of the reconstituted hydrochloride salt of NSC-82196 stored at 25° in dark or light. The apparent $t_{1/2}$ was 65 hr. for the same vials stored at 4° in the dark.

REFERENCES

(1) G. Hoffman, I. Kline, M. Gang, D. Tyrer, J. Vendetti, and A. Goldin, *Cancer Chemother. Rep.*, **52**, 715(1968).

(2) *University of Michigan College of Pharmacy Interim Progress Report*, January 14, 1969.

(3) Y. F. Shealy, C. A. Krauth, L. B. Holum, and W. E. Fitzgibbon, *J. Pharm. Sci.*, **57**, 83(1968).

(4) Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, *J. Org. Chem.*, **27**, 2150(1962).

(5) Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *ibid.*, **26**, 2396(1961).

(6) T. L. Loo and E. A. Stasswender, *J. Pharm. Sci.*, **56**, 1016 (1967).

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TECHNICAL ARTICLES

Automated Dual Extraction Procedure for Analysis of Phenmetrazine Hydrochloride Tablets

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Abstract □ An automated method of analysis, based on dual extraction of phenmetrazine hydrochloride, has been developed for analysis of phenmetrazine hydrochloride tablets. The method requires use of a continuous digestor along with other more familiar modules of an automatic analyzer. A total of 520 individual tablets was analyzed by this method. Of all the tablets analyzed, 99.8% were within ±10% of the indicated dosage and 100% were within ±15% of the indicated dosage.

Keyphrases □ Phenmetrazine HCl tablets—analysis □ Automated extraction procedure—phenmetrazine HCl analysis □ Diagram—automated system, phenmetrazine HCl analysis □ UV spectrophotometry—analysis

Automated analytical methods have been limited generally to dissolution and/or extraction of active ingredients from the formulation, filtration, and dilution to suitable concentration for analytical determinations. Manual methods involving evaporation of the organic solvent, followed by dissolution of the residue in suitable aqueous solvents, have been considered difficult to automate. One semiautomated approach to the solution of this problem has been reported by Feller *et al.* (1) for analysis of ethopabate in poultry feeds. This approach should provide a valuable means of automating pharmaceutical methods of analysis, where such extractions are frequently used.

A variety of manual methods (2–9) has been used for analysis of phenmetrazine hydrochloride.[1] For several years, a manual dual-extraction procedure (9) has been used in the authors' laboratories for analysis of 25-mg. tablets of this compound. The tedious and time-consuming manual procedure was automated by the use of the continuous digestor[2] along with other more familiar modules of the automatic analyzer.[2]

Table I—Recoveries and Precision with the Automated Method

Number	Percent Phenmetrazine Hydrochloride Recovered
1	99.2
2	101.2
3	100.4
4	103.2
5	101.2
6	98.0
7	101.2
8	103.2
9	99.2
10	100.4
Average	100.7
Relative *SD*	±1.7

EXPERIMENTAL

Materials and Methods—The flow diagram of the analytical system, including tubing sizes, is shown in Fig. 1. The Solidprep sampler is programmed to operate at a rate of 13 samples/hr. The sample (tablet) is deposited in a cup placed on the turntable of the sampler. In turn, each sample is dumped into the homogenizer and homogenized with 100 ml. of water; a 0.9-ml./min. sample (segmented with air) is pumped from the sampler. The sample is made alkaline with 1% w/v NaOH and filtered through a continuous filter. About 50% is resampled and extracted with chloroform, and the chloroform extract is washed with water and fed into the continuous digestor. Simultaneously, dilute hydrochloric acid (4 in 100)

[1] Preludin, Geigy Pharmaceuticals, Ardsley, N. Y.

[2] Technicon Corp., Tarrytown, N. Y.

