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RESEARCH PAPER

Wet Spheronization by Rotary Processing—A Multistage Single-Pot Process for Producing Spheroids

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ABSTRACT

Spheronization is an agglomerative size enlargement process for producing spherical agglomerates that have many technological and therapeutical advantages. Rotary processing is an efficient multistage, single-pot spheroid production method. The rotary processor can be used for spheroid production, drying as well as coating. In the course of spheroid production, centrifugal, fluidizing, and gravitational forces act upon the product from different directions and collectively contribute to the spheroid formation process during rotary processing. The outcome of the process depends on the complex interactions between the equipment, formulation, and process variables.

Key Words: Rotary processing; Spheroids; Wet spheronization.

INTRODUCTION

Granulation, also known as pelletization, agglomeration, or spheronization, is a size enlargement process during which fine powders or particles are aggregated into small, free-flowing, spherical and/or semispherical units that are referred to as granules, pellets, agglomerates, or spheroids.[1] For pharmaceutical purposes, useful agglomerates range from about 0.5 to 1.5 mm as they are usually intended for oral administration.

The general terms ‘‘granulation’’ and ‘‘pelletization’’ are sometimes used synonymously and no clear distinction is made between them. Generally, if a size enlargement process produced agglomerates of a wide size distribution within the range of 0.1 to 2 mm, the process may be called granulation. Pelletization is often referred to as a size enlargement process that involves the manufacture of agglomerates with a relatively narrow size range, usually with mean size from 0.5 to 2 mm.[2] Spheronization is a more specific term usually associated with spherical units formed by a size enlargement process that includes a spheronization step where extrudates or agglomerates are rounded as they tumble on a rotating frictional base plate. Due to the spheronization step,

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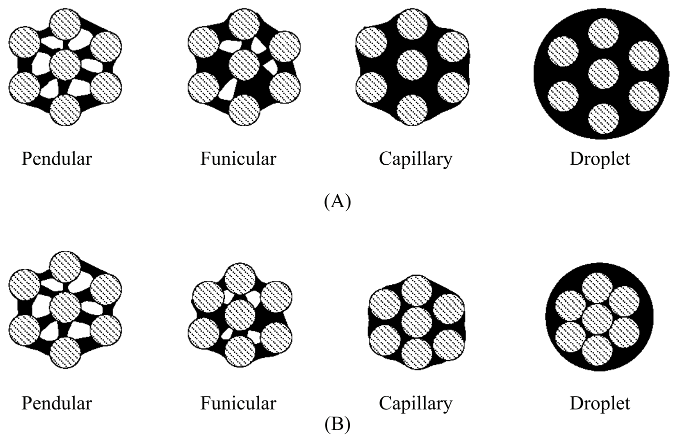

Figure 1. Changes in states of liquid saturation caused by (A) addition of binder liquid or (B) densification of the agglomerate (□ Air, ■ Liquid, ▨ Solid).

spheroids normally have optimal mean size, uniform size distribution, and highly spherical shape when compared with granules or pellets.[3] During spheronization, powders are converted into spheroids with certain properties that are suitable for use as the final product or for further processing by coating. The highly spherical shape of spheroids confers certain technological advantages. The technological advantages of spherical particles include the following:

1. Good flowability due to uniform size and spherical shape. This allows accurate capsule filling with minimal unit dose variation.
2. High physical integrity of spherical agglomerates. For spheroids, flow with minimal friction and dust generation during processing is expected as compared to flow of other powders or granules.
3. Superior qualities for coating application due to spherical shape, low surface area to volume ratio, smooth surface, and ability to withstand mechanical stresses.

Spherical granules or spheroids have become more popular in the pharmaceutical industry as a result of increased interest in multiparticulate dosage forms for controlled drug delivery.[4] Controlled-release oral solid dosage forms are usually products with drugs intended for delivery either at a specific site within the gastrointestinal tract or over an extended period of time. For controlled release spheroids, the desired goals mentioned can be achieved through the application of a drug release-limiting coating or by the formulation of matrix spheroids. These multiparticulate dosage forms are also known as multiunit doses. Multiparticulate drug delivery systems can be prepared by blending particles containing drugs that may not be chemically compatible or containing the same drug but with different release rates in an appropriate ratio to achieve the desired overall drug release profile. These delivery systems may affect drug release at the same site or at different sites within the gastrointestinal tract. Modified-release multiparticulate dosage forms prepared using spherical particles have several therapeutic advantages over single unit dosage forms such as tablet or powder-filled capsule dosage forms.[5] Some examples of therapeutic advantages are listed below:

1. Spherical particles can disperse freely throughout an area of the gastrointestinal tract after consumption. The drug will be released over a wider area. Drug absorption is maximized as a large gastrointestinal surface can be involved in the absorption process, assuming uniform drug absorption throughout the gastrointestinal tract.
2. Peak plasma level of the drug can be reduced by the use of spherical particles with different release rates. Potential side effects are minimized without markedly lowering drug bioavailability.
3. The wide distribution of spherical particles in the gastrointestinal tract limits localized buildup of the drug. Dangers of mucosa lining damage caused by certain irritant drugs can be alleviated.
4. Modified-release multiparticulate delivery systems are less susceptible to dose dumping than single-unit dosage forms.[1,6]

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Several manufacturing techniques are used for producing spherical particles. Broadly, they can be grouped in different ways, according to the type of equipment used, the intensity of mechanical forces involved, or the production techniques of the spherical particles.[1] The outcome of the process depends on complex interactions between the equipment, formulation, and process variables.[7−9] One of the more recent methods for the production of spheroids is rotary processing, where the whole cycle of wet spheronization, drying, and coating can be performed in one closed system.[10−19] Centrifugal granulator, rotary fluidized bed granulator, rotary fluid bed, rotary processor, and rotor granulator are some of the terms used to describe this single-pot spheronizer system.

The process of spheroid formation is identical with the wet granulation process, requiring the moistening liquid. The surface energy in a three-phase system of solid, liquid, and gas tends to be reduced by the formation of liquid bridges between the particles.[20] The states of liquid bridging depend on the liquid saturation of the agglomerate expressed as the ratio of pore volume occupied by liquid to the total volume of pores within the agglomerate. The liquid saturation is affected by the amount of binder liquid presented and the intragranular porosity. A state of liquid saturation can be brought about by gradual addition of liquid or a combination of liquid addition together with bulk densification (Fig. 1). Liquid saturation can be classified into four stages, namely, pendular, funicular, capillary, and droplet stages.[21,22]

This article will review the equipment, formulation, and process parameters that may influence spheroid properties in the process of rotary spheronization.

EQUIPMENT USED DURING WET SPHERONIZATION BY ROTARY PROCESSING

The rotary processor was modified from the conventional fluidized bed granulator, as granules formed by the top spray fluidized bed granulation method were usually not highly spherical and had comparatively lower densities.[18] A rotating plate granulator combines centrifugal, high intensity mixing with the efficiency of fluid bed drying. The basic design of the modified fluidized bed equipment includes air handling system, rotating plate, product chamber, extension chamber, and spray system.

There are three better known manufacturers of rotary processors: GEA-Aeromatic, Glatt Air Technique, and Vector/Freund Corporation.[23] The basic designs of these units contain some very different features. The prototype of this equipment was first developed in the 1970s.[13] The progressive changes and modifications to the basic design resulted in the rotor granulator (Glatt), roto-processor (Aeromatic), spir-a-flow (Freund), and centrifugal granulator (Freund).[13] For some designs, drying may not be possible since the centrifugal-granulators were not enclosed in a fluidized bed system.[24] The width of the gap between the rotating plate and chamber wall and the height of the rotating plate may be adjusted in some models to provide a control of the air velocity without involving a change in the air volume.

The rotary processor may be used for producing spherical particles, via several processing techniques such as powder layering, solution layering, and wet spheronization, as well as for coating. In recent years,

