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A REVIEW: GRANULATION TECHNOLOGY FOR PHARMACEUTICAL PRODUCT DEVELOPMENT

Rahul Shirode* and Dr. Ashish Gorle

Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dhule, Maharashtra, India.

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***Corresponding Author**
Rahul Shirode
Department of Pharmaceutics, R. C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Dhule, Maharashtra, India.

ABSTRACT

Granulation, it is a technique of particle enlargement by agglomeration; it is one of the most useful unit operation in the production of pharmaceutical dosage forms, mostly tablets and capsules. Although granules used in the pharmaceutical industry have particle size in the range of 200µ- 4000µ, they are primarily produced as an intermediary with a size range of 200µ- 500µ to be either packed as a dosage form or be mixed with other excipients before tablet compaction or capsule filling. Three type of granulation techniques are mostly used in pharmaceutical industry- 1. The Direct Compression Process, 2. Dry Granulation and 3. Wet granulation. Direct compression process is used when all the ingredients can be blended and placed in a tablet compression to make a tablet without any of the ingredients having to be changed. In dry granulation process the compression of the powder blend is without the use of heat and solvent. Roller compactor (Chilsonator) is most commonly used machine to produce powder blend to slugs. It is the most desirable method of all methods of granulation. Wet granulation is a way for size enlargement which involves any process whereby small particles are agglomerated into larger, relatively permanent structures with the help of liquid binder. Several methods are used to determine the end point in wet granulation process. Like Torque vs Power, Impeller torque profile. This review is give general overview regarding granulation techniques and its advantages and limitations.

KEYWORDS: Granulation Technology, Direct Compression Process, Dry Granulation, Roller Compactor, Wet Granulation, Torque vs Power, Impeller Torque Profile.

INTRODUCTION

Granulation, it is a technique of particle enlargement by agglomeration; it is one of the most useful unit operation in the production of pharmaceutical dosage forms, mostly tablets and capsules. During the granulation process, small fine particles or coarse particles are converted into large agglomerates called granules.

Generally, granulation starts after initial dry mixing of the necessary powder ingredients along with the active pharmaceutical ingredient (API), so that a uniform distribution or mixing of each ingredient throughout the powder mixture is achieved. Although granules used in the pharmaceutical industry have particle size in the range of 200µ- 4000µ, they are primarily produced as an intermediary with a size range of 200µ- 500µ to be either packed as a dosage form or be mixed with other excipients before tablet compaction or capsule filling.[1]

Wet granulation is a way for size enlargement which involves any process whereby small particles are agglomerated into larger particles, relatively permanent structures with the help of liquid binder. The wet granulation process generally achieves the desired granule properties intended for specific purposes. Granule voidage controls strength, and controls tablet and capsule dissolution behavior, as well as compaction behavior and tablet hardness.[2]

Granulation is an example of particle design. The desired attributes and requirement of the granule are controlled by a combination of the formulation and the process. The development of pharmaceutical granulation technology was driven by the invention of the tablet press machines. The demands on the granulation properties and technology were further enhanced in the 1970s as high-speed tablet and capsule filling machines with automated controls were developed. The continuous refinements in the regulatory requirements such as low-dose products requiring blend uniformity/content uniformity necessitated knowledge and technology to produce the required granule characteristics. The high-speed compression and capsule filling machines require a uniform flow of material from hopper to the dies or filling stations that produce ideal pharmaceutical dosage form.

