Available Online through
www.ijpbs.com (or) www.ijpbsonline.com

IJPBS |Volume 2| Issue 3 |JULY-SEPT |2012|223-239

Review Article
Pharmaceutical Sciences

REVIEW: SCALE UP PROCESS OF TABLET PRODUCTION: A PROSPECTIVE DISCUSSION

Kamya Chaudhary, A.C.Rana, Rajni Bala, Nimrata Seth*

Department of Pharmaceutics, Rayat College of Pharmacy, Ropar, India
***Corresponding Author Email: kamya0058@gmail.com**

ABSTRACT

Scale up is generally defined as the process of increasing batch size. In process scale up a formula is transformed into a viable, robust product by the development of a reliable and practical method of manufacturing that effect the orderly transition from laboratory to routine processing in a full-scale production facility. It must include a close examination of the formula to determine its ability to withstand batch-scale and process modification. In moving from R&D to production scale, it is sometimes essential to have an intermediate batch scale. This is achieved at the so-called pilot scale, which is defined as the manufacturing of drug product by a procedure fully representative of and simulating that used for full manufacturing scale. In tableting applications, the process scale-up involves different speeds of production in what is essentially the same unit volume (die cavity in which the compaction takes place). So process scale up of tablets includes Trial Batches, Exhibit Batches and Validation Batch. After these batches produce large scale up of tablets. During the scale up process controls are evaluated, valuated and finalized in addition, appropriate records and report are issued to support good manufacturing practices and to provide the historical development of the production, formulation, process equipments train, and specification.

Pilot Plants are the part of the pharmaceutical industry where lab scale formula is transformed into viable product by the development of liable practical procedure for manufacture. Pharmaceutical pilot plants that can quickly numerous short-run production lines of multiple batches are essential for ensuring success in the clinical testing and bougainvilleas study phases. Drug formulation research time targets are met by having a well-designed facility with the appropriate equipment mix, to quickly move from the laboratory to the pilot plant scale 1. In pilot plant, a formula is transformed into a viable, robust product by the development of a reliable and practical method of manufacture that effects the orderly transition from laboratory to routine processing in a full scale production facility where as the scale up involves the designing of prototype using the data obtained from the pilot plant model. 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. In addition, appropriate records and reports issued to support Good Manufacturing Practices and to provide historical development of the production formulation, process, equipment train, and specifications2. A manufacturer's decision to scale up / scale down a process is ultimately rooted in the economics of the production process, i.e., in the cost of material, personnel, and equipment associated with the process and its control. [1]

Why conduct pilot plant studies?

- A pilot plant allows investigation of a product and process on an intermediate scale before large amounts of money are committed to full-scale production
- It is usually not possible to predict the effects of a many-fold increase in scale.
- It is not possible to design a large scale processing plant from laboratory data alone with any degree of success.[3]

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-life and storage stability studies
- 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. [3]

Pilot plant design for tablets:

- Each stage considered carefully from experimental lab 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 either unavailable or unsuitable on a lab scale.[3]

Process scale up:

Scale-up is generally defined as the process of increasing the batch size. Scale-up of a process can also be viewed as a procedure for applying the same process to different output volumes. There is a subtle difference between these two definitions: batch size enlargement does not always translate into a size increase of the processing volume. In mixing applications, scale-up is indeed concerned with increasing the linear dimensions from the laboratory to the plant size. On the other hand, processes exist (e.g., tableting) for which "scale-up" simply means enlarging the output by increasing the speed. To complete the picture, one should point out special procedures (especially in biotechnology) in which an increase of the scale is counterproductive and "scale-down" is required to improve the quality of the product. In moving from R&D to production scale, it is sometimes essential to have an intermediate batch scale. This is achieved at the so-called pilot scale, which is defined as the manufacturing of drug product by a procedure fully representative of and simulating that used for full manufacturing scale. This scale also makes possible the production of enough product for clinical testing and samples for marketing. However, inserting an intermediate step between R&D and production scales does not in itself guarantee a smooth transition. A well-defined process may generate a perfect product in both the laboratory and the pilot plant and then fail quality assurance tests in production.[2]

It is procedure of transferring the results of R&D obtained on laboratory scale to the pilot plant and finally to production scale. Process scale up can also be viewed as procedure for applying the same process to different output volume. Process of changing the equipment ,machine speed or process steps to enable large scale manufacturing scale up of a process that involve powder handling is especially difficult because the

dynamic behavior of powders is not very well understood.

Process scale up is done to give the quality to the product and for extensive scientific knowledge of the physiochemical process that transform the incoming materials into the finals products, hence Scale up gives a clear cut idea about the formulations and help us to control the critical process parameters by proper process optimization.

When scale up is applied to granulation process, the effects of the operational variable on powder properties and granule growth is not clearly known. So, scale up process of material in the solid state can be based on dimensional analysis, mathematical modeling, and computer simulation, most of the work in this field still depends on trial and error and the principles of geometric similarity. Ratio of some variables in small scale equipment should be equal to that of similar variables in equivalent larger-scale equipment. Dimensional analysis is a algebraic treatment of variables affecting a process. It does not result in a numerical equation, but experimental data are fitted to an empirical process equation that result in scale up being achieved more readily.

