Nonaqueous Titration of Methaqualone and Its Dosage Forms

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Abstract □ The use of glacial acetic acid alone as a solvent for the nonaqueous titration of methaqualone dosage forms gives unsatisfactory overestimation due to interference of titratable excipients. A nonaqueous system of equal parts of chloroform and glacial acetic acid does provide a suitable medium for the visual and potentiometric titration of methaqualone and its hydrochloride. When applied to analysis of the dosage forms, the method gives recoveries that compare favorably with those of the manufacturer. The pKb of methaqualone, when determined potentiometrically, is 10.44.

Keyphrases □ Methaqualone and methaqualone hydrochloride tablets and capsules—nonaqueous titration □ Titrimetry, nonaqueous—analysis, methaqualone and methaqualone hydrochloride tablets and capsules

Since its advent on the market some 10 years ago, the hypnotic methaqualone has received considerable attention. Much work has focused on the detection and determination of the drug in various biological specimens. However, there are few reports concerned with the quantitative analysis of methaqualone and its hydrochloride in pharmaceutical dosage forms. Although the BP (1) offers a nonaqueous method with glacial acetic acid as the solvent system for the analysis of the raw material, no monograph is provided for the pharmaceutical dosage forms. This solvent does not give either a sharp visual or potentiometric end-point; however, it can be used for the titration of this weakly basic material provided no interfering excipients are present.

In 1969, King and Perry (2) published a nonaqueous titrimetic method for methaqualone tablets that employed glacial acetic acid as the solvent system and crystal violet as the indicator. Because of the solubility of a large number of interfering excipients, it has been demonstrated that this is not a suitable solvent to use when assaying tablets and capsules. On the other hand, very few excipients interfered with nonaqueous titrations when chloroform was first used to extract the active constituent from the tablet or capsule mass (3). Therefore, the use of this latter solvent system was investigated and its use as a means of eliminating the overestimation caused by interfering excipients when glacial acetic acid is employed as the extracting solvent is suggested.

EXPERIMENTAL

Apparatus—The following were used: a potentiometer[1] equipped with a glass–calomel electrode pair, a pH meter[2] fitted with a glass–calomel electrode system, a magnetic stirring apparatus, conventional laboratory glassware, and a platinum-tipped microburet graduated to 0.01 ml.

Reagents and Solutions—All of the following chemicals employed were ACS quality: acetone, chloroform, dioxane, glacial acetic acid, 0.1 *N* perchloric acid in dioxane (standardized against primary standard potassium acid phthalate), 3% mercuric acetate in glacial acetic acid, 1% crystal violet in glacial acetic acid, and 0.1 *N* HCl. The purity of the methaqualone free base and of the hydrochloride was determined by the BP procedure.

Procedures—*Pure Drugs*—Approximately 75 mg of the reference methaqualone or methaqualone hydrochloride was accurately weighed into a 150-ml beaker and dissolved in 25 ml of chloroform; then 25 ml of glacial acetic acid was added. Prior to commencing the titration for the hydrochloride salt, 2 ml of 3% mercuric acetate solution was added. The titrant was 0.1 *N* perchloric acid in dioxane. The end-point was determined potentiometrically using the pH meter for one set of samples and visually using crystal violet indicator for another set of samples.

Dosage Forms—The contents of 20 capsules were weighed or 20 tablets were weighed and then powdered to a very fine state. A uniform sample of the dosage form calculated to contain approximately 50 mg of methaqualone or its salt was accurately weighed into a 150-ml beaker. (For combinations with diphenhydramine hydrochloride, samples were calculated to contain 75 mg of methaqualone.) Twenty milliliters of chloroform was added and the mixture was stirred magnetically for 10 min to ensure dissolution of the active constituent. The solution was filtered under suction, the beaker was rinsed, and the filter was washed with an additional 5 ml of chloroform. The filtrate was transferred quantitatively to a clean 150-ml beaker by rinsing the flask with two 10-ml and one 5-ml aliquots of glacial acetic acid. When the hydrochloride salt was present, 2 ml of 3% mercuric acetate was added prior to the titration. The titrant was 0.1 *N* perchloric acid in dioxane and the end-point was detected from the first derivative plot of the potentiometer.

