Analysis of Certain Phenothiazines and Their Dosage Forms by Photometric Titration with Ceric Sulfate

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Abstract □ A photometric titration procedure is described for the determination of a number of phenothiazine derivatives and their dosage forms. An acidic solution of the drug or dosage form is titrated with standard ceric sulfate solution. The end point is determined photometrically at 420 mμ. Quantitative recoveries are reported for 14 phenothiazine derivatives and three dosage forms.

Keyphrases □ Photometric titration—phenothiazines □ Phenothiazines and dosage forms—analysis □ Colorimetric analysis—spectrophotometer □ Ceric sulfate—titrant

Phenothiazine derivatives in a variety of dosage forms are used extensively as psychopharmacological agents in the treatment of psychotic patients and in controlling anxiety and tension neuroses. A multitude of procedures for the analysis of these compounds involving titrimetry, spectroscopy, and chromatography have been reported in the literature. These have been reviewed by Blazek (1) and Blazek *et al.* (2).

Milne and Chatten (3) and Mainville and Chatten (4) analyzed a number of phenothiazines and their dosage forms by nonaqueous titration using perchloric acid in dioxane as the titrant. Anhydrous acetone, acetonitrile, or a mixture of hexane and acetone were used as the solvent. Methods involving titration in nonaqueous solvents have been reviewed by Gyenes (5).

DeLeo and Stern (6, 7) suggested a thermometric titration procedure for phenothiazines. Chlorpromazine hydrochloride was determined quantitatively by this technique using 2.0 *M* sodium hydroxide solution as the titrant. Satisfactory recovery was achieved for a sustained-release capsule dosage form, but a syrup dosage form gave enthalpograms with end points not indicative of the active constituent content.

Dusinsky (8, 9) and Dusinsky and Liskova (10) investigated oxidation procedures for the analysis of phenothiazines. Permanganate, bichromate, iodine, nitrate, and bromate did not yield quantitative results. However, the bromide-bromate couple (Koppeschaar's reagent) and ceric sulfate in sulfuric acid produced good recoveries. The *British Pharmacopoeia* (11) assay procedure for chlorpromazine tablets is based on oxidation with ceric ammonium sulfate.

Spectrophotometric procedures are used extensively in the analysis of phenothiazine derivatives. The *United States Pharmacopeia* (12) assay for a number of dosage forms containing salts of phenothiazines is based on the UV absorption properties of the phenothiazine base. Included here are chlorpromazine hydrochloride injection, syrup, and tablets; prochlorperazine edisylate injection and syrup; prochlorperazine maleate tablets; and promethazine hydrochloride injection, syrup and tablets. The *National Formulary* (13) utilizes UV absorption procedures for prochlorperazine suppositories, promazine hydrochloride, and the injection, syrup, and tablet dosage forms.

The present study describes a simple photometric titration procedure for the determination of a number of phenothiazine derivatives as pure drugs and as several dosage forms.

EXPERIMENTAL

Apparatus—Photometric titrations were performed with a spectrophotometer (Carl Zeiss model PMQ II) equipped with a special cell carriage capable of holding large silica titration cells (13 ml.; 18 × 35 mm.). Provision was made for magnetic stirring of the solution during titration. A special cell cover was provided which permitted the introduction of the buret tip through a small aperture in the cover. A 5-ml. buret (Kimax) graduated in 0.01 ml. was employed for delivery of titrant.

Materials—All phenothiazine derivatives used in this study (listed in Table I) were obtained from commercial sources. All reagents and solvents were reagent grade. Dosage forms (listed in Table II) were obtained from commercially available sources.

