exposed to the solvent. During ultrasonic extraction, this physical separation is further enhanced by the localized stirring occurring as a consequence of cavitation. The combination of this stirring effect and the repeated washing of the drug with solvent is far superior to the simple washing procedure in Soxhlet extraction. Again, the effect of ultrasound is most noticeable during short-term extractions. For if the drug is washed often enough in the conventional procedure, all of the alkaloids eventually will be separated from the residue.

These results lead us to propose that at least two different mechanisms may be involved in the liberation of alkaloids during the isolation procedure. One of these mechanisms, occurring during the process of maceration, is stimulated or enhanced by the higher frequencies of ultrasonic energy. The other mechanism, active during the extraction process, is promoted by low frequencies of ultrasonic energy. Although the evidence supporting this hypothesis is only indirect, the experiments reported here have clearly demonstrated that it is possible to evaluate critically the effect of ultrasound on *both* phases of the procedure involved in alkaloid isolation—maceration and extraction. Furthermore, these exploratory studies indicate that the utilization of ultrasonic energy during the isolation procedure may yield valuable information concerning the exact mechanisms involved in the liberation of medicinal products from natural sources.

Ultrasonic energy definitely has utility in the extraction of alkaloid containing plants, providing that the ultrasound is of sufficient intensity and is correctly applied. Ultrasonic energy shortens considerably both the duration of the maceration and extraction process while simultaneously yielding extracts containing greater quantities of alkaloid than can be obtained by conventional procedures. Although quantitative differences in alkaloid yield have been noted, our experience has been that the maceration process lends itself most readily to the application of ultrasound. We suggest that ultrasonic treatment on a commercial scale could be utilized profitably and simply by applying ultrasound to the macerating mixture.

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Development of a Simple Automated Film-Coating Procedure

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Information obtained in a series of manually controlled coating experiments was applied in developing a simple automated procedure for film-coating tablets. The equipment consists of a group of interconnected timers which signal a solenoid valve controlling the hydraulic atomization of the coating solution. The film compositions were based on mixtures of hydroxypropyl methylcellulose and ethylcellulose and were applied to tablets automatically in both 18 and 42-in. coating pans. The apparatus and coating procedure offer advantages in both research and production film-coating operations.

FILM-COATED TABLETS have gained increasing acceptance in the pharmaceutical industry; a growing number of tablet products coated in this way have reached the market. Numerous reports describing new and useful film-coating compositions have appeared in both the scientific and patent literature (1–5). The advantages of the film-coating technique include (among others) speed and convenience of operation and good control over tablet-to-tablet uniformity. A general review of the coating procedure has appeared in the reports by Wagner (6) and by Gross and Endicott (7). Recently, Lachman described a procedure for automating the film-coating operation (8). This technique was based on the use of punched-tape electronic instrumentation and may be overspecialized for general applications.

The present report describes the development of a simplified, inexpensive procedure for automatic film coating.

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EXPERIMENTAL

Materials.—The coating agents used in this study were based on mixtures of hydroxypropyl methylcellulose and ethylcellulose (9, 10) as shown in Table I.

Coating solutions were prepared by dissolving the

TABLE I.—FILM-COATING COMPOSITION

Ingredients	% w/v
Hydroxypropyl methylcellulose,[a] 60 HG, 50 cps.	3.75
Ethylcellulose N.F., 10 cps.	1.25
Propylene glycol U.S.P.	0.75
Titanium dioxide U.S.P.	1.98
Cab-o-sil,[b] M-5	0.02
Chloroform U.S.P.	
Isopropyl alcohol U.S.P.	
Equal parts by volume	*q.s.*

[a] Marketed as Methocel HG by the Dow Chemical Co., Midland, Mich. [b] Marketed by Cabot Corp., Boston, Mass.

film formers and glycol in a portion of the mixed solvent. A suspension of the pigment materials in a second portion of the solvent then was added. The mixtures were agitated with an Eppenbach homomixer to insure good dispersion.

Colors were included in the composition by substituting lakes and pigments for part of the titanium dioxide. Lakes of FD&C Blue No. 1, Green No. 1, Red No. 2, Red No. 3, and Yellow No. 5 were employed. Pigment materials included black and brown iron oxide and chrome green.[1] Generally, the colorant was added at a concentration of 0.2 to 0.4 w/v %.

A variety of tablet cores was used in the present experiments. Placebo tablets were formulated with spray-dried lactose and generally were compressed using $^{11}/_{32}$-in. standard concave punches. Deep concave, standard concave, square, and capsule-shaped tablets containing one or more active ingredients also were coated.

