components with chloroform. However, it is imperative to use 0.01 *N* NaOH, because a stronger concentration of the base can change the CAF structure (17), and, therefore, cause erratic results.

Automation for the analysis of the four components can be performed by following the above procedures (extraction, rather than differential spectrophotometry is preferred for CAF). The results would be directly obtainable from the responses of the recorders without need of any computers or calculating devices. The proposed schematic diagram for the automated system is shown in Fig. 7.

The tablet is crushed and dissolved in 85% methanolic solution, which is filtered into a central reservoir. From this container, three portions are taken. One aliquot is colorimetrically titrated for ASA in the presence of dye indicator with 0.02 *N* KOH. A second aliquot is automatically diluted with a given quantity of 0.01 *N* sodium hydroxide, and the CAF is extracted into chloroform, which is read at 276 mμ *versus* chloroform on a spectrophotometer. A third portion is automatically diluted and separated into two segments. To one portion, a pH 6 buffer solution is added and passed through a reference flow cell located in a spectrophotometer. Simultaneously, a pH 10 buffer solution is added to the other segment of the solution and passed through a sample flow cell in the spectrophotometer. The wavelength scale is programmed rapidly to two wavelengths—263.5 and 330 mμ. The APAP and SAL are determined at 263.5 and 330 mμ, respectively.

The advantage of using these methods is that each specific procedure is independent of the concentrations of the other components, and therefore, can be used either in the presence of large quantities or in the absence of any of the other ingredients, with very good accuracy and precision.

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*Keyphrases*

Analgesic tablets, powders—analysis
Aspirin determination—analgesic mixture
Colorimetric titration—analysis
Salicylamide, acetaminophen determination—analgesic mixture
Caffeine determination—analgesic mixture
UV spectrophotometry—analysis

# Application of Sugar Coating to Tablets and Confections by Means of an Automated Airless Spray System I

## Investigation of the Direct Coating of Tablets

By G. M. KRAUSE and T. L. IORIO*

**The practicability of directly applying sugar coating to unsubcoated tablets has been studied. Initial work performed indicates that such a procedure may be feasible when used in place of current sugar-coating techniques.**

THE DEVELOPMENT of automated airless-spray film-coating methods has shown signs of significant growth in recent years (1–5). Although there is considerable information pertaining to film coating by this method, particularly with coating solutions consisting of organic solvents and polymeric materials, there is little if any descriptive literature pertaining to the use of aqueous solutions of sugar or syrups as the coating medium. At the present time, sugar

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coating is still the principal method used for coating tablets and also confections. Nevertheless, the time involved and the uncertain reproducibility are reflected in high costs of operation. It would seem that an investigation of the practicability of modifying the traditional sugar-coating method of tablets would be desirable.

One of the drawbacks of the traditional sugar-coating procedure has been the necessity of subcoating tablets (6). This procedure is time consuming, and in some instances, an untidy operation. Tablets and confections of odd shapes, having sharp corners and thick edges, generally require subcoating to facilitate the application of a sugar coat. Those with well-rounded edges or corners do not present too much difficulty. This discussion will deal primarily with products of standard round shapes and normal curvatures.

## DESIGN AND EQUIPMENT

**Hydraulic Systems**—A hydraulic system was employed that was capable of developing 1400 psig, although most of the work was done at about 500 psig. The coating solutions were heated, circulated, and sprayed by an airless pump through nozzles as described by Lachman and Cooper (1).

**Coating Pan**—A 40.6-cm. (16-in.) diameter round stainless steel coating pan, unbaffled, was used because a reasonable quantity of tablets, about 8 kg., could be coated easily, and there was also room to accommodate the spray nozzle. Initial tumbling of the tablets was simplified by previously coating the inner surface of the pan with a thin coat of liquid latex, or syrup, and drying. The speed of the pan was 28 r.p.m. and was constant for all trials.

**Ventilation and Air System**—A conventional air delivery system was used capable of drying the tablets during the drying cycles. An exhaust system capable of greater air capacity than the air supply was used.

**Programmer**—The programmer was constructed similar to that described by Mody, Scott, and Lieberman (2), but modified to provide auxiliary controls that could be used to suspend any of the automated functions as desired. A series of neon lights was provided for the timers to indicate sequence of operation, primarily as an instructional aid. All wire connections were made to readily accessible terminal strips for any changes or modifications in circuitry.

