DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(9), 981-998 (1993)

EVALUATION OF DRUG LAYERING AND COATING: EFFECT OF PROCESS MODE AND BINDER LEVEL

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Top-spray layering and Wurster coating are common techniques for layering and coating operations, respectively. In the present study, the efficiency of these techniques was compared with rotolayering and rotocoating in the Niro-Aeromatic MP-1 Rotoprocessor. Also, three different polymers were evaluated as binding agents in the layering procedure. A solution containing drug and a suitable binder was layered onto non-pareil seeds followed by coating with a water-insoluble polymer. The pellets were evaluated for physical properties, surface characteristics and drug content (assay). The process efficiency was evaluated from process time, assay, and SEM data of the pellets. Efficiency of layering was compared between toplayering and rotolayering processes while efficiency of coating was compared between Wurster coating and rotocoating processes. The physical properties of pellets were used to explain the influence of binder nature and level of use in the layering process.

INTRODUCTION

Pellet dosage forms (1) provide excellent flow properties and ease of handling, less variations in gastric emptying rates and ideal shape for coating applications. Layering is one of the techniques for pelletization shown in Fig.1. In Liquid Layering, a

1. fluid-bed rotary granulation
2. drug layering
   a. top spray fluid-bed layering
      1. solution
      2. suspension
   b. rotary fluid-bed layering
      1. solution
      2. suspension
      3. powder feed
   c. pan layering
3. extrusion and spheronization

FIGURE 1
Techniques of Pelletization

solution or suspension of the drug containing a suitable binder ("fixing-agent") is sprayed onto non-pareil seeds in a fluidized bed (2,3,4). In addition to the top spray and Wurster, a relatively new mode of layering is the rotary spray (5) where the liquid is sprayed radially to the flow of particles. In this mode, the particle cycling time is very short and drug levels of up to 75% are achievable (6).

OBJECTIVES

The literature available on layering is limited. In a comparative study of Wurster and toplayered pellets, the recovery on assay was 79.6% and 64.7% respectively, indicating that both modes of layering are deficient (7). The binder used in layering influences liquid penetration and rate of wetting of the final product (8) as also the choice of equipment used for the process. In the MP-1 Rotoprocessor (9), the tip of the spray nozzle is at the periphery of the product chamber with a large volume that supposedly minimizes agglomeration. Also, a central partition in the product chamber forms the granulation zone. The area between the partition and chamber wall houses a screen through which fluidizing air passes into

the chamber. This area is higher than that of the slit width between the wall and rotor plate resulting in a high air volume.

The objectives of this investigation are:

a. to compare layering by top-spray and rotary spray in the MP-1 Rotoprocessor.
b. to compare Wurster and rotocoating processes.
c. to study the effect of binders on pellet properties.

EXPERIMENTAL

Materials

Phenylpropanolamine HCl (PPA), Lot H736176, NU-PAREILS 18/20 mesh (Lot 071-029, Ingredient Technology Corporation, Pennsauken, New Jersey), POVIDONE^R K 29/32 (Lot TX - 40809, GAF Corp. New York), HPMC E-5 (USP grade 2910, Methocel^R Lot MM9007-3121-E, Dow Chemical Co., Midland, Michigan), Gelatin 5A (Pharmagel B Lot Y2418A05, Amend Drug & Chemical Co., Irvington, New Jersey), PEG 400 (Lot B 13600, J.T.Baker Chemical Co.), Ethylcellulose (SURELEASE^R, Lot 600033, Colorcon, PA).

An experimental design for this study is shown in Fig. 2. Aqueous systems were used to facilitate handling and minimize hazards (10). Formulation and process conditions are given in Tables 1 and 2. The layering solution was prepared by dissolving the drug in warm water (40°C) and mixing with an aqueous solution of binder and PEG 400. Where needed, the binder was hydrated before mixing. 480 g of SURELEASE^R (25% solids) was mixed with 320 g of water to obtain 800 g of the coating dispersion (15% solids).

