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THE ROLE OF MOISTURE AND GAP AIR PRESSURE IN THE FORMATION OF SPHERICAL GRANULES BY ROTARY PROCESSING

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ABSTRACT

Spheroids are usually produced by a multi-step extrusion-spheronization process. The single-step production of spheroids may be carried out in a rotoprocessor. The use of feed materials in powder form requires an adaptation of the spheronizer machinery. This study investigates the formation and growth of spheroids and the changes in the spheroid moisture content in a single-step agglomeration-spheronization method. There was a rapid increase in size and formfactor values when spheroids started to form and grow from the powder mix. Although there was a continual and considerable loss of moisture with time, this did not have an appreciable effect on spheroid size and shape after the spheroid formation stage as the spheroid structure had already been determined. Spheroid size increased with higher liquid spray rates. The use of higher gap air pressures resulted in a greater rate of moisture loss and the production of smaller spheroids.

INTRODUCTION

Spherical granules have many advantages in the pharmaceutical industry (1,2). Besides their superior flow properties, the spherical shape allows for the application of a uniform layer of coating. The widely-known process for the production of spheroids is a multi-step operation. It generally involves four stages, i.e., granulation, extrusion, spheronization and drying.

The use of 'a rotoprocessor in the production of spheroids had been reported by Robinson and Hollenbeck (3). In a single-step procedure, the whole operation of spheroid formation, drying and coating may be confined to a single equipment. Spheroids are formed directly from materials in the powder form by an agglomeration-spheronization process. The powder handling capacity requires a modification of the spheronizer chamber. A positive pressure must be maintained between the annular gap to prevent powder slippage between the frictional plate and the rotor housing.

This study investigated the changes in spheroid characteristics with time during spheronization in the single-step rotoprocessor. The role of moisture and the influence of gap air pressure were also studied.

MATERIALS

Lactose monohydrate (Pharmatose 200M, De Melkindustrie Veghel, The Netherlands) and microcrystalline cellulose (MCC; Avicel PH-101, Asahi Chemical, Japan) were used as supplied. Distilled water was used as the moistening liquid.

METHODS

Preparation of Spheroids in the Rotoprocessor

MCC and lactose (1:3) were dry-mixed in a laboratory double cone mixer (J. Engelsmann A.G., JEL, Germany) for 30 minutes. A powder mix of 500 g was then transferred to a rotoprocessor (Niro Aeromatic, MP-1, Switzerland). The frictional plate had a cross-hatch design of square studs with rounded edges (diameter, 9 mm; height, 2 mm) arranged in a 10 mm square grid pattern at alternate intersections. It had a diameter of 30 cm and was spun at 480 rpm.

The moistening liquid was sprayed onto the rotating powder mix at a rate of 20 mL/min using a peristaltic pump (Watson Marlow, 503S1, U.K.). The atomizing pressure was set at 0.8 bar. Unless otherwise stated, a gap air pressure of 0.8 bar was used. The inlet air temperature was set at 30°C.

The changes in spheroid size, shape and moisture content with time during spheronization were examined. Samples of spheroids (about 10 g) were removed periodically during spheronization runs, beginning with the sample collected immediately after spraying was completed. Not more than seven samples were collected from each run.

Several runs were carried out at various spray rates to determine the effect of liquid spray rate on the spheroid size.

In the investigations on the effect of varying gap air pressures, samples were collected when the process was stopped 20 minutes after the complete addition of water.

Spheroid Characterization

Moisture Content Determination - Samples of spheroids were collected on pre-weighed petri-dishes. The initial weights of petri-dishes with samples were noted before the samples were dried at 115°C for 4 hours. The samples were then cooled to room temperature in a vacuum chamber. The dried samples were re-weighed. The difference in the initial and final weight of a sample represented the amount of moisture lost. The moisture content is the quotient, expressed as a percentage, of the amount of moisture lost and the weight of the dried sample. The moisture content of the powder mix was also similarly determined. It was found that the powder used for spheronization contained 1.34% w/w moisture. Therefore, it was necessary to correct the moisture content attributed to the granulating liquid by subtracting the basal moisture content.

