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TECHNICAL ARTICLES

Construction and Operation of an Automated Dispensing Analyzer for the Assay of Individual Tablets

WILLIAM F. BEYER* and EDWIN W. SMITH†

Abstract □ An automated system of modular design has been developed for the assay of single tablets. Commercially available proportioning pumps, continuous filter, tablet homogenizer, spectrophotometer, and recorder are mated to specially designed components for unattended operation. The system is constructed to analyze automatically up to 300 identifiable tablets with standards inserted prior to tablets, after any selected number of tablets, and at the end of the particular type of tablet being assayed. Up to six different concentrations or types of tablets can be automatically processed sequentially, each with its own standard insertion. Provisions are made to alter automatically the dilution of samples as tablet strengths vary. Under normal program conditions the system can operate unattended for approximately 18 hr.

Keyphrases □ Tablets, individual—automated analysis □ Automated dispensing analyzer, tablet—construction, operation □ Diagram—automated analyzer, individual tablets □ UV spectrophotometry—analysis

The assay of single tablets and single units in other dosage forms is recognized as an important feature in the quality control of manufacturing processes. Compendia requirements for content uniformity of selected tablets containing 50 mg. or less of drug substance has placed additional burdens on the quality control chemist. To make data available in the quantity needed for statistically valid results, analytical procedures have been automated to varying degrees. The majority of automated assay systems that include sample preparation have incorporated a commercially available solid sampler,[1] as evidenced by symposia of the New York Academy of Sciences and Technicon Corp. (1–5). Papers presented at the 1967 New York Academy of Sciences included a presentation by Rehm *et al.* (2) describing an automated system for the UV analysis of single tablets.[2]

An automated system constructed in these laboratories for UV analyses of individual tablets has been in routine operation for more than a year. The system is of modular design and consists of commercially available components wherever possible. Provisions have been made for the introduction of liquid standards, dilution, and

[1] SOLIDprep, Technicon, Inc., Tarrytown, N. Y.
[2] Available commercially as the Assayomat, American Instrument Company, Inc., Silver Spring, Md.

