**PILOT PLANT SCALE UP TECHNIQUES**

**Correspondent author 1.D.Reshma Banu, Assistant professor, Department of Pharmaceutics, Dr. K.V.Subbareddy Institute of Pharmacy.**

**Author ; 2. K.Rajasekhar reddy, Dr. K.V.Subbareddy Institute of Pharmacy**

**Abstract:**

In modern context, as per market demand there is surely an augmentation or decrease in production, this is called SUPAC. Distinct recommendations are made for those diverse sorts of SUPAC in by various regulating organizations for manufacture of items. Here SUPAC guidelines and post approval adjustments are provided for production in this review study. determined that SUPAC guideline line offer benefits as: This Review Focus on Reduced processing period for site transfers, saving operational overhead & maintenance expenditures. More quicker deployment of equipment and method improvements, better yield & Reduce failure investigations. More quicker adoption, increase in lot sizes and Manufacture of fewer un commercial stability batches and Reducing stability testing/costs.

Keywords : Pilot plant techniques ,solid dosage form, tablet compression, SUPAC, Post approval changes lot size, site transfer, stability.

**★ INTRODUCTION :**

**•Pilot plant:**

“Defined as a part of the pharmaceutical industry where a lab scale formula is transformed into a viable product by the development of liable practical procedure for manufacture.” R & D Production

Pilot Plant

•A pilot plant is a pre-commercial production system that 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 knowledge 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 (non-technical) purposes include gaining public support for new technologies and questioning government regulating Pilot plant studies must includes a close examination of formula to determine its ability to withstand batch scale and process modifications; it must includes a review of range of relevant processing equipment also availability of raw materials meeting the specification of product and during the scale up efforts in the pilot plant production and process control are evaluated, validated and finalized.

**☆ pilot plant can be used for:**

•Evaluating the results of laboratory studies and making product and process corrections and improvements.

•Producing small quantities of product for sensory, chemical, microbiological evaluations, limited market testing or furnishing

samples to potential customers, shelf-live and storage stability studies.

• Determining possible stable by-products or waste stream requiring treatment before discharge.

• Providing data that can be used in making a decision on whether or not to proceed to a full-scale production process; and in the

•case of a positive decision, designing and constructing a full-size plant or modifying an existing plant.

**☆Considerations in pilot plant development:**

• Kind and size – depends on goals; evaluating product and process; producing samples of product for evaluation; market testing or furnishing to potential customers.

• Location: near R&D facility? At an existing plant? Close liaison between R&D and pilot plant staff is essential.

• Laboratory requirements and costs: engineering staff, skilled operations and maintenance staff- pilot plant costs may exceed those of usual plant production costs. The pilot plant may be used for training personnel for a full- scale plant.

**☆Objectives:**

•To try the process on a model of proposed plant before committing large sum of money on a production unit.

• Examination of the formula to determine it’s ability to with stand Batch-scale and process modification.

•Evaluation and Validation for process and equipment.

• To identify the critical features of the process

•Guidelines for production and process controls.

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

• To avoid the scale-up problems.

**☆Significance of Pilot Plant:**

• Standardization of formulae.

• Review of range of relevant processing equipment.

• Optimization and control of production rate.

• Information on infrastructure of equipment during the scale up batches physical space required.

• Identification of critical features to maintain quality of a product.

• Appropriate records and reports to support GMP

• Optimization and control of production rate.

• Information on infrastructure of equipment during the scale up batches physical space required.

• Identification of critical features to maintain quality of a product.

• Appropriate records and reports

**☆ SUPAC guidelines- History:**

➢ Two workshops were held in 1991 and 1992 by the American Association of Pharmaceutical Scientists (AAPS), the United States Food and Drug Administration (FDA), and the United States Pharmacopoeia (UPS). The purpose of these Workshops was to discuss the fundamentals of modifying the procedure or composition of drug products after they Have been approved by the appropriate authorities.

➢ In the end, these adjustments included adjustments to the formulation or composition of the product, alterations to The processes, modifications to the size of the processes, and adaptations to the site or campus where the operations Were performed.

➢ The contents of the workshop were finally made public by the FDA in the form of a guideline paper titled “Scale-Up And Post-Approval Changes,” or SUPAC for short.

➢ The term “Scale-Up and Post Approval adjustments,” abbreviated as “SUPAC,” refers to both the process of scaling up As well as the modifications that are made to the product’s composition, production technique, manufacturing Equipment, and location after it has been approved.

**☆ Purpose of SUPAC guidance:**

The United States Food and Drug Administration (FDA), the American Association of Pharmaceutical Scientists (AAPS), And the United States Pharmacopeia Convention (USP) are all organisations that have made contributions to the SUPAC Proposal. The rule evaluates the process of developing pharmaceutical drugs, as well as their formulation and any Post approval modifications. In pharmaceutical technology, the process of going from a small scale (research) to a large scale(manufacturing) is referred to as “scale-up.” This results in an increase not only in the size of the samples that are collected But also in the quantity of goods that are created at the same time. Increasing production is what we mean when we talk About “stepping up” or “scaling up.” It is imperative that you follow this approach to collect all of the data needed for the Mass production of a product. After a product has been given its certification, changes may be made to the production Process, as well as the apparatus and supplies used in the process. These changes are referred to as SUPAC. Verify that the Method can generate the product to the desired quality and that the physical and chemical qualities of the product have not Changed as a consequence of the increase in production. Also ensure that the process can manufacture the product to the Desired quantity. If the author of a new drug application (NDA), an abbreviated new drug application (ANDA), or an Abbreviated antibiotic drug application (AADA) in the pharmaceutical industry wishes to make adjustments, they can refer to The advice that is provided in the following paragraphs (Mali et al 2022).