Scale up give us the various information about the product like physically and chemically stable therapeutic dosage forms, evaluate the formulation and process suitability for large scale, review of processing equipment, to identify the production and process control parameters, to identify the critical features of product and process, to provide the master formula and formulation evaluation for assessing criticality of ingredients. Identify the role of ingredient in formulation - decide criticality. E.g.a) HPMC film coating material or rate controlling polymer in matrix. b) Starch- diluents or disintegrate. c) Aesthetic or reservoir CR system. Scale up provide us the process monitoring and its control like complex city of process/formulation, process time limit, reproducibility, Simplicity for execution and Identifying processing stress on product quality, example a) Loss of viscosity during colloid milling, b) Evaporation of alcohol during processing. c) Capping during high speed compression.[2]

Stages of production of tablets:

- Material handling
- Dry blending
- Granulation
- Drying
- Reduction of particle size
- Blending

➢ Dry blending
➢ Direct compression
➢ Slugging (dry granulation)

Material handling: In 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: vaccum 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 no/minimal loss of material. The lengthy 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.[4]

Dry blending process:

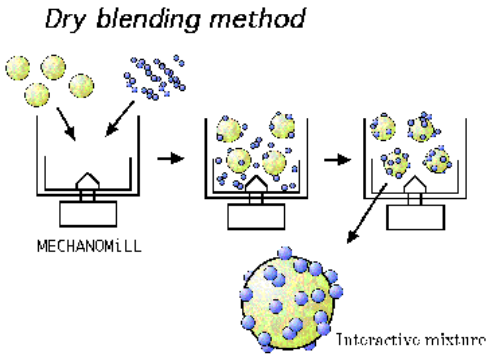

Figure 1: Dry blending method

In the dry blending process using a binary cohesive-powder mixture 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, however, the coating particles randomly adhere onto the surface of the core particles.[4]

Problems of improper blending:

- Flow problem through the equipment
- Non- reproducible compression
- No content uniformity

Screening and/or milling of the ingredients prior to blending done to make the process more reliable and reproducible. The equipments 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 [2]

Scale up considerations:

- Time of blending
- Blender loading
- Size of blender [2]

Granulation: Granulation process is a ‘‘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. In ancient times the granulation process used within the pharmaceutical industry but in modern time, granulation technology has been widely used by a wide range of industries, such as Pharmaceutical. ‘‘granulated’’ material is derived from the Latin word ‘‘granulatum,’’ meaning grained. The fundamental research on mixing, segregation mechanisms of powder, surface chemistry, and material science are necessary to develop the theoretical framework

of granulation technology. The granulated material can be obtained by direct size enlargement of primary particles, or size reduction from dry compacted material. These industries employ agglomeration techniques to reduce dust, provide ease of handling, and enhance the material's ultimate utility. Granulation is process of particle designing.[3]

Granulation methods: Two types

1. Wet methods which utilize some form of liquid to bind the primary particles.
2. Dry methods which do Granulation Minimizes the technical risks.

1. Wet granulation technology: It is employed 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.[11]

2. Dry methods: Dry compaction technique like roller compaction is commonly used in the Pharmaceutical industry. There are a number of drug substances which are moisture sensitive and cannot be directly compressed.[5]

Application of Granulation technology in Pharmaceutical Industry: Pharmaceutical granulation process is used for tablet and sometimes capsule dosage forms; however, in some applications the process is used to produce spherical granules for the modified release indications or to prepare granules as sprinkles to be used by pediatric patients.

Granulation of Pharmaceutical Compounds: Pharmaceutical compounds are granulated due to:

1. To increase the uniformity of drug distribution in the product
2. To densify the material
3. To enhance the flow rates and rate uniformity
4. To facilitate metering or volumetric dispensing
5. To reduce dust
6. To improve the appearance of the product.
7. Granulation encountered the incomplete description behavior of powders in general.[5]

Various Drying Techniques for Granulation

Sr. No.	Granulation Techniques	Drying techniques
1	Wet granulation	Tray or fluid-bed dryer
		Tray or fluid-bed dryer
		Vacuum/gas stripping/microwave
		Spray dryer
		Extrusion/ Spheronization /Pelletization
2	Dry granulation Process	Direct compression
		Slugging Mill
		Roller compactor Compacts milled

Granulation Mechanisms: These include wetting and nucleation, coalescence or growth, consolidation, and attrition or breakage. Initial wetting of the feed powder and existing granules by the binding fluid is strongly influenced by spray rate or fluid distribution as well as feed formulation properties, in comparison with mechanical mixing.

Role of Binders in wet-granulation process: Binders are adhesives that are added to solid dosage formulations. The primary role of binders is to provide the cohesiveness essential for the bonding of the solid particles under compaction to form a tablet. In a wet-granulation

process, binders promote size enlargement to produce granules and thus improve flowability of the blend during the manufacturing process. Binders may also improve the hardness of the tablets by enhancing intragranular as well as intergranular forces. In a direct compression process, binders often act as fillers and impart compressibility to the powder blend. The cohesive properties of binders may reduce friability of the tablets and thus aid in their durability and elegance.

Examples:

Natural Polymers: Starch, Pregelatinized Starch

Synthetic polymers: PVP, Methyl cellulose, HPMC

New Natural and Synthetic binders: Khaya gum, Leucaena leucocephala seed gum, Anacardium occidentale gum, Gellan gum, Combination of detarium gum and veegum.

New synthetic binders: Maltrodextrins, Chitosan derivatives [11]

Granulation techniques: The choice of granulation technique depends on various factors such as chemical and physical stability of the final dosage form, intended biopharmaceutical performance.