Evaluation Techniques.—Film-coated tablets were evaluated by visual inspection of film smoothness, uniformity of color, edge coverage, luster, and tablet to-tablet uniformity. The disintegration time of the film on the tablets was measured in the U.S.P. disintegration apparatus using simulated gastric fluid U.S.P. The end point was taken when the first distinct signs of film disintegration, rupture, or separation were evident.

Stability observations were obtained after storage at room temperature, 37 and 45° for various time intervals.

Hydraulic Coating Equipment.—The hydraulic coating system developed for these studies is shown schematically in Fig. 1. Basically, the system consisted of an air-driven hydraulic pump (paint sprayer type), a hand-operated spray gun, baffled coating pans, and auxiliary duct work for supply of warm air, cool air, and exhaust to the pans. Three different sized coating pans including 18, 28, and 42-in. units were used. The 18-in. pan was rotated at 30 r.p.m. The speed of the other pans was adjusted to 15 r.p.m.

The spray gun was held just within the coating pan approximately 12 in. from the surface of the (rotating) tablet bed. The air pressure to the hydraulic pump was maintained at 70 to 75 psig in all experiments.

For runs in the 18-in. pan, the batch size was approximately 30,000 tablets. Batch sizes of 75,000 and 300,000 tablets were coated in the 28 and 42-in. pans, respectively. These pan loads varied slightly with the size and shape of the tablets.

Manual Coating Procedure.—The coating procedure was based on an intermittent spraying and drying technique. The tablets were sprayed for a short interval (less than 5 seconds), then tumbled for several seconds. This "spray-on–spray-off" cycle was continued for several minutes. Cool air at ambient temperature then was admitted to the rotating pan for 5 minutes. This was followed by a 5-minute drying interval with warm air (approximately 50°). The "spray-on–spray-off" cycle then was started again and the total sequence of steps continued until the desired film weight had been applied. The run was terminated when an increase in tablet weight of 2.0% was obtained.

Coated tablets were allowed to dry completely for 8 to 12 hours in an oven at 110° F. and finished by standard polishing procedures.

Under manual operation of the equipment, the duration of the various time cycles was adjusted occasionally at the discretion of the tablet coater. For automating the film-coating operation, standardized spraying and drying cycles were established. These were accomplished by measuring the time intervals employed for each step of the process carefully in a series of successful, operator-controlled coating runs. Replicate trials in which each selected time interval was duplicated (and monitored by an observer, in addition to the tablet coater) then were conducted. The results of these experiments showed that film-coated tablets with reproducible characteristics were obtainable in separate coating runs when spraying and drying cycles were duplicated. The time cycles developed for several different tablet batch sizes are listed in Table II.

Automated Coating Procedure.—The hydraulic coating operation was automated by including a solenoid valve in the system to control the flow of the coating solution and by introducing a group of interconnected timers to control the various time cycles. The automated equipment is illustrated schematically in Fig. 2 which shows the relationship between the timer components, the solenoid valve, and the auxiliary units. The timer panel was designed to control the cool air and warm air blowers, the start and stop of the coating pan, the total coating time, and the spray-on, spray-off, and spray-repeat cycle time. The panel included stand-by switches for manual control of each function and appropriate signal lights.

The automated coating system was put in operation by closing a master power switch on the timer panel. This activated the spray-on and spray-repeat timers. The spray-on timer energized the solenoid valve for a given preset interval. The solenoid, in turn, actuated a needle control valve on the spray gun allowing flow and atomization of the coating solution. The solenoid valve was de-energized at

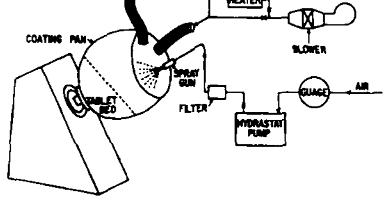

Fig. 1.—Schematic diagram of hydraulic coating system. Ten gallon hydrastat spray unit (24:1 pressure ratio), supplied by Alemite of New Jersey, Inc., Union, N. J.

[1] Lo-Micron pigments supplied by Whittaker, Clark, and Daniels, Inc., New York, N. Y.

TABLE II.—SPRAYING AND DRYING CYCLES FOR VARIOUS BATCH SIZES COATED BY MANUAL OPERATION

Batch Size, Tablets	Coating Pan, in.	Spray-On,[a] Sec.	Spray-Off,[a] Sec.	Spray-Repeat, Min.	Cool Air, Min.	Warm Air, Min.	Total Coating Time, Hr.
30,000	18	1	9	5	5	5	3 to 3.5
75,000	28	2	8	5	5	5	3.5 to 4
300,000	42	4	6	5	5	5	5.5 to 6

[a] Spray-on and spray-off operations alternated back and forth until the time period indicated in the column marked *Spray Repeat* was completed.

