THE APPLICATION OF TITRATION IN NON-AQUEOUS MEDIA TO PHARMACEUTICAL ANALYSIS

PART I. THE DETERMINATION OF ALKALI METAL SALTS OF ALIPHATIC AND AROMATIC ACIDS

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THE method of determination by titration in non-aqueous media of bases and acids which are too weak to be titrated in aqueous solution has been investigated and applied in analysis for many years.[1,2,3,4,5] It is only recently, however, that the method has received considerable attention, and it is now proving to be of wide applicability in the control of the purity of many diverse types of chemicals. Although many solvents have been used, glacial acetic acid has found the widest acceptance as a solvent for the titration of basic materials, and perchloric acid in glacial acetic acid has proved to be the most satisfactory titrant. This method allows not only of the titration of weak bases, but also of salts, because in many cases the anion is sufficiently basic under these conditions to give a good end-point.[6,7,8] It has recently been shown that hydrochlorides can also be titrated provided that mercuric acetate is added to the solution.[9] Titration in non-aqueous media does not require expensive equipment, and has been shown to be quick and accurate.[8,9,10] The completion of the titration can be determined either by the use of indicators or potentiometrically.

An examination of the B.P. and B.P.C. shows that many chemicals, at present being analysed by different procedures, some of which require a few hours to perform, could probably be analysed in non-aqueous media by a direct titration involving only a few minutes work. If this should prove to be possible, then the standardisation of the analytical procedures, and the simplicity, accuracy and speed of the method should be of great value in its application to pharmaceutical analysis, and this approach we have been investigating. Despite the fact that it has recently been demonstrated by other workers[8] that many of the compounds discussed in this communication can be titrated in non-aqueous media, we now present some of our results to show a comparison between the values obtained by this method and the values obtained by the procedure adopted in the B.P. and B.P.C., and to indicate the advantages and disadvantages associated with the method. We feel it necessary to place these results on record to emphasise the simplification of the B.P. and B.P.C. procedures which is possible. During the course of this work a number of publications have appeared showing the wide range of compounds, many being of pharmaceutical importance, which can be titrated in non-aqueous solvents.[9,11,12,13,14,15,16]

THEORY

By making use of the Brønsted-Lowry concept of acids and bases, the

titration of a base (B) in a solvent (SH) with an acid (HA) can be represented as follows:—

$$\begin{array}{rl} HA + SH \rightleftharpoons & SH_2^+ + A' \\ & \Updownarrow + B \\ BH^+ + SH + & A' \end{array}$$

If the reaction to BH^+ is to be complete (complete neutralisation) upon mixing one equivalent of base (B) and acid (HA), then B must be a stronger base than either SH or A′. For the titration of a very weak base in aqueous solution, the solvent ($SH = H_2O$) is too strong a proton acceptor, but it may be possible to titrate in glacial acetic acid (CH_3COOH) which has less tendency to accept a proton to become $CH_3COOH_2^+$. Thus titrations with perchloric acid of the base B in glacial acetic acid solution can be represented as follows:—

$$\begin{array}{rl} HClO_4 + CH_3COOH \rightleftharpoons & CH_3COOH_2^+ + ClO_4' \\ & \Updownarrow + B \\ BH^+ + CH_3COOH + & ClO_4' \end{array}$$

and so complete neutralisation of B to BH^+ becomes possible.

An aliphatic or aromatic carboxylic acid anion is also sufficiently basic to be titrated under these conditions because the equilibrium is considerably to the right in the following:—

$$RCOO' + CH_3COOH_2^+ \rightleftharpoons RCOOH + CH_3COOH$$

In the titration of hydrochlorides in glacial acetic acid,

$$BH^+ + Cl' + CH_3COOH_2^+ \rightleftharpoons BH^+ + HCl + CH_3COOH$$

the anion Cl′ is too weakly basic compared with CH_3COOH to result in a good end-point. However, by heating to remove HCl[17], or by adding mercuric acetate to remove the chloride anion as follows[9]:—

$$Hg(CH_3COO)_2 + 2Cl' \rightleftharpoons HgCl_2 + 2CH_3COO'$$

it is possible to obtain good results.