Size Analysis by Sieving - A nest of sieves (Endecotts test sieves, England) was used to separate granules into various size fractions. The mass median diameter is the diameter at the 50 percentile mark on a cumulative percent oversize plot.

Image Analysis - At least 60 dried spheroids were randomly selected for image analysis. The image analyzer (Dapple System, Imageplus, U.S.A.) consists of a computer system connected to a videocamera mounted on a stereomicroscope. The perimeter, area, length and breadth of the spheroids were obtained from their digitized images. Formfactor and size values were derived from these basic parameters. Formfactor measures the degree of spheroid sphericity. A perfect circle has a formfactor value of unity.

$$\text{Formfactor} = \frac{4\pi(\text{Area})}{(\text{Perimeter})^2}$$

Spheroid size is the average of the spheroid length and breadth.

RESULTS AND DISCUSSION

Spheroid Formation and Growth

In the formation of spheroids by the extrusion-spheronization method, the granulation, extrusion and spheronization processes are three separate but consecutive stages. The powder mix was first granulated with a moistening agent before extrudates could be formed. These extrudates were then spheronized to produce spherical granules. In the rotoprocessor, spheroids are formed directly from a powder mix by an agglomeration-spheronization method. The intermediate extrusion stage was omitted. Unlike the extrusion-spheronization method, the granulation and spheronization stages were not distinctly demarcated as the process was a single-step procedure.

During the liquid addition phase, the moistening liquid wets the powder particles. This gives rise to the formation of liquid bridges between the particles (4). When a low volume of moisture was added, there was inadequate interparticulate binding. With an increase in the amount of moistening liquid, there was an increase in the liquid saturation of the granules (5). More moisture was available for the formation of bonds between the particles. This increases the strength of the particulate mass. The presence of surface moisture improves particle surface plasticity. It aids the deformation and coalescence of particles during collisions. Consequently, the moistened particles agglomerated and consolidated to form granules. The surface plasticity also assists in the rounding off of granules. In preliminary investigations on the amount of moistening liquid required to form spheroids for this study, an increase from 10% to 40% water was found to be sufficient for transforming the powder mix from a powdery state to a granular mass suitable for spheroid production (Figure 1).

After the liquid addition phase, mean spheroid size continued to increase rapidly (Figure 2a). Besides agglomeration due to coalescence of spheroids, size reduction of granules may also occur. These two different mechanisms counteract each other and determine the extent of spheroid growth. The predominance of coalescence by collisions of spheroids in the presence of sufficient moisture favored spheroid growth. Simultaneously, the rolling motion of granules on the rotating frictional plate and the spheronizer wall supported the smoothening of granule surfaces as shown by the rising formfactor values of spheroids which were collected after the addition of water (Figure 2b). In this study, spheroid size and sphericity increased until an optimum was reached about 10 to 15 minutes after the complete addition of the moistening liquid.

Influence of Gap Air Pressure on the Moisture Content of Spheroids

In a study on the change in moisture content of spheroids during a granulation/extrusion/spheronization process (6,7), it was reported that the differences between the theoretical amount of water and the water measured from granules and extrudates were minimal as there was neither moisture evaporation nor temperature increase during the granulation and extrusion stages. The spheroid moisture content remained relatively constant until the