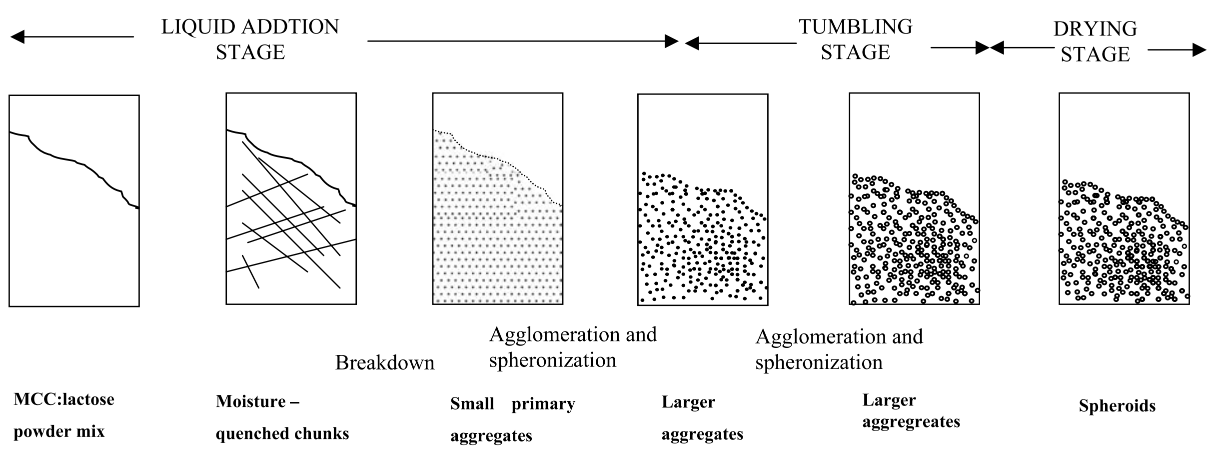

Figure 2. Schematic diagram reprsenting proposed mechanism for spheroid formation and growth during single-step spheroid production by rotary processing. (From Ref. [22].)

there had been comparatively more intensive rotary processor studies on wet spheronization than on powder layering techniques. The formation of spheroids by wet spheronization in rotary processing consists basically of three stages: liquid addition, tumbling, and drying (Fig. 2).[25] It involves the conversion of a powder mix into spheroids by the spraying of a moistening liquid onto the powder mass while it moves in a coil-wreath shaped or rope-like motion. During rotary processing, three forces (centrifugal, gravitational, and fluidizing) act on the product from different directions. The centrifugal forces are generated from the revolution of the rotating plate and tend to push material towards the wall of the processing chamber at the periphery of the rotating plate.[6,26] Incoming air from the gap between the rotating plate and wall aids the upward movement of material. As the lift velocity exerted by the airflow above the gap dissipates with distance, the material loses its upward momentum and cascades downwards and inwards due to gravitational force. The centrifugal force is a function of the rotational speed of the plate while the vertical distance transversed by the particles in the tumbling mass depends on gap air velocity and bulk volume of the powder mass. The combined action of the three forces produces a rope-like tumbling motion of the moistening powder mass on the rotating plate. A rapid turnover production rate is responsible for the high production efficiency of the equipment. The spray gun is located at the lower portion of the wall such that it is fully immersed in the spheronizing powder mass. With a tangential spray mode, spray droplets travel in a tangential path concurrent to the motion of the material on the rotating plate. Agglomeration proceeds with the addition of the atomized moistening liquid onto the revolving material. Dense spheroids of narrow size

