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Potentiometric and pHmetric Studies of Paracetamol

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Abstract

Acid-base titration of paracetamol in nonaqueous solvents was done. Procedure was followed for titration of paracetamol in different media like acetic acid, pyridine, dimethlformamide and ethyl alcohol with standard perchloric acid in glacial acetic acid, sodium ethoxide in ethyl alcohol using plantinum-calomel as well as glass-calomel electrode system. The equivalence point was located as accurately as possible by a differential graph of ΔE/ΔV or ΔpH/ΔV against V and concentration of test solution was computed.

The acid-base titration of paracetamol is rapid and reproducible, and permits its determination in medicinal sample. The electrode systems vary with the solvent employed. The platinum-calomel electrode system is suitable where the solvent is glacial acetic acid in this case perchloric acid in glacial acetic acid is the titrant while the glass-calomel electrode system is suitable where the solvent is either pyridine, an alcohol or dimethyiformamide, the titrant consists of sodium ethoxide in ethyl alcohol.

Keywords: Acetic acid; Dimethlformamide; Ethyl alcohol; Paracetamol; Pyridine

Introduction

Paracetamol (acetaminophen) is one of the most popular analgesic and antipyretic drugs. Paracetamol is available in different dosage forms: tablet, capsules, drops, elixirs, suspensions and suppositories. Dosage forms of paracetamol and its combinations with other drugs have been listed in various pharmacopoeias [1,2]. The combination of paracetamol with dipyrone is used as an antipyretic, analgesic and anti-inflammatory drug. Numerous methods have been reported for the analysis of paracetamol and its combinations in pharmaceuticals or in biological fluids. Paracetamol has been determined in combination with other drugs using titrimetry [3,4], voltammetry [5], fluorimetry [6], colorimetry [6], UV-spectrophotometry [7-9], quantitative thin-layer chromatography (TLC) [10], high-performance liquid chromatography (HPLC) [11-16] and gas chromatography (GC) [17] in pharmaceutical preparations. Effect of electrophilic and electrodotic groups on the potentiometric titration of amides and other weak bases was studied [18]. Electrodotic groups enhance the potentiometric end point and electrophilic groups depress it, sometimes to the extent that the compound is not titratable. A combination of chloroform and acetic anhydride is a useful alternative medium for the titration of weak bases. A potentiometric method for determination of p-acetamidophenol was reported [19].

Analytical data are given for a representative number of amides, acetylated amines, and formylated amines [20]. In acetic acid, amides show little tendency toward salt formation with $CH_3COOH_2^+$; however, upon addition of acetic anhydride, additional acidic species become evident and measurable end points are observed [21].

$$CH_3COOH_2^+ + (CH_3CO)_2O \leftrightarrows (CH_3CO)_2{-}OH^+ + CH_3COOH \leftrightarrows CH_3CO^+ + (CH_3COOH)_2$$

Considerable evidence for this equilibrium has been presented by a number of investigators [21-25].

An accurate, simple, reproducible and sensitive method for the determination of paracetamol, caffeine and dipyrone was developed and validated [26].

In present study acid-base titration of paracetamol in nonaqueous solvents was done. Procedure was followed for titration of paracetamol in different media like acetic acid, pyridine, dimethlformamide and ethyl alcohol with standard perchloric acid in glacial acetic acid, sodium ethoxide in ethyl alcohol using plantinum-calomel as well as glass-calomel electrode system. The equivalence point was located as accurately as possible by a differential graph of ΔE/ΔV or ΔH/ΔV against V and concentration of test solution was computed.

Methodology

All chemicals were of A.R. grade. Solvents were purified before use. Medicinal samples of paracetamol were collected from local market of different make. OSAW direct reading potentiometer was used to carry out redox titrations using bright platinum wire and saturated calomel electrodes. The pH-titrations were made with an ELICO LI-10 pH-meter in conjuction with Glass (EM-42) and calomel (ER-70) electrodes.

Acid-base titration of paracetamol in nonaqueous solvents was done by taking 0.2 g of Crocin paracetamol (Duphar) tablet in a 250 ml beaker and was dissolved in 25 ml of glacial acetic acid. A bright platinum wire electrode was dipped; the solution was connected to a calomel electrode via salt bridge and titrated with 0.1 N perchloric acid in acetic acid. Similar procedure was followed for titration of paracetamol in other media like pyridine, dimethlformamide and ethyl alcohol with standard sodium ethoxide in ethyl alcohol using plantinum-calomel as well as glass-calomel electrode system. The equivalence point was located as accurately as possible by a differential graph of ΔE/ΔV or ΔH/ΔV against V and concentration of test solution was computed.