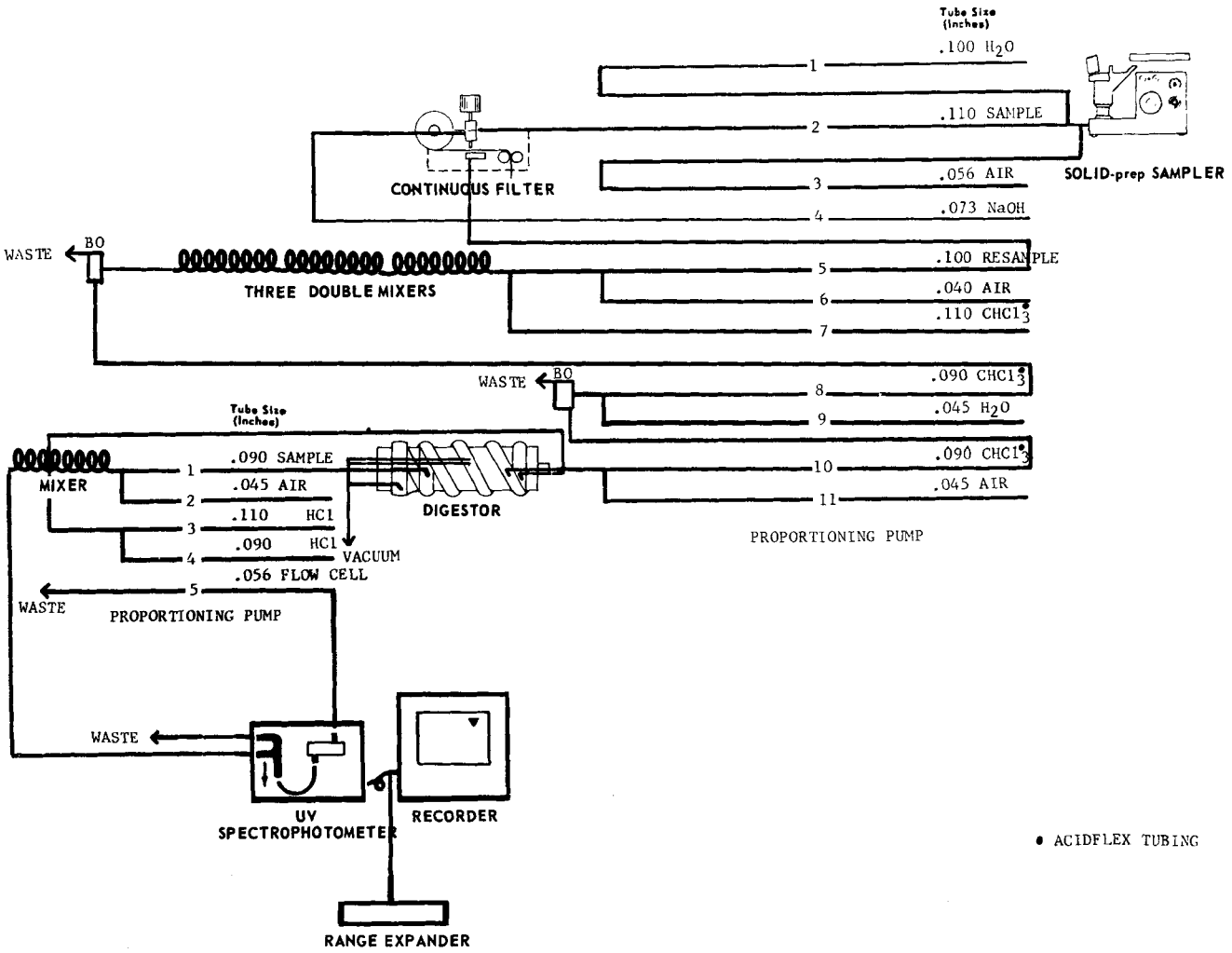

Figure 1—*Flow diagram of the analytical system.*

is fed into the continuous digestor where chloroform is evaporated in a heated rotating helix, with subsequent solution of the residue in the dilute hydrochloric acid. A portion of the dilute hydrochloric acid solution is sampled on the other end of the rotating helix (the rest of the sample and chloroform are sent to waste) and passed through a mixing coil; its absorbance is determined at 256 mμ in a 15-mm. tubular flow cell with the range expander set at the 2× setting. Standards are run at various intervals to provide a means for calculation of sample concentration and to check any instrumental fluctuations.

RESULTS AND DISCUSSION

Tablets are initially extracted with water instead of the dilute hydrochloric acid (4 in 100) used in the manual method. The latter solvent was undesirable for use with the automatic analyzer. After investigating various alternate solvents, it was found that water was the solvent of choice because of its greater suitability for further extractions.

In the manual method, 50% NaOH w/v solution is used for alkalinization of dilute hydrochloric acid (4 in 100) prior to chloroform extraction. The use of such a strong alkaline solution was considered neither desirable nor necessary in the automated method. A much lower concentration, such as a 1% w/v NaOH solution, was found very suitable for alkalinization in the automated method.

Beaded mixing coils are generally used for liquid/liquid extraction in automated methods. For this work, these coils were found unusable because they yielded very heavy emulsions which could not be resolved. This problem was solved by using three mixing coils in a row along with two separators. The first separator provides the separation of chloroform from the aqueous phase. In the second separator, chloroform is washed with water, whereby emulsion problems are completely eliminated.

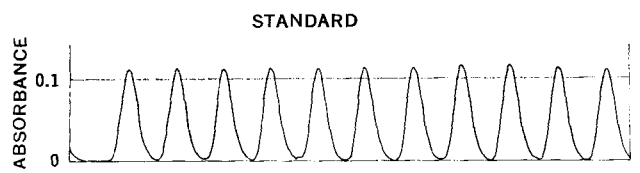

Figure 2—*Typical recording of phenmetrazine tablets, 25 mg.*

Table II—Comparison of Results Obtained by Automated and Manual Methods

Sample	Phenmetrazine Hydrochloride, mg. Automated Method	Manual Method	Deviation, mg.
A	25.0	25.3	−0.3
B	24.8	24.8	0.0
C	24.3	24.0	+0.3
D	23.8	23.9	−0.1
E	24.4	25.1	−0.7
F	24.7	24.3	+0.4
G	24.3	24.6	−0.3
H	25.1	24.7	+0.4
I	24.5	24.6	−0.1
J	24.6	24.5	+0.1
Average	24.6	24.6	±0.3

