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RESEARCH PAPER

Application of Powder-Layering Technology and Film Coating for Manufacture of Sustained-Release Pellets Using a Rotary Fluid Bed Processor

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ABSTRACT

The main objective of this study was to prepare pellets in a Roto-processor using the powder-layering process onto inert nonpareils and to evaluate the applicability of the Roto-processor setup for film coating. Nonpareils were loaded with phenylpropanolamine hydrochloride and film coated with ethyl cellulose polymeric dispersion (Surelease®). The drug loading was analyzed to test the efficiency of powder layering. The effect of polymer level on the drug release from the pellets and the pore size distribution in the membrane were studied. The yields for powder layering were greater than 90%. The dissolution studies on the film-coated pellets showed sustained release over a 10-hr period. The time required for 50% of drug release increased and the mean pore diameter decreased with an increase in polymer coating.

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INTRODUCTION

Pellets have gained importance in the prolonged action type formulations for oral administration. They owe their popularity to limited risk of dose dumping, improved flow properties, and flexibility in formulation development and manufacture.

One of the oldest processes for the manufacture of spherical pellets is agglomeration granulation in coating pans, which involves a layering process. Layering involves the deposition of successive layers of an active compound onto inert core particles or crystals/granules of the active compound. This process follows the principles of sugar coating as used in making nonpareil seeds (1). In order to obtain particles of uniform size, repeated particle size classification is necessary. The pelletization process changed dramatically after the introduction of the extruder/spheronizer (2). The process involves various stages such as wet massing, extrusion, spheronization, and drying followed by coating if required. The pelletization can also be done by spraying liquid (solution or suspension) using a top spray in a fluidized-bed dryer, using a bottom spray with Wurster insert in a fluid bed, or using a radial spray mode in a rotary fluid-bed granulator (3–6).

Bauer et al. (7) described the installation of bottom rotary disks into fluidized-bed units, which resulted in improved drying air efficiency and increased mixing. A novel agglomeration granulating system utilizing centrifugal fluidizing drive was reported by Funakoshi et al. (8), where the layering was done using a powder, and the binder solution was sprayed tangentially in the same direction as the moving bed of particles. Jager et al. (9) studied the effect of material motion on agglomeration in the rotary fluidized-bed granulator and showed that there was improved mixing efficiency, better reproducibility, increased binder solution spray rates, and formation of denser and more spherical granules. Gajdos (10) compared two different rotary granulators for the production of pellets and reported that both rotary granulators shortened the manufacturing process and were a major improvement in conventional pellet production methods. Ghebre-Sellassie et al. (11) evaluated a centrifugal pelletization equipment with different types of binders and concluded that this process is quicker and more easily reproducible. Regardless of which manufacturing process is used, pellets have to meet the following requirements:

- They should be of near spherical shape and have a smooth surface, both considered optimum characteristics for subsequent film coating.
- The particle size range should be as narrow as possible. The optimum size of pellets for pharmaceutical use is considered to be between 600 and 1000 μm.
- The pellets should contain as much of the active ingredient as possible to keep the size of the final dosage form within reasonable limits.

Even though the rotary granulators were proved efficient for making pellets, the utilization of the system for film coating was not studied extensively.

OBJECTIVE

The objective of the present study was to study the applicability of rotary fluid-bed processor for making sustained-release pellets in a two-step process: (a) loading of drug by powder layering onto inert nonpareils and (b) subsequent film coating of drug-loaded pellets with ethyl cellulose polymer dispersion in the same equipment.

MATERIALS AND EQUIPMENT

Phenylpropanolamine hydrochloride (PPA) (BASF Corp. Pharma Chemicals Dept., Mount Olive, NJ), nonpareils (Nu-Pareils® PG, 18/20 sieve cut, Crompton & Knowles, Mahwah, NJ), hydroxypropylcellulose, NF (HPC) Type-LF (Dow Chemical Co., Midland, MI), ethyl cellulose polymeric dispersion (Surelease®, Colorcon, West Point, PA), fumed silica (Cab-O-Sil, Cabot Corporation, Cab-O-Sil division, Tuscola, IL), and hydroxy propyl methyl cellulose (HPMC) (Opadry®, Colorcon Inc., West Point, PA) were used as received.