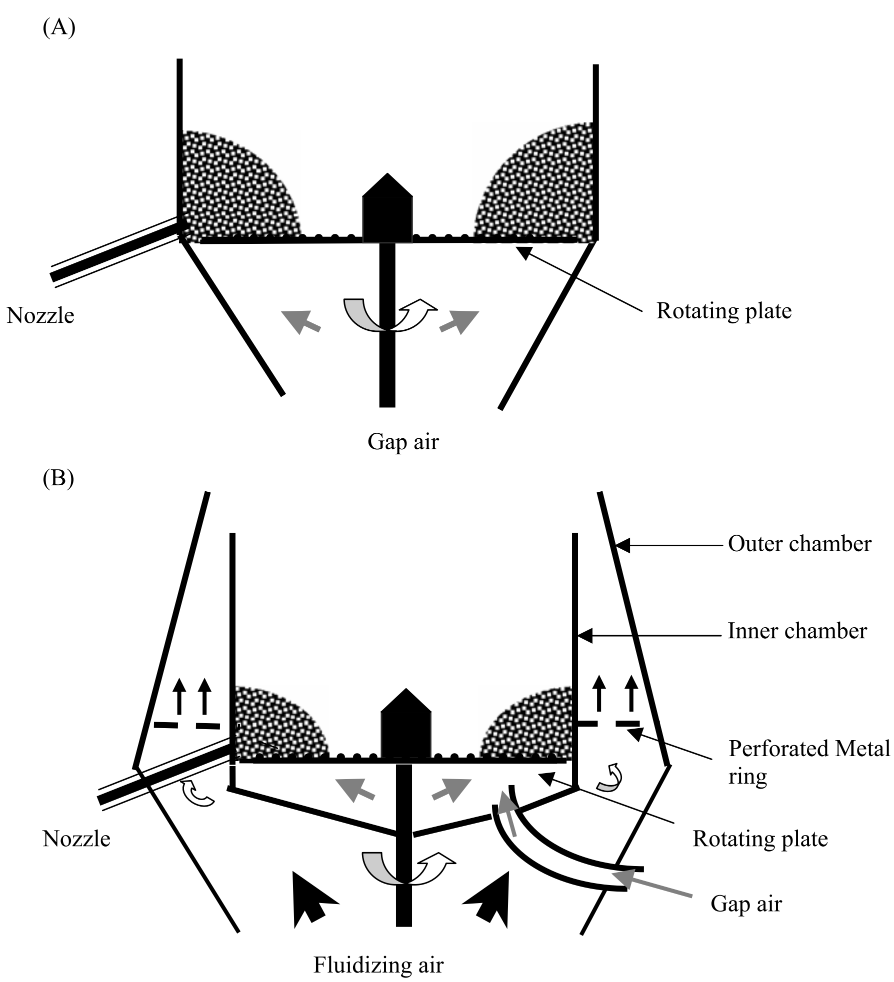

Figure 3. Schematic diagram of single chamber (A) and double chamber (B) designs of rotary processor. (*View this art in color at www.dekker.com.*)

distributions can be prepared by rotary spheronization.[27–29]

Chamber Design

The rotary processor can be considered as a hybrid of a fluidized bed and a spheronizer. There are two basic designs, single chamber and double chamber systems (Fig. 3). The single chamber processor is comparatively simpler in design. However, drying and coating are to take place within a single chamber processor, and the limited drying capacity of the processor extends the processing time considerably, especially with coating applications. Some of the single chamber processors have the motor housing separated from the processor itself. The double chamber design is more complicated but offers the flexibility of drying of spheroids and even spheroid coating. The rotary processor with a double chamber design consists of an inner metal chamber housed inside a larger outer chamber. The rotating plate resides within the inner chamber, with a narrow gap between the base plate and inner chamber wall. A perforated metal ring encircles the circumferential area separating the two chambers. Fluidizing air may be introduced into the outer chamber via the perforations on the metal ring. Drying of spheroids after preparation may be affected by lifting the inner chamber pneumatically, thus presenting a gap for spheroids to move to the outer circumferential area to be dried by the fluidizing air. The second chamber equipped the rotary processor with a highly efficient fluidized bed drying capacity.

Rotating Plate Design

The uniqueness of the rotary processor lies mainly with the rotating plate. In the absence of specialized tools for mixing and breakdown of agglomerates, material movement in the processor relies largely on the forces set up by the rotating plate to bring about liquid distribution and mixing during the liquid addition stage in spheroid production.

The surface of the rotating plate may be specially designed to meet specific applications. In cases when the rotary processor is used for powder layering with nonpareil seeds or coating with core spheroids, rotating plates used are those with smoother surfaces or completely smooth plates instead of plates with protuberances required for spheroid production. The reason for the use of smooth surface plates is that nonpareil seeds and core spheroids generally have better flow properties than fine powders and are able to tumble in a rope-like motion on plates with smooth surfaces. A smooth plate is also best for avoiding material adhesion but it does not supply sufficient shear for effective spheronization.[30] Patterned plates can supply higher shear but have a greater tendency to cause material adhesion. Surface pattern of the rotating plate is an important design consideration for a spheronizer. In conventional extrusion-spheronization, rotating plates with grooved surfaces are used to aid break up of rod-shaped extrudates and to reshape the short rods into spheres.[3,31] The edges on the grooves facilitate the initial cutting up of extrudates to form shorter and almost uniform length segments. The cross-hatch pattern (Fig. 4a), where grooves vertically intersect each other, is a common plate design. For plates with grooves arranged in a radial pattern (Fig. 4b), radiating grooves move outwards from the center with increasing distances between them. The manufacture of these radial patterned rotating plates is technically more difficult and costs more. However, it is claimed that the application of frictional forces from a radial patterned rotating plate is more uniform over the rotating powder mass, and energy transfer is greater.[32]

For rotary processing, a rotating plate with protuberances on the surface was also required. However, the edges of these protuberances need not be angular. Studs with a smooth but undulating design are desirable as the production of rotary processed spheroids does not involve an extrusion stage and there is no necessity for cutting up extrudates during spheronization. Studs described as pyramidally shaped elevations (Fig. 4c) or square studs with rounded edges positioned in a cross-hatch pattern on the surface of the rotating plate have been used in spheroid production by rotary processing.[25,28,29,33–35] With symmetrical studs on the plate, moist materials have a tendency to be trapped in the valley between two adjacent studs and around the wake region of the stud as the powder mass slides over. Following these observations, teardrop-shaped studs (Fig. 4d) were designed such that they provide the necessary shear force with minimal material adhesion for wet spheronization.[36,37] Due to their asymmetrical, streamline, and tapering nature, these teardrop shaped studs limit adhesion to the valley area at the stud head where stud height and width are at their largest dimensions.

