Potentials of the Dry Granulation by Roller Compaction

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Abstract: The latest trends in the field of pharmaceutical engineering are regarding roller compaction. Roller compaction technology is a well-established strategy particularly involved in the medical industry. This developing process has a great impact on the manufacturing of oral solid dosage forms while containing high-quality active pharmaceutical ingredients (API). When the medical industry tends to develop a tablet, there are three basic processing routes that have been considered: direct compression, dry granulation, and wet granulation. Among these three high-efficiency productive ways, dry granulation is a process that compresses powdery ingredients into tablets without adding any liquid solution. Dry granulation is carried out using either slugging or roller compaction techniques. This pharmaceutic process has potentials for drug development as it has been proved to continuously manufacture tablets by working with compaction machines. Roller compaction employed to dry granulation can provide more advantages compared with other processing methods. However, there are still have some challenges that this technology and researchers need to face. Improvements on the dry granulation by roller compaction technology would give a great contribution to drug development and goods production.

1 INTRODUCTION

The manufacture of processing solids into pharmaceutical tablets is a multi-stages assembly line whereby scientist has used this process for hundreds of years. Most compressed tablets are required to go through several procedures started from ingredient dispensing. The ingredients will be divided by accuracy, mixed with excipients through blenders, and powders aggregated into granules. The dry granulation is then compressed and coated into tablets by using compaction techniques. Nowadays, there are typically three similar routes for solid dosage processing, including direct compression, dry granulation, and wet granulation. Three alternative procedures share similarities and differences. Among these routes, direct compression is the simplest process by bleeding the powder of API with excipient particles and then compressing them directly into a tablet machine. Although direct compression is the most economical way in the manufacturing industry, it cannot apply in many cases due to the segregation of particles during routine processing. Most manufacturing industries prefer granulation instead of direct compression.

Granulation is a process which helps to avoid segregation within particles. It is carried out in order to let powder particles adhere to each other, resulting in a high density of products which is known as granules. Dry granulation is processed with no aid of liquid blenders whereas wet granulation is required. In the dry granulation process, powder particles compacted by a force, causing adhesion. The powder would be dried and physically milled to form granules (Stutzman, 2020). Dry granulation is suitable in the case of APIs that are hydrophilic and sensitive to heat, which wet granulation cannot approach. Granulation is a more challenging process than direct compression because it requires higher techniques and more complex steps. Researchers need to consider the impact of high pressure from compaction machines whether it would induce physical or chemical change on APIs. However, the advantages of dry granulation cannot be ignored, especially involved roller compaction technology.

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2 DRY GRANULATION BY ROLLER COMPACTION

Roller compaction technology is considered a well-known and economic granulation method for drug development. Dry granulation is a continuous method with a low amount of energy required and suitable for compounds that are sensitive to heat (Peter et al. 2010). During the process of dry granulation, intragranular excipients would be compacted through a roller compaction machine and result in granules. Dry granulation has the same prior procedures with direct compression, but the resulting powder would continue to go through additional compaction and sequentially form dried granules. The most important parameters involved in this process are powder feeding, pressure control, roll surface, and gap region, which take place in the machine of roller compaction. The common way for manufacturing granulation is roller compaction, where the powder is compressed into a ribbon before segregation happens. The powder is fed into a feed hopper first and then passes through a tube named screw feeder. After that, particles with a bleed of the API and the excipients would load through two counter-rotating rollers within the compactor machine (Stutzman, 2020). Two rollers keep rotating in order to squeeze the powders within a small gap between rollers, generating a dried, solid ribbon. The solid ribbon is then milled into small fragments by crusher, blended with extragranular excipients, and given an end product of tablets by compressing the mixture, the process can be seen in Figure 1, raw material is fed into the machine with a final product of tablet (Hudon et al. 2019).

