Chapter-9

Kinetic and Mechanistic Study on Oxidation of Phenylephrine hydrochloride by Chloramine-T in Hydrochloric acid Medium
9.1 Introduction

Phenylephrine hydrochloride (PHE), 3-[1-hydroxy-2(methylamino)ethyl] phenol is a medication commonly used for treating nasal and sinus congestion and pressure due to allergies (such as hay fever) or the common cold. There are various forms of this drug, as well as a variety of conditions it can be used to treat. The medication works by causing the blood vessels to constrict, allowing less fluid to leave the blood vessels and decreasing inflammation [1-4]. Medication can cause side effects, such as nervousness, dizziness, insomnia, nervousness, dizziness and high blood pressure (hypertension) [5].

Theia’a N. Al-Sabha [6] developed a new spectrophotometric method for determination of phenylephrine hydrochloride. The method is based on the coupling of 4-aminoantipyrine (4-AAP) with phenylephrine hydrochloride (PHE) to give a new ligand that reacts with copper (II) in the presence of sodium tetraborate buffer solution of pH 9.00 at 50 °C to give an intense red colored chelate having maximum absorption at 480 nm. The optimization of the experimental conditions is described. The method has been used for the determination of 2.0.50.0 ig/ml of PHE. The molar absorptivity is $5.34 \times 10^3$ L.mol.$^{-1}$cm.$^{-1}$ and the accuracy of the method is achieved by the value of average recovery (101.28 %) and the precision is supported by relative standard deviation (RSD=1.25 %) values. The results of the method was compared with those of the standard method. The interference of excipients was studied. The mechanism of the
chemical reaction has been proposed. The proposed method was successfully applied for
the determination of the PHE in pharmaceutical syrup formulations.

Ramesh Sawant, Rupali Joshi, Manisha Sawant, Prashant Lanke and Lokesh
Bhangale [7] developed a method by without resolving mixtures of paracetamol,
phenylephrine hydrochloride, chlorpheniramine maleate and caffeine, simultaneous
estimation has been successfully achieved by spectrophotometry. Method I employ
formation and solving of mathematical simultaneous equation using 256.8 nm, 236.8 nm,
222.4 nm and 272.0 nm as the Imax of paracetamol, phenylephrine hydrochloride,
chlorpheniramine maleate and caffeine respectively in 0.1N NaOH. Method II is a
multiwavelength spectrophotometric analysis in which the instrument is preprogrammed
to collect and compile the spectral data from the scan of standards and matrix
calculations. These methods were validated for accuracy, precision, linearity, specificity
and sensitivity as per ICH norms. Calibration curves were linear over the concentration
ranges of 0-35 μg/mL for all drugs. The validation study is statistically significant as all
the statistical parameters are within the acceptance range (% COV < 2.0 and S.D. < 2.0)
for both accuracy and precision. Both the methods are successfully applied to
pharmaceutical formulation, with no interference from excipients as indicated by the
recovery study. The proposed methods are simple, rapid, economic and accurate for
routine simultaneous estimation of paracetamol, phenylephrine hydrochloride,
chlorpheniramine maleate and caffeine.

A validated, specific, stability indicating reverse phase liquid chromatographic
method has been developed by Safeena Sheikh, Suhail Asghar, Showkat Ahmad Patni [8]
for simultaneous quantitative analysis of Phenylephrine HCl, Lignocaine HCl and
Betamethasone valerate in pharmaceutical ointment base products. The method was optimized by analysis of the samples and sample solutions spiked with each analyte for recovery study. Good resolution between the analytes was achieved in formulation and combined standards on Merck' C18 (250mm X 4.6mm, 5μ) column with mobile phase constituted of phosphate buffer (0.01M) and acetonitrile (46: 54% v/v) further the pH of the mobile phase was adjusted to pH = 7.0 (± 0.05) with triethylamine. Detection was performed at 270nm. The method was validated in accordance with ICH guidelines and validation data showed that the assay is sensitive, specific and reproducible for the simultaneous estimation of Phenylephrine HCl, Lignocaine HCl and Betamethasone Valerate in the presence of other pharmaceutical excipient. The developed liquid chromatographic method is specific, precise, accurate and robust. It can be used as an alternative method for the rapid and routine simultaneous determination of Phenylephrine hydrochloride, Lignocaine hydrochloride and Betamethasone Valerate in semi solid pharmaceutical preparations.

M V B Rao et al [9] worked on a simple and rapid dissolution test method for Phenylephrine Hydrochloride Pellets - 20%W/W has been developed and validated. Based on the stability and nature of the drug, dissolution experiments were conducted in different mediums in various time intervals with Basket at 100 rpm (resolution per minute). Dissolution was found to be NMT 25% over a period of one hour, 30-50% in 2nd hour, 50-70% in 4th hour, at 8th hour NTL 75%. The quantitative recoveries of the drug from semi formulations were established indicating non interference of excipients. The dissolution profiles for pellets were considered satisfactory and this could be utilized for the Quality control Analysis of Phenylephrine Hydrochloride Pellets 20%W/W.
Literature survey revealed no information in oxidation of phenylephrine by any other oxidants. Kinetics of oxidation of Phenylephrine by CAT in hydrochloric acid medium has been studied at 303K.