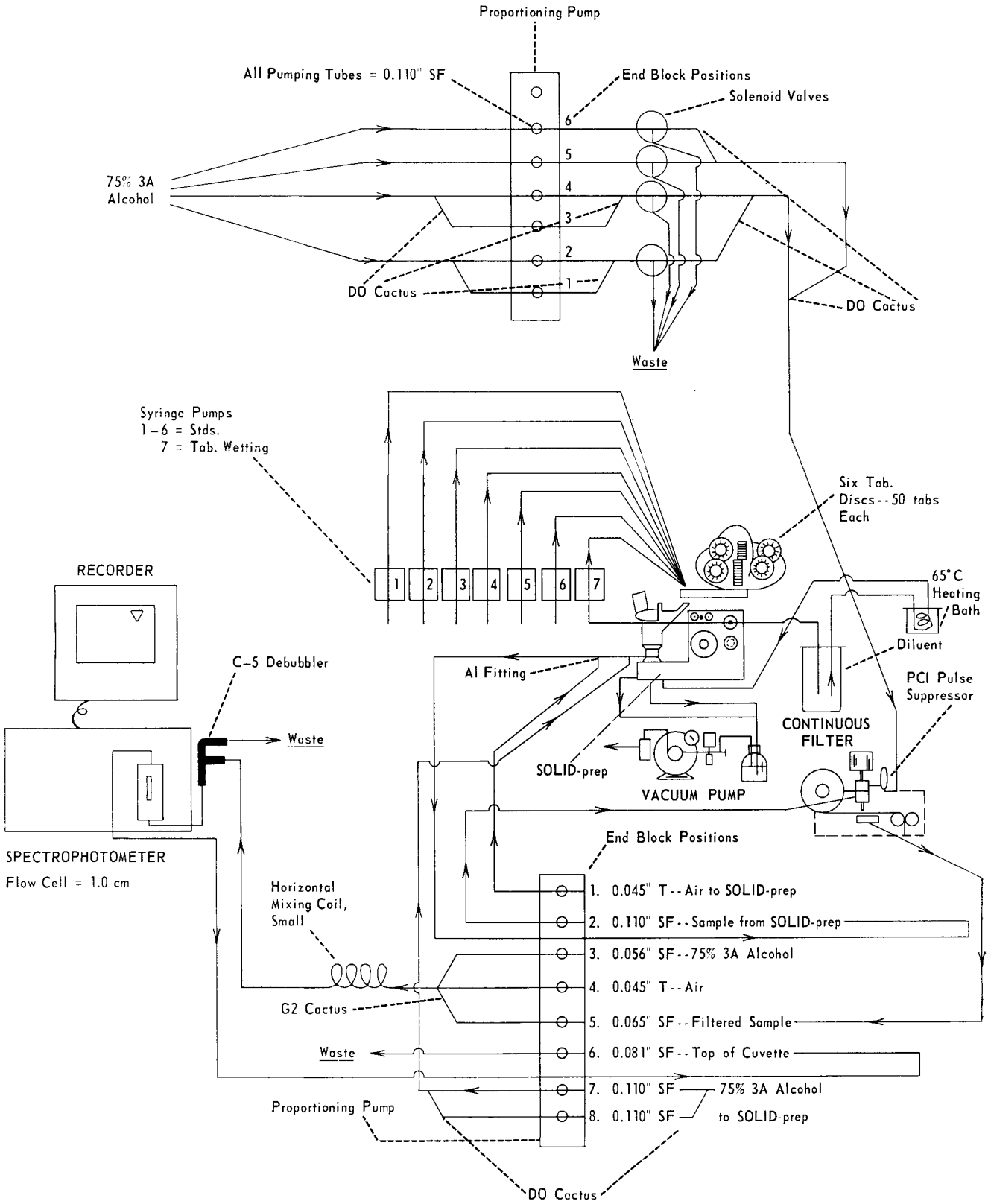

Figure 1—*Manifold flow system and associated equipment used with the automated dispensing analyzer. Solvaflex and Tygon pumping tubes are denoted as SF and T, respectively.*

filtration of tablet samples. Modifications in commercial modules, construction of new units, and the operation of the authors' automated dispensing analyzer (ADA) are the subjects of this report.

EQUIPMENT

The modules and manifold system are schematically illustrated in Fig. 1, with the modular design shown in Fig. 2. Teflon tubing is used throughout except for pumping tubes and heating bath coil.

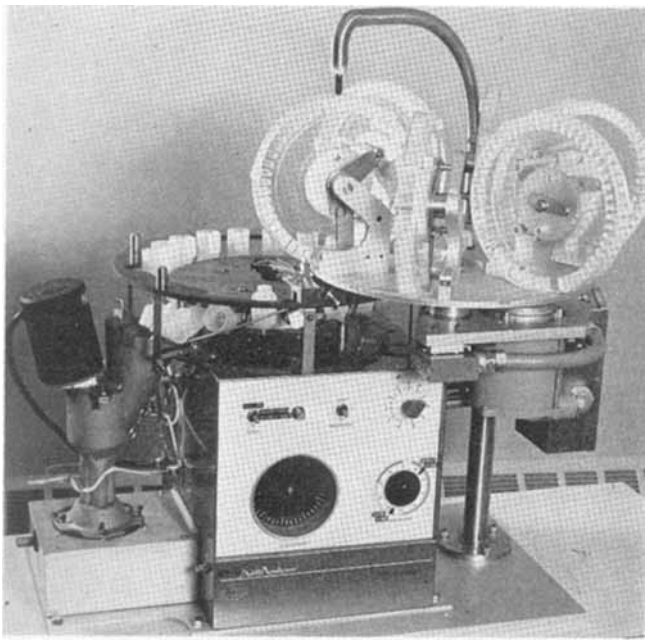

Figure 2—*Instruments comprising the automated dispensing analyzer, showing its modular design.*

the mixing block is replaced with a polyethylene tube having a capillary opening and attached to a pulse suppressor (PCl),[3] into which diluting lines are fed (Fig. 1).

