A NOTE ON THE TITRATION OF CAFFEINE IN PHARMACEUTICAL PREPARATIONS

By A. Anastasi, U. Gallo and L. Novacic
Laboratorio Controllo Stabilimento Farmitalia–Milano

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Caffeine is a largely used drug and its quantitative determination has been the subject of a large number of studies. As a purine base, it can be determined by different classical methods; Wallrabe's method of determination by weighing the precipitated periodide[1], and the iodimetric method of Wolff and Blister[2]. However, due to the fact that caffeine is seldom used alone in pharmaceutical preparations but is usually mixed with other drugs which may interfere in the usual analytical methods, titration in non-aqueous solvents has been considered.

Fritz[3] suggested a method of anhydrous titration with 0·1 N perchloric acid in glacial acetic acid, using as solvents chlorobenzene, acetonitrile, nitrobenzene, and other organic compounds. He reported that the method is applicable for the determination of caffeine; the only detail given is that caffeine gives an insoluble perchlorate and therefore the change of colour of the indicator is clearly seen.

Pifer and Wollish[4] reported a potentiometric method and Gautier and Pellerin[5] underlined the difficulties met during their titration of caffeine in an anhydrous medium. Poulos[6] reporting on the determination of theobromine in mixed solvents, such as acetic acid and carbon tetrachloride, mentions being unable, after many trials, to obtain satisfactory results with caffeine.

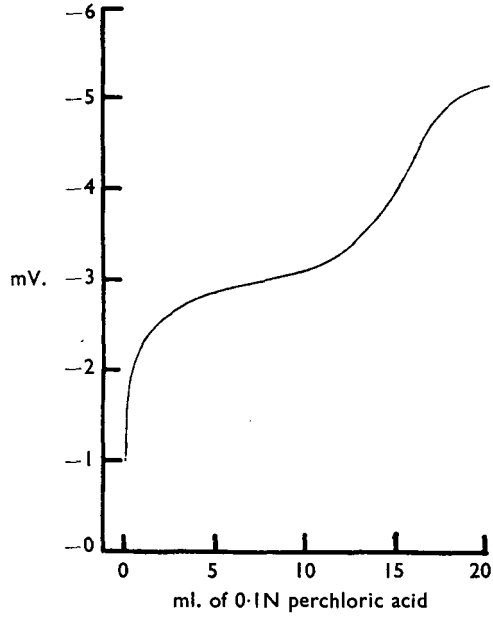

Fig. 1. Potentiometric titration of caffeine in acetic acid with perchloric acid (after Ekeblad *loc. cit.*).

Examination of the curve obtained by Ekeblad[7] during the potentiometric titration of caffeine in acetic acid with acetous perchloric acid 0·1 N shows that the end-point of the reaction is not clear. (Fig. 1). Pernarowsky[8] titrated with 0·1 N perchloric acid in anhydrous acetone using a mixture of chloroform and benzene as solvent and a 1 per cent. solution of α-naphtholbenzeine in acetic acid, as indicator.

On account of the importance of the problem and the possibility of introducing into the Pharmacopœias the method of titration in anhydrous media, we thought it worth while to investigate the various methods of analysis. We first confirmed the potentiometric data of Ekeblad (Fig. 2) on the titration of caffeine solution in anhydrous acetic acid with 0·1 N acetous perchloric acid, simultaneously following the colour change of crystal violet.