Observation

Potentiometric methods embrace two major types of analyses: the direct measurement of an electrode potential from which the concentration of an active ion may be derived, and the changes in the electromotive force of an electrolytic cell brought about through the

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addition of a titrant. Two types of potentiometric titrations, Oxidation-Reduction and Acid-Base titrations in nonaqueous solvents, have been performed, and interest is focused upon changes in the e.m.f. of an electrolytic cell as a titrant of precisely known concentration is added to a solution of the analyte namely paracetamol.

Acid-base titration data for paracetamol against perchloric acid and C_2H_2ONa in different media - glacial acetic acid, pyridine, dimethyl formamide and ethyl alcohol are shown in Table 1.

An end point is located more precisely by plotting successive values of the rate of change of cell e.m.f. vs each increment of titrant in the vicinity of the inflection point. The position of the maximum on the first derivative curve, Figures 1-6 corresponds to the inflection point on the normal titration curve.

Results and Discussion

The results of estimation of paracetamol by potentiometric method are represented in Table 2. It is found that paracetamol can be easily titrated by potentiometric method in nonaqueous media like glacial acetic acid with perchloric acid and in pyridine, dimethylformamide and ethyl alcohol with sodium ethoxide. Good inflection point is obtained, results are reproducible and recovery is nearly 100%.

Acid-base reactions of paracetamol in nonaqueous solvents

Many acids or bases such as paracetamol that are too weak for determination in water become susceptible to titration in appropriate nonaqueous solvents. The major considerations in the choice of a solvent for acidimetric reactions are its acidity and basicity, its dielectric constant, and the physical solubility of a solute. Acidity is

Potentiometric Titration of Paracetamol in glacial acetic acid with 0.1 N $HClO_4$ in glacial acetic acid, using platinum - calomel electrodes			
Volume of 0.1 N HClO4, ml	**Potential, Volts**	**Volume of 0.1 N HClO4, ml**	**Potential, Volts**
5	0.49	15	0.525
5.5	0.49	16	0.525
6	0.49	17	0.53
7	0.49	18	0.53
8	0.495	19	0.53
9	0.5	20	0.535
10	0.5	21	0.535
11	0.504	22	0.535
12	0.514	23	0.535
13	0.514	24	0.535
14	0.525	25	0.535
Potentiometric Titration of Paracetamol in pyridine with 0.075 N soldium ethoxide in ethyl alcohol, using platinum – calomel electrodes			
Volume of 0.075 N C2H5ONa, ml	**Potential, Volts**	**Volume of 0.075 N C2H5ONa, ml**	**Potential, Volts**
4	0.22	15	0.279
5	0.22	16	0.293
6	0.225	17	0.305
7	0.225	18	0.314
8	0.232	19	0.317
9	0.232	20	0.317
10	0.232	21	0.326
11	0.239	22	0.326
12	0.243	23	0.326
13	0.249	24	0.326
14	0.26	25	0.326
Potentiometric Titration of Paracetamol in dimethylformamide with 0.075 N sodium ethoxide in ethyl alcohol, using platinum-calomel electrodes.			
Volume of 0.075 N C2H5ONa, ml	**Potential, Volts**	**Volume of 0.075 N C2H5ONa, ml**	**Potential, Volts**
2	0.22	17	0.262
3	0.224	18	0.273
4	0.227	19	0.28
5	0.227	20	0.282
6	0.227	21	0.285
7	0.227	22	0.288
8	0.227	23	0.291
9	0.227	24	0.291
10	0.223	25	0.291
11	0.223	26	0.291

