the cast film.

Industrial scale filling: the machines for industrial-scale filling of hard gelatine capsules come in great variety of shapes and sizes, varying from semi- to fully automatic and ranging in output from 5000 to 15000 per hour. Automatic machines can be either continuous in motion, like a rotary tablet press, or intermittent, where the machine stops to perform a function and then indexes round to the next position to repeat the operation on a further set of capsules. The capsule filling process is illustrated in figure 1.6 and 1.7.

EQUIPMENT SELECTION FOR LIQUID ORALS

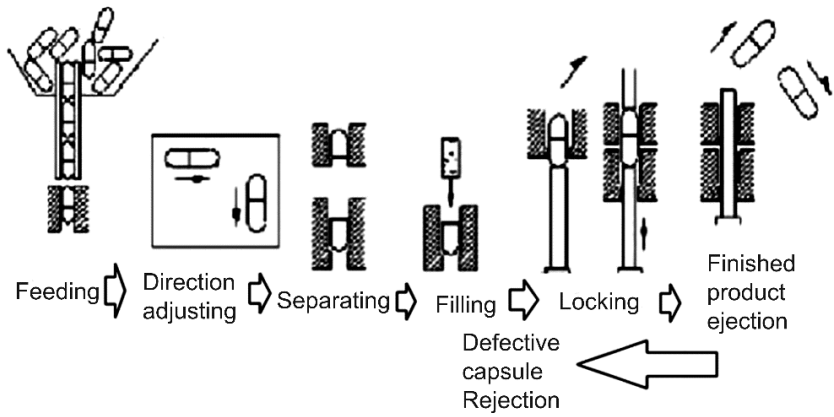

Fig.1.6 Flow diagram of capsule filling.

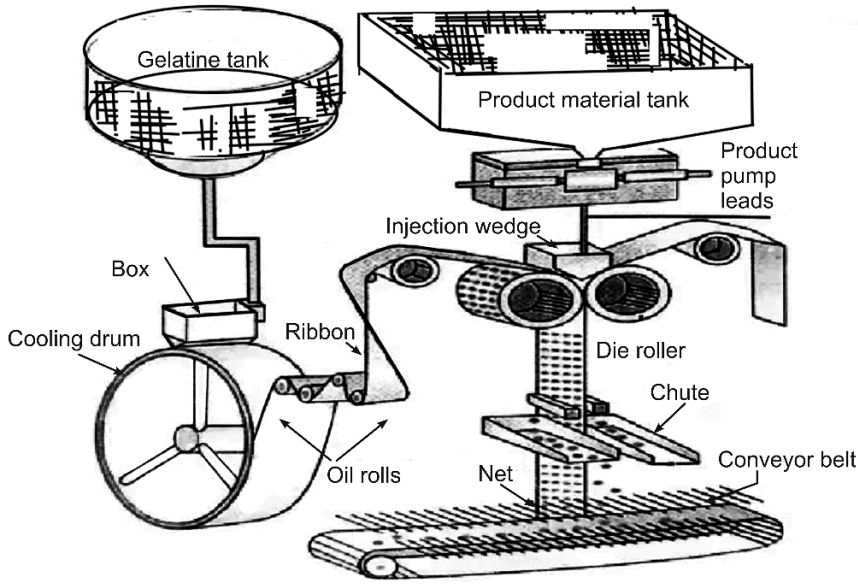

Fig.1.7 Schematic diagram of automatic soft gelatin capsule filling machine.

The liquid dosage forms may be classified as per their application as follows:

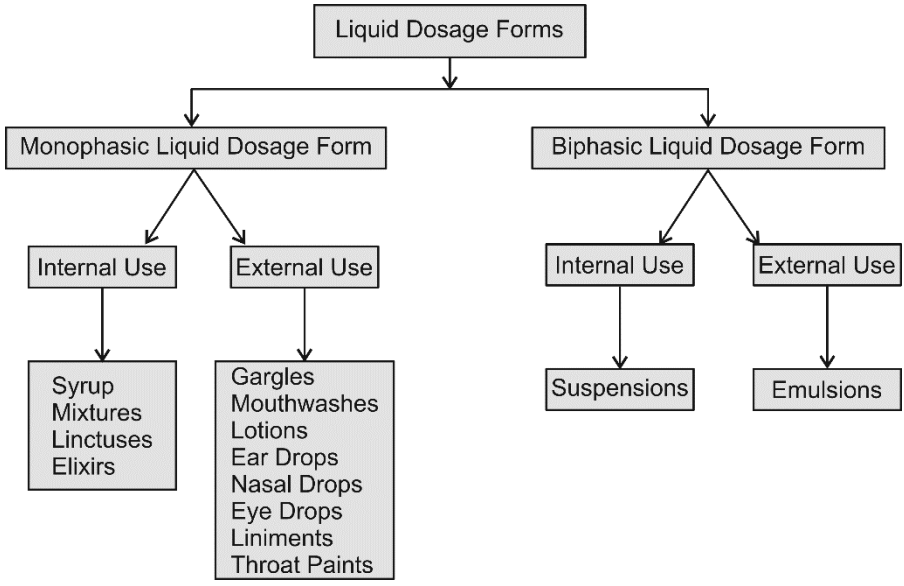

Fig.1.8 Classification of liquid dosage form.

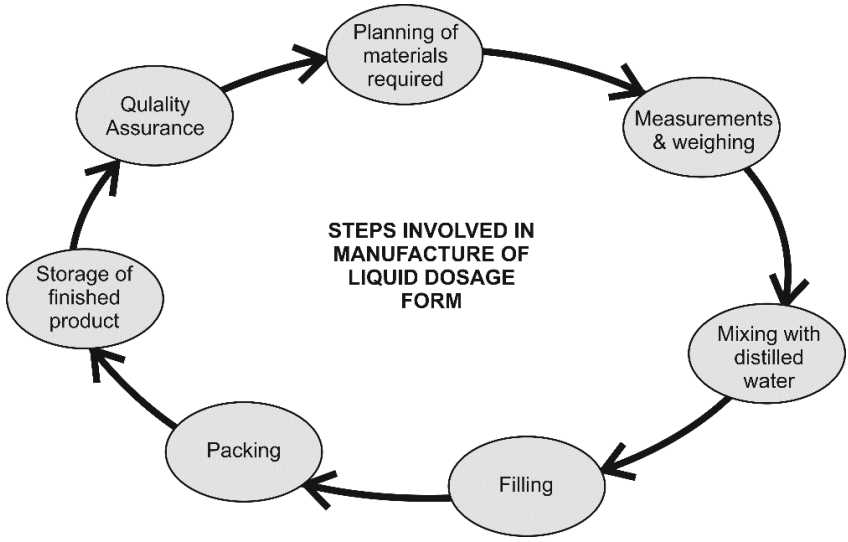

Fig.1.9 Schematic diagram of steps involved in manufacture of liquid dosage form.

Steps involved in liquid manufacturing process:

- Planning of material needs.
- Measurements and weighing
- Filling and Packing.
- Quality assurance.
- Critical features of liquid manufacturing
- Physical Plant.
- Heating, ventilation and air regulating system.

The impact of extended processing durations at suboptimal temperatures should be evaluated in terms of repercussions on the physical or chemical stability of components as well as product.

Solution: The parameters to be considered are for scaling up of solutions are;

- Impeller diameter.
- Tank size (diameter)
- Number of impellers.
- Impeller type.
- Mixing capabilities of impeller.
- Rotational speed of the impeller.
- Height of the filled capacity of the tank.
- Number of baffles.
- Transfer system.
- Clearance between Impeller Blades and wall of the mixing tank.

Filtration device should remove desirable elements but should not eliminate active or adjuvant substances. It should remove desired materials but should not remove active or adjuvant ingredients. Passivation of Stainless Steel (Pre-reacting the SS with acetic acid or nitric acid solution to eliminate. the surface alkalinity of the Stainless Steel. Pre-reacting the SS with acetic acid or nitric acid solution removes the surface alkalinity of the Stainless Steel.