Fluid-bed Roto-processor Model MP-1 (Niro Inc, Columbia, MD), powder feeder (Accurate Dry Material Feeder, White water, WI), moisture analyzer (Computrac, CT Instruments Inc., Tempe, AZ), and peristaltic pump (Masterflex, Cole–Parmer Instruments Co., Chicago, IL) were used during the manufacture of the pellets. Dissolution apparatus type I (Vankel Industries, Edison, NJ), spectrophotometer (Beckman Model 35, Beckman Instruments, Allendale, NJ), mercury

porosimeter (Poresizer Model 9305, Micromeritics Instrument Corp., Norcross, GA), and scanning electron microscope (Jeol Technics Ltd., Tokyo, Japan) were used in the evaluation of the manufactured pellets.

EXPERIMENTAL

Description of the Manufacturing Equipment

Aeromatic MP-1 can be utilized for several processes such as fluid-bed granulation and drying, Wurster coating and pelletization, and layering using appropriate inserts or modules. One of these inserts is the Roto-processor, which is dedicated to the production and coating of pellets. It differs from other centrifugal machines by utilizing an inner wall that allows for two modes of operation, forming and drying. The design consists of two chambers: the inner one, called the forming zone, which consists of a rotating disk and a spray nozzle opening; and the outer chamber, called the drying zone. These two chambers are divided by a movable wall. The rotating disk comes in various surface textures including a smooth surface. In the present study, a smooth plate was used for layering and coating operations. During the initial stages of the pelletization process, the wall was kept in a lower position in a forming mode until simultaneous binder spraying and powder application produced pellets. Once pellets were formed, the Roto-processor wall was lifted pneumatically to produce a gap through which the pellets were propelled into the drying zone as a result of the centrifugal force created by the rotating disk. The pellets were fluidized by drying air flowing upward along the outside of the inner wall. The geometry of the unit caused pellets to fall back into the inner chamber where they were again forced out through the gap and recirculated. The outline of the setup is shown in Fig. 1.

Setup for Powder Layering

The powder was transported from a dry powder feeder into the inner bowl through a nozzle fitted with a horizontal screw (1 in. diameter). The powder feeder was mounted on specially fabricated platform fixed at the view port of the MP-1. The powder was fed under gravity through a stainless steel tube (1 in. diameter) positioned at 120° away from the spray nozzle. The tip of the tube was immersed to about 1 cm into the bed of the beads. Space was left between the tube and the wall

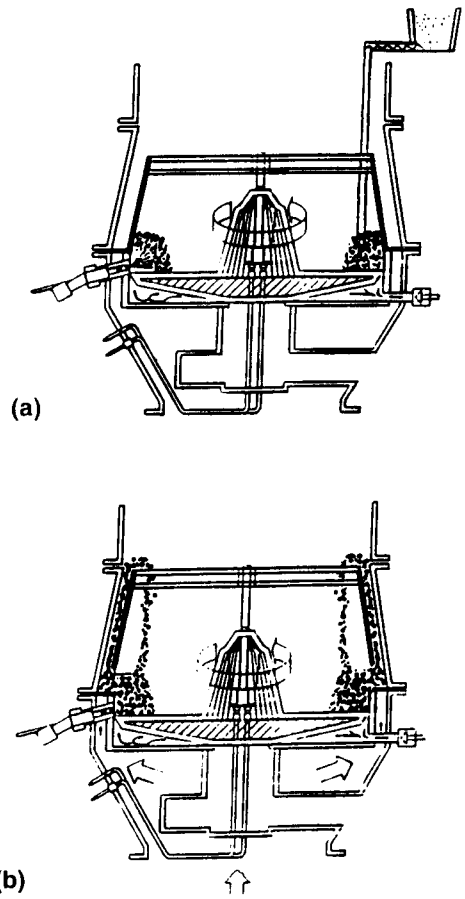

Figure 1. Schematic diagram of the Roto-processor depicting (a) powder layering and (b) drying.

of the inner chamber to allow free movement of the pellets.

Preparation of Solutions

HPC solution (4% w/w) was prepared by the addition of the powder to cold deionized water under stirring. The stirring was continued for 15 min and set aside for the foam to dissipate. HPMC solution was made by dissolving the powder in sufficient deionized water to make a 10% w/w solution. Surelease was diluted to 15% w/w solids, level with sufficient deionized water and used for film coating.