- High- and low-shear granulation
- Roller compaction
- Spray drying
- Fluid-bed granulation
- Extrusion spheronization
- Melt granulation and Pelletization
- Effervescent Granulation

Granulation Characterization: Granulation is a process used to prevent segregation of formulation components in a powder blend, bulk volume of granulation, improve blend flow, content uniformity, compressibility, and other properties. Chemical properties are equally important due to their impact on specifications of a dosage form such as content uniformity, chemical purity, and in vitro performance. In vivo performance such as bioequivalence done because it determines whether a pivotal bioequivalency batch passes or fails. Granule Size affect the dissolution performance which ultimately affect bioequivalence study. Physical characterization can be performed at molecular, particulate, or bulk (macroscopic) levels. [5]

Different Parameters and Methods for Characterization of Granules

Sr. No.	Parameters	Method
1	Particle Morphology	Optical microscopy
2	Particle Size Distribution	Sieve analysis, laser light scattering
3	Nature	Powder X-Ray Diffraction
4	Thermal Analysis	DSC, TGA, DTA
5	Identification	Near-infrared (NIR) spectroscopy
6	Surface Area	Gas adsorption
7	Granule Porosity	Mercury intrusion methods
8	Granule Strength	Development of a Formulation
9	Granule Flowability and Density	Mechanical Method, Hopper Method, Density Appratus

Drying: It is the most common conventional method. It involves circulating hot air oven, which is heated by either steam or electricity.

Scale up considerations for oven drying operation are:

- Airflow
- Air temperature
- The depth of the granulation on the trays

Too deep or too dense 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 and for each particular oven load. Fluidized bed dryers are an attractive alternative to the circulating hot air ovens. The important factor considered as part of scale up fluidized bed dryer 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 2-5µm 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. [6]

Problems encountered due to improper particle size are:

- Too large particle size leads to the insufficient filling of the die cavity that results in weight variation of the tablets.
- In case of colored granulation the coarser the granulation, greater are the chances of mottling.
- The very fine particle size leads to the flowabilty problem that results in the weight variation of the tablets.
- Capping (also occurs if the speed of the press is increased)

Equipments used are:

- Oscillating granulator (for not too hard oversize granulation)
- Hammer mill
- Mechanical sieving device
- Screening device

Determining factors for a particle size: Particle size distribution needs to be small enough to go through an 18 mesh screen yet big enough as to not go through a 200 mesh screen. While machine type and condition play a role, the following list of items should also considered.

Flowability: Generally speaking the smaller the particle the worse the flow. Compare powdered sugar with granular sugar. The fine small particles in powdered sugar aide dissolution but not flow.

Feeder clearance: Particle size must be larger than the feeder clearance to prevent leakage.

Die table run-out: If die table run-out increases, feeder clearance and particle size must also increase proportionately. To check run-out, use a dial indicator to determine the variation of the die table.

Die fill: Wide variations in particle sizes can cause inconsistent fill volumes.

Weight control: Final volume is final weight. Larger particles pulled out of the die can reduce the final weight. Fine particles require more precise scrape-off and increase the need for a good scraper blade.

Compressibility: Improves with increased particle size and decreases as particles become smaller and smaller. Small particles have less ability to lock together during compaction.

Hardness: Smaller particles are more sensitive to over-compression.

Ejection force: Small particles decrease interstitial space and increase drag and friction.

Lubrication levels: In general higher percentages of small particles require increased quantities of lubricant. Magnesium stearate is the most commonly used lubricant and should be de-agglomerated before use.

Disintegration & Dissolution: Small particles decrease disintegration time, and increase dissolution.

Friability: Larger particles usually lock together better which results in reduced friability while small particles often increase the potential for failure (higher friability).

Electro Static effects: Electro static charge is increased as the percentage of small particles increases.

Dust control: Fine particles create a dusty operation, creating a need for frequent production stoppages and press clean-ups.

Environmental conditions: Many products are hygroscopic and sensitive to heat. Variations in room conditions can result in poor flow, compression and ejection conditions.

Lamination & Capping: Small particles are the heart of the most common defects.

Punch lubrication: Dust and super fine particles become airborne and combine with the oils and greases which can produce black specks in tablets.

Tooling condition: Punch tip & die clearance are designed to control air release allowing for improved compaction.

Machine condition: Cleaning and maintenance are downtime issues. A high percentage of fine particles and dust increases the potential for greater wear, increased cleaning frequency, reduced yield, greater particle segregation, and more tablet defects.

Cost: Fines (small dusty particles) increase operating costs, require increased levels of dust collection, decreased yields, increased frequency of cleaning, and generate greater machine & tool wear. Reducing fines will improve tablet quality.[7]

Blending: Blending in solid dose manufacturing has two objectives;

1) To achieve blend uniformity and
2) to distribute the lubricant.

In (objective 1) the blend step(s) are designed to achieve homogeneity of all components prior to the final blend of the lubricant (objective 2). 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 – 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.[7]

Characteristics of material:

- Fragile particles or agglomerates: more readily abraided – more fines – improper mixing – flow problems; fill problems, content uniformity problems.
- Particle abbraision is more when high shear mixing with spiral screws or blades are used.
- Tumble blenders: for prolonged mixing.
- Bulk density of raw materials considered in selection of the blender and determining optimum blender load.
- Excessive granulation: poor content uniformity, poor lubrication, & improper color dispersion.

Direct compression: The term "direct compression" is defined as the process by which tablets are compressed directly from powder mixture of API and suitable excipients. No pre-treatment of the powder blend by wet or dry granulation procedure is required.[8]

Merits

- Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.
- The most important advantage of direct compression is economical process. Reduced processing time, reduced labor costs, fewer manufacturing steps, and less number of equipments are required, less process validation, reduced consumption of power.
- Elimination of heat and moisture, thus increasing not only the stability of the process for thermolabile and moisture sensitive API's.
- Particle size uniformity.
- Prime particle dissolution.
- The chances of batch-to-batch variation are negligible, because the unit operations

required for manufacturing process is fewer.
- Chemical stability problems for API and excipient would be avoided.
- Provides stability against the effect of aging which affects the dissolution rates.[8]