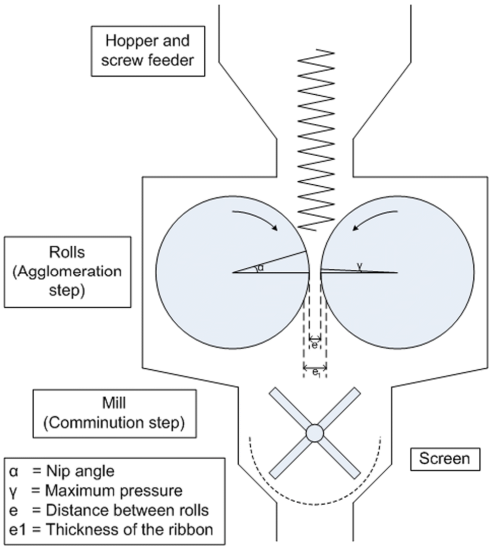

Figure 1: Process of roller compaction within the compactor.

Dry granulation by roller compaction is separated into two alternative steps. The first step is agglomeration started from putting the raw material into the machine. The flowing powder is passed through the feed hopper by using a feed screw to transport it into the rollers, result in a solid form of a ribbon. The second step is called the size reduction step which compresses the ribbon into granules (Teng et al. 2009). Each step plays an important role in the granulation process. Variation happens during the dry granulation that would affect the final quality of tablets. Granulator speed is a possible variable that would decrease the production of fine materials (Rana et al. 2011). By understanding the principles of compaction roller press, different zones are shown within the compactor, as can be seen from Figure 2. Two rotating rollers are the key point by applying a force to compact powder into the solid ribbon. Unique angle and specific shape of rollers that would allow producing the amount of solid product. During the agglomeration step, powder pass through the compaction zone starts at the first zone, the nip region. Particles within the power would break down under the force of two plates. Then, powders would be squeezed into small pieces of fragments under the pressure of two rolls. Fragmentation takes place in the roll gap and releases ribbon that bonds by dried particles into the next stage (Rana et al. 2011). In this whole process, the main compaction force is carried out by the two rollers as it solves the big problem about adhesion between particles.

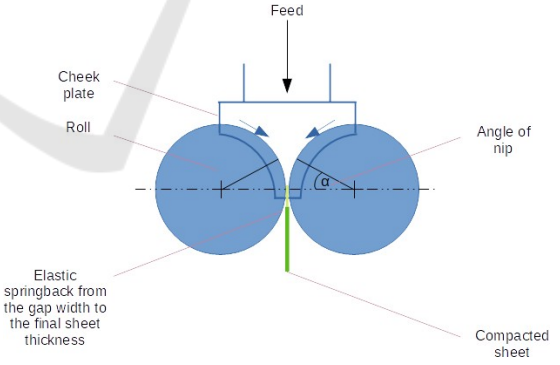

Figure 2: Compaction zone of two rollers within the compaction machine.

Instead of using liquid binders to stick each particle, dry granulation depends on the compound itself. During the compaction process, the power suffered from great pressure would become easier to be broken down. It has been indicated that materials pass through the two rolls which give a very high pressure, allowing to completely compact powder and result in dried flakes. Also, the smooth surface of

rollers is beneficial for particles sticking and reduced the use of lubricant. The different surfaces of rolls would have more or less gripping force for the compaction (Pietsch, 2002). The technology of manufacturing granules from raw material has been adapted to many industries since it was considered as an economic way. Researchers need to control parameters in roller compaction so that the machine would effectively produce tablets. The density of the ribbons is a relative parameter that has the ability to control the flowability of granules and the compactibility of final products (Peter et al. 2010). Many results show that a large density of the ribbon would manufacture a small number of fine granules after granulation, thus there would have a better flowability but a low rate of compactibility. Comparing the quality of granules with the products obtained from direct compression, there would be a reduction in tablet strength due to the loss of compactibility.

