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EVALUATION OF A HIGH-SPEED PELLETIZATION PROCESS AND EQUIPMENT

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ABSTRACT

A single step high-speed centrifugal pelletization procedure is described. Pellets of three model drugs of varying solubilities were prepared and characterized. Scanning electron microscopy showed that the external layer which is composed of binder and drug is very porous relative to the non-pareil seed core material. Bulk density measurements also confirmed the loose structural makeup of the drug layer. Preparation of pellets from small non-pareil seeds provided particles that have high drug content and are amenable to high dose formulations. Common wet granulation binders such as polyvinylpyrrolidone, sodium carboxymethylcellulose and gelatin exhibited good binding capacities and generated excellent pellets.

INTRODUCTION

Due to the numerous advantages that solid spherical pelleted products possess, incorporation of drugs in pellets has been a prevalent practice in the pharmaceutical industry. Pellets are not only attractive in appearance as a result of the various shades of color which can be imparted to them, but they also have a free flowing property that can alleviate handling problems. Furthermore, they are easily mixed when either a combination of ingredients or various drug release rates from a particular drug delivery

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system is desired. Specially significant, however, is the role which pelleted products play when injested into the body. When they are formulated as multiple unit formulations in controlled-release preparations, pellets maximize drug absorption (1), reduce variations in gastric emptying rate and over-all transit times (2), eliminate local irritative or anesthetizing effect of an active substance and avoid dose-dumping (3). Consequently, pelletization, or the manufacturing of pellets, has been the subject of intensive research both in terms of innovative formulations and process equipment.

One method of manufacture that has been used extensively is spheronization. Spheronization which is a form of pelletization refers to the formation of spherical particles from wet granulations (4). The spheronization equipment generally operates by extruding wetted material into cylindrical segments, breaking the segments and then rolling them into solid spheres (5). The main processing steps are (a) dry blending, (b) wet granulation, (c) extrusion and (d) rolling in a marumerizer. Although spherical particles with a high drug content can be generated by this process, each of the steps are critical and should be controlled very carefully. A much simpler and less time-consuming pelletization process that utilizes high speed centrifugal equipment is the subject of this paper.

EXPERIMENTAL

Instrumentation: A laboratory scale, centrifugal, fluidized-bed coater/granulator[1] that is composed of a rotation apparatus, liquid spray and powder feed units, a control panel and a source of heated fluidizing air was used to prepare the pellets. The rotation apparatus consists of a stationary cylinder or stator, a variable speed rotor and a preset, non-adjustable slit between the rotor and stator through which heated fluidizing air is forced. Thorough and uniform mixing of the contents is achieved by a combination of centrifugal force, gravity and fluidizing air.

Materials: Hydroxypropylcellulose[2], sodium carboxymethylcellulose[3], polyvinylpyrrolidone[4], gelatin[5], non-pareil seeds[6], Kaolin[7] and Eudragit E 30

D[8] were employed as received. Theophylline[9], pseudoephedrine hydrochloride[10] and diphenhydramine hydrochloride[11] were passed through a 60 mesh standard sieve[12] prior to use.

Preparation of Binder Solution: All the binders except gelatin were dissolved in cold distilled water immediately before use to provide an eight percent solution. Air bubbles formed during the mixing process were driven out by sonication. Gelatin was first hydrated in cold water and then dissolved by heating the mixture to 50°. The temperature of the solution was maintained at 35° during the pelletization process to avoid gelation.

Preparation of Pellets: About 900 gms of non-pareil seeds were placed in the granulation chamber and allowed to tumble for a maximum of 3-5 minutes prior to the addition of the binder solution. Once spraying was initiated and the seeds became barely moist, powder was fed at an appropriate rate. After the required amount of powder was added, spraying of the binder solution was terminated. The pellets were partially dried while they were still in the chamber using the fluidizing air. After about three minutes the particles were transferred to a paper-lined tray and further dried in an oven at 45° for twenty-four hours. The dried pellets were screened in portions of 250 grams, weighed and stored in plastic bags. The general operating conditions are given in Table I.

Sieve Analysis: The size distribution of the pellets was evaluated by the sieve analysis technique using 12-30 mesh screens. The sieve nest was shaken using an automatic shaker[13] until no further change in weight distribution of the particles was observed with continued shaking. The sieve load was 250 grams.

Bulk Density: The bulk densities of the starter seeds and pellets were measured using an automatic tapper[14]. A specially designed, 250 ml graduated cylinder was tared and enough particles were transferred to the cylinder to give a net weight of 50 grams. The cylinder was then placed on the tapper and automatically dropped from a height of about 0.5 cm two thousand times. The volume of the particle bed was measured to the

TABLE I

General Operating Parameters of the CF-Granulator and Their Settings During the Manufacture of the Drug Pellets from Non-pareil Seeds

OPERATING PARAMETER	SETTING
Rotor speed	150-170 rpm
Atomizing spray air velocity	14 Nl per min.
Atomizing air pressure	0.3 kg per cm^2
Inlet temperature	50°
Binder solution flow rate	8 ml per min.
Powder feed	80 g per min.
Product bed static pressure	0.3 mm
Slit width	0.2 mm
Fluidizing air velocity	400 Nl per min.
Product bed temperature	26°-30°

nearest 0.5 ml. The bulk densities were determined from the weight and volume of the particles.

True Density: The true densities of the non-pareil seeds and pellets were determined using an air comparison pycnometer[15]. The true volume of a ten gram sample was obtained directly from a digital read out and the density computed in the usual manner.