Successful processing for the agglomeration of primary particles depends on proper control of the adhesion force between particles, which encourage agglomerate formation and growth and provide adequate mechanical strength in the product. Furthermore, the rheology of the particulate system can be critical to the rearrangement of particles necessary to permit densification of the agglomerate and the development of an agglomerate structure appropriate

for the end-user requirements. If the particles are close enough then the surface forces such as van der Waals forces and electrostatic forces can interact to bond particles. Decreasing particle size increases surface–mass ratio and favors the bonding. Van der Waals forces are sevenfold stronger than electrostatic forces and increase substantially when the distance between them is reduced, which can be achieved by applying pressure as in dry granulation method.[8]

Table 1- Frequently used granulation techniques and their processing[8]

	PROCESS	DRYING TECHNIQUES
Wet granulation	Low-shear mixer	Tray or fluid-bed dryer
	High-shear mixer	Tray or fluid-bed dryer
	Fluid-bed granulator/dryer	Fluid-bed granulator/dryer
	Extrusion/ spheronization	Tray or fluid-bed dryer
Dry granulation	Direct compression	Blend and process further
	Slugging	Mill slugged tablets and process further
	Roller compactor	Compacts milled/blend/process further

Ideal characteristics of granules

The ideal characteristics of granules include

Spherical or round shape,

Small particle size,

Distributed with sufficient fines to fill void spaces between granules,

Sufficient moisture (between 1-2%),

Good flow property,

Good compressibility,

Sufficient hardness (3)

The effectiveness of granulation depends on the following properties

Particle size of the API and excipients,

Type of binder solution (strong or weak)

Volume or amount of binder solution (less or more)

Wet massing time (less or more)

Amount of shear force applied

Drying rate and drying time (Hydrate formation and polymorphism).[3]

Type of granulation

1. The Direct Compression Process

This method is used when all the ingredients can be blended and placed in a tablet compression to make a tablet without any of the ingredients having to be changed. This is not so common because many tablets have active pharmaceutical ingredients which will not allow for direct compression due to their concentration in blend or the excipients used in formulation are not contributory to direct compression.

Advantages

- Economic process,
- Less stability issues,
- Achieves faster dissolution as compared to other method.

Disadvantages-

- Segregation,
- Dosage variation,
- Variation in functioning.[4]

2. Dry Granulation

In dry granulation process the compression of the powder blend is without the use of heat and solvent. It is the most desirable method of all methods of granulation. The two basic steps are 1.The formation of compact of material by compression, 2.Then to mill the compact to obtain the granules. Two methods are used for dry granulation. The most commonly used method is **slugging** in which powder blend containing API is recompressed and resulting tablet or slugs are milled in co-mill to obtain the granules. The other method is to precompress the powder blend containing API with pressure rolls using a machine such as **Chilsonator**.

Roller Compaction (Chilsonator)

The compaction of powder blend by use of pressure roll can also be done by a machine called Chilsonator. Unlike tablet compression machine, the Chilsonator turns out a compacted mass in a steady continuous flow. The powder is filled in between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled to produce granules.

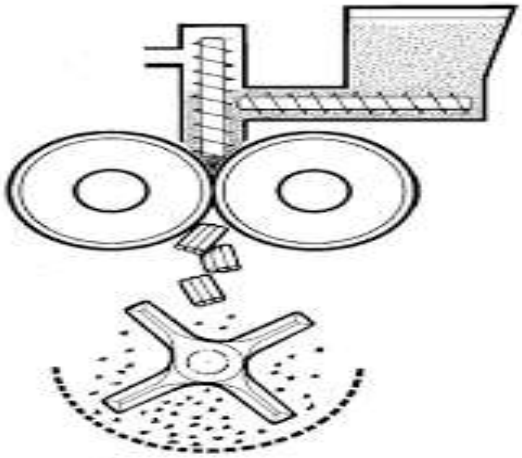

Fig. 1 Schematic diagram of roller compactor

Advantages

- Less equipments and space is required,
- Useful for heat sensitive material,
- Also useful for moisture sensitive material,
- It eliminates the need of binder solution,
- It does not required any heavy mixing equipment,
- It eliminate time consuming drying step required for wet granulation.