9.2. Oxidation of Phenylephrine hydrochloride by Chlormaine-T in acid medium.

The kinetics of oxidation of PHE with CAT in hydrochloric acid solution has been studied at 303 K discussed in this chapter.

9.2.1. Stoichiometry and product analysis

Reaction mixtures containing varying ratios of CAT and PHE, in the presence of HCl were equilibrated at 303 K for 24 hours. The results of estimation of unreacted CAT indicated 1:1 stoichiometry, that is one mole of PHE consumed one mole of Chloramine-T.

\[
\begin{align*}
\text{Ts} = \text{CH}_3\text{C}_6\text{H}_4\text{SO}_2^- \\
\text{2-hydroxy-2-(3-hydroxyphenyl) acetaldehyde was detected by spot tests [10] i.e., 2, 4- dinitrophenyl hydrazine test and sodium nitroprusside test and was further confirmed by GC-MS analysis. The GC-MS data were obtained from 17A Shimadzu gas chromatograph with a QP-5050 Shimadzu mass spectrometer. The mass spectra showed a molecular ion peaks at at 151 amu [Fig. 9.6] confirming the above product.}
\end{align*}
\]

Reduction product of the oxidant, p-toluenesulphonamide was detected by thin layer chromatography [11] using light petroleum-chloroform-butan-1-ol (2:2:1 v/v) as
solvent and iodine as spray reagent (Rf = 0.88). The reported Rf value is consistent with that given in the literature. Further it was confirmed by its melting point 150-151°C (melting point: 149-151°C) and the molecular ion peak in the mass spectrum at 171 amu confirms p-toluene sulfonamide. It was also observed that no further oxidation of these products under the present experimental kinetic conditions.

9.2.2. Kinetic results

The oxidation of PHE by CAT in the presence of hydrochloric acid carried out in a measurable rate. The reaction orders have been determined from the slopes of log k' versus respective logarithemic concentration of PHE, HCl and MeOH except [CAT], by keeping the other concentrations constant.

9.2.3. Effect of Reactants on the rate of the reaction

With invariable concentration of [PHE], [HCl], The CAT concentration was varied in the range 5 × 10⁻⁴ to 20 × 10⁻⁴ mol dm⁻³. All kinetic runs exhibited identical characteristics. The linearity of plots of log [CAT] versus time, for different concentrations of CAT, indicates order in CAT concentration as unity. This was also confirmed by the constant values of pseudo-first-order rate constants, k' for variable [CAT] [Table 9.1]
The PHE concentration was varied in the range $5 \times 10^{-3}$ to $30 \times 10^{-3}$ mol dm$^{-3}$ at constant [HCl], [CAT] and temperature, it is observed that rate constants $k$ values increased with increase in PHE concentration range as in [Table 9.1]. The plots of log $k$ vs. log [PHE] were linear with unit slopes showing first order (+1.25) dependence of the rate on the [PHE] [Fig. 9.1].

The oxidation of PHE by CAT was studied by keeping PHE, CAT concentration and temperature at constant values by varying the concentration of HCl in the range $0.5 \times 10^{-3}$ to $5 \times 10^{-3}$ mol dm$^{-3}$ The rate constants increased with increase in the [HCl]. The plots of log $k$ versus [HCl] were linear with positive slopes (1.0) [Table 9.1 and Fig. 9.2] indicating a first-order dependence of rate on [HCl].
Table 9.1 Effect of varying [CAT], [PHE] and [HCl] on the reaction rate at 303 K.

<table>
<thead>
<tr>
<th>$10^4$ [CAT]/M</th>
<th>$10^3$ [PHE]/M</th>
<th>$10^3$ [HCl]/M</th>
<th>$k' \times 10^4$ s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>05</td>
<td>10</td>
<td>05</td>
<td>2.76</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>05</td>
<td>2.80</td>
</tr>
<tr>
<td>15</td>
<td>10</td>
<td>05</td>
<td>2.85</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>05</td>
<td>2.88</td>
</tr>
<tr>
<td>10</td>
<td>05</td>
<td>05</td>
<td>1.20</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>05</td>
<td>2.80</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>05</td>
<td>6.70</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>05</td>
<td>11.48</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0.5</td>
<td>0.28</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>01</td>
<td>0.56</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>02</td>
<td>1.12</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>05</td>
<td>2.80</td>
</tr>
</tbody>
</table>
Fig. 9.1 Effect of variation of [PHE] on the oxidation of PHE by CAT in HCl at 300 K
(Conditions as in Table.9.1)
9.2.4. Effect of PTS, Halide ions and Ionic strength

During the oxidation reaction, oxidizing agent CAT gets reduced. The reduction product of CAT is p-Toluene sulphonamide (PTS). In order to study the effect of reduction product during the oxidation reaction of PHE by CAT, the reduction product of CAT was added to the reaction mixture. The rate constants for different PTS concentrations are shown in [Table 9.2]. The data of [Table 9.2] showed that the rate constant remains same in the range of studied PTS concentration. It indicated the rate constants on the oxidation of PHE by CAT does not depend on PTS concentration, and hence PTS has no effect on the rate of the reaction.

