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## Review

### A Review On Non Aqueous Titrations Used In Assay Of Various Drugs

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	<b>Abstract</b>
Published on: 8 May 2024	<p>Various titrimetric methods are available for estimation of acids and bases, except very weak acids and bases which can only be estimated by non-aqueous methods of titration or potentiometry. Non aqueous means of titrimetric analysis involves the conversion of weak acid to strong acid or weak base to strong base by exerting the differentiating effect when dissolved in basic or acidic solvents. The Non aqueous titration method was carried out using 0.1 N Perchloric acid. The end point of the titrations is determined via non aqueous indicator solutions such as crystal violet, Nile blue A, 1-Naphtholbenzein, oracet blue B.</p>
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 <a href="https://creativecommons.org/licenses/by/4.0/">Creative Commons Attribution 4.0 International License.</a>	<p><b>Keywords:</b> Non-aqueous titration, weak acid, weak base, crystal violet, perchloric acid, alkalimetry, acidimetry, solubility.</p>

## INTRODUCTION

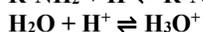
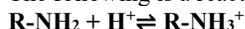
For decades, acids have been described as bitter-tasting substances that turn the cyanide solution/paper red. Similarly, the bases are bitter-tasting substances and the colored toner/paper is red. Acids and bases dissociate and form their corresponding ions in solution. Non-aqueous titration refers to a form of titration in which the analyte is dissolved in a solvent that no longer contains water. This method is crucial for determining the pharmacopoeia. It is a very simple, qualitative and very accurate method. Organic acids and bases that are insoluble in water are soluble in non-aqueous solutions. It is useful for titrating very weak acids and bases when water cannot be used. It can also be used to titrate an acidic mixture. A non-aqueous titration is the titration of a solute in a solvent other than water. Non-aqueous titrations are those in which the titration of weakly acidic or basic substances is carried out using non-aqueous solutions to achieve a steep dropping point. Most titrations are performed in an aqueous medium in the same way that water is used as a solvent. Problems can arise when the precursor is insoluble in water or the reactant is reactive with water or the analyte (sample) is both an overly sensitive acid and an overly sensitive base. Acids or bases that are too sensitive cannot be titrated in aqueous solution due to the amphoteric conductivity of water. So water competes with the template if it is a very sensitive acid or base. A simple answer to that problem is to make water the solvent with some other non-aqueous solvent, so this kind of titration is called "non-aqueous titration".<sup>(1)</sup>

25 years ago Consant, Hall and Werner showed that many substances with little or no basic properties in water behave as relatively strong bases in glacial acetic acid and can be quantitatively determined in this solvent by titration with a strong mineral acid. Unfortunately, the potential of this method and its clear advantages over many volume measurement methods performed in the aquatic environment have not been realized. In just the last two years, anhydrous titrimetry has found a significant number of new applications and has become a valuable broad-spectrum analytical method. The studies described in this article show that the quantitative evaluation of narcotic substances and alkaloids, which are very different in terms of structure and degree of alkalinity, can also be achieved by anhydrous titration, during which acetic acid is used as a solvent and perchloric acid. is used as a titrator.<sup>(2,3)</sup>

### Theory behind Non-Aqueous Titrations

The need for a non-aqueous titration arises because water behaves as both a weak acid and a weak base. Thus, when other weak acids or weak bases are dissolved in it, water effectively competes for the proton donor to accept the proton. However, the exact end point cannot be obtained during the titration. This method is useful for the correct titration of weak acids and bases and the ability of an anhydrous solvent to dissolve natural compounds. Many reactions in anhydrous titration techniques can be defined using the Bronsted-Lowry theory and its definition of acids and bases. Basically, acids can be thought of as proton donors, while bases can be thought of as proton acceptors. Theory why anhydrous titration is necessary:

The following is a reaction in which water is not a suitable solvent



get the correct end point Hence the need for anhydrous titration.<sup>(4,5,6)</sup>

**Non-Aqueous Solvents:** Examples - benzene, toluene, carbon tetrachloride, chloroform, ethyl acetate, dioxane, etc. Solvents used in anhydrous titrations are known as non-aqueous solvents.