Friability: Exactly fifty grams of pellets were placed in a Friabilator[16] and rotated for ten minutes or 250 revolutions. The pellets were then screened to remove the fines, reweighed and compared to their initial weight. Non-pareil seeds of comparable mesh size (14-16) were used as reference.

Scanning Electron Microscopy: The pellets and non-pareil seeds were embedded in a mixture of purified paraffin and a synthetic polymer and sliced to provide cross-sectioned views of the particles. The embedded and sliced samples were then mounted on a metal stub, coated with gold and

examined using a scanning electron microscope[17] at a magnification of 100X and a 20° tilt.

RESULTS AND DISCUSSION

The operating conditions of the equipment were selected after investigation of the effects of the inlet temperature, powder feed rate, speed of the rotor and flow rate of the binder solution. An inlet temperature of 50° was found to be optimum and selected to process the pellets. At higher inlet temperatures, the water in the binder solution evaporated so fast that the powder did not adhere to the core material and, consequently, was blown off the product bed, while at lower temperatures, the rate of evaporation of water was so low that the particles became wet and got aggregated. Once the processing inlet temperature was chosen, the powder feed rate and the flow rate of the binder solution were fixed. Non-pareil seeds were placed on a rotor which, when turned on, created, together with the fluidizing air, a circular flow pattern promoting uniform mixing of the seeds. While the seeds were being acted on by centirfugal force, the spray gun applied a constant spray of binder solution. Simultaneously, the drug powder was fed through the powder spray unit. The rates of powder feed and the flow of binder solution were varied until constant values of the two parameters provided spherical pellets devoid of aggregation as well as a product bed free of excess powder or binder solution. The pelletization process is amenable to all hydrophilic drug candidates irrespective of their physico-chemical properties. When diphenhydramine hydrochloride and pseudoephedrine hydrochloride pellets were prepared, the most critical independent variables, binder solution flow-rate and powder feed-rate, were kept constant at 8 ml/min and 80 gm/min respectively. The similar processing conditions for the two drugs can be attributed basically to the similarity in their water-solubilities. Theophylline which has limited water-solubility was processed under a different set of conditions. Satisfactory pellets were generated only when the flow-rate was increased to 15 ml/min and the powder feed-rate was initially set at 30 gm/min and progressively increased to 60 gm/min.

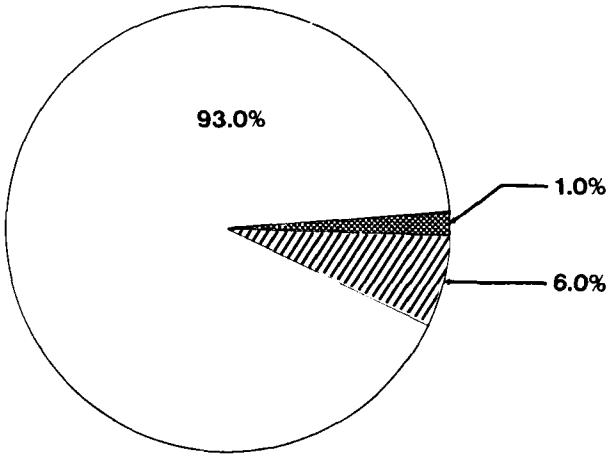

FIGURE 1
Percent weight distribution of pellets prepared from 20-25 mesh starter seeds:
■ ≥12 mesh, ☐ 14-16 mesh, ▨ 18-20 mesh.

Pellets were prepared from various mesh sizes of starter seeds. As expected, larger seeds provided larger pellets, although overlap of certain mesh sizes were observed (Figs. 1-3). As the mesh size of the non-pareil seeds was increased or decreased, the mesh size of the primary pellets in the product was altered correspondingly (Fig. 4). Moreover, the bulk densities of the pellets were found to be proportional to the size distribution and bulk densities of the starter seeds (Figs. 5 and 6). Smaller seeds and pellets derived from these seeds provided higher bulk densities mainly due to small intraparticle porosities. More specifically, bulk density is indicative of the packing properties of particles and, as such, is greatly influenced by the diameter of spherical seeds or pellets. In contrast, true density indicates the extent of densification or compactness of substances and, therefore, is influenced by the diameter of spherical particles to a lesser extent. Generally, the true densities of the starter seeds were found to be slightly higher than the respective pellets (Table 2).

Scanning electron photomicrographs of sectioned pellets and the corresponding starter seeds revealed significant differences in the porosities of the particles (Figs. 7-12). While the core material in the pellets and the starter seeds had, as expected, identical and relatively dense structures, the

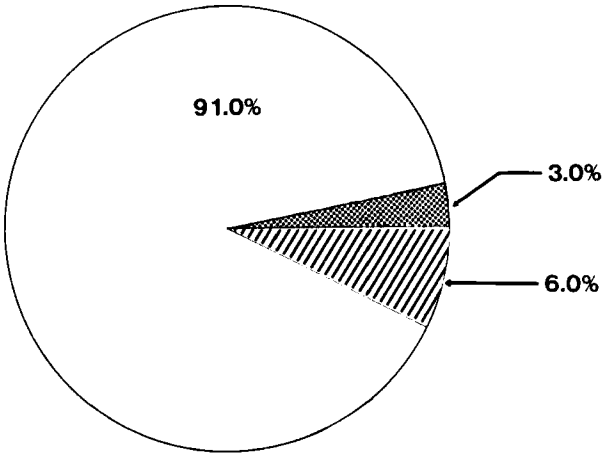

FIGURE 2
Percent weight distribution of pellets prepared from 25-30 mesh starter seeds:
■ ≥ 14 mesh, □ 16-18 mesh, ▨ 20-30 mesh.