 Throughout the post approval phase, changes can pertain to components or composition, manufacturing location, Scale-up/scale-down of production, or the manufacturing of a modified release solid oral dosage form. The guidance outlines The levels of change, recommended chemistry, manufacturing, and controls (CMC) tests for each change level, recommended In vitro dissolving tests and/or in vivo bioequivalence tests, and the necessary documentation to substantiate the change

 The Centre for Drug Evaluation and Research (CDER) should obtain the application information that is supplied in this Suggestion. This will guarantee that the product quality and performance features of a modified release solid oral dosage Formulation are maintained for specified adjustments after approval. This guideline does not cover the CDER’s Office of Compliance or the FDA’s Office of Regulatory Affairs, both of which have their own document review and compliance Standards. Neither of these offices are covered in this publication .



This guideline is irrelevant to any additional adjustments, with the exception of the specific changes that have been mentioned. After looking at the extra data, the FDA came to the conclusion that the adjustments that were reported in the Changes Being Effected (CBE) update (21 CFR 314.70(c)) are not acceptable. If a sponsor wants information on testing and application documentation for modifications that are not included in this guideline or if numerous changes are submitted concurrently or in a short period of time, they can contact the relevant CDER review division or look at other CDER guidelines. Additionally, if a sponsor requires information on changes that are not included in this guideline, they can look at other CDER guidelines .

 Formulation and quality performance can be influenced by changes at various levels, with Level 1 suggesting an impact that is unlikely to be noticeable, Level 2 indicating the potential for a significant influence, and Level 3 signifying a probability of exerting a substantial influence. Recommendations for post approval changes are encompassed within these guidelines, including alterations in manufacturing (process and equipment), modifications in the manufacturing site, adjustments in the scale-up of manufacturing, and changes in components or composition, as outlined in Sherman (2015).

**☆ Advantages and Disadvantages of SUPAC:**

Incorporating SUPAC presents several advantages, including the ease with which scale-up runs can be observed by personnel within the departments of production and quality assurance. Furthermore, within the more capacious workspaces of the production division, the acquisition of excipient and medicinal supplies, already sanctioned by the quality control division, is made possible. Additionally, the installation, maintenance, and repair of equipment become attainable with the assistance of experts from the engineering department in contrast, there are certain disadvantages associated with SUPAC. First, it results in diminished face-to-face interaction opportunities between the formulator and production personnel throughout the manufacturing process. Second, in cases of position), any packaging activities, any analytical testing laboratories, or any changes in the location of the site where the product is manufactured.

**☆ The systematic aspect of SUPAC :**

The adjustments that need to be made are separated into their own categories in the SUPAC advice summary. The following characteristics can be used to characterise each stage of change:

1. An analysis that is being offered of the chemistry, manufacturing, and control (CMC),

2. In vivo bioequivalence testing or in vitro dissolution testing

3. The NDA, ANDA, or AADA must be submitted along with the supporting papers that are requested by the FDA.

It is possible for the annual report to contain both 'Moderate' and 'Major' post approval pharmaceutical CMC adjustments.

1. Moderate: If the changes are moderate, the applicant must submit a supplement called the Change Being Effected (CBE)-30 no later than 30 days before the drug product is supplied, or in some cases, the CBE-0 supplement can be submitted at the time of provision.

2. Major: In the event of significant changes, the applicant must seek and receive FDA approval of a prior approval supplement (PAS) prior to distribution of the drug product.

**Drug products manufactured with the proposed changes are as follows:**

1. Modification of the constitution or parts

2. A different production location

3. Manufacturing on and off-scale

4. Modification of the equipment and production process

**SUPAC guidance defines a different level of changes as per below:**

1. The proposed chemical

2. Manufacturing and quality control tests are performed at each tier transition.

3. Third, in vitro dissolution and/or in vivo bioequivalence studies must be performed at each concentration level.

4. Required filing materials

SUPAC's help is crucial for the scale-up procedure of the chemical manufacturing and quality control processes. During the process of manufacturing pharmaceutical prescription goods, an essential and expected stage known as scale-up takes place. During this step, the batch size may need to be raised or lowered depending on the circumstances. It speeds up production, boosts yield, and reduces expenses all at the same time.

**1.1. The components or composition changes:**

 Section 4 discusses alterations to the components or composition, with a focus on evaluating the need for Excipient SUPAC-MR in achieving modified drug release. Additionally, it underscores the capacity to exert control and prevent unintended release through modifications to the excipients. Furthermore, it addresses changes in preservatives within semisolid formulations, categorised under SUPAC-SS. The section also encompasses adaptations to the SUPAC-IR Criteria for Solid Oral Dosage Forms, specifically designed for immediate release, as extensively documented in the work by Xiaowen et

al. (2023).

**1.2. The site changes of manufacture**

Do not include any adjustments to the scale-up process, any manufacturing (including process and/or equipment changes, changes in components or composition), any packaging activities, any analytical testing laboratories, or any changes in the location of the site where the product is manufactured.

Examination for Compliance with the Most Recent Good Manufacturing Practises (CGMP).

**1.2.1. Level I Changes**

Classification: Single building with the same tools, standard operating procedures (SOPs), environmental factors (such as temperature and humidity) and controls, and employees.