Preparation and Standardization of 0.02 N Ceric Sulfate Solution—Ceric sulfate solution (0.1 *N*) was prepared according to the *United States Pharmacopeia* (12). This solution was diluted quantitatively with distilled water to yield a 0.02 *N* solution. The diluted solution was standardized in the following manner: about 120 mg. of reagent grade arsenious trioxide, previously dried at 100° for 1 hr. and accurately weighed, was transferred to a 100-ml. volumetric flask. Five milliliters of sodium hydroxide solution (8% w/v) was added to the flask which was then swirled until the arsenious trioxide dissolved. Fifty milliliters of distilled water and 2 ml. of sulfuric acid (33% w/v) were then added. The solution was shaken thoroughly and diluted to the mark with distilled water and again shaken. Ten milliliters of this solution was transferred by pipet to the titration cell, 1 drop of osmium tetroxide solution (1 in 400) was added, and the solution was titrated with 0.02 *N* ceric sulfate solution. Titrant was added in 0.2-ml. portions and absorbance readings at 420 mμ were taken after each addition of titrant. Absorbance measurements were plotted against volume (ml.) of titrant. A typical plot is shown in Fig. 1.

Analysis of Phenothiazine Derivatives—A stock solution of phenothiazine derivative was prepared by transferring 0.4 to 0.5 meq., accurately weighed, to a 100-ml. volumetric flask. Sufficient diluted sulfuric acid (10% w/v) was added to dissolve the drug. Additional sulfuric acid was added to bring the volume to the mark.

A 10-ml. aliquot of the stock solution was transferred to the titration cell. The instrument was set at a wavelength of 420 mμ and the solution, magnetically stirred, was titrated with 0.02 *N* ceric sulfate solution. Initially titrant was added continuously until the absorbance reached a maximum. Titrant was then added in 0.04-ml. aliquots and the absorbance reading was recorded after

Table I—Analysis of Phenothiazine Derivatives by Photometric Titration

Compound	Trade Name	Proposed Method Recovery, %	Nonaqueous Method Recovery, %
Trimeprazine tartrate	Temaril	100.55 ± 0.30[a]	99.16[b]
Chlorpromazine	Thorazine	98.71 ± 0.30	98.55
Chlorpromazine hydrochloride USP		97.79 ± 0.75	101.38
Fluphenazine dihydrochloride	Prolixin	97.86 ± 0.36	97.60
Methdilazine hydrochloride	Tacaryl	101.33 ± 0.90	100.39
Thiopropazate dihydrochloride	Dartal	101.38 ± 0.90	98.55
Prochlorperazine NF	Compazine	96.92 ± 0.11	97.48
Prochlorperazine dimaleate USP		98.84 ± 0.49	100.65
Prochlorperazine ethanedisulfonate USP		99.00 ± 0.24	98.46
Perphenazine BP	Trilafon	100.24 ± 0.30	97.59
Acetophenazine dimaleate	Tindal	100.69 ± 0.62	98.74
Trifluoperazine BP	Stelazine	98.84 ± 0.40	98.17
Mepazine hydrochloride	Pacatal	97.84 ± 0.50	100.56
Mepazine acetate		101.28 ± 0.24	98.39

[a] Standard deviation based on at least four determinations. [b] Average of two determinations by official method or by general nonaqueous titration procedure.

each addition of titrant. The end point was determined by plotting absorbance *versus* volume of titrant. A typical titration curve is shown in Fig. 2.

Because of the poor solubility of mepazine acetate in sulfuric acid, the solvent mixture, acetone–diluted sulfuric acid, 1:1, was used in this instance.

Each phenothiazine derivative was analyzed by nonaqueous titration according to the procedure described in the USP, NF, or BP. Those derivatives which are not official were analyzed by dissolving about 1 meq., accurately weighed, in 50 ml. of glacial acetic acid. The solution was titrated visually with 0.1 *N* acetous perchloric acid using methyl violet as the indicator. In the case of the hydrochloride and dihydrochloride salts, 10 ml. of 6% mercuric acetate in acetic acid was added to the titration mixture. Acetophenazine dimaleate is a yellow-colored compound. Its solutions were analyzed by potentiometric titration with a titrimeter (Fisher) equipped with a glass-calomel electrode system.

Analysis of Dosage Forms—Several representative dosage forms containing phenothiazine derivatives were analyzed. The dosage forms selected for study did not require preliminary extraction of the active ingredient.

