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Pilot Plant Scale up Techniques of Solid Dosage Form (Tablet): An overview

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ABSTRACT: Pilot plant is a section part of the Pharmaceutical Industry where a laboratory scale formula is transformed into a viable product by the development of a liable practical procedure for manufacture. This technique is a pre-commercial production system that employs new production technology which produces small volumes of new technology based products. After adopting new Technology, the knowledge thus obtained is utilized for designing of large scale production of commercial products. It is also extended for identification of further research objectives and support of investment decisions. The drug discovery and development of processes for new medicinal plants are subsequent integral and critical parts of the Pilot plant and scale-up techniques. In Scale up technique, several important decisions are targeted on the points where the idea or process is advanced from a research oriented program targeted towards commercialization. The new drug applications (NDAs) and abbreviated new drug applications (ANDA) are all-time high. The preparation of several clinical batches in the pilot plant provides its personnel with the opportunity to perfect and validate the process. Also different types of laboratories have been motivated to adopt new processes and technologies in an effort to stay at the forefront of scientific innovation.

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INTRODUCTION:

Plant is a place where the 5 M's like money, material; man, method and machine are brought together for the manufacturing of the products. Pilot plant is a part of the Pharmaceutical industry where an idea from the laboratory scale as formula is transformed into a viable, robust product by the development of a reliable and practical method of manufacture. It affects the transition from laboratory to routine processing in a full scale production in definite order form. The scale up is an art of designing a prototype using the data obtained from the pilot plant model. In modern manufacturing technology, the pilot plant scale up utilized technology transfer tool to explore the researcher ideas [1].

Need of Pilot Plant Studies:

The pilot plant studies offer several necessities that are demonstrating the process on a continuous basis, including yields and product purity. It provides the design data for scaling the commercial-scale plant. The scale up provides the data for evaluating process economics, including capital and operating costs. It determines the potential for scale build up in processing equipment and methods to minimize scaling. The Pilot Plant studies provides the product for customer evaluation representative of what will be made in the Commercial plant and it also provides the design data for scaling the commercial-scale plant [1].

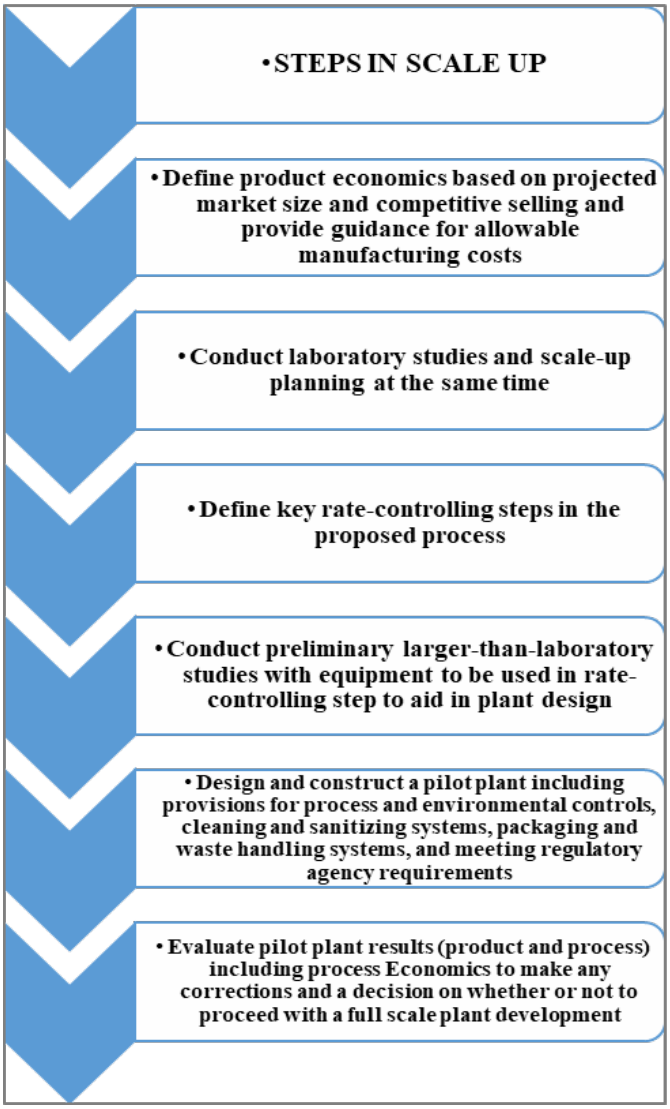

Fig 1. The Step in Scale up Technique.

