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# THE PREPARATION OF ASCORBIC ACID PELLETS USING THE WET PELLETIZATION PROCESS IN LIQUID MEDIA

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## ABSTRACT

The pellets of ascorbic acid were prepared from wet granulation using modifided spherical agglomeration technique, named as wet pelletization, in liquid media. The wet granules made by conventional method were placed into the baffled cylinderical vessel which was previously filled with water saturated ethylether. The wet granules were composed of ascorbic acid, microcrystalline cellulose and 3% of aqueous PVP K-30 solution as binding agent. To prepare highly spherical pellets with narrow size distribution, the system, at first, was agitated strongly about 1,500 rpm for 10 min with screw type agitator. Then the medium was changed to an anhydrous ethylether and agitated slowly about 900 rpm until pellets are shaped and densified. The shape and size distribution of pellets depend largely on the amounts of binding solution and the proportion of microcrystalline cellulose at fixed agitation speed. This wet pelletization technique was simple, reproducible and might have application for the spheronization of other hydrophilic drugs.

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## INTRODUCTION

Solid spherical pellets for pharmaceutical uses are of interest for the both conventional dosage form and controlled release drug delivery system. The manufacture of pharmaceutical pellets has been a prevalent practice in pharmaceutical industry since the successful introduction of pellet-type sustained release products, particularly for capsule fills, in early 1950s. Various techniques and equipments have been used to obtain spherical granular materials, with newer pieces of granulation equipment being the Marumerizer and Centrifugal Granulator(1-4).

In the present study, we developed a simple and inexpensive method using a modified wet spherical agglomeration technique, named as the wet pelletization, to prepare spherical pellet as an alternative to extrusion- spheronization method.

The wet spherical agglomeration technique has been developed mainly at the National Research Council of Canada to establish a novel method of agglomeration of fine particles in a liquid suspension (5-7). By this process, finely divided solid in liquid suspension are agglomerated and separated from the suspending liquid by the addition of small amount of a second liquid which preferentially wets the solid and is immiscible with the first liquid. Subsequent agitation causes the agglomerates to become sphere as a balance between the destructive force and cohesive force acting on the agglomerates (8-9).

Recently, Kawashima et al. developed the spherical crystallization technique using the spherical agglomeration technique and recrystalization method for obtaining pharmaceutical crystals with improved micromeritic properties, dissolution rate and bioavaiability (10-11).

The objective of this study was to elucidate the possibility of manufaturing of pellets in liquid media. The binary mixture of ascorbic acid and microcrystalline

cellulose have been processed and evaluated the effect of diluent in preparing ascorbic acid pellet. We also investigated the effect of other manufacturing factors on the formation and properties of pellets.

## EXPERIMENTAL

### Materials

The following materials were used: Ascorbic acid (Chin Hwa Pharm. Co.) was used after screening with a 100-mesh sieve. Microcrystalline cellulose (Avicel PH101 ; Asahi chem. Ind. Co.) was used as a diluent and binder. Polyvinyl pyrrolidone (Collidon 30; BASF) was used as a binder. Ethylether (Tedia Co. Japan) was used as a suspending liquid.

### Perparation of Ascorbic Acid Pellets

The dry powders, ascorbic acid and microcrystalline cellulose, were preblended and sieved through 80 mesh screen. Batch size was held constant at 20 g of dry solid. Binding solution, 3% PVP K-30 aqueous solution saturated with ascorbic acid,was added to the mixed powders to achieve the proper consistency and kneaded properly. The wetted mass was passed twice through 18 mesh screen to evenly distribute the binding solution. This conventional wet granules were placed into the 6-baffled cylinderical vessel which was previously filled with 200 ml of ethylether saturated with water. The system ,at first, was agitated strongly about 1,500 rpm for 10 min with screw type six blade mechanical stirrer. Then the medium was changed to an anhydrous ethylether and was agitated slowly about 900 rpm until pellets shaped and densified. The resultant pellets were seperated by decantation and washed twice with an anhydrous ethylether and dried in a desiccator for overnight.

### Measurement of Pharmaceutical Characteristics of Pellets

Following physical properties were measured to evaluate and characterize the final products.

Sieve Analysis - Particle size distribution was evaluated by a sieve analysis using 16-, 18-, 20-, 25-mesh screens and pan. The charge weight on the 7.5 cm diameter screen was 20 g.

Repose Angle - Repose angle was measured using a funnel with a 0.5 cm diameter orifice. 20 g of pellets were placed in funnel and allowed to fall 4 cm onto a hard level surface covered with arithmatic grid paper. The repose angle was determined by the height and radius of the resulting granule file.

