

Permanganate and Cerimetric Methods in Pharmaceutical Assays

A Study of the Relative Merits

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INTRODUCTION

Potassium permanganate has been the most generally accepted oxidant in volumetric analysis for the past fifty years. This supremacy has been seriously challenged during the past decade by the introduction of ceric salts.

As early as 1861, Lange (1) suggested the use of acidified solutions of ceric salts as volumetric oxidizing agents. Further work on this subject was neglected until the systematic studies of Atanasiu (2, 3) in 1928. This work did not attract wide attention as it was confined to electrochemistry. Since 1928, additional developments in the use of cerimetric methods have been devised by Willard and Young (4, 5), Furman (6-10) and others. As a result of these investigations and the introduction of a satisfactory indicator by Walden (11), which eliminated the necessity of electrometric titrations, the practicability of ceric solutions as oxidants has been established.

Since much of Willard's and of Furman's work dealt with a comparison of the results obtained with the use of ceric solutions and those obtained with permanganate and dichromate solutions, and in view of the growing popularity of cerimetric methods, it appeared desirable to the authors of this paper to compare them with methods now in use in the United States Pharmacopœia.

Quadrivalent cerium is a powerful oxidizing agent in acid solutions. The normal oxidation potential (12), referred to hydrogen, is 1.46 volts (Ce^{IV} to Ce^{III}), while that of potassium permanganate (13) is 1.52 volts (Mn^{VII} to Mn^{II}) and that of potassium dichromate (13) is 1.30 volts (Cr^{VI} to Cr^{III}), each at a concentration of 1*N* sulfuric acid.

Advantages of Cerimetric Methods.—The respective merits and limitations of ceric

sulfate, potassium permanganate and potassium dichromate are as follows:

1. The solutions of this salt are exceedingly stable (14).

2. Ceric solutions can be used in the presence of a high concentration of hydrochloric, sulfuric or perchloric acids. Its use in strong hydrochloric acid is a distinct advantage over potassium permanganate.

3. Ceric solutions can be standardized against the same primary standards as potassium permanganate, namely: electrolytic iron (15), sodium oxalate (16), arsenous oxide (17).

Recent announcement (18) proposes the use of a pure ceric salt, hexanitro ammonium cerate, $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$, which makes possible the preparation of a standard solution by direct weighing. The authors of this paper have not as yet substantiated this claim.

4. There is only one change in valence, Ce^{IV} to Ce^{III} , and therefore no intermediary products are possible.

5. The high oxidation potential has already been cited.

6. The reduced form, cerous ion, is colorless and hence offers no interference with indicators.

Disadvantages of Cerimetric Methods.—1. Until recently cerate methods were limited to electrometric titrations. While this disadvantage has been eliminated by the development of a satisfactory indicator (11), the necessity of using a catalyst is still essential in most titrations.

2. The change of color of Ce^{IV} to Ce^{III} is from yellow to colorless but the end-point is not easily discernible necessitating, in most cases, the use of an indicator.

3. Cerate methods are less economical than those involving the use of potassium permanganate or potassium dichromate.

At current prices, 1939, it costs \$0.27 to prepare 1 liter of 0.1*N* $\text{Ce}(\text{SO}_4)_2$, \$0.37 for $\text{Ce}(\text{NH}_4)_2(\text{SO}_4)_2 \cdot 2\text{H}_2\text{O}$, \$0.005 for KMnO_4 and \$0.008 for $\text{K}_2\text{Cr}_2\text{O}_7$.

Advantages of Potassium Permanganate.—

1. Its reactions generally occur with marked rapidity.

2. It serves as its own indicator.

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3. It can be used in acid, alkaline and neutral solutions.

4. It is very inexpensive.

5. It has a high oxidation potential.

Disadvantages of Potassium Permanganate.—1. It cannot be obtained pure enough to warrant its use as a primary standard.

2. The solutions of this salt must be allowed to stand for a considerable time and must be filtered before standardization is possible.

3. The oxidation reduction reactions involving this salt in acid media are limited to sulfuric and perchloric acids. The presence of hydrochloric acid is not desirable and cannot be used in the titration of ferrous iron.

4. The change in valence of potassium permanganate is Mn^{VII} to Mn^{II} with the possibility of forming compounds of variable valence, *i. e.*, Mn^{VI} , Mn^{IV} , Mn^{III} , Mn^{II} .