Utilization of Pilot plant:

It permits close examination of laboratory formula to determine its ability to withstand batch scale and process modification. It permits to produce minimum quantities of product for chemical, microbiological evaluation and to study the shelf-life of products. It provides data which can be used for making a decision to proceed to a full scale production process, designing and constructing a new full size plant [1].

Objectives of the Pilot Plant Scale up:

The prime objective of the Pilot Plant study was to find out the mistakes on small scale and committed to make profit on large scale. In addition to this other objectives are to try the process on a model of proposed plant before committing large amount of money on a production unit, to produce a stable therapeutic dosage form, ability of the formula to be examined to withstand Batch scale and modification of process, to guide production and process control, validation of process, to identify the several critical process parameters and to prepare the master manufacturing formula [2].

Significance of Pilot Plant:

The Pilot plant study offers several significance that are formulae standardization; review of equipment for their most simple, reliable, compatibility and most economical; adjustment of production rate after considering marketing requirement; it provide rough idea about physical space required; different parameters to be taken in to account for maintenance of quality of product and to satisfy the Good Manufacturing Practice (GMP) [3].

Steps in Scale up:

Scale-up is the migration of a process from the Laboratory scale to the pilot plant scale and then to the commercial scale. Detail steps illustrated in Fig 1 [4].

GENERAL CONSIDERATIONS [4-6]:

Reporting Responsibility:

In order to facilitate smooth transfer of a product from laboratory scale to commercial Scale, there is a need for adequate records and reporting systems. To achieve the same, there should be a good relation and effective communication between the pilot plant group and R & D group as shown in Fig 2.

Personnel Requirement:

Person employed for scale up process should be qualified as required for position in a pilot plant organisation. It should be a blend of good theoretical of Pharmacy and some experience in Pharmaceutical Industry. The type and level of education within the group is equally important as they have to understand the intent of the formulator as well as understand the

perspective of the production personnel. Engineering principles and Knowledge of computers and electronics are also required.

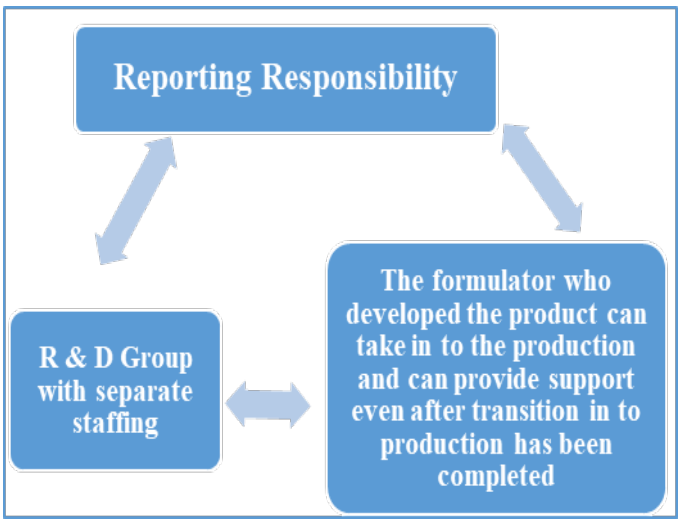

Fig 2. The Reporting Responsibility in the Pilot plant Scale up.

Space Requirements:

***Administration and Information Process*:**

There should be adequate space for working personnel to facilitate proper documentation of their activities and observations. This should be nearby to the working area and sufficiently isolated.