Demerits

Excipient Related

- Problems in uniform distribution of low dose drugs.
- High dose drugs having high bulk volume, poor compressibility and poor flowability are not suitable for direct compression.For example, Aluminium Hydroxide, Magnesium Hydroxide.
- The choice of excipients for direct compression is extremely critical. Direct compression diluents nad binders must possess both good compressibility and good flowability.
- Many active ingredients are not compressible either in crystalline or amorphous forms.
- Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.
- Non- uniform distribution of color, especially in tablets of deep colors.[10]

Process Related

- Capping, lamination, splitting, or layering of tablets is sometimes related to air entrapment during direct compression. When air is trapped, the resulting tablets expand when the pressure of tablet is released, resulting in splits or layers in the tablet.
- In some cases require greater sophistication in blending and compression equipments.
- Direct compression equipments are expensive.[10]

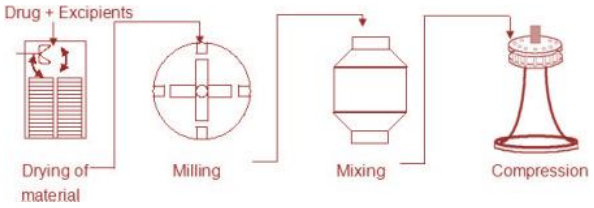

Figure 2. Manufacturing Steps for Direct Compression

Control factors:

- Particle characteristics (mixing and segregation): size, size distribution, shape, static charge
- Blender load
- Optimum mixing speed
- Blending time
- Optimizing the process and validation of its performance

Aspects for optimization:

- Order of addition of components to the blender
- Mixing speed: can be varied with the original direction as necessary
- Mixing time: excessive mixing may fracture the fragile excipients and ruin their compressibility
- Use of auxiliary dispersion material within the mixer (chopper blade within a twin shell mixer):
    a) Increase efficiency
    b) Reduce agglomerates

Mixing action: The mixing action is determined by the mechanics of the mixer. It is changed by converting from one blender to the other or by modifying the blender through addition of baffles or plates, which would alter the mixing characteristics.

Blender load: The size of blender load affects the efficiency to greater extent. The blender overload reduces free flow of granules and reduced efficiency. The localized concentration improves the content uniformity where as the small loads improves sliding and rolling of powders in the blender, no proper mixing & increased time for mixing.

Slugging (dry granulation): when tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying and when the tablet ingredients

have sufficient inherent binding or cohesive properties,slugging may be used to form granules. This method is reffered to as dry granulation, pre-compression or double compression. The active ingredient, diluents (if required) and the part of the lubricant are blended. One of the constituents either the active ingredient or diluents, must have cohesive properties. Powdered material contains a considerable amount of air;under pressure this air is expelled and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug.[13]

Diameter of slugs:

- 1 inch for more easily slugged material
- ¾ inch for materials difficult to compress

Materials of very low density require roller compaction to achieve a bulk density sufficient to allow encapsulation or compression. E.g. densification of aluminium hydroxide.

Parameters influencing the process and granule quality: The micro-level interactions between the powder particles and liquid binder have been shown by many researchers to play important roles in granulation phenomena (Ennis et al., 1991; Iveson and Litster, 1998a; Liu et al., 2000; Simons and Fairbrother, 2000; Iveson et al., 2003).

Fluidized bed granulation is an intricate process and the factors affecting the process and granule quality are classified into three categories for discussion below. The first category involves the nature and characteristics of the ingredients in the formulation. Even though the discussed scope on this category is focused on fluidized bed granules, the findings for this category are generally applicable to all other wet granulation processes. Process factors during liquid binder addition phase and process factors during the drying phase constitute the second and third categories respectively, and are more specific to the fluidized bed equipment.[14]

Material related factors: The properties of the raw materials involved in granulation, namely the feed powder, binder and granulating liquid, will affect granule formation and growth.

- **Ability of powder particles to be wetted:** Wetting is an essential phenomenon needed to form initial liquid bonds between the particles to enable agglomerative growth. The feed powder must have reasonably good wetting properties if there is to be uniform granulating liquid distribution. In fluidized bed granulation, the initial spreading of the binder in the powder bed is very crucial (Faure et al., 2001). This is because of the rather low shear forces present in the fluidized bed and liquid within agglomerates would be less likely to be squeezed out for growth by coalescence. The initial wetting conditions therefore determine the size distribution of the granule batch. The important role of this interaction has been emphasized by different groups of researchers in literature. Pont and co-workers (Pont et al., 2001; Hemati et al., 2003) have illustrated that granule growth was favoured with an increase in interfacial tension and a decrease in contact angle between the particles and the liquid binder. Danjo et al. (1992) reported that harder and less porous granules were formed when the adhesion-tension of the liquid binder was increased. Spreading coefficients of the liquid binder over the particles were similarly observed by Planinsek et al. (2000) to be in good correlation with granule friability.
- **Solubility of powder particles:** Surface dissolution of lactose was proposed to behave as a secondary binder after solidification upon drying, and contributed to the sphericity of the granules (Wan and Lim, 1989). An increase in granule hardness with a decrease in pore volume was reported by Danjo et al. (1992) with increased solubility of lactose particles in the solvent used to prepare the liquid binder. Rohera and Zahir (1993) also found that part dissolution of excipients being granulated was desirable for granule growth and affected granule size distribution.
- **Type of powder:** The different deformation behavior during coalescence exhibited by different types of powder was shown to influence the kinetics of the process (Abberger, 2001). Powder load: Due to a

larger load to binder ratio, whereby a smaller extent of wetting took place, an increment in feed load resulted in more of the smaller size granules being produced (Wan and Lim, 1988; Cryer and Scherer, 2003).