One or two kg of non-pareil seeds was layered with the drug-binder solution in the MP-1 Rotoprocessor and processing time and yield were noted. Each batch of pellets was sifted through a 16 mesh sieve and those with no more than 5% agglomerates were used further. The

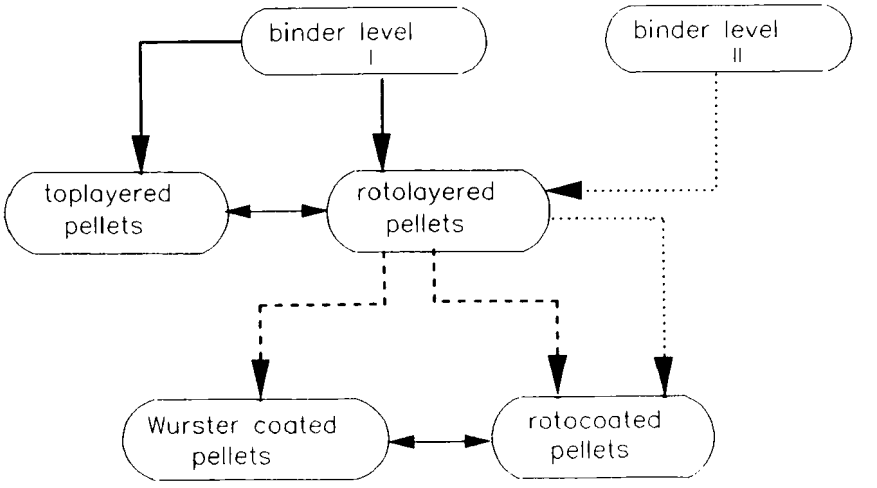

FIGURE 2
Processing Flow Chart

TABLE 1

Process Parameter Levels for Coating and Layering in the Niro-Aeromatic MP-1 Rotoprocessor

Process parameter	Level	Comments
LAYERING		
Solids content	22.8 %	constant
Batch size	1 or 2 kg	
Spray rate	up to 20 g/min.	varying
COATING		
OPADRY®		
solids content	10% w/w	
qty. applied	1% w/w	
Batch size	1 kg	
SURELEASE®		
solids content	15% (w/w)	
amount sprayed	800 g	
Spray rate	up to 20 g/min	varying
EQUIPMENT		
Inlet temp.	50°C	
Exhaust temp.	37 - 41°C	
Nozzle dia.	0.8 mm	
Atomization press.	1 Bar	
Air volume	80 - 150 cfm	

TABLE 2

Composition of Layering Solution

Ingredients (for 1 kg non-pareils)	Quantities (g) level I	level II
PPA HCl	150	150
Binder	8	20
PEG 400	2	5
Distilled Water	540	591

layered material was assayed in duplicate and those batches whose drug content was within ±10 % of theoretical were used for subsequent coating. In this study, each run is a single batch of layered pellets.

An "overcoat" was applied to the layered pellets before coating to minimize leaching of drug into the aqueous coating. One kg of layered pellets was coated with the polymer dispersion by spraying to a specified weight gain. As above, each run is a single batch of coated pellets.

Processing parameters were held constant as outlined in Table 1. The exhaust temperature was maintained during the process by independently varying spray rate and air volume.

Evaluation of pellets

The pellets were sifted through 14 mesh sieve to remove agglomerates. The layered pellets were assayed for drug content in duplicate by dispersing an equivalent of 100 mg drug in 200 ml distilled water and measuring the absorbance of a supernatant aliquot in a Perkin Elmer Model 3 D spectrophotometer at 256 nm. A helium pycnometer (Micromeritics, Narcoss, GA.) with a 5 cm^3 sample chamber was used to obtain the true density. Particle size analysis was done by placing a 20 g sample

over a set of sieves (# 14, 18, 25 and 30) in an Allen-Bradley Sonic Sifter and sifting for 7 mins. Specific surface area of pellets was obtained from surface area measurements in a Flowsorb II 2300 instrument (Micromeritics Inc., Narcoss, GA.) using krypton as the adsorbing gas (He-Kr mixture with 0.01% Kr) at the temperature of liquid nitrogen and atmospheric pressure. Coated pellets were evaluated as above except that in the assay procedure, the sample was crushed before dispersion as ethylcellulose is water insoluble. Drug release studies were performed in a six-spindle Model 3000 Dissolution System (Distek Inc.) equipped with USP basket apparatus and manual sampling ports. About 5 g of pellets was weighed accurately in the USP basket and placed in the dissolution vessel containing 900 ml of distilled water as the medium held at a temperature of 37°C. The stirring speed was maintained at 100 ± 2 rpm and sampling was done at specific intervals over a 10 h time period and absorbance recorded. Each data point was obtained as a mean of six runs (n = 6).