***Physical Testing Area*:**

Adequate working area as per guideline should be provided where the analysis and physical testing of samples can be performed that is the in-process quality control analysis and it helps in early identification of production error. This area should provide permanent bench top space for routinely used physical testing equipment like balances, pH meters and viscometers.

***Storage Area*:**

Separate provision should be made for the storage of active ingredients and excipients. Different areas should be provided for the storage of the in-process materials, finished bulk products from the pilot plant and materials from the experimental scale-up batches made in the production. Storage areas for packaging materials should also be made available.

Review of the Formula:

This step is more important. It includes review of each ingredient, formulation and final product manufactured on the small scale laboratory equipment so that the stresses of different types and degrees can more readily be predicted or recognized.

Raw Materials:

The raw materials used during small scale formulation trials may not meet the requirements of large volume shipments of materials used in full manufacturing scale. Also active ingredients used in a laboratory scale need to meet up with the rising needs of the product when subjected to scale up. So it is the responsibility of the pilot plant to approve and validate the active ingredients and excipients used in the formulation keeping view of their particle size, shape, morphology, density, static charges, solubility rate and flow properties.

Equipments:

During scale-up, alternative manufacturing equipment should be considered since most development work has been performed on small and simple laboratory equipment. The equipment that promises to be the most economical, the simplest, the most efficient and the most capable of consistently producing products within the proposed specifications should be evaluated based on the known processing characteristics of the product. The size of the equipment should be optimized and the ease of cleaning should be considered especially if multiple products are to be manufactured in the equipment.

Production Rate:

Production rate mainly depends upon immediate requirement and future market trends.

PROCESS EVALUATION:

Process is validated only when there are no changes in the formulae, quality of the ingredients and the equipment configuration. Revalidation needs to be done to ensure that changes have not taken place. Process validation steps illustrated in Fig 3 [5].

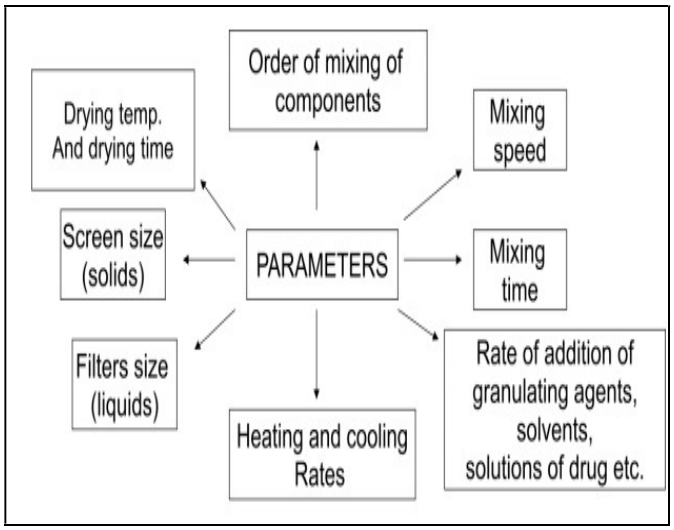

Fig 3. The Steps of Process Validation.

Master Manufacturing Procedure:

The master manufacturing procedure consists of three major aspects that are [5,6];

***Weight Sheet*:**

It is the working sheet where the chemicals or active ingredients required for a batch should be clearly mentioned.

***Process Directions*:**

Ti should be precise, stated clearly and in detail, leaving no room for confusion or doubt.

***Manufacturing Procedure*:**

It is the manufacturing protocol written by Operator which indicates the various specifications such as rate of addition, mixing time, mixing speed, heating and cooling rates of a finished product.

PRODUCT STABILITY AND UNIFORMITY:

The physical and chemical factors influencing stability of a product. Formulation and manufacturing procedure of each pilot batch should be studied. The protocol for stability testing includes batches, containers and closures, Orientation of storage of containers, sampling time points, sampling Plan and test storage conditions [5, 6]. The batches used for stability study must meet all the testing requirements including heavy metals, residue on ignition and residual solvents. Some of these are required at the time of product release but not required to be repeated during stability testing [7]. We have to follow FDA guidelines, for submitting documentation for the stability studies of Human Drugs and Biologics.