## EXPERIMENTAL

**Tablets and Materials**—The initial trials were conducted on ball-shaped, uncoated confections obtained from a commercial producer. They averaged 0.50 in. in diameter and weighed 1.36 g. each. The compressed tablets used during these experiments were prepared from terra alba, using the wet granulation method. They weighed 385 mg./-tablet, with a diameter and gauge of 95.4 mm. (0.375 in.) and 4.43 mm. (0.174 in.), respectively, and were compressed on a Colton 216 single rotary, using extra deep, cup-shaped punches. Approximately 1,250,000 tablets were used during this work. Coating solutions used were 4-lb. cut pharmaceutical glaze (shellac), subcoating solution according to Clarkson (6), and sugar syrup colored with 0.1% F.D. & C. Red No. 3. With the exception of batch series A and I, Table I, all batches used received two coats of glaze, and weighed 8 kg. initially. Batch series A and I received no precoat, and series C was subcoated over the shellac coat. The initial trial coating weight of series C was therefore correspondingly greater, *i.e.*, 9.27 kg. All shellac coats and subcoats were applied by the conventional pan-coating method (6). All sugar coats, with the exception of series B, Table I, were applied by the automated airless-spray method.

Four different kinds of sugar-coated commercial tablets were purchased from local pharmacies. They were in original unopened containers and were of about the same size and weight as the tablets coated by the automated method during this experiment.

**Sampling Plan**—Samples were removed from the coating pan at the end of 10, 20, 30, and 40 cycles, or 20, 40, 60, and 80 cycles, depending on whether the coating process was for 40 or 80 cycles. The tablets were weighed and measured for diameter and gauge increase individually. The data are seen in Figs. 1 and 2, and Tables II and III.

**Coating Procedure**—The ball-shaped confections received 60 applications of syrup by means of the automated airless-spray method. The average weight of sugar delivered per confection was 0.350 g., with an increase in diameter of 0.75 mm (0.030 in.), Total coating time was 90 min. The trials were repeated twice, and data are presented in Table I (series I) and in Fig. 3, which represent an average of the three batches.

**Subcoated Tablets**—Shellac-coated tablets were subcoated and then sugar coated by the automated method. The operation was continued through 40 cycles per batch for the series and sampled according to plan. The average cumulative gain, diameter and gauge are shown in Figs. 1 and 2. Additional data are summarized in Table I (series C).

**Shellac-Coated Tablets**—These were sugar coated directly by the automated process, with part of the series going through 40 cycles, and the remainder through 80 cycles. In both instances complete coverage took place after 20 cycles, and the process continued through 40 cycles and 80 cycles in order to note uniformity of coating application. Data are presented in Table I (series D, E, F, G, and H).

**Uncoated Tablets**—This batch series received no precoating, only the usual processing to remove any dust and loose particles. These tablets coated well, and the data are seen in Table I (series A).

**Conventional Method**—In order to compare the results of sugar-coating tablets by the automated-spray method with those sugar coated by the traditional pan-coating method, several batches of shellac-coated tablets were coated under conditions approximating the spray method as closely as possible. Forty coats were applied, using the same amount of sugar per coat as per cycle in the automated method. Each application was timed with a stopwatch for uniformity of conditions. With the exception of the increased drying time, all other conditions were met, and the results were almost compa-

TABLE I—WEIGHT OF SUGAR ACQUIRED BY TABLETS PER BATCH SERIES USING AUTOMATED AIRLESS-SPRAY SYSTEM

| Sample series[a] | A | B | C | D | E | F | G | H | I |
|---|---|---|---|---|---|---|---|---|---|
| Number of cycles | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 80 | 40 |
| Initial weight/batch, kg. | 8 | 8 | 9.27 | 8 | 8 | 8 | 8 | 8 | 8 |
| Weight increase/batch, kg. | 1.46 | 1.45 | 1.46 | 1.24 | 1.56 | 1.56 | 1.56 | 3.14 | 2.06 |
| Sugar delivered/cycle, g. | 36.80 | 36.80 | 36.80 | 31.50 | 39.50 | 39.50 | 39.50 | 39.50 | 23.00 |
| Total operating time, min. | 88 | 137 | 104 | 89.5 | 88 | 102 | 107 | 201 | 90 |

[a] Series A, no precoat; series B, conventional pan sugar coating; series C, subcoat; series I (confections), no precoat; all series except A and I were shellac coated.