RESULTS AND DISCUSSION

Process Efficiency (top spray liquid layering vs rotary spray liquid layering)

Rotolayered pellets had a smooth, spherical surface with no loss of drug as seen from Fig. 3 and assay results in Table 3. However, top layered pellets had a rough surface morphology (SEM in Fig. 4), lower yield, a drug content varying from 82% to 88% and a smaller particle size. This was true for all three binders studied. This may be due to loss of drug from spray drying of solids inside the walls of the expansion chamber and due to agglomeration of pellets from the improper distribution of material on substrate during spraying. The process efficiency in both modes, however, was the same as process variables and time (Table 1) were

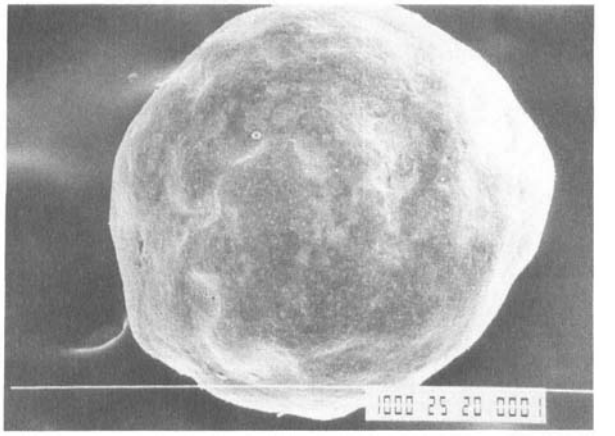

FIGURE 3
SEM of rotolayered pellet - HPMC binder

TABLE 3

Evaluation of Rotolayered and Toplayered Pellets
Binder Level I

Binder	Mode[a]	Density (g/cc)	Size (microns)	Assay (%)	Process time (min.)
HPMC	RL	1.454	896	103	90
	TL	1.400	903	82.4	85
Gelatin	RL	1.456	909	102	90
	TL	1.395	886	86.2	90
PVP	RL	1.434	1013	99.1	83
	TL	1.414	925	88.3	85

[a] RL - rotolayering TL - toplayering

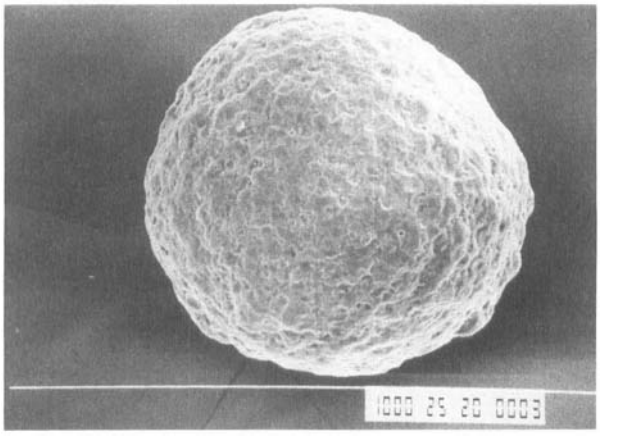

FIGURE 4
SEM of toplayered pellet - HPMC binder

constant. A key variable in toplayering is the distance from nozzle to bed: too close a distance can result in agglomeration while too far can result in spray drying. A slower spray rate in the top spray mode may achieve the desired result at the expense of process time. In the rotolayering mode, a shorter particle cycling time and greater volume for material movement enabled a higher spray rate and shorter process time. Also, no loss of drug by spray drying or agglomeration was observed. Comparatively, the volume for fluidization and material movement in toplayering is limited.

The true density of the pellets decreased in the order of non-pareils, layered pellets and then coated pellets (Table 3). The presence of cracks or fissures on the surface of the pellets can lead to a lower volume of displacement for helium and a higher density. A lower density on progression from non-pareils to coated pellets implies fewer surface defects. The density of coated pellets was lower presumably due to the low density (1.14 g/cm^3) of the polymer, ethylcellulose.