Test documentation:

Standards for applications and compendia in chemistry, dissolving, and in vivo bioequivalence - None.

Putting away paperwork: Annual report.

**1.2.2. Level II Changes**

Classification: Same continuous campus, Common personnel, No other changes.

Test Documentation: Application/compendia requirements; Notification of the location of the new site; Updated batch records.

SUPAC - MR - Multipoint dissolution profiles (15, 30, 45, 60, and 120 min) USP buffer medium at pH 4.5-7.5 for sustained release.

It is recommended to utilise three distinct media (such as water, 0.1 Cl, and USP buffer media at pH 4.5 and 6.8 for delayed release) until 80% of the medication has been released (metre et al 2022).

Filing Documentation- Annual report.

**1.2.3. Level III Changes**

Classification: Different campus, Different personnel.

Test Documentation:

The application and compendia requirements, a notation of the location of a new site, and updated batch data are all

included in this package.

SUPAC and IR both feature prominently in the profile of the medium's breakdown at various stages.

Multiple breakdown profiles on USP buffer medium at 15, 30, 45, 60, and 120 minutes for SUPAC-MR, with a prolonged release pH range of 4.5–7.5. Until 80% of the medication is released, you need to utilise three distinct media, such as water, 0.1 N Cl, and USP buffer media at pH 4.5 and 6.8 for delayed release. This should be done until the drug is completely released.

Filing Documentation- Annual report prior approval of supplement (Vasquez et al 2021).

**1.3. Changes in Batch Size (Scale-Up/Scale-Down)**

If the size of a batch is changed from a pivotal/pilot-scale bio batch to a larger or smaller production batch after approval, the application must include more details.

This suggestion does not apply to dose reductions of less than 100,000 dose units.

**1.3.1. Level I Changes**

Changes in batch size of up to and including a factor of ten times the size of the pilot or bio batch qualify for this classification.

Test Documentation - Ensured that all batch records were brought up to date and that all application and compendia criteria were met.

Documentation to be Filed: Annual Report (including Data on Long-Term Stability) (Wu et al 2023).

**1.3.2. Level II Changes**

Classification: No other alterations, batch size changes greater than 10 times the size of the pilot or bio batch.

Chemistry Documentation Application/Compendia Release Requirements for Test Documentation. notification of the modification and batch records that have been modified. Testing for stability: two batches, one testing for long-term stability and the other testing for accelerated stability over three months.

Testing for Dissolution Documentation-Case B

There is no in vivo bioequivalence.

Filing Documentation: Annual Report (Long-Term Stability Data) and Supplement for Changes Being Effected.

**1.4. Manufacturing Changes**

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself (Jered et Al 2020).

**1.4.1. Equipment**

**1.4.1.1. Level I Changes**

Alternate equipment with the same concepts and classification as automated equipment.

Updated batch records, application/compendia requirements, and stability are all included in the test documentation. Submission of Documentation: Annual Report (Long-Term Stability Data); Prior Approval Supplement with Justification For Chan**Leve 1.4.1.2. Level II Changes**

Classification: switch to machinery with a new design and operating system.

Updated batch records, application/compendia requirements, and stability are all included in the test documentation. Multipoint dissolution profiles in various media using SUPAC IR. Multipoint dissolution profiles in various media using SUPAC MR. Annual Report and Changes Being Effected Supplement Filing Documentation (Kenmore et al 2022).

**1.4.2. Process**

**5.4.2.1. Level I Changes**

Alternate equipment with the same concepts and classification as automated equipment. Updated batch records, application/compendia requirements, and stability are all included in the test documentation. Annual Report Documentation Filing.

**&**

Classification: The modifications to the process that are included in this category are those that have an effect on the Mixing durations and operating speeds but are not permitted by the application or validation. The test documentation includes all of the most recent batch records, as well as requirements for applications and Compendia, as well as stability (Mustafa et al 2022).

A dissolution profile obtained from many points using SUPAC and IR. Using SUPAC-MR, we were able to generate Multipoint dissolution profiles in a variety of media. Documentation for the in vitro release test may be found in the SUPACSS. Documents must be filed, including an annual report with long-term stability data and a supplement for modifications Currently being made.

**1.4.2.3. Level III Changes**

Changes made to the type of process being carried out (for example, moving from direct compression to wet Granulation) fall under this category. The test documentation includes everything from up-to-date batch data to application And compendia criteria, as well as stability, bio study, and IVIVC information.

A dissolution profile obtained from many points using SUPAC and IR. Using SUPAC-MR, we were able to generate multipoint dissolution profiles in a variety of media. Documentation Required for Submission: Annual Report (Long-Term Stability Data); Prior Approval Supplement with Justification Annual Report (Long-Term Stability Data) (Denktash et al 2022).