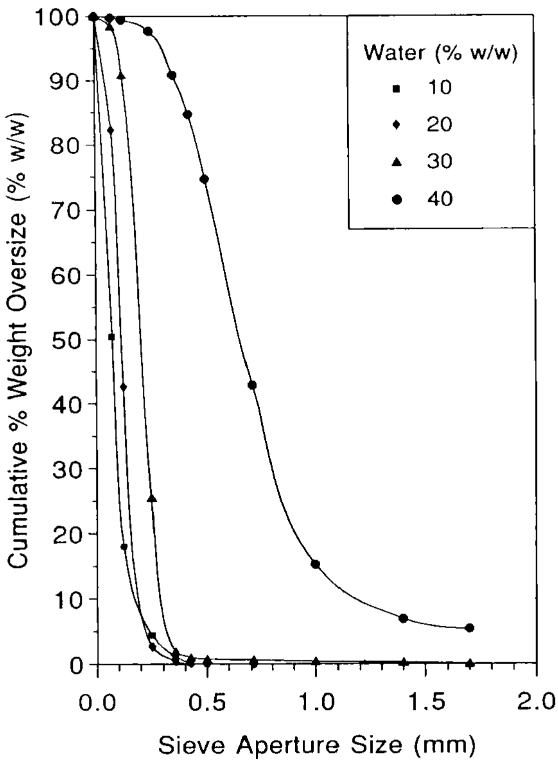

FIGURE 1

The size distribution of products formed with varying amounts of moistening liquid after the liquid addition phase.

spheronization stage when it started to decrease. In the rotary processing method, the moisture content of spheroids sampled immediately after the liquid addition stage was less than the theoretical amount. The spheroid moisture content was found to decrease linearly with time after the complete addition of water (Figure 3). The presence of a positive pressure between the annular gap had a drying effect which would account for the continual loss of moisture during the process.

Spheronization runs carried out at various gap air pressures in the rotoprocessor was used to study the effect of gap air pressure on the spheroid moisture content. At each sampling time, a drop in spheroid moisture content was observed with an increase in gap air pressure (Figure 3). The drying effect of the compressed air was greater at a higher air pressure. Therefore, the rate of moisture loss displayed an increasing trend following an increase in the gap air pressure (Figure 4).

Role of Moisture and the Influence of Liquid Flow Rate on Spheroid Size

The amount of moistening liquid plays an important role in determining the size of spheroids (8). In the present study, the influence of moisture was most critical at the stage when spheroids

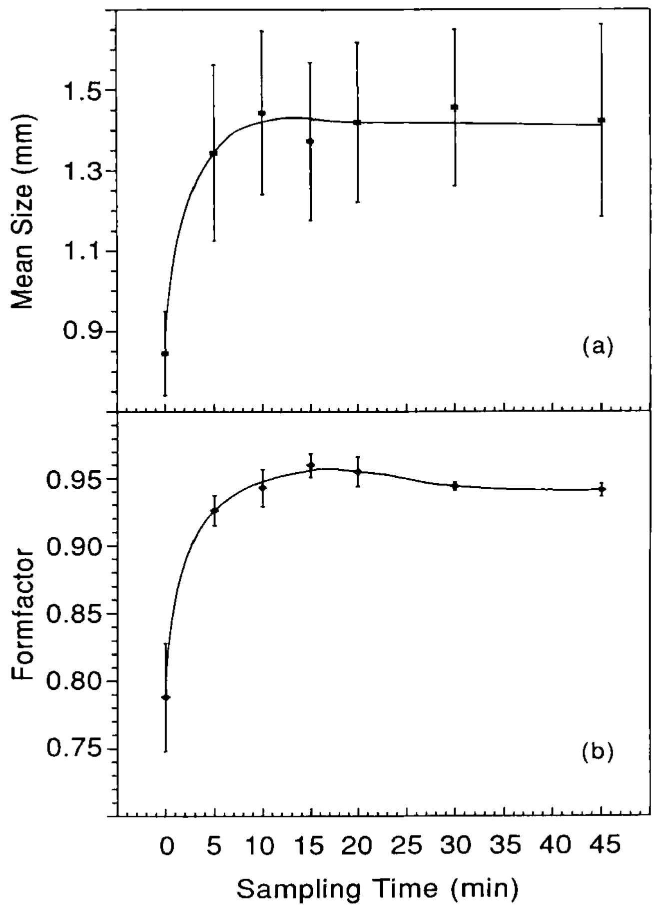

FIGURE 2

The changes in spheroid size and shape with time after the complete addition of water during spheroid production. Standard deviations are denoted by the vertical lines.