Selection of solvents for anhydrous titration:

**Solubility of the drug:** Weak acids or basic drugs must be soluble in solvents that must also mix with the titration.

**Nature of the drug:** The solvent is used according to the nature of the drug, whether it is a weak acid or a weak base.<sup>(7)</sup>

**Reactivity:** The solvent must not react with the drug. Four types of solvents are used in such titrations and these include:

**Aprotic solvents:** These are chemically inert materials including benzene, chloroform, etc. They are added to ionizing agents to reduce solvolysis of the neutralization product, leading to a sharpening of the endpoint.

Examples: benzene, toluene, carbon tetrachloride, chloroform, ethyl acetate, dioxan etc.

1. **Primary Solvents:** These solvents are acidic and readily donate protons. They are used to increase the basicity of weak acids and increase the strength of weak bases. Examples - sulphur, acetic acid and formic acid.
2. **Protophilic solvents:** These solvents are basic and accept protons. They react with acids and form solvated protons. Examples - liquid ammonia, amines ketone, pyridine, ethylenediamine and ethers.<sup>(8)</sup>
3. **Amphiprotic Solvents:** These consist of sites of each protogenic and protophilic solvent. Examples - contains alcohols and acetic acid.

### Types of non aqueous titrations

**Acidimetry:** It involves the quantitative determination of weak bases by anhydrous titration.

**Alkalimetry:** It involves the quantitative determination of weak acids by anhydrous titration.

## METHODS AND METHODOLOGY

### Alkalimetry

As basic solvents, pyridine and n-butylamine add an acidic character there, other widely used solvents are methanol, ethanol, acetone, methyl ketone, methyl isobutyl ketone. These substances can be analyzed with potassium, sodium or lithium methoxide prepared by dissolving the metal in toluene-methanol or tetrabutylammonium hydroxide solution in methanol. One disadvantage of using metal methoxides is the formation of gelatinous precipitates and their toxicity. To avoid this problem, tetrabutylammonium hydroxide was introduced because titrated benzoic acid is a widely used basic standard in non-aqueous alkali measurement, while tubulin blue and azo violet are visual indicators. In the absence of a visual indicator, the endpoint of the titration is determined by potentiometry.<sup>(9,10)</sup>

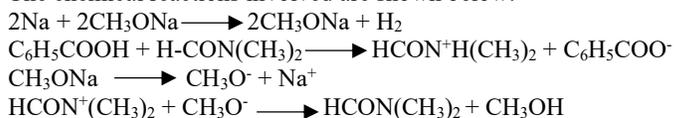
**Estimation of acids****Preparation of 0.1N Alkali Methoxide**

2.3-2.6 g of freshly cut sodium or 0.7-1.0 g of lithium with absolute methanol should be washed. To an ice-cold mixture of 50 ml of toluene and 40 ml of absolute methanol, the metal must be added with constant stirring. When the metal is dissolved, add methanol to homogenize the solution, then add toluene until the solution is cloudy. Continue adding methanol and toluene alternately until the final volume is 1 liter. Mix the solution in a pyrex or polyethylene bottle and standardize it against benzoic acid.

**Standardization of 0.1N Alkali Methoxide**

An accurately weighed 200-300 mg of benzoic acid is dissolved in 25 ml of N,N-dimethylformamide (DMF) in an Erlenmeyer flask. A few drops of thymol blue are added, a stream of nitrogen is introduced and titrated with alkaline methoxide solution until the color of the solution becomes blue. Take at least three uniform readings and a blank using 25 mL of DMF.

The chemical reactions involved are shown below:

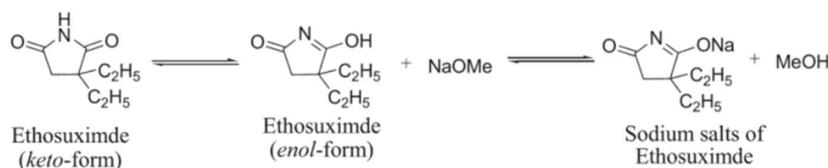
**net reaction**

Therefore, 1ml 0.1N lithium methoxide = 0.01221 g of benzoic acid.

