a CV value for weight of 3.4 or less. In consequence, the producer must make every effort to produce batches with a CV whose upper fiducial limit is 3.4 or less. This borderline CV, evaluated on a sample of 30, corresponds to 2.7, because in this case the fiducial limits ($p = 0.05$) are 3.4 and 2.0. Batches meeting these CV specifications are therefore very likely to be accepted by the consumer's control. In fact a batch with a CV of 2.7 has already 0.57 probabilities of being accepted at the first of the proposed inspection steps, *i.e.*, that asking for no defectives in a sample of nine.

Going by the authors' experience of suppository production, it should not be too difficult to meet the requirement that the CV must be lower than 2.7. In fact, the highest CV values observed in the authors' samples was of 2.05 (bis suppositories of the C type, Table II), a value substantially smaller than 2.7, which is critical for the producer.

Specification Limits on Control Charts—The critical CV of 2.7 corresponds to an upper-range specification limit of 0.088 m for the 12 specimens sample, and of 0.083 m for the 10 specimens sample considered by the control charts (m = average weight). As already said, in most instances these specification limits are outside the upper ORL (outer range limit).

In a few instances they are between the ORL and the WRL (warning range limit), and even so the limits can still be met. For two drugs they are below the WRL. In these cases it is necessary either to adjust the production process, or to accept a higher probability of rejection of the product by the outgoing or by the consumer's quality control.

REFERENCES

(1) Deutsches Arzneibuch, VII, **1**, 1964, p. 13.0.02.
(2) "State Pharmacopoeia of the USSR," IX, 1961, p. 487.
(3) "Pharmacopoea Nordica," **3**, 1964, pp. 309, 328.
(4) E. S. Pearson, "Statistical Methods. British Standard 600: 1935." British Standard Institution, London, England, 1960, p. 80.
(5) J. M. Airth, D. F. Bray, and C. Radecka, *J. Pharm. Sci.*, **56**, 233(1967).
(6) W. N. French, F. Matsui, D. Cook, and L. Levi, *ibid.*, **56**, 1622(1967).
(7) C. W. Dunnett and R. Crisafio, *J. Pharm. Pharmacol.*, **7**, 314(1955).
(8) K. L. Smith, *ibid.*, **7**, 875(1955).
(9) A. R. Rogers, *ibid.*, **8**, 1103(1956).
(10) K. Ilver, "Tabletters Doseringsnøjagtighed," Kandrup & Wunsch, København, Denmark, 1966, pp. 32, 83, 106.
(11) H. F. Dodge and H. G. Romig, "Sampling Inspection Tables," Wiley, New York, N. Y., 1959, Appendix 3, p. 176.
(12) Svenska Farmacopèn, 1946, p. 584.

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Assay of Quinacrine Hydrochloride

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Abstract □ Comparison of USP method for the assay of quinacrine hydrochloride involving precipitation of the dichromate salt and determination of the excess dichromate with the nonaqueous titration using a visual end point and a proposed nonaqueous titration with a potentiometric end point, shows that all three methods give the same results, with the nonaqueous methods superior in reproducibility and rapidity. The proposed method is also satisfactorily applied to the assay of quinacrine hydrochloride tablets.

Keyphrases □ Quinacrine HCl and tablets—analysis □ Titration, nonaqueous—analysis □ Mercuric acetate T.S.—reagent □ Potentiometric determination—titration end point

Many types of analytical methods have been proposed for the determination of quinacrine hydrochloride including fluorescimetric (1–10), absorptimetric (11, 12), gravimetric (13), polarographic (14), amperometric (15), complexometric (16, 17), chloridometric after Parr bomb fusion (18), and various titrimetric methods (19–21). The method of Auerbach (22), has been the basis for the official methods of assay in the "United States Pharmacopeia" (23–28), since the compound was first recognized as official. This method has been adopted by other compendia (29–31). The procedure involves precipitating quinacrine dichromate from a buffered aqueous solution by addition of an excess of standard dichromate solution, removal of the precipitate by filtration, and determination of the excess dichromate in an aliquot of the filtrate by addition of potassium iodide and titration of the liberated iodine with standard thiosulfate solution, using starch indicator. The procedure is lengthy and involved and requires correction of the results for the solubility of quinacrine dichromate. In this laboratory, the reproducibility was not as good as desired.

