Original Article

A Review on the Development of Granulation Technology in the Past Two Decades

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Abstract

Granulation is a technique that convert fine powder particles to granules which form appropriate agglomerate. It's main function is to improve the powders flow and compressibility properties as well as to prevent segregation of the blend components. Traditionally, there are three types of granulation methods namely dry granulation, wet granulation and direct compressing. But, each one of these traditional methods has different disadvantage which prompted the researchers to modify and find new technique to granulate the powder. Among the new granulation technique are steam granulation, melt granulation, moisture activated dry granulation, foam granulation, pneumatic dry granulation technology and thermal adhesion granulation. Choosing a technique depends on the knowledge of advantages and disadvantages of each technique and how appropriate it is to the characteristics of each ingredient. This review mainly focusses on new techniques in granulation technologies for granules production.

Keywords: Granulation, Steam Granulation, Melt Granulation, Moisture Activated Dry Granulation, Foam Granulation.

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INTRODUCTION

Granulation is a technique that convert fine powder particles to granules which form appropriate agglomerate.[1] The normal size for drug granules ranges between 0.2 and 4.0 mm. The granules produced from granulation will be used in tablet compaction or capsule filling after mixing with suitable excipients.[2] The main function of granulation is to improve the powders flow and compressibility properties as well as to prevent segregation of the blend components. Traditionally, there are three types of granulation methods namely dry granulation, wet granulation and direct compressing. But, each one of these methods has different disadvantage. For instance, direct compressing is one of the least suitable technologies for many active substances if the active substances are in high dosages or in fine powder form as it may cause splitting, lamination, capping, or layering of tablets. Air might be entrapped during direct compression process and causing friable tablet. This is resulted from the entrapment air, causing the tablets to expand and release of pressure of the tablet which resulted in splitting or layering in the tablet. Greater sophistication in blending and compression equipment is required in some cases. In addition, direct compression equipment are generally expensive.[3] On the other hand, cost is the greatest disadvantage of wet granulation method. Wet granulation process involves a great deal of time, labor, equipment, space, energy and the loss of material at different stages. For moisture sensitive or thermos labile drugs where the stability may be a major concern, more processing steps are required resulting in higher complexity and as a result, the validation and control of the process is more difficult. Consequently, this aggravation of incompatibility between formulation has become a significant inherent limitation of wet granulation.[4] Finally, a specialised heavy-duty tablet press is need to form slug in dry granulation. In wet granulation, coloring agent can be dispersed in granulating fluid. However, this is not the case for dry granulation. Besides, the dry granulation process also results in more dust being created and thus increasing the contamination risk.[5] In view of the advantages mentioned above, formulators are developing and exploring improvised granulation technologies to overcome the shortcomings. In this report, we are going to discuss about new advances in granulation technologies.

NEW GRANULATION TECHNOLOGIES

Steam Granulation

It is similar to wet granulation. But, the difference here is the binder used is a pure steam instead of liquid. Furthermore, this steam will occupy around 1,600 times the volume of an equal mass of the liquid, under standard temperature and pressure. Main process in steam granulation is inject the desired amount of liquid in the form of steam. The purpose of steam injection is to provide a suitable heat and wet to the particles, hence give rise to form masses in the granulated product. Applying steam granulation gives some advantages such as: uniformly distributed in the powder particles,

optimal spherical granule formation, save time, improve of dissolution of granules due to larger surface area created. However, this process has disadvantages such as need special machine to generate steam, thermolabile products are not recommend and it is not appropriate for all binders.[6]

Melt Granulation

Melt granulation is a technique help to achieve agglomeration of powder particles through adding of either a molten binder or meltable binder which can melt within temperature range between 50-80 ˚C. Reducing agglomerated powder temperature leads to drying the molten binder to make it ready for sizing the granular mass, in order to obtain final dry granules. Melt granulation has some benefits over wet granulation such as suitable for moister sensitive materials, save time and money because there is no addition of liquid and drying procedure. However, the main drawback is that this technique is not suitable for heat sensitive drugs.[7]

Moisture Activated Dry Granulation (MADG)

MADG is a method that does not apply direct heat to dry granules but only using heat as in form of steam to activate granule formation. The first stage in MADG is agglomeration of required powder. In this stage, the binder and diluents are mixed with drug, to yield a uniform mixture. In order to wet the binder and make it tacky, small droplets of water is sprayed onto the powder during mixing process. Present of binder in the formulation, facilitates mixing drug and excipients specially when the mixer blades mix them in a circular motion. Agglomerates have a common particle size range of 150-500 μm. Then, the second stage is moisture absorption. During mixing, microcrystalline cellulose or silicon dioxide are added to mixture to absorb the moisture. The moisture absorbents help to absorb moisture so that the moisture is redistributed within the mixture. As a result, the relative humidity of the whole mixture remains low. Sufficient level of moisture is required as internal binder to avoid granules become too brittle and easily break up. This process has help to produce more uniform sized granules. The main advantages of this technique are using a small amount of granulating fluid and decreasing drying time and producing granules with excellent flow ability. However, it is not suitable for moisture-sensitive drugs and not easy to develop formulations contains large drug dosing.[8]