**Assay of ethosuximide**

**Materials Required:** Ethosuximide: 0.2 g; dimethylformamide: 50 ml; azo-violet (0.1% w/v in DMF): 2 drops; sodium methoxide 0.1 N.

**Procedure:** About 0.2 g is accurately weighed, dissolved in 50 ml of dimethylformamide, 2 drops of azo violet solution are added and titrated with 0.1 N sodium methoxide to the deep blue endpoint. Precautions are taken to prevent absorption of carbon dioxide from the atmosphere. Run a blank configuration and make the necessary corrections. Each ml of 0.1 N sodium methoxide corresponds to 0.01412 g of C<sub>7</sub>H<sub>11</sub>NO<sub>2</sub>.



Therefore 0.01417 g C<sub>7</sub>H<sub>11</sub>NO<sub>2</sub> = 1 ml 0.1 N NaOMe.

**Preparation of 0.1N Tetrabutylammonium Hydroxide**

Dissolve 80 grams of accurately weighed tetrabutylammonium iodide (Bu<sub>4</sub>NI) in 180 mL of analytical reagent grade anhydrous methanol in a stoppered flask. Place the bottle in an ice bath, add 40 g of powdered silver rust and shake occasionally for one hour. The solution is filtered through a sintered glass crucible. Wash the bottle and residue three times with 50 ml of cold, dry benzene. The filtrate and washings are combined and diluted to 2 liters with dry benzene.

**Standardization 0.1N Tetrabutylammonium Hydroxide**

Weigh accurately 0.1 g of benzoic acid which has previously been dried at 100°C for 30 minutes and dissolve in 50 ml of analytical grade pyridine. Place the electrodes in the solution, start the mixer and adjust the reading on the millivolt scale to zero. Titrate potentiometrically with tetrabutylammonium hydroxide solution. Also prepare a millivolt balance according to the added titration volume.

For calculations,

Therefore, C<sub>6</sub>H<sub>5</sub>COOH = H = 1000 ml N or 0.01221 g C<sub>7</sub>H<sub>6</sub>O<sub>2</sub> = 1 ml of 0.1 N Bu<sub>4</sub>NI.

**Assay of chlorthalidone**

**Materials Required:** Chlorthalidone 0.3gr, pyridine (dehydrated) 50ml, 0.1 N tetrabutylammonium hydroxide.

**Procedure:**

Weigh accurately about 0.3 g and dissolve in 50 ml of dehydrated pyridine. Titrate with 0.1 N tetrabutylammonium hydroxide, determining the endpoint potentiometrically and protecting the solution and titrant from atmospheric carbon dioxide during the determination. Run a blank configuration and make the necessary corrections.

Therefore, Each ml of 0.1 N  $C_{16}H_{37}NO$  is  $\cong 0.03388$  g of  $C_{14}H_{11}ClN_2O_4$ .

