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Exploration of Pilot Plant Scale Up Consideration For Solids

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Abstract: *Pilot Plant - It can be understood as a small- scale production system or a pre-commercial system of the giant pharmaceutical industry. Here, a small preliminary lab-scale formula is developed and transformed into an operational product by the development of the liable and practical procedure of manufacture.*
Scale-up The art designing of a prototype to increase the batch size of a product using the data obtained from the pilot plant model.
Before investing a large sum of money on a production unit this small preliminary lab-scale formula can be carried out on a model of the proposed plant.
To conduct an examination of the formula to check its robustness and ability to withstand large scale or Batch-scale production and if process modification is needed. To conduct an evaluation of equipment and process validation.
Evaluation of a product and process validation on an intermediary scale can be carried out by a pilot plant setup before investing large amounts of money to full- scale production. It is not feasible to predict the effects of a many-fold increase in the scale of batch production without a pilot plant study. It is beyond everyone's scope to design a large-scale manufacturing unit from laboratory data alone without any degree of relevant success.

Keywords: Pilot plant, scale up, production, TAM, tablet, granulation, slugging and blending

I. INTRODUCTION

Pilot plant is part of pharmacectical industry in which a lab scale formula is converted to a feasible product by developing a liable practical method for manufacture. The scale-up is helpful in designing a prototype by utilising the information obatainned from pilot plant model. In this technique, a formula is examined and shifted to a most suitable formulation by developing a reliable and useful manufacturing procedure which affects the organised transition from laboratory to regular processing in a large scale production facility.

Definition

Pilot plant can defined as the pre-commercial production system which includes new production technology and produces small volumes of new technology based products.
Scale up is the process of increasing the batch size or a procedure for applying the same processs to different output volumes.
Pilot plant scale updefined as a technique that involves developmet of a practical procedure for manufacturing dosage forms that may result into transformation of lab scale process into a viable product.

Objective

- It determines the steps involved in raw material processing.
- It enables handeling of raw materials as per their specification.

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- It implroves various parameters required in the formulation and development of physically and chemically stable therapeutic dosage forms.
- It generates stratergies for production and process control.
- It develops the master manufacturing formula.
- It allows any sort of modification in the process.
- It evaluates, validates, and finalises the production and process controls.
- It develops the pilot plant studies to form an identifical examination of the formula to tolerate batch scale.
- It properly evaluates and validates the developed product.
- It makes the process more economical and less time consuming.
- It ensures the physical and mechnical compatibility between the equipment and preparation.
- It overcomes the problems in small-scale techniques by developing large- scale techniques.
- It develops modern marketing stratergies.