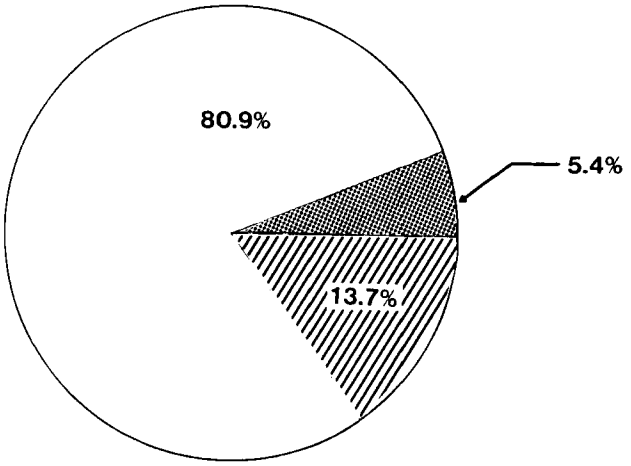

FIGURE 3
Percent weight distribution of pellets prepared from 30-35 mesh starter seeds:
■ ≥ 16 mesh, □ 18-20 mesh, ▨ 20-30 mesh.

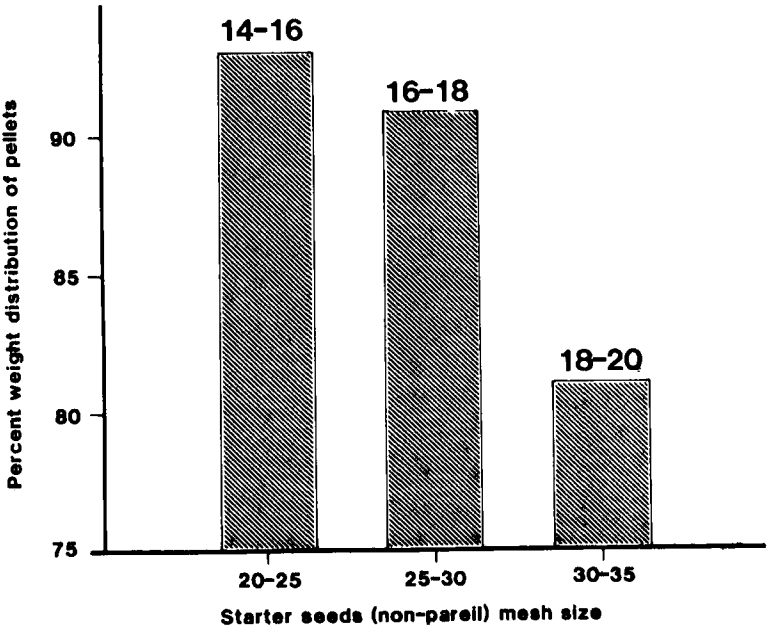

FIGURE 4
Comparison of the percent weight distribution of the primary pellet composition produced from three different starter seeds.

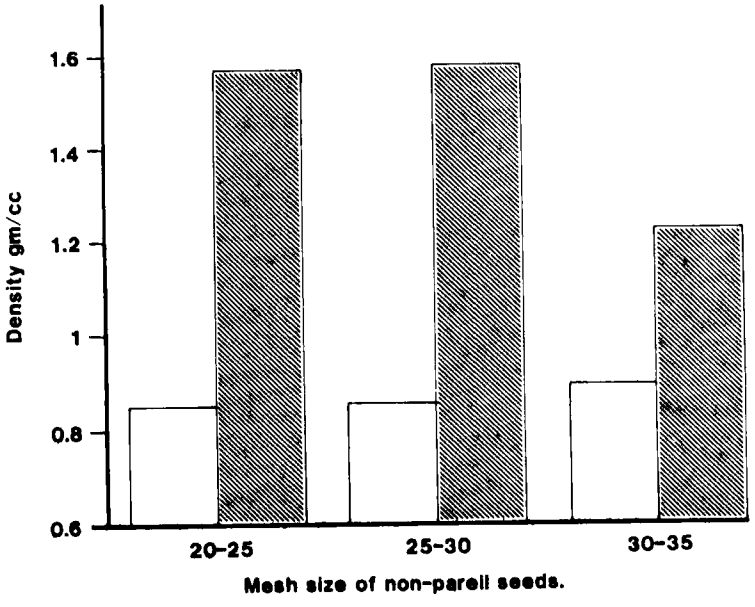

FIGURE 5
Relationship between densities and sizes of starter seeds: ▨ true density, □ bulk density.

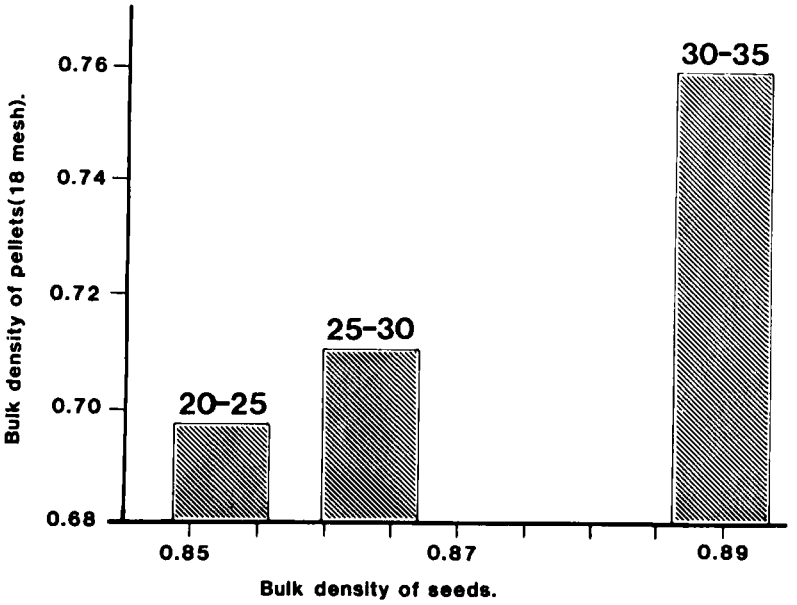

FIGURE 6
Relationship between bulk densities of seeds and the corresponding 18 mesh pellets.