Disadvantages

- It requires a specialized heavy duty tablet press machine to form slug.
- The process create more dust than wet granulation, increases the potential contamination.
- It will not permit uniform color distribution as we achieved with wet granulation where the dyes can be incorporated into binder liquid.[4]

Steps involve in Dry Granulation

1. **Milling of drug and excipients-** In dry granulation process the drug and excipients are milled to produce uniformity in powder and excipients.

2. **Mixing of milled granules-** Mixing of Drug and excipients are the most important step in dry granulation. After milling the drug and excipients, the milled drug and excipients are mixed well in blender to avoid blend uniformity and segregation problem.

3. **Compression into large, hard tablets to make slug-** After mixing, the blend is compressed into large size, hard tablets to make slugs. Then these slugs are milled

through multi- mill to produced granules (also called as de-slugging). This step is very important because fine powder get converted into granules.

4. **Mixing with lubricant and disintegrating agent-** After de-slugging, the granules get mixed with disintegrant and lubricating agent.

3. Wet Granulation

Wet granulation is a way for size enlargement which involves any process whereby small particles are agglomerated into larger, relatively permanent structures with the help of liquid binder. The wet granulation process must generally achieve the desired granule properties intended for specific purposes Granule voidage controls strength, and controls capsule and tablet dissolution behavior, as well as compaction behavior and tablet hardness.

In wet granulation methods, liquid added to dry powders has to be distributed through the powder blend by the mechanical agitation created in the granulator. The particles adhere to each other because of liquid addition, and further agitation and/or liquid addition causes more particles to adhere.

Advantages

1. It Permits mechanical handling of powders without loss of quality of blend.
2. The flow properties of powder blend are improved by increasing particle size and sphericity.
3. Increases and improves the uniformity of powder density.
4. Minimize air entrapment between granules.
5. Reduces the level of dust and cross contamination.

Limitations

1. Processing stages is more so losses are more during handling.
2. Stability may be major issue for moisture sensitive or thermo labile drugs.
3. Number of processing steps adds complexity and makes validation and control difficult.
4. It is an expensive process because of labor, time, equipment, energy and more space requires.[4]

The precise mechanism by which a dry powder is transformed into a bed of granules varies for each type of granulation equipment.

Mechanism of Granule formation-

The granulation mechanism can be divided into three stages-

1. Nucleation
2. Transition
3. Ball growth

Nucleation

Granulation starts with adhesion among particles due to liquid bridges between them and the formation of agglomerates at capillary state. A number of solid particles will join to form the pendular state. Further agitation densifies the pendular bodies to form the capillary state, and these bodies then act as nuclei for further granule growth.

Transition

Nuclei can grow in two possible ways:

- single particles added to the nuclei by pendular bridges, or
- combining two or more nuclei

The combined nuclei will be reshaped by the agitation of the bed. This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Provided that this distribution is not excessively large, this is a suitable end-point for granules used in capsule and tablet manufacturing, as relatively small granules size will produce a uniform tablet die or capsule fill. Larger granules may give rise to problems in small-diameter dies fill owing to bridging across the die and uneven fill.

Ball growth

Further granule growth produces large, spherical shape granules and the mean particle size of the granulating system will increase with time. If agitation is continued, granule coalescence will also continue and produce an unusable, over-massed system, although this is dependent upon the amount of liquid added, impeller speed and the properties of the material being granulated.

Although ball growth produces granules that may be too large for pharmaceutical purposes, some degree of ball growth will occur in planetary mixers and it is an essential feature of some spheronizing equipment.[5]

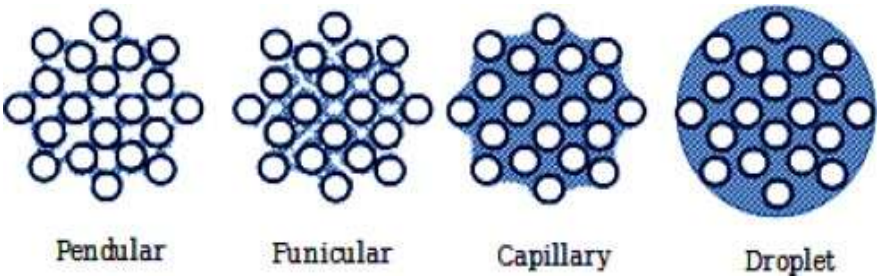

Fig. 2 Stages in wet granulation process

Steps involved in wet granulation

1. **Weighing and Blending-** Specified quantities of active ingredient, diluent or filler, and disintegrating agent are mixed by mechanical powder blender or mixer until uniform mixing is not done.