- **Powder particle size:** It was implied by Hemati et al. (2003) that an increase in the initial particle size led to an increment in particle growth rate and affected the mechanism of growth. Powder particle shape: Contact surface between the less spherical particles was reportedly enhanced as compared to the highly spherical particles. This resulted in different growth kinetics (Hemati et al., 2003).
- **Powder particle surface roughness:** Growth kinetics was also found to have a strong dependence on the surface roughness of the particles by Stepanek et al. (2009).
- **Type of binder:** Binder is an essential part of the granulating fluid. Yuksel et al. (2003) reported that granules prepared using polyvinylpyrrolidone were observed to have lower mechanical strength than those prepared using pregelatinized starch and gelatin. In another study by Rohera and Zahir (1993) where polyvinylpyrrolidone, acacia, and gelatin were investigated, it was found that different binders had different influences on granule growth.
- **Binder concentration and viscosity:** In general, increasing the concentration and viscosity of the liquid binder increased mean granule size and increased granule strength, as reported in several studies. The types of binders investigated in these reports included gelatin, acacia, polyvinylpyrrolidones and cellulosic binders (Davies and Gloor, 1972; Alkan and Yuksel, 1986; Lim, 1989; Rohera and Zahir, 1993; Ling,1995; Wan et al., 1996; Kokubo et al., 1995, 1998; Bouffard et al., 2005). Other physical properties such as drug release (Haldar et al., 1989), granule morphology and porosity (Rajniak et al., 2007) were also found to be influenced by binder concentration.
- **Mode of binder addition:** Binder addition, either suspended in the spray liquid or dry mixed in the powder was shown to affect the granular characteristics of the end product. Binder distribution was found to be more uniform when suspended in the spray liquid with a smaller amount of oversized granules produced (Kokubo et al.,1995, 1998; Wan and Lim, 1988).
- **Volume of liquid binder:** The volume of granulating liquid needed depends primarily on the solubility of the drug and/or components of the binder. Larger granules resulted when bigger volumes of binder solution were used (Rohera and Zahir, 1993; Merkku et al., 1994; Wan et al., 1996). This was likely to be due to promoted wetting of particles during growth.[14]

Process related factors during the liquid binder addition phase: The sensitivity of the process to its bed humidity has been identified by many researchers, and control of this bed condition is primary for process reliability (Kokubo and Sunada, 1997; Watano et al., 1997; Hu et al., 2007). Bed humidity is an indication of the availability of liquid binder at the particle surfaces. A more humid bed indicates wetter conditions, more liquid binder is available to the surfaces of the particles and this enhances nucleation and growth. However, if the moisture content in the granule bed is too high, excessive granule growth can result and the bed can even collapse by wet quenching due to the poor fluidizing capacity of the wetted mass (Schaafsma et al., 1999). Accordingly, parameters that affect the temperature and moisture content of the powder bed play important roles in influencing process and granule quality.

- **Binder spray rate:** An increase in binder spray rate availed more liquid binder to the particles and resulted in a more humid bed. Thus, granules of larger size and lower bulk density typically formed as reported by many researchers (Rankell et al., 1964; Davies and Gloor, 1971; Lipps and Sakr, 1994; Wan et al., 1995; Menon et al., 1996; Gao et al., 2002; Cryer and Scherer, 2003; Hemati et al., 2003; Bouffard et al., 2005).

Pulsed spraying of the liquid binder had also been tried by Ehlers et al. (2009) as a method to control granule growth.

- **Binder droplet size:** A direct relation between droplet size and granule size at the early stage of the growth process was reported by Schaafsma et al. (2000). Bigger spray droplets were found to produce more granules in the larger mass size fractions.
- **Atomizing air pressure:** The degree of atomization of the liquid binder depended on the air to liquid mass ratio at the nozzle head. A decrease in atomizing air pressure was extensively shown to result in granules of larger size and lower bulk density. This is because of the resultant decreased air-to-liquid mass ratio that caused the formation of bigger spray droplets (Davies and Gloor, 1971; Merkku et al., 1994; Gao et al.,2002; Rambali et al., 2001; Bouffard et al., 2005). An optimum pressure was found to be necessary for promoting uniform distribution of a low dose drug, when the drug was incorporated in the granulating liquid (Wan et al., 1992). The degree of atomization was also observed to affect granule structures and consequently, granule strength by Wang et al. (2003).
- **Spray nozzle position from bed:** The position of the spray nozzle in TG was reported to significantly influence granule growth and granule friability (Rankell et al., 1964; Davies and Gloor, 1971; Rambali et al., 2001). The nearer the nozzle was placed to the powder bed from the top, the larger were the granules formed.[4]
- **Spray nozzle tip protrusion from air cap:** This determined the angle at which the binder solution was sprayed onto the powder bed by changing the airflow rate through the nozzle. Rambali et al. (2001) found that a higher protrusion resulted in more granules in the smaller mass size fractions and higher process yield.
- **Spray nozzle tip diameter:** A wider nozzle tip diameter caused larger spray droplets to be formed, promoted granule growth and resulted in bigger granules (Rambali et al.,2001). Product chamber geometry: Particle flow pattern and distribution were shown to be affected by the shape of the product chamber, and is an important factor to consider during process design (Yang et al., 1992; Schaafsma et al., 2006).
- **Airflow rate:** Smaller granules were observed when the airflow rate was increased (Cryer and Scherer, 2003; Bouffard et al., 2005). This was explained by a more rapid removal of water from the wetted particles by the air that caused slower growth kinetics with higher airflow rate. It was also found by Wang et al. (2003) that airflow rate affected granule size and process yields.
- **Inlet air temperature:** As the inlet air temperature increased, there was faster mass transfer of water from the wetted particles to the air (i.e. evaporation). This reduced the binder layer surrounding the powder particle, created fewer opportunities for coalescence and resulted in smaller granules (Lipps and Sakr, 1994; Schinzinger and Schmidt, 2005).