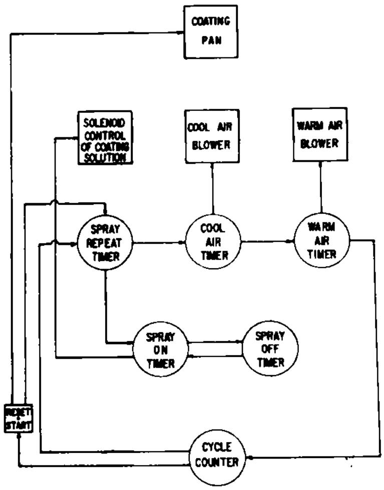

Fig. 2.—Schematic diagram of control system for automated coating operation. Solenoid valve controls the flow of the coating solution by actuating a needle valve on the spray gun (three-way solenoid valve-115 v./60c/AC and No. 22AUHPSSTC Autojet with 0.011-in., 40° angle nozzle). The cycle counter normally energizes the spray-repeat timer. On the last count, the counter ends the operation through the reset starter switch.

TABLE III.—TIMER PANEL SPECIFICATIONS[a]

Components	Dial Range	Dial Divisions
Spray-on timer	10 sec.	$^1/_6$ sec.
Spray-off timer	30 sec.	1 sec.
Spray-repeat timer	60 min.	1 min.
Cool air timer	60 min.	1 min.
Warm air timer	60 min.	1 min.
Cycle counter	80 counts	1 count

[a] Panel constructed by Ribble Engineering Co., Hackensack, N. J.

the end of the time period set on the spray-on timer. At this point, the spray-off timer was energized and continued to run for a preselected time interval. At the completion of this period, the spray-off timer reactivated the spray-on timer. These components alternated their operation in this manner until the time interval programmed on the spray-repeat timer was complete. The cool air timer controlling the cool air supply blower then was activated for a preset time period. At the completion of this step, the warm air timer was energized, which in turn started the flow of warm air to the pan. When the time interval set on this component was complete, the timer signalled the cycle counter, and one count was registered. The entire sequence of steps then was repeated until the total number of cycles preset on the counter had been completed. At this point the counter signalled a reset switch, and the pan and all other operations were stopped automatically.

The specifications for the timer components utilized in the automated system are listed in Table III.

Automated film-coating runs were conducted in the 18 and 42-in. coating pans. For these studies, the spray gun was held in a fixed position by suitable clamps and stand arrangement. Two spray guns were used for studies in the 42-in. pan. In these cases, the guns were positioned so that their spray patterns did not overlap. All time cycles and operating conditions reproduced those developed for manual coating as listed in Table II.[2]

RESULTS AND DISCUSSION

The film-coating solution could not be applied successfully by pouring or pneumatic spray techniques. In the latter case, the difficulties were believed to result from the premature evaporation of solvent at the nozzle. This led, in turn, to the deposition of pigment agglomerates on the tablet and "pimpled" surfaces. Application of the coating solution by pouring procedures led to mottled, uneven film coats, presumably caused by excessive film tackiness during the dry down phase. These difficulties were corrected with the hydraulic coating system.

In the present series of experiments over 1,500,000 tablets constituting 30 individual batches were coated with the hydraulic system operating under manual control. The results of these studies were used to demonstrate the flexibility of the coating solution, the reliability of the equipment, and the reproducibility obtained when duplicate time cycles were employed. In all cases, smooth and elegant film coats were obtained. Coated tablets showed complete edge coverage and high tablet-to-tablet and batch-to-batch uniformity. These qualities were evident particularly when colored film compositions were applied to white-core tablets.

No difficulties were experienced in scaling up the system for operation in the 42-in. coating pans. These experiments generally were limited, however, to tablets with a hardness of 10 Strong Cobb units or more and friability values of less than 0.2% (measured with the Roche Friabilator). At present, it is not known whether the described system has utility with softer or more friable tablets.

The application of a film thickness equal in weight to approximately 2% of the tablet core weight generally was sufficient to obtain good tablet coverage. At this thickness, the disintegration time of the film was 5 to 10 minutes. These disintegration rates did not change materially after aging the tablets at room and elevated temperatures for extended periods. No significant changes in other film characteristics were noted over these storage intervals. In two cases, however, some fading of the film color was observed. Stability results are summarized in Table IV for several representative products.

[2] To compensate for the increased flow rate obtained with the use of two spray guns with the 42-in. pan, the spray-on and spray-off cycles were changed from those established under manual operation (4 seconds on, 6 seconds off) to 2.5 seconds on and 9 seconds off.