3 ADVANTAGES OF DRY GRANULATION

The most obvious difference between dry granulation and wet granulation is that dry granulation is not required for liquid content. The major advantage of dry granulation is that the process is suitable for the API or excipients which are sensitive to heat and moisture. This dry formulation of the drug satisfies the compound which has a low melting point or contains hydrophilic contents. Dry granulation is the benefit to the manufacturing industry which progresses a more economic and less equipment way compared with wet granulation. Another advantage of roller compaction is that the technique improves the flow properties of powders. Throughout many pharmaceutical applications, the main goal is to increase the flowability of medical powder to achieve a fast compressing of tablets. Researchers usually use the compressibility index to calculate the flowability of granules, with a method named The United State Pharmacopeia (USP) (Anshul et al. 2017). Results and data would then be collected from the compressibility index calculation by using the equation in Figure 3.

$$CI(\%) = 100 \times \left[\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}}\right]$$

Figure 3: An equation used to calculate compressibility index (CI).

The equation shows that bulk and trapped densities can be determined per the procedure within the USP. By calculating the compressibility index (CI) in a different situation, results indicate that the roller speed has an impact on CI. Variables include roller forces that would change the flowability, suggesting stronger ribbons produce by the strong roller forces (Anshul et al. 2017). Furthermore, roller compaction prevents particle segregation during the granulation. The process of granulation forces the powder to pass through two rotating rollers. By squeezing and milling the mixtures, the density of granules would increase so that each particle would stick to the other tightly (Rana et al. 2011).

4 DISADVANTAGES AND CHALLENGES

Roller compaction becomes a new trend in the drug manufacturing industry. Although dry granulation by roller compaction presents many benefits to the economy and productivity, there are still have some challenges that researchers need to overcome. One of the major challenges during dry granulation is the loss of compactibility in the double compaction (Heiman et al. 2017). Researchers found the details of the loss of tabletability by using microcrystalline cellulose (Sun et al. 2007). Granules size enlargement on tabletability would change the bonding within the tablets. In the paper of Sun and Changquan Calvin (2008), phenomenon of larger particles perform a lower tabletability after the granulation process has been addressed. To verify the phenomenon of loss of compactibility, Sieve analysis has been introduced which is a common method that used to detect the powder particle size. Levels of different variables in the designed experiments are showed in Table 1 (Herting et al. 2007). Experiments used fraction of Theo and porosity of the ribbons to obtain the levels of Microcrystalline cellulose (MCC) and theophylline (Theo) since MCCs affect the flowability of granules and Theo is another API ingredient used in particle size (Herting et al. 2007). Sieve method can divide granules in order to make a comparison between variables in the granules of roller compaction. The results of sieve analysis are usually presented in median diameter of particles (μm). Based on the results in Table 1, there was a relationship between Fraction of Theo and MCC, with an increasing percentage of fraction of Theo, the change on granules size enlargement influenced by MCC is less but significant (Herting et al. 2007). Subsequently,

the results shown that enlargement of granules also reduced the tabletability after the granulation process (Sun et al.2006). Therefore, granules size enlargement plays an important role in causing the reduced tabletability and this become one of the major disadvantages of roller compaction through dry granulation.

Table 1: Levels of variables for measuring the influence of particle size in the designed experiments.

Level	-1	-0.33	0	+0.33	+1
MCC (μm)	21	-	56	-	106
Theo (μm)	7	-	-	-	110
Fraction (%)	25	41.67	50	58.33	75
Porosity (%)	20	26.67	30	33.33	40

Other disadvantages including the process is too slow compare with direct compression. Direct compression has the same characteristic as an absence of liquid binder within the process. However, dry granulation has additional steps of transforming the raw materials into granules by go through the compactor. The machine would cost more money and time which is a burden for some drug industries.

5 CONCLUSIONS

In conclusion, the dry granulation technique has drawn the attention of many pharmaceutical industries because of the advantages of dry granulation by roller compaction compared with other compaction technology. The agglomeration step of drug formulation briefly illustrates how powder of APIs and excipients pass through the compactor and result in dried granules. During the dry granulation, the absence of liquid content gives a major advantage to this process which becomes suitable for heat and moisture products. Dry granulation also prevents particle segregation and contributes to flowability. Although the dry granulation process may lose tabletability, researchers still believe the process has the potentials to overcome the disadvantages.

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