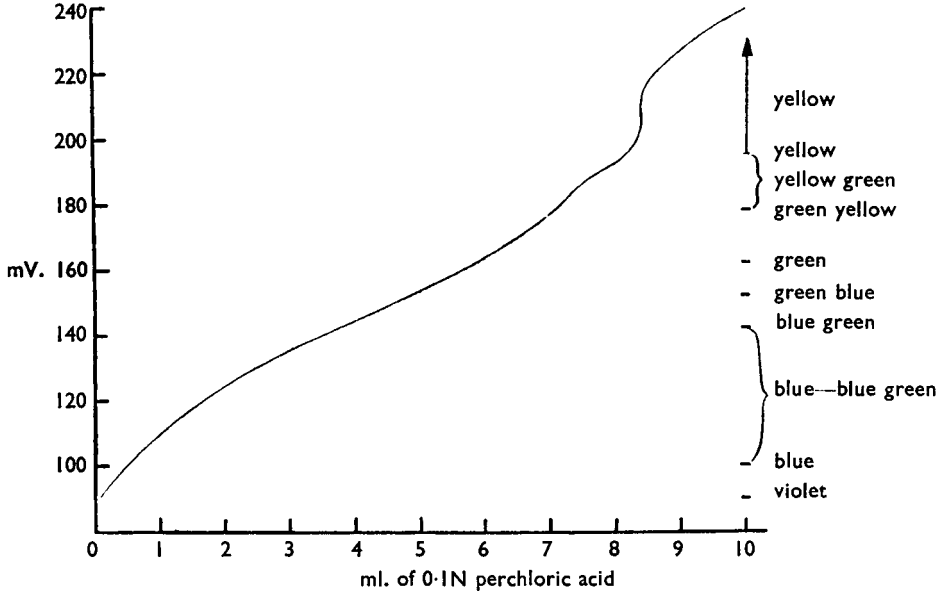

FIG. 2. Colour change of crystal violet during the titration of caffeine in acetic acid with perchloric acid.

It is clearly seen that an indicator, whose end-point is reached long before the equivalence point, cannot therefore be used.

It can also be clearly seen that it is difficult to locate exactly the end-point of the titration, in the potentiometric curve, on account of its gradual slope and the small magnitude of the potential break at the end-point.

To obviate these difficulties we tried dissolving the base in other solvents such as dioxane, acetone and chloroform, pure or mixed together, and titrating with a solution of perchloric acid in anhydrous acetic acid or in dioxane, without, however, obtaining better results.

We considered the use of acetic acid as the solvent of the substance to be titrated, and of perchloric acid, to be necessary for the determination of caffeine in tablets in the presence of acetylsalicylic acid in order to obviate tedious separations which constitute an obstacle in the routine analysis of products manufactured on a large scale. We therefore made experiments to see whether a change in the experimental conditions would improve the results already obtained with this solvent. We found that mixing acetic acid with other solvents such as dioxan or chloroform did

not produce any advantage, but adding an excess of acetic anhydride allows the potentiometric titration to proceed with more precision, by producing a sharper potential break with a greater slope.

In these conditions the movement of the galvanometer needle is rather slow and it is better to wait a few minutes before reading. The greater

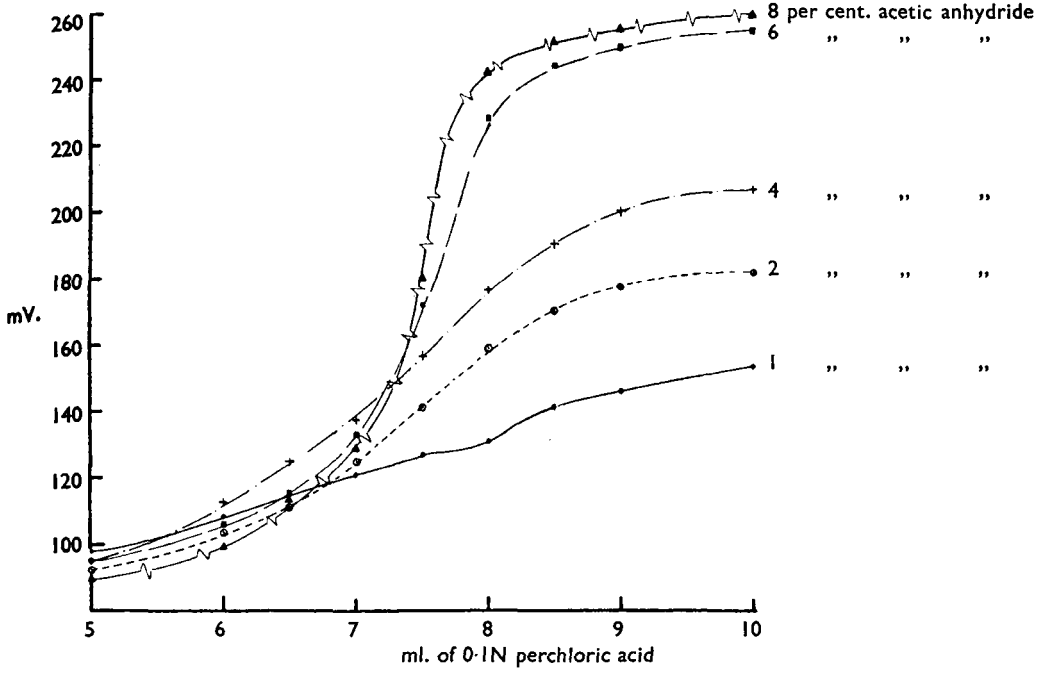

FIG. 3. The effect of increasing the amount of acetic anhydride on the precision of the potentiometric titration.