Comparative values were obtained by the method of King and Perry (2).

pKb Determination—The pKb of methaqualone was determined by the method according to Chatten and Harris (4) by using acetone–water solvent mixtures. Three concentrations of methaqualone were used (0.002, 0.0015, and 0.001 *M*). Each concentration was prepared in three different acetone–water

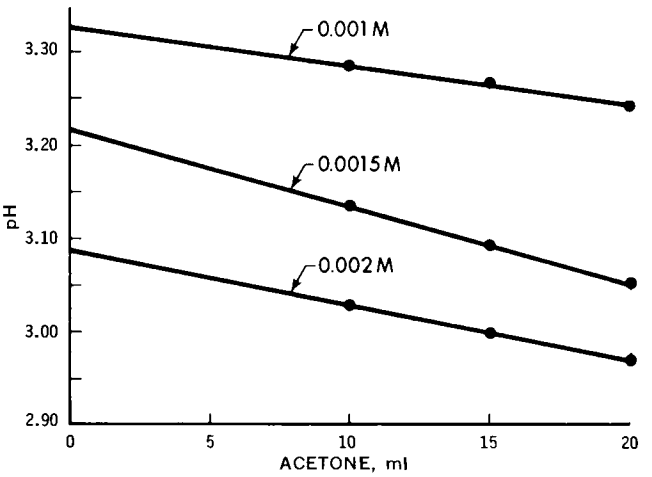

Figure 1—*Theoretical pH values obtained by extrapolation to 0 ml of acetone for three concentrations of methaqualone.*

[1] Model E336 Metrohm Potentiograph.
[2] Fisher model 230.

Table I—Comparison of Results Using Proposed Solvent System with Those of BP Method for Methaqualone and Its Hydrochloride Salt

	Chloroform–Glacial Acetic Acid (1:1), Recovery, %		BP 1973, Recovery by Visual Determination[a], %
	Potentiometric[a]	Visual[a]	
Free base	99.3 ± 0.3	98.6 ± 0.4	99.4 ± 0.9
Hydrochloride salt	99.9 ± 0.1	99.7 ± 0.3	98.2 ± 0.8

[a] Each figure is the average of five determinations.

mixtures, and the total volume of each mixture was constant at 50 ml. Thus, the acetone–water ratios were 10:40, 15:35, and 20:30 ml, respectively.

The solutions were titrated to the half-neutralization point with standardized 0.1 *N* HCl and the pH was measured. Because of the dilutions employed, no corrections were made for differences in activities.

RESULTS AND DISCUSSION

Since methaqualone and its hydrochloride are both readily soluble in chloroform, it was found to be a useful and convenient solvent for the extraction of the active constituent from pharmaceutical dosage forms. After filtration to remove the excipients, an equal quantity of glacial acetic acid was added to produce a stable, readily detectable potentiometric end-point. Simultaneous use of crystal violet indicator during the potentiometric titration of methaqualone or its hydrochloride revealed that the emerald-green color of the indicator corresponded to the maximum potentiometric inflection point. Although the indicator color change is not sharp, careful titration can produce good, reproducible results (Table I).

The following additional indicators were investigated in this and other solvent systems: malachite green, metanil yellow, methylene blue, methyl red, α-naphtholbenzein, neutral red, oracet blue B, phenol red, quinaldine red, and tropaeolin OO. None gave color changes that corresponded to the potentiometric end-point. Since the potentiometer plots a first-derivative curve, potentiometric end-point detection with this instrument is as rapid as a visual titration. Consequently, the indicator was not used with the dosage forms.

Comparative analyses between the results obtained with the proposed solvent system and those using the BP (1) method are presented in Table I for methaqualone and the hydrochloride. Other solvents investigated for the free base were various combinations of: *(a)* chloroform and acetonitrile, *(b)* chloroform and nitromethane, *(c)* acetone and hexane, and *(d)* benzene and nitromethane. In addition, both *(a)* and *(b)* were investigated for the hydrochloride. All of these combinations failed to yield quantitative results with the pure drugs.