5. Unless special precautions are taken potassium permanganate solutions are unstable and must be standardized at frequent intervals (19, 20, 21).

Advantages of Potassium Dichromate.—

1. Solutions of this salt are stable over a long period of time.

2. The salt can be obtained pure enough to be used as its own primary standard.

Disadvantages of Potassium Dichromate.—

1. The use of this salt as an oxidant is practically limited to the determination of iron.

2. The titrations with this salt require the use of either an external or an internal indicator. Satisfactory results are obtained by the use of an external indicator although internal indicators are receiving favorable attention (22, 23).

EXPERIMENTAL

Electrolytic iron wire (Mallinckrodt 99.86 per cent iron) was used to standardize the oxidizing solutions of ceric ammonium sulfate, potassium permanganate and potassium dichromate. Samples weighing approximately 0.2 Gm. were dissolved in enough concentrated sulfuric acid (96 per cent) to make the final volume of 200 cc. $2N$ in acid. These solutions were reduced by the use of the Jones reductor and titrated against the respective oxidizing solutions, which were approximately $0.1N$.

The following chemicals, which are typical of The United States Pharmacopœia XI assays, were assayed by each of the three oxidizing solutions where possible: Ferrous Ammonium Sulfate, Sodium Perborate U. S. P., Solution of Hydrogen Peroxide U. S. P., Calcium Bromide U. S. P., Calcium Chloride U. S. P. and Calcium Gluconate U. S. P. Since ferrous ammonium sulfate is more stable than ferrous sulfate U. S. P., this salt was included in the group of substances assayed. Because potassium dichromate could not be used in the assay of calcium bromide and of calcium chloride, the Volhard method was used for the determination of these salts.

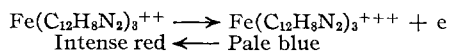
The method used in the analysis of the salts was that of The United States Pharmacopœia XI,¹ substituting the several oxidizing solutions as required for potassium permanganate, which is the oxidizing solution in the official methods of assay.

In the use of ceric ammonium sulfate, osmium tetroxide, in the form of a $0.01M$ solution in $0.1N$ sulfuric acid, was the catalyst used (0.15 cc.), excepting the determinations involving the oxalate ion in which iodine monochloride (5 cc.) served as the catalyst.

The iodine monochloride used was prepared as follows: 0.279 Gm. of potassium iodide and 0.178 Gm. of potassium iodate were dissolved in 250 cc. of distilled water and 250 cc. of concentrated hydrochloric acid were added immediately (4).

The indicator used in all the determinations involving the ceric salt was the ortho-phenanthroline ferrous sulfate complex (11). This was prepared by dissolving the calculated quantity of ortho-phenanthroline, $C_{12}H_8N_2 \cdot H_2O$, in $0.025M$ ferrous sulfate and $0.5M$ sulfuric acid so that the final solution is $0.25M$ in respect to the indicator.

The indicator color change is:



The oxidation potential of the indicator is 1.14 volts producing a sharp end-point. The reaction is reversible as shown above.

The ceric ammonium sulfate determinations were carried out at room temperatures except in the case of the oxalate ion which required a temperature of about $50^\circ C$.

DISCUSSION OF RESULTS

In the determination of ferrous iron it appears that there is very little choice between the three oxidants used, as far as precision is concerned.²

The experimental data indicate that ceric ammonium sulfate is as precise as potassium

¹ In the analysis of calcium bromide the U. S. P. XI First Supplement method was used.

² In the Second Supplement to the U. S. P. XI, issued in September 1939, Pills of Ferrous Carbonate and Mass of Ferrous Carbonate are assayed by the use of ceric sulfate.