Solid Sampler—An externally mounted solenoid valve[4] replaces the internal wash water distribution solenoid valve carrying three associated rinsing lines. Two check valves[5] replace the check valve for solvent introduction. Only the cup rinsing jet and the hopper jet nearest the cabinet of the solid sampler are used.

Heating Bath, 65°[6]—The diluent passes through 0.95-cm. (0.375-in.) copper tubing fashioned into a 12-turn, 11.43-cm. (4.5-in.) coil, immersed in a 65° water bath. The temperature of the diluent remains above 55° while in the blender.

UV-Visible Spectrophotometer[7] with 1.0-cm. flow cell.[8]

Absorbance Recorder with event marker.[9]

Constructed Modules—*Instream Diluting System*—Four explosion-proof three-way solenoid valves[4] are mounted in an elevated stand to match the height of the proportioning pump. Stainless steel fittings to accommodate approximately 0.32-cm. (0.125-in.) tubing were made for all ports of the solenoid valves. Entrance ports are connected to Solvaflex pumping tubes[3] and exit ports to Teflon tubing leading either to the continuous filter or to waste.

Tablet-holding Disk and Tablet-dispensing Apparatus—Six disks of 50-tablet capacity were fabricated from 0.32-cm. (0.125-in.) and 1.27-cm. (0.5-in.) Plexiglas sheet stock. Numbered slots in the tablet-holding disk accommodate nearly all tablet shapes currently produced at the authors' company. Embedded in the rim of each tablet-holding disk is a strip of brass, sensed by a proximity probe, to signal that the last tablet has been dispensed. The disks, dispensing mechanism, turret, and proximity probe are shown in Fig. 3. The