**Table 1: Non - Aqueous titrations with perchloric acid using Mercuric Acetate and Different Indicators**

S.NO	Name Of Substance	Qty. Prescribed	Indicator Employed	Calculation
1	Amantadine hydrochloride	0.21 g	Crystal violet	Each ml of 0.1 M $HClO_4 \cong 0.01877$ g of $C_{10}H_{17}N.HCl$
2	Chlorpromazine hydrochloride	0.6 g	Methyl orange	Each mL of 0.1 M $HClO_4 \cong 0.3533G$ of $C_{17}H_{19}ClN_2S.HCl$
3	Clonidine Hydrochloride	0.4 g	1- Naphthol benzein	Each mL of 0.5 M $HClO_4 \cong 0.01333$ G OF $C_9H_9Cl_2N_3.HCl$
4	Cyproheptadiene hydrochloride	0.5 g	Crystal violet	Each mL of 0.1 M $HClO_4 \cong 0.0323g$ of $C_{21}H_{21}N. HCl$
5	Dehydroemetine hydrochloride	0.4 g	-do-	Each mL of of 0.1 M $HClO_4 \cong 0.02758G$ OF $C_{29}H_{38}N_2O_4.2HCl$
6	Dequalinium chloride	0.7 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.02918g$ of $C_{17}H_{21}NO.HCl$
7	Diphenhydramine Hydrochloride	0.75 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.02918$ g of $C_{17}H_{21}NO.HCl$
8	Ephedrine hydrochloride	0.5 g	-do-	Each mL of 0.1 M $HClO_4$ v $0.02017$ g of $C_{10}H_{15}NO.HCl$
9	Ethylmorphine Hydrochloride	0.3 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.03499$ g of $C_{19}H_{23}NO_3.HCl$
10	Fluphenazine Hydrochloride	0.6 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.02552$ g of $C_{22}H_{26}F_3N_3OS_2.HCl$
11	Imipramine Hydrochloride	0.5 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.03169$ g of $C_{19}H_{24}N_2.HCl$
12	Isoprenaline Hydrochloride	0.5 g	Crystal violet	Each mL of 0.1 M $HClO_4 \cong 0.2477$ g of $C_{11}H_{17}NO_3.HCl$
13	Lignocaine Hydrochloride	0.6 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.02708$ g of $C_{14}H_{22}N_2O.HCl$
14	Meclizine Hydrochloride	0.35 g	Quinaldine Red	Each mL of 0.1 M $HClO_4 \cong 0.02319$ g of $C_{25}H_{27}ClN_2.2 HCl$
15	Methadone Hydrochloride	0.5 g	Crystal Violet	Each mL of 0.1 M $HClO_4 \cong 0.03459$ g of $C_{21}H_{28}ClNO$
16	Methylamphetamine Hydrochloride	0.4 g	-do-	Each mL of 0.1 M $HClO_4$ v $0.01857$ g of $C_{10}H_{15}N.HCl$
17	Morphine Hydrochloride	0.4 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.03218g$ of $C_{17}H_{19}NO_3.HCl$
18	Morphine Sulphate	0.5 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.06688$ g of $(C_{17}H_{19}NO_3)_2.H_4SO_4$
19	Neostigmine Bromide	0.75 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.0303$ g of $C_{12}H_{19}BrN_2O_2$
20	Oxrenolol hydrochloride	0.4 g	1- Naphthol benzein	Each mL of 0.1 M $HClO_4 \cong 0.3018$ g of $C_{15}H_{23}NO_3$
21	Pentazoline Hydrochloride	0.65 g	Crystal Violet	Each mL of 0.1 M $HClO_4 \cong 0.03219$ g of $C_{19}H_{27}NO.HCl$
22	Pethidine Hydrochloride	0.5 g	-do-	Each mL of 0.1 M $HClO_4 \cong 0.02838$ g of $C_{15}H_{21}NO_2. HCl$
23	Pentobarbitone Sodium	0.5 g	1- Naphthol benzein	Each mL of 0.1 M $HClO_4 \cong 0.02542$ g of $C_{12}H_{11}N_2NaO_3$
24	Phenylephrine hydrochloride	0.5 g	Crystal Violet	Each mL of 0.1 M $HClO_4 \cong 0.02037$ g of $C_9H_{13}NO_2.HCl$
25	Phenytoin Sodium	0.4 g	1- Naphthol benzein	Each mL of 0.1 M $HClO_4 \cong 0.02743$ g of $C_{15}H_{11}N_2NaO_2$
26	Promethazine hydrochloride	1 g	Methyl orange	Each mL of 0.1 M $HClO_4 \cong 0.03209$ g of $C_{17}H_{20}N_2S.HCl$