TABLE 2

True Densities of Non-pareil Seeds and 18 Mesh Pellets Derived from Them.

Particle	True Density, gm/cc
1. 20-25 mesh non-pareil seeds	1.585
Pseudoephedrine hydrochloride pellets	1.255
2. 25-30 mesh non-pareil seeds	1.597
Pseudoephedrine hydrochloride pellets	1.279
3. 30-35 mesh non-pareil seeds	1.231
Pseudoephedrine hydrochloride pellets	1.230

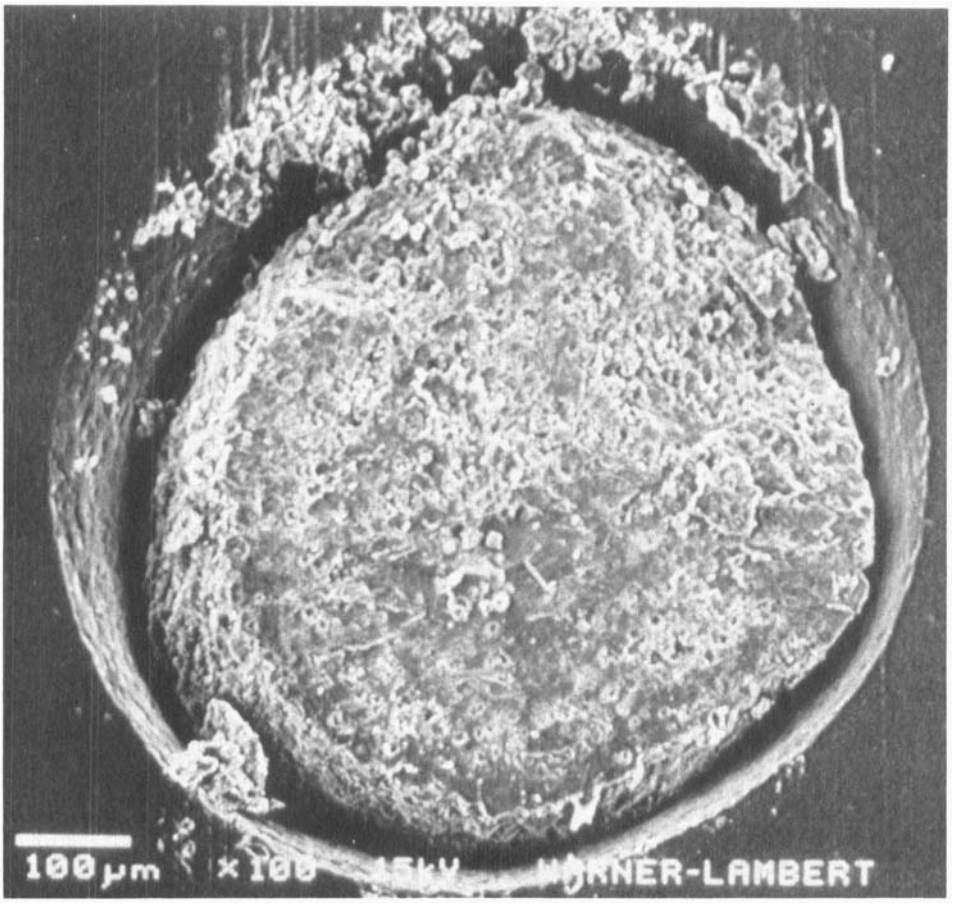

FIGURE 7
Scanning electron photomicrograph of a sectioned 20-25 mesh size non-pareil seed.

external layer of the pellets which is composed of the drug and binder was loosely packed and very porous, particularly at the core/drug-binder interface. The porosity appeared to get more pronounced as the mesh size of the non-pareil seeds increased, an observation that is in agreement with bulk density measurements. It is apparent, therefore, that densification does not occur during the pelletization process. Further examination of the surface morphology of the pellets clearly showed the effect of the difference in solubilities of the drugs on the structural makeup of the final