GMP Consideration:

In practice of GMP, personnel must be adequately trained, suitable premises, equipment used, correct materials used, approved procedures adopted, suitable storage, transport facilities available and appropriate records made accordingly. The essential components of GMP are summarized in Fig 4 [8].

PILOT PLANT DESIGN FOR TABLET:

Each stage for Tablet production is considered carefully from experimental laboratory batch size to intermediate and large scale production. Same process, same equipment but different performance when amount of material increased significantly. May involve a major process change that utilizes techniques and equipment that were unavailable on a lab scale [9].

Layout of pilot plant:

The layout of Pilot Plant systematically represented as in Fig 5.

Stages of Production of Tablet:

***Material handling*:**

In the laboratory, materials are scooped, dumped or poured by hand. It may work well for small or intermediate scale productions. For large scale productions, mechanical means is necessary. The simple means are: post hoist devices, devices for lifting and tilting drums but the sophisticated ones are: vacuum loading systems, screw feed system and meter pumping systems. The type of system selected depends upon the characteristics of the material e.g. density. Material handling system should cause minimal loss of material. The longer the transfer, the more is material loss. If one system being used for more than one material cross contamination should be avoided, accomplished by using validated cleaning procedures [10].

***Dry blending*:**

In this process a binary cohesive-powder mixture is used which contains two different sizes, it is well known that finer particles adhere preferentially on the surface of the coarse particles. This type mixture has been called an interactive mixture. The blending of fine and coarse particles breaks down the agglomerates of fine and coarse powders, and produces an electric charge by contact and collision between particles. Fine and coarse particles do not revert to the former agglomerates. The blending operation produces new agglomerates in which fine particles are adhered to the surface of the coarse particles. In the first step, the coating particles randomly adhere onto the surface of the core particles [10].

Problems of improper blending are flow problems through the equipment, non- reproducible compression and no content uniformity.

Screening of the ingredients prior to blending done to make the process more reliable and reproducible. The equipment used for blending are V-blender, Double cone blender, Ribbon blender, Slant cone blender, Bin blender, Orbiting screw blenders vertical and horizontal high intensity mixers [11]. The scale up consideration is time of blending, blender loading and size of blender.

Granulation:

Granulation is the process whereby small particles are gathered into larger, permanent masses in which the original particles can still be identified. Pharmaceutical granulation is the rapid breakdown of agglomerates is important to maximize the available surface area and aid in solution of the active drug. Granulation is a process of particle designing and it is of two types [9].