2. **Final** **considerations:**

It can be concluded that during the first half of 1997, interviews for the SUPAC-Industry Perspective were held with Representatives from a total of six different firms. It was shown that if the SUPAC standards were adhered to, site relocation Times could be cut down significantly, and the amount of money spent on maintenance could be reduced to an absolute minimum. There was a reduction in the number of equipment failure-related queries, which led to an increase in production, a quicker adaptation to process and equipment modifications, and an overall improvement in the situation. When the batch sizes are raised, there will be a subsequent decrease in the fraction of unstable amounts. It will ultimately bring down the costs that are involved in conducting safety tests

**☆Solid dosage form :**

Pilot plant scale up techniques for solid dosage form involve in the process for large scale manufacturing (Figure 2). It play vital role in large scale manufacturing. In past two decades pilot plants have particularly witnessed amazing inventions and innovations in pharmaceutical research, resulting in the ability to produce new drug faster than before. The scale up of solid dosage form would be better appreciated if one understands the pilot plant scale up techniques used in pharmaceutical manufacturing. It is considered to be intermediate form of batch size in large scale production; various types of size and equipment are used. Solid dosage form refers essentially to pharmaceutical drug products in the form of tablets, capsules, powders, granules containing active drug component or a mixture of active drug component (Active pharmaceutical ingredient) and non-drug component (excipients) (Allen L and Ansel HC, 2013). Tablets are composed of solid unit dosage form containing medicament. Which are usually circular, may be flat or biconvex in shape. It contains medicament with or without excipients. They are prepared by compressing drugs or mixture of drugs with or without diluents. Types of tablets are compressed tablets, sugar coated tablets, and film coated tablets, effervescent tablet, enteric coated tablets, and chewable tablets, buccal and sub-lingual tablets (Ennis BJ and Litter JD, 1997). Capsules are solid dosage form in which the drug substance is present either in hard or soft soluble container or shell of suitable form of model like gelatine. The drug which is in powder or any other forms encloses gelatine or other polymers. Hard capsules are generally used for powder or solid fills. Soft capsules are generally used for semisolid or liquid fills. Powders are intimate mixture of drug that may be intended for internal or external use. The flow properties of powder are depends upon the particle size, nature of particle, shape and moisture content. It can be determined by angle of repose, bulk or tapped density. Granules are small powder particles are gathered together to form agglomerates. It is necessary to include adhesive substances to achieve cohesion between the powders. It increases the flow properties of powders. During tabulating it prevents segregation of powder components. During manufacture process it reduces cross contamination and hazard associated with generation of toxic dust. All the formulation ingredients should be uniformly distributed in the granules (Boylan JC and Swarbrick J, 2001).

Dosage



 Figure:1Preparation of solid dosage forms

Equipment’s of solid dosage form (Tablets) are material handling, it is mechanical equipment used for movement, storage, protection, of material and products throughout the process of manufacturing, distribution, consumption. System proper handling of material is necessary for large scale production ingredients should be delivered to the destination in accurate quantity. The characteristic of the materials depends on the selection of the type of system. It has four different types they are transport equipment, positioning equipment, unit load formation equipment and storage equipment (Faure A, et al., 2001).

Conveyor:

Belt conveyor: It is a simple device that is very useful here a motor is used to turn the pulleys, thus moving the belt.

Chain conveyor: It consists of moving chain to carry products instead of having rollers or a belt it is used to carry large items.

Blending: It is the action of mixing or combining things together (Schwartz Bach H, 2010).

Dry blending: It is the process to produce a well-mixed dry product by in-cooperating dry ingredients. If desired it is also possible to add controlled amount of liquids for some blenders. It also have temperature control can be used to heat the bed of powder furthermore temperature controls which can heat the liquid stream that is added to the bed. To ensure proper distribution of drug granulated powder are well blended. Due to insufficient blending of powders could result in uneven portion of the batch which result in either high or low in potency. All ingredients should be free of lumps and agglomerates prior to blending. The proper steps should be taken care or else flow problems can occur. Before blending, screening of the ingredients should be done (Gomel MC, et al., 2007).

Ribbon blender: The machine consists of U-shaped horizontal trough. It rotates up to approximately 300 feet/min. the liquid ingredient can be added through a charge port on the cover but for critical application. It is also used in preparation of flow able slurries or pastes such as food extrusion operation.

Paddle blender: It is U-shaped trough. It provides low shear and less heat development.

Tumble blender: It is a double cone or V-shaped. It is designed with asymmetric vessels to reduce blend time and improve uniformity. It operates a speed of 5 to 25 rpm (Stomped JP, et al., 2013).

Granulation: It is a unit operation where powder particles are combined together to form granules.

• Dry granulation is the process of granulating without the use of liquid. It is slugging and roll compaction method.

• Wet granulation method is the process of granulating with use of liquid. It also involves additional steps of wet massing, wet screening and drying (Meyer T, 2003).

Drying: It is the process which removes the presence of solvents in the formulation with presence of heat. The final product of drying is a dry solid mass or powders. This process impact on the quality attributes of the API. It will not have impact on the drug safety and efficiency, thus providing high quality final product. Drying of granulation takes place by heating either by steam or electricity in a hot air oven. For each product drying times as specified temperature and air flow rates. Drying of wet soils is done by fluidized bed dryer to obtain good contact between the warm drying air and wet particles. It improves the efficiency of heat transfer and vapour removal, as compared with the older static tray dryer. It also allows the efficient transfer of the latent heat of evaporation from the air and into the drying solid. For solutions and suspensions spray drying is most useful method. As it disperse the liquid to a spray of small droplets. In spray dryer it atomizes the liquid into small droplets thus creating a large surface area for heat and mass transfer. It is most beneficial for terminable materials. Spray drying is capable of producing spherical particles in the irrespirable range of 1-7 micro meter that are necessary for the delivery of drugs from dry powder inhalers (Benedek I, 1998).

Reduction of particle size: During hand screening with a small scale mill in equipment is used to obtain the desired particle size distributions prior to compression or encapsulation.