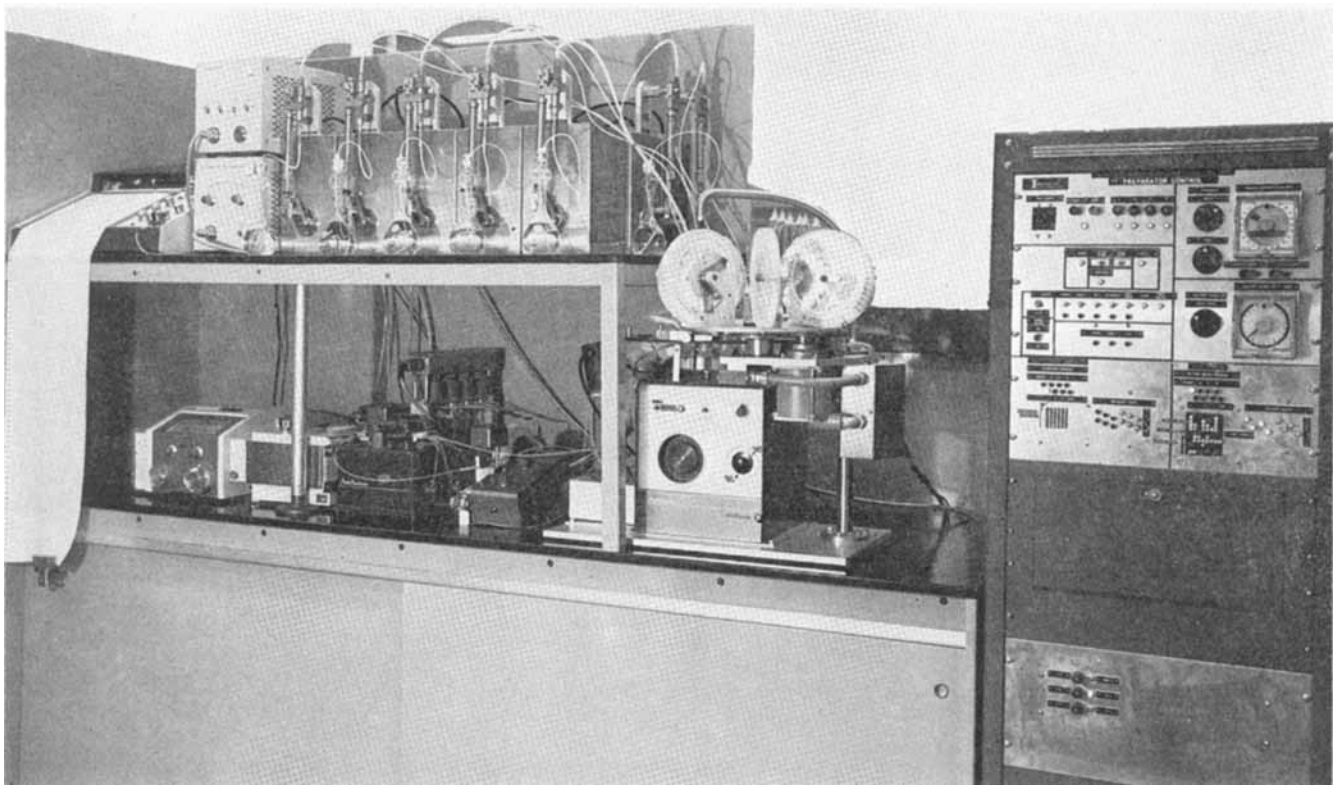

Figure 3—*Sample preparation and dispensing system: solid sampler; turret with six tablet disks, dispensing mechanism, and proximity probe; and the seven-figured tubing attachment unit for standards and tablet-wetting lines.*

Commercially Available Modules, Modified in Some Instances—*Proportioning Pumps (Two)*[3] *and Continuous Filter with Paper T-014*[3]—The chamber of the mixing block is enlarged to accommodate the large volumes of diluent required on occasion. The small nipple used to attach the sample line to the mixing block is replaced with a larger one (N-4)[3] to prevent plugging of the nipple with tablet excipients after prolonged pumping of sample. The upper nipple of tablet-dispensing mechanism is powered by a synchronous motor.[10] A pulse signal from the programmer causes the motor to rotate the

[3] Technicon Inc., Tarrytown, N. Y.

[4] Asco Red Hat, No. 832043, Automatic Switch Co., Florham Park, N. J.

[5] Circle Seal, No. 119T-lpp, Anaheim, Calif.

[6] Tamson Bath, Witt Sales, Cleveland, Ohio.

[7] Hitachi-Perkin Elmer 139, A. H. Thomas, Philadelphia, Pa.

[8] Catalog No. 9120-NO5, A. H. Thomas, Philadelphia, Pa.

[9] Model TRL, Sargent, Chicago, Ill.

[10] Hurst Manufacturing Co., Princeton, Ind.