27	Propoxyphene hydrochloride	0.6 g	Crystal Violet	Each mL of 0.1 M HClO <sub>4</sub> $\cong$ 0.03759 g of C <sub>22</sub> H <sub>29</sub> NO <sub>2</sub> .HCl
28	Propranolol hydrochloride	0.7 g	1- Naphthol benzein	Each mL of 0.1 M HClO <sub>4</sub> $\cong$ 0.02058 g of C <sub>16</sub> H <sub>21</sub> NO <sub>2</sub> .HCl
29	Pyridoxine hydrochloride	0.4 g	Crystal Violet	Each mL of 0.1 M HClO <sub>4</sub> $\cong$ 0.02056 g of C <sub>8</sub> H <sub>12</sub> ClNO <sub>3</sub>
30	Succinylcholine chloride	0.5 g	-do-	Each mL of 0.1 M HClO <sub>4</sub> $\cong$ 0.018078 g of C <sub>14</sub> H <sub>30</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>
31	Tetramisole hydrochloride	0.5 g	1- Naphthol benzein	Each mL of 0.1 M HClO <sub>4</sub> $\cong$ 0.02408 g of C <sub>11</sub> H <sub>22</sub> N <sub>2</sub> S.HCl
32	Thiabendazole	0.16 g	Crystal Violet	Each mL of 0.1 M HClO <sub>4</sub> $\cong$ 0.02013 g of C <sub>10</sub> H <sub>7</sub> N <sub>3</sub> S
33	Verapamil hydrochloride	0.5 g	Crystal Violet	Each mL of 0.1 M HClO <sub>4</sub> $\cong$ 0.04911 g of C <sub>27</sub> H <sub>38</sub> N <sub>2</sub> O <sub>4</sub> .HCl

### Acidimetry

To save weakly basic substances, neutral or acidic solvents are used, similar to the alkali meter. The solvent for anhydrous acidity is glacial acetic acid. For very weak bases (eg: amides), however, acetic anhydride is used. Other solvents used in anhydrous titrations are dioxane, perchloric acid, acetonitrile, benzene, chloroform, a glycol-hydrocarbon mixture (eg, a 1:1 solution of propylene glycol and chloroform or a solution of ethylene glycol and n-butanol). Perchloric acid, the strongest acid available, is the most commonly used anhydrous acid titral. Commercially available perchloric acid is a concentrated aqueous solution. Water is removed from the solution by adding acetic anhydride to increase its sensitivity to the titration. The primary non-aqueous acidity standard is potassium biphthalate. The chemical reaction between potassium biphthalate and perchloric acid is shown below. Other substances used as primary standards are tris(hydroxymethyl) aminomethane, sodium carbonate and diphenylguanidine. Crystal violet, methyl violet, p-naphtholbenzene, quinaldine red, malachite green are visual indicators commonly used in anhydrous titrations of weak bases. In the absence of a visual indicator, the endpoint of the titration is determined by potentiometry<sup>(1,3)</sup>.

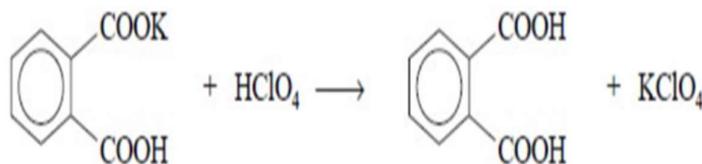


### Preparation of 0.1 N perchloric acid

Dissolve 8.5 ml of 72% HClO<sub>4</sub> in it, add 900 ml of glacial acetic acid with constant stirring, and add about 30 ml of (CH<sub>3</sub>CO)<sub>2</sub>O (acetic anhydride) to 1000 ml adding glacial acetic acid and keep the mixture for 24 hours. .500 mg of potassium hydrogen phthalate dissolved in 20 ml of glacial acetic acid, add a few drops of 5% (w/v) crystal violet indicator and titrate with 0.1 N HClO<sub>4</sub> to change the color from blue to blue-green.<sup>(11)</sup>

$$V_1N_1 = V_2N_2$$

Therefore, Each ml 0.1 N perchloric acid  $\cong$  0.0204 g potassium hydrogen phthalate.