Hammer mill: the material is impacted by the hammer bars and is there by shredded and expelled through screens in the drum of a selected size (Marshall K, 1986).

Compression: It is the process of granulation can be compressed on high speed tablet press and produce tablets with the help of compressing machine. Granules are compressed and produce tablets. By combined pressing extinction of two punches and die tablet formation takes place. The principle behind tablet compression is hydraulic pressure. It is divided into 4 distinct stages filling, metering, compression and ejection.

Coating: To a solid dosage form a thin polymer-based coat is applied. The thickness of a coating is typically between 20-100 micrometres.

Standard coating pan: It contains a metal pan which is circular in shape rotated on its horizontal axis by a motor. Heated air is directed into the pan and on to the tablet bed surface and is exhausted by means of ducts through the front of the pan. It is improved by Pellegrino pan, the immersion sword, and immersion tube system (Hoag SW, 2017).

### Capsules

Two types of gelatines are hard gelatine and soft gelatine. Hard gelatine capsules are made up of two separate parts called body and cap where soft gelatine capsules are hermetically sealed one piece capsule which cannot be separated. The manufacturing of hard gelatine capsule are produced in two steps where shell is manufactured by one type of machine and then filling is done by another machine but soft are manufactured in one step.

The manufacturing process of hard gelatine capsule Is shell composition-gelatine which is used for shell composition it is produced from the collagen by hydrolysis or by extraction process. Generally they are two types of gelatine, which are differentiated by isoelectric point and by nature of viscosity and film forming capacity. To produce optimize shell the combination of pork skin and bone gelatine is often used. Here the colouring agent is used for colour the drug, piquing agent such as titanium dioxide is preferred for protection against light. Preservatives such as paraben are often used.

Shell manufacture:

Dipping: The pairs of stainless pins are dipped in solution to form caps and bodies. The pins will be at ambient temperature; where solution temperature is about 50°C in a heater, jacketed dipping pan.

Rotation: After dipping the pins are elevated and rotated continuously for 2-12 times until they are faced upward.

Trimming: The stripped portion are delivered and collected which are firmly held. Then it will rotate, and then knives are brought against shell to cut them for equal length.

Joining: The two portions are aligned concentrically in channels and then pushed together slowly.

Sorting: The moisture content of capsule as from the machine they will be in the range of 15%-18% w/w then they are passed through light moving conveyor and examined for defects.

Printing: They are printed just before filling which are done by offset rotator presses which have a high capability of printing. Size and shapes they are different range of capacities.

Sealing: They are sealed and reshaped by a seal process. This is a thermal welding process where cap overlap the body.

Storage: They are normally containing moisture content 13%-16%, relative humidity 40%-60%.

Soft gelatine capsules-plasticizer: It is made up of soft shell which is elastic and pliable. Commonly used plasticizer is made up of glycol, orbital, and propylene glycol-400. It is should be minimum interaction between liquid fill material and soft gel shell. The presence of water is 30%-40% of the wet formulation and it is presence is importance during gel preparation (Augsburg LL, 1990). The colorants which may be natural and synthetic for desire shell colour. An pacifier is also added for preparation of opaque shell commonly used pacifier is titanium dioxide. The preservative which is used to prevent growth of microbes is of concentration range of 0.2% commonly used preservative is methyl paraben and propyl paraben. The following agent which is used to mask bitter taste commonly used flavouring are ethyl vanillin, essential oil and sucrose is used.

Manufacturing plate process: Here the warmed sheet of gelatine sheet is placed over die plates which have moulds then sheet is drawn into the moulds by vacuum. A measured liquid medicament is pour over. Then another plate of mould is placed and then by applying pressure the plate is combined. Then it will shape, filled, sealed and cut into individual unit. Here it has moisture content of 20%-40%.

Rotary die process: Here the production of gel mass by dissolving gelatine in water at 80°C under vacuum, followed by adding excipients like pacifier, flavour, colour, preservative are added. Here the 57°C-60°C is maintained in melting tank. Then hot gel transfer into encapsulate machine by heated transfer pipes by casting method. This forms two separate gelatine ribbons. Then production of gelatine ribbons by metering device. Then checked correct thickness where two ribbons are then carried by roller and rotator die encapsulation (Augsburg LL, 1990). The liquid fill matrix is prepared separately. The drug which is a non-liquid vehicle filled using a conventional mixer homogenizer. The two ribbons of gelatine are fed between rollers and it sealed after pass through roller with pressure forms capsule encapsulation. Liquid gelatine which is passing overhead tank is passed through continuous ribbon by rotating drum and then it brought together by twin rotating dies. The injection of liquid between the ribbons, thereby gel expands and into the packets of die, which is used in maintaining the size and shape of soft gel.

Reciprocatingdieprocess:This is similar to rotator process but different encapsulating process.

Actonel: It is another rotator process which consists of measuring roll, die roll and sealing roll. Here the measuring roll rotates directly over the die roll and the pockets in two rolls are aligned. With each other powder fill material in pockets by applying vacuum. Then plasticized sheet is placed over as measured roll and die roll rotate which is transfer to gelatine lined pockets of die roll.

Seamless gelatine capsules: The apparatus consist of two concentric tubes, where inner tube is filled with medicament and through surrounding outer tube, the gelatine solution. The formed capsules are dropped into liquid paraffin where gelatine becomes insoluble. The capsules are subsequently degreased and dried. Generally soft gelatine capsules are used as ophthalmic soft gelatine capsule/ ophthalmic ointments, chewable soft gelatine capsule, enteric coated soft gelatine (Augsburg LL, 1990).

