fer, these recoveries are considered adequate to indicate the lack of any significant interferences.

An additional way to indicate lack of interference and also to demonstrate the applicability of the method is to analyze other ophthalmic solutions[5]. Decongestant ophthalmic drugs contain preservatives, vasoconstrictors, and other ingredients such as buffers and cleaning agents. Hard contact lens cleaning solutions do not contain the vasoconstrictors (8).

The common vasoconstrictor drugs available for over-the-counter use in ophthalmic preparations include phenylephrine, naphazoline, and tetrahydrozoline. The common preservatives are chlorobutanol, benzalkonium chloride, thimerosal, and edetic acid. Table III lists the combinations present in Solutions A–F, and Table IV lists the results for titration of these solutions by the proposed method. There were no problems with the titrations, and curves with end-point breaks similar to Figs. 1 and 2 were obtained. The low result for Solution E might be due to the more viscous nature of this solution, but sampling in triplicate did produce identical results.

CONCLUSION

This spectrophotometric titration procedure for determining edetic acid in ophthalmic solutions is simple and accurate. A complete analysis can be accomplished in 15 min using the automated equipment described herein. The precision and accuracy of the method have been quantitatively demonstrated.

[5] The commerical solutions used in this work were: A, Clear Eyes; B, Lensine; C, Degest; D, Visine; E, Adapt; and F, Soquette.

REFERENCES

(1) F. J. Welcher, "The Analytical Uses of Ethylenediaminetetraacetic Acid," Van Nostrand, Princeton, N.J., 1958, p. 1.

(2) M. R. W. Brown, *J. Pharm. Sci.*, **57**, 389(1968).

(3) D. C. Monkhouse, *Australas. J. Pharm.*, **48**, S70(1967).

(4) M. E. Richards, *ibid.*, part II, **48**, S96(1967).

(5) M. E. Richards, *J. Pharm. Pharmacol., Suppl.*, **23**, 136S (1971).

(6) G. W. Brady and J. R. Gwilt, *J. Appl. Chem.*, **12**, 79(1962).

(7) J. S. Fritz, J. P. Sickafoose, and M. A. Schmitt, *Anal. Chem.*, **41**, 1954(1969).

(8) P. W. Lofholm, in "Handbook of Non-Prescription Drugs," G. B. Griffenhagen and L. L. Hawkins, Eds., American Pharmaceutical Association, Washington, D.C., 1973.

ACKNOWLEDGMENTS AND ADDRESSES

Received June 18, 1973, from *Abbott Laboratories, North Chicago, IL 60064*

Accepted for publication March 4, 1974.

The authors thank Dave Williamson and Tom Eng for their assistance.

x To whom inquiries should be directed.

Titrations of Barbiturates and Sulfa Drugs in 3-Methyl-2-oxazolidone

GARY M. DAVIS, JOHN E. TAPHORN, III, and JOSEPH A. CARUSO x

Abstract □ 3-Methyl-2-oxazolidone was evaluated as a solvent for the titration of selected barbiturates and sulfa drugs. Its high dielectric constant and wide liquid range contribute to its outstanding solvent properties. Tetrabutylammonium hydroxide was used as the titrant. End-points were determined potentiometrically using a glass–calomel electrode system. Data evaluation was performed by suitable computer programs, and relative acid strengths were determined.

Keyphrases □ 3-Methyl-2-oxazolidone—evaluated as solvent for titration of barbiturates and sulfa drugs, determination of relative acid strengths □ Barbiturates—potentiometric titration using 3-methyl-2-oxazolidone as solvent, relative acid strengths determined □ Sulfa drugs—potentiometric titration using 3-methyl-2-oxazolidone as solvent, relative acid strengths determined

Information is available concerning the physical properties, preparation, and pharmacological usefulness of highly substituted 2-oxazolidones. Since most of these compounds are solids at room temperature, they have little usefulness as analytical solvents. However, a few *N*-alkyl-substituted derivatives of the parent compound are liquids and have a wide liquid range. Little is known regarding 2-oxazolidones as possible solvents for acid–base titrations (1). Some liquid *N*-substituted 2-oxazolidones were suggested as promising solvents (2).