The rotating plate can be made of stainless steel or polytetrafluoroethylene (PTFE). The PTFE rotating plate produced higher spheroid yields compared to the stainless steel rotating plate.[38] However, a stainless steel rotating plate (Fig. 4e) allows for greater heat conduction, and consequently gives rise to better drying of the mass compared to a PTFE rotating plate.[38]

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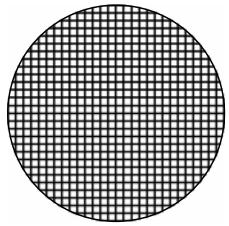
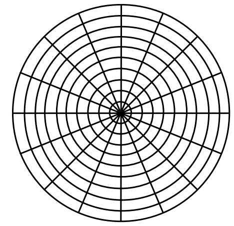
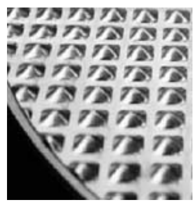



(a) Studs in cross-hatch pattern (b) Studs in radial pattern




(c) Pyramidally shaped studs in cross-hatch pattern (d) Teardrop shaped studs in radial pattern

(e) Smooth surface plate with wide spaced baffles

Figure 4. Depiction of rotating base plates with different designs of surfaces. (*View this art in color at www.dekker.com.*)

Agitator Blade, Baffle, and Chopper

Besides a rotating plate, an agitator blade may be added to a rotary processor to exploit the combined advantages of high shear mixing and fluidization techniques.[39–42] The addition of an agitator blade introduces a tumbling and compacting action to the conventional fluid-bed system. This facilitates the production of spheroids of higher densities due to an increase in the magnitude of shear forces involved and can also prevent lumping formation.[23] Two baffles were installed to ensure that the powder mass traveled in a tumbling rope-like motion on the rotating plate.[43–45] The first baffle directed the upper part of the powder mass downward to the rotating plate and inward toward the center of the inner chamber, thus prevented the division of wetted powder mass into two parts moving at different speeds. The second baffle guided the material toward the center of the inner bowl. The baffles, together with the PTFE lining of the inner wall, ensured a coil-wreath shaped movement of the moist mass in the inner bowl. The idea of using a chopper to prevent localized overwetting and to facilitate breakdown of large agglomerates into smaller fragments has been investigated. The chopper was found to have no significant influence on mean size, size distribution, and amount of agglomerates. The optimal spiral, rope-like movement of the moistened mass ensured the orderly movement and spread of moistening liquid over the powder mass, making the use of a chopper superfluous.[43]

Polytetrafluoroethylene Lining

Several investigators have described the use of PTFE in high shear mixers for reducing adhesion of moist material on granulator walls.[9,46–50] Polytetrafluoroethylene was also widely used in lining the product chamber wall to reduce material adhesion during wet spheronization by rotary processing.[25,33,43,44,51–54]

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Without the PTFE lining, part of the moistened powder mass occasionally formed stationary layers or cakes that periodically detach from the wall and return to the wet mass undergoing spheronization. These pieces can become the cores for lump formation.[25,33] This phenomenon is undesirable as it gives rise to product yields with wide size distributions. A removable PTFE film formed by applying PTFE tap onto the chamber wall had the disadvantage of dislodging from the wall after several runs when materials slipped underneath and loosened the film. A permanent PTFE coating is thus preferred when compared to an applied-on tape.

The PTFE lining influenced the quality of spheroids produced using starting materials of different particles.[25] The effect of the PTFE lining was found marginal for formulations containing 200-mesh lactose. For the coarser 100-mesh lactose, larger spheroids were formed at equivalent moistening levels when the chamber wall was lined with PTFE tape. The spheroids made from microcrystalline cellulose (MCC) and 100-mesh lactose agglomerates are more fragile than those made from MCC and 200-mesh lactose. The softer, low friction, and nonstick properties of the PTFE lining made the chamber surface impact by spheroids made of MCC and 100 mesh lactose less likely to fragment on collision and thus enabled them to grow to a larger mean size.

