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A HIGH FREQUENCY OSCILLOMETRIC TECHNIQUE FOR THE ANALYSIS OF VARIOUS CHLORIDES

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Abstract

This study involved the use of an oscillometric technique for the quantitative analysis of various chlorides such as sodium, potassium, calcium and aluminum chlorides. This technique depends on the determination of the capacitance of aqueous solutions of varying normality and the generation of a calibration curve as a function of concentration. These calibration curves for each salt were computerized by means of a modeling equation of a nonlinear type. This gave a parameter set of values which were iterated to constant value and uniquely defined for a particular calibration curve. The results of the quantitative assay of various chlorides was found to be accurate to within two percent and compared favorably with and is somewhat more accurate than a silver nitrate titration with a fluorcein indicator.

Introduction

In this study an oscillometric technque was investigated and utilized for the analysis of various chloride salts and compared to a colorimetric method using silver nitrate and a fluorscein indicator.

The various salts chosen were sodium, potassium,calcium and aluminum chloride which provided for mono, di, and trivalent cationic species. This was done in order to discern the effect of these various cations and normal solutions were used to provide isonormal concentrations of the anionic chloride species. Thus the generated curves could be compared to the relative conductance of these solutions.

The sodium, potassium and calcium chlorides are found in many types of pharmaceutical dose forms including many which are used for parenteral administration.

The basic objective of this study was to quantitate the application of the oscillometric technique for the analysis of various chlorides or chloride ions.

There is a vast amount of literature available on the analysis of chlorides and chloride ions. Only the most pertinent and most current methods will be cited here. There are available titrametric methods such as that reported by Krincic (1) in which mercuric nitrate is used with a diphenyl-carbazone indicator used for infusion solutions. Other reports (2-4) basically utilize titration methods. Trace chloride determinations have been reported by Music (5) and a argentometric technique given by Singh and Nathan (6). With the advent of ion-specific electrodes (7), many reports on their use for chloride determinations have appeared of which more recent ones are cited. These are reports by Speights et al (8), Popp and Pungor (9), Florence (10) and Washizuka (11). The use of high frequency oscillometric analysis or titrations are exemplified by the studies of Blaedal (12, 13,) and Jensen (14, 15) and a general overview of oscillometric techniques given by Sherrick et al (16).

Theory of Operation

Utilization of a high frequency oscillator as a power source with coupling to a capacitive circuit of chemical sample is the underlying principle of this technique. The resonant circuit (tuning oscillator) is employed and a test sample is introduced such that there is a change in the capacitance or resistance or both contributed by the sample.

In this case, a sample cell acts as a conductive arm between electrodes and measures the relative capacitance of a test solution. The advantage of the Model V Oscillometer is the isolation of the sample from the circuit elements. Further, this advantage eliminates the unwanted effects of electrolytic alteration and electrode potential in other common electrometric methods.

In this study, various chloride salts were used and in each of these solutions, the change in conduction from sample to sample would result in an energy loss from the circuit. This energy loss then would cause additional capacitance that would be required to null the resonant frequency. Since the chloride ion was common to all these halide salts, the differences in a portion of the added capacitance would depend upon the ion size, charge and hydration of the cationic species. Therefore, isonormal solutions of various chlorides should produce similar calibration curves as a function of concentration and should be slightly different from one another depending upon the cationic species.

Experimental

Chemicals - The following chemicals were used:

Sodium Chloride[1], Potassium Chloride[2], Calcium Chloride[3], Aluminum Chloride[4], Sodium Hydroxide[5], 2, 7' dichlorofluorscein[6], and distilled water.

Equipment - The following equipment was used:

Burettes with 0.01 ml. increments, Sargent Model V Chemical Oscillometer, Mettler Balance Type H16 volumetric flasks, pipettes and erhlenmeyer flasks.

Preparation of Solutions - Solutions of salts were prepared from accurately weighed samples by a difference method. The various chloride salts were dried to constant weight at 55° in a convection oven prior to use. The reagent solutions were freshly prepared in distilled water and were discarded after 24 hours. Commercial samples of Bacteriostatic Chloride Injection, USP was used directly and diluted to the operating range of the oscillometer.

Operation of Oscillometer

In the course of study, it was found that in order to obtain the most accurate and reproducible results, several operating characteristics for this instrument were determined and should be adhered to.

The procedure that was adopted is given as follows. The Model V Oscillometer was allowed to warm up for at least two hours prior to use. The room temperature was ambient at about 23° and the temperature was taken prior

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[1] Lot X2466109, Amend Drug and Chemical Co.