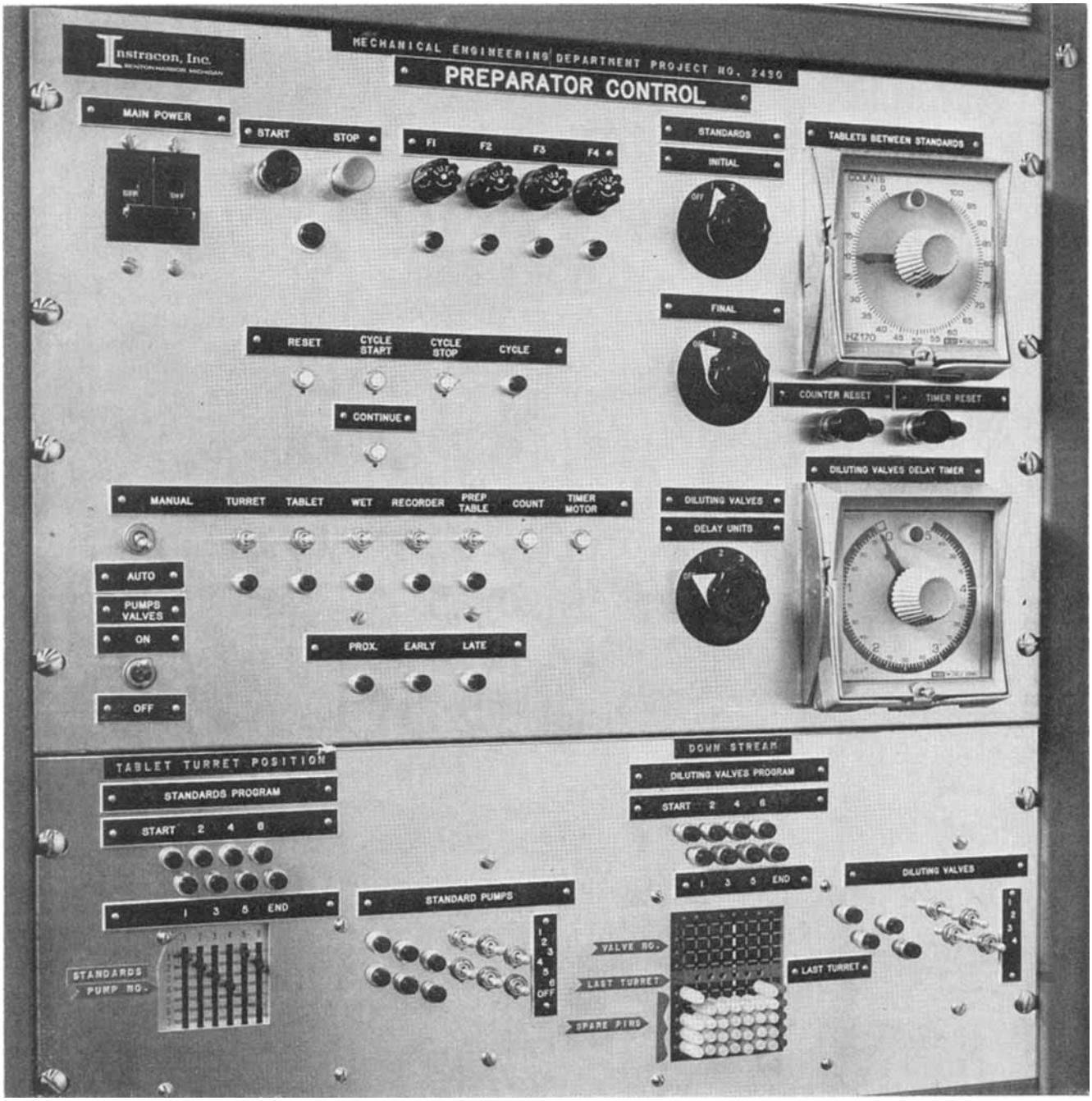

Figure 4—*Control panel of the preparator control.*

disk to the next slot and automatically brake to a stop. The turret mount for the six tablet-holding disks is indexed to the next position by a motor.[11] A pulse signal from the programmer causes this motor to move the turret and brake to a stop when the next disk is in the proper position ready to dispense tablets.

Standards and Tablet-wetting Pumps—Seven pump units consisting of stainless steel pumps, adjustable crank throws, and upper posts were purchased.[12] One-revolution drive and brake units with synchronous motors[10] were constructed to provide braking of the pumps and nonburnout (if stalled) features. Six pumps are used for the six different standards and one pump for tablet wetting (Figs. 1 and 2). The upper and lower valve casings of the pumps containing the tubing attachment nipples were replaced with valve casings having stainless steel tube fittings in order to accept approximately 0.32-cm. (0.125-in.) Teflon tubing. Standards and diluent for tablet wetting are dispensed from each particular pump to a special ring, located above the cup at the point where the tablet is dispensed from the tablet disk, as shown in Fig. 2. A pulse signal from the programmer results in only one filling and diluting cycle of the pump.