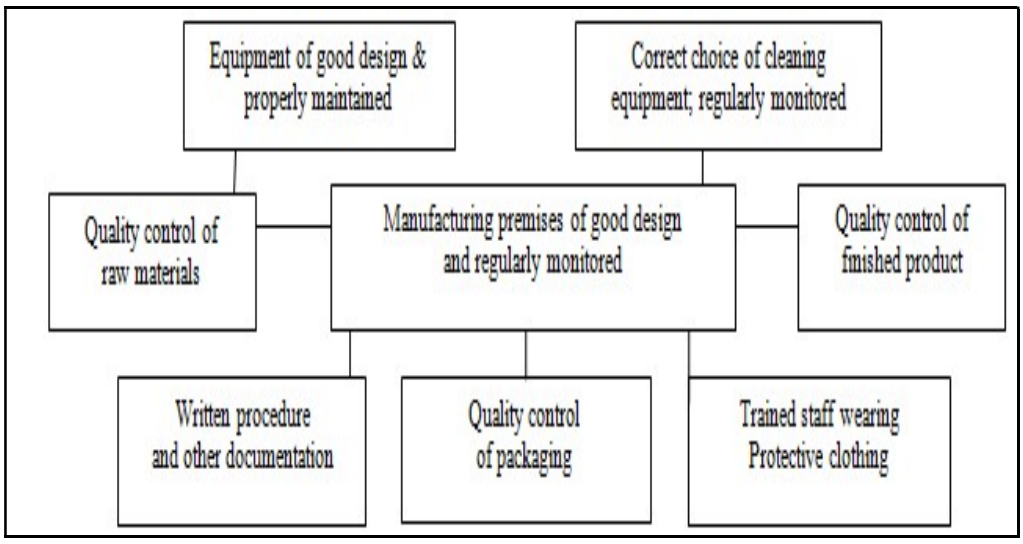

Fig 4. The Components of Good Manufacturing Practice.

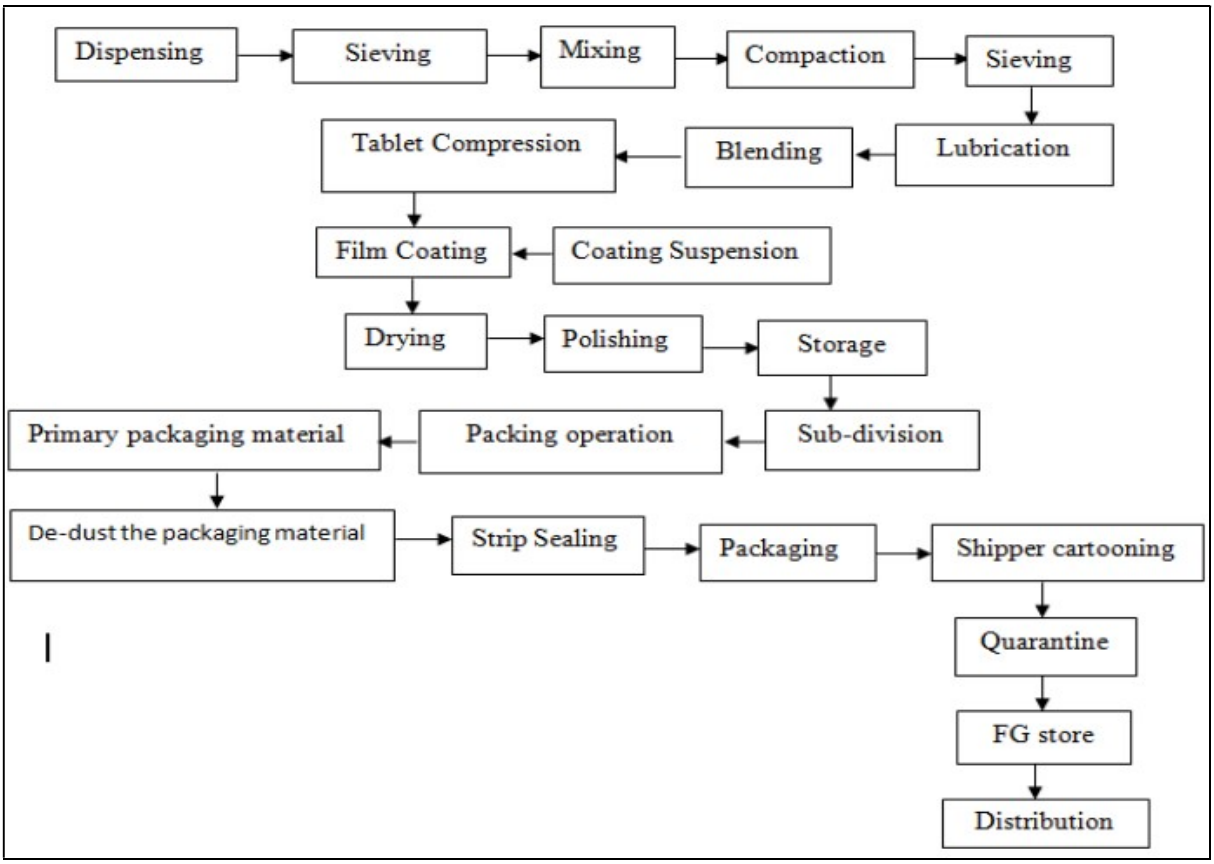

Fig 5. The Layout of pilot plant Scale up Technique.

