exhibit different R_f values. Table III shows the average R_f value of vancomycin and factor A in the two solvent systems.

Vancomycin and factor A could be determined semiquantitatively by densitometry over a range from 2 to 10 mcg. Reliable scanning was difficult with greater amounts because of streaking, especially where mixtures of the two components were involved. Figure 2 shows the linear curve of vancomycin (USP reference standard) concentration *versus* average spot density calculated from five plates and the effect of factor A on this curve. Factor A has little or no effect on the lower range (3 to 6 mcg.) but appears to inhibit color development at higher levels.

The vancomycin factor A used in this work was impure, as it contained approximately 20% vancomycin as estimated by TLC. The R_f values quoted as "factor A" are for the major, slower running spot. In making the densitometer readings for vancomycin in mixtures it was necessary to begin the scan from the lowest background reading between the spots for vancomycin and factor A.

The Folin-Ciocalteau assay is obviously not specific for vancomycin hydrochloride and should not be used in the absence of other criteria of identity. One such procedure is thin-layer chromatography which also detects the presence of interfering materials including factor A. Where nonphenolic impurities occur, the Folin-Ciocalteau method is recommended as the most convenient assay. Where impurities such as factor A are encountered, the semiquantitative assay of vancomycin by TLC with Folin-Ciocalteau spray followed by densitometry provides an alternative.

These data show that the chemical methods may supplement the current microbiological procedures for the qualitative and quantitative determination for this drug.

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Keyphrases

Vancomycin HCl
Colorimetry—analysis
Folin–Ciocalteau reaction
Microbiological analysis
TLC–densitometric scanning
Factor A–vancomycin—TLC separation

Technical Articles

Design and Evaluation of a Miniature Air-Suspension Coating Apparatus

By HAL N. WOLKOFF, GEORGE PINCHUK, and PAUL H. SHAPIRO

Experiments were conducted, using a miniature air-suspension coating apparatus designed and built in these laboratories, to determine the feasibility of uniformly coating gram quantities of various sized and shaped particles. The coating chamber used has an inner diameter of 1.22 in. and an overall length of 4.875 in. A schematic drawing of the apparatus is presented and the function of each component as well as its critical dimensions are discussed. The coating capabilities of the apparatus were explored using nonpareil seeds, tablets of several sizes and shapes, and hard gelatin capsules. Data are presented to compare the relative coating efficiency of the miniature unit with the widely used 6-in. Wurster apparatus. The results indicate that minor differences do exist in terms of coating efficiency but that the two units are comparable with respect to the uniformity of coating which can be achieved.

AIR-SUSPENSION coating techniques have generated considerable interest since Wurster's disclosures in 1953 and 1957 (1, 2). The process has been widely used on an experimental basis and, to a lesser extent, in commercial production. It has as its major advantages simplicity of operation, versatility, rapidity, and uniformity of the final product. As opposed to conventional pan coating techniques, this process provides for rigorous control over the many factors responsible for batch-to-batch variability.

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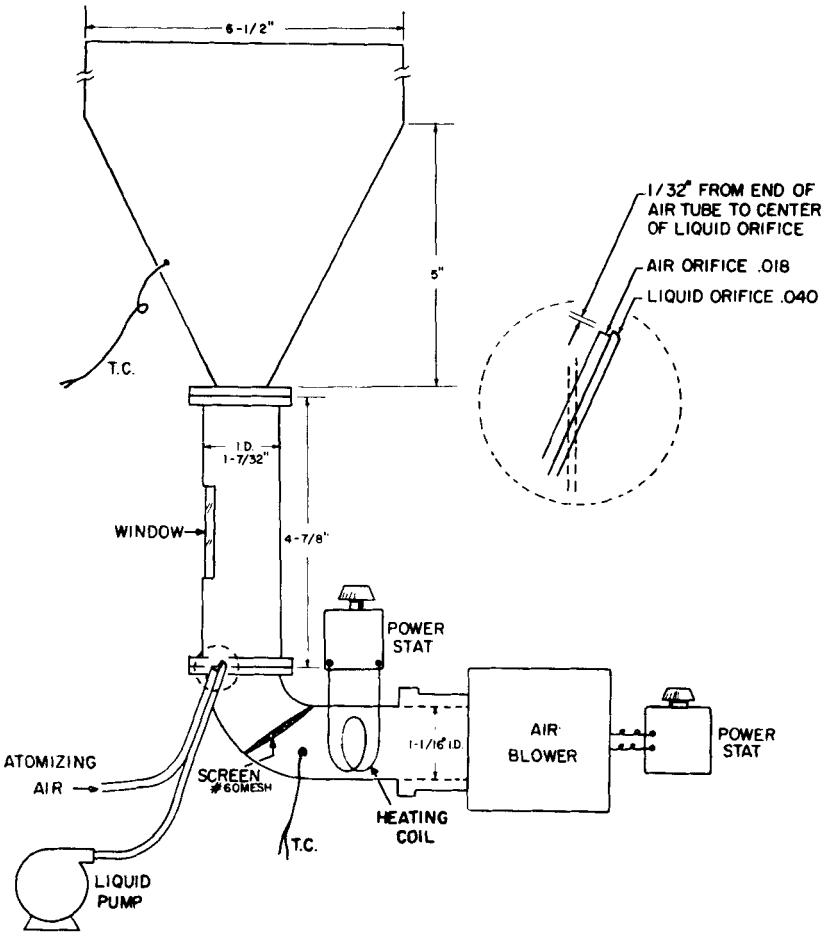