Stepsi Scale-Up

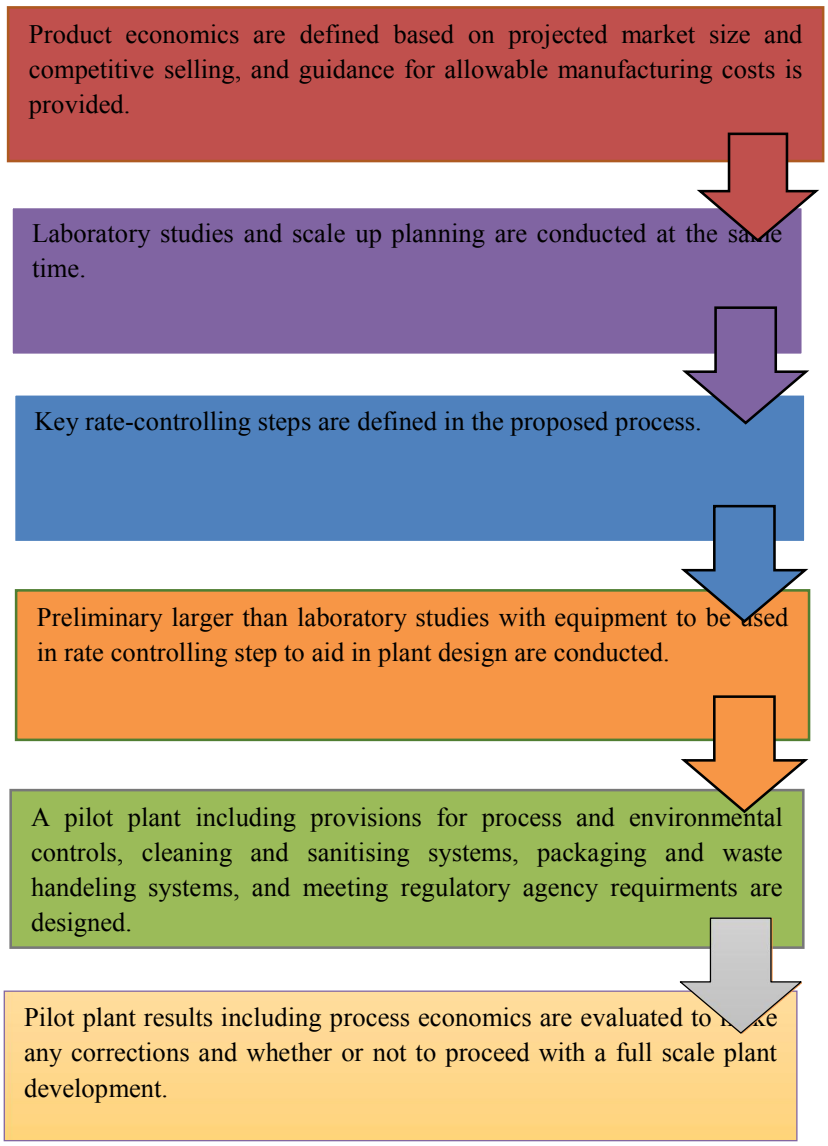

Figure 1

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II. GENERAL CONSIDERATION

Reporting requirement:

The pilot plant function can be a part of the R and D or operation - orientation groups. If it is a part of R and D , there is a need of separate staff and importance also given on consideration of hierachy of responsibility to scaleup forrmulations ,anufactured by the R and D department and that emerges as the product.some industries implement combination of the R and D and the operationa-oriented systems to achieve the best qualities of both.

Fig. 2

Personnel Requirement

Scientists with experience in pilot plant operations as well as in actual production area are the most preferable. As they have tounderstand the perspective of the production personnel. Experience of formulation process and equipment in the production environment is also important. Pilot plant personnel should know the objective of the formulator and also recognise the view point of production personnel. Due to these reasons, pilot plant organisations include scientists having experience in both areas. The group should have some personnel with engineering knowledge as well as scale up also invloves engineering principles. Knowledge of computers and electronics.

Space requirements

Administration and Documentation: the data from every experiment and trial performed in a pilot plant scale up of a product are recorded and documented. The documentation area should be near to the work area, but should be located remotely so that the people can work without any interruptions.

Physical Testing Area: There should be an adequate working area where the analysis and physical testing of samples can be performed (in-process quality control analysis) which 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, viscometers etc.

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Standard Pilot Plant Equipment Floor Space: This has to do with where all the relevant equipment used in the pilot plant scale up techniques is kept. The equipment should be available in a variety of sizes known to the representative of all production capability. This arrangement helps make sure of the quality of the scale up data collected, as well as being prudent with expensive materials.

Intermediate size and large or full scale production equipment are essential in evaluating the effects of scale up on research formulations and processes. Equipment should be made portable where possible since the utilization of pilot plant equipment is occasional or sporadic and dependent on project assignments. Utilization of this area is most effective when it is subdivided into areas for different dosage forms (solid, semi-solid, liquid and sterile products).

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-upbatches made in the production. Storage area for packaging materials should also be made available.

Raw Material:

One responsibility of pilot plant operation is to approve and validate the active and excipient raw materials used in the formulation of pharmaceutical products. This should not be taken for granted. This is because pilot scale up, in itself, does not guarantee a smooth transition. 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.

Relevant Processing Equipment:

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.

Processing Equipment:

The equipment size should be appropriate for conductiong experimental trials that are significant to the production size batches. The method developed will not scale up well if incurred if the equipment is very large; new and costly active ingredients will also get wasted in large quantities. Upone development of a practical process on the pilot plant equipment, medium sized and economical experiment should be caried out. If the equipment is not present im house, one can reach out to equipment vendors. Choice of equipment depends on the ease of cleamimg, especially if multiple products are manufactured in the same equipment. The time needed to break down the equipment for cleaning and changing from one product to another should be estimated. Trials should be conducted at the vendor's facility for assessing these parameters. This aids in establishing the real capabilities of the equipment and the quality of technical support available from the vendors.