Wet methods:

Wet granulation technology is employed in low-shear mixers or the mixers/blenders normally used for dry blending such as ribbon mixers. There are a number of products currently manufactured using these low-shear granulators. The process control and efficiency has increased over the years; however, the industry has embraced high-shear granulators for wet granulation because of its efficient and reproducible process and modern process control capabilities [12].

Dry methods:

Dry compaction techniques like roller compaction are commonly used in the Pharmaceutical industry. There are a number of drug substances which are moisture sensitive and cannot be directly compressed [13].

It is the most common conventional method, which includes circulating hot air ovens, which is heated by either steam or electricity. Scale up considerations for oven drying operation is airflow, air temperature and depth of the granulation on the trays.

Too deep or too dense a bed makes the drying process inefficient and if soluble dyes are involved migration of the dye to the surface of the granules. Drying times at specified temperatures and air flow rates must be established for each product. Fluidized bed dryers are alternative to the circulating hot air ovens. The important factors considered the scale up fluidized bed dryers are optimum loads, rate of airflow, inlet air temperature and humidity.

Reduction of particle size:

Particle size influences many properties of particulate materials and is a valuable indicator of quality and performance. This is true for powders, suspensions, emulsions, and aerosols. The size and shape of powders influences flow and compaction properties. Larger, more spherical particles will typically flow more easily than smaller or high aspect ratio particles. Smaller particles dissolve more quickly and lead to higher suspension viscosities than larger ones. Smaller droplet sizes and higher surface charge (zeta potential) will typically improve suspension and emulsion stability. Powder or droplets in the range of 2 to 5 µm aerosolize better and will penetrate into lungs deeper than larger sizes. For these and many other reasons it is important to measure and control the particle size distribution of many products [14]. The **e**quipment used are Oscillating granulator, Hammer mill, Mechanical sieving device and Screening device.

Blending:

Blending in solid dose manufacturing has two objectives that are to achieve blend uniformity and to distribute the lubricant. In the first objective, the blend step(s) are designed to achieve homogeneity of all components prior to the final blend of the lubricant and in the second objective, blending powders is more of a challenge due to particle size, moisture content, structure, bulk density and flow characteristics. The first step in achieving predictable results in a blend is to introduce the proper particle profile within a range; between 40 to 180 mesh for most oral solid dosages. We do not want any particles larger than 20 mesh and try hard to limit the percentage of fines to less than 20 % smaller than 200 mesh. The next step is to complete pre-blending steps in a carefully planned order of addition [15].

Compaction and Compression of Tablet

Compaction and tableting are associated with scale-up issues despite the availability of other good technologies. Generally, tablets are made up of compressed powder in a die by punches in a rotary tablet press. During this process the die table, along with punches, rotates and pushes each set of upper and lower punches between compression rollers [16]. This results in the punches travelling inside the die and bringing about the compression of powder. Thus the process of production of tablets briefly involves two processes: compaction and compression (Fig 6).

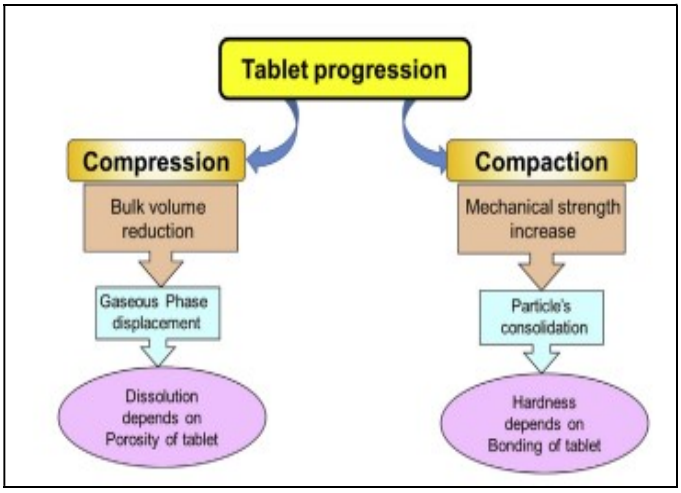

Fig 6. Compression and compaction processes involved in tablet manufacturing.