began to form and grow in size during the liquid addition phase and thereafter until an optimum size was reached. The amount of moisture available determined the strength of the particulate mass, the extent of agglomeration and the smoothening of the spheroid surfaces. Thus, it established the spheroid structure. After the formation phase, the further loss of moisture did not appear to affect spheroid size and sphericity as the structure had already been built up. Similar findings were also reported by other workers (9).

At any point in time, the moisture content of granules depended on the extent of wetting and evaporation (10). It was reported that these two factors were primarily controlled by liquid flow rate and inlet air temperature respectively. In the present study, it was found that the gap air pressure also contributed to evaporation of moisture. Using the same amount of moistening liquid (40% w/w), spheroid size was found to increase linearly (r^2 value = 0.96) with an increase in the

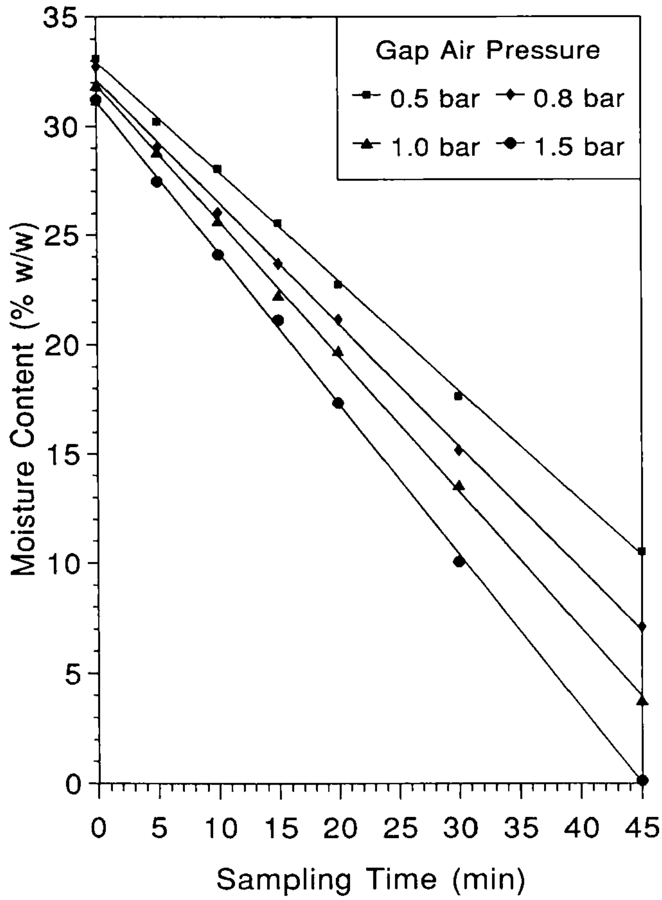

FIGURE 3
The change in moisture content of spheroids with time after the complete addition of water during spheroid production.

liquid spray rate (Figure 5). When the atomizing pressure was kept constant, a higher liquid spray rate allowed for a larger amount of moistening liquid to be delivered to the powder mix per unit time. This resulted in an increased availability of moisture for wetting of the powder mix. The higher spray rates also reduced the liquid addition period. Consequently, there was a decrease in the total amount of moisture loss due to evaporation during the granulating phase. These factors were conducive for the formation of more liquid bonds which facilitated a greater granule growth during the spheroid formation stage.