Suspension:

The criteria to be considered are for scaling up of suspension are;

- Versator that avoids air entrapment prevent air entrapment
- Wetting of suspending agent.
- Addition and dispersion of suspending agents.
- Selection of the equipment according to batch size.
- Time and temperature necessary for hydration of the suspending agent.
- Mixing speeds, high speed should not be utilised since it leads to air entrapment.
- Mesh size should be able to remove the foreign particles and sieve determines depending on the manufacturing batch size testing.

Emulsion:

The parameters to be examined are for scale up of emulsion are:

- Homogenizing equipment.
- Temperature.
- Mixing equipment
- Phase densities.
- In-process or final product filters.
- Phase volumes.
- Screens, pumps and filling equipment.
- Phase viscosities.

The following equipment are recommended for the manufacture of oral/internal use preparations i.e. Syrups, Elixirs, Emulsions and suspensions, whichever is applicable, namely: -

1) Mixing and storage tanks (stainless steel),
2) Jacketed Kettle / Stainless steel tank (steam, gas or electrically heated).
3) Portable stirrer (electrically operated)
4) A colloid mill or suitable emulsifier (electrically operated)
5) Suitable filtration equipment (electrically operated)
6) Semi-automatic/automatic bottle filling machine

7) Pilfer proof cap sealing machine.
8) Water distillation unit or deioniser
9) Clarity testing inspection units.

A minimum area of thirty square meters for basic installation and ten square meters for Ancillary area is recommended.

EQUIPMENT SELECTION FOR PARENTERALS

The whole operation of manufacture of parenteral preparations (small volume injectables and large volume parenterally in glass and[24,25] plastic containers may be divided into the following separate areas/rooms, namely

Parenteral preparations in glass containers:

1) Water management area: this includes water treatment and storage
2) Containers and closures preparation area: This includes washing and drying of ampoules, vials, bottles and closures.
3) Solution preparation area: This includes preparation and filtration of solution.
4) Filling, capping and sealing area: This includes filling and sealing of ampoules and/or filling, capping and sealing of vials and bottles.
5) Sterilization area
6) Quarantine area
7) Visual inspection area
8) Packaging area

The following equipment is recommended for above-mentioned areas, namely

(a) Water management area,
    1) De-ionised water treatment unit
    2) Distillation (multi-column with heat exchangers) unit.
    3) Thermostatically controlled water storage tank.
    4) Transfer pumps.
    5) Stainless steel service lines for carrying water into user areas.

(b) Containers and closures preparation area,
    1) Automatic rotary ampoule/vial/bottle washing machine having separate air, water distilled water jets.
    2) Automatic closures washing machine,
    3) Storage equipment for ampoules, vials, bottles and closures.
    4) Dryer/sterilizer (double ended)
    5) Dust proof storage cabinets.
    6) Stainless steel benches/stools.

(c) Solution preparation area.
    1) Solution preparation and mixing stainless steel tanks and other containers.
    2) Portable stirrer

EQUIPMENT SELECTION FOR SEMISOLID PREPARATION

The following parameters have to be addressed during the scale up of semisolids:

- Mixing speed.
- Mixing apparatus (Could be able to transport semisolid substance from outer walls to the middle and from bottom to top of the kettle) (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 proper handling system at its most viscous stage) (Drive mixing system with appropriate handling system at its most viscous stage).
- Heating and cooling procedure.
- 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 transport viscous material without producing excessive shear and free of entrapped air) (Easily must move viscous material without applying excessive shear and free of entrapped air).
- Pumping rate.
- Pumping pressure necessary should be considered.
- Product compatibility with the pump surface.