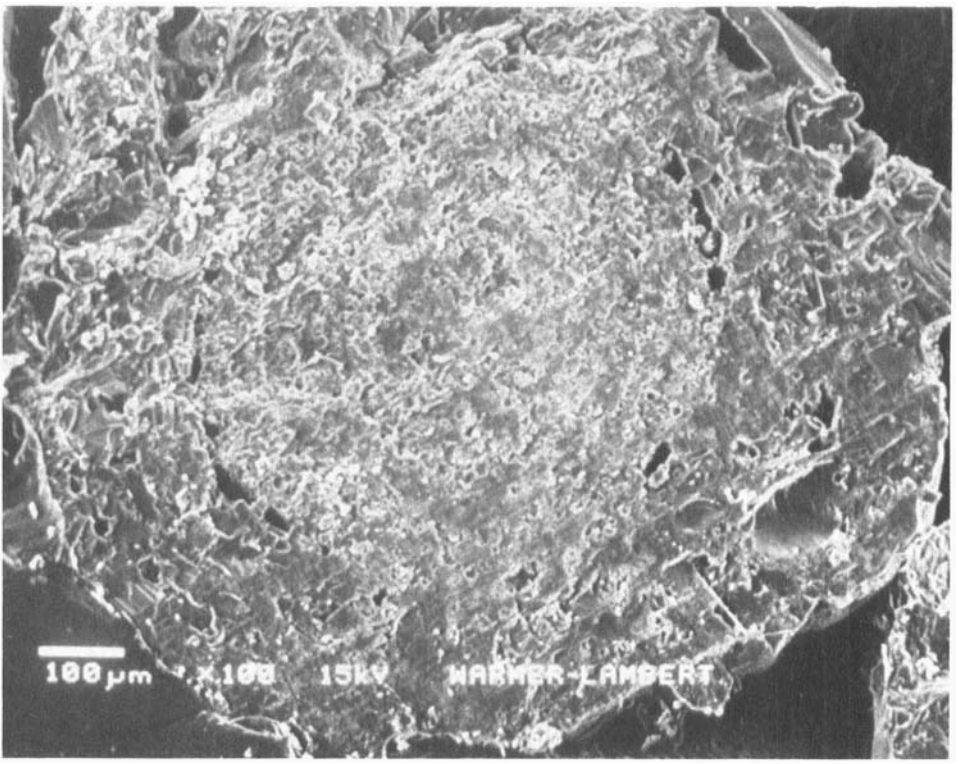

FIGURE 8
Scanning electron photomicrograph of a sectioned pseudoephedrine hydrochloride 18 mesh pellet prepared from 20-25 mesh non-pareil seeds.

product. Theophylline crystals were readily observed on the surface and are believed to exist in the same pattern throughout the body of the pellets (Fig. 13). In contrast, diphenhydramine hydrochloride and pseudoephedrine hydrochloride pellets showed no drug crystals on the surface, indicating complete dissolution and intimate mixing of the drugs with the binder solution (Figs. 8, 10, 12, 13, and 14). The surfaces of the pellets, however, were rough and irregular.

Hydroxypropylcellulose was employed as a binder for the most part of the work. Other potential binders such as polyvinylpyrrolidone, sodium carboxymethylcellulose and gelatin were also evaluated. All of these binders are routinely used in the pharmaceutical industry as binders in wet

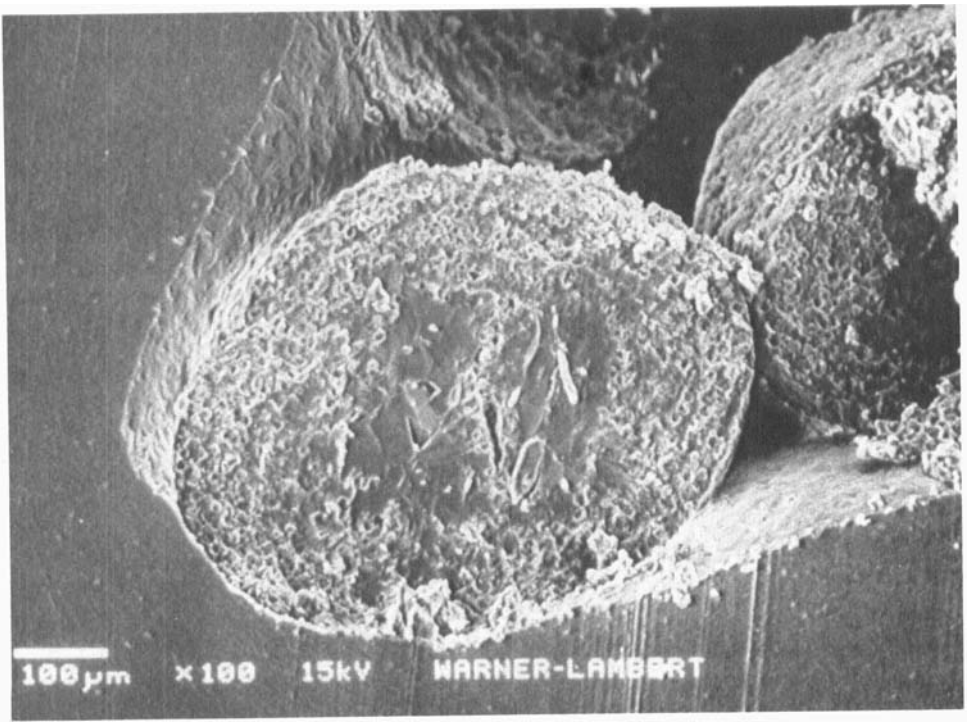

FIGURE 9
Scanning electron photomicrograph of a sectioned 25-30 mesh non-pareil seed.

granulations. Although the concentrations of the binders were arbitrarily fixed at 8% and were not separately optimized, the use of these binders during the preparation of diphenhydramine hydrochloride pellets established their unequivocal application in pelletization. No significant change in operating conditions, including feed-rate and binder solution flow-rate, was required to obtain the desired pellets. Gelatin was an exception, however. The powder feed rate had to be increased to 100 gm/min and the liquid flow-rate had to be lowered to 5 ml/min. It appears that lower concentrations of gelatin would be needed to maintain the general operating conditions, implying that gelatin probably is a stronger binder. In addition, a mixture of kaolin and Eudragit^{R} E 30 D generated high quality pellets when employed

