Single-Tablet Assays

Automated Assay of Single Tablets of Isoxsuprine Hydrochloride

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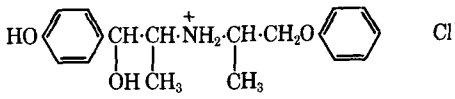
An automatic analyzer system was used to determine the amount of isoxsuprine hydrochloride in single tablets. The intensity of the ultraviolet absorbance of isoxsuprine hydrochloride was a measure of its concentration in the tablet.

ISOXSUPRINE HYDROCHLORIDE[1] (I) is a myovascular relaxant that acts directly and specifically on the smooth muscle of the blood vessels and the myometrium to increase blood flow in vascular disorders, and to reduce uterine hypermotility (1, 2). Isoxsuprine hydrochloride is readily assayed in tablets by means of its characteristic ultraviolet spectrum: $\lambda_{max.}$ 218 mμ (0.1 *M* H_3PO_4) (*a*, 42.2).



The literature on the application of automated analyses to pharmaceutical formulations, including tablets, is extensive, and several comprehensive literature compilations exist (3–5). The application of an automated ultraviolet assay to single tablets of isoxsuprine hydrochloride is now reported. Using this method the probability of meeting the USP test for content uniformity (6) was found to be greater than 99%.

EXPERIMENTAL

Apparatus—The analytical train consisted of the following modules: (*a*) Solidprep Sampler, proportioning pump, and dialyzer, from Technicon Instruments; (*b*) Hitachi Perkin-Elmer spectrophotometer, model 139; (*c*) Microflow cell 9120 No. 5; and (*d*) Sargent model TR-05 recorder.

Reagents—(*a*) Phosphoric acid (H_3PO_4), 0.1 *M*; and (*b*) phosphoric acid (0.1 *M*) containing 0.01% polysorbate 20.[2]

Standards—Aqueous solutions of isoxsuprine hydrochloride were made up at three levels of concentration (0.871, 1.09, and 1.31 Gm./L.) (Table I). Ten-milliliter aliquots of each solution were equivalent to an 8-mg., 10-mg., or 12-mg. tablet, respectively, when they had been diluted with 110 ml. 0.1 *M* H_3PO_4 in the Solidprep sampler. This correction was necessary to compensate for volume differences.

Samples—Production lots of tablets were obtained at both front and back punches of the tableting machine. Theoretical content of each tablet was 10 mg. of isoxsuprine hydrochloride.

Procedure—A schematic of the automatic analyzer[3] system is shown in Fig. 1. Each tablet was individually disintegrated in the presence of 0.1 *M* phosphoric acid. An aliquot of the resulting suspension was dialyzed to remove extraneous solid and the dialyzate passed through the spectrophotometer where its ultraviolet absorbance was measured and recorded (Fig. 2).

Approximately 120 tablets could be analyzed in an 8-hr. day.

The three standard solutions were analyzed several times during the day to check the variation of absorbance. No significant variation was found.

Calculation—The average absorbance for each level of standard was determined. A standard curve [average absorbance *versus* tablet equivalent (mg.)] was prepared. Reference to the standard curve gave for each sample the mg. of isoxsuprine hydrochloride per tablet.

TABLE I—CONCENTRATION AND AVERAGE ABSORBANCE OF STANDARDS

Concn. of Standard, Gm./L.	10 ml. of Standard Equivalent to	Av. Absorbance at 220 mμ
0.871	8 mg. Isoxsuprine HCl	0.253
1.09	10 mg. Isoxsuprine HCl	0.311
1.31	12 mg. Isoxsuprine HCl	0.369

DISCUSSION

Interference at the dialysis stage due to dibasic calcium phosphate (a tablet excipient) was overcome by the use of phosphoric acid. Other acids (*e.g.*, sulfuric acid, hydrochloric acid) were found unsuitable. Sulfuric acid resulted in anomalous dialysis rates; hydrochloric acid attacked the automatic analyzer's stainless steel.

RESULTS

Standard Curve—The average absorbance for each of the three standards was determined. A plot of the values (see Table I) gave a straight line, indicating adherence to Beer's law.

Reproducibility of Standards—The reproducibility of the method was checked by the analysis of 10 standards (Table II).

Reproducibility of Sample Suspension—The precision of the method was checked by the analysis of nine aliquots of a sample suspension (Table II).

Statistical Results[4]—The results of nine lots of 50 tablets have been evaluated. The data are presented in Table III.

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[1] Marketed as Vasodilan by Mead Johnson Laboratories, Division of Mead Johnson & Co.

[2] Tween 20, Atlas Chemical Industries, Inc., Wilmington, Del.

[3] AutoAnalyzer, Technicon, Ardsley, N. Y.

[4] The statistical program was prepared by the Systems Department, Mead Johnson & Co. Results were obtained using an IBM 360 computer.