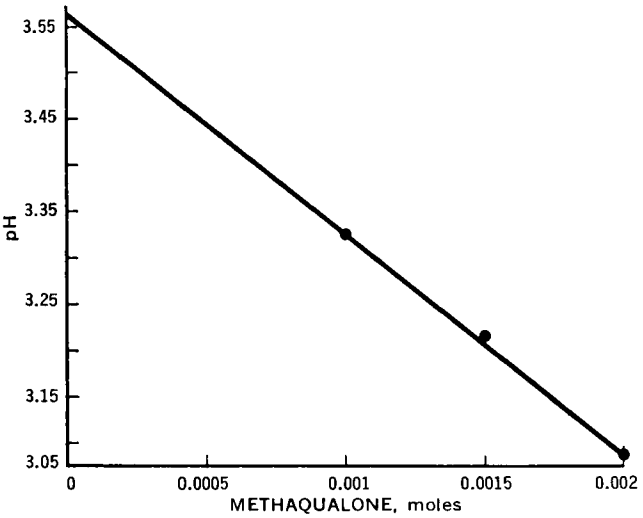

Figure 2—*Determination of pKa of methaqualone. The pH values from Fig. 1 are extrapolated to infinite dilution of methaqualone (pKa = 3.56).*

Table II lists the results obtained for the dosage forms, using the chloroform–glacial acetic acid (1:1) solvent system in which the end-point was determined from the first-derivative plot of the potentiometer. Comparative data were supplied by the manufacturer's quality control laboratory and are presented with the results obtained by the King and Perry (2) procedure. Although the values obtained with the proposed method generally agree well with those of the manufacturer, the use of glacial acetic acid alone (2) apparently resulted in serious overestimation in several instances. If the dosage form did not contain titratable excipients, the results of the glacial acetic acid procedure agreed with those of the proposed method. In addition, King and Perry (2) did not include a filtration step prior to the titration. This resulted in the presence of slowly soluble titratable excipients, which caused a fading or reversible indicator change in the vicinity of the end-point.

Synthetic mixtures of methaqualone and diphenhydramine hydrochloride (10:1) were analyzed for both constituents by the proposed method. When the end-point for methaqualone was passed, 1 ml of 3% mercuric acetate was added and the titration was continued. Based on the average of five determinations, the recovery for the methaqualone was 100.3 ± 0.7%. This compares favorably with the recovery of 99.3% reported in Table I for pure methaqualone. However, the recoveries for diphenhydramine hydrochloride were erratic. It is possible that the chloride ion furnished by the diphenhydramine hydrochloride, although small in amount, may

Table II—Comparison of Recoveries of Active Constituent from Commercial Dosage Forms Expressed as Percent Potency

Form	Product[a]	Labeled, mg	Proposed Method[b]	Manufacturer Data	King and Perry (2) Method
Capsule	A Methaqualone hydrochloride	150	99.7 ± 0.9	103.3	120.0
Capsule	B Methaqualone hydrochloride	250	98.9 ± 1.5	98.9	120.3
Capsule	C Methaqualone hydrochloride	300	99.9 ± 0.7	97.2	105.4
Tablet	D Methaqualone	300	99.5 ± 0.7	100.8	102.5[c]
Tablet	E Methaqualone hydrochloride	150	98.1 ± 1.2	Not available	107.7[c]
Tablet	F Methaqualone hydrochloride	300	99.5 ± 0.6	Not available	103.6[c]
Capsule	G Methaqualone hydrochloride	200	98.1 ± 1.4	98.6	101.7[c]
Capsule	H Methaqualone hydrochloride	400	95.4 ± 0.7	100.4	94.8
Capsule	I Methaqualone hydrochloride	300	100.0 ± 0.4	Not available	100.8
Capsule	J Methaqualone hydrochloride	150	101.1 ± 0.5	101.8	104.5[c]
Capsule	K Methaqualone hydrochloride	300	97.8 ± 1.9	100.5	96.7
Capsule	L Methaqualone	250	102.9 ± 0.3	103.3	98.8[c]
Tablet	M Methaqualone	250	102.9 ± 0.7	103.5	101.8[c]

[a] Trade names and suppliers of the products: A and B, Mequelon, Charles E. Frosst; C, Pexaqualone, Therapex; D, Quaalude, Rorer; E and F, Rougualone, Rougier; G and H, Somnafac, Cooper; I, Triador, Trianon; J and K, Tualone, ICN; and L and M, Mandrax, Roussel. [b] Each figure is the average of five determinations. [c] Indicator color reverses due to presence of excipients.

be responsible for the 1% discrepancy obtained for methaqualone in the mixtures. This would result in a significant error in calculating the diphenhydramine hydrochloride recoveries. Although samples equivalent to 75 mg of methaqualone were taken for the mixture, the procedure works equally well with mixtures containing 50 mg of methaqualone. The larger samples were used in the hope of being able to estimate accurately the antihistamine.