The following equipment is recommended for different above-mentioned areas, for example:

a) Water management area
    1) De-ionised water treatment unit
    2) Distillation (multi-column with heat exchangers) unit.
    3) Thermostatically controlled water storage tank.
    4) Transfer pumps.
    5) Stainless steel service lines for carrying water into user areas.

b) Containers and closures preparation area
   1) Automatic rotary ampoule/vial/bottle washing machine having separate air, water distilled water jets.
   2) Automatic closures washing machine,
   3) Storage equipment for ampoules, vials, bottles and closures.
   4) Dryer/sterilizer (double ended)
   5) Dust proof storage cabinets.
   6) Stainless steel benches/stools.

c) Solution preparation area
   1) Solution preparation and mixing stainless steel tanks and other containers.
   2) Portable stirrer.
   3) Filtration equipment with cartridge and membrane filters/ bacteriological filters.
   4) Transfer pumps.
   5) Stainless steel benches/stools

d) Filling, capping and sealing area
   1) Automatic ampoule/vial/bottle filling, sealing and capping machine under laminar air flow workstation.
   2) Gas line (Nitrogen, Oxygen, Carbon dioxide) wherever required.
   3) Stainless steel benches / stools

e) Sterilization area
   1) Steam sterilizer preferably with computer control for sterilization cycle along with trolley sets for loading/unloading containers before and after sterilization).
   2) Hot air sterilizer (preferably double ended).
   3) Pressure leak test apparatus.

f) Quarantine area
   1) Storage cabinets.
   2) Raised platforms/steel racks.

g) Visual inspection area
   1) Visual inspection units (preferably conveyor belt type and composite white and black assembly supported with illumination).
   2) Stainless steel benches/stools.

h) Packaging area
   1) Batch coding machine (preferably automatic)
   2) Labelling unit (preferably conveyor belt type)
   3) Benches/stools

Exercise

Multiple Choice Questions

1. Fill in the blank with correct word given below

   Pilot plant is a ——- where 5M's like money, material, man, method & machine are utilised to produce the product

   a) Place
   b) Room
   c) Area
   d) Plant

2. Fill in the blank with correct word given below

   During scale up experiment in a pilot plant production & process control are evaluated, ——- and finalised.

   a) Done
   b) Evaluated
   c) Calibrated
   d) None of the above

3. Which of the following statements is correct?
   a) The main objective of a pilot plant is to prepare the product
   b) The main objective of a pilot plant is to optimise the operating parameters of the process
   c) The main objective of a pilot plant is to measure the process parameters
   d) The main objective of a pilot plant is to develop the method

4. Which of the following statements is correct?
   a) Pilot plant should be designed as per requirements of the company
   b) Pilot plant should be designed as per factory rules
   c) Pilot plant should be designed as per the WHO-GMP norms
   d) Pilot plant should be designed as per the pollution control norms

5. Which of the following statements is correct?
   a) Research pharmacist is responsible for initial scale up & initial production run
   b) Pharmaceutical Research team is responsible for pilot plant scale up technology
   c) Production department is responsible for pilot plant & scale up technology
   d) All the above

6. Which of the following statements is correct?
   a) The manufacturing sheet must be signed by any two no production personnel

b) The manufacturing sheet must be signed by two persons, one from manufacturing and other from Quality Control departments
c) The manufacturing sheet must be signed by two persons, one from manufacturing and other from R & D department
d) The manufacturing sheet must be signed by one who is directly responsible for manufacturing and other who is responsible for check up

7. Which of the following six things are to be thought before selecting equipment for manufacturing a tablet
   a) Scaleability, return of investment, versatility, ease of use, operator safety & strong service network
   b) Scaleability, return of goods, operator safety, ease of use, versatility & strong service network
   c) Scaleability, return of investment, ease to use, versatility, operator safety, & strong service network
   d) Scaleability, return of goods, ease to reprocess, operator safety, versatility, & strong service network
8. Which of the following liquid preparations is filled into a hard gelatine capsule?
   a) Aqueous liquid
   b) Nonaqueous liquid
   c) Mixture of aqueous and non-aqueous liquid
   d) None of the above
9. Fill in the blank with suitable word given below

   The specification for standard moisture content of hard gelatine capsules——- to ——-
   a) 13 percent to 16 percent
   b) 13 percent to 15 percent
   c) 10 percent to 15 percent
   d) 9 percent to 15 percent
10. Fill in the blank with suitable word given below

    A versatile R & D tablet press is ———— for flexible drug development
    a) Important
    b) Frequent
    c) Casual
    d) Required
11. What for CDMO stands?
    a) Construction of Drug Manufacturing Organisation
    b) Construction, Development & Manufacturing Office
    c) Contract Development & Manufacturing Organisation
    d) Contract Drug Manufacturing Office