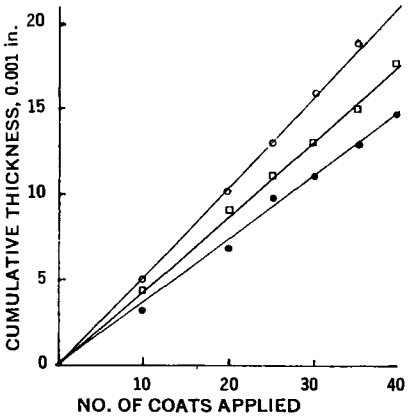


*Fig. 1—Comparison of gain in tablet wall thickness of tablets coated by automated method and tablets coated by conventional method. Key: ○, diameter (automated); ●, gauge (automated); □, diameter and gauge (conventional).*

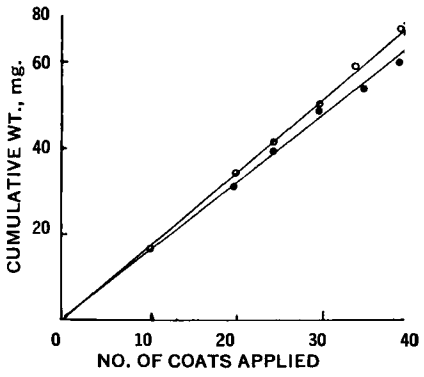


*Fig. 2—Gain in weight of tablets coated by automated method and tablets coated by conventional method. Key: ○, automated; ●, conventional.*

rable to those of the automated method. Data are presented in Figs. 1 and 2, and Table I (series B).

**Total Operating Time**—The total operating time for each batch series was dependent on (*a*) the type of tablet coated, *i.e.*, whether it was not precoated, subcoated, or shellac coated, (*b*) quantity of sugar delivered per cycle, (*c*) type of coating method employed, *i.e.*, conventional pan coating or automated airless-spray method, and (*d*) deliberate change in length of drying time increments per cycle in order to determine operating ranges for the production of a satisfactory coat. These changes are reflected in the figures for total operating times in Table I. All sugar coats entered in Table I were judged satisfactory.

**Comparison of Coating Variability to Commercial Samples**—Twenty tablets were chosen at random from each of four commercial samples and then individually weighed and measured. Thirty tablets each from the lots spray coated by the automated method were also selected at random and weighed and measured. The data are presented in Tables II and III.

## RESULTS AND DISCUSSION

The ball-shaped confections were used as the initial samples for coating because objects of such shape roll readily in the coating pan and are rather easy to coat, since they also have no edges or corners that generally cause difficulty in coating. The settings of the programmer for sugar delivery for this ball-shaped confection could be made over a rather wide range, consistent within reasonable limits. The ease of coating experienced with ball-shaped objects would indicate that they could be used for familiarization with the operation of the automated airless-spray system. Normally, baffles are used in the coating pan to produce tumbling with the automated system. However, it was found that the application of a thin coating of liquid latex or syrup to the pan and drying it, would permit good tumbling during the initial stages when tablets generally have a

TABLE II—MEANS ($\bar{X}$), RANGES ($R$), STANDARD DEVIATIONS ($S$), AND COEFFICIENTS OF VARIATION ($CV$) OF TABLET DIAMETER

| Type of Sugar Coating | Sample[a] | No. of Tablets | Tablet Diameter, in. $\bar{X}$ | $R$ | $S$ | $CV$ |
|---|---|---|---|---|---|---|
| Conventional | A | 20 | 407.5 | 25 | 6.38 | 1.57 |
| | B | 20 | 404.4 | 16 | 3.74 | 0.93 |
| | C | 20 | 430.5 | 10 | 2.60 | 0.60 |
| | D | 20 | 436.6 | 11 | 2.78 | 0.64 |
| Automated airless spray | E | 30 | 408.0 | 9 | 2.06 | 0.51 |
| | F | 30 | 400.8 | 12 | 2.52 | 0.63 |
| | G | 30 | 416.4 | 10 | 2.89 | 0.69 |

[a] Samples A–D were commercial tablets, and samples E–G, were tablets included in study.