2. **Preparing the Damp Mass-** A liquid binder is added to the powder mixture to facilitate adhesion of the powder particles. Either a dampened powder formed into granules or a damp mass resembling dough is formed and used to prepare the granulation. A good binder results in appropriate tablet hardness and does not hinder the release of the drug from the tablet.

3. **Screening the Damp Mass into Pellets or Granules-** The dampened powder granules are screened or the wet mass is pressed through a screen (usually 6 or 8 mesh) to prepare the granules. This may be done by hand or with special equipment that prepares the granules by extrusion through perforations in the apparatus. The resultant granules are spread evenly on large lined trays and dried to consistent weight or constant moisture content.

4. **Drying the Granulation-** Granules may be dried in thermostatically controlled ovens that constantly record the time, temperature, and humidity. Instruments used for drying is Rapid dryer, Fluid bed dryer, Trey dryer, etc.

5. **Sizing the Granulation by Dry Screening-** After drying, the granules are passed through a screen of a smaller mesh than that used to prepare the original granulation. The degree to which the granules are reduced depends on the size of the punches to be used. In general, the smaller the tablet to be produced, the smaller the granules. Screens of 12- to 20-mesh size are generally used for this purpose. Sizing of the granules is necessary so that the die cavities for tablet compression may be completely and rapidly filled by the

free-flowing granulation. Voids or air spaces left by too large a granulation result in the production of uneven tablets.

6. **Adding Lubrication and Blending-** After dry screening, a dry lubricant is dusted over the spread-out granulation through a fine mesh screen. Lubricants contribute to the preparation of compressed tablets in several ways: They improve the flow of the granulation in the hopper to the die cavity. They prevent adhesion of the tablet formulation to the punches and dies during compression. They reduce friction between the tablet and the die wall during the ejection of the tablet from the machine. They give a shine to the finished tablet.

End point determination in wet granulation-

End-point can be defined as a target particle size mean or distribution. Alternatively, the end-point can be defined in rheological terms. It has been shown that once we have reached the desired end-point, the granule properties and the subsequent tablet properties are very similar regarding of the granulation processing factors, such as impeller, chopper speed or binder addition rate.

The aim of any measurement in a granulation process is to estimate the density and viscosity of the granules, and perhaps, to obtain an indication of the particle size mean and distribution. One of the method is to obtain the information is by measuring the load on the main impeller.

1. **Torque vs Power**

When we say "power consumption", we usually refer to the main motor. It reflects the load on the motor due to useful work, as well as the power required to run the motor itself.

It is possible to talk about the power consumption of the impeller, which is, obviously, quantitatively less than the power consumption of the motor and relates directly to the load on the impeller.