Layering

Experiments were performed with 1000 g of nonpareils as nuclei and PPA as model drug for powder lay-

ering. The PPA was blended with 0.5% w/w fumed silica in a plastic bag for 2 min and transferred into the powder feeder. A 1 in. diameter screw was used on the feeder to deliver the powder. The powder feeder was calibrated by monitoring the weight dispensed per unit time at various settings. Binder solution was continuously sprayed using a peristaltic pump and Schlick-type nozzle with a 1-mm orifice. The powder addition was started with a 30-sec lag time to the binder addition. Once the desired drug loading was achieved, both binder and powder additions were stopped, and the inner wall was raised pneumatically to let the pellets enter the drying zone. The pellets were dried for 2 min at 60°C and cooled for 1 min before they were discharged. The weight of the pellets was noted. Moisture content of the dried pellets was determined on a moisture balance. The processing conditions and yields are given in Table 1. The equipment was cleaned to remove the traces of the drug and the binder before film coating.

Seal Coating

The drug-loaded pellets of "16/20-sieve cut" were preheated to 45°C in the Roto-processor and coated with HPMC solution to a weight gain of 1%. The liquid addition rate was adjusted to keep the bed temperature around 45°C. The processing conditions for seal coating are given in Table 2.

Surelease Coating

HPMC-coated pellets of "16/20-sieve cut" were preheated to 45°C. The ethyl cellulose dispersion was sprayed onto the pellets using the same nozzle used for binder spray. Three separate batches were made with coating levels at 10, 12.5, and 15% weight gain. After coating was completed, the pellets were dried for 2 min at 60°C and cooled for 1 min before they were discharged. The processing conditions are shown in Table 3.

Table 1

Processing Conditions for Powder Layering Using HPC as Binder

Batch size (nonpareils) (g)	1000
Target quantity of drug to layer (g)	500
Rotor speed (rpm)	200
Binder spray rate (g/min)	4.8 ± 0.2
Powder addition rate (g/min)	15 ± 1
Amount of binder sprayed (g)	168 ± 8
Total time of layering (min)	37 ± 2
Inlet air temperature (°C)	25
Outlet air temperature (°C)	20–22
Bed temperature (°C)	23–14[a]
Gap air pressure (bar)	2–3
Atomization air pressure (bar)	1
Yield (%) calculated after processing	90–95

[a]The bed temperature dropped as the powder layering progressed.

Table 2

Processing Conditions of Seal Coating Using HPMC Solution on Drug Loaded Pellets

Batch size (g)	1350
Quantity of liquid sprayed (g)	135
Rotor speed (rpm)	200
Spray rate (g/min)	6–9.6
Inlet air temperature (°C)	60
Bed temperature (°C)	44–49
Gap air pressure (bar)	3
Atomizing air pressure (bar)	1.5
Fluidizing air volume (cfm)	140

EVALUATION ANALYSIS

Analysis

From each stage of the experiment, pellets having an equivalent weight of 40–50 mg of the drug were weighed and powdered in a glass mortar. The powder was carefully washed into a 50-ml volumetric flask with the help of distilled water. The flask was sonicated for 15 min and the volume was adjusted to 50 ml with distilled water after the flask was allowed to cool to room

Table 3

Processing Conditions of Film Coating Using Ethyl Cellulose Dispersion to Polymer Levels of 10, 12.5, and 15% Weight Gain

Batch size (g)	1000
Rotor speed (rpm)	200
Spray rate (g/min)[a]	10–16
Inlet air temperature (°C)	60
Bed temperature (°C)	45
Gap air pressure (bar)	3
Atomizing air pressure (bar)	1.5
Fluidizing air volume (cfm)	140

[a]The spray rate was increased to keep the bed temperature around 45°C.

temperature. The liquid was then centrifuged for 30 min at 3000 rpm. The absorbance of the supernatant clear liquid was measured at 256.6 nm using a UV spectrometer.

Scanning Electron Microscopy (SEM)

The surface characteristics of the pellets were observed by taking scanning electron micrographs using a scanning electron microscope. The pellets were dried overnight in a vacuum oven and fixed on an aluminum stub using double-sided tape. The pellets were sputter coated with Au/Pd alloy for 7 min in a Hummer sputter-coating machine. The pictures were taken at an excitation voltage of 25 kV using a TMAX 100 speed film.