Process Evaluation:

Understanding the outcome of key processes such as mixing speed, time, rute of addition of granules, granulating agent, solution of drugs, solvents, heating and cooling rates, etc., is a major requirement for optimising and verifying the quality of in-process and finished product. The aim of process validation is to check whether the chosen manufacturing method ensures the product quality at numerous critical stages in the process and in the finished form. This can be achieved by monitoring the within-batch variation of measurable parameters, and the data acquired shows if the process is performed as planned and where problem areas could be found. Review of the manufacturing process and quality control data should be done annually, and if required, some revalidation studies should be performed to confirm that alterations have not ensued.

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Production Rates:

While estimating the production rates and the type/sizes of production equipment to be used in the production, the current and future market demands of a product should be kept in mind. The equipment size should be proportional to its utilisation. The selection of equipment and process to be used depends on the loss of product in equipment during manufacturing, time needed for cleaning the equipment between batches, and the number of batches required for testing.

Preparation of Master Manufacturing Procedure:

The master process records are made for the optimised formulation, in which the manufacturing directions, chemical weigh sheet and in-process and finished product specifications are recorded. The processing steps should be accurate and written in a style which uses language and terms well known to the operators. For writing the manufacturing procedures, sufficient input should come from the operators or from someone having knowledge and experience in the modern weighing and processing areas.

The batch record steps should include specification for mixing time, addition rates, mixing speed, temperature, heating and cooling rates. The record should also bear proper ranges. The batch process record should follow the master process record instructions. The manufacturing process and quality control data should be reviewed annually and if required, some revalidation studies should be performed to make sure that alterations have not ensued.

The accurate time, speed, and temperature used in batch process should be recorded. These can be monitored and recorded using suitable controller recorders. GMPs, periodic revalidation, and monitoring of finished product test results through control charts are required for maintaining constant product quality.

Transfer of Analytical Methods to Quality Assurance:

The analytical test procedures developed in research during scale up of a s product should be moved to the quality assurance department. The staff of t department should assess the process to ensure that proper analys instrumentation is present and personnel are trained to do the assigned activiti Research personnel should analyse the susay method and the data acquit during the validation studies for confirming that the analytical procedures ha not been changed in a way that may alter the reliability and accuracy of the fest

III. ADVANTAGES

- Members of the production and quality control divisions can readily observe scale up runs.
- Supplies of excipients & drugs, cleared by the quality control division, can be drawn from the more spacious areas provided to the production division.
- Access to engineering department personnel is provided for equipment installation, maintenance and repair.
- A pilot plant provides important process data collection.
- A pilot plant allows you to test commercial-grade materials and equipment.
- A pilot plant produces useable product.
- A pilot plant is a viable long-term solution for small-quantity products.

IV. DISADVANTAGES

- The frequency of direct interaction of the formulator with the production personnel in the manufacturing area will be reduced.
- Any problem in manufacturing will be directed towards it's own pilot-plant personnel's.

V. PLANT SCALE UP CONSIDERATIONS FOR SOLIDS

INTRODUCTION

In scaling up the production of solid dosage forms (like tablets and capsules) from experimental laboratory batch sizes to medium- and large-scale production every operation step should be considered suitably. A method using the same

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type of equipment produces different results when the equipment size and the material quantity are changed considerably. Following are the consideration for the pilot plant scale up of solid dosage forms:

1) The major responsibility of the pilot plant staff is to make sure that the recently formulated tablets manufactured by the product development personnel are efficiently, economically, and regularly reproducible on a production scale .
2) Design and building of the pharmaceutical pilot plant for tablet manufacturer should include all the necessary features to assist maintenance and cleanliness.
3) The tablet manufacturing area should be present on the ground floor to facilitate handling and transportation of supplies.
4) The following specifications should be included in the pilot plant design to avoid microbiological contamination:
    i) Fluorescent lighting fittings should be the ceiling flush type.
    ii) The operating areas should have floor drains for simplifying cleaning.
    iii) The area should be air-conditioned and humidity controlled.
    iv) The floors should be of high-density concrete.
    v) The walls of the processing and packaging areas should have enamel cement finish on concrete.
5) Equipment used in the pharmaceutical pilot plant for manufacture of tablets should be similar to that used by production division.