Granule Density - the granule density was determined by pycnometer method for solid using hexane as displaced liquid. 5 g of pellets was placed in a 50 ml of pycnometer and air bubbles were driven out by sonification for 1 min.

Bulk density - 20 g of pellets was poured gradually through a funnel into a 50 ml graduated cylinder, tapped lightly 100 times on a hard surface and the volume measured. Bulk density was calculated as the quotient of the weight and volume of pellets.

Friability - The strength of pellets was assessed by determining the resistance to abrasion using tablet friabilator. 10 g of the size fraction (18-16 mesh) of pellets and 10 glass bead (6 mm in diameter) were placed in a friabilator and rotated for 4 min. The pellets were screened with 18 mesh screen to remove the fines, reweighted and compared to there initial weight. Friability index is the loss in weight expressed as a percentage.

Microscopic studies - The surface and cross-sectional characteristic of pellet was studies by scanning electron microscopy. The shape and size of pellet was observed with enlarged photography.

## RESULTS AND DISCUSSION

### Operating Conditions and Procedure of the Wet Pelletization

In preliminary experiment, the various operating conditions were selected after investigation of the effect of the size and shape of vessel, the degree and type of

TABLE 1. Operation Conditions of the Wet Pelletization

| |
|---|
| 1. Setting Conditions |
| 1) The size and shape of vessel<br>6-baffled cylinderical form; 7.5cm in diameter, 16cm long and 400ml in volume |
| 2) The size and shape of agitator<br>6-blade screw type impeller, 6cm in diameter |
| 3) The volume of suspending liquid<br>200ml of ethether |
| 4) The weight of solid<br>20g of mixed powder (ascorbic acid, Avicel PH101) |
| 5) Agitation speed<br>1,500 rpm for 10 min and 900 rpm for about 1 hr. |
| 2. Variable Conditions |
| 1) The proportion of Avicel PH101<br>0, 5, 15, 30, 50 (w/w) % |
| 2) The amouts of binding solution |

agitation, the amounts of binding solution and suspending liquid (Tab.1). Formation of pellet took place in the specially designed cylinderical vessel which have a 6-baffled, a inside diameter of 7.5cm and over-all length of 16 cm. And the inside surfaces of the vessel were smooth and free from sharp corners so that no pockets would be avaiable in which the solid could accumulate. It is important to properly select shape of blade and agitation speed to prepare small spherical pellet with narrow size distribution. Agitation was provided by centrally located 6-bladed screw type impeller which was 6 cm diameter and operated 2 cm from the bottom of the vessel. And agitation speed was carried out, at first, 1,500 rpm for 10 min and then 900 rpm for about 1 hr. When system was agitated strongly 1,500 rpm in water saturated ethylether, the conventional wet granules was formed to the irregular shaped granules having a narrow distribution of particle size. Then the suspending medium was changed to an anhydrous ethylether and system was agitated slowly about 900 rpm until pellets

are shaped and densified. At agitating 900 rpm, the irregular shaped granules was not destrupted further, but collided with the vessel wall and became gradually to spherical and compacted pellets. And the reason for changing to suspending medium as follows; water of inside part of pellet migrated to surface according to the densification by continuous agitation, then these water acted as a liquid bridge, the second agglomeration could be occurred between pellets, therefore bizzare shaped larger pellets was formed. The anhydrous ethylether absorbed these free water and eliminated this phenomena.

Sticking problem could happen in separating and drying step. The spherical pellets separated individually in a suspending medium, but they had tendency to stick together during drying in a air. This phenomena was ,also, caused to the remaining small amounts of free water on the surface of pellets. Therefore the pellets must be washed with anhydrous ethylether twice before drying. The shape of ascorbic acid pellets which were made by this process was highly spherical and particle size distribution represent a narrow distribution.

Effect of Microcrystalline Cellulose

Microcrystalline cellulose(Avicel PH101) has been shown to be an effective diluent in granulation to be spheronized (12-13). At the preparing conventional wet granule of binary mixture of ascorbic acid and Avicel PH101 with 3% PVP k-30 aqueous solution, increasing the Avicel PH101 content proportionally increased the amount of binding solution because Avicel PH101 could accomodate a lot of water. The physical appearance of the products varied as the amount of Avicel PH101 increased, as shown Fig. 1. At only ascorbic acid used, the shape of pellets were irregular and the particle size distribution represent a wide distribution. In this case, the irregular shaped pellets generated by first agitating of 1,500 rpm did not deform to spherical pellet during a continuous agitation at 900 rpm. This lack of deformation

