Advantages and Challenges of Roller Compaction Process for Dry Granulation

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ABSTRACT
Granulation, which is a technology of expanding particles by coagulation, is one of the most significant unit operations for the production of drug dosage forms (mainly capsules and tablets). In the granulation process, fine or coarse particles are transformed into large aggregates called particles. Granulation processes can be divided into two types: wet granulation and dry granulation (also called RC). The difference between the two processes is whether utilize liquid. Granulation has many advantages and has made considerable success, especially for dry granulation. However, because the formed particles have high-quality requirements in terms of content uniformity, physicochemical properties and stability of drugs, which bring dry granulation many challenges. Among currently available technologies, dry granulation can be achieved by rolling or slug granulation. This review focuses on the roller compaction process for dry granulation. This review summarizes the development, significance, and limitations of the roller compaction process for dry granulation. This review focuses on the roller compaction process for dry granulation. Through the retrieval and reading of relevant literature, this paper puts forward the advantages and challenges of the roller compaction process for dry granulation.

Keywords: *Roller compaction; advantages and challenges; dry granulation*

1. INTRODUCTION

Granulation is one of the most significant unit operations in the production of pharmaceutical dosage forms. The general process of granulation is to make the mixed powder containing pharmaceutical excipients and APIs into granules through direct compression or agglomeration granulation technology, and then compressed into tablets. Granulation technology can be widely divided into two types, dry granulation and wet granulation. Dry granulation uses mechanical compression (Slug) or roller compaction to promote the agglomeration of dry powder particles, while wet granulation uses granulation liquid to form wet agglomerates by adhesion. Among the two granulation technologies, wet granulation technology is the most widely used granulation technology. Although it involves multiple unit processes such as wet aggregate, drying and screening, it is so complex and expensive that it will cost large space, time, and multiple types of equipment[1]. This review summarizes the development, significance, and limitations of roller compaction process for dry granulation. This review puts forward the unsolved problems for the development of dry granulation in the future by comparing dry and wet granulation.

2. DRY GRANULATION

Dry granulation is a method in which drugs are evenly mixed with diluents, disintegrating agents and lubricating agents in an agglomeration process; then compressed into strips or flakes and crushed into the required particle size[2]. Unlike wet granulation, dry granulation does not require water or any organic solvent, therefore, this method is particularly suitable for drugs sensitive to moisture or heat and excipients' poor fluidity. This type of method is environmentally friendly with no waste gas emission. Its simple operations are efficient and automated, which can be scaled at a low cost. After dry granulation, the finished product has uniform particle size, improved fluidity and controllable disintegration, which is convenient for subsequent processing, storage and transportation[3]. Compared with the more mature wet pelletizing technology, solid preparation is still the most common to improve the powder properties such as fluidity and stability of products, eliminate the degradation caused by wet granulation, and prevent

delamination between materials by increasing bulk density.

The latest development of dry granulation can be achieved by rolling or slug granulation. These two different types are shown in Figure 1. Compared with wet granulation, dry granulation technology has not made great progress except for an important innovation of dry granulation technology known as roller compaction. Compared with slugging, the advantage of roller compaction is that they can increase the bulk density, improve the flow characteristics and ensure the uniformity of particulate formulations by preventing segregation[2].