12	0.223	27	0.291
13	0.226	28	0.291
14	0.231	29	0.291
15	0.235	30	0.291
16	0.247		
Potentiometric Titration of Paracetamol in Pyridine with 0.09 N sodium ethoxide in ethyl alcohol.			
Volume of 0.09 N C2H5ONa, ml	**Potential, Volts**	**Volume of 0.09 N C2H5ONa, ml**	**Potential, Volts**
3	0.385	15	0.415
4	0.385	16	0.415
5	0.385	17	0.42
6	0.385	18	0.42
7	0.385	19	0.42
8	0.395	20	0.42
9	0.395	21	0.42
10	0.395	22	0.42
11	0.4	23	0.42
12.1	0.405	24	0.42
13	0.415	25	0.42
14	0.415		
Potentiometric Titration of Paracetamol in dimethyl formamide with 0.09 N sodium ethoxide in ethylalcohol.			
Volume of 0.09 N C2H5ONa, ml	**Potential, Volts**	**Volume of 0.09 N C2H5ONa, ml**	**Potential, Volts**
0.5	0.395	13	0.415
1	0.395	14	0.42
2	0.395	15	0.42
3	0.395	16	0.42
4	0.395	17	0.42
5	0.395	18	0.42
6	0.395	19	0.42
7	0.395	20	0.42
8	0.4	21	0.42
9	0.4	22	0.42
10	0.4	23	0.42
11	0.405	24	0.42
12	0.405	25	0.42
pH-metric Titration of Paracetamol in ethyl alcohol with 0.083 N sodium ethoxide in ethylalcohol.			
Volume of 0.083 N C2H5ONa, ml	**pH**	**Volume of 0.083 N C2H5ONa, ml**	**Potential, Volts**
4	12	14.5	13.3
5	12.1	15	13.4
6	12.15	16	13.5
7	12.25	17	13.6
7.5	12.3	18	13.65
8	12.4	19	13.7
9	12.5	20	13.75
10	12.6	21	13.75
11	12.7	22	13.8
12	12.8	23	13.8
13	12.9	24	13.8
14	13.2	25	13.85

Table 1: The acid-base titrations of paracetamol in nonaqueous solvents.

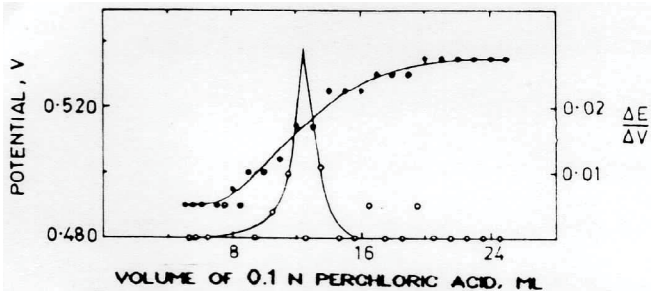


Figure 1: Potentiometric Titration curves for Paracetamol in glacial acetic acid with 0.1 N $HClO_4$ in glacial acetic acid, using platinum - calomel electrodes.

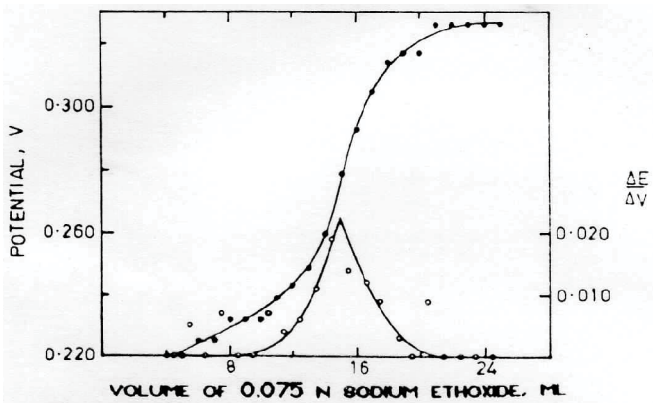


Figure 2: Potentiometric Titration curves for Paracetamol in pyridine with 0.075 N soldium ethoxide in ethyl alcohol, using platinum – calomel electrodes.

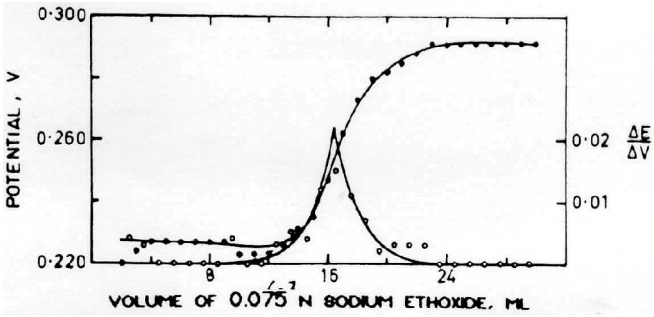


Figure 3: Potentiometric Titration curves for Paracetamol in dimethylformamide with 0.075 N sodium ethoxide in ethyl alcohol, using platinum-calomel electrodes.