Foam Granulation

Foam granulation is a technology using liquid binder as aqueous foam instead of spraying or pouring liquid onto the powder particles (Fig 1). Comparing with wet granulation, it has many advantages, for example less binder required as compared to spray granulation, less water required compared to wet granulation, shorten processing times by reducing water requirements, elimination of the use of spray nozzles and thus no plugging problems as well as no over wetting issues. Moreover, this method is suitable for moisture sensitive material by shorten drying and manufacturing time overall. It improves the distribution of binder homogeneously throughout the powder bed with lesser binder is required for solid dosage form. [9]

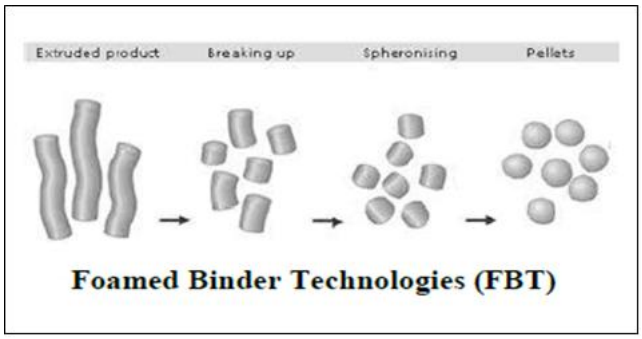

Fig. 1: The Process of foam granulation

Thermal Adhesion Granulation (TAG)

Thermal adhesion granulation is similar to moist granulation by making agglomeration by using a little amount of granulation liquid and heat. The powder blend is mixed and maintained at temperature between 30 ˚C -130 ˚C in a tumble rotator. Granules are formed after cooling and screening of the dried mass. The granules formed in this method has good flowability and binding property. With this, tablet with sufficient hardness, low friability and high drug loading can be obtained. The pros of this method is that it uses less water compared to wet granulation method. In addition, due to the process is in a closed rotator, the dust generated is minimum. This method is suitable if the process involves expensive material in small quantity as the lost needs to be controlled. The shortcomings of this method is that it requires considerably high energy input and special equipment for heat generation and regulation. Furthermore, TAG is not suitable for all types of binder and thermo labile drugs are not suitable to be used with this method. [9, 10]

Pneumatic Dry Granulation Technology (PDG)

This technology produces porous highly compressible and free flowing granules. The granules produced are suitable for various applications such as sustained release, immediate release or coating. The tablets produced have an enhanced drug loading capacity, disintegration time and tablet hardness. This method is a good news for heat sensitive excipients and active pharmaceutical ingredient. PDG Technology has been proven in various types of tablet applications including immediate release, controlled release and orally disintegrating tablets. This granulation technology basically is suitable for all solid dosage pharmaceutical product.[11] This technology provides many advantages such as decreased production cost through reduced waste via recycling and higher drug loading through good granulation even for those materials that are known to be difficult to handle historically.[12] Moreover, it offers potential for fast release dosage form as the granules and tablets produced showed fast disintegration properties. Further, release time

can be tailored to requirements. In addition, the system offers safety advantages through lower dust levels as it is a closed system and this is a potential for the production of sterile products and handling of toxic materials.[13] Comparison between PDG and wet granulation showed that PDG granules have excellent properties and less steps (Fig 2).

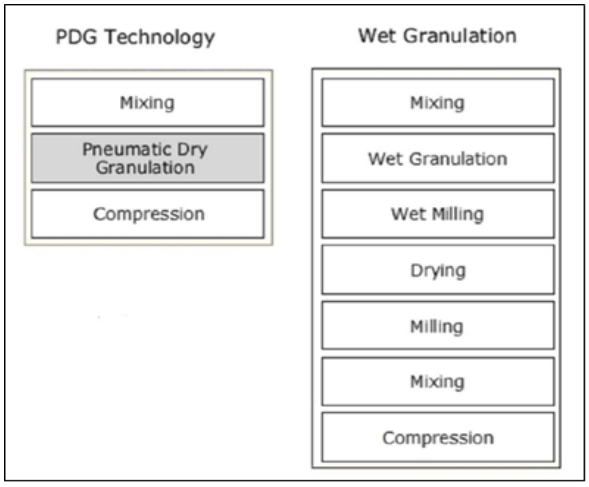

Fig. 2: Comparison between PDG and wet granulation

Freeze Granulation Technology

Freeze granulation method was proposed by Swedish Ceramic Institute. In this method, a suspension was formed and sprayed into liquid nitrogen to form dry granules when the granules drop freeze instantaneously in liquid nitrogen pool.[14] The granules were further dried using freeze drying. The granules formed were spherical in shape, having good flowability and good homogeneity.[15-16]

CONCLUSION

This report mainly focusses on new advances in granulation technologies for granules production. Choosing a technique depends on the knowledge of advantages and disadvantages of each technique and how appropriate it is to the characteristics of each ingredient and the ability of the technique to improve flow, compression, ejection, and disintegration properties. Then the proper method can be applied.

Conflicts of Interest: The authors declare no conflict of interest.

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