Process related factors during the drying phase: After complete spraying of the liquid binder, the granules formed are dried for a further period of time. This is to remove remaining moisture contained in them down to a moisture level best suited for the stability of the constituent actives and requirements of the ensuing downstream process. Inefficient or poor process control of this drying phase will lead to inconsistent end product quality. For instance, attrition of the formed granules was reported to occur paradoxically, resulting in unwanted size reduction (Niskanen and Yliruusu, 1994). Formation of fines by attrition is, in practice, an important parameter because excessive fines generation can affect granule flow and should be avoided (Nieuwmeyer et al., 2007b).

- **Inlet air humidity:** Zoglio et al. (1975) reported that the humidity of the drying air strongly impacted the drying rate for aqueous based granulations. This was attributed to the diffusion of water vapor through the stagnant air film surrounding the granule and into the neighboring fluidizing air - the rate-limiting step in the

drying phase. Based on the findings that an increase in inlet air humidity resulted in higher product temperatures (Lipsanen et al., 2007, 2008), concern in scenarios where a fixed product, temperature was used as a drying end-point criterion was highlighted by the authors. This is because the residual moisture content in the dried granules could vary between batches if the inlet air humidity is not controlled and this would affect the quality of the product attained at the end of processing. Their findings also implied stability issues when using a fixed product temperature as a drying end-point criterion for granulating moisture sensitive and heat sensitive materials.[4]

- **Inlet air temperature:** Reductions in drying time was reported to be possible with employment of higher inlet air temperatures, and the lower temperatures were found to cause higher equilibrium moisture content in the granules.
- **Airflow rate:** Increments in airflow rate was observed to lead to the enhancement of evaporation rates (Hlinak and Saleki-Gerhardt, 2000) and possibly drying. However in practice, practical use of airflow rate to enhance the evaporation rate might be limited due to its potential influence on the particle size distribution of granules (Faure et al., 2001). Too high an airflow rate may result in an unacceptable level of attrition.
- **Atomizing air pressure:** High atomizing air pressure, especially when maintained during the drying phase was shown to contribute substantially to granule breakage (Bouffard et al., 2005). As the atomizing air is counter-current to the fluidizing air, it is best switched off after completion of liquid addition. The atomizing air may also disrupt the fountain like flow of the granules in the fluidized bed.
- **Liquid binder:** Niskanen and Yliruusu (1994) observed that attrition was dependent on both the amount and the wetting tendency of the liquid binder.
- **Moisture content:** The moisture content of granules during fluidized bed drying was found to affect the hydrodynamic behavior (Wormsbecker and Pugsley, 2008) and granule size (Nieuwmeyer et al., 2007b).
- **Duration of drying phase:** The duration of drying was widely shown to affect granule size properties (Banks and Aulton, 1991). Extended duration of drying may result in excessive granule attrition. The drying time was recently shown by Tomuta et al. (2009) to influence the residual moisture content, bulk and tapped density of the granules.[4]

Fluidized Bed Granulation:

Fluidized bed technology has its origins from the petroleum industry in the 1940s. Since its successful implementation for coating in the pharmaceutical industry by Wurster (1959), this air suspension technique has been used widely in coating, granulating, pelletizing and drying processes. As shown in Figure 1, a fluidized bed processing system typically consists of a Inlet air filter, Condenser, Humidifier, Inlet air Heater, HEPA filter, Inlet air, Inlet air plenum, Gas distributor plate, Product container, Conical expansion zone, Filter housing, Product filter, Outlet air, HEPA filter, Fan and a Spray gun. *In-line* monitoring of process conditions is also often possible to facilitate process control. In this system, a bed of powder particles, supported over a fluid distribution plate, is made to behave like a liquid by the passage of the fluid, typically air, at a flow rate above a certain critical value. The phenomenon of imparting the properties of this fluid to the bed of particulate solids by passing the fluid through the latter at a velocity which brings the stationary bed to its loosest possible state just before its transformation into a fluid-like bed is termed fluidization (Gupta and Sathiyamoorthy, 1998).

During granulation, the powder particles circulate within the product chamber and provide a constant flow of bed particles through a defined spray granulation zone. At the spray granulation zone, a fine spray of liquid binder is usually atomized and deposited onto the fluidizing particles. Particle wetting brings about granule formation. Partial drying of the wetted particles by the fluidizing air occurs continuously during granulation. When the spraying of liquid

binder is completed, the granules are quickly dried by the hot air stream and complete drying is achieved.[14]

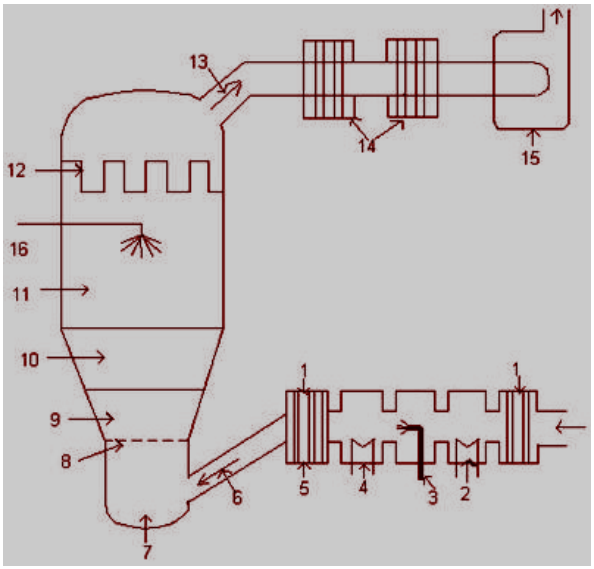

Figure 3: Fluid bed granulator

1. Inlet air filter
2. Condenser
3. Humidifier
4. Inlet air Heater
5. HEPA filter
6. Inlet air
7. Inlet air plenum
8. Gas distributor plate
9. Product container
10. Conical expansion zone
11. Filter housing
12. Product filter
13. Outlet air
14. HEPA filter
15. Fan
16. Spray gun