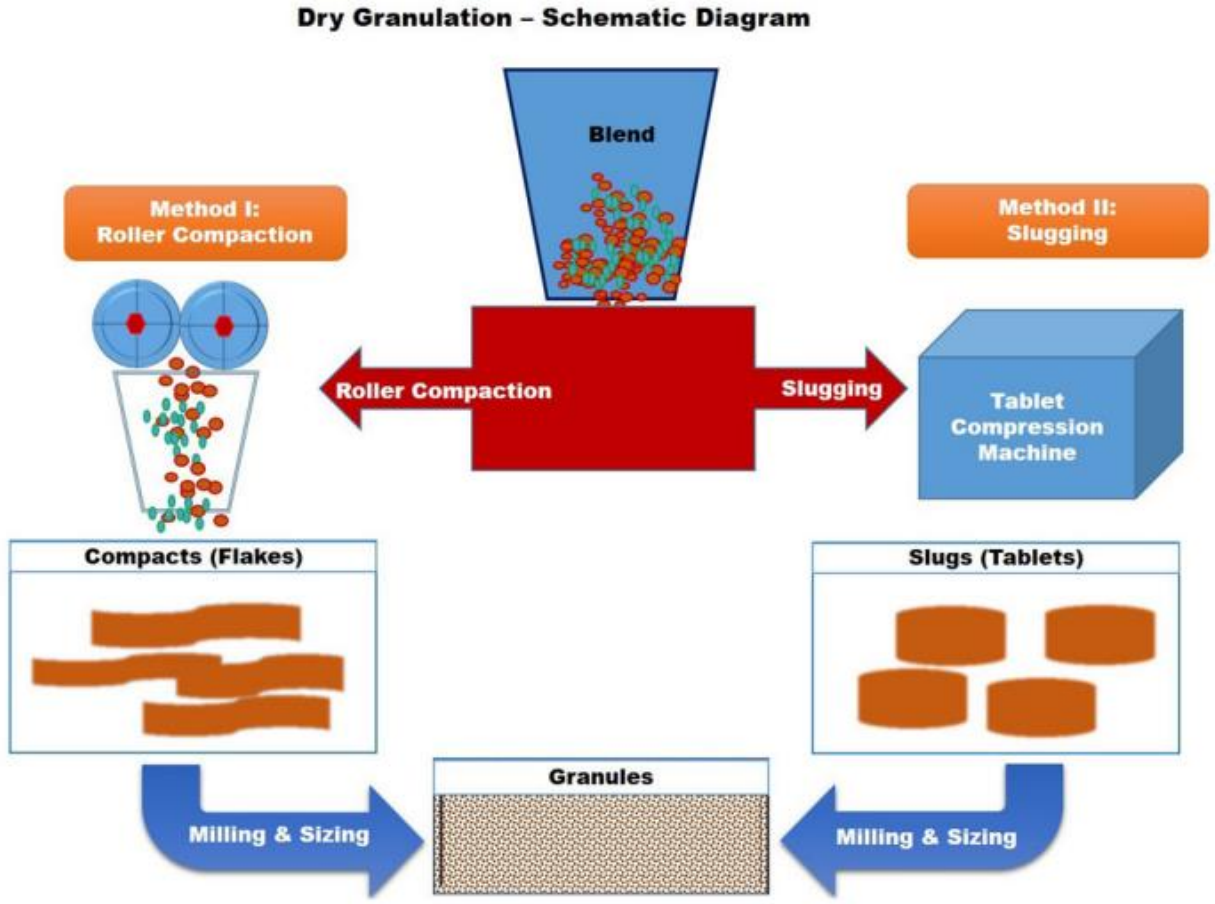

Figure 1. Schematic diagram of dry granulation and two different techniques. Method I is roller compaction and Method II is slugging

The most common dry granulation technology is rolling, which is combined with a subsequent gentle grinding of thin sheets. The selection of the rolling drying granulation process has both product advantages and process advantages. Although the RC process has been used for many years, it has become more and more popular recently on a small-scale[3]. Its use in pharmaceutical solid doses has increased considerably. Although it has all the benefits that the wet granulation process can provide, including improving material flow behavior and content uniformity, RC also provides better thermal sensitivity than wet granulation in moisture, solvent or drug. In addition, RC technology plays a very important role in supplying competitive cost control, because it has the minimum operator presence and high throughput of floor space. There are still many problems such as the large number of fine particles and poor particle fluidity in the roller compaction, but it can be made into particles to improve the fluidity of materials[3]. In general, the main advantage of dry granulation over wet granulation is that there is no water or any organic solvent. Therefore, this method is particularly attractive for drugs sensitive to water or heat. In addition, this process is environmentally friendly. In addition, rolling technology provides an efficient and easy to automate the process. The process is easy to expand, simple in concept and low in operation cost. However, compaction in the roller press is still not fully understood[4]. The dry granulation tablet pressing method is to mix drugs and dressings, press them into large pieces with the appropriate equipment, then break them into particles of appropriate size, add lubricants, etc., and then press them. The process for dry granulation: Drug + excipients crushing - sieving - mixing - pressing - crushing a whole - mixing - pressing tablet[1]. Dry granulation is to add the mixed dry powder materials into