precision of the method due to more exact determination of the equivalance point is clearly seen from Figure 3. The best results are obtained with a quantity of acetic anhydride corresponding to 8 per cent. of the acetic acid used. This method which has been standardised with pure caffeine, has been successfully used in the analysis of some specialities and galenical products containing caffeine mixed with acetylsalicylic acid.

EXPERIMENTAL

Reagents

(*a*) Anhydrous acetic acid, reagent grade.
(*b*) Acetic anhydride, reagent grade.
(*c*) 0·1 N perchloric acid in anhydrous acetic acid. (For the preparation and standardisation of these reagents see Gallo and Ventura[9]).

Procedure

(1) Caffeine (0·15 to 0·20 g.) is added to a mixture of acetic acid (50 ml.) and acetic anhydride (4 ml.) and the whole is stirred electromagnetically, until a solution is obtained which is potentiometrically titrated with perchloric acid using glass-calomel electrodes.

Each ml. of 0·1 N perchloric acid is equivalent to 0·01942 g. of $C_8H_{10}O_2N_4$.

(2) Samples of tablets of 3 different pharmaceutical preparations were examined. 10 tablets are powdered and 2 g. of the powder is dispersed in a mixture of anhydrous acetic acid (50 ml.) and acetic anhydride (4 ml.); the above procedure is then followed.

The analytical data are reported in Tables I and II.

TABLE I

TITRATION OF PURE CAFFEINE

Weighed	Found	Error per cent.
0·1618	0·1621	+0·18
0·1743	0·1735	−0·46
0·1697	0·1713	+0·94
0·1625	0·1624	−0·07
0·1730	0·1724	−0·35
0·1690	0·1715	+1·47

TABLE II

TITRATION OF CAFFEINE IN TABLETS WITH ACETYLSALICYLIC ACID

PRODUCT A. Theoretical 8 per cent.		PRODUCT B. Theoretical 7·25 per cent.		PRODUCT C. Theoretical 6·5 per cent.	
Found		Found		Found	
7·95	7·82	7·40	7·15	6·48	6·51
8·10	7·95	7·27	7·25	6·52	6·43
8·02	7·94	7·10	7·37	6·45	
8·27	7·98				
8·12	7·99				
8·10					

DISCUSSION

The precision of the method, as is clearly seen from the results obtained, and its simplicity recommend it especially for the routine control of pharmaceutical specialities (tablets, powders, capsules, etc.) containing caffeine, alone or mixed with substances having an acid character, such as acetylsalicylic acid.

A preliminary separation is however necessary when substances such as amidopyrine, ethylmorphine and similar substances having a basic character in acetic acid solution, are mixed with caffeine.

It is difficult to explain the better results obtained by adding acetic anhydride to the acetic acid used as solvent. It appears however clearly that the anhydride does not act as a dehydrator because:

(1) It has been found, according to the method of Karl Fischer, that the quantity of water present in the acetic acid used was not higher than 0·25 per cent. and would not require more than 1·3 per cent. of acetic anhydride.

(2) The caffeine used, being anhydrous, does not introduce water into the solution tested.

(3) Only a very slow reaction can take place between acetic anhydride and water at normal temperature; the solution must be brought to

boiling at least for a few minutes to complete it. Numerous tests were carried out, treating the boiling solution with different quantities of acetic anhydride in precisely the exact stoichiometric quantity or with a small or a large excess. It was observed that also in this case, good results are obtained only on adding 6 to 8 per cent. of acetic anhydride. The necessity of maintaining a constant temperature during the test in order to obtain repeatable results is also to be noted as heating would complicate the procedure.

Summary

1. A new potentiometric method for the titration in non aqueous solvents of caffeine, alone or mixed with acetylsalicylic acid, is suggested.

2. This method is based on the use of a mixture of acetic acid and 8 per cent. of acetic anhydride, as solvent, and acetous perchloric acid as the titrating solution.

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