Pifer and Wollish (32), state that they have titrated quinacrine hydrochloride as a base in nonaqueous systems but present no supporting data. Phoryles and Cohen (33), report the nonaqueous titration of quinacrine hydrochloride in glacial acetic acid after the addition of mercuric acetate using crystal violet indicator. The end point is a change from red to green when the solution is viewed by transmitted light. No end point is detected by reflected light. The "British Pharmacopoeia" (34), calls for a similar titration in chloroform, but omits directions for viewing the end point by transmitted light.

EXPERIMENTAL

Quinacrine Hydrochloride—*Method A*—USP XVII method for quinacrine hydrochloride (28).

Method B—Nonaqueous titration with visual end point, performed concomitantly with Method C by adding 3 drops of crystal violet T.S. (35). The end point is a color change from red to green when the sample is viewed by transmitted light.

Method C—Proposed potentiometric determination of end point. Accurately weigh about 600 mg. of quinacrine hydrochloride into a 150-ml. beaker. Add 60 ml. of glacial acetic acid. Add 10 ml. of mercuric acetate T.S. (36) reagent with stirring. Insert a combination electrode[1] (saturated solution of potassium chloride and silver chloride filling solution; glass-silver, silver chloride electrode pair) connected to a pH meter[2] and titrate potentiometrically with 0.1 *N* perchloric acid in dioxane (37), determining the end point potentiometrically by using the second derivative of the potential with respect to volume (38).

Quinacrine Hydrochloride Tablets—*Method D*—Weigh accurately a portion of crushed tablets containing about 600 mg. of quinacrine hydrochloride and dissolve this sample in 60 ml. of glacial acetic acid. Proceed as in Method *C* starting with "Add 10 ml. of mercuric acetate, T.S....." Concomitantly determine the end point visually with crystal violet T.S. indicator. The end point is a color change from red to green when the sample is viewed by transmitted light.

Method E—Weigh accurately a portion of crushed tablets containing about 600 mg. of quinacrine hydrochloride and transfer to a separator. Add about 25 ml. of water and 1 ml. of hydrochloric acid. Extract the suspension with two 15-ml. portions of chloroform and wash the chloroform extracts with 10 ml. of water. Discard the washed chloroform, and add the water to the suspension of tablet material. Make the suspension strongly alkaline with ammonia (about 10 ml.). Extract with successive 20-ml. portions of chloroform until the last extract is colorless (about five portions required). Filter the combined chloroform extracts through purified cotton moistened with chloroform and wash the cotton with a few milliliters of chloroform. Gently evaporate the filtrate to dryness on a water bath. Take up the residue in 60 ml. of glacial acetic acid and proceed as in Method *C* starting with "Add 10 ml. of mercuric acetate, T.S....."

RESULTS

Quinacrine Hydrochloride—*Method A*—Nine assays of the sample gave 100.6 ± 1.30% (range: 98.53 to 103.30%).

Method B—Eleven assays of the sample gave 99.96 ± 0.26% (range: 99.25 to 100.18%).

Method C—Eleven assays of the sample gave 99.95 ± 0.41% (range: 99.22 to 100.27%).

Method D—Four aliquots of the same crushed tablet mixture gave 100.99 ± 0.26% of the labeled amount potentiometrically (range: 100.72 to 101.16%) and 101.16 ± 0.36% visually (range: 100.79 to 101.90%).

Method E—Six aliquots of the same crushed tablet mixture as in Method *D* gave 100.44 ± 0.67% of the labeled amount potentiometrically (range: 99.47 to 101.14%) and 100.82 ± 0.86% visually (range: 99.82 to 101.97%).

DISCUSSION

Preliminary experiments with solvents including chloroform, glacial acetic acid, acetonitrile, and an equivolume mixture of glacial acetic acid and acetic anhydride showed that a blank correction was necessary only for acetonitrile. The largest change in potential in the region around the end point was found in chloroform, but the plot of potential against volume of titrant was asymmetric. The large potential change (about 100 mv./0.2 ml. of titrant in the equivalence-point region) and a symmetrical plot obtained in glacial acetic acid led to its choice as the solvent.