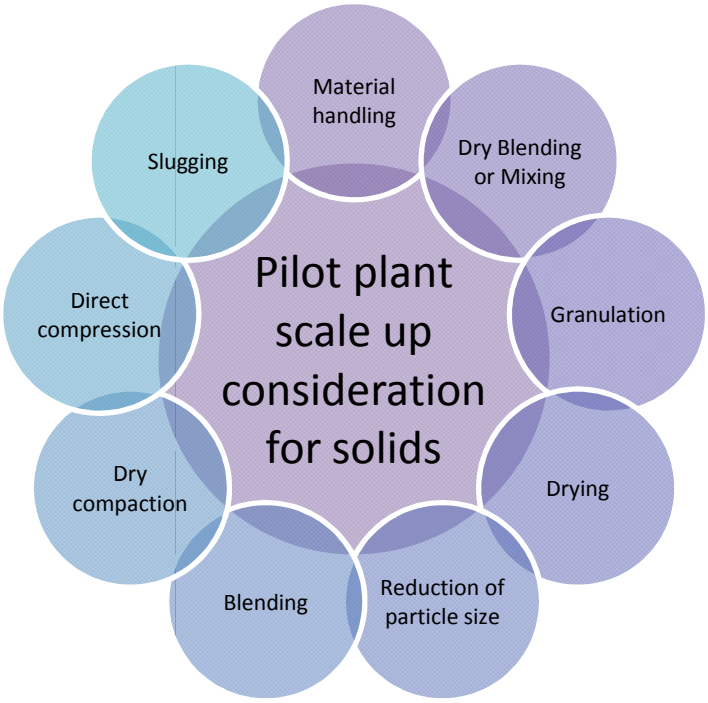

Figure 3

Material Handling

On a laboratory scale, materials can be handled through scooping, dumping or pouring by hand. These manual handling practices may prove satisfactory for small or intermediate-scale productions, but for large-scale productions, mechanical devices are required. The simple forms of material handling procedures include post hoist devices, devices for lifting and tilting drums; while the modern pro include vacuum loading systems, screw feed system, and meter pumping system. The material characteristics (like density and static change) influences the selection of a definite system There should be minimal or no material loss in material handling system. Lengthy transfer processes facilitate

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material loss. Validated cleaning procedures prevent cross-contamination during the transfer of more than one material by a single system. Every material handling system" should supply ingredient to the formulation in precise quantity.

Dry Blending Or Mixing

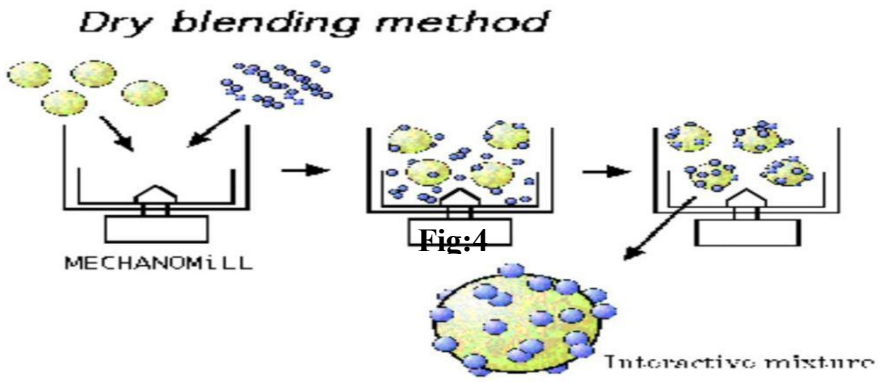

Fig:4

The dry blending process utilises a binary cohesive powder mixture containing particles of two different sizes, the finer particles stick to the surface of the coarse particles. This mixture is also known as Interactive mixture. The agglomerates of fine and coarse powders break down when the fine and coarse particles are blended. During blending, the particles interact and collide with each other, thus, generating an electric charge. This process is irreversible, Le., the fine and coarse particles do not return to their agglomerate states. New agglomerates. containing finer particles that stick to the coarse particles' surface, are produced as a result of blending. However during the first step, the coating particles stick randomly on the core particles' surface. Processes like screening and/or milling are performed initially to make blending more dependable and reproducible.