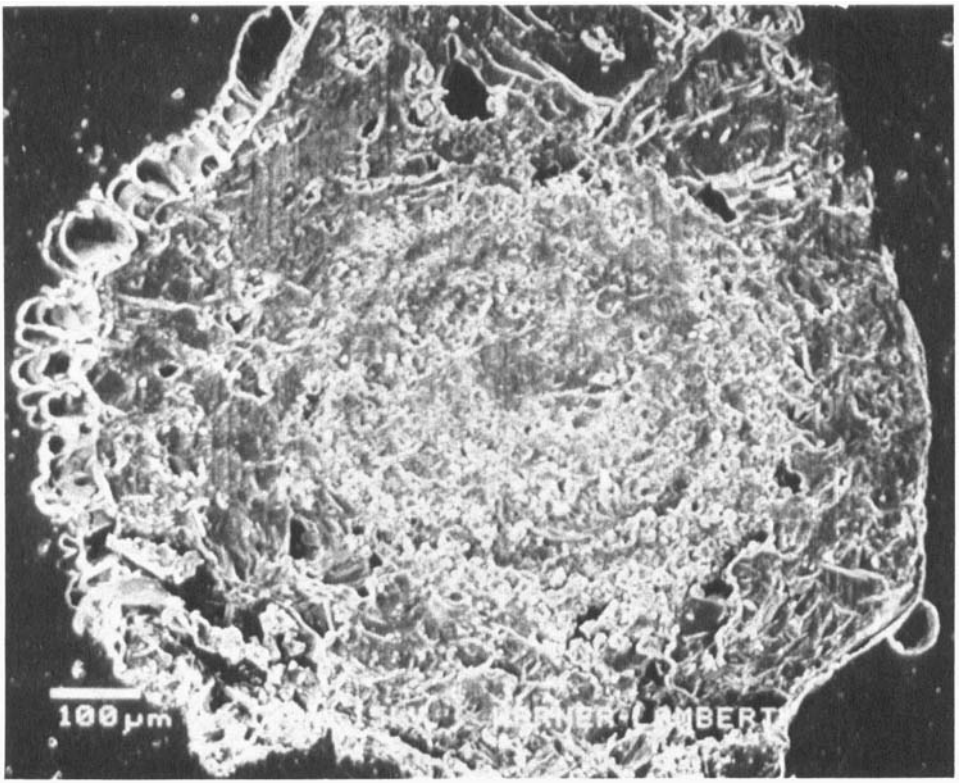

FIGURE 10
Scanning electron photomicrograph of a sectioned pseudoephedrine hydrochloride 18 mesh pellet prepared from 25-30 mesh non-pareil seeds.

as a binder. Since friction and shock during coating can lead to abrasion and cause pellets to chip or break, friability was selected to be a measure of the extent of "goodness." A weight loss of less than 0.8% is generally considered satisfactory for tablets. For pellets, however, the acceptable value could be higher to compensate for the higher surface area per unit weight and the subsequent frictional forces involved. Whatever the cutoff value, friability tests provided good comparative values (Table 3). Considering the weight loss that was observed with non-pareil seeds as a

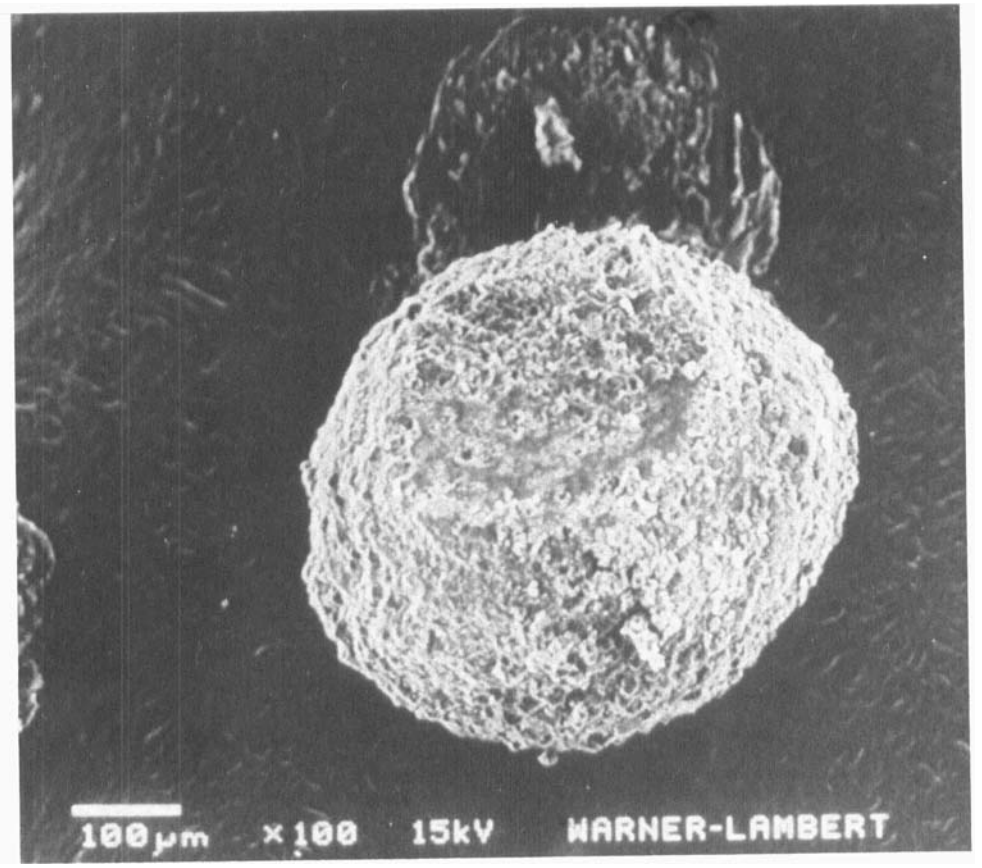

FIGURE 11
Scanning electron photomicrograph of a sectioned 30-35 mesh non-pareil seed.

reference, gelatin appears to be the best binder followed by sodium carboxymethylcellulose, hydroxypropylcellulose, kaolin/Eudragit^{R} E 30 D mixture and polyvinylpyrrolidone. Based on friability as a sole criterium for the measure of good quality pellets, polyvinylpyrrolidone would probably be the least acceptable binder. It can be extrapolated from these data that all wet granulation binders can, in general, be used as binders in the pelletization process.