Advantages and challenges

Fluidized bed granulation is efficient and convenient to use, offering many advantages over the multistage process of conventional wet granulation (Banks and Aulton, 1991). Powder can be mixed, granulated and dried in a single container, thereby avoiding cross-contamination. Since fluidized bed granules are formed and dried within the same piece of equipment, it cuts cost by saving time needed for transfers and greatly simplifies the process. By virtue of the air or gas required to fluidize the solids, the fluidized bed typically provides high rates of heat and mass transfer, leading to uniform temperature distribution within the bed and relatively short processing times(Turton et al., 1999). High process yields of 97 to 100 %, w/w with typically less than 1 %, w/w fines and 3 %, w/w lumps can be attained (Olsen, 1985).

In comparison to high shear granulation, a popular wet process to employ for granulation in the industry, the size distribution of fluidized bed granules is often narrower with the absence of large size compact granules. This indicates a less frequent need for re-granulation and a less problematic drying step. Fluidized bed granules have also been generally shown to be more porous, less dense, and more compressible than high shear granules (Tobyn et al., 1996; Horisawa et al., 2000; Gao et al., 2002; Hausman,2004). As mixing and fluidization quality in the fluidized bed is highly dependent on the characteristics and properties of the powder particles, the process is more sensitive to the filler characteristics and properties. The filler type was reported to have a more pronounced effect on granule properties in the conventional fluidized bed granulator than in the rotary processor (Kristensen and Hansen, 2006). It has also been shown that a wider selection of feed material can be used in rotary processing (Kawaguchi et al., 2001) and high shear granulation (Stahl, 2004). The mixing effect in a fluidized bed is generally good for particle sizes between 50 to 2000 µm. However, for fine particles less than 50 µm and particles which are difficult to fluidize when wet, vibratory forces have to be applied to the powder bed, increasing equipment, cleaning and maintenance costs (Law and Mujumdar, 2007). A lower critical size where the usual pharmaceutical powders can be discretely processed will be around 20 µm. Lower than this size, steady fluidization without any retardation is difficult as indicated by Geldart's fluidization map (Geldart, 1973). To process powder mixture containing components of vastly different densities is another difficult task, as the different fluidization behaviour of the individual components may result in bed segregation and non-uniform mixing. Without

the aid of mechanical forces in distributing the liquid binder, the spreading of the liquid binder droplets in the powder bed is more crucial compared to other wet granulation processes that are aided by mechanical forces. As such, agglomeration in the fluidized bed granulation process is highly dependent on this spreading phenomenon (Faure et al., 2001).

Coupled with the inter-relation of variables that influence the agglomerative process, it is challenging to obtain good control of the process. As an illustration, a myriad of factors such inlet air temperature, inlet air absolute humidity, temperature of liquid binder, volume of liquid binder and the extent of evaporation (itself a function of droplet size, binder spray rate and airflow rate) would influence powder bed humidity. This is due to the fact that mixing, wetting and drying of particles take place simultaneously in the same apparatus, and therefore these different elementary processes play influential inter-dependent roles on each other (Hemati et al., 2003). [15]

REFERENCES

1. The theory & practice of industrial pharmacy by Leon Lachman, Herbert A. Lieberman, Joseph L. kenig, 3rd edition, published by Varghese Publishing house.
2. www.google.com
3. www.slideshare.net
4. Rambali B, Baert L, Using experimental design to optimize the process parameters in fluidized bed granulation on a semi-full scale, International Journal of Pharmaceutics,220,2001,149-160.
5. Aulton ME Pharmaceutics: The Science of Pharmacy, Churchil Livingstone Pub, 13th Edition.
6. Michael Levin,Metropolitan Computing Corporation,East Hanover, New Jersey, Pharmaceutical Process Scale-Up, Marcel Dekker, Inc,2001.
7. http://www.rs.kagu.tus.ac.jp/~honda/om.html
8. http://freepaharmaresearchpaper.blogspot.in/2011/06/role-of-granulation-process-in.html
9. Horiba scientific, A Guide to particle size analysis,1-2.
10. Mike,Techceuticals, solution for pharma and nutra manufacturers since 1989™, march 9th, 2009.
11. Faurea P, York RC, Process Control and Scale Up of Pharmaceutical Wet Granulation Process: a review, European Journal of Pharmaceutics and Biopharmaceutics,52,2001,269-277.
12. http://www.pharmainfo.net/tablet-ruling-dosage-form-years/manufacturing-methods-tablets
13. Lippincott Williams and Wilkins, Remington, "the science and practice of pharmacy", 21st edition,900-901.
14. Elsevier, Identifying fluid-bed parameters affecting product variability, Anil Menon ,Narinder Dhodi, William Mandella, Sibu Chakrabarti, International Journal of Pharmaceutics, volume 140, issue 2, 30 august, pages 92-102.
15. S.Henrick, The Possibilities and Challenges of Spray Drying, Advancing Process Solution Pharmaceutical Technology, Europe, Reprinted May 2010.
16. Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. Ist ed. vallabh prakashan, 2002,156-189.
17. Shargel L, Yu ABC. Modified release drug products. In: Applied Biopharmaceutics and Pharmacokinetics. 4th ed. McGraw Hill. 1999; 169-171.
18. Ratner BD, Kwok C. Characterization of delivery systems, surface analysis and controlled release systems. In: Encyclopaedia of Controlled Drug Delivery, Vol-I. Published by John Wiley & sons. 1999; 349-362.
19. Nandita GD, Sudip KD. Controlled-release of oral dosage forms, Formulation, Fill and Finish 2003, 10-16.
20. Malamataris S, Karidas T, Goidas P. Effect of particle size and sorbed moisture on the compression behaviour of some hydroxypropyl methylcellulose (HPMC) polymers, Int J Pharm 1994, 103, 205-215.
21. Gohel MC, Parikh RK, Padshala MN, Jena GD. Formulation and optimization of directly compressible isoniazid modified release matrix tablet, Int J Pharm Sci 2007, 640-644.
22. Levina M, Palmer F, Rajabi-Siahboomi A. Investigation of directly compressible metformine HCl 500 mg extended release formulation based on hypromellose, Controlled Release Society Annual Meeting 2005, 1-3.
23. Jonathan, Bouffard, "Drug Development and Industrial Pharmacy, Influence of Process Variable and Physicochemical Properties on the Granulation Mechanism of Mannitol in a Fluid Bed Top Spray Granulator", 2005, Vol. 31, No. 9 , Pages 923-933.
24. Schaefer.T.and Worts.O.,"Control of Fluid Bed Granulation-5,"Arch.Pharm.Chem.Sci.Ed.,Vol.6,1978,78-81.
25. Schaefer.T.and Worts.O.,"Control of Fluid Bed Granulation-3,"Arch.Pharm.Chem.Sci.Ed.,Vol.6,1978,12.
26. Elsevier, Discrete element modelling of fluidised bed spray granulation, M.J.V Goldschmidt, Volume 138, Issue 1, 30 November 2003,World Congress of Particle Technology, pages 39-45.
27. Characterization of Wet Granulation Process Parameters Using Response Surface Methodology. Top-spray fluidized bed, Douglas M. Lipps, Adel M. Sakr, Journal of Pharmaceutical Sciences, volume 83, Issue 7, July 1994, pages 937–947.
28. Elsevier, Experimental Study of Wet Granulation in fluidized bed: Impact of the binder properties on granule morphology, P. Rajniak,International Journal