In both chloroform and acetic acid a yellowish-green precipitate separates from the solution during the course of the titration and obscures the visual end point, a color change from red to green. As demonstrated by Phoryles and Cohen (33), it is essential that the end point with crystal violet indicator be viewed by transmitted light, thus necessitating the positioning of an intense light source behind or below the titration vessel. Directions to this effect were omitted in the British Pharmacopoeia (34), and no end point can be detected using the published method. Even with a proper light source the precipitate must be allowed to settle before the color of the solution can be determined, thus unnecessarily prolonging the titration and adding to operator eye fatigue. It was found that potentiometric determination of the end point was as rapid and more convenient than the visual method.

Although direct titration of quinacrine hydrochloride tablets by Method *D* was applicable to the product of the single manufacturer, tested, it might not be universally applicable. For this reason Method *E*, which separates organic bases from other substances in the tablet mixture, is to be preferred.

CONCLUSIONS

On the basis of data presented, it is suggested that the currently official methods for the assays of quinacrine hydrochloride and quinacrine hydrochloride tablets be changed to Method *C* and Method *E*, respectively.

REFERENCES

(1) J. M. Masen, *J. Biol. Chem.*, **148,** 529(1943).

(2) L. C. Craig, *ibid.*, **150,** 33(1943).

(3) M. E. Auerbach and H. W. Eckert, *ibid.*, **154,** 597(1944).

(4) T. C. Butler, *J. Pharmacol. Exptl. Therap.*, **80,** 70(1943).

(5) A. J. Henry and D. N. Grindley, *Ann. Trop. Med. Parasitol.*, **39,** 1(1945).

(6) J. A. Garudo and G. P. Gil, *Med. Colonial (Madrid)*, **9,** 148(1947); through *Chem. Abstr.*, **41,** 3498*d*(1947).

(7) B. B. Brodie, S. Udenfriend, W. Dill, and G. Downing, *J. Biol. Chem.*, **168,** 311(1957).

(8) A. Bernanose and P. Vouaux, *J. Chim. Phys.*, **52,** 509 (1955).

(9) A. E. Mshvidobadze, B. I. Chumburidze, and O. V. Sardjeveladze, *Aptechn. Delo*, **12,** 36(1963).

(10) S. Udenfriend, D. E. Duggan, B. M. Vasta, and B. B. Brodie, *J. Pharmacol. Exptl. Therap.*, **120,** 26(1957).

(11) J. Carol, *J. Assoc. Offic. Agr. Chemists*, **27,** 360(1944).

(12) P. Spacu, C. Gheorghiu, and E. Cristurean, *Z. Anal. Chem.*, **210,** 436(1965).

(13) H. C. Heim, *J. Assoc. Offic. Agr. Chemists*, **27,** 354(1944).

(14) A. Blazek, R. Kalvoda, and J. Zyka, *Casopis Ceskeho Lekarnictva*, **63,** 138(1950).

(15) R. Kalvoda and J. Zyka, *Pharmazie*, **7,** 535(1952).

(16) F. T. Wilkomirsky, G. N. Meier, and A. J. Brieva, *Anal. Real Acad. Farm.*, **28,** 311(1962).

(17) Y.-Y. Chou, J.-L. Chen, and J.-C. Hsu, *Acta Pharm. Sinica*, **8,** 61(1960); through *Anal. Abstr.*, **7,** 4458(1960).

(18) H. C. Heim, *J. Assoc. Offic. Agr. Chemists*, **31,** 538(1948).

(19) K. Thoma, E. Ullmann, and P. Loos, *Pharmazie*, **21,** 172 (1966).

(20) O. Motl, *Cesk. Farm.*, **1,** 630(1952).

(21) F. O. Gundersen, R. Heiz, and R. Levstrand, *J. Pharm. Pharmacol.*, **5,** 608(1953).

(22) M. E. Auerbach, *J. Am. Pharm. Assoc., Sci. Ed.*, **26,** 231 (1937).

(23) "United States Pharmacopeia," 12th rev., Mack Publishing Co., Easton, Pa., 1942, pp. 283–284.

(24) *Ibid.*, 13th rev., 1947, p. 434.

(25) *Ibid.*, 14th rev., 1950, p. 499.

(26) *Ibid.*, 15th rev., 1955, pp. 599–600.

(27) *Ibid.*, 16th rev., 1960, p. 610–611.

(28) *Ibid.*, 17th rev., 1965, p. 552.

(29) "Pharmacopoea Internationalis," 1st. ed., vol. 1, World Health Organization, Geneva, Switzerland, 1951, pp. 135–136.