[2] Lot WNRS, Mallinckrodt Chemical Works

[3] Anhydrous, #4128 Mallinckrodt Chemical Works

[4] Lot 6066066, Amend Drug and Chemical Co.

[5] Analyzed, Eastman Organic Chemicals, Inc.

[6] Lot WI83J, Pellets, Allied Chemical Co.

to and after each run with the largest variation of 1° for all reported results.

The small unstoppered 10 ml. cell was used in a constant configuration marked on the cell holder, and all sample solutions were at least 2 cm. above the electrode surface. A 180° turn of the cell produced no change in the observed readings. All solutions were prepared with distilled water since there was no difference in the readings with deionized distilled water.

The temperature of all solutions was measured prior to and after measurement with no change in temperature and all readings were taken when thermal equilibrium had been reached.

For each sample, 3 readings were taken within about two minutes by determining the capacitance units added, removing the cell, reinserting it into the cell holder again in a particular configuration and remeasuring the capacitance units added.

It was observed that the null balance sometimes had a slight drift which may have been due to line current fluctuations or variations in room temperature. This drifting did not cause any problems of measurement of the capacitance of the samples.

There were day-to-day variations in the calibration curves for the various salts but these variations were uni-directional and constant in magnitude.

Each sample cell would have its own unique characteristics and properties (cell constant); thus 2 small 10 ml. unstoppered cells were used in many of these experiments in order to compare their individual consistency and reproducibility of results.

For each salt solution, at least 8 runs of 3 sample readings for each concentration were determined by this technique. These calibration runs for a particular cell were repeated on the same day, one week and two weeks later with a maximum deviation of 200 units over the entire sets of results which resulted in an error of less than one percent error in capacitance units added.

Procedure for Colorimetric Titration

In general, a given volume of solution was placed in a volumetric flask with a magnetic stirrer, about 3 drops of the fluroscein T.S. added and titrated with the appropriate normality of freshly prepared silver nitrate (less than 24 hours old) and titrated in a burette with .01 ml. divisions. The greenish yellowish fluorescent color was titrated by the addition of silver nitrate to a reddish brown coloration with 15 second stops after each 0.01 ml. increment added near the end point.

The fluorscent T.S. was prepared by dissolving 100 mg. of 1,7' dichlorofluorscein in 60 ml. of 95% ethanol, adding 2.5 ml. of 0.IN freshly prepared NaOH, mixed and diluted with distilled water to 100 ml.[a]

For these titrations, duplicate sets of 3 samples per set were run for the various concentrations of the chloride salts used in this study.

Results and Discussion

Determination of Calibration Curves

Each salt solution was prepared at a given concentration and subsequent dilutions were made in order to prepare concentrations of 1×10^{-3}N to 6×10^{-3}N.

For a given sample at each concentration, 3 instrument readings were taken, the cell rinsed 3 times with the next most concentrated sample and the process repeated. The precautions on the operational technique as given in the experimental section were adhered to.

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[a] USP XIX p. 764

In Figure 1, a plot of instrument reading or capitance units added is plotted versus concentration expressed in normality. These types of nonlinear curves were found for all the chlorides used in this study. Typical calibration curves are shown in Figure 1 for the experimentally determined readings for two of the salts studied, sodium chloride and potassium chloride in 2 different 10 ml. unstoppered cells. The calibra-