### Assay of Adrenaline

In general, the reaction taking place between a primary amine and perchloric acid may be expressed as follows:





17	nikethamide	0.2g	-do-	Each ml of 0.1 M HClO <sub>4</sub> ≅0.01782g of C <sub>10</sub> H <sub>14</sub> N <sub>2</sub> O
18	Noscapine	0.5g	-do-	Each ml of 0.1 M HClO <sub>4</sub> ≅0.04134g of C <sub>22</sub> H <sub>23</sub> NO <sub>7</sub>
19	Nicotinamide	0.2g	Crystal violet	Each ml of 0.1 M HClO <sub>4</sub> ≅0.01221g of C <sub>6</sub> H <sub>6</sub> N <sub>2</sub> O
20	Metronidazole benzoate	0.5g	Brilliant green	Each ml of 0.1 M HClO <sub>4</sub> ≅0.02753 g of C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub>
21	metronidazole	0.45g	1-naphthol benzein	Each ml of 0.1 M HClO <sub>4</sub> ≅0.01712g of C <sub>6</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub>
22	Levodopa	0.6g	Oracet blue-B	Each ml of 0.1 M HClO <sub>4</sub> ≅0.01972g of C <sub>9</sub> H <sub>11</sub> NO <sub>4</sub>
23	Ethambutal hydrochloride	0.2g	Crystal violet	Each ml of 0.1 M HClO <sub>4</sub> ≅0.01386g of C <sub>10</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> .2HCl

### Detection of Endpoint

Indicators used for non-aqueous titration are:

**Crystal Violet:** It is considered as the most common indicators in the titration of the bases. It is used as 0.5% solution in glacial acetic acid it gives violet colour in basic medium and yellowish-green in acidic medium. It is maximum broadly use for the titration of pyridine with perchloride acid.

**Oracet Blue B:** It is prepared 0.5% glacial acetic acid. It offers blue colour in basic medium at the same time as pink colour in acidic medium.

**Quinaldine Red:** It is employed as indicator in the determination Of the drug substance in dimethylformamide (DMF). It is used as 0.1% w/v solution in ethanol. The shade alternate is from red to pale green.

**Thymol Blue:** It is used as 0.2% w/v solution in methanol. The colour change is from yellow to blue. Used as an indicator for the titration of substances acting as acids in DMF.

**Alpha naphtholbenzein:** Alpha naphtholbenzeins are also used as indicators.

### Advantages of Non-Aqueous Titrations

- 1) It is a very simple, qualitative and highly accurate method.
- 2) Organic acids and bases, which are insoluble in water soluble in non-aqueous solvents.
- 3) It is useful for titrations of very weak acids and bases where water cannot be used.
- 4) It can be used in the titration of a mixture of acids as well.
- 5) It is a very important procedure in pharmacopoeial assays.
- 6) Substance compositions that can't be one after the other decided in aqueous media may be titrated in a non-aqueous medium.<sup>(12,13)</sup>

### Disadvantages of Non-Aqueous Titrations

- 1) Solvents are relatively expensive and less stable than those used in aqueous titrations
- 2) Indicators must be prepared in an anhydrous medium.
- 3) Solvents require adjustment after each use.
- 4) Volatile solvents can contaminate the medium.
- 5) This titration is non-specific; therefore, it is possible that impurities may affect.<sup>(13,14)</sup>

### Applications of Non-aqueous Titration

Non-aqueous titration has several applications in many fields. Especially in the medical field, non-aqueous titration can be very useful. We have indexed some applications of anhydrous titration here.

- 1) Non-aqueous titration is used to determine the purity of analytes.
- 2) It is used to define focus expressions.
- 3) Used to determine hydrophobic compounds, phenobarbitone, diuretics, steroids.
- 4) Used to determine the composition of tuberculosis drugs and adrenergic drugs.<sup>(15)</sup>

## CONCLUSION

The involvement of water molecules in titration is one of the reasons why non-aqueous titrations are relevant. A water molecule retains both weak acid and weak basic characteristics. Water molecules interact with various bases and acids dissolved in them for proton donation and proton acceptance.

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