From Fig. 5 it is seen that layering retains the pellets in the same size range as before (> 80%) while the transition to the next oversize range was seen only after the coating. Thus, after coating, the volume gain is significant enough to increase the mean particle size by one sieve size, i.e. from 18/25 to 14/18. Also, that this increase is not due to agglomeration may be observed from density and size analysis data as follows (using HPMC data):

Mean size for non-pareils is taken as mean of # 18 and # 25 mesh size, i.e. 855 micrometers. Assuming perfect spheres, the volume of a particle with this diameter is 3.27×10^{-4} cc. Since the density is 1.541 g/cc, the weight of one particle may be approximated at 5.04×10^{-4} g. The layering and coating processes result

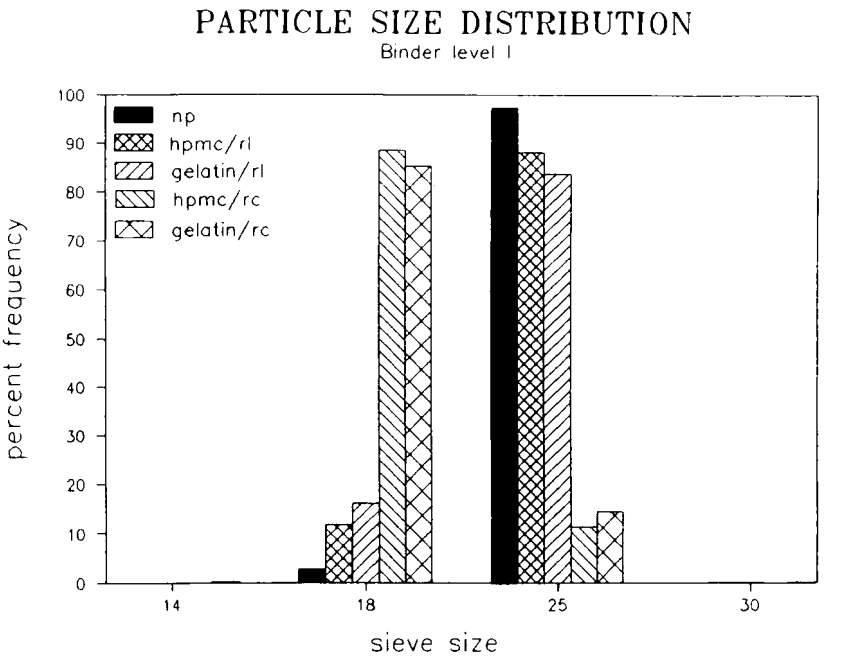

FIGURE 5
Particle size distribution of pellets
binder level I

in particle buildup of about 32% which for one particle is then estimated at 6.61 x 10^{-4} g. The volume of one such particle, based on the density of final pellets (1.369 g/cc) is 4.82 x 10^{-4} cc. Assuming spherical shape, the diameter of such a particle becomes 975 micrometers, greater than the mean size for 18/20 mesh. For non-pareils, the particle size is distributed mainly between #18 and #25 mesh. If it is assumed that two particles in this range agglomerate, the least possible size of the agglomerate will be the sum of two 25 mesh particles (i.e. 1710 microns). Since more than 90% of the coated particles are within #18 mesh size (1000 microns), the increase in particle size to the next sieve cut is due to actual material buildup on the non-pareils and not agglomeration.

TABLE 4

EVALUATION OF ROTOLAYERED PELLETS AT BINDER LEVELS I &II

Binder	Mode	Density (g/cc)	Size (microns)	Assay (%)
HPMC	I	1.454	896	103
	II	1.472	1057	101.2
Gelatin	I	1.456	909	102
	II	1.454	1081	103.5
PVP	I	1.434	1013	99.1
	II	1.455	1094	103

Binder Evaluation

Results from the evaluation of rotolayered pellets are shown in Table 4. The SEMs of pellets in Figs. 3, 6 and 7 indicate a smooth surface except for those with PVP as the binder that had an uneven, rough surface. Since aqueous solutions of PVP are extremely tacky, it is possible that at the spray rate used, the material formed "lumps" instead of coalescing around the non-pareils. A lower spray rate and antitack additives could possibly have reduced this effect. The uneven surface of PVP layered pellets may explain the apparent greater particle size compared to that of pellets layered with gelatin or HPMC.