<u>Influence of Gap Air Pressure on Spheroid Size and Shape</u>

When the gap air pressure was not used, the load size of the powder mix was significantly reduced as a substantial amount of powder collected in the rotor housing under the frictional plate. Overwetting occurred with the production of large spheroids (Figure 6). This gave rise to the need

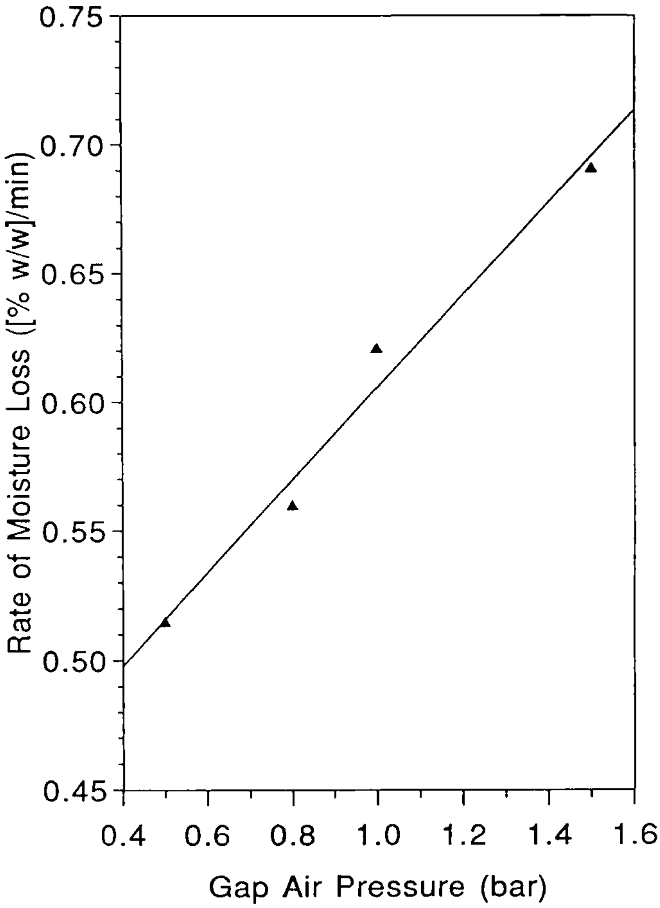

FIGURE 4
The effect of gap air pressure on the rate of moisture loss in the rotoprocessor.

for introducing compressed air through the annular gap. The compressed air created an air resistance against powder entry into the clearance between the frictional plate and the rotor housing. When a positive pressure was maintained below the annular gap, the powder slippage under the frictional plate was minimal. Smaller spheroids were formed as the bulk of the powder mix was available for agglomeration-spheronization.

There was a reduction in spheroid size with an increase in gap air pressure as shown by the decreasing trend in the mass median diameter values (Figure 6). A higher gap air pressure subjected the powder mix to greater agitation. This increased the tendency for powder to rise and swirl while the rotating powder mix was sprayed with water. The gap air pressure may influence the wetting pattern of the powder mass during the agglomeration phase. Increased gap air pressures could also result in increased attrition of spheroids. Moreover, the different rates of