Fig. 1—Schematic diagram of the miniature air-suspension coating apparatus.

Several reports have appeared in the literature concerning the design and utility of laboratory air-suspension coating devices (3–6). The optimum load for each of these units is in the kilogram range. In the authors' experience, it has been frequently desirable to work with much smaller quantities of material. This may be the case when a drug is in short supply during early biopharmaceutical studies, or when new coating agents which are not yet available in sizeable quantities are being evaluated.

An air-suspension coating apparatus, capable of processing gram quantities of material, ideally satisfies these needs. This report deals with the design and evaluation of such a unit, referred to as a miniature air-suspension coating apparatus.

EXPERIMENTAL

Apparatus—A schematic diagram of the miniature air-suspension coating apparatus is shown in Fig. 1. The air supply is provided by a Master heat gun, model HG 301 (Master Appliance Corp., Racine, Wis.). The heating element and blower were rewired to allow for independent control of air volume and temperature. The unit has a maximum capacity of approximately 35 cu. ft. of air per min. Air output can be controlled by either varying the voltage delivered to the blower or by adjusting the air intake shield.

A Sigmamotor, model T8, equipped with a Westinghouse hi-torque speed control, type 902, was used to deliver the coating solutions through Tygon tubing ($^1/_{32}$ or $^1/_{16}$ in. i.d. × $^1/_{32}$ or $^1/_{16}$ in. wall thickness) to the atomizing nozzle. The coating solution was aerosolized at the point of entry into the coating chamber by the construction shown in the insert of Fig. 1. The air-liquid tubes of the atomizer head, coating chamber, and expansion chamber were constructed of No. 316 stainless steel. A clear, solvent-resistant plastic window[1] was inserted into the coating chamber to permit observation of the coating process.

The inlet and outlet air temperatures are determined by the use of electrical thermometers model 380 (Radio Frequency Labs, Inc., Boonton, N. J.).

A photograph of the apparatus and auxiliary equipment are shown in Fig. 2. The panel board is equipped with inlet and outlet air temperature gauges, atomization air pressure control knob and gauge, and a master on-off switch. The variable transformers shown on the right side of the photo-

[1] Saranex, trademark of Dow Chemical Co.

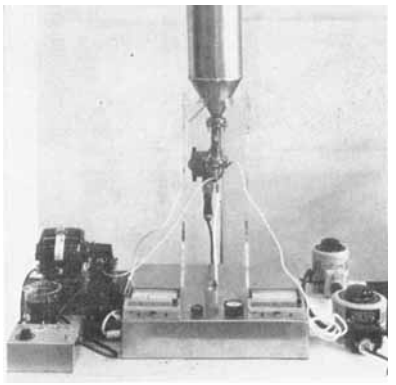

Fig. 2—Miniature air-suspension coating apparatus and ancillary equipment.

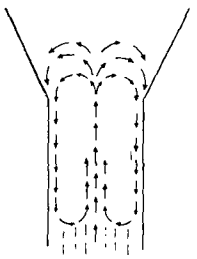

Fig. 3—Schematic representation of optimum particulate flow pattern.

graph are for air volume and temperature control. The control box to the left governs the race at which the Sigmamotor delivers coating solution to the atomizing head.