It is evident that the method therefore holds out considerable promise for the analysis of pharmaceutical substances because of the vast range of compounds which can be considered as falling within its scope.

Reagents, Solutions and Apparatus

Perchloric acid, Analar (72 per cent.).

Glacial acetic acid. Before use as a solvent it was treated with the theoretical amount of acetic anhydride to render it anhydrous.

Acetic anhydride. Redistilled before use.

Potassium hydrogen phthalate, Analar.

Crystal violet indicator solution (0.5 g. of crystal violet in 100 ml. of anhydrous acetic acid).

Standard solution of perchloric acid (0·1N). Perchloric acid (20·5 ml.) was added slowly, with stirring, to approximately 2000 ml. of anhydrous acetic acid in a large flask cooled in ice. Then acetic anhydride (50·5 ml.) was slowly added to react with the water in the perchloric acid, and the solution made up to approximately 2500 ml. with anhydrous acetic acid.

The solution was allowed to stand 24 hours before use, and then standardised against potassium hydrogen phthalate both potentiometrically and by using crystal violet indicator solution (2 drops).

Potentiometric titrations were carried out using a Morton D.C. Amplifier,[18] calibrated in *p*H and millivolt readings, and a glass electrode and a saturated calomel electrode (sleeve or fibre type). A mechanical stirrer was used.

Consideration of Various Factors Associated with the Titrations

In this paper we are dealing only with titrations with perchloric acid using glacial acetic acid as solvent.

Standardisation. Diphenylguanidine, sodium carbonate, and potassium hydrogen phthalate have been used by different workers as basic standards, and Seaman and Allen[10] studied the last standard in detail. We have found potassium hydrogen phthalate to be a reliable standard. The standardisation was performed both potentiometrically and using crystal violet as indicator, the indicator change at the end-point being blue→blue-green as shown in Figure 1.

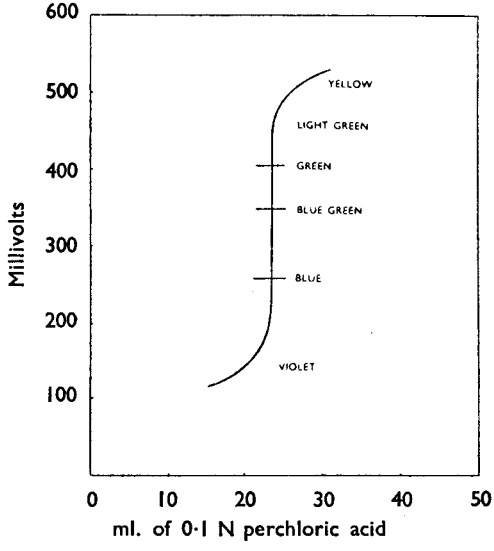

Fig. 1. The titration of potassium hydrogen phthalate using crystal violet as indicator.

Effect of Water-content upon the End-point. The results used in the preparation of the curves in Figure 2 were obtained with known percentages of water in solutions of 0·5 g. of potassium hydrogen phthalate in 50 ml. of acetic acid solution. The standard solution of perchloric acid was water-free. These results demonstrate that the presence of water must be avoided. A small percentage of water, even less than 1 per cent., leads to a slight flattening of the titration curve. The sharpness of the indicator end-point is impaired by 1 per cent. of water, and larger amounts of water ruin the end-point completely. The presence of excess of acetic anhydride has no effect upon the potentiometric titration or upon the indicator end-point. Consequently we have used an excess of 1 per cent. of acetic anhydride in all the acetic acid used in subsequent work to obviate the necessity of taking any precautions to exclude atmospheric moisture.