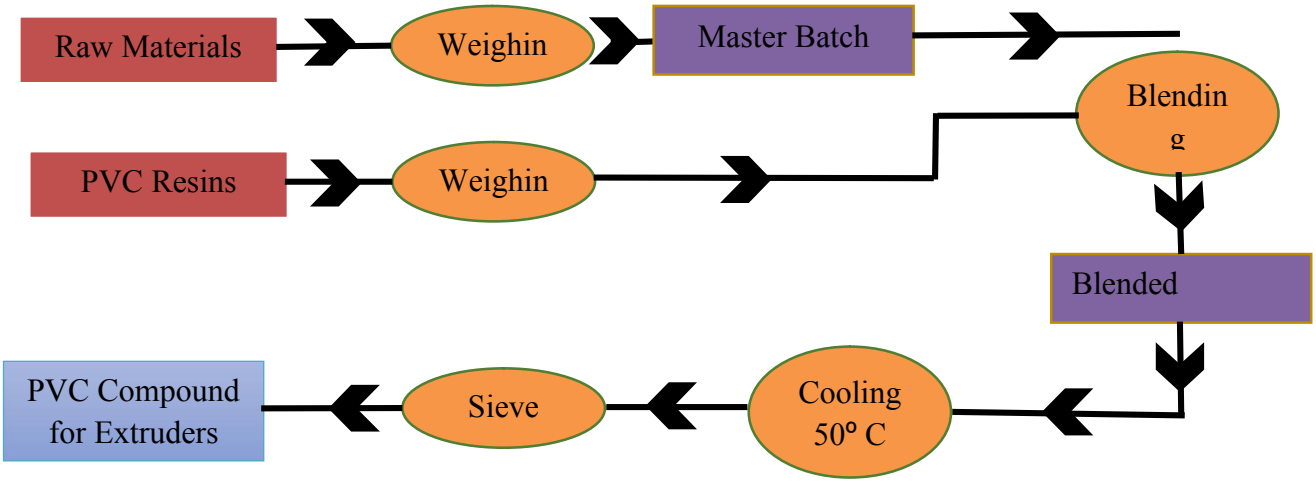

Fig: 5

Problems Associated with Improper Blending
1) Flow problem through the equipment.
2) Non-reproducible compression.
3) No content uniformity.

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Equipment Required for Blending
1) V-blender
2) Double cone blender
3) Ribbon blender
4) Slant cone blender
5) Bin blender
6) Orbiting screw blenders vertical and horizontal high intensity mixers.

Parameters to be Considered for Improving the Blending Process
1) Blending time
2) Blender loading
3) Blender size.

Granulation

The process of granulation involves agglomeration of smaller particles into larger ones, in which the original particles can still be recognised. Pharmaceutical granulation involves enhancing the surface area and dissolutionof API by rapidly breaking down the agglomerates Granulation process is a form of particle designing.

Functions of Granulation Process
1) facilitates uniform drug distribution throughout the product.
2) It increases material density.
3) It improves flow rates and rate uniformity.
4) It aids in metering or volumetric dispensing of drugs.
5) It reduces dust production.
6) It enhances product appearance.

Types of Granulation Methods
1) Wet granulation method, and
2) Dry granulation method.

Table 1.1: Drying Techniques for Granulation

Granulation Techniques	Drying Techniques
Wet Granulation Method	Tray or fluid-bed dryer Vacuum/gas stripping/microwave Spray dryer Extrusion/spheronisation/pelletisation
Dry Granulation Method	Direct compression Slugging mill Roller compactor

Different processes involved in granulation mechanism are wetting, nucleation, coalescence (or growth), consolidation, and attrition (or breakage). Spray rate (or fluid distribution) and feed formulation properties affect the initial wetting of feed powder and the existing granules by the binding fluid.

Table 1.2: Different Parameters and Methods for Characterisation of Granules.

Parameters	Methods
Panicle morphology	Optical microscopy
Particle size distribution	Sieve analysis and laser light scattering
Nature	Powder X-ray diffraction
Thermal analysis	DSC, TGA, and DTA
Identification	Near-Infrared (NIR) spectroscopy
Surface area	Gas adsorption

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Granules porosity	Mercury intrusion methods
Granules strength	Development of a formulation
Granule flowability and density	Mechanical method, hopper method, density apparatus

Drying

Circulation of granules in a hot air oven (heated by either steam or electricity) is one of the most commonly used methods for drying granules Factors like air flow, air temperature, and depth of granulation on trays are considered as essential part of scale up in an oven drying operation. The drying process will be unproductive if the granulation bed is too deep or too dense, or if the soluble dyes (present in granules) migrate to the surface. Each and every product or a particular oven load should have a specific and definite air flow rates, and drying times and temperatures.An alternative to circulating hot air oven is fluidised bed dryer Optimum loads. air flow rate, inlet air temperature, and humidity are the factors that play an important role in scale up of a fluidised bed dryer.

Reduction of Particle Size

Particle size indicates the product quality and performance. It also affects the other properties associated with particulate materials The flow rate of larger and spherical particles is more than that of the smaller or high aspect ratio particles Dissolution of smaller particles occurs more rapidly (forming suspensions of higher viscosities) than that of the larger particles Therefore, control and measurement of the particle size distribution of several products is necessary.