Materials—Eastman cellulose acetate phthalate, Distillation Products Industries; ethylcellulose, 50 cps., pharmaceutical grade, Dow Chemical Co.; isopropyl alcohol, acetone, and chloroform, reagent grade; castor oil USP; syrup USP; D&C Red No. 21, H. Kohnstamm and Co.; chlorpheniramine maleate tablets, 4 mg.;[2] and nonpareil seeds coated with chlorpheniramine maleate, 4.0 mg./1.64 Gm. (prepared by applying a sugar solution containing the drug to 20-mesh nonpareil seeds in a coating pan).

Coating Solutions—Ethylcellulose solution was prepared by dissolving 12.5 Gm. of polymer and 0.05 Gm. D&C Red No. 21 in 1 L. of a 50/50 acetone–isopropyl alcohol mixture.

Cellulose acetate phthalate solution was prepared by dissolving 25 Gm. of CAP and 7.5 Gm. of castor oil in 500 ml. acetone and then adding sufficient isopropyl alcohol to adjust the volume to 1 L.

RESULTS AND DISCUSSION

Equipment Characteristics—The feasibility of coating particles using the air-suspension technique depends, in addition to the surface characteristics and strength of the particle, on establishing an appropriate flow pattern. The desired flow pattern is schematically presented in Fig. 3. The extent to which a circulation pattern of this type can be established is determined by the particle size, shape, and density, the total weight of material in the coating chamber, and the air distribution in the operating parts of the unit.

The general utility of the miniature air-suspension apparatus was determined by evaluating the flow patterns established with a number of particles having different sizes and shapes. This information is presented in Table I. Obviously, variations in either the atomization air pressure or fluidizing air velocity would result in different optimum and maximum chamber loads. As the load is decreased from optimum, the circulation pattern becomes erratic.

TABLE I—CONDITIONS FOUND TO ESTABLISH CIRCULATORY FLOW PATTERNS WITH VARIOUS SIZED AND SHAPED PARTICLES[a]

Particle Description	Optimum Load, Gm.	Max. Load, Gm.
$^5/_{16}$ in. Std. concave tablet Av. gauge = 0.145 in. wt. = 200 mg.	4.00	8.00
$^7/_{16}$ in. Std. concave tablet Av. gauge = 0.220 in. wt. = 550 mg.	1.65	5.50
Oval concave tablet (0.200 × 0.300 in.) Av. gauge = 0.150 in. wt. = 170 mg.	4.00	8.00
Clover leaf tablet ($^5/_{16}$ in.) Av. gauge = 0.150 in. wt. = 170 mg.	3.91	7.82
Hexagonal tablets ($^7/_{16}$ in.) Av. gauge = 0.220 in. wt. = 570 mg.	2.85	5.70
No. 1 gelatin capsule wt. = 410 mg.	2.05	2.46
No. 0 gelatin capsule wt. = 530 mg.	1.59	2.12
Nonpareil seeds (20 mesh)	10.00	16.00

[a] The atomization air pressure was maintained constant at 20 p.s.i. and the transformer setting for the fluidizing air was 90 (intake shield at maximum opening).

Coating Studies—During the course of biopharmaceutical testing, it is often desirable to evaluate enteric-coated dosage forms. At this stage of new drug research materials are frequently in short supply, and therefore a technique for handling small amounts of material is highly desirable. The miniature air-suspension coating apparatus was evaluated as a tool for applying cellulose acetate phthalate (CAP) to a variety of solid dosage forms.

The typical coating procedure used was as follows. The fluidizing air is turned on and brought to the appropriate temperature range by the adjustment of the heating coil transformer. The coating solution is pumped through the feeding tube to the atomizer head. The atomization air is turned on and the particles introduced into the coating chamber by way of the exhaust air duct. The coating rate is controlled so that about a 20° differential exists between the inlet and outlet air temperatures. When all of the solution has been applied, the pump and atomization air is turned off. A few minutes of additional drying time are provided to minimize solvent retention. The heating coil and fluidizing air are then turned off, the unit disassembled, and the coated material recovered.

The enteric properties of the CAP-coated tablets and capsules were evaluated using the USP XVII procedure (7).

A modification of this procedure was used to evaluate the enteric-coated nonpareil seeds. The seeds were placed into a stainless steel cylinder

[2] Chlor-Trimeton Maleate, trademark of Schering Corp.

(25 × 64 mm.) covered at each end with an 80-mesh stainless steel screen. The cylinder was moved in a vertical plane beneath the surface of the test fluid by means of a Stoll-Gershberg apparatus (8). The nonpareil seeds were examined after 1 hr. in simulated gastric fluid at 37 ± 2°. Any visual evidence of nonpareil seed disintegration was interpreted as a failure of the enteric coating. The same procedure was repeated using simulated intestinal fluid and the time for total disintegration (more than 90% of material passing through the screen) was recorded.