(30) "Pharmacopoea Danica," Addendum, Nyt Nordisk Forlag Arnold Busck, Copenhagen, Denmark, 1952, p. 105.

[1] Beckman Instruments, Inc., Fullerton, Calif.

[2] Fisher Accumet model 210, Fisher Scientific Co., Chicago, Ill.

(31) Pharmacopoea Suecica," 11th ed., Addendum, Apoteckarsocietetens Forlag, Stockholm, Sweden, 1958, p. 132.
(32) C. W. Pifer and E. G. Wollish, *Anal. Chem.*, **24**, 300(1952).
(33) L. A. Phoryles and N. Cohen, *Drug Standards*, **27**, 92 (1959).
(34) "British Pharmacopoeia 1963," The Pharmaceutical Press, London, England, 1963, p. 472.
(35) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, p. 1074.
(36) *Ibid.*, p. 1077.
(37) *Ibid.*, p. 1085.
(38) G. H. Ayres, "Quantitative Chemical Analysis," Harper, New York, N. Y., 1958, pp. 537–541.

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Gas Chromatographic Assay for Benzyl Alcohol and Phenylethyl Alcohol in Pharmaceutical Formulations

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Abstract □ A gas chromatographic method has been developed for the determination of benzyl alcohol and phenylethyl alcohol in pharmaceutical formulations. The method employs a column made of a silanized copolymer of ethylvinylbenzene–divinylbenzene and uses cyclohexanol as the internal standard. The method is applicable to various formulations which contain either benzyl alcohol or phenylethyl alcohol or the combination. Each analysis requires 10 min. This method showed a relative standard deviation of ±0.85% for benzyl alcohol and ±1.41% for phenylethyl alcohol.

Keyphrases □ Benzyl alcohol—analysis in dosage forms □ Phenylethyl alcohol—analysis in dosage forms □ Cyclohexanol—internal standard □ GLC—analysis

Pharmaceutical preparations frequently contain benzyl alcohol and/or phenylethyl alcohol as preservatives. Gas chromatographic methods for benzyl alcohol have been reported by Gallo and Chiesa (1), by Ragone and LaFata (2), and by Rhodes *et al.* (3), using columns other than a silanized copolymer of ethylvinylbenzene–divinylbenzene.[1] Burger (4) has reported the retention times of a large number of organic compounds on this copolymer; however, neither benzyl alcohol nor phenylethyl alcohol was included. This report describes a simple and rapid gas chromatographic method for the assay of benzyl alcohol and phenylethyl alcohol, singly or in combination, using a silanized copolymer of ethylvinyl–divinylbenzene column.

EXPERIMENTAL

Apparatus—A Micro-Tek MT 220 gas chromatograph equipped with a dual hydrogen-flame ionization detector was used for the experimental work. The 76.2-cm. (2.5-ft.) × 0.31-cm. (1/8-in.) o.d. stainless steel column was packed with a silanized copolymer of ethylvinylbenzene–divinylbenzene, 80–100 mesh. The column was operated at a temperature of 228° and the injection port was maintained at 275°. A Hamilton 10-μl. syringe with a 7.6-cm. (3-in.) needle was employed for injection of sample. The hydrogen gas flow was 48 ml./min., the air 1.2 cu. ft./hr., and the helium 120 ml./min.

Solutions and Reagents—A standard stock solution of benzyl alcohol and phenylethyl alcohol was prepared by weighing accurately 200 mg. of both benzyl alcohol and phenylethyl alcohol into a 200-ml. volumetric flask and diluting to volume with distilled

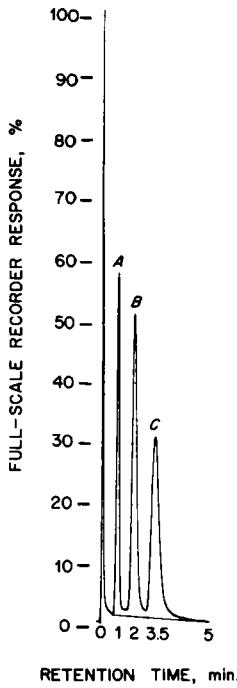

Figure 1—*Typical chromatogram of: A, cyclohexanol; B, benzyl alcohol; and C, phenylethyl alcohol.*

[1] Porapak Q. S., Waters Associates, Framingdam, Mass.