12. Fill in the blank with a suitable word given below

    A significant amount of water present in capsule shell acts as ——- to the gelatine film.

    a) Coat
    b) Lubricant
    c) Disintegrant
    d) Plasticizer

13. Fill volume of standard 5 size capsule is….?

    a) 0.13 ml
    b) 0.15 ml
    c) 1.3 ml
    d) 0.21 ml

14. Fill in the blanks with suitable words given

    The most common type of one piece capsule is produced by —— ——- process

    a) Die and pin
    b) Rotating die and pin
    c) Rotary die
    d) Multiple dies

15. what is a criterion for scaling of suspension?

    a) Mixing equipment
    b) wetting of suspending agent
    c) In process or final product filler
    d) Phase volume

16. Which of the following criteria is related to emulsion manufacturing?

    a) Time and temperature necessary for hydration of the suspending agent
    b) Addition and dispersion of suspending agent
    c) Temperature
    d) Wetting of suspending agent

17. What is the minimum area required for installation of basic equipment?

    a) Fifteen square meters
    b) Thirty square foot
    c) Thirty square meters
    d) Fifteen square foot

18. Which of the following equipment is placed in water management area?

    a) Transfer pump
    b) Dust proof storage cabinet
    c) Portable stirrer
    d) Product transfer

19. Which of the following equipment is required for solution preparation area?

    a) Steriliser
    b) De-ionised water treatment unit
    c) Transfer pump
    d) Stainless steel benches

20. What is the equipment required for quarantine area?

    a) Storage tank
    b) Batch coding machine
    c) Pressure leak test apparatus
    d) Storage cabinets

Short Questions

1. What is pilot plant, define it. Do you think that pilot plant must mimic all the flow sheets? If not, what does it include? A pilot plant should be designed for what?
2. What are the significance of a pilot plant? What are the objectives of a pilot plant?
3. What are the basic requirements for designing a pilot plant?
4. Write down the activities of the machine for capsules, tablets and liquid filling and mention their capacities.
5. Give a floor plan for small pilot plan for tablet manufacturing, mention the areas required for each equipment.
6. Give a floor plan for tablet dosage form, not small one.
7. What do you mean by the specification sheets for active ingredients? Explain with the help of a specific example.
8. What are the main characteristics for selecting the equipment for tablet manufacturing. Briefly explain these.
9. What are the parameters for producing emulsion and suspension.
10. How do you select the equipment for manufacturing the parenteral products?

Long Questions

1. What is a pilot plant? How is it relevant to pharmaceutical industry? Explain the silent feature of a pilot plant.
2. What are the facilities required for a pharmaceutical pilot plant?
3. Explain how the communication between pilot plant and Quality Control and Production departments take place.
4. Explain how the equipment required for tablet manufacturing can be selected.
5. Write down how the equipment can be selected for liquid orals manufacturing.
6. How can you select the equipment for manufacturing the capsules and parenterals?
7. Discuss how can the equipment be selected for manufacturing of semisolid preparations.
8. Explain the preparation of a floor plan for manufacturing the tablets with the help of the relevant diagram.
9. Present in a tabular form the manufacturing instructions to prepare tablet and also the list of ingredients required.
10. Prepare the list of final tests to be performed for different types of Pharmaceutical products.

Answers

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
a	b	b	c	d	d	c	b	a	a	c	d	a	c	b	c	c	a	b	d

