Potentiometric and pHmetric Studies of Paracetamol

Swaroopa Rani N. Gupta*
Department of Chemistry, Brijlal Biyani Science College, Amravati, Maharashtra, India

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, dimethylformamide 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 dimethylformamide, the titrant consists of sodium ethoxide in ethyl alcohol.

Keywords: Acetic acid; Dimethylformamide; 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], volumetry [5], fluorimetry [6], colorimetry [7], 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$_3$COOH$_2^{+}$ however, upon addition of acetic anhydride, additional acidic species become evident and measurable end points are observed [21].

\[ \text{CH}_3\text{COOH}^+ + (\text{CH}_3\text{CO})_2\text{O} \rightleftharpoons (\text{CH}_3\text{CO})_2\text{O}^- + \text{CH}_3\text{COOH} \]

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, dimethylformamide 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.
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 C₃H₂ONa 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 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 sodium ethoxide in ethyl alcohol, 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, 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 |
### 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                            | 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 ethyl alcohol.

| 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             |
| 13                            | 0.415            |                                |                  |
| 14                            | 0.415            |                                |                  |

### pH-metric Titration of Paracetamol in ethyl alcohol with 0.083 N sodium ethoxide in ethyl alcohol.

| 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.
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:

\[
\text{pH} - \text{metric Titration curves for Paracetamol in ethyl alcohol with 0.083 N sodium ethoxide in ethyl alcohol.}
\]

In less acid solvents, such as dimethylformamide or pyridine, this titration can be carried out readily with a stronger basic titrant, the alkoxide ion:
the acid-base titration of paracetamol is rapid and reproducible, and as follows.

While titrating with perchloric acid/sodium ethoxide can be represented sodium ethoxide. Acid-base reaction involved in case of paracetamol pyridine, and alcohol or dimethylformamide, the titrant consists of the glass-calomel electrode system is suitable where the solvent is either pyridine, an alcohol or dimethylformamide, the titrant consists of sodium ethoxide in ethyl alcohol.

Acid-base reaction involved in case of paracetamol while titrating with perchloric acid/sodium ethoxide can be represented as follows.

\[
\text{OH} + \text{RO}^- \rightarrow \text{O}^+ + \text{ROH}
\]

The platinum-calomel electrode system is suitable where the solvent is pyridine, an alcohol or dimethylformamide. The titrant is sodium ethoxide. The platinum-calomel electrode system is suitable where the solvent is pyridine or an 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.

\[
\text{OH} + \text{CH}_3\text{COO}^- \rightarrow \text{CH}_3\text{COOH} + \text{Na}^+
\]

\[
\text{OH} + \text{HClO}_4 \rightarrow \text{H}^+ + \text{ClO}_4^- + \text{H}_2\text{O}
\]

\[
\text{OH} + \text{H}^+ + (\text{H}_2\text{C}_2\text{N})_2\text{N}^- + \text{HCHO} \rightarrow \text{NH}_3\text{COOH}^+ + \text{H}_2\text{O}
\]

\[
\text{OH} + \text{H}_2\text{O} \rightarrow \text{OH}^- + \text{H}_3\text{O}^+
\]

\[
\text{OH} + \text{Na}^+ + \text{C}_2\text{H}_5\text{OSO}_2\text{Na} \rightarrow \text{Na}^+ + \text{C}_2\text{H}_5\text{OSO}_2^- + \text{H}_2\text{O}
\]

\[
\text{OH} + \text{H}_2\text{O} \rightarrow \text{OH}^- + \text{H}_3\text{O}^+
\]

\[
\text{OH} + \text{CH}_3\text{COO}^- \rightarrow \text{CH}_3\text{COOH} + \text{Na}^+
\]

\[
\text{OH} + \text{HClO}_4 \rightarrow \text{H}^+ + \text{ClO}_4^- + \text{H}_2\text{O}
\]

\[
\text{OH} + \text{H}^+ + (\text{H}_2\text{C}_2\text{N})_2\text{N}^- + \text{HCHO} \rightarrow \text{NH}_3\text{COOH}^+ + \text{H}_2\text{O}
\]

\[
\text{OH} + \text{H}_2\text{O} \rightarrow \text{OH}^- + \text{H}_3\text{O}^+
\]

\[
\text{OH} + \text{Na}^+ + \text{C}_2\text{H}_5\text{OSO}_2\text{Na} \rightarrow \text{Na}^+ + \text{C}_2\text{H}_5\text{OSO}_2^- + \text{H}_2\text{O}
\]

\[
\text{OH} + \text{H}_2\text{O} \rightarrow \text{OH}^- + \text{H}_3\text{O}^+
\]

\[
\text{OH} + \text{CH}_3\text{COO}^- \rightarrow \text{CH}_3\text{COOH} + \text{Na}^+
\]

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 dimethylformamide, the titrant consists of sodium ethoxide in ethyl alcohol.

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