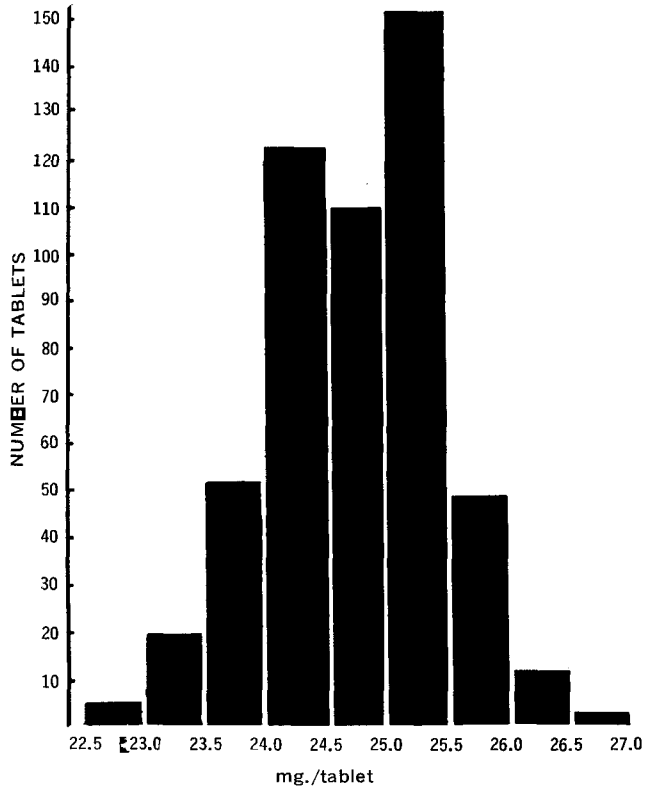

Figure 3—*Histogram of phenmetrazine tablets, 25 mg.*

The second extraction step, involving reextraction of phenmetrazine into dilute hydrochloric acid (4 in 100) from chloroform, is automated by the use of the continuous digestor. This is accomplished in a heated rotating helix. The chloroform and the dilute hydrochloric acid are introduced in such a proportion as to create thin layers of both of these phases. The organic phase is volatilized by heat and vacuum (which is applied on the other end), and the aqueous acid phase is aspirated into the automated system and processed as shown in Fig. 1. The use of the continuous digestor provides increased sensitivity (1) and eliminates the emulsification problems commonly encountered in manual liquid/liquid extraction methods.

A linear relationship was observed between the concentration of phenmetrazine hydrochloride and absorbance in the range of concentration studied. The precision and recoveries obtained by the method were checked by running "synthetic" formulations (prepared in a manner similar to the commercial formulation). The percentage recovery results on the synthetic formulation are shown in Table I. No significant interference from the excipients was observed when placebos of this formulation were run by this method.

A typical recording is shown in Fig. 2. The average of 10 individual tablets compared favorably with the results obtained manually (Table II), thus suggesting that the automated method provides an acceptable alternate means of assaying phenmetrazine hydrochloride in phenmetrazine hydrochloride tablets.

To study tablet-to-tablet variation, a very large number of individual tablets was analyzed by these methods. The tablets used were selected randomly from several production batches to obtain a good overall picture of tablet-to-tablet variation. The distribution of dosage in these tablets is presented in the form of a histogram (Fig. 3). Of all the tablets analyzed, 99.8% were within ±10% of the indicated dosage and 100% were within ±15% of the indicated dosage (±15% is the present limit in the NF for content uniformity of tablets).

REFERENCES

(1) B. Feller, W. A. Boyd, B. E. DiDario, and A. Ferrari, "Automation in Analytical Chemistry," Mediad Inc., White Plains, N. Y., 1967, p. 206.

(2) E. Vidic and J. Schuette, *Arch. Pharm.*, **295,** 342(1962).

(3) E. Smith, L. F. Worrell, and J. E. Sinsheimer, *Anal. Chem.*, **35,** 58(1963).

(4) J. Kracmar and J. Pokarny, *Cesk. Farm.*, **11,** 7(1962).

(5) W. N. French and J. R. Truelove, *J. Pharm. Sci.*, **54,** 306 (1965).

(6) H. Kolb and P. W. Patt, *Arzneim.-Forsch.*, **15,** 924(1965).

(7) A. Heyndrickse and A. de Leenheer, *J. Pharm. Belg.*, **22,** 109 (1967).

(8) G. P. Quinn, M. M. Cohn, M. B. Reid, P. Greengard, and M. Weiner, *Clin. Pharmacol. Ther.*, **8,** 369(1967).

(9) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, p. 542.

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