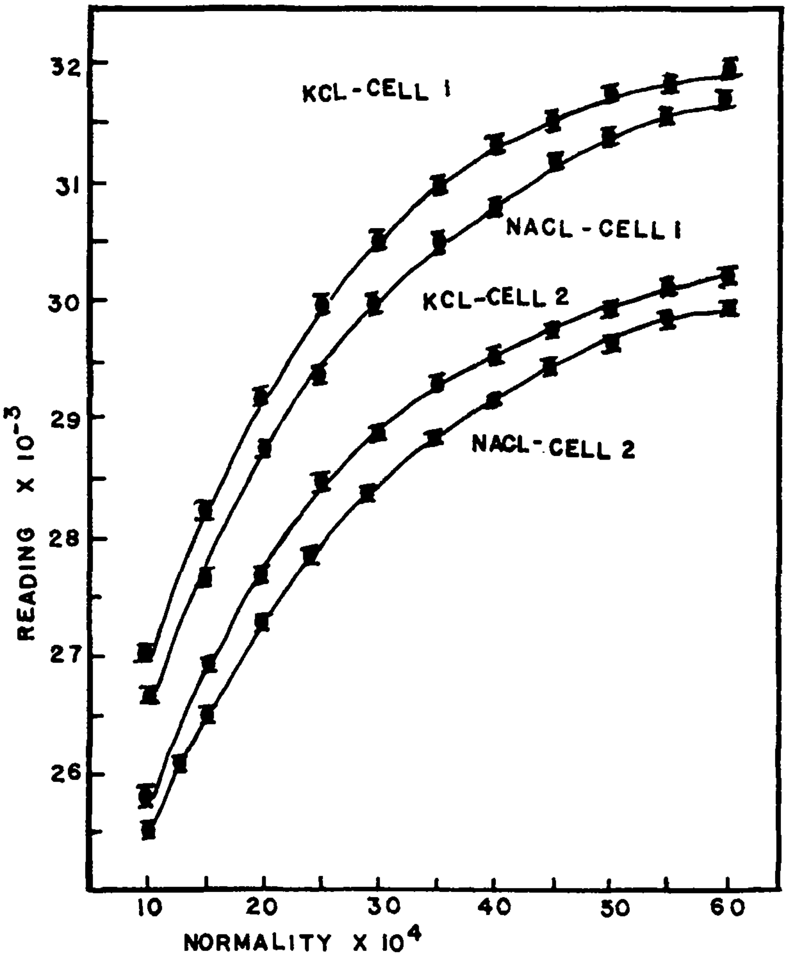

FIGURE 1 A plot of Oscillometer Reading for Sodium and Potassium chlorides in Cell 1 and Cell 2 as a function of concentration expressed as Normality.

tion curves produced for these salts in the 2 cells are completely superimposable but the difference in the magnitude of the plotted readings illustrates the effect of the cell characteristics. The above held as well for the calibration curves of calcium and aluminum chlorides. There were day-to-day variations in these readings for a particular concentration range of any of the salts, and these variations were unidirection and constant in magnitude. The magnitude of these variations is also shown in Figure 1 by horizontal lines above and below the average value being plotted.

Obviously either cell 1 or cell 2 could be used to test future known or unknown samples as long as all the constraints described previously for instrument operation are adhered to.

Unfortunately, during this study a hairline crack was observed near the electrode surface of cell 1 and most of the latter work described herein utilized cell 2.

Computer Analysis of Calibration Curves

Once the calibration curves for the various chlorides had been determined, an attempt was made to fit various analytical expressions to the data obtained. One such expression was found (17) which gave an excellent fit to the calibration curves. The data for each solution concentration was averaged using a minimum of six individual determinations and analysis performed by a Nonlin program on an IBM 360/155 computer. The equation which fitted the calibration curves could be represented as follows:

$$R = P_1 + P_2 (\log_{10}C - P_3) \qquad \text{Equation 1}$$

where R = instrument reading, C is concentration expressed in normality and P_1, P_2 and P_3 are parameters which by a iterative process become constant. When the parameter set (P_1, P_2 and P_3) have been determined for a particular chloride salt, these P values are used in a subroutine, by typing in the instrument reading for an unknown concentration of the same salt, the computer would then calculate and print out the normality.

It is important to note that each set of self consistant instrument readings for any given salt will produce a calibration curve which by computer analysis will generate a parameter set of P_1, P_2 and P_3 which are uniquely defined for that calibration curve.

In order to illustrate these characteristics, a typical computer printout for varying normalities of sodium chloride is shown in Table I. In this case, a data bank is created (normalities and instrument readings) and stored. The data is called out and the Nonlin program operates on the data. Part of the printout of data and data analysis is shown in Table I.

For each individual calibration curve in different cells for the same salt a different parameter set would be generated. In Table II, the parameter set P_1, P_2 and P_3 for each salt in either cell 1 or cell 2 were obtained from computer analysis and are given in this table. The values listed under R^2 and cor. are considered to give estimates of "goodness of fit" to a nonlinear function. All of these values have magnitudes of 0.99 and greater indicating a very good fit of the modeling equation and raw experimental data.

Results and Discussion

In order to test this model equation and its ability to predict the normality of unknown concentrations of any given salt, samples of sodium chloride in the concentration range of 1×10^{-3}N to 5×10^{-3}N

Table I - A typical computer printout data for sodium chloride solutions of varying normalities for cell 2 with iterated values of parameters P_1, P_2 and P_3

Normality x 10^2	Observed Reading	Calculated Reading	Obs.-Calc. Reading	% Deviation
.1011	25,805	25,787	18	0.07
.2023	27,661	27,778	127	-0.46
.3033	28,858	28,763	95	0.33
.4045	29,520	29,414	106	0.36
.5055	29,906	29,902	4	0.01
.6064	30,199	30,194	95	-0.31

were prepared and coded. These solutions were then measured on the oscillometer in cell 1, the instrument reading inputted into the subroutine and the normality printed out. In Table III, the results of the prepared (unknown) normality and the computed normality are shown and very good results are obtained. For this "blind" study, the percent error varied from about 1 to 2.5 percent.

