Direct Acidimetric Analysis of Papaverine in Concentrated Lithium Chloride Solution

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Hydrochloric acid was used as the titrant for papaverine base in two different media: (*a*) 18.5% ethanol and 81.5% 8 *M* lithium chloride solution, and (*b*) 10% tetrahydrofuran, 5% ethanol, and 85% 8 *M* lithium chloride solution. Per cents were calculated on a weight to weight basis. All of the titrations were carried out potentiometrically and the end points were determined by the first derivative method. It was found that bromophenol blue indicator could also be used to determine end points in medium *a*. The mean per cent recovery for the titrations in medium *a*, with the end points determined by the first derivative method, was 98.85 with a standard deviation of 0.69. In the same medium, using bromophenol blue for end point determination, the recovery was 99.48 with a standard deviation of 0.96. In medium *b*, the recovery was 100.02 with a standard deviation of 1.27.

CRITCHFIELD and Johnson (1) have found that the potentiometric break in the titration of a weak base with aqueous hydrochloric acid is greatly enhanced if a concentrated aqueous solution of a neutral salt is used as the titration medium. (Neutral salts, for the purpose of this work, are defined as those derived from strong monobasic inorganic acids and strong mono- or diacidic inorganic bases.) Aniline, for example, with an ionization constant of 3×10^{-10}, is too weak to be titrated satisfactorily in water. By titrating the same compound in 7 *M* sodium iodide solution, a potentiometric break is obtained which is satisfactory for precise analytical measurements.

The present study was undertaken with the purpose of investigating the possibility of analyzing certain pharmaceuticals by the above method. Many pharmaceutical compounds contain tertiary amine structures and can be classed as weak bases. It would appear, therefore, that they might lend themselves to this type of analysis.

Papaverine, which is representative of the type of compound to which this method of analysis may be applied, was selected as the base for this investigation. First, the compound had to have an ionization constant between 1×10^{-8} and 1×10^{-11} (1). It has been observed that compounds with ionization constants greater than 1×10^{-8} can be acidimetrically titrated very satisfactorily in water either by a direct or an indirect method. Compounds with ionization constants smaller than 1×10^{-11} cannot be titrated satisfactorily even in concentrated salt solutions.

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Another reason for the selection of papaverine was that it was desired to choose a compound for which this method of analysis might be compared to the official procedure. The U.S.P. XVI method of analysis of papaverine hydrochloride preparations is a gravimetric one.

Lithium chloride was selected as the salt to be used in the titration medium because of its high heat of solution and because it has been successfully employed in titrations of this kind (1). Critchfield and Johnson have attempted to correlate the heat of solution of a salt with its effect on an acid solution. Their experimental data indicate that salts with high heats of solution exhibit the most pronounced effect of increasing the acidity of aqueous mineral acids. They have suggested that these salts have strong affinities for water and, therefore, compete with the hydronium ion for water of hydration (2). This, in effect, decreases the hydration of the hydronium ion and causes it to be more active.

The object of this investigation was to devise a direct acidimetric method of analysis of papaverine. The experimental work required to meet this objective was carried out in three main steps. The first was finding a cosolvent which would solubilize the papaverine in concentrated lithium chloride solution and not interfere with end point detection. The second step was establishing the accuracy and precision which could be obtained by this direct titration procedure. This was done by titrating known samples of papaverine and calculating per cent recovery. The third step was comparing the accuracy of the titration and the gravimetric methods. This was done by analyzing several official papaverine preparations by both methods and comparing the results.

EXPERIMENTAL

General Titration Procedure

All titrations were carried out potentiometrically using a Leeds and Northrup line-operated pH meter[1] equipped with glass and calomel electrodes. The titrant was added from a 5-ml. buret and the titration mixture was stirred throughout the process with Sargent magnetic stirrer.[2] The applicability of the potentiometric curves to end point determination was judged intuitively. Unless otherwise indicated, end points were determined by the first derivative method. That is, the volume at which the greatest value of dpH/dV occurred was taken as the end point.

Reagents

Hydrochloric acid, at a normality near 0.05, was used as the titrant. This acid was standardized against a 0.1 N sodium hydroxide solution which was standardarized using potassium acid phthalate. The lithium chloride was a Baker analyzed reagent.[3]

Preparation of Samples

Ion Exchange.—Papaverine hydrochloride was converted to the free base by means of an ion exchange resin. The procedure proposed by Levi and Farmilo (3) was used with the following alterations: Dowex 1-X4[4] resin was substituted for Amberlite IR-4B[5] and the sample size was reduced from 75 mg. to 65 mg. Individual samples were prepared by dissolving 0.6500 Gm. of papaverine hydrochloride in 100 ml. of the solution in a 100-ml. volumetric flask and pipetting 10-ml. aliquots. The solvent used in this step consisted of two parts by volume of chloroform and one part by volume of ethanol. The aliquots were introduced onto the ion exchange column and a solution of the free papaverine base was eluted. The solvent was removed by evaporation on a water bath, and the sample was then ready to be dissolved in the appropriate solvent and titrated with acid.