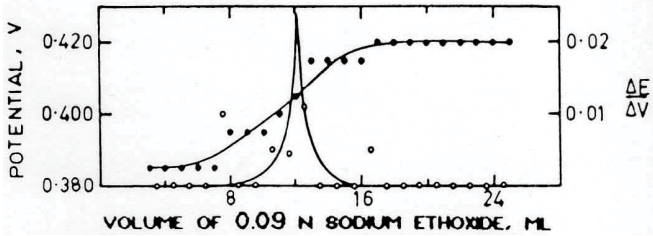


Figure 4: Potentiometric Titration curves for Paracetamol in Pyridine with 0.09 N sodium ethoxide in ethyl alcohol.

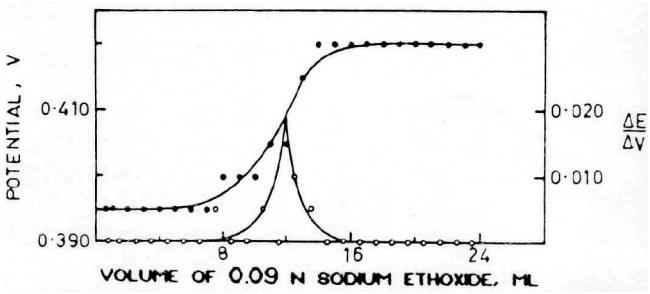


Figure 5: Potentiometric Titration curves for Paracetamol in dimethyl formamide with 0.09 N sodium ethoxide in ethylalcohol.

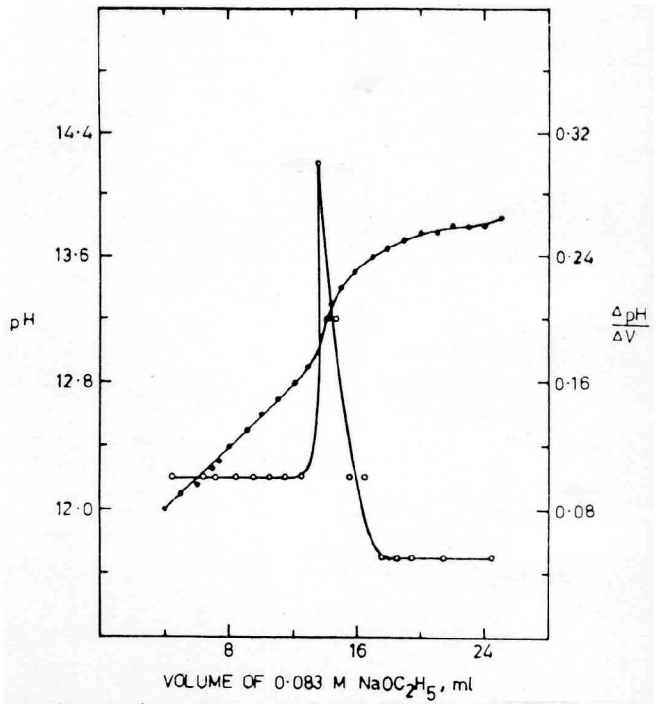
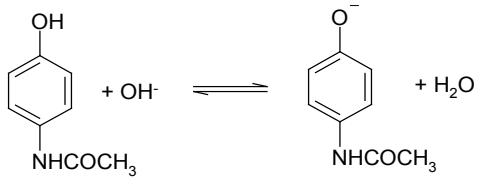


Figure 6: pH-metric Titration curves for Paracetamol in ethyl alcohol with 0.083 N sodium ethoxide in ethyl alcohol.

important because it determines to a large extent whether or not a weak acid can be titrated in the presence of a relatively high concentration of solvent molecules. Paracetamol, for example, cannot be titrated as an acid in aqueous solution because water is too acid and present in too high a concentration to permit the p-oxyacetanilide ion to be formed stoichiometrically by titration with a base. In other words the intrinsic basic strength of the p-oxyacetanilide ion and hydroxide ions are not sufficiently different for the reaction:



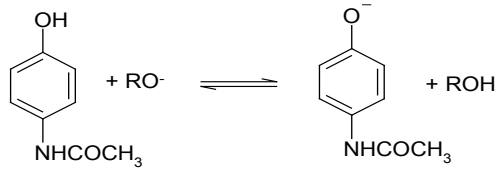
In less acid solvents, such as dimethylformamide or pyridine, this titration can be carried out readily with a stronger basic titrant, the alkoxide ion:

S No	Solvent	Titrant	Electrode system	Inflection Point	Weight of Tablet	Amount of Paracetamol per Tablet, g	
1	Glacial acetic acid	0.1 N HClO4 in acetic acid	Platinum - Calomel	12.5	0.6	0.5	0.5669
2	Pyridine	0.075 N C2H5ONa in ethyl alcohol	Platinum - Calomel	15	0.5915	0.5	0.5029
3	Dimethyl formamide	0.075 N C2H5ONa in ethyl alcohol	Platinum - Calomel	16.5	0.5965	0.5	0.5579
4	Pyridine	0.09 N C2H5ONa in ethyl alcohol	Glass - Calomel	12.5	0.6097	0.5	0.4997
5	Dimethyl formamide	0.09 N C2H5ONa in ethyl alcohol	Glass - Calomel	12	0.6132	0.5	0.5
6	Ethyl alcohol	0.083 N C2H5ONa in ethyl alcohol	Glass - Calomel	13.5	0.5875	0.5	0.4975

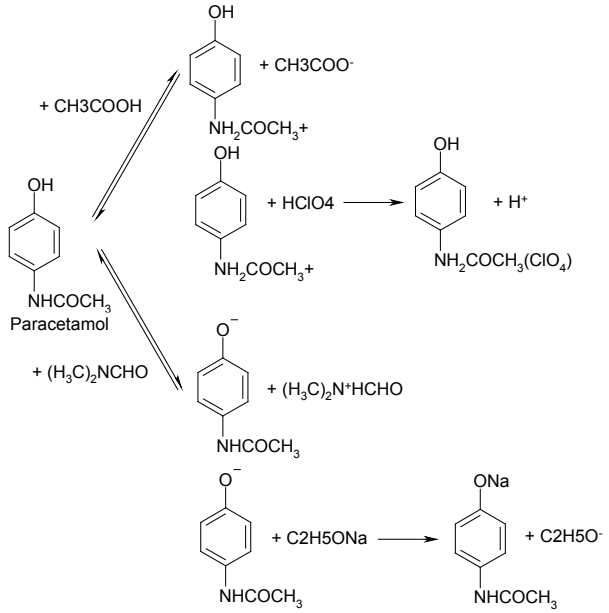
Note: Amount of Paracetamol per tablet,

$$g = \frac{\text{Inflection Point} \times \text{Mol. wt. of Paracetamol} \times \text{Normality of Titrant}}{1000 \times 1} \times \frac{\text{Weight of Tablet}}{\text{Weight of Tablet taken}}$$

Table 2: Analysis of crocin (duphar) paracetamol tablet by potentiometric acid – base titration methods.



Acidic properties of solvent such as acetic acid produce a pronounced levelling effect on the weak base (p-hydroxyacetanilide) and thus it gets converted into strong base which then can be titrated with strong acid. The titrant is a solution of perchloric acid in glacial acetic acid which has been standardized with potassium hydrogen phthalate. In an analogous fashion, basic solvents enhance the properties of weak acid (p-oxyacetanilide). It produce distinctive end point in dimethylformamide. The titrant is sodium ethoxide. The electrode systems vary with the solvent employed. The platinum-calomel electrode system is suitable where the solvent is glacial acetic acid in this case perchloric acid in glacial acetic acid is the titrant while the glass-calomel electrode system is suitable where the solvent is either pyridine, and alcohol or dimethylformamide, the titrant consists of sodium ethoxide. Acid-Base reaction involved in case of paracetamol while titrating with perchloric acid/sodium ethoxide can be represented as follows.



Conclusion

Based on potentiometric studies of paracetamol it is concluded that the acid-base titration of paracetamol is rapid and reproducible, and permits its determination in medicinal sample. The electrode systems vary with the solvent employed. The platinum-calomel electrode system is suitable where the solvent is glacial acetic acid in this case perchloric acid in glacial acetic acid is the titrant while the glass-calomel electrode system is suitable where the solvent is either pyridine, an alcohol or dimethyiformamide, the titrant consists of sodium ethoxide in ethyl alcohol.

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