Effect of Temperature. One of the disadvantages associated with titration in glacial acetic acid, and with non-aqueous solvents in general, is the rather large coefficient of expansion of these solvents. Seaman and

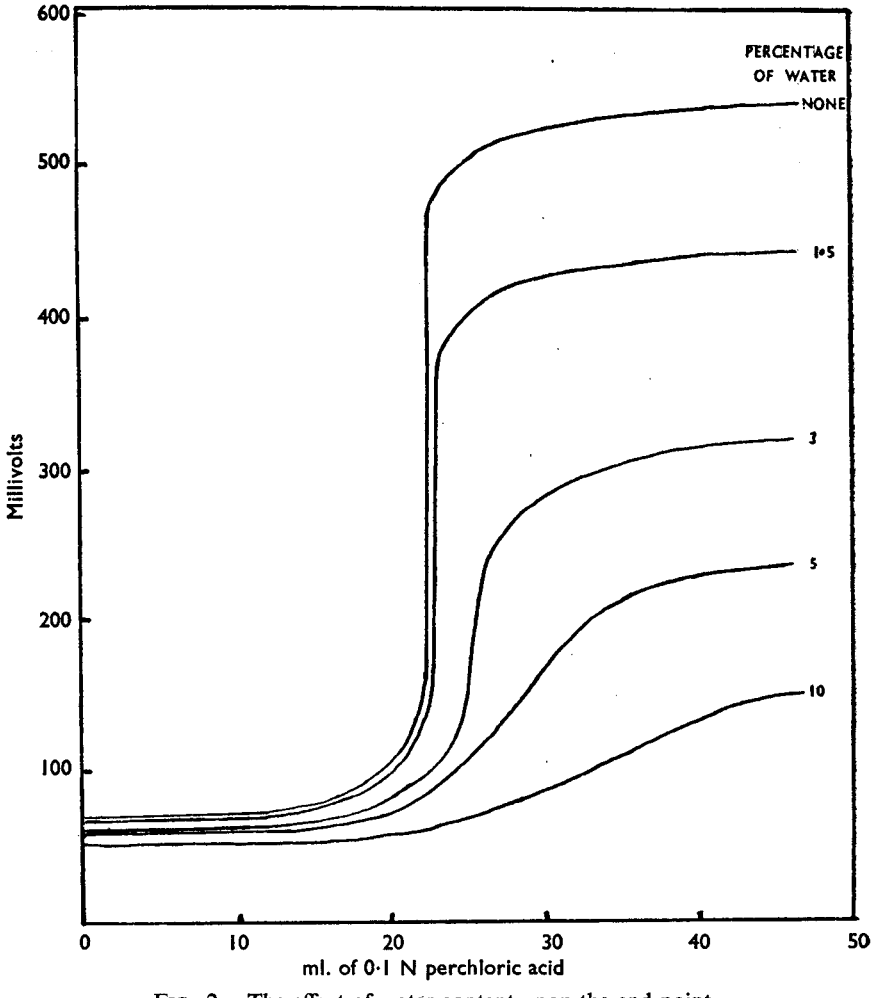

FIG. 2. The effect of water-content upon the end-point.

Allen[10] applied a factor of 0·11 per cent. per ° C. to the observed volumes of titrating solution, because the coefficient of expansion of glacial acetic acid is 0·0011 per ° C. We have determined the volumes of perchloric acid solution (0·1N) required at different room temperatures by 0·5 g. of potassium hydrogen phthalate dissolved in acetic acid (50 ml.), both the solution and the titrant being at room temperature before the commencement of the titration. The results are shown graphically in Figure 3 which indicates that a correction of 0·11 per cent. per ° C. is required. Thus, for accurate work, the perchloric acid must be standardised and used at the same constant temperature, or the burette readings must be multiplied by $1 - (n \times 0{\cdot}0011)$ if the temperature is above the standardisation temperature, and $1 + (n \times 0{\cdot}0011)$ if below, where n is the difference in ° C. from the standardisation temperature.