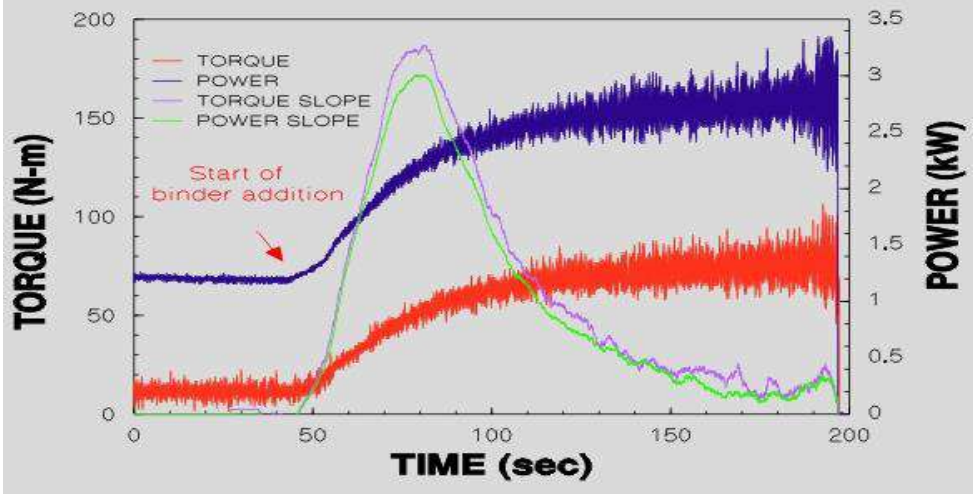

Fig. 3 Impeller torque and motor power consumption

Fig.3 illustrates the classical power and torque profiles that start with a dry mixing stage, rise steeply with binder solution addition, level off into a plateau, and then exhibit over-granulation stage. The power and torque signals have similar shape and are strongly correlated. The pattern in graph shows a plateau region where power consumption or torque is relatively stable.

2. Impeller torque profile

In a mixing process, changes in torque on the blades and power consumption of the impeller occur as a result of change in the cohesive force or the tensile strength of the agglomerates in the moistened powder bed.

The analysis was done by effect of impeller speed on the shape of torque profile, at constant formulation.

Firstly the torque value increases linearly with water or binder addition, suggesting a progressive densification of the wet mass. A decrease in the slope is then observed which can be explained by an increased lubrication of the mass which causes a decrease of stress on impeller.

A sudden increase in the slope can be noted when the added water volume is larger than critical value. This abrupt increase in slope denotes the formation of liquid bridges and achieves the pendular state.[10]

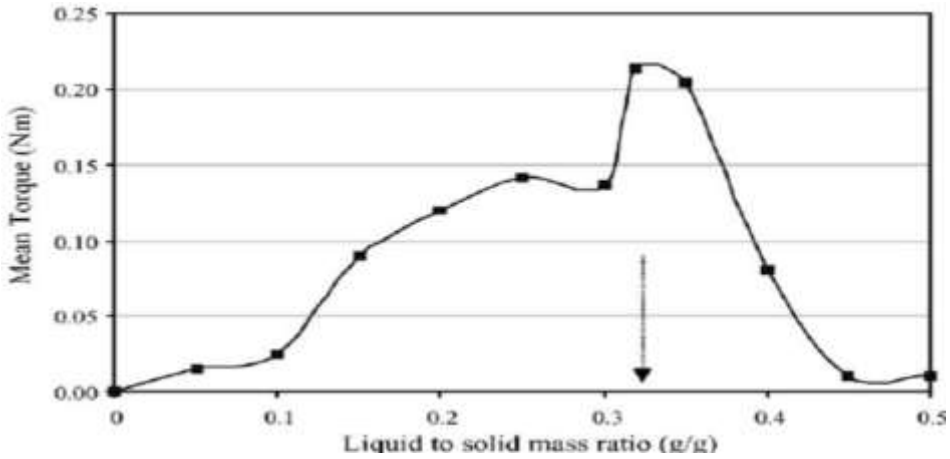

Fig. 4 Impeller Torque profile

CONCLUSION

The advance in granulation leads to the formulation of better dosage forms in terms of content uniformity and stability aspects. Each technique has its own merits and demerits. Which method is chosen depends on the ingredients individual characteristics and ability to properly flow, compresses, eject, and disintegrate. Mixing torque rheometry (MTR) has strongly replaced hand squeeze test for end point determination of wet granulation. MTR is a valuable tool for preformulation evaluation and scale up of wet granulation products.

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