PARAMETERS INFLUENCING THE PROCESS AND FINAL SPHEROID QUALITY

Rotary spheronization shares many similarities with fluid-bed granulation and with the spheronization stage of the extrusion-spheronization process. Formulation and processing variables that influenced fluid-bed granulation and spheronization, such as moistening liquid type and content, MCC type and content, filler type and particle size, drug particle size, speed of rotating plate, spheronization time, moistening liquid addition rate, atomizing and gap air pressures, and load size also affected the rotary spheronization process.[6,10,14,34,44,45,52,55]

Moisture Content of Wet Mass

The most critical and influential variable for spheroid growth was the amount of liquid binder present for wet spheronization.[3] Some studies had demonstrated the importance of the amount of moistening liquid in controlling size, size distribution, shape, friability, and other physical characteristics of spheroids produced by rotary processing.[34,36–38,44,51,55,56] Water content can be calculated based on dry mixture[25,28,29,33,38,55] or water/MCC ratio since MCC was used as the spheronization aid in many studies.[51–54] With an increase in the amount of moistening liquid, there was an increase in the liquid saturation of spheroids. More moisture was available for the formation of bonds between particles. The presence of surface moisture improved particle surface plasticity and aided the deformation and coalescence of particles during collisions. Consequently, the moistened particles agglomerate and consolidate to form spheroids. The surface plasticity enhanced deformation, assisting the rounding of spheroids.[1,28] With the increase in water-MCC ratio, spheroid mean size increased and spheroids produced were less friable but of wider size distribution.[44,52]

The moisture content of wet mass should be precisely controlled within very narrow limits to ensure the production of spheroids of appropriate size and size distribution. The amount of moistening liquid added should reach the required level so that spheroids with a suitable mean size can be obtained.[55] When too much moistening liquid was added, a large amount of undesired, oversized lumps was produced due to a less controlled agglomeration. The products had a skewed size distribution. The quantity of water to be added should take into consideration the moisture contents of the starting materials, which depended on storage conditions prior to usage. During the water addition phase, a small proportion of the added water will be removed by the gap and atomization air streams.

Physical Properties of the Starting Material

Rotary processing was found to be affected by formulation variables such as MCC type and content, type of filler, and particle size of constituents.[34,44,45,52,55] The unique properties of MCC made it a very efficient spheronization aid for spheroid preparation by rotary processing and extrusion-spheronization.[57] Microcrystalline cellulose can be used with or without additional binding agents.[58] It is available in various powdered and colloidal grades from several suppliers. Among all types of MCC supplied, Avicel PH 101 is the most commonly used grade.[19,25,28–30,33,36,37,39,45,51–54,57,59,60] Avicel RC-581 and CL-611 grades had been used for producing spheroids but no difference of mean size and size distribution of spheroids produced was seen between grades.[38] Emcocel 50M was also successfully used.[55]

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Three grades of MCC were used to prepare theophylline spheroids, and the differences of MCC in the formation of spheroids and the effects on spheroid quality were investigated.[61] The spheroids were characterized by size, density, friability, flowability, drug content, and shape. Only minor differences were seen during processing. Avicel PH 200 was slightly superior in the ability to successfully form theophylline spheroids (83% success rate) to Avicel PH 101 (75% success rate) and PH 200 was about equal to PH 102. Holm found there was no difference in porosities of spheroids prepared using different MCC grades.[62]

The MCC content had the most significant impact on spheronization efficiency. The amount of MCC required depended on the other components in the formulation.[34] The working range of MCC content can be as low as 10% of the total starting materials.[34,61] However, a controllable spheronization process for producing spheroids with consistent and acceptable characteristics required the content of MCC to be at least 20% (w/w) of the starting materials.[57] A decrease in the proportion of MCC resulted in higher deposition and adhesion of moistened material, the formation of large, irregularly shaped lumps, and augmentation of electrostatic charges causing material to stick on the product container.[45] The amount of MCC present was found to influence the mean size, size distribution, friability, and shape of spheroids produced by rotary processing.[14,38,44,52] Increased MCC content led to a narrowing of spheroid size distribution and increased mean size and sphericity but decreased spheroid friability.[34,35] However, porosity of the final product was not influenced by the amount of MCC in the formulation.[62] The MCC content was also found to play the most dominant role in determining the overall dissolution rate of a very slightly water soluble drug administered in low doses.[51]

Fillers were also incorporated into the spheroids, although many formulations contained only the model drug and MCC.[30,61] Lactose was shown to be more suitable as a substitute for a portion of MCC than mannitol or calcium carbonate.[45] The formulation containing calcium carbonate produced a wet sticky mass while mannitol gave rise to larger granules with a more evident development of electrostatic charges. Lactose 200 mesh was most commonly used in related studies.[25,28,29,33,55,57] It was found that formulations containing lactose were more sensitive to small changes in moisture content and speed of rotating plate than those containing dicalcium phosphate.[34] The aqueous solubility of lactose enhanced the binding properties of the moistening liquid and plasticized the moistened mass, thereby increasing the potential for granule growth with small moisture increment. Lactose formulations had lower porosities in the final product as they were more easily densified to a lower level of porosity than formulations containing dicalcium phosphate.[35]