References

1. Baekeland, L.H., J. Ind. Eng. Chem. 8, 184, 1916.
2. Constant, L.G., Pilot plants for medium-sized companies, Chem. Eng. Prog. 56, Feb. 1984.
3. Floter, W., "Pressure leaching", Uranium Extraction Technology: Current Practice and New Developments in Ore Processing, OECD, Paris; 54-58, 1983.
4. Lowenstein, J.G., The pilot plant, Chem. Eng. 92 25, 62-76, 1985.
5. Leon Lachman, Herbert A Lieberman, Joseph L Kanig: The Theory and Practice of Industrial Pharmacy: Section IV: Chapter 23: Pilot Plant Scale-Up Techniques: 3rdedition, published by Varghese Publishing house,; 681-710, 2009.
6. James Swarbrick, James C Boylan: Encyclopaedia of Pharmaceutical Technology: Pilot Plant Design, Volume 12 New York,; 171-186, 2001.
7. Gomez AL, Strathy WA. Engineering Aspects of Process Scale-Up and Pilot Plant Design. In: Michael Levin, editor. Pharmaceutical Process Scale-Up. New York: Marcel Dekker Inc; p.311-324, 2002.
8. Roop K Khar, Farhan J Ahmad, A Vashishtha, S. Harder, GV Buskirk, JV Battista. Pilot Plant Scale-up and Production Management. In: Roop K Khar, SP Vyas, Farhan J Ahmad, Gaurav K Jain, Editors. Industrial Pharmacy. 4 th edition. New Delhi: CBS Publishers & Distributors Pvt Ltd,; pp. 947-1002, 2013.
9. Dhobale AV, Mahale AM, Shirsat M, Pethkar S, Chakote V. Recent Advances in Pilot Plant Scale Up Techniques - A Review. Indo Am J Pharm Res; 8(4): 1060-1068, 2018.
10. Gomez AL, Strathy WA. Engineering Aspects of Process Scale-Up and Pilot Plant Design. In: Michael Levin, editor. Pharmaceutical Process Scale-Up. New York: Marcel Dekker Inc; p. 311-324, 2002.
11. Pharmaceutics – The Science of Dosage form Design by M.E. Aulton, 2 nd Edition, Page no: (515-538).
12. Remington – The Science and Practice of Pharmacy, 20 th Edition, Volume – 1, Page no: (918-922).
13. The Theory and Practice of Industrial Pharmacy by Leon Lachman, Page no: (374-411).

14. Shah VP, Skelly JP, Barr WH, Malinowski H, Amidon GL. Scale-up of Controlled Release Products - Preliminary Considerations. Pharm Technol; 16(5):35-40, 1992.
15. FDA. Center for Drug Evaluation and Research, Guidance for Industry: Immediate Release Solid Oral Dosage Forms. Scale-up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation [SUPAC-IR]; 1995.
16. Walker, S. E., et al.: The filling of molten and thixotropic formulations into hard gelatine capsules. J. Pharm. Pharmacol. 32, 389-393, 1980.
17. Bauer, K. H.: Die Herstellung von Hart- und Weich gelatine kapseln, in: Die Kapsel, ed. Fahrig, W., Hofer, U., Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, 1983.
18. Cole, E.T.: Liquid filled and sealed hard gelatine capsules. Capsugel Library, BAS 210 2000.
19. Mounica, NVN, Sharmila, RV, Anusha, S, Evangeline, L, Nagabhushanam, MV, Nagarjuna Reddy, D; Scale up and Post approval changes (SUPAC) Guidance for Industry: A Regulatory note. Int J Drug Regul Aff.; 5(1): 13-19, 2017.
20. Sherman R. Technology & Product Architectures. In: Business Intelligence Guidebook. Science Direct; 2015.
21. Ogura T, Furuya Y, Matuura S. HPMC capsules: an alternative to gelatine. Pharm Tech Europe.; 10(11): 32-42, 1998.
22. D. Aviad Shapira, M.ASCE; and Marat Goldenberg Associate Professor, Dept. of Civil and Environmental Engineering, Technion–Israel Institute of Technology, Haifa 32000, Israel. Submitted: 11 November, 2003.
23. Marcelo M. Azambuja; and William J. O'Brien Assistant Professor, Dept. of Construction, Southern Illinois University Edwardsville.
24. David Arditi, Member, ASCE, Prof., Dept. of Civ. and Arch. Engineering, Illinois Inst. of Technol., Chicago, IL 60616.
25. Serdar Kale and Martino Tangkar Grad. Student, Dept. of Civ. and Arch. Engineering., Illinois Inst. of Technol., Chicago, IL. Published: 01 December 1997.