Preparator Control[13] *(6)*—This unit (Fig. 4) is an electrical hybrid, having conventional limit switches interfaced with integrated solid-state circuit logic. Output for motors and solenoids comes through contacts on conventional d.c.-driven plug-in relays. The sequence of programmed operations inherent in the solid sampler is not disturbed. Two spare switches in the solid sampler programmer (as

[11] Slo-Syn, Superior Electric Co., Bristol, Conn.
[12] Unit No. FUS-15, National Instrument Co., Baltimore, Md.

[13] Instracon, Inc., Benton Harbor, Mich.

Table I—Diluting Lines and Solenoid Valves Required for Various Steroids

Steroid	Number Diluting Lines	Solenoid Valve No.	Average Absorbance	Coefficient of Variation %
Fluprednisolone, 0.75 mg./10 ml.	None	None	0.219	0.65
Prednisolone, 2.5 mg./10 ml.	None	None	0.705	0.62
Methylprednisolone, 4.0 mg./10 ml.	1	1	0.485	0.64
Hydrocortisone, 10.0 mg./10 ml.	4	1,2,3	0.497	1.21
Methylprednisolone, 16.0 mg./10 ml.	6	1,2,3,4	0.499	1.23
Hydrocortisone, 20.0 mg./10 ml.	6	1,2,3,4	0.703	1.23

purchased) are utilized to sequence the preparator control. The latter unit coordinates the actions of five separate pieces of equipment: (*a*) the solid sampler unit; (*b*) the turret which supports six tablet-holding disks; (*c*) the pumping system for six separate standards and one tablet-wetting pump; (*d*) the instream diluting system which determines the extent of sample dilution after aspiration from the homogenizer; and (*e*) the event pen of the recorder, energized upon delivery of standard.

The preparator control automatically governs functions of the system once started, yet permits the following actions manually by the operator: (*a*) selection of the number of standards dispensed prior to any tablets, numbers of tablets dispensed between the introduction of additional standards, and whether or not a standard is dispensed after the last tablet in each tablet-holding disk; (*b*) selection of the proper times for diluting valves to open or close in order that exact correspondence may be maintained after the introduction of a new series of tablets; (*c*) rotation of the turret to any one of the six tablet-holding disks for correct startings; (*d*) dispensing of standards and tablet-wetting medium prior to initiation of a run in order to purge the lines; and (*e*) testing for malfunction of individual components by activating selected switches or observing pilot lights as the entire sequence of operational events is simulated.

Table II—Individual Tablet Assay of Corticosteroids with the Automated Dispensing Analyzer and Comparison with a Semiautomated Blue Tetrazolium Procedure

Lot No.	Automated Dispensing Analyzer, UV High %	Low %	Mean %	Semiautomated B.T.Z.,[a] %
	Prednisone, 5 mg.			
1	105	98.8	102	96.4
2	105	97.2	101	98.4
3	108	98.4	102	98.0
4	109	96.4	103	98.2
5	110	101	104	98.2
6	105	96.0	99.8	100
7	105	95.4	99.6	100
8	104	96.0	100	97.8
9	105	96.8	101	97.4
10	105	97.0	102	97.4
11	104	94.8	99.4	98.0
12	104	96.8	100	97.0
13	112	98.6	102	98.8
14	110	99.6	104	100
15	105	93.4	100	98.8
16	107	98.0	103	98.6
17	106	97.6	102	101
18	105	97.2	101	99.4
19	107	97.0	101	99.2
20	107	100	103	101
	Methylprednisolone, 4 mg.			
21	106	98.2	102	98.2
22	105	98.5	102	102
23	104	99.8	102	99.0
24	108	97.2	102	98.8
25	104	98.2	101	96.2
26	104	97.8	100	99.8
27	104	97.5	100	98.5
28	102	91.0	97.8	97.8
29	105	98.8	101	98.0
30	108	98.5	103	98.0
31	107	97.8	102	96.5
32	104	95.5	99.5	98.5
33	105	96.0	98.5	97.5
34	106	95.2	100	98.0
35	103	93.8	98.0	97.5
36	102	96.0	98.8	99.5
37	104	96.0	100	98.2
38	106	101	104	98.2
39	113	105	108	103
40	108	99.2	103	98.7

[a] Blue tetrazolium.