Dissolution Studies

Drug release was determined using pellets containing 800 to 900 mg of PPA. The dissolution studies were performed using a USP XXII type I apparatus (rotating basket) with basket rotation at 50 rpm and 900 ml of distilled water at 37°C ± 0.5°C as dissolution medium. Drug release from 6 samples of each batch was determined by measuring the absorbance at 256.6 nm using a UV spectrometer with 1-cm path length quartz flow cells. Dissolution medium was continuously circulated through the flow cells and returned to the dissolution vessels by a peristaltic pump.

Porosity Measurements

Porosity of the pellets at various stages was determined using a mercury intrusion porosimeter. The pellets were dried overnight in a vacuum oven to remove moisture and any adsorbed gases. A computer was interfaced with the poresizer to collect the intrusion data. The intrusion volumes were collected up to 30,000 psi.

Powder Layering Efficiency

Total yield was defined by subtracting the charge load, polymer weight, and the moisture content from the final weight, and dividing with weight of powder added. Moisture contents were determined as a percentage loss of drying at 100°C using a moisture analyzer. The actual drug loading was determined by analysis for the drug in the pellets.

RESULTS AND DISCUSSION

To produce successful powder-layered pellets, three factors that need to be addressed are binder application on the substrate to create uniform wetted surface, balancing the powder and binder application rates, and the densification of pellets by rolling in a rotary fluid bed. All these factors can be achieved by setting proper processing parameters.

The disk speed was set at 200 rpm for layering and coating. Higher speeds caused the loss of the rope-like motion of the pellets and caused the bed to slide on the rotating disk as the binder was added. This, in turn, caused uneven distribution of the binder and agglomeration of pellets. Lower disk speeds caused similar problems due to uneven distribution of the binder.

The nozzle position in the MP-1 Roto-processor is perpendicular to the flow of the pellets. Making droplet size finer results in coverage of greater surface area on the pellets, resulting in more uniform wetting. When the ratio of binder spray rate to the powder addition rate was high, the bed became wetter and resulted in agglomeration. The binder spray rate and powder addition rate had to be optimized in order to reduce the agglomeration of the pellets and improve the layering efficiency. The binder spray rate should be based upon the surface area of the pellets over which binder gets distributed. Even though the effect of the particle size of the powder in relation to the substrate was not studied, the surface area and the particle size of the powder are critical in determining the binder spray rate.

The powder addition rate and point of application are equally important. The powder was introduced into the bed of pellets at an angle of 120° from the spray nozzle. After passing the spray zone, the pellets rolled out at about 120° from the spray nozzle when the rotor speed was at 200 rpm. If the point of powder application was moved to a different position, the yields were decreased. The yields for powder layering were around 95%, calculated as a percentage of drug used for powder layering. The assay results were in close agreement with the calculated yields and are shown in Table 4.

Another aspect to consider during yield evaluation is the amount of fines and small agglomerates generated during the process. Even though the drug loading was about 50% of the starting material, less than 0.5% of agglomerates smaller than 30 mesh were formed, thus showing the efficiency of powder layering in the Roto-processor. The total processing times for loading 500 g of drug on 1000 g of nonpareils was between 35 and 40 min. These times were far less than the processing times

Table 4

Comparison of the Theoretical Yield and Chemical Assay After Powder Layering

	Theoretical Yield (%)	Spectrophotometric Assay (%)
Batch 1	95	94.6
Batch 2	93.3	92.8
Batch 3	90.7	90.1

for solution layering of similar quantity of drug in the same equipment, reported by Iyer et al. (6).

Drug release from the coated pellets depends on the uniformity of the coating. The success of any coating process is based on the uniformity of coating on the pellets within a batch and reproducibility from batch to batch. When coating is based on weight gain, the thickness of the membrane is controlled by the surface area of the pellets on which the coating is applied. To reduce the variability, similar sieve-cut pellets were taken for coating. The porosity of the drug-layered pellets was very high, resulting in high surface area. The migration of drug and other components of the core material into the film coating have been reported by Aulton et al. (12) and Simpkin et al. (13). In a separate study, Dansereau et al. (14) suggested that the surface dissolution of the drug or excipient into the film coating could be controlled by choosing proper inlet air temperature and spray rate. Yang et al. (15) reported that application of a seal coat totally eliminated or minimized drug migration into the sustaining functional coat during the coating operation. In order to eliminate or minimize the migration or leaching of the drug into the functional membrane, the drug-layered pellets were initially coated with HPMC to form a seal coat. The seal coat also provides an added advantage of protecting the powder layer from losing the drug during further handling. The seal-coated pellets were further coated with ethyl cellulose dispersion at three levels of weight gain. The rate of drug release from the pellets decreased with an increase in the coating level. The release profiles are shown in Fig. 2 and the time to release 50% ($t_{50\%}$) of the drug is shown in Table 5. The low variability in the release profiles of the 6 samples during the dissolution was an indication of the uniformity of the layering and coating operations. In a fluid-bed dryer, even though fluidization is efficient, there can be blind spots during the coating operation which may cause uneven distribution of the coating solution. In a Roto-processor, the centrifugal forces imparted by the rotating disk to the pellets in association with the upward forces generated by the gap air cause intense agitation. These intense forces may completely eliminate the blind spots in the bed, resulting in even drug layering and uniform film coating.