The specific surface area of the layered and coated pellets from Table 5 are lower for gelatin and HPMC than for PVP which could be due to permeation of the adsorbed gas into the pellets through cracks on the surface. The coated pellets had a lower surface area.

Among the three binders used, HPMC provided pellets with the slowest release (maximum t_{50}), smallest particle size and best content uniformity.

Pellets obtained at binder level II had a rough surface compared to level I as seen from Figs. 6 and 8.

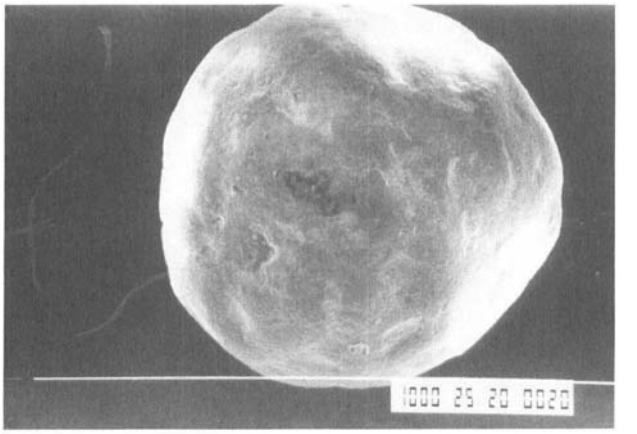

FIGURE 6
SEM of rotolayered pellets - gelatin binder

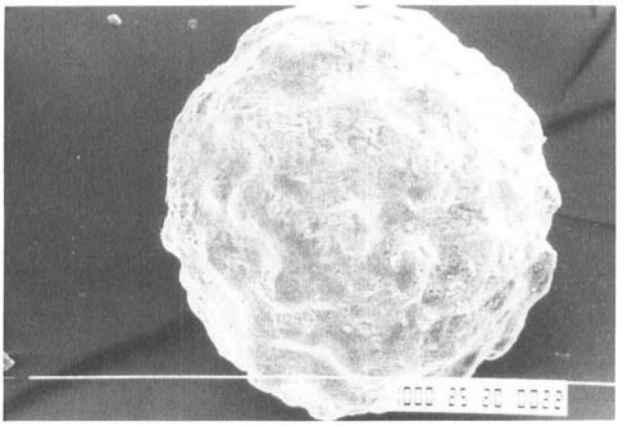

FIGURE 7
SEM of rotolayered pellets - PVP binder

TABLE 5

Specific Surface Area (m^2/g) of Pellets

Binder	Level	Rotolayered	Rotocoated
HPMC	I	0.106	0.043
Gelatin	I	0.099	-
PVP	I	0.145	-
HPMC	II	-	0.047

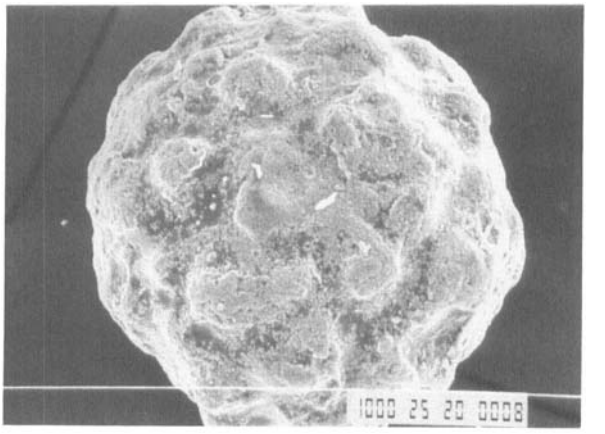

FIGURE 8
SEM of rotolayered pellets - gelatin level II

In fluidized beds, the viscosity of binder solution and contact angle at the surface of the solids influence droplet size and granule growth (8). Since drying takes place simultaneously with liquid addition, the binder concentration increases and the liquid bridges gradually become viscous and immobile. A very viscous binder solution can give rise to an uneven surface if it is immobilized before complete bridging. Thus the amount of binder should be enough to adhere the drug on the non-pareils and also provide a uniform surface on drying. In the present study, binder level II appears to exceed the minimum requirement.