The columns were checked for completeness of recovery by processing a sample in the above manner, collecting the eluted papaverine solution in ten 10-ml. fractions, and testing these fractions for papaverine by the U.S.P. XVI identification test (4). Recovery was found to be essentially complete. Samples prepared in this way are referred to as column samples.

Extraction.—Papaverine was extracted from papaverine hydrochloride according to the method described in U.S.P. XVI under the assay of papaverine hydrochloride injection. Individual samples were prepared by weighing portions of the dried free base. Samples prepared in this way are referred to as extracted samples.

Solubilization of Papaverine in 8 *M* Lithium Chloride

The very low solubility of papaverine in water requires the use of cosolvents to produce a homogeneous system in 8 *M* lithium chloride solution.

Tetrahydrofuran-Ethanol (Alcohol U.S.P. XVI).—Tetrahydrofuran (THF) is a good solvent for papaverine. However, it is immiscible with 8 *M* lithium chloride and hence a third solvent, ethanol, is required to solubilize certain concentrations of THF in 8 *M* lithium chloride. These three comprise a typical ternary system, the compositions of which can be described graphically by means of a triangular plot. This plot was constructed by the following procedure: a series of seven solutions was prepared containing known amounts of ethanol and 8 *M* lithium chloride, and these were titrated with THF. The end point was taken as the first perceptible cloudiness. A second series of seven solutions was prepared containing known amounts of ethanol and THF. These were titrated to cloudiness with 8 *M* lithium chloride. The per cent composition of each sample at the end point was calculated on a weight basis and these compositions were plotted on triangular graph paper. This plot is shown in Fig. 1. At any point above the curved line, the system is homogeneous. At any point below the line, the system consists of two phases.

From the triangular plot, different compositions were selected with the objective of keeping the THF and ethanol concentration at the lowest possible value which would solubilize the papaverine and produce a satisfactory titration curve. The combination which gave the best results with respect to solubility and per cent recovery was 10% THF, 5% ethanol, and 85% 8 *M* lithium chloride solutions. A convenient volume was chosen to be 5.6 ml. of THF, 3.2 ml. of ethanol, and 36 ml. of 8 *M* lithium chloride. Ten column samples were analyzed using this system.

It was observed that when column samples were dissolved in this medium, the solution was slightly turbid. This cloudiness was caused by a small amount of insoluble residue eluted from the ion exchange resin.

It was found that ethanol alone would solubilize a column sample of papaverine. This solution also had a slightly turbid appearance which was again attributed to the presence of an insoluble residue eluted from the resin. However, when the first

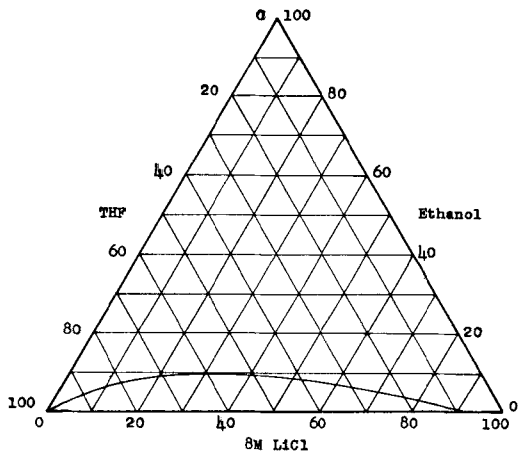

Fig. 1.—Three-component system consisting of tetrahydrofuran, ethanol, and 8 *M* lithium chloride solution.

[1] Leeds and Northrup Co., Philadelphia, Pa.
[2] E. H. Sargent Co., Chicago, Ill.
[3] J. T. Baker Co., Phillipsburg, N. J.
[4] Dow Chemical Co., Fair Lawn, N. J.
[5] Fisher Scientific Co., Fair Lawn, N. J.

increment of acid was added, a small amount of precipitate formed. This did not occur when the three-component system was used as the titration medium. The precipitate was slight and did not interfere with the end point determination. It was not identified.

Ethanol.—Ethanol also proved to be a good co-solvent for extracted samples. A system consisting of 18.5% (12 ml.) of ethanol and 81.5% (36 ml.) of 8 *M* lithium chloride solution gave good results with 5 samples. Volumes of ethanol less than 12 ml. failed to keep the papaverine in solution. Volumes greater than 15 ml. tended to flatten the curve and cause erratic pH meter response.