Potentiometric or Indicator End-point? The use of the Morton D.C. Amplifier[18] makes it possible to perform potentiometric titrations in a few minutes. However, because we consider it desirable to make the titration method applicable to general pharmaceutical analysis, without having to resort to instruments, we are attempting to find suitable indicators for the proposed analyses. It has been pointed out previously[10] that the slope of the curve at the end-point, and the colour change of crystal violet indicator at the end-point, are not only influenced by the strength of the base being titrated, but possibly by the concentration and nature of the ions in solution at this point.

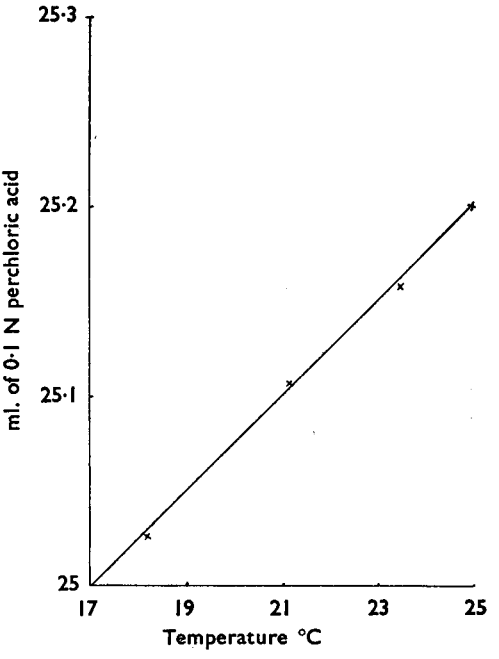

FIG. 3. The effect of temperature.

THE DETERMINATION OF ALKALI METAL SALTS OF ALIPHATIC AND AROMATIC CARBOXYLIC ACIDS OF THE B.P. AND B.P.C.

It has been shown[6,8] that salts of this type can be titrated in non-aqueous media. In the B.P. and B.P.C. are found three different procedures for the analysis of these substances, namely:—

(1) Ignition to alkali metal carbonate, addition of excess of 0·5N sulphuric acid, filtration and back titration with 0·5N sodium hydroxide, e.g., sodium potassium tartrate.
(2) Titration in almost boiling solution with 0·2N sodium hydroxide, e.g., potassium acid tartrate.
(3) Titration with 0·5N sulphuric acid, involving shaking with ether to remove most of the aromatic acid from the aqueous phase before a correct end-point can be obtained, e.g., sodium salicylate.

We suggest a simple standard analytical procedure for these substances as outlined later.

In Table I we present the mean results of analyses using the official procedures, and titration with perchloric acid in glacial acetic using the potentiometric and indicator methods.

The determinations were made on chemicals supplied as of B.P. or B.P.C. quality. The aqueous standard solutions, and the perchloric acid

TABLE I

Chemical	Determined purity percentage		
	Official method	Potentiometric method	Indicator method
Lithium citrate	99·40	99·56	99·52
Lithium salicylate	98·79	98·95	98·86
Potassium acetate	99·86	99·95	99·92
Potassium citrate	99·94	99·93	99·92
Potassium tartrate.. ..	100·16	99·97	99·95
Potassium acid tartrate ..	99·95	99·80	99·80
Sodium acetate	99·93	99·90	99·89
Sodium benzoate	99·83	99·92	99·90
Sodium citrate	99·64	99·75	99·68
Sodium acid citrate ..	100·04	99·93	99·90
Sodium potassium tartrate	100·3	100·2	100·2
Sodium salicylate ..	99·91	99·91	99·88

solutions in anhydrous acetic acid, were standardised against the same sample of potassium hydrogen phthalate. Many titrations were performed on the above salts in anhydrous acetic acid containing 1 per cent. of acetic anhydride, and the results indicated a reproducibility of ± 0·15 per cent. on a 25 ml. titration using either the potentiometric or indicator method.

