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Short Communication

Determination of halide acid salts of organic bases and quaternary ammonium compounds by titration

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Introduction

It is the policy of the Commission of the European Pharmacopoeia to avoid, whenever possible, the use of mutagens, carcinogens and environmentally toxic substances as reagents in the monographs of the European Pharmacopoeia. For many years the determination of the halide acid salts of organic bases and quaternary ammonium compounds has been accomplished in many pharmacopoeias by perchloric acid titration after the addition of mercuric acetate according to the method first described by Pifer and Wollish [1]. Therefore, substances subject of already published monographs using this method of determination, and like substances still under study, have been determined by a number of other procedures which may be suitable as replacement methods. Alteration of the medium employed for the perchloric acid titration from glacial acetic acid to acetic anhydride such that the dissociation constants were altered sufficiently to permit the titration of the strong halide acids with perchloric acid has been described [2–6] as has the replacement of mercuric acetate by bismuth nitrate [7]. Another approach is to dissolve the salt in an alcoholic medium and titrate with sodium hydroxide solution. Some recently published monographs of the European Pharmacopoeia (Table 1) include this type of titration.

The reactions are thought to proceed in the following manner:

(a) *Perchloric acid titration in glacial acetic acid in the presence of mercuric acetate*

$$2B\ HCl + Hg(CH_3COO)_2 \rightarrow HgCl_2 + 2B\ CH_3COOH$$

$$B\ CH_3COOH \rightarrow BH^+ + CH_3COO^-$$

$$CH_3COO^- + HClO_4 \rightarrow CH_3COOH + ClO_4^-$$

where B represents the base.

Table 1
Substances included in the European Pharmacopoeia which are determined by titration with sodium hydroxide in an alcoholic medium

Substance	European pharmacopoeia monograph
Amantadine HCl	463
Amitriptyline HCl	464
Chlorpromazine HCl	475
Clonidine HCl	477
Desipramine HCl	481
Levomepromazine HCl	505
Bupivicaine HCl	541
Propranolol HCl	568

(b) *Perchloric acid titration in acetic anhydride*

$(CH_3CO)_2O \rightleftarrows CH_3CO^+ + CH_3COO^-$

$B\ HCl + CH_3CO^+ + CH_3COO^- \leftrightarrow B\ CH_3COOH + CH_3COCl$

$BCH_3COOH \rightarrow BH^+ + CH_3COO^-$

$CH_3COO^- + HClO_4 \rightarrow CH_3COOH + ClO_4^-$

(c) *Perchloric acid titration in glacial acetic acid/dioxan in the presence of bismuth nitrate*

$3BHCl + Bi(NO_3)_3 \rightarrow BH^+(NO_3)^-.\ BiCl_3 + 2BH^+(NO_3)^-$

$BH^+(NO_3)^-.\ Bi\ Cl_3 + 2\ BH^+\ (NO_3)^- + 3HClO_4 \rightarrow BH^+(ClO_4)^-.\ Bi\ Cl_3 + 2\ BH^+\ (ClO_4)^- + 3\ HNO_3$

A number of proposed and existing monographs of the European Pharmacopoeia has been examined with a view to the possible replacement of the perchloric acid titration in the presence of mercuric acetate with another titration method less environmentally damaging.

Experimental

Reagents

All solvents and reagents were of analytical grade supplied by Merck (Darmstadt).

Apparatus

The titration assembly consisted of a research pH-meter, PHM64, an autoburette ABU 80, a servograph recorder REC80 with the titrimetric module REA 160 and derivatization module REA 260 (all from Radiometer, Copenhagen). The electrodes employed were a calomel, containing a saturated solution of lithium chloride in alcohol, (K9040, Radiometer) and a glass electrode (G 0204B, Radiometer).

Methods

(a) *Titration by perchloric acid after addition of mercuric acetate.* This method was carried out as described by the European Pharmacopoeia [8].

(b) *Perchloric acid titration with acetic anhydride as solvent.* Between 50–100 mg of the substance were weighed into the titration vessel and dissolved, with the aid of heat if necessary, in 40 ml of acetic anhydride. A few drops of 0.5% solution of malachite green in acetic anhydride were added and the solution was titrated with 0.1 N perchloric acid

(end-point, blue to yellow). The titration was also carried out with potentiometric detection of the end-point.