In this study, 3-methyl-2-oxazolidone was chosen due to its high dielectric constant and relatively low melting point. When pure, the compound is odorless and colorless. Some of its important physical properties at 25° (2) are: mp, 15.9°; bp at 1 mm, 74–75°; dielectric constant at 1 MHz, 77.5; viscosity, 2.450 cps; density, 1.1702 g/ml; and refractive index, 1.4522. A series of important weak acids of pharmaceutical interest was used to determine the suitability of 3-methyl-2-oxazolidone as a solvent for such analyses.

EXPERIMENTAL

Apparatus—A digital pH/mv meter[1] equipped with an electrode switch[2] was used for potential measurements. Glass indicator electrodes[3] were used in conjunction with porous ceramic junction calomel reference electrodes[4]. The saturated aqueous potassium chloride solutions of the calomel electrodes were replaced with a saturated solution of potassium chloride in ethanol. The electrodes were soaked for several days in 3-methyl-2-oxazolidone prior to use. To stabilize potential readings, any one pair of electrodes was resoaked in 3-methyl-2-oxazolidone before reuse.

The titrant was dispensed from a 5-ml microburet[5] graduated in 0.01-ml divisions, which meets National Bureau of Standards Specification NNN-B-789. The storage vessel was fitted with a

[1] Orion model 601.
[2] Orion model 605.
[3] Sargent 30050-15c.
[4] Sargent 30080-15c.
[5] Kimax model 17110 Class A.

Table I—Acid–Base Titration Data in 3-Methyl-2-oxazolidone

Acid[a]	Milliequivalents Taken	Found	Recovery[b], %
Sulfamerazine	0.1307	0.1320	99.34 ± 1.59
	0.1128	0.1103	
	0.1122	0.1112	
Sulfadiazine	0.1231	0.1260	101.92 ± 1.38
	0.2261	0.2267	
	0.1086	0.1117	
Sulfapyridine	0.2017	0.2052	100.92 ± 0.83
	0.1438	0.1452	
	0.1647	0.1649	
Barbituric acid	0.4121	0.4152	100.94 ± 0.29
	0.2589	0.2616	
	0.1363	0.1377	
Phenobarbital	0.1717	0.1712	100.50 ± 0.89
	0.1246	0.1264	
	0.1490	0.1495	
Secobarbital	0.1226	0.1239	100.08 ± 1.77
	0.1581	0.1601	
	0.1812	0.1777	
Amobarbital	0.1487	0.1479	100.75 ± 1.17
	0.1653	0.1682	
	0.2234	0.2256	
Barbital	0.1662	0.1665	99.99 ± 0.46
	0.2449	0.2437	
	0.2595	0.2605	

[a] Barbituric acid was Eastman reagent grade; barbiturates and sulfa drugs were Eli Lilly USP grade. [b] Standard deviation based on three reported values.

rubber stopper and nitrogen purge line. The titrations were performed in a 200-ml beaker[6] fitted with a rubber stopper with provisions for the electrodes, nitrogen purge line, and buret tip. To prevent titrant loss or evaporation, the buret height was adjusted so that the delivery tip just penetrated the titration solution.

Reagents—3-Methyl-2-oxazolidone was prepared by the Homeyer (3) method and purified by fractional freezing as described earlier (4). Tetrabutylammonium hydroxide[7] was diluted with methanol and standardized against benzoic acid, which was previously purified by sublimation. All samples were dried *in vacuo* prior to use and stored over anhydrous calcium sulfate. Further purification was not attempted due to limited quantities.

Procedure—Each sample weight was determined to four significant figures using an electrobalance[8]. To provide quantitative transfer of samples, all weights were determined by difference. Once the solid was transferred to the titration vessel, it was dissolved in approximately 50 ml of 3-methyl-2-oxazolidone. To avoid atmospheric contamination, the head space was flushed with nitrogen which was passed through asbestos coated with sodium hydroxide[9] to remove carbon dioxide and through anhydrous magnesium perchlorate to remove any residual traces of water.

The electrodes were allowed to stabilize for 10 min before the addition of titrant. Readings were taken after the potential had stabilized (which generally occurred in 2 min or less) to ±0.2 mv. The average time per titration was 20 min. The determination of the equivalence point and inflection point was accomplished with the use of suitable FORTRAN programs[10] by a first and second derivative *versus* volume technique.

RESULTS AND DISCUSSION

Table I lists the recovery data for all drugs studied, and Figs. 1 and 2 show the titration curves. At the present time there is no established indicator for acid–base titrations in 3-methyl-2-oxazolidone.