The results presented in Table II demonstrate the versatility with which the apparatus can be used to enteric coat a spectrum of solid pharmaceutical dosage forms. It should be pointed out, however, that the uniform disintegration times of the various dosage forms in simulated intestinal fluid is probably best interpreted as due to the high solubility of cellulose acetate phthalate in this media rather than as an indication of uniform film thickness.

The data presented in Table III clearly demonstrate the effect of coating suboptimal chamber loads. Coating efficiency decreases markedly with decreasing chamber loads, probably due to an erratic flow pattern and decreased bed density. Coating efficiency for very small chamber loads can be increased by decreasing the diameter of the coating chamber. This was done by inserting a 0.75-in. i.d. tube mounted with rubber stoppers into the coating chamber. One gram of 5/16-in. standard concave tablets was coated with 2.5 ml. of 2.5% CAP solution. The coated tablets weighed 1.065 Gm., indicating a coating efficiency of approximately 80% as opposed to 12% when the same quantity of tablets was coated in the 1.22-in. chamber.

Table II—Enteric Dosage Forms Prepared in Miniature Air-Suspension Coating Apparatus

Batch No.	Chamber Load, Gm.	CAP Coating Applied, %	Disintegration After 1 hr. in Simulated Gastric Fluid at 37°	Disintegration Time (min.) in Simulated Intestinal Fluid at 37° (Range)
	Std. Concave Tablets, 5/16 in.			
1	4.0	8	none	12–15
2	4.0	8	none	12–15
3	4.0	16	none	12–15
4	4.0	16	none	12–15
5	4.0	16	none	12–15
6	2.0	16	none	10–11
7	2.0	16	none	8–9
8	2.0	16	none	8–9
9	1.0	16	none	11–12
10	1.0	16	none	11–12
11	1.0	16	none	11–12
12	1.0	16	none	11–12
13	1.0	16	none	11–12
14	1.0	16	none	11–12
	Oval Concave Tablets, 0.2 × 0.3 in.			
15	4.0	12	none	10–15
	Clover Leaf Tablets, 5/16 in.			
16	3.91	12	none	10–15
	Hexagonal Tablets, 7/16 in.			
17	5.70	9	none	10–15
	Std. Concave Tablets, 7/16 in.			
18	2.75	9	partial	...
19	2.75	18	none	10–15
	No. 1 Gelatin Capsules			
20	2.05	16	none	5–10
	No. 0 Gelatin Capsules			
21	1.60	20	none	5–10
	Nonpareil Seeds, 20 mesh			
22	10.00	5	partial	...
23	10.00	7	none	5–10
24	10.00	13	none	5–10
25	10.00	16	none	5–10

Table III—Relative Efficiency of Coating 5/16-In. Standard Concave Tablets as a Function of Chamber Load

Expt. No.	Chamber Load, Gm.	Solids Applied, mg.	Wt. Gain, mg.	Coating Time, min.	Coating Efficiency,[a] %
1	4.0	650	390	8	60
2	4.0	650	400	8	62
3	2.0	325	130	4	40
4	2.0	325	130	4	40
5	1.0	162	20	2	12
6	1.0	162	20	2	12

[a] Defined as wt. gain (mg.)/solids applied (mg.) × 100.

Correlation with 6-in. Wurster Apparatus—Experiments were carried out to determine whether information generated using the miniature unit could be extrapolated to larger air-suspension coating units. The quantity of ethylcellulose required to retard the release of chlorpheniramine maleate from tablets and seeds was determined in the miniature unit. Tablets and seeds were then coated in the 6-in. unit using an amount of coating solution proportional to the increased batch size.

Coating Procedure—Twenty milliliters of 1.25% ethylcellulose applied to 10 Gm. of seeds yielded a product which released chlorpheniramine maleate for over 16 hr. Four liters of the same solution was then applied to 2 Kg. of seeds in the 6-in. unit.

Twenty chlorpheniramine maleate tablets (5/16-in. standard concave, 200 mg.) were coated with 3 ml. of 1.25% ethylcellulose solution in the miniature coater. Similarly, 750 ml. was applied to 5,000 tablets in the large unit.