The solid packaging area as per schedule ‘M’ for culinary area square meters 60, 30, 20, 10 area requirement, environment requirement, temperature requirement 25°C-5°C humidity, 55%-10% RH pressure in ware house area, 10 Pascal pressure in weighing area, 20 Pascal pressure in tabulating area, 15 Pascal pressure in central corridor. The advantages of solid dosage form are they have strong onset of action, formulation is simpler than liquid and semisolid dosage forms, it has high precision, lowest variability and accurate dosing, doses available according to patients requirements, easy for packaging, transport and does not require special conditions for storage, it does not harm the GIT due to its easy and rapid digestion, unpleasant taste and odour can be marked by using capsules and sugar coating for tablets, they are stable in chemical, physical and microbiological properties. The disadvantages of solid dosage form are it is not easy to swallow, it cannot be given to the unconscious patient, encapsulation of tablets, complex process of capsules may increase production cost and hygroscopic drugs are not suitable for these types of dosage forms.

☆**Liquid dosage form :**

The Physical form of a drug product that is pourable displays Newtonian or Pseudo plastic flow behaviour and conforms to its container at room temperature. Liquid dosage forms may be dispersed systems or solutions. In dispersed systems there is two or more phase; where one phase is distributed in another (World Health Organization, 2007) (Figure 3).

Layout.

 Figure 2: Pilot plant layout for liquid

The oral liquid dosage forms classify as Monophasic and Biphasic. The Monophasic is of simple solutions. The Biphasic is suspension and emulsion. Liquid preparation for oral use is usually Solutions, Emulsions or Suspensions containing one or more drug forms in suitable vehicle. The preparation for oral use are either supplied in finished form or with excipients or it may also prepare just before use by dissolving powder in vehicle stated on label.

The liquid preparation for oral use consists of antimicrobial preservative, antioxidants, dispensing agent, suspending agent, thickening agent, emulsifying agent, buffering wetting, solubilizing, stabilizing, flavouring and sweetening with suitable colouring agent. They may be single dosage or multiple dosage preparation. The devices used are spoon or cup, oral syringe, dropper, etc. The liquid of should be uniformity of mass, uniformity of mass of doses delivered by measuring devices, container with proper labelling.

The Oral suspension consists of active ingredient suspended in suitable liquid or vehicle. It should be readily dispersed when shaking and stable to give or enable correct dose to be delivered. Oral emulsion is active ingredients which are stabilized in oil in water dispersion or water in oil dispersion. It also readily disperses while shaking. Oral drops which are used in small volumes with the aid of suitable measuring device. The drops should be free from precipitate. The instability can be seen through flocculants, sediments, change in colour, etc. Powders for oral solutions consists one or more dose preparation consist of solid loose, dry particle with high degree of fitness. It should be readily disperse in solution and should not form cake and the instability can be check through texture. Examples are clumping. Presentation for granules for oral solutions are intended to be issued to patient as granules to be swallowed, as such to be chewed or taken through water. They are dry aggregate of powder particles sufficiently resistant to withstand handling. It has noticeable changes in physical appearance when there is disability in the drug (Remington JP, 2006).

Formulation aspects of liquid orals are suspensions, emulsions, solutions. They are facilitating the connection between API and Vehicle. Steps involved in manufacturing process include planning of material requirements, liquid preparation, filling and packing, quality assurance (World Health Organization, 2007).

The Equipment’s used are mixers or mixing tank, homogenizer, filtration assembly, bottling assembly. The mixing tank and storage tank for liquid oral contains a bottom out let with electric or steam heating also available. Storage tank is manufactured from stainless steel 304/stainless steel 316 and is argon welded. They are made up with suitable thickness with smooth finish. It has a valve at bottom and lid at top. It has capacity of 50-10000 litters. The tank will be mounted on 4 legs with castors for movement. It is used or proper mixing of drug with excipients. Stainless steel tank with stirrer is with stainless steel steam jacketed and insulating with stainless cladding. They are different types of stirrer such as paddle/anchor/propeller. The electric heating of liquid is possible for small scale. It has capacity of 100-10000 litres. Colloidal mill is use for superfine grinding and simultaneous emulsifying, dispersing and homogenizing within one process. The homogenizer spring crude mixture inlet outlet homogenized liquid valve cover, valve seating. It is used for making suspension and emulsion. It consists of head of spring arrangement made out of stainless steel ultrasensitive inlet orifice vibrating blade outlet. The filter press is where the liquid to be filtered is pumped to tank where it enters into individual plates then passes through filter media like paper and crystal clear filtrate comes out through a central channel formed by interlocking cup then the pure form of liquid is obtained. Bottle washing machine consists of four inner and one outer wash. The first wash with water, second wash with detergent then wash with demineralized water and dry in inverted position or dry under hot air oven.

The liquid packaging area as per schedule ‘M’ include bottle washing area, filling and capping area, bottle labelling and box filling area. Bottle washing area here the tank should be filled with fresh demineralized water and then place in bottle into aluminium tray and then for washing area. The bottles should be inspected and rejected. Then the correct size should be chosen and fix on stainless steel platform and washing process is semiautonomous platform and washing process is semi-automatic. The washed bottles should be inverted on empty nozzles and then unloading of washed bottle in aluminium clean perforated tray in inverted position. So the water should be drained completely then dried at oven for 120°C for 1 hour. The filling and capping area contains the bulk containers which are used for filling. Only washed bottles and cleaned caps are used. The filled volumes record should be recorded and maintained as prescribed. The box filling area consists of the sealed and filled bottles are passed through convey belt and filled boxes consists labelling.