Tablets—Twenty tablets were weighed and reduced to a fine powder. An accurately weighed portion of the powder equivalent to 0.4–0.5 meq. of drug was transferred to a 100-ml. volumetric flask, and about 75 ml. of diluted sulfuric acid was added. The flask was shaken thoroughly for 10 to 15 min. Additional acid was added to bring the volume to the mark and flask was again shaken for 10 to 15 min. The contents of the flask were filtered. The first 20 ml. of filtrate was discarded. Ten milliliters of the remaining filtrate was transferred to the titration cell and was titrated as described earlier.

Syrup—Exactly 25 ml. of the syrup was transferred by pipet to a 100-ml. volumetric flask. The flask was filled to the mark with diluted sulfuric acid. Ten milliliters of this solution was titrated as described previously.

Concentrate—Exactly 5 ml. of the concentrate was transferred by pipet to a 100-ml. volumetric flask and was diluted to the mark with diluted sulfuric acid. Ten milliliters of this solution was titrated as described above.

RESULTS AND DISCUSSION

Photometric titrations combine the simplicity of titration with the accuracy and specificity of spectroscopy. The principles underlying photometric titrations, instrumentation, applications, advantages, and shortcomings have been reviewed recently by several authors (14–16). A significant advantage of photometric titration is that it can be applied to the determination of individual compounds in a multicomponent mixture. Hummelstedt and Hume (17) were able to determine as many as four components in a single mixture. This aspect of photometric titrations is of major interest in analytical pharmacy since it offers distinct possibilities in the assay of a particular component in a complex dosage form. In the present study a number of phenothiazines were determined successfully as pure compounds as well as components in representative dosage forms.

An acidic solution of phenothiazine drug or an aliquot of a dosage form was titrated photometrically at a wavelength of 420

Table II—Analysis of Typical Dosage Forms Containing Phenothiazine Derivatives by Photometric Titration

Compound	Dosage Form	Labeled Amount per Unit Dose	Recovery, %
Thiopropazate dihydrochloride	Tablet	5 mg.	98.77 ± 0.26[a]
	Tablet	10 mg.	101.62 ± 0.33
Chlorpromazine hydrochloride	Syrup	10 mg./5 ml.	100.70 ± 1.61
Prochlorperazine ethanedisulfonate	Concentrate	10 mg./ml.	96.13 ± 0.13

[a] Standard deviation based on at least four determinations.

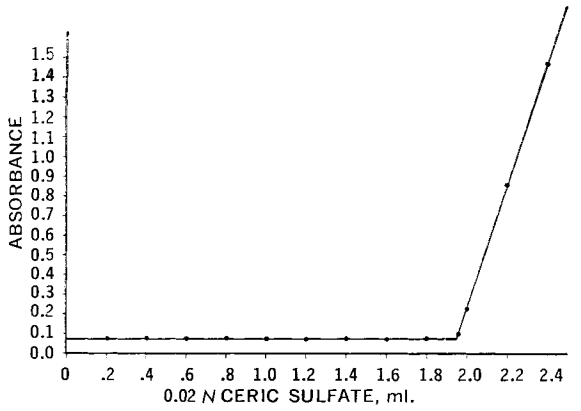

Figure 1.—*Photometric titration of arsenic trioxide with standard ceric sulfate solution at 420 mμ.*

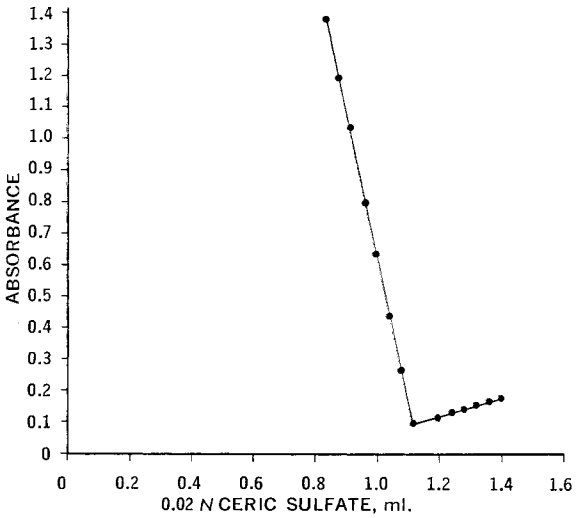

Figure 2—*Photometric titration of prochlorperazine edisylate with standard ceric sulfate solution at 420 mμ.*