OPERATING PROCEDURE

A zero base line with 75% 3A alcohol is established using the manifold flow system of Fig. 1 and with all instruments operating (recorder, UV spectrophotometer at a wavelength at 242 mμ, two proportioning pumps, vacuum pump, continuous filter, 65° heating bath, solid sampler, and preparator control). Sixty milliliters of 75% 3A alcohol is used in the solid sampler. From 1–50 tablets are placed in numbered slots of each of the six disks, and the disks are mounted on the turret and secured. The tablet-wetting pump and all standard pumps used in the analysis are rinsed with solutions to be used to ensure that the lines are free of air and previous liquid. Programs for the standard pumps and associated tablet disks, diluent valves, and number of disks used in the assay are selected on the preparator control panel.

The recorded peak heights resulting from tablets and standards bracketing the tablets are used in conjunction with the concentrations of the standards to calculate the amount of active ingredient in each tablet.

RESULTS AND DISCUSSION

The manifold tubing and flow system of the automated dispensing analyzer is very similar to that reported for the automated UV assay of tolbutamide tablets (7). The durability of Solvaflex tubes during prolonged pumping with 75% 3A alcohol and the ability of this solvent to remove or minimize UV-absorbing material from the tubes were established in the tolbutamide studies (7).

A much better flow of liquid and more uniform air segmentation of the sample stream occurred when the diluent and air lines connected to the blender assembly of the solid sampler were interchanged in the manner described by Kuzel (8). The ratio of rinse to sample was increased (also suggested by Kuzel) so that during the wash cycle a portion of the rinse enters the sample line and the remainder enters the blender, blocking off seepage of sample. Directing the diluent from the solenoid valves to the mixing block of the continuous filter permitted the addition or interruption of diluent without changing sample flow rate. This was particularly important in programming the correct moment for the solenoid diluting valves to be activated. Placing a pulse suppressor in the diluent line at the mixing block of the continuous filter eliminated surging which gave poor mixing of unfiltered sample and diluent.

Standards, tablets, and tablet-wetting diluent are dispensed into the sample cups of the solid sampler 45 min. prior to homogenization. Complete dissolution of drug from the tablet is ensured by a combination of the 45-min. period and by the use of heated diluent in the homogenizing vessel of the solid sample. Delivery volumes of the six standards and one tablet-wetting pump were adjusted so that each pump filled ten 10-ml. volumetric flasks to the mark. Automatic addition of standards and manual pipeting gave equivalent results for steroids when analyzed by ADA.

Table I gives results for six levels of various steroids, four of which require the use of diluting valves. The data are the result of 10 replicate analyses with the automated system. The coefficients of variation ranged from 0.62% for prednisolone to 1.23% for hydrocortisone at concentrations of 2.5 mg./10 ml. and 20.0 mg./10.0 ml., respectively.