The mean particle sizes of the drug and filler also affected the spheronization process. In MCC and theophylline binary system, finer grades of theophylline were more difficult to spheronize than the coarser grades. Only the coarsest grade of theophylline formed spheroids containing 90% drug.[61] However, the particle sizes of lactose or dicalcium phosphate did not have any influence on the porosity of the resultant spheroid products.[35]

Type of Moistening Liquid

Purified water was the most commonly used moistening liquid for formulations containing MCC as a spheronization aid in rotary processing.[25,28,29,33,44,51,52,55] Binders are usually not incorporated, as the addition of MCC provides sufficient adhesive strength for forming agglomerates. However, researchers had attempted to incorporate various binders in the moistening liquid in addition to MCC. Aqueous polymer solutions/suspensions containing Eudragit NE 30D,[30] hydroxypropyl methyl cellulose (HPMC),[38] polyvinylpyrrolidone (PVP),[14,58] and gelatin[14] had been used in the moistening liquid. Polyvinylpyrrolidone was reported to produce spheroids of higher sphericity when compared with gelatin.[14] As a binder, HPMC improved product yield.[38]

Speed of Rotating Plate

The speed of the rotating plate can be kept constant during the whole process run, and the speed used affected spheroid particle size.[14,34,38,44,51,52] Some studies showed that spheroid size increased with an increase in rotating speed,[33,36,37] but contrary results were also reported.[63] A possible explanation for these contradictory findings was attributed to differences in methods and/or equipment used. For successful spheronization, there has to be a balance between the agglomeration of powder particles and the breakdown of large oversized agglomerates or lumps. Strong centrifugal forces can supply sufficient energy into the system to bring about coalescence, and these forces can concurrently contribute to size reduction of large opportunistic quenched aggregates developing by attrition or breakage. A low-high-low speed variation protocol was developed to produce spheroids with a narrow size distribution and with a minimum amount of oversized particles in the total product yield.[33,36,37]

Higher speeds have been reported to give rise to spheroids of narrower size distribution,[34] slightly wider size distribution,[44] higher sphericities,[52] lower friability,[44] smoother surface,[52] reduced pore volume,[53] higher crushing strength, and greater total spheroid yield (but lower useable yield).[14] When a high rotating plate speed was used, improved liquid addition would reduce lump formation, and thus, fewer lumps and a narrow size distribution spheroid batch were produced. In cases where the resultant spheroids are more fragile, high rotating plate speed may result in increased breakdown of the spheroids and wider size distribution may be resulted. Lumps were formed at the low rotating speed during the wet massing phase as wetted material adhered to the plate due to lower centrifugal forces and less impact of the mass.[34] Rotating speed was also found to have a major influence on the overall dissolution rate since overall dissolution rate was linked to spheroid size.[51]

An interrelationship between the surface of the rotating plate and rotating speed has also been observed.[38] With a textured surfaced rotating plate, an increase in rotating speed produced spheroids with smaller size, lower sphericity, and rough surface. Larger, more spherical and smooth-surfaced spheroids were produced with an increase in speed when a smooth surfaced rotating plate with wide spaced baffles was used.

Spheronization Time

Spheroid size was found to be related to spheronization time[14,33,34,36–38,44] Extended spheronization time resulted in spheroids with narrower size distribution,[34,44] higher sphericity shape,[44,52] lower friability,[44] smoother surface,[52] reduction in pore volume,[53] and higher crushing strength.[14]