Figure 2 shows curves obtained in the titration of extracted samples. Curve 1 is the titration in the ethanol-8 *M* lithium chloride system and curve 2 is the titration with the same amount of ethanol but with the 8 *M* lithium chloride solution replaced by water.

It was found that bromophenol blue indicator gave satisfactory end points in this system. The color change is from blue to faint yellow.

For the solubilization of a column sample, 15 ml. of ethanol was required. The need for this increased volume might possibly have been due to the presence of the insoluble column residue. At this concentration of ethanol, the potentiometric curve was leveled somewhat and the end point was not as clearly indicated. Therefore, the tertiary mixture was used as the titration medium of choice for column samples. It was observed, when calculating the per cent recovery of a series of samples, that the results were consistently high. This suggested that the medium was contributing a certain amount of basicity. A series of titrations performed on the components of the system indicated that the lithium chloride was the source of error and demanded that a blank value be determined. This blank value was not strictly reproducible by direct titration of the lithium chloride solution with acid so a back titration procedure was tried. Standard acid was added to the lithium chloride solution and the excess was titrated with sodium hydroxide. The milliequivalents of acid equivalent to the basicity of 36 ml. of 8 *M* lithium chloride solution was calculated. Reproducible results were obtained by this procedure and it was accepted as a satisfactory method for the determination of the blank value. A certain amount of variation can be observed in the blank values recorded in Tables I, II, and III. This is accounted for by the fact that the 8 *M* lithium chloride solution was only approximate and, therefore, a new blank value had to be determined for each batch of solution which was prepared. Another reason for the variation is that all the lithium chloride used did not come from the same lot.

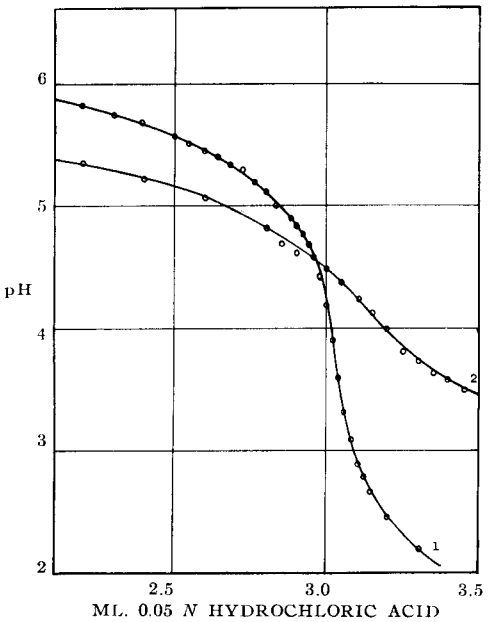

Fig. 2.—Potentiometric titration of papaverine. 1, In 18.5% ethanol and 81.5% 8 *M* lithium chloride solution; 2, In 18.5% ethanol and 81.5% water.

TABLE I.—POTENTIOMETRIC TITRATION OF PAPAVERINE IN 10% TETRAHYDROFURAN, 5% ETHANOL, AND 85% 8 *M* LITHIUM CHLORIDE

Sample No.	Sample Wt., Gm.	Acid Used, meq.	Blank, meq.	% Recovery
1	0.0587	0.1896	0.0188	98.75
2	0.0587	0.1933	0.0188	101.54
3	0.0587	0.1896	0.0188	98.75
4	0.0587	0.1933	0.0188	101.54
5	0.0587	0.1933	0.0188	101.54
6	0.0587	0.1834	0.0092	100.71
7	0.0587	0.1964	0.0233	100.09
8	0.0587	0.1934	0.0233	98.35
9	0.0587	0.1907	0.0198	98.83
10	0.0587	0.1929	0.0198	100.08
			Mean	100.02
			Standard Deviation	1.27

TABLE II.—POTENTIOMETRIC TITRATION OF PAPAVERINE IN 18.5% ETHANOL AND 81.5% *M* LITHIUM CHLORIDE SOLUTION

Sample No.	Sample Wt., Gm.	Acid Used, meq.	Blank, meq.	% Recovery
1	0.0581	0.1977	0.0276	99.36
2	0.0598	0.2002	0.0276	97.90
3	0.0589	0.1997	0.0276	99.13
4	0.0514	0.1783	0.0276	99.50
5	0.0590	0.1986	0.0276	98.36
			Mean	98.85
			Standard Deviation	0.69