During compaction flow, the pattern or behavior in the blender or hopper could be predicted through mathematical approaches, whereas powder flow analysis in a hopper is achieved through dimensionless relations and it can be redundant. To prevent arching, a minimum outlet size is required in case of gravity discharge and it is also based on the type of flow pattern of powder. Irrespective of the flow pattern of the powders the outlet size of the hopper is determined by the powder's flow function which is reflected by measuring the cohesive strength tests. The size of the outlet required to overcome no-flow conditions is merely based on the flow pattern. In order to overcome arching in the funnel, flow develops in place of mass flow and thus the minimum diameter of the outlet is given through the propensity for a stable rat hole to the formation, due to a larger diameter that is required for arching [17]. Hopper angle basically depends on two factors namely wall friction angle and internal friction of the material. Proper angle of hopper is required for mass flow and also determines the level of powder within the hopper or the diameter or height of the bin, especially for minimum outlet size. With lower normal pressure the wall friction increases and if the outlet size is larger, it

discharges and exhibits a mass flow pattern. Additionally, the mass flow of powder is highly reliant on conditions beneath the hopper which are the presence of a throttled valve, a lip or other protrusion, or anything that can does a zone of stationary powder into funnel flow, irrespective of the angle of the hopper or surface finish [18]. Earlier a bench-scale compression model was developed by Gereg and Capolla which is able to translate parameters to scale compactors. The objectives of this study were to characterize the ingredients as per their properties and categorize the process parameters in order to attain the essential particle size and density using the dry granulation process [19]. Powder granules formed by a roller compactor are similar to those obtained from the Carver press. Lactose monohydrate or spray-dried lactose monohydrate were utilized as the model compounds. Authors observed that parametric association exists between the laboratory bench Carver press and the production-scale compactor and thus several process parameters can be shifted directly [20].

The compact which has been milled generated slightly larger particles and the associated round slugs that have been formed by the Carver press produced a greater number of fines. Further, in the case of roller compacted material, flow rate was twice as fast as that for the Carver press' granules, although both flow rates were thought to be satisfactory [21].

The authors have also used the wet granulation procedure but it was not feasible due to the high solubility of the active bulk molecules. Further, it was observed that the granulating pockets had highly wetted areas preventing uniform moisture distribution and granule formation. To solve these problems, it was possible to carry out granulation with a solution of drugs. However, this is not a standard protocol as it results in the formation of an amorphous form of the compound after drying. Another method was to perform a dry slugging granulation procedure to overcome the problems that arise in wet granulation [22].

Slugging was a good alternative but it had limitations, like difficulty in compressing slugs owing to low bulk density and poor blend flow properties. From batch to batch, weight and hardness variation of the slugs vary in a wide range during the slugging process. Furthermore, non-consistency in particle size distribution, bulk, and tap densities make it difficult to compress slugs [23].

The compaction procedure was scaled-up to a rate of 100150 kg/h using the same parameters as set at the pilot scale. Granules made from the compactor scale-up created a tablet with excellent physical properties paralleled to the slugging process. The roller compaction method maintained predictable powder properties and consistency with a slugging process.

CONCLUSION:

The traditional process of product development of pharmaceuticals involves many experiments, observations, challenges, and resolutions before the drug reaches the global market. Most of the solid dosage forms contain both the mixture of active ingredients/drugs and excipients. The large-scale production of solid dosage forms requires well proven and documented formulae for production. Dry powder blending and mixing is a crucial step for the manufacturing of tablets that directly have an impact on the uniformity of content. So Pilot plant scale up techniques of different parameters such as granulation, feed rate, lubricant, blending and compression play an important role as well as important tools for large scale production as discussed above.

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