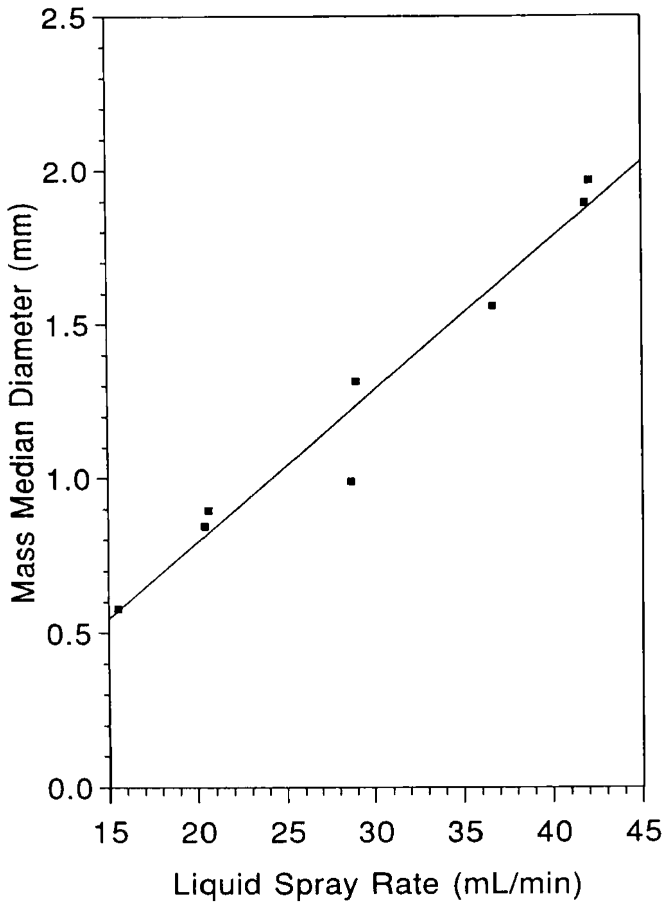

FIGURE 5

The effect of liquid spray rate on the mass median diameter of spheroids formed by rotary processing.

moisture loss may be an indirect contributing factor in the determination of spheroid size at the formation stage as the rate of moisture loss influenced the amount of moisture in the spheroid interior and exterior.

The formation of a stationary layer of material on the spheronizer wall occasionally occurred during a run. The layer may be made up of moistened powder or spheroids which had been flung against the wall. The layer was usually dislodged and broken up rapidly during the course of the run. However, if a significant part of the stationary layer remained on the wall without breaking up, the participating load was reduced in size and it may be overwetted by the moistening liquid. Moreover, the smooth rolling motion of spheroids on the rotating plate may be disrupted by the presence of the stationary layer. Spheroids with much larger mass median diameters were observed in some spheronization runs where substantial wall adhesion occurred (Figure 6).

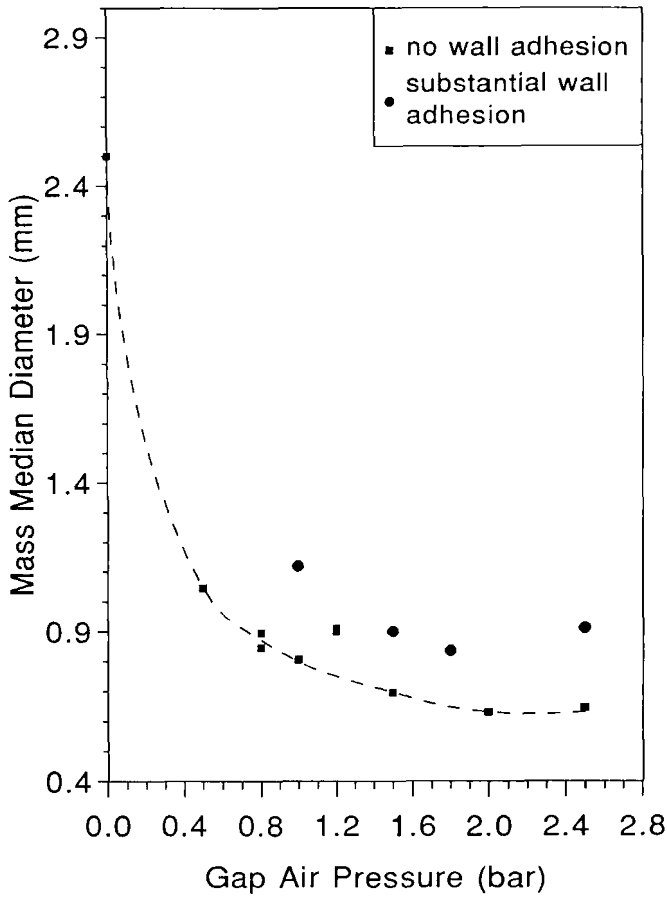

FIGURE 6
The influence of gap air pressure on the mass median diameter of spheroids formed by rotary processing.