Substance	Theory	Experimental Data				
		Cerate	KMnO ₄	K ₂ Cr ₂ O ₇	Volhard	
Ferrous ammonium sulfate	14.24% Fe	14.31	14.18	14.23	
		14.28	14.15	14.16	
		14.25	14.27	14.18	
		14.22	14.21	14.25	
		14.19	14.19	14.24	
		14.20	14.17	14.18	
		14.24	14.14	
		14.34	14.17	
		Av. % Fe	14.25	14.19	14.21
		Ferrous ammonium sulfate ^a		5.12	5.05	5.04
5.12	5.00			5.09	
Av. % Fe	5.12			5.03	5.07
Sodium perborate, U. S. P.	Not less than 9% free O ₂ , U. S. P.	9.63	9.66	
		9.64	9.64	
		9.66	9.64	
		9.65	9.63	
		9.66	9.65	
Av. % O ₂	9.65	9.65		
Solution hydrogen peroxide, U. S. P.	2.5 to 3.5% H ₂ O ₂ , U. S. P.	2.93	2.95	
		2.93	2.95	
		2.95	2.97	
		2.96	2.96	
		2.94	2.96	
		2.94	2.95	
Av. % H ₂ O ₂	2.94	2.96		
Calcium bromide, U. S. P.	84.73% CaBr ₂ (84-89% U. S. P.)	88.33	89.44	88.68	
		88.62	88.96	88.61	
		88.77	89.24	88.65	
		Av. % CaBr ₂	88.57	89.21	88.65
Calcium chloride, U. S. P.	75.49% CaCl ₂ (75-85% U. S. P.)	74.15	74.45	Modified Volhard ^b 74.19	74.04	
		74.30	74.17	74.23	74.02	
		74.30	74.29	74.07	74.04	
		74.21	74.24	
		74.15	74.35	
		Av. % CaCl ₂	74.22	74.30	74.16	74.03
Calcium gluconate, U. S. P.	12.51% CaO (12.4-12.8% CaO U. S. P.)	12.23	12.58	
		12.22	12.46	
		12.17	12.50	
Av. % CaO	12.21	12.51		

^a A specially prepared sample used for student analysis.

^b The modified Volhard method using nitrobenzene eliminates the necessity of filtering. Caldwell and Moyer, *Ind. Eng. Chem., Anal. Ed.*, 7 (1935), 38.

permanganate in the determination of oxygen in solutions of hydrogen peroxide and in sodium perborate.

Although the literature³ indicates that the toxic properties of osmium tetroxide have been recognized for a long time, none of the references dealing with cerate methods, in which this substance was used as a catalyst, mentioned precautions for handling it. A vial of osmium tetroxide was accidentally broken and the contents falling on the

³ "Textbook of Inorganic Chemistry," J. N. Friend, Vol. IX, Part I, page 221, Griffin and Company.

operator's hands caused a black deposit of metallic osmium. The fumes given off were highly irritating to the eyes and nasal passages.

The data relative to the assay of calcium bromide indicate that the method of assay as outlined in the First Supplement of the United States Pharmacopœia XI does not give as consistent results as do the cerate and the Volhard methods. Discrepancies in weighing, caused by the deliquescent nature of this salt, were eliminated by the use of aliquot samples.

Each of the four methods used to assay calcium chloride gave results which were in satisfactory agreement. The low results obtained for the analysis of this salt may be attributed to the fact that the sample was taken from a stock bottle which had been in the laboratory for several years.

The standards specified by The United States Pharmacopœia XI for calcium bromide dihydrate, 84–94% CaBr_2 (by theory 84.73%), and for calcium chloride dihydrate, 75–85% CaCl_2 (by theory 75.49%), would indicate that these salts, as obtained on the market, contain less water of hydration than their formulas show. If the dihydrates are obtained as such, and in view of the fact that they are strongly deliquescent, the query is raised as to why their present standards should not be adjusted to agree with this fact.

In the assay of calcium gluconate, it appears that potassium permanganate gives results which are in somewhat better agreement with the theoretical composition of the salt, than does the use of ceric ammonium sulfate. Since calcium gluconate monohydrate is a stable salt, it appears that the present Pharmacopœial standard, 12.4–12.8% CaO (by theory 12.51%), might properly be adjusted to the mean of limits corresponding more closely to the theoretical composition.

SUMMARY

It has been shown in this study that ceric ammonium sulfate can be substituted for potassium permanganate as an oxidant in pharmaceutical assays; however, the cost of the cerate method is such that its general substitution for potassium permanganate does not appear to be warranted at the present time.

From the viewpoint of simplicity, speed and precision the Volhard method appears to be preferable to the methods now used in the United States Pharmacopœia for the assay of calcium chloride and of calcium bromide.

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Adaptation of Assay Methods for Some N. F. Pastes*

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There are six pastes in the Sixth Edition of the *National Formulary* for which there are no assay requirements. Since these pastes are contained in an official book, it is important that standards be adopted for them, fixing definitely the content limits of their active ingredients.

In some cases the assay methods used for certain drugs and chemicals can be adapted for use in the assay of official preparations containing these ingredients. This appears to be especially feasible in the case of four of the six pastes referred to.

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