The layout of pilot plant of liquid” consists of the equipment such as tanker, mixer, homogenizer, filtration assembly.

Tanker: It should be according to batch size preparation of the drug. It should not produce any additive to the product. It is made up of stainless steel of different grades and lined with Teflon and glass if high viscosity liquid then high electrical stirrers are used.

Mixer: Here simple mixing is done to increase mixing of liquid. There should be proper adequate clean up procedure. At high viscosity air entrapment occur it can be minimized by reduce agitator speed by caring out mixing process in closed tank under vacuum homogenizer. There should be a variety of equipment should be used for better results. Filtration and Clarification should require careful evaluation to exhibit high purity of drug as their laboratory counterparts. It should be checked periodically to know the purity of substance.

The advantages of liquid dosage form are immediate available for absorption in the body, easy route of administration, they can be taken easily and can be add colour, flavour, sweetener as per required, they are used to change the dose daily easily, they can be given for children and old people, better for patient who have trouble swallowing, expiration, than other, more flexibility in achieving the proper dosage of medication. The disadvantages of liquid dosage form are they are bulky form than capsules or tablets, so they are difficult to carry, they are less stable and some are cannot store in room temperature, they are incompatibility than solid dosage form, there will be accident breakage of container, they have shorter half-life, they are harder to measure accurate dose, they are easily affected by microbes. “The visual inspection of solution is should be clear and free from any precipitation. A change in physical or chemical form of drug such as cloudiness of solutions may indicate chemical degradation or microbial contamination. It should be avoided for safety of the patient.”

☆**Semi-solid dosage forms :**

Semi solid dosage forms are the topical dosage forms that are intended for the therapeutic, protective or cosmetic functions. Few examples are Ointments, paste, creams, plasters, suppositories, gels and rigid foams. Semisolids are the complex formulations which are having complex structural elements. They are of two phases-oil in water one is a continuous phase also known as external phase and the other is a dispersed phase also known as internal phase. Semi solid dosage form products are mostly administered topically or by the insertion method into an orifice of the body. During mixing process an active ingredient of a semi solid product attains uniformity. The consistency and viscosity of these products, once the active pharmaceutical ingredient is distributed in the manufacturing batch, the API is less prone to segregation than solid dosage form. The physical properties of the semi-solid dosage form depends upon numerous factors such as interfacial tension between the phases, size of the dispersed particles, partition coefficient of the active ingredient between the phases and also the product rheology. These factors merge to determine the release characteristics of the drug, as well as other characteristics.



 Fig : 3 Layout for semisolid

The semi-solid dosage forms are classified as Suppositories. Suppositories are introduced into orifices of human body, which are of various weights and shapes these are the solid drug delivery systems. When suppositories are introduced into orifice, the external membrane will typically melt or dissolve at the body temperature that allows the active ingredient absorbed by the surrounding tissue. Suppositories bases that are usually employed are hydrogenated vegetable oils, mixtures of polyethylene glycols, glycerinated gelatine, fatty acid esters of polyethylene glycol. The suppository base has a marked impact on the release of active ingredient which is incur ported in it. Ointments are semi solid preparations. Ointments are homogenous, viscous, translucent semi solid preparations that are intended for external applications to the skin or mucus membranes. Ointments may be medicated or non-medicated. The bases of ointments are used as vehicle for transfer of drug into skin. Depending on the carrier of the drug or base used for its formulation, ointments can be classified as follows Hydrocarbon or oleaginous bases, absorbent or anhydrous base, emulsion or water miscible base and water soluble base. Creams are viscous semi solid emulsion with an opaque appearance. Creams are emulsions of water and oil classified as oil in water (o/w) or water in oil (w/o) emulsions. Oil in Water creams spread easily and do not leave the skin greasy and sticky, whereas Water in Oil creams is greasy and more emollient. Medical topical cream formulations also contain the suitable excipients such as emulsifiers and preservatives. Pastes generally contain a larger portion of solid material (such as 25%) than ointments and therefore they are stiffer. Pastes are prepared by incorporating the solids directly into a congealed system by levitation with a portion of base to form the paste like mass. They have good adhesion on skin and are less greasy. Gels are typically transparent or translucent, water-based semisolid dosage forms. They exhibit good spreading properties. Many gel products are turbid (Sod S and Kamath A, 2013).

☆**The** **Equipment’s** **used** **in** **semi**-**solid** **dosage** **form** **are**:

Agitator mixer: This agitator is a machine used in a tank for mixing numerous process media together. It works through mechanical mean by rotating an impeller to impart energy to the media which interact and mix the ingredients. An agitator consists of shaft, impellers, motor and gear box.

Roller mill: It is a form of compression mill which use single, double or triple cylindrical wheels arranged horizontally. It is rotated through there long axis in opposite pairs or against flat plates which is used to crush or grind several materials. One roller is run by motor and other by friction. The stress and attrition are employed in the procedure of milling which are rotate at distinct speeds.

Ribbon agitator: The mechanism involved is shear that is transfer by moving blades in a fixed shell. The functions are paste mixers, vacuum dryer, granulators. The mixing is completed within 15 mins or less. It consists of U-shaped shell containing a double helical ribbon agitator.