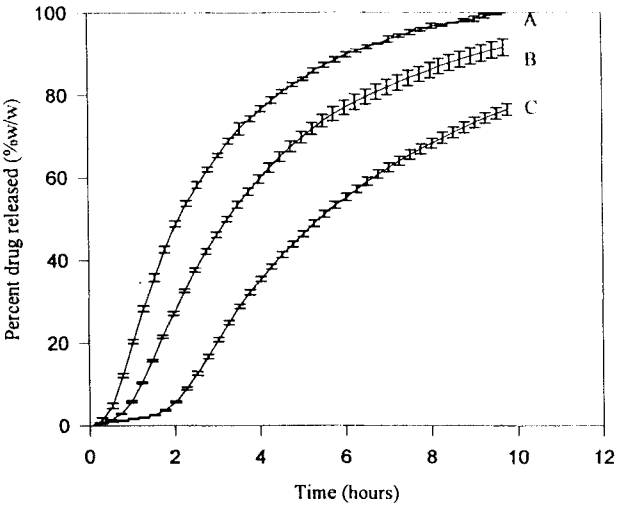

Figure 2. Dissolution profiles of phenylpropanolamine hydrochloride pellets coated with ethyl cellulose dispersion: A represents 10% coat level, B represents 12.5% coat level, and C represents 15% coat level.

Drug release through ethyl cellulose membrane is expected to occur by diffusion through the membrane and the micropores in the membrane. Therefore, drug release depends on the thickness and the porosity of the membrane. The mean pore diameter and porosity measured on the coated pellets showed that they were indirectly correlating to the $t_{50\%}$ values of the three formulations studied. It can be seen from that data that with increasing the level of ethyl cellulose coating, the mean pore diameter and the porosity decreased and the pore size distribution shifted toward smaller pores. The porosity and the mean diameters are given in Table 6.

The SEMs are shown in Figs 3–6. Figure 3 shows the surface morphology of the powder-layered pellet at

Table 5

Dissolution Data

Batch Type	$t_{50\%}$ (min)
Pellets coated with Surelease to a 10% wt. gain	126
Pellets with Surelease coating at 12.5% wt. gain	206
Pellets with Surelease coating at 15% wt. gain	325

Table 6

Porosity Data from the Mercury Intrusion Porosimeter

Type of Formulation	Mean Pore Diameter (μ)	% Porosity
Nu-pareils (blank)	0.6009	16.3
PPA layered pellets	0.4871	16.3
Opadry-coated pellets	0.2743	14.5
Pellets with Surelease coating at 10% wt. gain	0.0256	14.9
Pellets coated with Surelease at 12.5% level	0.0232	13.6
Pellets coated with Surelease at 15% level	0.0141	7.3

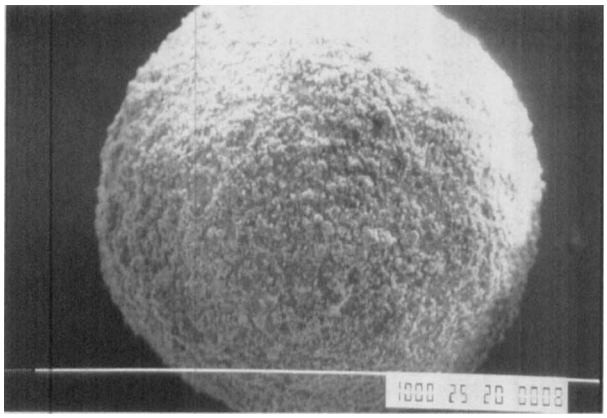

Figure 3. SEM of intact powder layered pellet (original magnification 100×).