of Pharmaceutics,volume 334, issues 1-2 , 4 April 2007, pages 92-102.
29. Elsevier,Identifying fluid bed parameters affecting product variability, Anil Menon, International Journal of Pharmaceutics, volume 140, issue 2, 30 august, pages 92-102.
30. Ibrahim Khattab, Anil Menon, Adel Sakr, Effect of Mode of Incorporation of Disintegrants on the Characteristics of Fluid-bedWet-granulatedTablets,Journal of Pharmacy and Pharmacology,Volume 45, Issue 8, August 1993, pages 687–691.
31. Katta S and Gauvin W (1976) basic concept of spray dryer design. AICHE J, 22(4), 713-724.
32. Keey RB and Pharm QT (1976) Behaviour of spray driers with nozzle atomizers. Chem. Engg. 311, 516-521.
33. Elsevier, powder technology, volume 120, issues 1-2, 8 october 2001, third European conference on fluidization, pages 76-81.
34. Chien YW. Novel Drug delivery systems. Second edition (Revised & Expanded), Marcel Dekker Inc 1992 160- 64, 139-96.
35. Ghosh TK, Jasti BR. Theory and practice of contemporary pharmaceutics. CRC press; 2005, 282-367, 150-155.
36. Kasture PV, Parakh SR, Gokhale SB, Hasan SA. Pharmaceutics-I. Nirali prakashan; 1993, 23.
37. http://www.australianprescriber.com/magazine.
38. H C Ansel, L V Allen, Jr. N C Popovich, Pharmaceutical dosage forms and drug delivery systems., Lippincott Williams and Wilkins; Baltimore 7th edition. 2000: 231.
39. The drug development process, Edited by: Peter welling and Umesh. V. Banakar. Published in: United State of America.
40. Theory and Practice of Industrial Pharmacy: Third edition, Edited by: Leon Lachman. Published by: Varghese publishing house, Bombay.
41. Introduction to Pharmaceutical Dosage Forms: Third edition, Edited by: Howard Ansel Published by: K.M Varghese Company, Bombay.
42. Kibbe AH., Handbook of pharmaceutical excipients; American Pharmaceutical
43. Association and Pharmaceutical Press, Washington London; 2000; 3rd Ed; 102- 106.
44. Chowhan ZT. Role of binders in moisture-induced hardness increase in compressed tablets and its effect on in vitro disintegration and dissolution. J Pharm Sci 1980; 69: 1–4.
45. Rowe RC. The adhesion of film coatings to tablet surfaces – the effect of some direct compression excipients and lubricants. J Pharm Pharmacol 1977; 29: 723– 726.
46. Alderman DA, Schulz GJ. Method of making a granular, cold water dispersible coating composition for tablets. United States Patent No. 4,816,298; 1989.
47. Pollock D., Sheskey P., Micronized ethylcellulose: opportunities in direct compression controlled-release tablets; Pharmaceutical Technology; 1996; 20(9); 120–130.
48. Lachman L., Lieberman HA., Kanig JL., The theory and practice of Industrial pharmacy, Varghese Publishing House Bombay; 1987; 171-293.
49. Cooper J, Gun C, Powder Flow and Compaction. Inc Carter SJ, Eds. Tutorial Pharmacy. New Delhi, hidix CBS Publishers and Distributors; 1986:211-233.
50. Martin A, Micromeretics, In: Martin A, ed. Physical Pharmacy.Baltimores, MD: Lippincott Williams and Wilkins; 2001:423-454.

***Corresponding Author:**
Kamya Chaudhary*
Department of Pharmaceutics,
Rayat College of Pharmacy, Ropar, India