Table II - A summary of the Nonlin computer analysis of parameters P_1, P_2 and P_3 for the various salts used in this study for cell I and cell 2

Cell 1 - Parameter Set 1

Salt	P_1	P_2	$P_3 \times 10^3$	R^2	Cor.
Sodium Chloride	46,257	6413	.1419	.995	.998
Potassium Chloride	44,397	5445	.3945	.993	.993
Calcium Chloride	46,069	6368	.1236	.996	.998
Aluminum Chloride	45,194	5963	.2047	.995	.998

Cell 2 - Parameter Set 2

Salt	P_1	P_2	$P_3 \times 10^3$	R^2	Cor.
Sodium Chloride	42,303	5458	.1683	.994	.997
Potassium Chloride	40,572	4560	.4275	.997	.998
Calcium Chloride	42,513	5580	.0833	.990	.995
Aluminum Chloride	40,784	4778	.3181	.994	.997

Since there is variability in both the calibration curve and the parameter set, it would be possible to determine a maximum error for this technique by a cross-over variability design. This is illustrated in Table IV for sodium chloride solutions in cell 2 in which the percent error is shown when the instrument reading is constant and the parameter set is varied. In the lower half of this table, the parameter sets are the same but the instrument reading is varied. From this tabulation,

Table III - Summary of a comparison of prepared normalities and computed normalities of sodium chloride solutions and the percent error found for cell 1

Prepared Normality x 10^2	Instrument Reading	Computed Normality x 10^2	% Error
.1002	25,789	.0990	1.2
.1396	26,312	.1380	1.2
.1470	26,466	.1440	2.5
.2504	27,854	.2470	1.4
.2613	28,080	.2650	1.4
.4990	29,608	.4890	2.1
.5030	29,713	.5100	1.4

the most likely maximum error in any determination without recalibration would be about 3.7% with the most likely error around 2.5%.

In the case of the other chlorides used in this study, unknowns were prepared and coded, instrument

Table IV - A summary of a crossover variability of instrument readings and test parameters for sodium chloride solutions of varying normalities

	Instrument Reading		Computed Normality		Percent Error	
Normality Prepared x 10^2	$P(set_1)$	$P(set_2)$	$P(set_1)$	$P(set_2)$	$P(set_1)$	$P(set_2)$
.1370	26,446	26,446	.1335	.1413	2.6	3.1
.2507	28,080	28,080	.2519	.2548	0.5	1.7
.5013	29,713	29,713	.5001	.5106	0.3	1.8

	Instrument Reading		Computed Normality		Percent Error	
Normality Prepared x 10^2	$P(set_1)$	$P(set_2)$	$P(set_1)$	$P(set_2)$	$P(set_1)$	$P(set_2)$
.1370	26,312	26,312	.1371	.1344	0	1.9
.2489	27,854	27,854	.2399	.2422	3.7	2.7
.4976	29,608	29,608	.4893	.4880	1.4	2.0

readings were taken in cell 2 on the same day the calibration runs in cell 2 were performed. The results of these determinations are given in Table V. The percent error of the prepared (unknown) normality and the computed normality is striking, the average error is only about 1.0% which compares quite favorably with other techniques of chloride determination by titrametric and electrometric methods. In this "blind" technique, a

Table V - A Summary of results obtained for Potassium Chloride, Calcium Chloride and Aluminum Chloride of varying normalities in cell 2 with constant values of parameters P_1, P_2 and P_3 (Parameter Set 2)

Potassium Chloride

Normality Prepared x 10^2	Inst. Reading	Computed Normality	% Error
.1012	25,809	.1006	0.6
.2503	28,325	.2489	0.6
.5010	29,892	.4986	0.5

Calcium Chloride

Normality Prepared x 10^2	Inst. Reading	Computed Normality	% Error
.1006	25,607	.1017	1.1
.2511	27,869	.2479	1.3
.5007	29,683	.5013	0.2

Aluminum Chloride

Normality Prepared x 10^2	Inst. Reading	Computed Normality	% Error
.1022	25,691	.1012	1.0
.2507	27,886	.2461	1.8
.5031	29,627	.4989	0.5

conclusion can be made about an increase in accuracy in samples with a recalibration of instrument readings with known solution normalities over a short time span.