In addition to the good analytical results, it is possible to determine relative acid strengths from the size of the break in the titration curve in the vicinity of the equivalence point. The relative acid strengths of the barbiturates studied are barbituric acid > phenobarbital > secobarbital > amobarbital > barbital. Similarly, the relative strengths of the sulfa drugs are sulfamerazine > sulfadiazine > sulfapyridine. The samples were readily soluble in 3-methyl-2-oxazolidone. The recoveries were as good or better than those reported previously (5–8). With respect to barbital and phenobarbital, the recoveries and precision are especially encouraging. The recoveries and precision of the sulfa drugs deviate

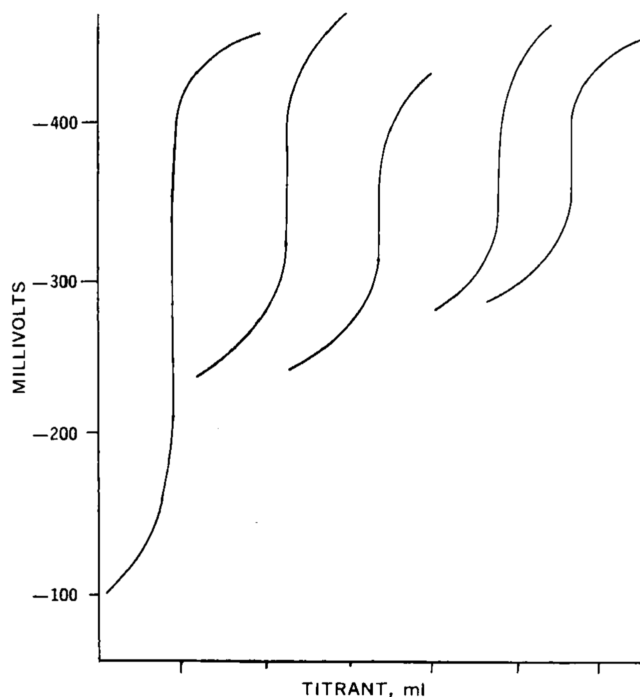

Figure 1—*Typical titration curves for (left to right) barbituric acid, phenobarbital, secobarbital, amobarbital, and barbital.*

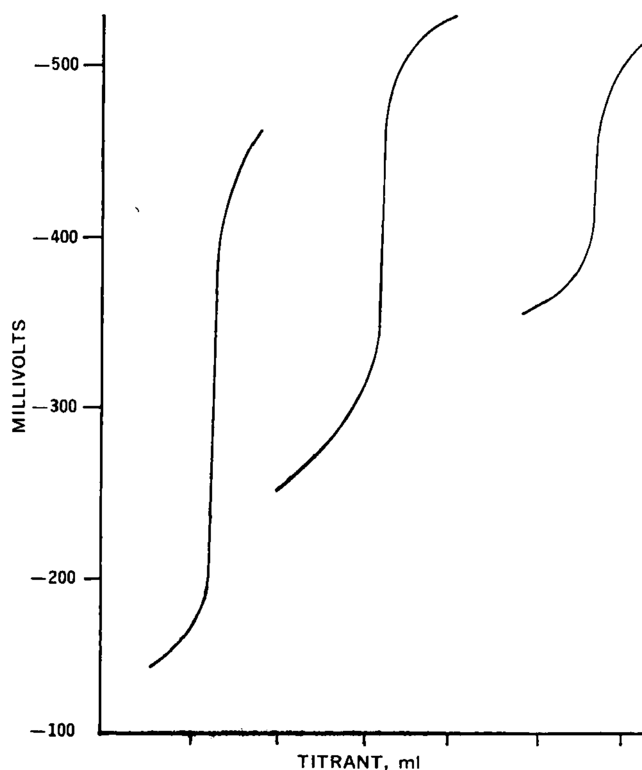

Figure 2—*Typical titration curves for (left to right) sulfamerazine, sulfadiazine, and sulfapyridine.*

[6] Berzelius.
[7] Eastman No. 7774, 25% solution in methanol.
[8] Cahn model G-2.
[9] Ascarite.
[10] University of Cincinnati IBM 370/165 Computer System.

more than expected. To explain such deviations, several blank determinations were performed to ascertain if any solvent-titrant reaction occurred. No discernible reaction was observed, which suggests that the precision might be improved by further purification of these materials.