Release Rate Determination—The release rates were determined at 37 ± 0.1° in 150 ml. of 0.01 *N* HCl in a 3.5 × 16-cm. test tube. The sample (one tablet or 1.64 Gm. of seeds) was placed in a 24 × 64 mm. stainless steel cylinder covered at each end with an 80-mesh screen. The cylinder was oscillated in a vertical plane with a Stoll-Gershberg apparatus. The chlorpheniramine maleate was assayed spectrophotometrically at 264 mμ with a Beckman DU spectrophotometer modified with a Gilford model 220 absorbance converter. A continuous record was made of chlorpheniramine maleate from the seeds by pumping the solution through a 1-cm. flow cell with a Sigmamotor pump and recording the output of the absorbance converter on a Gilford-Honeywell recorder. In the case of the tablets, only a single point determination was made at 4 hr.

Discussion—The chlorpheniramine maleate release rates from the nonpareil seeds are shown in Fig. 4. The results of the tablets are given in Table IV. The variation in release rates is much smaller with the nonpareil seeds than with the tablets be-

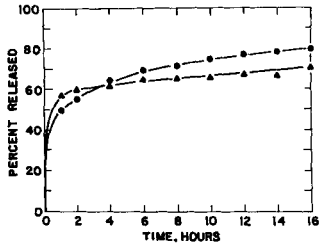

Fig. 4—Release of chlorpheniramine maleate from ethylcellulose-coated nonpareil seeds in 0.01 N HCl maintained at 37 ± 0.1°. Key: ●, miniature; ▲, 6-in. model.

TABLE IV—MINIATURE *Versus* 6-in. WURSTER CHLORPHENIRAMINE MALEATE TABLETS COATED WITH 1.25% ETHYLCELLULOSE SOLUTION

Expt. No.	1.22-in. Chamber	6-in. Chamber I	6-in. Chamber II
	% Release in 4 hr.		
1	54	18	17
2	33	18	14
3	50	17	33
4	46	36	31
5	60	51	50

cause the measurement of the release rates from 1.64 Gm. of seeds gives the average of a large number of individual assays, while the tablets were assayed individually. However, although the release rates are not precisely identical, the results do show that it should be possible to scale-up from the 1.22-in. coater to the 6-in. model with very little additional experimentation.

SUMMARY

An apparatus has been described which is capable of processing gram quantities of material in much the same manner as the larger 6-in. model Wurster unit. The miniature device has been evaluated and found to be highly versatile with respect to the types of discrete particles for which it can effect a continuous coating. Coating experiments indicate the miniature unit to be qualitatively comparable with the larger 6-in. model, although some quantitative differences were observed. The data suggest that minimal scale-up problems would probably accompany transition to the large unit.

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Keyphrases

Air-suspension coating apparatus, miniature
Coating apparatus—schematic diagram
Ethylcellulose–coating solution
Cellulose acetate phthalate–coating solution
Tablet coating
Capsule coating
Enteric dosage forms–coating
Drug release–coated dosage forms

Notes

Pharmacology and Toxicology of Potassium Perrhenate and Rhenium Trichloride

By THOMAS J. HALEY and FRANK D. CARTWRIGHT

A pharmacologic and toxicologic investigation of potassium perrhenate and rhenium trichloride showed that these compounds exhibited the same delayed acute toxicity previously reported for other rare elements. Rhenium trichloride was 10 times more toxic than potassium perrhenate but the latter compound was among the least toxic of all of the rare inorganic compounds studied. Potassium perrhenate was not irritating to the eyes and rhenium trichloride produced only a minimum of such irritation. Neither compound was irritating to the skin. Potassium perrhenate had no effect on isolated intestine while the liberation of acid from rhenium trichloride caused an intestinal spasm. Potassium perrhenate caused death by cardiovascular collapse coupled with respiratory failure. The compound also affected the superior cervical ganglion. Decomposition of aqueous solutions of rhenium trichloride and their extreme acidity prevented any pharmacodynamic studies.

IN 1933, HURD *et al.* (1) reported that they were unable to determine the LD_{50} for $KReO_4$ in mice or rats. They found wide distribution of the chemical in body tissues of the rabbit but no pharmacological effects in the dog. In 1940, Maresh *et al.* (2) reported that the i.p. lethal range for Re metal, given as $NaReO_4$, was 900–1,000 mg./Kg. for rats. Symptoms of toxicity included: cyanosis, increased respiration, and tonic convulsions. Rhenium trichloride was very toxic but the LD_{50} was not determined. Rhenates had no effect on the

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