One of the basic objectives of this study was to compare the usefulness and accuracy of the oscillometric technique to another technique such as a colorimetric titration with silver nitrate and a fluorescein indicator. Standard solutions of the various chlorides were prepared and carefully titrated with silver nitrate in the manner previously described. In Table VI, the results of these titrations is shown is shown expressed

Table VI - A summary of the Silver Nitrate - 2, 7'dichlorofluorscein calorimetric tertration of standard solutions of the various chlorides used in this study.

	mls of .IN Soln.	Silver Nitrate mls of 0.IN	% Error
Sodium Chloride	5.00	.50-.51	2
Potassium Chloride	5.00	.51-.52	2-4
Calcium Chloride	5.00	.49-.50	2
Aluminum Chloride	5.00	.50-.51	2

	mls of .OIN Soln.	Silver Nitrate mls of 0.IN	% Error
Sodium Chloride	5.00	.51-.52	2-4
Potassium Chloaride	5.00	.50-.52	4
Calcium Chloride	5.00	.49-.52	2-4
Aluminum Chloride	5.00	.51-.52	2-4

as the deviation from the required volume, i.e., 5.00 ml. of 0.1N sodium chloride requires 0.50 ml. of 1N silver nitrate. Here it can be observed that errors in these determinations vary over a range of about 2-4% which is somewhat less accurate than the oscillometer. It is important to note here that this titrametric technique is fairly accurate at higher concentrations but one might expect that at lower concentrations the color change would be difficult to observe. In the oscillometric technique with an operating range of .001N to .006N, any more concentrated solution could be accurately diluted which is an advantage over the silver nitrate method.

In order to illustrate these points, 3 commercial samples of sodium chloride injection bacteriostatic, USP were obtained, dilutions prepared and the average concentrations determined by both the oscillometric and colorimetric methods. The results of these determinations are shown in Table VII. In the oscillometric technique, very good correlation was obtained with a maximum error of 1.3% and a minimum error of 0.5% For the colorimetric technique, good results were also obtained with a slightly higher error on the order of 1-3%. Again, the oscillometric technique is somewhat more accurate than the titration method.

In the oscillometric method, the sodium chloride injection and the calibration runs were done on the same day again providing relatively accurate results. In the titration method, higher errors are found at the lower concentrations but the accuracy at the highest concentration of about .005N is the same as the oscillometric technique.

Further, this technique can be applied to concentrated solutions of various chlorides (0.01 - 1N by

Table VII - A summary of test results from the oscillometric and titration method for Sodium Chloride Injection Bactierostatic, USP

Oscillometric, Cell 2, Parameter Set 2

Dilution	Calc. Normality x 10^2	Average Inst. Reading	Determined Normality	% Error	% NaCl in USP Sample
1-100	.1550	26,940	.1571	1.3	.909
1-60	.2583	27,967	.2550	1.2	.882
1-30	.5166	29,893	.5140	0.5	.896

Colorimetric Titration Method

Dilution	Calc. Normality x 10^2	Determined Normality	% Error	% NaCl in USP Sample
1-100	.1550	.1597	3.0	.925
1-60	.2583	.2653	2.6	.920
1-30	.5166	.5207	1.0	.910

accurate dilutions into the operating range of the oscillometer.

Additionally, this technique could provide a "second" method for chloride analysis in which this instrumental method could back up a titrametric method. The effect of pH and non-aqueous solvents on the applicability of this method is planned for future studies. There has been some preliminary work on other halide determinations by this oscillometric technique and these results will be considered in a future communication.

The oscillometric technique as described in this study can be used as a rapid, reliable, reproducible and relatively accurate method for the analysis of various chlorides or chloride ions.

Conclusions

A high frequency oscillometric method for the quantitation of various chloride salts has been presented.

The accuracy of this method depends on the careful use of the operating characteristics of the Model V Oscillometer and cell characteristics.

The computerization of and analysis of parameter sets and data was accomplished by the use of a nonlinear modeling equation. The "goodness of fit" to this equation was excellent, all values of R-squared and cor. being greater than 0.99.

The analysis of various unknown and bacteriostatic sodium chloride injection, USP were found to be quite accurate to within a maximum error of about 2 percent.

This technique compared very favorably with a silver nitrate titration method using 2, 7' dichlorofluorscein as the indicator, the oscillometric technique being somewhat more accurate.

Finally, the oscillometric technique as described herein can be used as a rapid, reliable, reproducible and relatively accurate method for the determination of aqueous solutions of the chloride salts used in this study.

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