the upper hopper by a special feeder (pneumatic or motorized) and transport them to the pressure chamber by a screw conveyor. Two high-pressure extrusion wheels press the material into high-density flakes, cut them into small pieces through the cutting system, and make particles of the required size through the two-stage granulation system, so as to complete the granulation process[5].

3. ADVANTAGES OF THE ROLLER COMPACTION PROCESS FOR DRY GRANULATION

There are considerable advantages, especially about the roller compaction process for dry granulation, which makes it the most widely used dry granulation technology.

3.1 About increasing efficiency and reducing costs

Roller compaction can shorten the production time and reduce the production equipment, especially for drugs that are easy to deteriorate by moisture and heat, and can improve the product quality[6]. The Roller compaction process is a continuous process, which means it is relatively easy to scale up and improve the overall process efficiency, while reducing the operation cost[5]. Although it has all the benefits that the granulation process can provide, including improving material flow behavior and content uniformity, RC also offers advantages over wet granulation in terms of moisture, solvent or heat sensitivity of API[2]. Moreover, it does not require a drying stage, so it is suitable for use with compounds with a low melting point or rapid degradation after heating, making it a cost-effective manufacturing option[2].

3.2 About environmental protection and safety hazards

Since no granulation liquid is required, it has advantages in dealing with physically or chemically water sensitive materials compared with wet granulation. Roller compaction can also reduce bulk to minimize storage volume and improve transportation efficiency, which can also help reduce potential environmental and safety hazards[3].

3.3 About the discoloration of materials in the granulation process

The color of general materials after dry granulation will be different from that of the original powder. Because the surface area of powder is larger than that of particles, the reflection of light is also different. In addition, the bulk density of pressed particles is increased compared with that of the original powder, so the color of particles will also be deepened. Generally, the greater the pressure on the pressure roller, the darker the color will become[3]. The pressure on the pressure roller is not only the pressure of the oil pump, but also related to the feeding speed and tablet pressing speed. When the pressure and tablet pressing speed are constant, the faster the feeding speed, the greater the pressure between the pressure rollers, and vice versa. Similarly, when the pressure and feeding speed are constant, the slower the tablet pressing speed is, the greater the pressure acting on the pressure wheel, and vice versa. Therefore, when using the dry granulator, we should choose a great pressure and speed according to the actual situation of materials, so as to improve the primary yield of products on the basis of ensuring product performance[6].

4. CHALLENGES OF THE ROLLER COMPACTION PROCESS FOR DRY GRANULATION

4.1 About the mechanical properties of the material

The design of the experiment should consider the mechanical properties of the material. For example, materials that can significantly form strips even at low pressure. If this material is used for dry granulation in a relatively high pressure range, the effect of dry granulation pressure on the strip characteristics of the material and the compressibility of the particles may not be observed[4].

4.2 About expensive generation cost and resource consumption

The dry granulation process is continuous, and any materials that leak from the drum must be recovered. Recovery can maintain high production to reduce costs, but it may also lead to poor particle fluidity[1]. Different ways of using lubricants, including internal and external lubricants, may lead to significant differences in material properties. Compared with external lubricant, internal lubricant often shows worse tablet compressibility. This requires careful consideration and evaluation in the process and formulation design process. In general, it is best not to use lubricants unless the powder needs to be treated, for example, to prevent the powder from sticking to the roller shaft[1]. The strips produced on the dry granulator usually show an uneven density distribution[6]. Although dry granulation is used to improve the fluidity of other powders with poor fluidity, the fluidity of the starting powder must meet the requirements, so that the feeding process of dry granulation can be carried out smoothly[3].