TABLE III—MEANS ($\bar{X}$), RANGES ($R$), STANDARD DEVIATIONS ($S$), AND COEFFICIENTS OF VARIATION ($CV$) FOR TABLET GAUGES

| Type of Sugar Coating | Sample[a] | No. of Tablets | Tablet Gauge, in. $\bar{X}$ | $R$ | $S$ | $CV$ |
|---|---|---|---|---|---|---|
| Conventional | A | 20 | 225.5 | 22 | 5.41 | 2.40 |
| | B | 20 | 240.7 | 19 | 5.14 | 2.14 |
| | C | 20 | 226.8 | 11 | 2.70 | 1.19 |
| | D | 20 | 253.5 | 15 | 3.98 | 1.57 |
| Automated airless spray | E | 30 | 204.6 | 11 | 2.24 | 1.10 |
| | F | 30 | 194.5 | 15 | 4.23 | 2.18 |
| | G | 30 | 208.5 | 12 | 3.19 | 1.58 |

[a] Samples A–D were commercial samples, and samples E–G were tablets included in study.

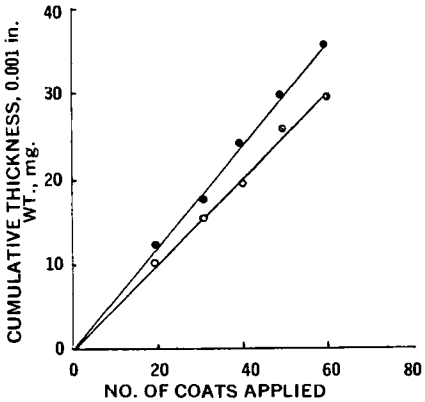


*Fig. 3—Gain in weight and tablet wall thickness of ball-shaped confections coated by automated airless-spray method. Key: O, wall thickness; ●, weight*

tendency to slide. Difficulty in tumbling is usually not experienced after the first or second cycle.

Each of the four samples obtained from commercial outlets represented a single production lot per sample, and the results therefore cannot be interpreted as being indicative of other lots of the same product. Variations of individual coated tablets within a single lot can be divided into three types: (*a*) those caused by inherent variations in the uncoated tablets, (*b*) those caused by the actual coating operation, and (*c*) the possibility of both *a* and *b* occurring at the same time. The standard deviation of all of the tablets coated by the automated process was equal to or less than that of the four commercial samples. These were used for comparison because they were similar in weight and dimensions to the spray-coated tablets. However, a greater standard deviation in the commercial tablets may not be objectionable if the weight variation is due only to nonmedicinal coating ingredients, and not active materials that might be included in the coats.

Tables II and III show the means, ranges, standard deviations, and coefficient of variations for tablet diameter and gauge, respectively. In all cases, tablets coated by the automated process compare favorably to those coated by the conventional method. The subcoated automated lot had less variation than any of the samples examined.

Batches of tablets weighing 8 kg. each were used because this was equivalent to about 8 l., the optimum working capacity of the 40.6 cm. (16 in.) coating pan. Standard concave-shaped tablets, particularly those with thick edges, are more of a problem than those with a curvature approaching roundness, such as the extra deep cup shape. It is well known to the arts that tablets possessing greater curvature and thin edges are coated with less difficulty than others.

During sampling, it was noted that coverage took place at about 20 cycles, as could easily be seen by examining the samples through a 7× lighted magnifier. The process was initially continued until 80 cycles, but since coverage was complete before this, and prior work indicated that additional coats could be applied readily, the operation was generally stopped at the end of 40 cycles. As was noted before, sugar was applied directly to tablets not precoated, with a reasonable degree of success. This area is being explored further.

Tablets coated by the automated process acquired a greater thickness on the edges (diameter) than on the surface (gauge). At the present time, the reason for this difference is unknown, and work is being done to determine the cause and if it can be controlled. The comparison is shown in Fig. 1.