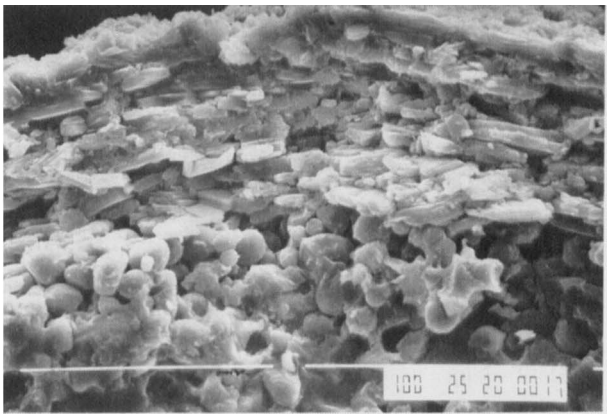

Figure 4b. SEM of cross section of a powder-layered pellet (original magnification 500×).

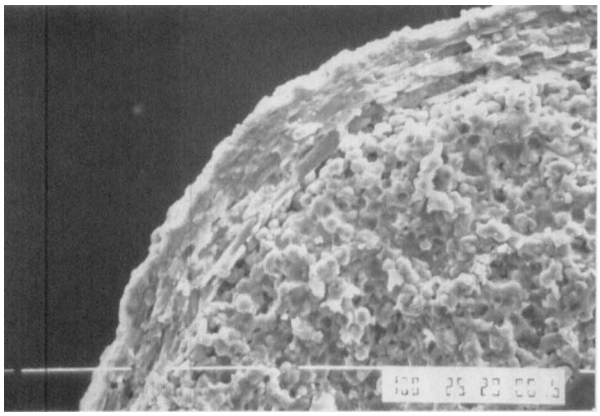

Figure 4a. SEM of a cross section of powder-layered pellet (original magnification 200×).

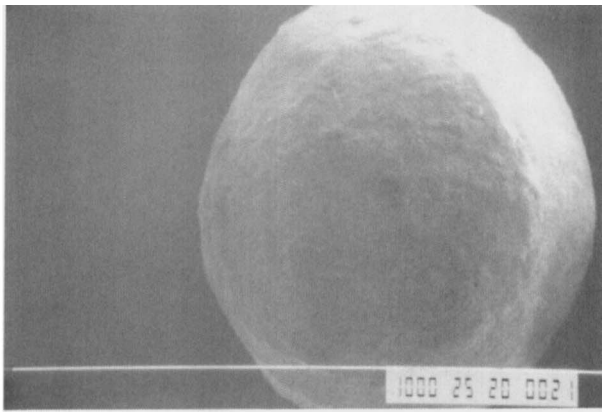

Figure 5. SEM of an intact ethyl cellulose coated pellet (original magnification 100×).

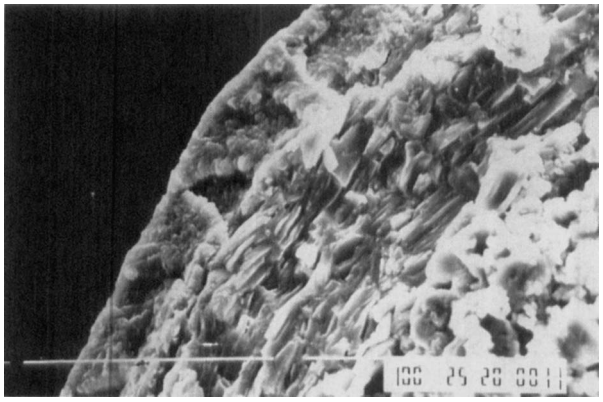

Figure 6. SEM of cross section of an ethyl cellulose coated pellet (original magnification 500×).

a magnification of 100×. The uniform layering of drug particles on the nonpareil core (spherical particles) can be seen in the dissected pellets under 200× and 500× magnifications in Figs. 4(a) and 4(b). Figure 5 shows the ethyl cellulose coated pellet, highlighting the smooth surface and round shape. The cross section of the same pellet in Fig. 6 shows distinct layers of ethyl cellulose, PPA, and the nonpareil core. The uniformity of ethyl cellulose membrane over the drug layer can be seen in this SEM.

CONCLUSIONS

In conclusion, drug-loaded pellets can be successfully made by powder-layering technology in a Roto-processor with excellent yields, and film coating can be done with the same setup without additional equipment. Sustained-release pellets with high drug loading and uniform coating can be made in short processing times in a Roto-processor.

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