TABLE III.—POTENTIOMETRIC TITRATION OF PAPAVERINE IN 18.5% ETHANOL AND 81.5% 8 *M* LITHIUM CHLORIDE SOLUTION

Sample No.	Sample Wt., Gm.	Acid Used, meq.	Blank, meq.	% Recovery
1	0.0581	0.1977	0.0276	99.36
2	0.0598	0.2008	0.0276	97.90
3	0.0598	0.2008	0.0276	100.20
4	0.0514	0.1794	0.0276	100.19
5	0.0590	0.2018	0.0276	100.19
			Mean	99.48
			Standard Deviation	0.96

TABLE IV.—RESULTS OF THE ANALYSIS OF PAPAVERINE HYDROCHLORIDE TABLETS (0.0324 GM./TAB.) BY GRAVIMETRIC AND TITRIMETRIC METHODS

Sample No.	Papaverine HCl Present,[a] Gm.	Gravimetrically		Titration	
		Found, Gm.	Recovery, %	Found, Gm.	Recovery, %
1	0.1022	0.1014	99.22	0.1017	99.49
2	0.1022	0.1046	102.36	0.1009	98.73
3	0.1026	0.1020	99.33	0.1021	99.45
4	0.1026	0.0989	96.31	0.1009	98.35
		Mean	99.31	Mean	99.00
		Standard Deviation	2.47	Standard Deviation	0.52

[a] Calculated from the labeled amount.

TABLE V.—RESULTS OF THE ANALYSIS OF PAPAVERINE HYDROCHLORIDE INJECTION (0.0320 GM./ML.) BY GRAVIMETRIC AND TITRIMETRIC METHODS

Sample No.	Papaverine HCl Present,[a] Gm.	Gravimetrically		Titration	
		Found, Gm.	Recovery, %	Found, Gm.	Recovery, %
1	0.128	0.1342	104.82	0.1274	99.51
2	0.128	0.1357	106.30	0.1321	103.16
3	0.128	0.1317	102.91	0.1297	101.34
4	0.128	0.1332	104.04	0.1305	101.95
		Mean	104.52	Mean	101.49
		Standard Deviation	1.01	Standard Deviation	1.15

[a] Calculated from the labeled amount.

Assay of Some Official Papaverine Preparations

Papaverine hydrochloride injection[6] (0.032 Gm./ml.) and papaverine hydrochloride tablets[6] (0.0324 Gm./tab.) were assayed according to the U.S.P. XVI procedures. After the samples were dried and weighed, they were dissolved in 20 ml. (18.5% w/w) of ethanol and 60 ml. (81.5% w/w) of 8 *M* lithium chloride solution and titrated with 0.1 *N* hydrochloric acid. Either titration medium previously outlined could have been used. The ethanol-THF combination will solubilize a greater amount of papaverine per unit volume than will ethanol alone. However, the preparation of the three-component medium requires one additional volume measurement, i.e., THF. Since both systems give satisfactory curves with extracted samples, the ethanol-8 *M* lithium chloride medium was selected because of its relative ease of preparation.

RESULTS

Table I lists the per cent recovery for 10 column samples of papaverine titrated in 10% THF, 5% ethanol, and 85% 8 *M* lithium chloride solution. End points were determined by the first derivative method. The mean per cent recovery indicates good accuracy. The deviation of 1.27% represents about 0.05 ml. of 0.05 *N* acid, about 0.002 meq., and about 0.7 mg. of papaverine.

Table II lists the per cent recovery obtained from the five extracted samples titrated in 18.5% ethanol and 81.5% 8 *M* lithium chloride solution. In this table the end points were determined by the first derivative method. Table III lists the recovery of the same five samples, but the end points were determined with bromophenol blue indicator. The alkaline form of bromophenol blue is bluish-purple in this system. The end point occurred at pH 2.8–3.5 and the color changed to an easily perceptible faint bluish-yellow. The change is abrupt enough to be used in routine analysis.

[6] Eli Lilly and Co., Indianapolis, Ind.

Tables IV and V list the per cent recovery obtained in the assay of two official preparations. End points for the titrimetric data were determined by the first derivative method. These same end points were also determined using bromophenol blue and the results obtained were essentially equivalent to those by the first derivative. Since the exact amount of papaverine in the samples is unknown, the mean per cent recovery is not as significant as that of the known samples. The standard deviation is, however, a valid measure of precision.

CONCLUSIONS

The data obtained in this investigation indicate that this method of analysis is suitable for the quantitative determination of papaverine and other alkaloids or pharmaceuticals whose properties are similar to those of papaverine.

The problem of solubilizing the free base was overcome by using cosolvents in either a binary or ternary system. The optimum volume of the cosolvent was that volume which would hold the papaverine in solution in 8 *M* lithium chloride and not cause excessive dilution. This investigation indicates that 8 *M* lithium chloride solution can be diluted 33% with cosolvent and still sufficiently enhance the potentiometric break when titrating papaverine.

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