Process Efficiency in Polymer Coating

Results from the evaluation of coated pellets are shown in Table 6. Since fluidization patterns vary in Wurster and rotary modes, mean air velocity in the chamber, process time and $t_{50\%}$ drug release were used as indices of process efficiency.

The inlet flap setting was calibrated for air flow in the MP-1 Rotoprocessor at zero resistance (no load)

TABLE 6

Evaluation of Rotocoated and Wurstercoated Pellets
Binder Level I

Binder	Mode[a]	Density (g/cc)	Size (microns)	Assay (%)	Process time (min)	$t_{50\%}$ (min)
HPMC	RC	1.369	1160	102	85	175
	WC	1.355	1171	109	93	125
Gelatin	RC	1.370	1146	99	80	135
	WC	1.397	1174	107	91	100
PVP	RC	1.360	1184	108	84	100
	WC	1.368	1182	104	95	125

a RC - rotocoating WC - Wurstercoating

and with a 1 kg. load for both Wurster and rotary inserts, as shown in Fig. 11. At a given flap setting, with a load in the chamber, the rotary insert provides a greater air volume indicating lower bed resistance. During coating, the inlet damper set point and actual air volume (cfm) were monitored. For each damper setting, the air flow was calculated from the calibration data. From the air flow, the mean air velocity was calculated as follows:

1. Rotary insert:

$$\text{Velocity (ft/s)} = \frac{\text{Air volume (cfm)}}{60 * \text{Air distribution area (ft}^2\text{)}}$$

$$\text{Drying area} = 0.025 \text{ sq.m}$$

2. Wurster insert:

Since material is essentially fluidized within the column, the pressure drop in the static bed outside the column is higher than inside. Thus, a considerable amount of fluidized air flows through the column. Since the ratio of column area to static bed area was about 0.13, the air volume through the column must be greater than

TABLE 7

Air Velocity for Wurster and Rotocoated Pellets
Binder Level I

Binder	Mode[a]	Calculated velocity (ft/s)
HPMC	RC	3.29
	WC	7.27
Gelatin	RC	1.50
	WC	6.81
PVP	RC	1.50
	WC	6.36

[a] RC - rotocoating WC- Wurstercoating

13% of the total volume. If roughly 50% of the air gets directed through the column, then

$$\text{Velocity (ft/s)} = \frac{0.5 * \text{Air volume (cfm)}}{60 * \text{Wurster plate area (ft}^2\text{)}}$$

Wurster column area = 0.0026 sq.m

The calculated velocities for Wurster and rotary inserts are shown in Table 7. For a given inlet damper setting, a higher air volume and lower velocity provide more efficient drying in the rotary insert than the uWurster. Also, no agglomeration was observed in this process. The Wurster coated pellets had a rougher surface than rotocoated pellets as seen from SEMs in Figs. 12 and 13.

The process time for both processes was almost the same although slightly shorter for rotocoating.

Release Studies

Release profiles of coated pellets layered at binder levels I and II are shown in Fig. 9 while that for Wurster and rotocoated pellets at binder level I are shown in Fig. 10. The drug release from the coated pellets was sustained over a 10 h period and since the drug is highly water soluble, the release is not limited by dissolution rate. Prolonged drug release from pellets