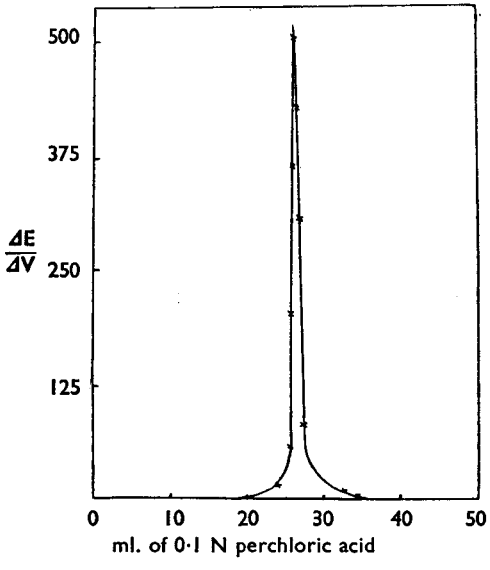

FIG. 4. A typical differential titration curve of alkali metal salts of aliphatic and aromatic carboxylic acids.

Potentiometric Titrations. Sufficient of the salt, to give a titration of approximately 25 ml. was dissolved in 50 ml. of anhydrous acetic acid. The change at the end-point was very sharp indeed in all cases, even when 0·01N perchloric acid solution was used as titrant. Figure 4 is a typical differential titration curve. In some titrations 2 drops of crystal violet indicator solution were added in order to observe the colour changes in the vicinity of the end-point. The millivolt readings recorded in the figures are meter readings (uncorrected).

Indicator Colour Changes. The colours near the end-point were affected by the type of cation present. For instance, the potassium salt produced a different colour from that of the corresponding sodium and lithium salt under comparable conditions, this fact being portrayed on the potentiometric curves in Figure 5. This may be connected with the fact that potassium perchlorate precipitates during the titration, whereas lithium and sodium perchlorates do not. When both sodium and potassium ions are present, the colour changes represent the mean of the changes produced