(c) *Titration with perchloric acid after addition of bismuth nitrate.* About 50–100 mg of the substance were weighed into a titration vessel and dissolved, with the aid of heat if necessary, in 40 ml of a mixture of glacial acetic acid and dioxan (1:1). To this 2.5 ml of a 5% solution of bismuth nitrate in glacial acetic acid was added and titrated with 0.1 N perchloric acid. The end-point was determined potentiometrically.

(d) *Sodium hydroxide titration in an alcoholic medium.* About 150 mg of the substance were weighed into a titration vessel and dissolved in 30 ml of alcohol. To this, 5.0 ml of 0.01 N hydrochloric acid was added and titrated potentiometrically with 0.1 N sodium hydroxide aqueous solution. The volume was read between the two points of inflexion on the recorded titration curve.

Results and Discussion

Quaternary ammonium compounds cannot be titrated with sodium hydroxide in an alcoholic medium so these substances were titrated with perchloric acid in acetic anhydride medium and also by the replacement of mercuric acetate with bismuth nitrate. It has already been shown that halide salts of phenothiazines can be directly titrated with perchloric acid, with acetic anhydride as solvent [2–5] and it has been indicated that this method is suitable for alkaloids [6]. Japanese workers have shown that mercuric acetate can be replaced by bismuth nitrate [7]. Several quaternary ammonium compounds were examined by these methods, and the results were compared to those obtained by Volhard's method and perchloric acid–mercuric acetate titration (Table 2). It can be seen that the results obtained for all seven quaternary ammonium compounds examined, which are already subject to a monograph (actual or proposed), by the different methods were in good agreement, except for the titration in the presence of bismuth nitrate where the titration could not be accomplished in all cases. Of the methods examined, the titration in the presence of bismuth nitrate exhibited the largest relative standard deviation (RSD). Titration curves of methylatropine bromide are shown in Fig. 1 from which it seems that the potential jump at the end-point is greatest for the titration in

Table 2
Determination of quaternary ammonium halide salts

Substance	Mercuric acetate–perchloric acid	Bismuth nitrate–perchloric acid	Acetic anhydride perchloric acid	Volhard's method
Butylhyoscine bromide	—	—	99.4*	99.8
Gallamine triethiodide	98.8	D	100.0*	100.0 (0.54)
Methylhomatropine bromide	100.3	—	100.0*	—
Methylatropine bromide	99.4 (0.11)	100.3 (0.9)	99.3 (0.67)	100.2 (0.18)
Pancuronium bromide	90.3	PPT	90.9	90.1 (0.57)
Propantheline bromide	99.7	99.9	99.5	99.0
Suxamethonium chloride	99.6	PPT	99.7	99.3 (0.20)

RSDs (n = 5) are given in parentheses, otherwise mean of duplicates.
D, solution discoloured, probable degradation.
PPT, precipitate formed.
*Substance dissolves only during titration.

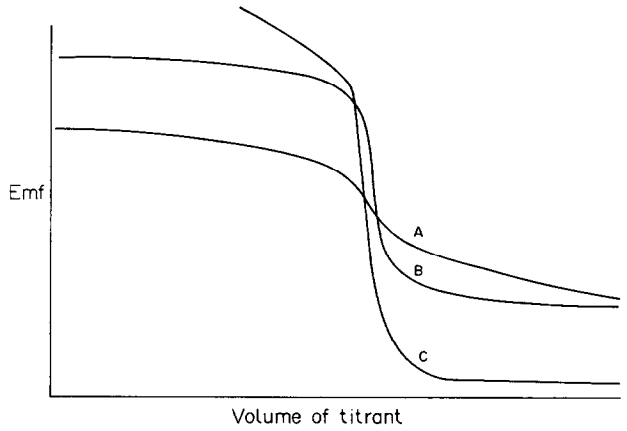

Figure 1
Potentiometric titration curves of methylatropine bromide.

acetic anhydride (C), and is rather weak for the titration in the presence of bismuth nitrate (A). It would seem that the method of choice for the titrimetric assay of quaternary ammonium compounds is titration with perchloric acid in acetic anhydride medium which can be carried out using an indicator (malachite green) or potentiometrically. Better repeatability was achieved by the latter method for detecting the end-point (RSD 0.31% compared with 0.67%).