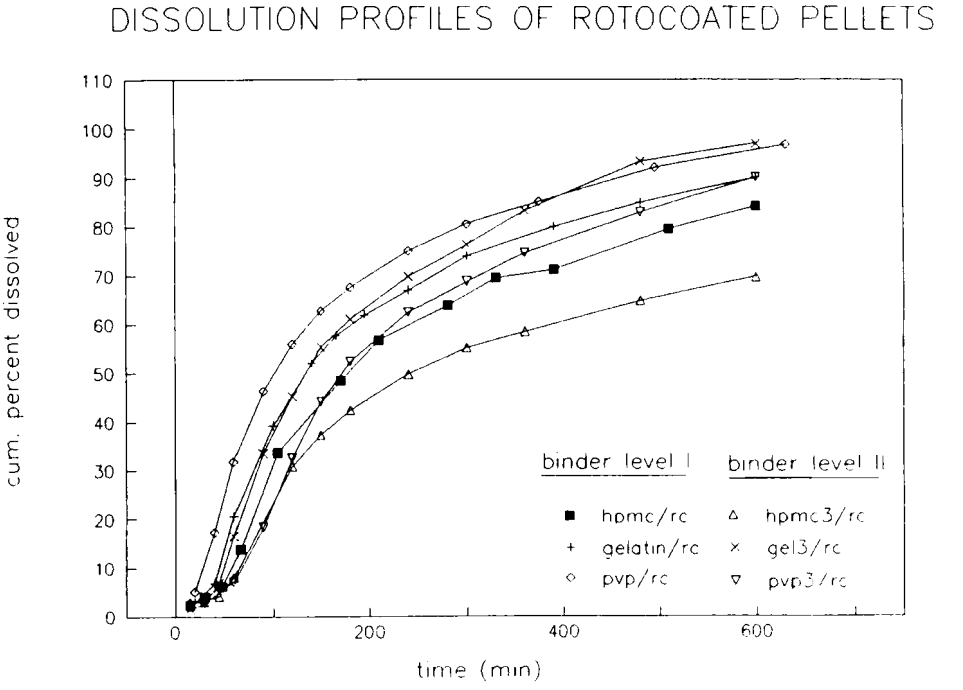

FIGURE 9
Dissolution profiles of rotocoated pellets (binder level I vs II)

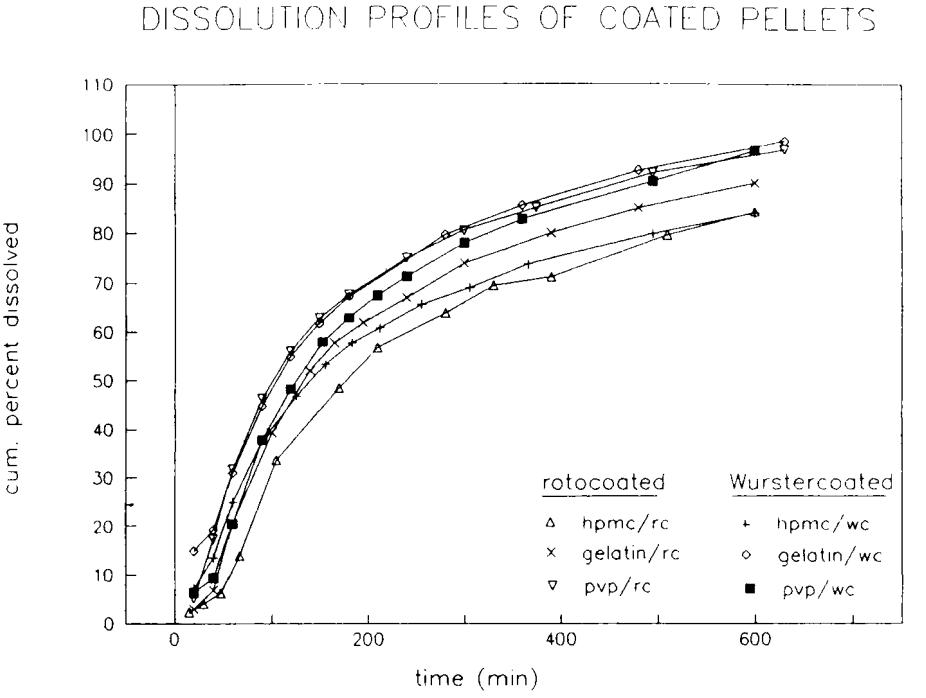

FIGURE 10
Dissolution profiles of coated pellets (Rotocoated vs Wurstercoated)