Moistening Liquid Addition Rate

It was found that the most critical and influential variable for granule growth was the amount of moistening liquid present after liquid addition.[14,51] A higher liquid addition rate increased spheroid crushing strength and ''useable'' yield (0.25–1 mm fraction). It was reported that the water addition rate had a considerable influence on the size and size distribution of spheroids prepared using a rotary processor.[44,45] Spheroid size was found to increase with increased spray rate when atomizing pressure and amount of moistening liquid delivered were kept constant.[29,34,45] If the level of agitation forces in the rotary processor was insufficient for ensuring a spiral, rope-like material movement, lower water addition rates enabled sufficient time for adequate spreading of the moistening liquid.[43] Inadequate spreading of the water added influenced the spheroid formation process. Regions with excessive amounts of water contributed to the formation of larger agglomerates. In addition, the influence of water addition rate on spheroid size was compounded by differences in the amount of water removed by the air streams. Increasing the water addition rate decreased the process time, and less water was removed by gap air. Consequently, more water remained in the formulation at the end of the water addition phase.[28,54] The amount of water removed from the agglomerating powder mass by the gap air and nozzle atomizing air can be estimated from the flow rate, temperature, and relative humidity measurements of the air stream and moisture content of the final product. With a fixed volume of moistening liquid sufficient for spheronization, larger spheroids were produced with increasing liquid addition rates.[29] With a constant atomizing air pressure, the atomized droplets became larger and had a wider size range when liquid addition rate was increased. The amount of oversized agglomerates was increased and a less uniformly sized yield may be produced with the use of relatively higher spray rate. However, changes in spray droplet size and size distribution attributed to variations in water addition rate may be offset by other spheroid parameters. As such, the effect of spray rate had also been found to be comparatively minor and overshadowed by the prevalent centrifugal forces.[37,55]

Atomizing and Gap Air Pressures

Higher atomizing pressures produced relatively smaller droplets with the same water addition rate and the range of droplet sizes tended to be narrower.[29] Changes in spray droplet size and atomizing pressure did not appear to greatly affect mean spheroid size.[29,58] However, the presence of an atomizing pressure was necessary and it should be maintained at an optimal level sufficient for the even dispersion of the moistening liquid to reduce both localized overwetting during spheronization and the amount of oversized particles formed. Excessively high pressures could disturb the material rope-like flow pattern. Small amounts of the material could also be entrained by an atomizing air if the pressure is too high.[30] At the start of a spheronization run, a positive gap air pressure is required to prevent powder slippage between the rotating plate and wall of the production chamber. Higher gap air pressure was reported to result in a greater rate of moisture loss, increased attrition of spheroids, and the production of smaller spheroids.[28,54]

Load Size

Depending on the equipment type, various load sizes, from 0.5 to 10 kg, had been used for spheroid production.[30,38,57,63] For example, in one study, 12-inch and 19-inch roto inserts were used for 1-kg and 5- or 10-kg loads of starting materials, respectively.[38] An increase in load size from 0.5 to 1 kg improved size distribution, yield, bulk density, and shape of spheroids produced in a 3.5-L rotary processor.[14] The design and size of the rotating plate also determined load size. With teardrop-shaped studs, the centrifugal forces supplied by a plate with shorter stud height may not be sufficient for supporting a high load of starting materials.[36]

Endpoint Monitoring

The identification of the spheronization endpoint in rotary processing appears to be critical to the success of the operation.[14] The moisture content of the product could be controlled in several ways. The first method attempted was to carefully control all factors influencing the rate of evaporation during liquid addition, such as product temperature, air flow to process unit, humidity of inlet air, and moisture content of starting materials.[34] The moisture removed by the atomizing air, gap air, and fluidizing air should be considered.[28] The second method studied involved monitoring the moisture content with the help of an infrared moisture sensor.[39] Another method proposed for determining the endpoint of wet spheronization in a rotary process was by measuring the torque and terminating liquid addition once a certain increase in torque value had been obtained.[57,59] The use of torque increase measurements was found to be suitable for predicting the stage of spheroid production in rotary processing because the water content of the mass was reflected by the torque value. Variations in moisture content of the materials being processed can be compensated for by adding an amount of liquid to reach a certain level of torque. As torque measurements were found to be influenced by the rotating speed of the friction plate and by batch size, a correlation was reported between torque increase and spheroid size if other process variables were kept constant.[57] Power consumption can also be used to monitor the endpoint of liquid addition.[62] The level of power consumption after liquid addition correlated with the mean size of the final product.

CONCLUSION

The process of converting powder into highly spherical spheroids in a single pot processor is a very efficient and attractive spheroid-making method. However, for the process of random opportunistic growth to be harnessed, stringent control in a predictable manner of all critical variables is needed. When all formulation and operational variables are well controlled, spheroids of high quality can be produced. Of the many variables, process variables such as the speed of rotating plate and rate of addition of the moistening liquid can profoundly influence the process and quality of the end product. The total volume of the moistening liquid added needed to be precisely controlled, taking into account the moistening liquid loss to the gap air. Factors that affect the flow of material undergoing moistening rotation in the rotary processor will undoubtedly have their influences, and these included the type of protuberances on the rotating plate, size of load added, and flow properties of starting materials used. The on-going studies in rotary processing will provide a better understanding of the spheroid-making process, and improvements in the processing methods, feed materials, and hardware can be made to enhance the robustness of spheroid production by rotary processing.

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