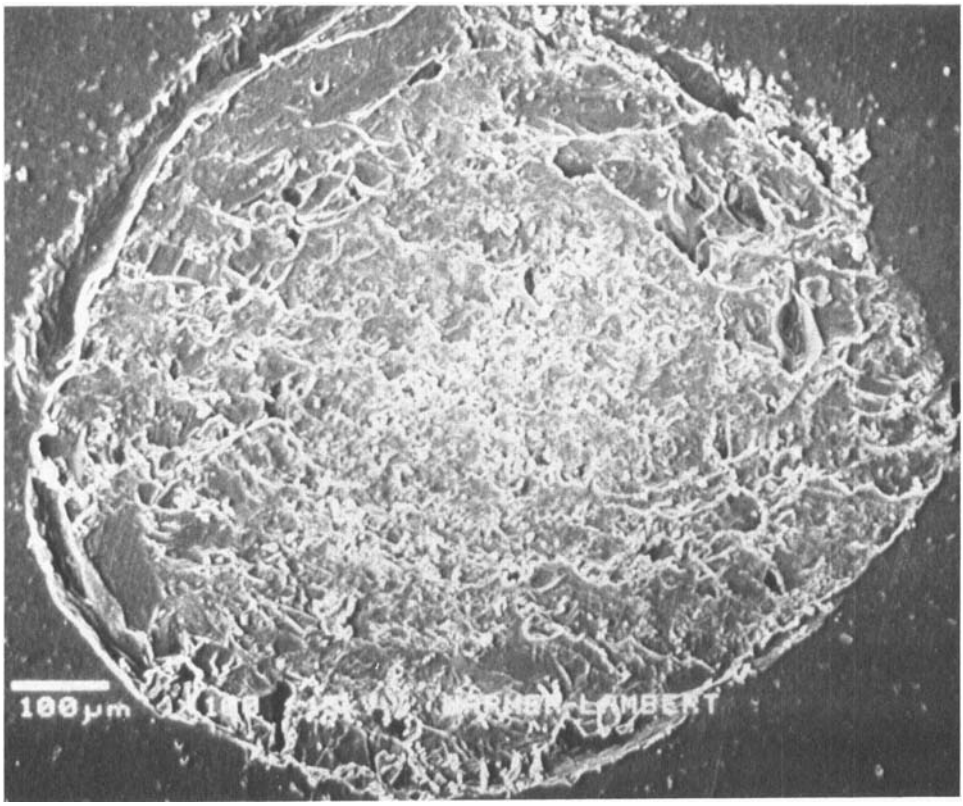

FIGURE 12
Scanning electron photomicrograph of sectioned pseudoephedrine hydrochloride 18 mesh pellet prepared from 30-35 mesh non-pareil seeds.

Since the size of pelleted products is proportional to the corresponding starter seeds, the drug content of the pellets vary accordingly. When a high dose product is desired, it is essential that the non-pareil seeds be extremely small. The drug content of 18 mesh pellets prepared from 40-60 and 20-25 mesh starter seeds was determined and the results are given in Table 4. As expected, pellets obtained from smaller seeds contained a higher drug load.

CONCLUSION

Manufacture of pellets using rotary equipment is not only convenient but also requires a very short time to accomplish the desired

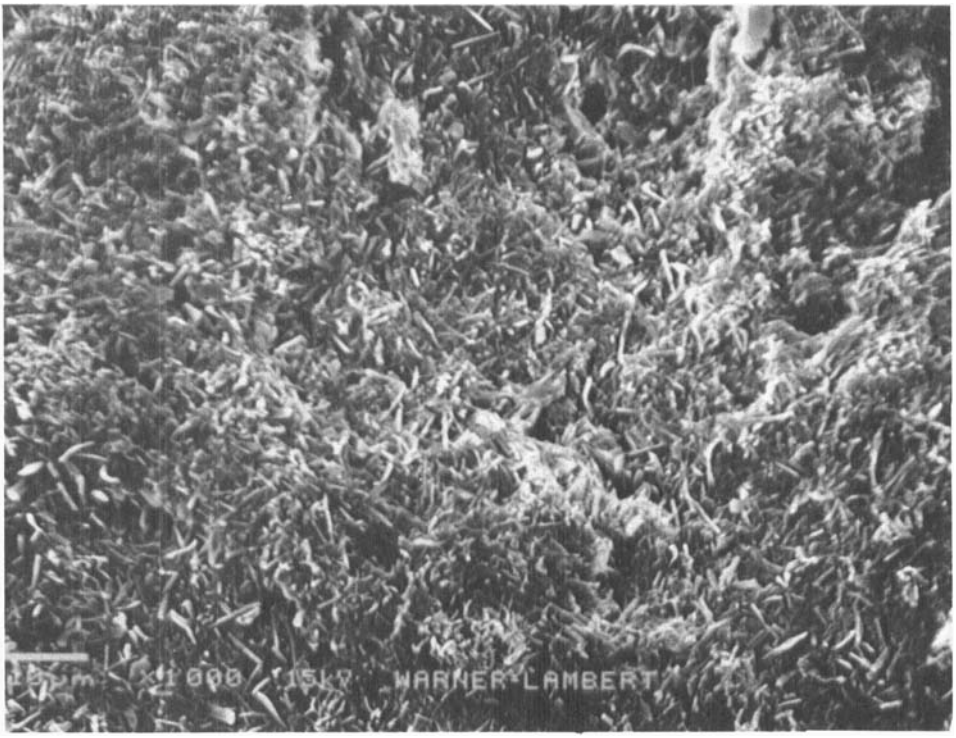

FIGURE 13
Scanning electron photomicrograph of the surface morphology of an 18 mesh theophylline pellet prepared from 20-25 mesh starter seeds.