The difficulties observed in the titration of quaternary ammonium compounds when using bismuth nitrate were also apparent with the halide acid salts of organic bases, and not all the salts examined could be titrated due to precipitation of the complex. When this method was applied successfully to a salt (e.g. amiodarone hydrochloride) the RSD was inferior to those of the other methods applied (Table 3). Titration of salts in a medium of acetic anhydride by perchloric acid was similarly not universally applicable. These procedures were considererd unsuitable as generally acceptable replacement methods, due to the insolubility of the substances in acetic anhydride and precipitation of the bismuth complex. It has been suggested that adding chloromethane to the acetic anhydride may overcome the problem of solubility but such a strategy proved to be unsuccessful. Similarly, altering the ratios of dioxan and glacial acetic acid had little effect on the solubility of the complexes examined.

No such problems of solubility were encountered when titration was carried out with sodium hydroxide solution with alcohol as the solvent. Direct titration of the salts of organic bases was considered inappropriate since some salts are obtained by the action of gaseous acid on the base so that a small amount of excess halide acid may be present and the final product may give falsely high results. By adding a small amount of acid to the titration medium, recording the titration curve and measuring the volume of titrant between the two inflexion points, such an error can be avoided. This, therefore, was the method chosen for examination, and the results are given in Table 3.

In conclusion, it has been shown that other methods may be successfully employed to replace the non-aqueous titration of halide salts of organic bases which employs mercuric acetate as the complexing agent, but of the methods employed for the substances examined, only the alkali titration method appears to be generally satisfactory. As

Table 3
Determination of halide acid salts of organic bases

Substance	Method			
	Perchloric acid–$HgCl_2$ (a)	Perchloric acid–acetic anhydride (b)	Perchloric acid–Bi $(NO_3)_3$ (c)	Sodium hydroxide (d)
Amiodarone HCl	100.5 (0.33)	99.8 (0.52)	99.5 (0.99)	100.4 (0.44)
Chlordiazepoxide HCl	99.4	NA	N/A	99.2
Diphenhydramine HCl	100.3	100.3	N/A	100.3 (0.10)
Emetine HCl	99.7 (0.28)	N/A	N/E	99.5 (0.31)
Ephedrine HCl	100.5	N/A	N/E	101.2
Ethambutol HCl	99.7 (0.41)	N/E	N/E	99.8 (0.28)
Homatropine HBr	100.8	N/A	N/E	101.5
Hyoscine HBr	99.6 (0.24)	100.0	N/E	100.2 (0.39)
Imipramine HCl	100.1 (0.16)	100.3	N/E	100.5 (0.15)
Lidocaine HCl	100.5 (0.26)	100.0	N/E	100.6 (0.15)
Naloxone HCl	100.0 (0.26)	N/E	N/E	100.3 (0.24)
Oxprenolol HCl	100.3 (0.73)	N/A	100.1	100.4 (0.31)
Phenylephrine HCl	99.6 (0.38)	N/A	99.9	99.6 (0.39)
Pilocarpine HCl	99.9 (0.66)	99.7	N/A	100.4 (0.22)
Pyridoxine HCl	100.5 (0.47)	N/A	N/E	99.2 (0.13)
Tetracaine HCl	99.9 (0.20)	99.9	N/E	100.8 (0.20)
Thiamine HCl	99.6	N/A	N/A	101.5
Trifluoperazine HCl	100.5 (0.21)	100.0	N/E	99.4 (0.25)

N/A, method not applicable under the given conditions due to insolubility (method b) or precipitation (method c).
N/E, not examined.
RSDs (n = 5) are given in parentheses, otherwise means of duplicates.

concerns the quaternary ammonium compounds, non-aqueous titration with acetic anhydride as solvent seems to offer a viable alternative to the use of mercuric acetate, albeit only a small number of such substances were examined.

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