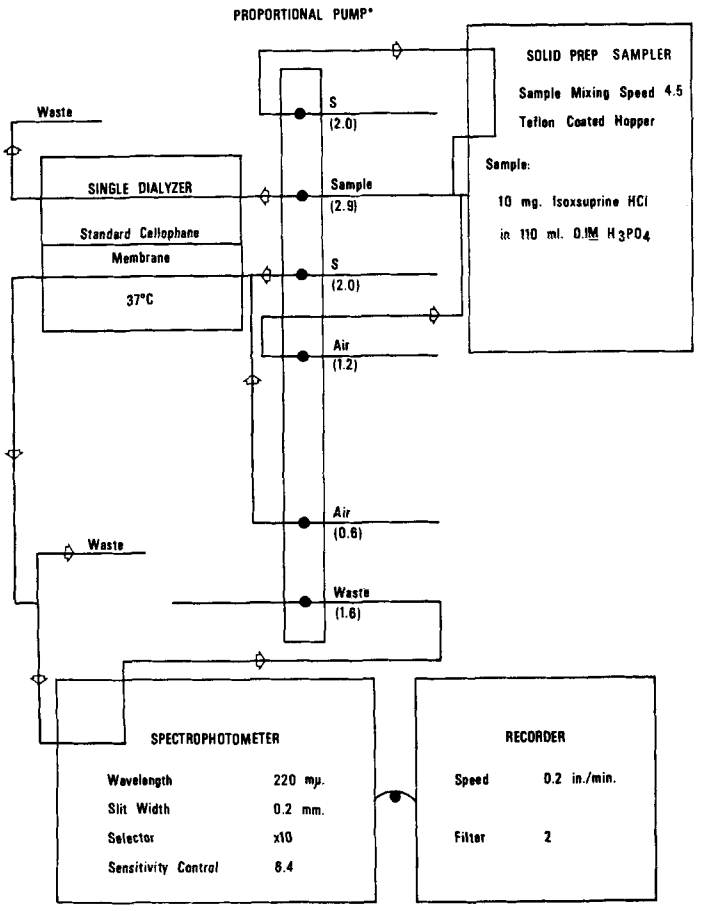

Fig. 1—Schematic for isoxsuprine hydrochloride (values in parentheses are flow rates in ml./min., S = 0.1 M H_3PO_4 with 0.01% polysorbate 20.)

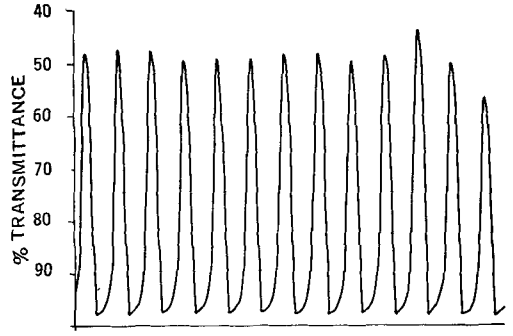

Fig. 2—Typical curve for isoxsuprine hydrochloride.

TABLE II—REPRODUCIBILITY OF STANDARDS AND SAMPLE SUSPENSION

10 ml. of Standard Solution Equivalent to Wt. of Isoxsuprine Hydrochloride			Tablet Suspension Equivalent to 10 mg. Isoxsuprine Hydrochloride
8.0 mg.	10.0 mg.	12.0 mg.	
8.2	10.0	12.0	10.1
8.0	10.0	12.0	9.9
7.9	9.9	12.0	10.0
8.0	10.0	12.0	10.0
7.9	10.0	12.0	10.1
8.0	10.0	12.0	10.2
8.0	10.0	12.0	10.2
8.0	10.0	12.0	10.4
8.0	10.0	11.9	10.4
7.9	10.0	12.0	
Av. 8.0 mg.	10.0 mg.	12.0 mg.	
Coefficient of Variation, %			
1.20	0.33	0.28	1.70

TABLE III—STATISTICAL RESULTS

Lot	Mean mg. Isoxsuprine HCl/Tablet	% Coefficient of Variation
1	9.9	2.4
2	10.1	2.5
3	10.4	3.1
4	10.0	2.5
5	10.3	3.0
6	10.4	1.6
7	10.4	2.3
8	10.6	2.6
9	10.2	1.6

SUMMARY

Single tablets of isoxsuprine hydrochloride have been analyzed using an automated procedure, with greater than 99% probability of meeting the USP content uniformity test.

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(6) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, p. 905.

Keyphrases

Automated analysis—isoxsuprine HCl tablets, single
Diagram—automatic analyzer system
Dialysis—separation
UV spectrophotometry—analysis

Evaluation of Factors Affecting the Encapsulation of Powders in Hard Gelatin Capsules I

Semi-Automatic Capsule Machines

By G. REIER, R. COHN, S. ROCK, and F. WAGENBLAST

A useful model has been developed which relates particulate properties, capsule size, and the operating rate of semi-automatic filling equipment to filled capsule characteristics. The mean capsule fill weight is dependent on machine speed, capsule size, and specific volume. The weight variation as expressed by the standard deviation is a function of machine speed, capsule size, specific volume, flowability, and the presence of a glidant. Particle size considerations of moderately coarse powders (USP designation) are not directly a part of the model because they are reflected in the other evaluated particulate properties. The model is applicable to powder systems other than those from which it was derived. Mean gross capsule weights of such systems may be calculated with an accuracy often exceeding 95 percent. The utility of the model lies in its ability to provide information concerning the relationship of machine speed, capsule size, powder specific volume, and flow to mean capsule fill weight from simple evaluations of small samples of the formulation to be encapsulated.

HARD GELATIN capsules have been known since 1848. They were first prepared in London (1), and quickly attained popularity in the United States where capsule manufacturing and filling operations were carried out manually (2). Hard gelatin capsules are today an important part of solid dosage form drug presentation. A variety of useful, elegant capsule products are available to the physician.

Curiously, the literature is devoid of any reports dealing with the encapsulation of dry powders on an industrial scale. The absence of reported works on this subject is even more marked when one considers the detailed investigations published, for example, by Higuchi *et al.* (3, 4), on the physical factors affecting the tableting process.

Current formulation of powders for encapsulation is carried out on an empirical basis and, while this method has apparently met the needs of the pharmaceutical industry, it would be extremely valuable to have a mathematical model which quantitatively defines the variables encountered in capsule filling. Once these variables are known and quantitated, their application to formulations can be assessed before laboratory work is begun.

The present work was conducted to develop a mathematical model which describes the effect of selected physical powder properties as well as mechanical operating conditions on the capsule filling operation, and to ascertain the relationships of these variables on the encapsulation process.

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