The build-up of sugar in the coating pan ranged from about 0.08–0.13%, with a mean of 0.10%. This was found to be dependent on the weight of sugar delivered per cycle and the drying time, and could be adjusted readily. Trials were conducted with the 40.6-cm. coating pan to determine the maximum and minimum load of shellac-coated tablets that would slide or tumble in this pan when the latter was coated with latex. As little as 2.5 kg. of these tablets would tumble in the treated pan, and as much as 10–12 kg. would slide in the uncoated pan. It should be pointed out that this latex or sugar coating was used only for the initial start of tumbling of the tablets, because once there is a slight quantity or sugar on the pan walls, tumbling will generally proceed normally.

It would appear that, within specific limitations, direct application of sugar to tablets and confections, with or without precoat, shows promise. Transfering this process to an automated airless-spray system permits greater uniformity of coating and decreased costs of operation because the operator need not be particularly skilled and can control more coating pans with greater precision than one skilled in performing his work in the traditional manner.

Smooth finish coats were obtained by the usual reduction and closed pan method as described in Clarkson (6), however, this requires the removal of the spray gun from the coating pan after the last cycle. The finished tablets can be polished by any conventional means, with the usual materials.

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Keyphrases

Tablets—sugar coating
Spray coating—automated airless system
Automated coating, pan coating—comparison

# Semiautomated Assay for the Simultaneous Determination of Propoxyphene Hydrochloride and Paramethasone Acetate in Coated Single Tablets

By C. E. STEVENSON and I. COMER

**A semiautomated method for the simultaneous determination of propoxyphene hydrochloride and paramethasone acetate is described for coated tablets. A novel device for the removal and dissolution of tablet coatings is outlined. Solutions are sampled with an automatic sampler at the rate of 20/hr. and fed to two independent systems for analysis. A modified blue tetrazolium procedure is utilized for the determination of paramethasone acetate producing essentially complete color development within 5 min. at room temperature. Working concentrations of 12.5 mcg. paramethasone acetate per ml. can be assayed without resorting to range expansion. Analysis of propoxyphene hydrochloride is accomplished by the formation of a complex with bromocresol purple with subsequent extraction and color measurement in ethylene dichloride.**

THE AUTOMATED analysis of single tablets has been reported by Wolski (1) as a useful tool in the concept of quality assurance. The product[1] involved in this study consists of an enteric 500-mg. acetylsalicylic acid (aspirin) core tablet coated with 32.0 mg. of the analgesic propoxyphene hydrochloride (DPH), and 0.250 mg. of the ketosteroid paramethasone acetate (PMA) (6$\alpha$-fluoro-16$\alpha$-methylprednisolone 21-acetate). For the quality assurance of this product, an automated single-tablet procedure for the simultaneous determination of DPH and PMA was developed using the automatic analyzer.[2]

A desirable condition involving methods for simultaneous determinations is that each component be capable of measurement in the presence of the other without significant interference. The automated method of Kuzel (2), based on the formation of a complex between tertiary amines and bromocresol purple (BCP), and the automated methods of Greely *et al.* (3) and Beyer (4), utilizing the reducing powers of the ketosteroids on blue tetrazolium (BTZ), meet this condition for the compounds in this study. Slight modifications of these procedures have been made in the development of this automated system.

## EXPERIMENTAL

**Reagents**—*BCP*—A 2% acetic acid–98% deionized water (v/v) solution containing 0.25 mg. of bromocresol purple (5′,5″-dibromo-*o*-cresolsulfonphthalein Na salt, Eastman No. 6266) per ml.; *BTZ*—A solution containing 0.15 mg. blue tetrazolium (Fisher Certified B-410) per ml. SD-3A alcohol; *Ethylene Dichloride*—Fisher Certified E-175; TMAH—A solution of 20% tetramethylammonium hydroxide (Eastman No. 1515)–80% SD-3A alcohol (v/v); *Wash*—A solution of 50% methanol–50% deionized water (v/v); *Theory Standard*—32.0 mg. propoxyphene hydrochloride and 0.250 mg. paramethasone acetate reference standard per 20 ml. of Wash solution.

**Sample Preparation**—Due to the relatively low steroid concentration in the formulation, it was desirable to limit the amount of solvent used in the dissolution of the active ingredients to as low a volume as possible. Utilization of an automatic[3] module

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[1] Marketed as Stero-Darvon with ASA by Eli Lilly and Co., Indianapolis, Ind.
[2] AutoAnalyzer, Technicon Corp., Chauncy, N. Y.
[3] Solidprep, Technicon Corp., Chauncy, N. Y.