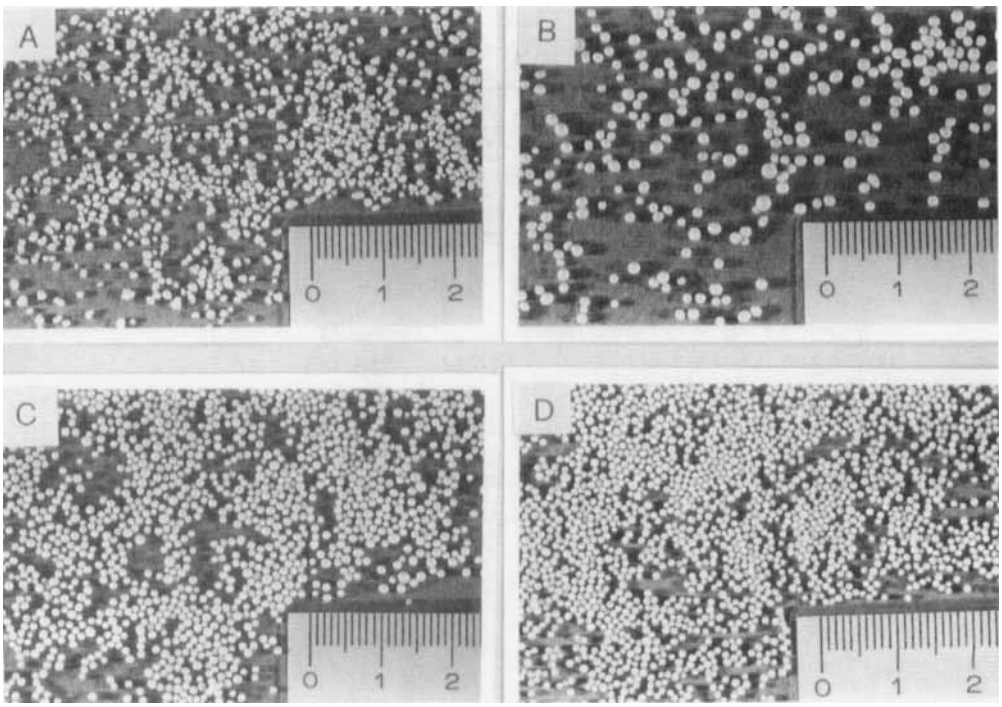


**FIGURE 1**

**Photographs of ascorbic acid pellets with different porportion of Avicel PH101.**
**proportion of Avicel PH101 : A) 0%, B) 5%, C) 15%, D)30%**

caused to be deprived of water to the anhydrous ethylether and lose the plastic nature. At a Avicel PH101 content of 5 %, spherical pellets are formed but particle size distribution showed wide. At a Avicel PH101 content of 15 %, products were very spherical and showed narrow size distribution. At a Avicel PH101 content above 30%, the average pellet diameter decreased somewhat and most pellets formed more spherical shape with even distribution of particle size. With increasing Avicel PH101 content, the surface of pellets had more plastic nature due to accomodate a lot of water. Thus, they could be easily deformed to spherical shape in a vessel during continuous agitation.

TABLE 2. Pharmaceutical Charateristic of Pellets with Different Proportion of Avicel PH101 as a Diluent.

| Sieve Analysis Percent Retained on Mesh# (um) | Avicel PH101 (%) | | | | |
|---|---|---|---|---|---|
| | 5 | 15 | 30 | 50 | |
| 16 (1,190) | 10.30 | 14.77 | 5.67 | 0.93 | 0.58 |
| 18 (1,000) | 30.81 | 31.22 | 24.74 | 17.95 | 21.27 |
| 20 ( 840 ) | 36.60 | 37.61 | 54.43 | 62.51 | 62.74 |
| 25 ( 710 ) | 15.58 | 14.14 | 13.38 | 16.74 | 14.53 |
| pan | 6.70 | 2.26 | 1.81 | 1.86 | 0.89 |
| Geo. Mean Diameter (um) | 873 | 900 | 851 | 810 | 833 |
| Granule Density (g/ml) | 1.5465 | 1.5589 | 1.5797 | 1.5061 | 1.5012 |
| Bulk Density (g/ml) | 0.896 | 0.900 | 0.877 | 0.865 | 0.856 |
| Friability (%) | 2.5 | 0.3 | 0.25 | * | * |

* negligible

Therefore, based solely on physical appearance, Avicel PH101 appears to be the effective diluent for the preparation of pellet containing ascorbic acid as a water soluble drug. The pharmaceutical characteristics of pellets are presented in Table 2 and log-normal distribution showed particle size distribution with different proportion of Avicel PH101 (Fig. 2). In general, the particle size distribution of these pellets represent a narrow distribution relative to that produced by conventional wet granuration. Greater than 90 % (by weight) of the pellets contained more than 15 % of Avicel PH101 were 18 - 25 mesh range. The slight decrease in granule density and bulk density with increasing the Avicel PH101 content must be due to the difference in density between ascorbic acid and Avicel PH101. All product had a much great bulk density as compared to conventional irregular granules. The friability appears to decrease with increasing Avicel PH101 content. At the presence of Avicel PH101, all pellets could be expected to withstand rough handling.