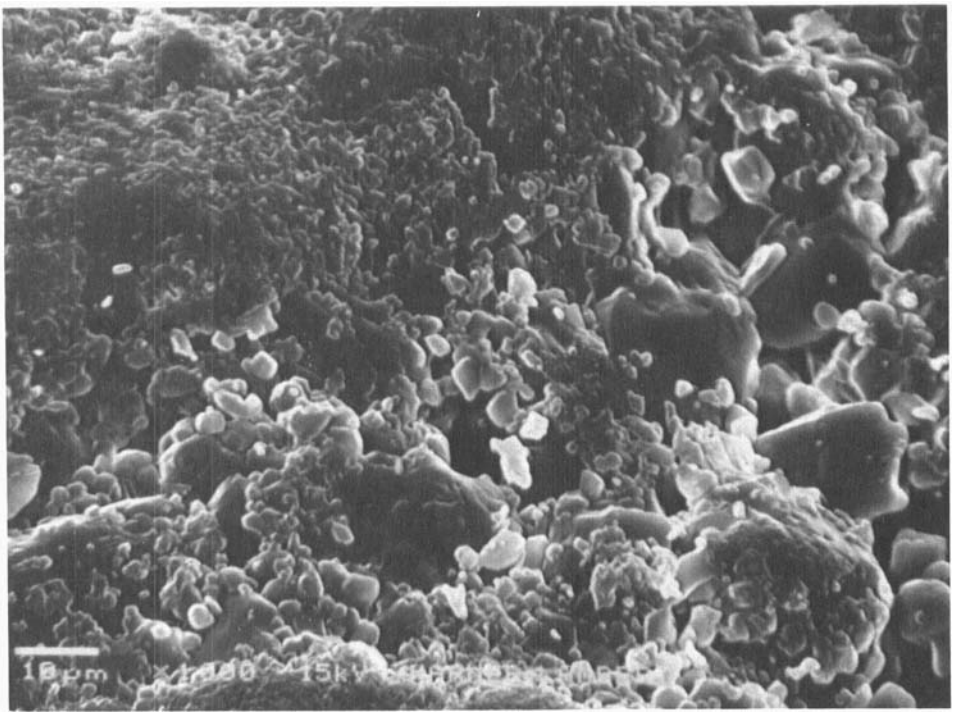

FIGURE 14
Scanning electron photomicrograph of the surface morphology of an 18 mesh diphenhydramine hydrochloride pellet prepared from 20-25 mesh starter seeds.

TABLE 3

Friability Results of Diphenhydramine Hydrochloride Pellets Prepared by Using Different Binders

Binder	Initial Wt. of Pellets	Final Wt. of Pellets	Percent Wt. Loss
Hydroxypropylcellulose	50 gm	49.75 gm	0.50
Gelatin	50 gm	49.91 gm	0.18
Sodium CMC	50 gm	49.81 gm	0.38
PVP	50 gm	49.39 gm	1.22
Kaolin/E 30 D (20/60)	50 gm	49.70 gm	0.60
Non-pareil Seeds	50 gm	49.94 gm	0.12

TABLE 4

The Drug Content of 18 Mesh Diphenhydramine Hydrochloride Pellets Prepared from 40-60 and 20-25 Mesh Non-pareil Seeds.

Mesh Size of Non-pareil Seeds	Percent Drug Content
20-25	67.3
40-60	82.5

product. The processing technique is simple, reproducible and involves a minimum number of steps. It is thus superior to the extrusion-marumerization process as well as to the pelletization process that utilizes coating pans.

ACKNOWLEDGEMENTS

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NOTES

1. CF-Granulator, Model CF-260, Freund Industrial Co., Ltd., Tokyo, Japan.

2. Hercules, Inc., Wilmington, Del.

3. Ruger Chemical Co., Inc., Irvington, NJ.

4. GAF Corporation, New York, NY.

5. Kind and Knox, Saddle Brook, NJ.

6. Beaver Food Products, Pennsauken, NJ.

7. Georgia Kaolin, Elizabeth, NJ.

8. Rohm Pharma GmbH Darmstadt, West Germany.

9. Knoll Fine Chemicals, Div. of Knoll Pharma Co., New York, NY.

10. Ganes Chemicals, Inc., Carlstadt, NJ.

11. Warner-Lambert, Holland, MI.

12. U. S. Standard Sieves, E. H. Sargent and Co., Chicago, IL.

13. Cenco-Meduzer Sieve Shaker, Central Scientific, Cenco Instruments Corp., Chicago, IL.

14. J. Englesmann A-G, Ludwigshafen am. Rh., West Germany.

15. Air Comparison Pycnometer, Model 930, Beckman, Lincolnwood, IL.

16. Type PTF, Pharma Test, Hamburg, West Germany.

17. SEM, Model 1200B, Amray, Bedford, MA.

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