4.3 About scope of application

RC may be inappropriate for substances that strongly adhere to metal surfaces or that are difficult to compact. The robustness of RC can also be affected by the variability in drug substance physical and mechanical properties; however, this is less than direct compression. In general, the drug load in RC can range from 2 to 50% according to the compression and flow characteristics of drug substances[2].

5. DISCUSSION

Although there are plenty of challenges of the roller compaction process for dry granulation, there exist solutions to addressing disadvantages with the roller compaction process for dry granulation. Firstly, about leakage of uncompacted material or fine powder. Concave roller is used for sealing, because the leakage between the roller side sealing rings will produce uncompacted material. The material can be granulated after recovery, but if the composition of the leaked fine powder is different from the total composition, it will lead to the non-uniformity of the final product. In addition, multiple rolling of materials will have a negative impact on the compressibility of materials. Vacuum around the equipment prevents powder splashing[4]. Secondly, material compression loss. The loss of compressibility of materials is a common problem in dry granulation, which is more obvious at higher grinding pressure. This mainly occurs in plastic materials and brittle materials. Generally, the roll pressure is high in dry granulation to achieve the required particle characteristics, but on the premise of meeting the quality requirements, the roll pressure should be reduced as much as possible to avoid the loss of material compressibility. Excessive compression can cause discoloration, overheating, severe cracking or plasticization of material strip[6]. Third, there is the issue of material adhering to the roll. Lubricant can be added to control the material moisture within the best range. Dextrin, maltodextrin and other auxiliary materials with high Tg can be selected, and cooling water can be used to effectively reduce the roller surface temperature, and appropriate roller pressure and relative humidity of production environment can be controlled to avoid roller sticking[5]. Last but not least, about pressing strip delamination. To reduce delamination, maintain consistency in particle size distribution, density, and other material properties[1].

6. CONCLUSION

In the past few years, rolling drying granulation has made considerable achievements. The use of dry granulation, that is, RC, has increased recently in the development and manufacturing of pharmaceutical dosage forms. However, there are still potential problems and inherent limitations with RC such as adequate powder flow and material density, and there is no universal way to solve all related problems. Even if there are still a number of challenges, the future of roll compaction is expected to achieve rapid and further results in the near future in the next few years.

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REFERENCES

[1]S. Shanmugam, “Granulation techniques and technologies: Recent progresses,” BioImpacts, vol. 5, no. 1, pp. 55–63, 2015, doi: 10.15171/bi.2015.04.

[2]N. Sandler and R. F. Lammens, “Pneumatic dry granulation: potential to improve roller compaction technology in drug manufacture,” Expert Opinion on Drug Delivery, vol. 8, no. 2, pp. 225–236, Feb. 2011, doi: 10.1517/17425247.2011.548382.

[3]M. T. A. Ende et al., “Improving the content uniformity of a low-dose tablet formulation through roller compaction optimization,” Pharmaceutical Development and Technology, vol. 12, no. 4, pp. 391–404, Jul. 2007, doi: 10.1080/10837450701369253.

[4]P. Kleinebudde, “Roll compaction/dry granulation: pharmaceutical applications,” European Journal of Pharmaceutics and Biopharmaceutics, vol. 58, no. 2, pp. 317–326, Sep. 2004, doi: 10.1016/j.ejpb.2004.04.014.

[5]C. S. Omar, R. M. Dhenge, S. Palzer, M. J. Hounslow, and A. D. Salman, “Roller compaction: Effect of relative humidity of lactose powder,” European Journal of Pharmaceutics and Biopharmaceutics, vol. 106, pp. 26–37, Sep. 2016, doi: 10.1016/j.ejpb.2016.02.016.

[6]J. Clarke et al., “Determining the Impact of Roller Compaction Processing Conditions on Granule and API Properties,” AAPS PharmSciTech, vol. 21, no. 6, Aug. 2020, doi: 10.1208/s12249-020-01773-2.