It has been found in these laboratories that the hydroxyl and phenolic protons of salicylic acid can be titrated separately in this solvent. Work on the differentiating ability of the solvent is currently in progress. This preliminary study shows 3-methyl-2-oxazolidone to be a promising solvent in pharmaceutical assays by titration.

REFERENCES

(1) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197(1967).

(2) H. L. Huffman and P. Sears, *J. Soln. Chem.*, **1**(2), 187 (1972).

(3) A. M. Homeyer, U. S. pat. 2,399,118 (1946); through *Chem. Abstr.*, **40**, 4084(1946).

(4) L. R. Dawson, J. W. Vaughn, G. R. Lester, M. E. Pruitt, and P. G. Sears, *J. Phys. Chem.*, **67**, 278(1963).

(5) M. S. Greenberg, B. J. Barker, and J. A. Caruso, *Anal. Chim. Acta*, **54**, 159(1971).

(6) J. S. Fritz and R. T. Keen, *Anal. Chem.*, **24**, 308(1952).

(7) C. H. Hsiao, H. J. Rhodes, and M. I. Blake, *J. Pharm. Sci.*, **60**, 1847(1971).

(8) T. L. Buxton and J. A. Caruso, *Talanta*, **20**, 254(1973).

ACKNOWLEDGMENTS AND ADDRESSES

Received December 17, 1973, from the *Department of Chemistry, University of Cincinnati, Cincinnati, OH 45221*

Accepted for publication February 20, 1974.

ˣ To whom inquiries should be directed.

PHARMACEUTICAL TECHNOLOGY

Automated Analysis of Riboflavin in Multivitamin Preparations

OMER PELLETIER ˣ and RENÉ BRASSARD

Abstract □ An automated procedure was developed for the determination of riboflavin by following the steps of the USP manual procedure. The automated procedure is applicable to different types of multivitamin products and yielded results equivalent to the manual procedure.

Keyphrases □ Riboflavin—automated analysis, multivitamin preparations, compared to official method □ Multivitamin preparations—automated analysis of riboflavin, compared to official method □ Automated analysis—riboflavin in multivitamin preparations

Methods recognized officially by the Association of Official Analytical Chemists (1) or USP (2) for the determination of riboflavin in pharmaceutical preparations are described exclusively as manual techniques. These determinations consist of measuring the fluorescence of riboflavin in an acetic acid medium after destroying interfering materials by permanganate oxidation and decolorizing excess permanganate with hydrogen peroxide. Other interfering materials are measured separately after reducing riboflavin with sodium hydrosulfite. Automated procedures (3–7) previously proposed differed from the official methods (1, 2) either by omitting some steps or by using different chemical principles. An automated system was developed that maintains the specificity and validity of the manual procedures by performing exactly the same steps.

EXPERIMENTAL

Equipment—The analytical system[1] consisted of the following modules: liquid sampler II, a proportioning pump (model II), a fluorometer II, and a recorder.

Reagents—*Hydrochloric Acid, 0.1* N—Dilute 8.5 ml of concentrated hydrochloric acid (analytical reagent) to 1 liter with distilled water.

Acetic Acid and Sodium Acetate Solution (pH 2.4)—Dissolve 10.25 g sodium acetate (analytical reagent) in 300 ml distilled water, add 600 ml acetic acid, and dilute to 1 liter with distilled water.

Potassium Permanganate, 0.2% (w/v)—Dissolve 0.4 g of potassium permanganate (analytical reagent) in 200 ml distilled water. Prepare fresh daily.

Hydrogen Peroxide, 0.15% (w/v)—Dilute 1 ml of 30% H_2O_2 (analytical reagent) to 200 ml with distilled water. Prepare fresh daily.

Sodium Hydrosulfite, 5% (w/v)—Dissolve 5 g of anhydrous sodium hydrosulfite (analytical reagent) in distilled water and dilute to 100 ml. Prepare daily just before use and keep in an amber bottle under toluene.

Ascorbic Acid, 4% (w/v)—Dissolve 4 g ascorbic acid[2] in 100 ml distilled water.

Standards—*Standard Riboflavin Stock Solution (10 μg/ml)*—

[1] Technicon.

[2] Nutritional Biochemicals Corp.