Colloidal mill: It is used to reduce the particle size of solid forms of the pharmaceutical ingredients which are present in different liquid or solid forms. It works on the principal of rotor-stator. Generally it is used in production of sterile products.

Sigma mixer: It works on the principle of shearing and tearing.

The plant layout requirements for semi solid dosage form as per schedule ‘M’ include external preparation, Quantitative layout, and Specific requirement for the manufacturing process. External preparation here it is recommended to have a minimum of 30 square meters area for basic installation of 10 square meters for ancillary area. It is necessary to provide a separate area for the formulation aimed for external and internal use, so that it can be avoidance of mix-up for suppositories, there should be a minimum area of 20 square meters for the basic installation. Quantitative layout for cream it has to be 18.5 square meters, 25 Lts to 10000 Lts for raw material strafing area; 40.8 square meters for the manufacturing area; tube and machine filling area should be 27 square meters; 46.8 square meters for packaging and labelling area and for the final product storage area should be 14 square meters. Specific requirements for the manufacturing of topical preparation here the manufacturing area temperature should not exceed 30°C. The area should be under suitable air lock. Insecticides shall be installed outside the air lock. The air is filtered through 20 micrometre air filters and air conditioning at the manufacturing area. A suitable capacity of an exhaust system is used. There should be no usage of rags and dusters in the cleaning and drying process. Water used in compounding should be purified and the powders are sieved suitably before use. The heating of vehicles and bases should be done in separate mixing area. The advantages of semi-solid dosage form are it can be applied directly on to the affected area, it can be administered easily at any conditions, the active pharmaceutical ingredient present in the dosage can be directly deliver to target system through skin or other physical membrane, it reduce risk of unwanted side effects, the first pass effect is avoided, it is stable than liquid dosage form, it is convenient for patients who have difficulty in oral administration, it is suitable dosage form for bitter drugs. The disadvantages of semi-solid dosage form are it cause irritation or allergy to some patients, the accuracy of dosage form cannot be measured, it is bulky to handle, the physiochemical properties are less stable than solid dosage form, it is easily contaminates when applied with fingers.

☆**CONCLUSION**:

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

**☆Reference:**

Ahmed P (2022) A current review on pilot plant scale up techniques: focus on supac (scale up and post approval changes). J.Xi’anShiyou Uni 18:575-600.Ankit T, Shrikalp D, Maitreyi Z, Praveen Kumar J, Kiran K (2021) Regulatory procedure of post approval changes and comparative requirements of EU and USA Regulatory regions. Journal of Pharmaceutical Research International 33:304-317.https://doi.org/10.9734/jpri/2021/v33i46B32944Chowdhary Y, Kumar B (2023) SUPAC-Post approval changes suggested by FDA to industry. Asian Journal of Research in Pharmaceutical Science 13.<https://doi.org/10.52711/2231-5659.2023.00005>Dhobale A, MA hale A M, Shirsat M, Pethkar S, Chakote V (2018) Recent advances in pilot plant scale up techniques-a review. Indo Am J Pharm Res 8:1060-1068Jereb R, Kristl A, Mitra A (2020) Prediction of fasted and fed bioequivalence for immediate release drug products using physiologically based Biopharmaceutics modelling (PBBM). European Journal of Pharmaceutical Sciences 155:105554.<https://doi.org/10.1016/j.ejps.2020.105554>Kamnoore K, Venkatesh M P, Kumar TM (2022) Study on post approval source change of active pharmaceutical ingredient in the finished product and its Regulatory requirements in EU and US. The Thai Journal of Pharmaceutical Sciences 46:11-19.Mali SM, Patil A, Saptal V, Phate N, Pathan F, Pawar P, Mali A (2022) An updated review on SUPAC-scale-up process and changes guidelines. Journal of Pharmaceutical Quality Assurance and Quality Control: 1-21.Metry M, Polli JE (2022) Evaluation of excipient risk in BCS class I and III bio waivers. The AAPS journal 24:20. <https://doi.org/10.1208/s12248-021-00670-1>Mounica NVN, Sharmila Reddy V, Anusha S, Evangeline L, Nagabhushanam MV, Nagarjunareddy D, Brahmaiah B (2017) Scale up and post approval changes (SUPAC) guidance for industry: a regulatory note. International Journal of Drug Regulatory Affairs 5:13-9.https://doi.org/10.22270/ijdra.v5i1.192Mustafa G, Mujtaba MA, Kotta S, Harebell A, Alhakamy NA, Aldawsari HM, Md, S (2022) Drug product performance and scale-up process approval Changes. In Regulatory Affairs in the Pharmaceutical Industry Academic Press:215-240. <https://doi.org/10.1016/B978-0-12-822211-9.00010-1>Sherman R (2015) Technology & product architectures. Business Intelligence Guidebook 143-169. <https://doi.org/10.1016/B978-0-12-411461-6.00007-1>Vásquez AGT (2021) Risk based approach of post approval changes in central America and Dominican republic, identifying opportunities for convergence with EMA and FDA.Wu D, Sanghavi M, Kollipara S, Ahmed T, Saini AK, Heimbach T (2023) Physiologically based pharmacokinetics modelling in biopharmaceutics: case studies For establishing the bioequivalence safe space for innovator and generic drugs. Pharmaceutical Research 40:337-357. <https://doi.org/10.1007/s11095-022->03319-6Xiaowen L, Zhen H (2023) Present situation and enlightenment of post approval change management of drugs in China, USA and EU 18:17-23