Table III—Statistical Results of Single Tablet Potency Assays

Product	Lot No.	No. Tablet	Steroid/Tablet, mg.	Coefficient of Variation (%)	95% Confidence Limits
Fluprednisolone, 0.75 mg.	41	50	0.78	3.74	0.72–0.84
	42	50	0.85	2.88	0.80–0.90
Fluprednisolone, 1.50 mg.	43	10	1.60	1.53	1.55–1.65
	44	10	1.58	3.01	1.49–1.68
Prednisolone, 2.5 mg.	45	50	2.50	2.40	2.38–2.62
	46	50	2.50	2.22	2.39–2.61
Prednisolone, 5.0 mg.	47	40	5.09	2.37	4.85–5.33
	48	25	5.01	2.27	4.78–5.23
Prednisone, 2.5 mg.	49	10	2.59	1.23	2.52–2.65
	50	10	2.57	1.70	2.49–2.67
Prednisone, 5.0 mg.	51	15	5.07	2.17	4.85–5.30
	52	20	5.10	1.74	4.93–5.28
Cortisone acetate, 5.0 mg.	53	10	5.13	1.21	5.00–5.25
	54	24	5.06	1.85	4.87–5.24
Cortisone acetate, 10.0 mg.	55	10	10.17	1.44	9.88–10.47
	56	10	9.41	3.13	8.82–10.00
Cortisone acetate, 25.0 mg.	57	8	24.73	2.60	23.45–26.02
	58	11	24.30	2.53	23.06–25.53
Hydrocortisone, 5.0 mg.	59	49	5.15	2.94	4.85–5.45
	60	25	5.02	1.99	4.82–5.22
Hydrocortisone, 10.0 mg.	61	50	10.0	1.64	9.67–10.33
	62	50	9.94	1.83	9.58–10.31
Hydrocortisone, 20.0 mg.	63	50	19.98	2.14	19.12–20.83
	64	41	20.32	2.63	19.25–21.39
Methylprednisolone, 2.0 mg.	65	10	2.00	1.35	1.94–2.05
	66	50	2.02	1.29	1.97–2.08
Methylprednisolone, 4.0 mg.	67	49	4.18	2.18	4.00–4.37
	68	50	4.12	2.00	3.95–4.28
Methylprednisolone, 16.0 mg.	69	19	15.98	2.15	15.29–16.67
	70	18	16.23	1.77	15.66–16.81
Fluoxymesterone, 1.0 mg.	71	10	1.03	1.59	1.00–1.07
	72	10	1.05	0.92	1.04–1.07
Fluoxymesterone, 2.0 mg.	73	15	2.04	1.70	1.97–2.10
	74	15	2.13	2.92	2.01–2.26
Fluoxymesterone, 5.0 mg.	75	10	5.19	2.38	4.95–5.44
	76	10	5.14	1.89	4.95–5.34
Fluoxymesterone, 10.0 mg.	77	10	9.79	1.10	9.57–10.00
	78	10	10.05	2.80	9.49–10.62
Medroxyprogesterone acetate, 2.5 mg.	79	15	2.54	2.22	2.43–2.65
	80	15	2.58	1.80	2.43–2.67
Medroxyprogesterone acetate, 10.0 mg.	81	10	9.93	3.00	9.34–10.53
	82	10	10.11	1.32	9.95–10.38

Numerous individual steroid tablet assays were carried out with the automated UV system. Representative data of prednisone, 5 mg., and methylprednisolone, 4 mg., are given in Table II. Approximately 50 tablets from each of 20 lots are shown with high and low tablets well within NF (9) and USP (10) limits for content uniformity (85–115% of the average of specified tolerances). Blue tetrazolium assays of composite samples of pulverized tablets are also shown in Table II.

Table III gives statistical data for individual tablet assays, with the steroid content varying from 0.75 mg. fluprednisolone to 25 mg. cortisone acetate. Steroid content, coefficients of variation, and 95% confidence limits were calculated for this series of tablets. Both production and assay precision determine the magnitude of the coefficient of variation and the spread of the 95% confidence limits. The highest coefficient of variation was 3.74% for 0.75 mg. fluprednisolone; the lowest was 0.92% for 1.0 mg. fluoxymesterone.

The tablet data of Tables II and III demonstrate the application of the automated system for unattended UV analysis of individual tablets. Changes only in manifold tubing and the addition or elimination of particular modules should permit the use of other endpoint detection methods.

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