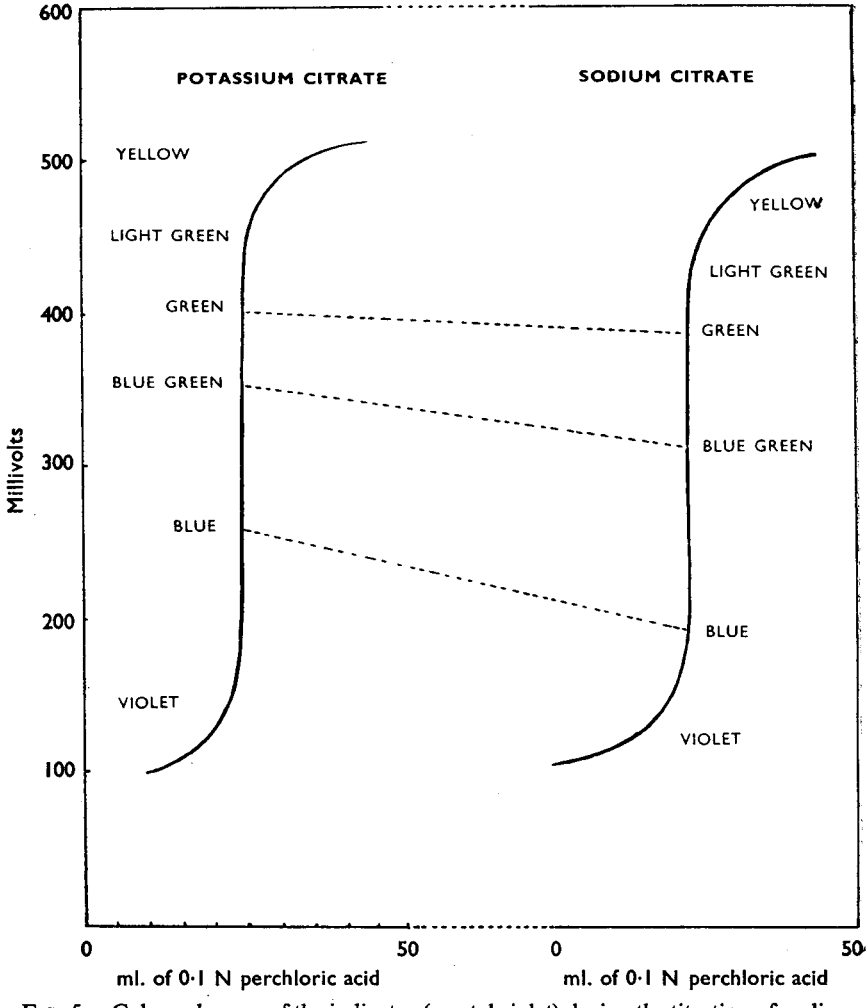

FIG. 5. Colour changes of the indicator (crystal violet) during the titration of sodium and potassium salts of organic carboxylic acids.

by these ions alone. However, in the determination of all the above salts, the end-point may be taken as the colour change from blue to blue-green, which is a sharp colour change. In fact, using sufficient salt dissolved in 50 ml. of anhydrous acetic acid to give a titration of 25 ml. of 0·1N perchloric acid solution a volume of 0·1 ml. of titrant is sufficient to change the colour from the last shade of blue to the full green.

Solution of the Salts. Sufficient of the salts could be dissolved in 50 ml. of anhydrous acetic acid to give a titration figure of 20 to 25 ml. of 0·1N perchloric acid, with the exception of the tartrates. Solution was affected in some cases by heating, with subsequent cooling before the titration. Too vigorous heating tended to cause charring in some cases. For the tartrates, more dilute solutions had to be employed, and 0·01N perchloric

acid was used as titrant. There is not sufficient water in the water of crystallisation of the salts to affect the end-point, and even if large percentages are present, the water may be removed prior to the titration by heating with glacial acetic acid containing excess acetic anhydride.

We consider the method of titration with perchloric acid in anhydrous acetic acid to offer considerable advantages over the official methods used for the determination of the salts mentioned in this communication, because of its speed, simplicity and standardisation of procedure without any loss of accuracy. Further communications will show its application to other groups of pharmaceutical substances. The major disadvantage is the effect of change of temperature upon the observed results, but a correction factor can readily be applied.

Recommended General Procedure

1. Use sufficient acetic anhydride to leave a 1 per cent. excess in the anhydrous acetic acid.

2. Record the room temperature at the time of standardisation of the perchloric acid solution and at the time of its use for determinations, and apply a correction factor.

3. For the salts (except tartrates) mentioned in this communication, weigh sufficient of the sample to give a titration of approximately 25 ml. of 0·1N perchloric acid, and dissolve in 50 ml. of anhydrous acetic acid, by the use of gentle heat if necessary. Cool to room temperature, add 2 drops of crystal violet indicator solution and titrate, taking the colour change from blue to blue-green as the end-point.

4. For tartrates, use 0·01N perchloric acid and proceed as above.

We have applied the general procedure to other alkali metal salts of organic acids such as sodium alginate, sodium glycerophosphate, sodium lauryl sulphate etc., with success. Although some of these substances are not pure material, and other analytical data will be required for the control of their purity, yet to specify a minimum figure for a determination in a non-aqueous medium such as outlined above, would certainly be of advantage.

Summary

1. Various factors concerned with titrations in non-aqueous media are examined, and the advantages and disadvantages of the method in respect to its application to the analysis of pharmaceutical substances are considered.

2. Comparative results are quoted for the determinations of alkali metal salts of aliphatic and aromatic carboxylic acids using the B.P. and B.P.C. methods, a potentiometric method, and an indicator method.

3. A general indicator method suitable for routine analysis is recommended.

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