mμ with standard ceric sulfate solution. Initially a red-colored semiquinone intermediate is formed which represents the first stage in the oxidation. Upon loss of a second electron, the solution becomes colorless as a result of the formation of the sulfoxide derivative of the phenothiazine. The mechanism of the oxidation of chlorpromazine hydrochloride in an aqueous medium was reported by Merkle and Discher (18).

Figure 1 illustrates the typical titration curve obtained in the standardization of ceric sulfate solution against arsenious trioxide. Two straight lines are obtained which intersect at the equivalence point. Prior to the equivalence point there is no change in absorbance due to ceric ion since it is reduced immediately to cerous at the expense of arsenious ion. At the equivalence point where ceric ion is in excess absorbance increased in proportion to the concentration of ceric ion.

The titration curve for the photometric titration of prochlorperazine edisylate with ceric sulfate is shown in Fig. 2. Absorbance values are recorded for the second stage in the oxidation or where the solution changes from a red color to colorless. The end point occurs when excess ceric ion remains in solution and is characterized by an increase in absorbance which increases with ceric ion concentration.

The data in Table I indicate that quantitative recoveries were obtained for 14 phenothiazines. Percent recovery is shown in the third column. In the fourth column are listed the percent recoveries for the methods of analysis based on nonaqueous titrimetry. The proposed procedure was applied to several representative dosage forms. The results are indicated in Table II. Undoubtedly certain dosage forms will not lend themselves to the proposed method because of interfering components or for other reasons. However, good agreement was realized between label claim value and recovered amount for the products reported. The proposed photometric titration procedure is simple, rapid, and accurate and since the method is sensitive, only small amounts of drug or dosage form are required for analysis.

REFERENCES

(1) J. Blazek, *Pharmazie*, **22,** 129(1967).

(2) J. Blazek, V. Spinkova, and E. Steijakal, *Anales Farm. Hosp.*, **10,** 7(1967).

(3) J. B. Milne and L. G. Chatten, *J. Pharm. Pharmacol.*, **9,** 686(1957).

(4) C. A. Mainville and L. G. Chatten, *J. Pharm. Sci.*, **53,** 154(1964).

(5) I. Gyenes, "Titration in Non-aqueous Media," D. Van Nostrand, Princeton, N. J., 1967, pp. 327–328, 356–361.

(6) A. B. De Leo and M. J. Stern, *J. Pharm. Sci.*, **53,** 993(1964).

(7) *Ibid.*, **55,** 173(1966).

(8) G. Dusinsky, *Cesk. Farm.*, **6,** 302(1957).

(9) G. Dusinsky, *Pharmazie*, **13,** 478(1958).

(10) G. Dusinsky and O. Liskova, *Chem. Zvesti*, **12,** 213(1958).

(11) "British Pharmacopoeia," The Pharmaceutical Press, W. C. 1, England, London, 1963, p. 175.

(12) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, pp. 128–130, 524–526, 528–530, 1082.

(13) "National Formulary," 12th ed., Mack Publishing Co., Easton, Pa., 1965, pp. 329–333.

(14) J. B. Headridge, "Photometric Titrations," Pergamon Press, New York, N. Y., 1961.

(15) S. P. Eriksen and K. A. Connors, *J. Pharm. Sci.*, **53,** 465 (1964).

(16) A. L. Underwood, in "Advances in Analytical Chemistry and Instrumentation," vol. 3, Interscience, New York, N. Y., 1964, pp. 31–104.

(17) L. E. I. Hummelstedt and D. N. Hume, *Anal. Chem.*, **32,** 576(1960).

(18) F. H. Merkle and C. A. Discher, *J. Pharm. Sci.*, **53,** 620 (1964).

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