TABLE IV.—STABILITY DATA FOR FILM-COATED TABLETS STORED AT ROOM TEMPERATURE FOR 1 YEAR

Product	Size, in.	Shape[a]	Pigment Compn.	Color Original	Color 1 Yr.	Luster Original	Luster 1 Yr.	Disintegration Time of Film, Min. Original	Disintegration Time of Film, Min. 1 Yr.
A	11/32	S.C.	100 parts titanium dioxide	White	N.C.[b]	G	N.C.	5	5
B (Placebo)	11/32	S.C.	80 parts TiO_2 + 20 parts FD&C Red No. 3 Lake	Pink	S.F.	G	N.C.	5–7	5–7
C (Placebo)	11/32	S.C.	80 parts TiO_2 + 20 parts FD&C Blue No. 1 Lake	Light blue	S.F.	G	N.C.	5–7	5 7
D (Placebo)	11/32	S.C.	80 parts TiO_2 + 20 parts oxide brown	Brown	N.C.	G	N.C.	5–7	5–7
E	5/16 × 5/16	P	28 parts TiO_2 + 20 parts D&C Red No. 3 Lake + 28 parts black + 24 parts oxide brown	Reddish brown	N.C.	G	N.C.	5	5
F	19/32 × 7/8	C	40 parts TiO_2 + 60 parts FD&C Yellow No. 5 Lake	Yellow	N.C.	G	N.C.	7–10	7–10
A[c]	11/32	S.C.	100 parts titanium dioxide	White	N.C.	G	N.C.	5	5
A[d]	11/32	S.C.	100 parts titanium dioxide	White	N.C.	G	N.C.	5	5

[a] S.C., Standard concave; P, pillow-shaped; C, capsule-shaped. [b] N.C., No change; S.F., some fading; G, good. [c] Product *A* coated by automated procedure in 18-in. pan (30,000 tablets). [d] Product *A* coated by automated procedure in 42-in. pan (300,000 tablets).

Automated coating experiments were conducted in the 18 and 42-in. coating pans. Since the operating conditions required for successful coating had been previously established in an extensive number of manual runs, only limited experiments were required to develop and confirm the automated system. Six runs were undertaken and completed successfully. The results showed that tablets coated by the automatic procedure were equivalent in terms of edge coverage, luster, and disintegration time to the film-coated tablets prepared by the manual technique.

The automated film-coating system developed in this study was relatively inexpensive to assemble and simple to operate. Only four tasks were left to the tablet coater. These included (*a*) the loading of tablet cores into the pan, (*b*) the charging of coating solution to the pump, (*c*) the pressing of the start button on the timer panel, and (*d*) the unloading of finished (unwaxed) tablets. It was useful, however, to wipe the tip of the nozzle with solvent from time to time to remove any dried film which may have accumulated at the nozzle orifice. This in no way complicated the coating operation and could be completed during the routine inspections of the operation.

The capacity of the automated system is sufficient to control the coating operation in four or more individual coating pans, provided the same time cycles and film compositions are used in each. The wide range of time settings which can be programmed on the timer panel adds considerable flexibility. Although the present results are limited to the use of one basic film composition, the available flexibility suggests that the total system will have utility with other film-coating agents. Since very close control can be exerted over the spraying and drying cycles by the introduction of the automatic time controls, standardized coating conditions from batch to batch can be maintained readily.

The automated apparatus appears to have additional utility as a research tool in developing new film-coating compositions. This advantage arises because the unit can be set to give exact and reproducible coating cycles, thereby removing the influence of operator variables. For example, it was shown in one experiment that an increase of only one quarter of a second in the spray-on time resulted in overwet tablets which required immediate drying before they could be processed further. The control of the nozzle operation within such narrow time limits is virtually impossible under manual operation, but is readily achieved with the automated equipment.

SUMMARY AND CONCLUSIONS

The film composition used in the present experiments has utility in coating a broad variety of tablet shapes and sizes. The basic film composition was easily colored by the addition of suitable lakes and pigments and showed good disintegration and stability characteristics. A hydraulic atomization technique was used in applying the film coat. The introduction of timer components to control the various cycles resulted in a simple and inexpensive method of automating the coating procedure.

Batch loads of approximately 300,000 tablets were coated automatically in a 42-in. coating pan. The total coating time was 5.5 to 6 hours. For approximately two-thirds of this time (4 hours), the tablets were undergoing drying, and no additional film coats were being applied. Although these time cycles were established on the basis of manual operation, the results of the automated experiments suggested that the drying intervals could be reduced significantly. This would lead to proportional reductions in the total coating time. The automated coating equipment provides a convenient tool for exploring these opportunities, and experiments are presently planned in these directions.

The automated system offers further advantages in improving batch-to-batch uniformity and in reducing production labor charges. The system also has particular utility in research studies with new film compositions.

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