Problems Produced by Improper Particle Size

1) Weight variation of tablets occurs because of inadequate filling of the die cavity due to large-sized particles
2) Weight variation of tablets may also occur due to flowability problems of very fine particles
3) Chances of mottling increases if the coloured granules are coarser
4) Capping may occur as a result of augmented press speed.

Equipment Involved in Particle Size Reduction

Oscillating granulator (for not too hard oversize granulation),
2) Hammer mill.
3) Mechanical sieving device, and
4) Screening device.

Blending

Two main purposes of blending in solid dose manufacturing arc
1) Achieving blend uniformity, and
2) Distributing the lubricant.

According to objective 1, blending should attain uniform size distribution of all the components before final blending with the lubricant (objective 2). Several features like particle size, moisture content, structure, bulk density, and flow characteristics may create problems in powder blending. The particle shape for most oral solid dosages should lie within the range of 40-180 mesh. it is the first step in attaining expectable results in a blend. The other step involves completing the pre-blending steps by carefully and sequentially adding the ingredients. The blending equipment used for scale up differs from that used in laboratory Particle size, shape, hardness, density, and dynamics of mixing action affect the blending process involving simultaneous occurrence of segregation and mixing use of high shear mixers with spiral screws or blades causes particle abrasion Blending of low dose API involves sandwiching the ingredient between two-portions of directly compressible excipients. Thus, API loss to the blend surface is prevented.

Dry Compaction

In dry compaction granulation process, materials are compressed by applyi pressure (up to 10 tons per linear inch) on the powder passing between t rollers. Sufficient bulk density required for tablet encapsulation or compressi can be attained by subjecting low density materials to roller compaction proce Densification of aluminium hydroxide is one of the best examples of t process. It is the responsibility of the pilot plant personnel to determine wheth or not the effectiveness of this API compaction technique for yieldi granulation (exhibiting the desired tableting or encapsulation characteristics) more as compared to other commonly used conventional processes.

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Direct Compression

This process involves direct compression of powder mixture of API and oth excipients into tablets. The Wet or dry granulation process requires no pr treatment of powder blend. Compression of granules on a high speed tablet press a crucial test performed to ensure proper tablet formulation and granulati process. Compression features of a formulation are evaluated by keeping the pre speed equal to that to be used in normal production during lengthy trial runs. Th will be helpful in detecting the problems, like sticking to the punch surface, tab hardness, capping, and weight variations. High speed tablet compression determined by the capacity of the press to interact with the granules.

In the die feed system, the die is passed under the feed frame during which die cavities are filled effectively within a short period. Uniform filling of smal tablets utilising a high press speed is more difficult. Induced die feed systems a necessary for high speed machines. These machines are provided with variab speed capabilities and a variety of feed paddles to achieve optimal feed for eve step of granulation.

Granulation compression is a single step involving passage of granules between the lower and upper punches and pressure rollers. The punches are thus allowed to penetrate the die to a pre-set depth and produce compact granulation with thickness equal to the gap set between the punches. The creation of bonds within the compressible material during compression of granulation results in sticking. thus, forms tablets. Soft tablet may occur due to utilisation of high level of lubricant or over blending which may result in decreased powder wettability with prolonged dissolution time. Utilisation of die with 0.001-0.005 inch wider upper portion than the center (to relieve pressure during ejection) prevents binding of granules to die walls. This operation is usually carried out by high speed rotary machine, multi rotary machine, double rotary machine, upper punch and lower punch machine, and single rotary machine.

Slugging

This process is utilised to produce granules for moisture- and heat-sensitive APIs. and when APIs exhibit sufficient binding or cohesive properties. The method of slugging is also known as dry granulation, pre-compression, or double compression. The APIs, diluents, and a portion of lubricants are mixed together to form a blend. It is essential that either the API or the diluents should be cohesive in nature.

Pressure is applied to remove significant amount of air present in powdered material to produce a dense product. The tablet or slug quality improves with increase in time allowed for the air to escape. This process is performed on a tablet press that functions at pressures of 15 ton which is much higher than the 4 tons pressure utilised in normal tablet press. The material that can be easily slugged produce slugs of 1 inch diameter, while the materials difficult to be compressed and require more pressure per unit area can produce slugs of ½ inch diameter. Roller compaction process is utilised for compacting very low density materials so that bulk density sufficient enough for encapsulation or compression is achieved, e.g., densification of aluminium hydroxide.

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