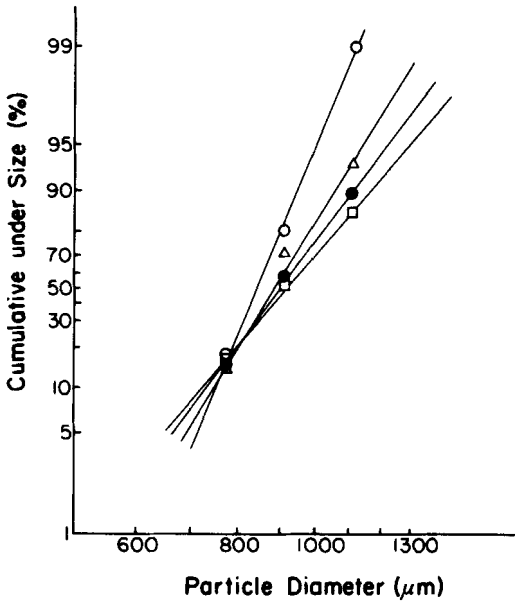


FIGURE 2

Particle size distribution of ascorbic acid pellets with different proportion of Avicel PH101. porportion of Avicel PH101 : △,0%; ○,5%; ●,15%;□,30%



## Effect of Binding Solution

Pellet formation was found to be so sensitive to the amount of binding solution incorporated, therefore its content should be controlled so that it will be optimal condition. It is reported that physical appeareance of the agglomerated product is critically dependent on the amout of bridging liquid used (6). For example, voluminous clusters of agglomerated product are created when a small amount of bridging liquid are employed, while compact spheres of much larger size will be formed if more bridging liquid is used. In this experiment, irregular shaped fine pellets are prepared when 6.5 ml of binding solution are employed at 20 g of binary mixture containing 15 % of Avicel PH 101. On the other hand, spherically compacted pellets are prepared when 7.2 ml and 7.8 ml of binding solution are used at the same amount of solid

TABLE 3. Pharmaceutical Characteristics of Pellets with Different Amounts of Binding Solution at 15% of Avicel PH101

| Sieve Analysis Percent Retained on Mesh # (um) | Amounts of Binding Solution (ml) | | |
|---|---|---|---|
| | 6.5 | 7.5 | 7.8 |
| 16 (1,190) | 1.41 | 5.67 | 83.25 |
| 18 (1,000) | 3.03 | 24.74 | 15.79 |
| 20 ( 840 ) | 26.36 | 54.41 | 15.79 |
| 25 ( 710 ) | 40.18 | 13.38 | 0.00 |
| pan | 29.01 | 1.81 | 0.00 |
| Geo. Mean Diameter (um) | 715 | 851 | 1,120 |
| Granule Density (g/ml) | 1.5149 | 1.5197 | 1.5214 |
| Bulk Density (g/ml) | 0.751 | 0.877 | 0.902 |
| Repose Angle | 28.30 | 24.74 | 23.30 |

and operating conditions. The results of physical testing for these amount of binding solution at 15 % Avicel PH101 are presented in table 3. As the amount of binding solution was increased, the average pellet diameter increased remarkably at same operating conditions. The increase in average pellet diameter could be due to the change from the pendular to the capillary state of wetting. This change of wetting state is accompanied also with rising of bulk density. Repose angle was decreaed with increasing the amount of binding solution. But granule density was not showed a difference because pellet were composed of same constitutive material.

## CONCLUSION

In this experiments, various operating conditions, such as the shape and size of vessel, the type of agitation, agitation speed, agitation time and suspending medium,

must be judiciously chosen to preparing ascorbic acid pellets by the wet pelletization process. Avicel PH101 was needed to prepare highly spherical and hard pellets with narrow size distribution. And average pellet diameter was increased with increasing the amount of binding solution at same operating conditions. The wet pelletization was simple, reproducible and could be produce more spherical pellet than other mechanical methods.

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