Spheroids formed under such conditions tended to deviate from those formed during runs with minimal adhesion.

Spheroid sphericity was not greatly affected by a change in the gap air pressure. The spheroids were generally spherical in shape. The formfactor values showed a slight decrease as the gap air pressure was increased (Figure 7).

CONCLUSION

In the rotoprocessor, spheroids may be produced by an agglomeration-spheronization method without the extrusion stage. Spheroids started to form during the liquid addition phase and continued to grow to an optimum size after the complete addition of the moistening liquid. There

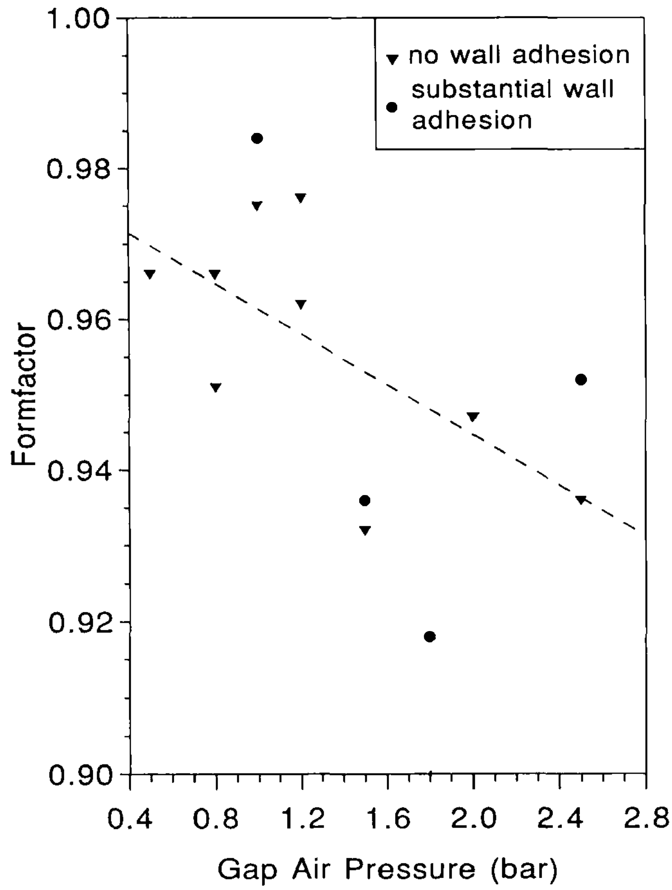

FIGURE 7
The formfactor of spheroids produced with different gap air pressures.

was a continual loss of moisture due to evaporation during the process. However, after the spheroid structure was built up, the further loss of moisture did not significantly affect the final spheroid size and shape. The moisture content of spheroids at the formation stage determined the spheroid structure. Consequently, the loss of moisture due to evaporation must be taken into account when deciding the amount of moistening liquid to be added. Besides the amount of moistening liquid, the spray rate of the moistening liquid also played a part in the determination of spheroid size. Increased delivery rates resulted in greater wetting and an increase in the extent of liquid binding.

Gap air pressure influenced the rate of moisture loss during the spheronization process and seemed to play a role in determining spheroid size. There was a range of gap air pressure settings over which spheroids may be produced successfully. A positive pressure was necessary to prevent powder from collecting under the frictional plate. However, when the gap air pressure was set above 2.5 bar, there was an increase in the tendency for the powder to be blown up and out of the inner spheronization chamber particularly at the initial stage of liquid addition before the powder mix was sufficiently moistened. Strong air pressures also caused some of the spheroids to fluidize and impinge against the spheronizer wall. This increases the likelihood for spheroids to adhere onto the wall. Consequently, suitable low gap air pressures should be chosen for use in the direct formation of spheroids from a powder mix in a single-step agglomeration-spheronization process using a rotoprocessor.

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