The visual and potentiometric end-points for methaqualone base are less distinct than are those for the CH_3COO^- species that is created from the hydrochloride by the addition of mercuric acetate. This indicates that methaqualone is a weaker base than the acetate anion. Furthermore, the presence of diphenhydramine hydrochloride further reduces the sharpness of the end-point with methaqualone base.

Because the pKb of methaqualone was not available from the literature for comparison, it was determined by a previously reported method (4). Figure 1 represents plots of pH *versus* milliliters of acetone for three concentrations of methaqualone. The pH values were measured at exactly half-neutralization. Figure 2 represents the three pH values obtained by extrapolation of the lines in Fig. 1 to 0 ml of acetone. Extrapolation to infinite dilution of the best straight line in Fig. 2 gives a resulting pH of 3.56. Since this is equal to pKa, the pKb of methaqualone was found to be 10.44.

REFERENCES

(1) "British Pharmacopoeia 1973," British Pharmacopoeia Commission, London, England, 1973, p. 296.

(2) E. E. J. King and A. R. Perry, *J. Ass. Pub. Anal.*, **7**, 55(1969).

(3) E. G. Clair and L. G. Chatten, *J. Pharm. Sci.*, **50**, 848(1961).

(4) L. G. Chatten and L. E. Harris, *Anal. Chem.* **34**, 1495(1962).

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Improved Method for Salicylazosulfapyridine Analysis and Partial Characterization of Impurities in Commercial Salicylazosulfapyridine

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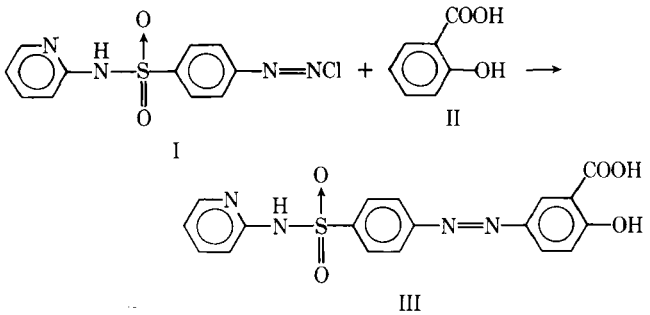
Abstract □ A column chromatographic system was developed that quantitatively separates salicylazosulfapyridine from impurities that contribute to the usual colorimetric method. The chromatographic–colorimetric method can be used to assay specifically for salicylazosulfapyridine as a raw material and in the final dosage form. Respective samples of two chromatographic mobile impurities were isolated, collected, and assayed by various means. Based on the data collected, partial characterizations of the chemical structure of these impurities were proposed. A third impurity, which was chromatographically immobile, was also studied and characterized as possibly being polymeric in nature.

Keyphrases □ Salicylazosulfapyridine bulk and tablets—chromatographic–colorimetric analysis, partial characterization of three impurities □ TLC—separation, salicylazosulfapyridine and three impurities □ Colorimetry—analysis, salicylazosulfapyridine and three impurities after TLC separation

The commercial synthesis (1) of salicylazosulfapyridine (III) involves the reaction between the diazonium salt of sulfapyridine (I) and *o*-hydroxybenzoic acid (II) (Scheme I).

The presence of the hydroxy *ortho–para*-director and the carboxy *meta*-director causes salicylazosulfapyridine to be the primary product. However, minor by-products which could interfere with the usual analytical method (2) are also expected to be present.

To determine if interfering impurities might be present, TLC analyses were performed on experimental salicylazosulfapyridine and commercial tablets, and it was possible to resolve three yellow-colored impurities in both types of samples. One impurity was essentially immobile (as indicated by the brown spot at the origin) and is speculated to be polymeric, resulting from the formation of a benzyne



Scheme I