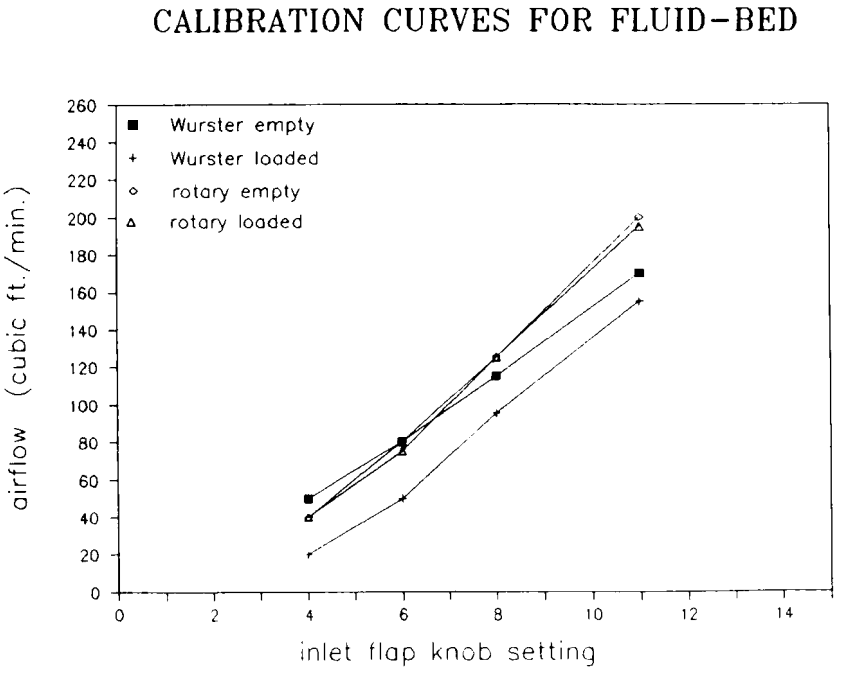

FIGURE 11
Calibration curves for fluidized bed in MP-1

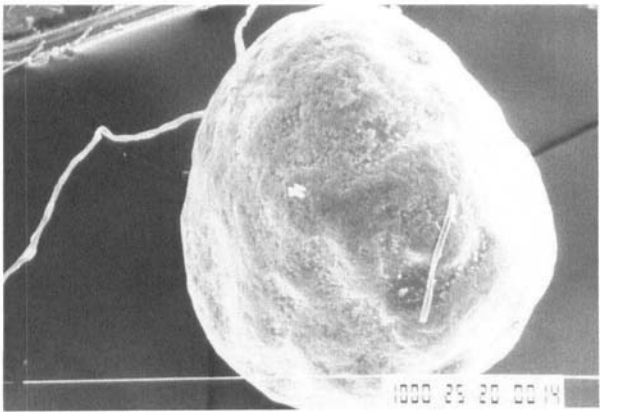

FIGURE 12
SEM of rotocoated pellets

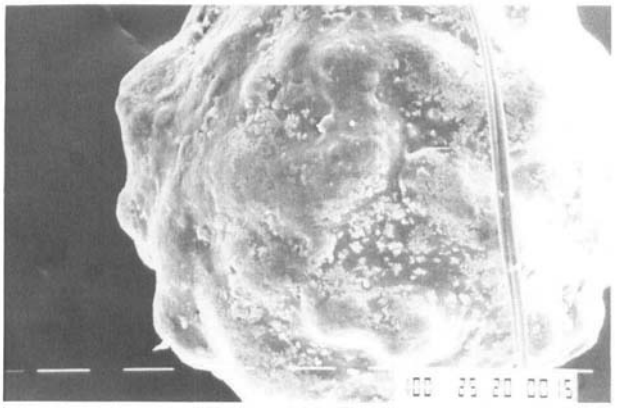

FIGURE 13
SEM of Wurstercoated pellets

layered with soluble or insoluble drugs and then coated, have been reported in the literature (2, 7).

The $t_{50\%}$ was the same for Wurstercoated pellets for all three binders but varied for rotocoated pellets depending on the binder chosen as seen from Table 6. Also, drug release was slower from rotocoated than from Wurstercoated pellets.

In a comparative study of different coating levels of ethylcellulose (11), drug release was presumed to be mediated via the tortuous matrix of the polymer layer at 2-10% coating while at levels from 12 - 20%, the release occurred by diffusion through the polymer film. At intermediate levels of 11 - 12%, as in the present study, both mechanisms are operative. Thus drug release occurs via the tortuosity of the drug-binder layer and concentration gradient across the polymer film.

CONCLUSIONS

Rotary spray offers a better mode of drug layering than top spray. Also, rotocoating is a viable alternative to the conventional Wurster process. The binder for layering

can influence the surface features of the pellets. The MP-1 Rotoprocessor was found to be amenable to layering and coating by the rotary process.

ACKNOWLEDGMENTS

We thank Niro-Aeromatic Inc. (Columbia, MD) for the equipment and a research grant to support this work.

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