In order to see the effect of halide ions such as chloride and bromide on the reaction rate, the experiments were performed taking halide salts at concentration in the range $1 \times 10^{-2}$ to $10 \times 10^{-2}$ mol dm$^{-3}$. The HCl concentration was kept at $5 \times 10^{-3}$ moldm$^{-3}$.
The rate constant for different NaCl and NaBr concentrations are shown in [Table 9.2]. The data of [Table 9.2] showed that the rate constant remains same in the range of studied halide concentration. It infer that the rate constants of the oxidation of PHE by CAT does not depend on halide ions concentration, hence halide ions show no effect on the rate of the reaction.

To see the effect of ionic strength on the oxidation reaction of PHE by CAT, ionic strength of the medium was varied in the reaction mixture by the addition of the solution of NaClO₄ in the range of $5 \times 10^{-3}$ to $20 \times 10^{-3}$ mol dm$^{-3}$. The rate constants for different NaClO₄ concentrations are shown in [Table 9.2]. The data in the [Table 9.2] shows that the rate constant remains same in the range of studied NaClO₄ concentrations. Hence the rate constant is independent of NaClO₄ concentrations. The ionic strength of the medium does not influence the present oxidation reaction.
Table 9.2 Effect of varying [NaCl], [NaBr], [PTS] and [NaClO₄] on the reaction rate.

<table>
<thead>
<tr>
<th>10^2[NaCl] / [NaBr] M</th>
<th>k' (×10^4 s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>2.91 (2.90)</td>
</tr>
<tr>
<td>05</td>
<td>2.95 (2.85)</td>
</tr>
<tr>
<td>10</td>
<td>2.93 (2.89)</td>
</tr>
<tr>
<td>10⁴ [PTS]/M</td>
<td></td>
</tr>
<tr>
<td>05</td>
<td>2.75</td>
</tr>
<tr>
<td>10</td>
<td>2.71</td>
</tr>
<tr>
<td>20</td>
<td>2.77</td>
</tr>
<tr>
<td>10³ [NaClO₄]/M</td>
<td></td>
</tr>
<tr>
<td>05</td>
<td>2.55</td>
</tr>
<tr>
<td>10</td>
<td>2.56</td>
</tr>
<tr>
<td>20</td>
<td>2.58</td>
</tr>
</tbody>
</table>

Values in parenthesis refers to the rate constants with NaBr

[CAT] = 10 × 10⁻⁴ mol dm⁻³; [PHE] = 10 × 10⁻³ mol dm⁻³; [HCl] = 5 × 10⁻³ mol dm⁻³;

T = 303 K

9.2.5. Effect of Dielectric constant of Medium

The dielectric constant (D) of the medium was studied by the addition of methanol to the reaction medium. The results obtained indicated that the increase in the concentration of methanol decrease of rate of the reaction. Plots of dielectric constant [D] vs. log k' are shown in [Fig. 9.3]. The slope of the plot is negative with a value of (1.10).
Table. 9.3 Effect of varying dielectric constant of medium on the reaction rate.

<table>
<thead>
<tr>
<th>[MeOH] % v/v</th>
<th>D</th>
<th>$10^7/D$</th>
<th>$k'(\times10^4 \text{ s}^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>76.73</td>
<td>1.3032</td>
<td>2.80</td>
</tr>
<tr>
<td>10</td>
<td>72.37</td>
<td>1.3817</td>
<td>2.47</td>
</tr>
<tr>
<td>20</td>
<td>67.48</td>
<td>1.4819</td>
<td>2.06</td>
</tr>
<tr>
<td>30</td>
<td>62.71</td>
<td>1.5946</td>
<td>1.56</td>
</tr>
</tbody>
</table>

[CAT] = $10 \times 10^{-4}$ mol dm$^{-3}$; [PHE] = $10 \times 10^{-3}$ mol dm$^{-3}$;

[HCl] = $5 \times 10^{-3}$ mol dm$^{-3}$; T = 303 K

Fig. 9.3 Effect of Dielectric constant [MeOH] on the oxidation of PHE by CAT in HCl at 303 K (Conditions as in Table. 9.3)
9.2.6. Effect of temperature

The rate constants for the oxidation of PHE with CAT at different temperature ranges from 293 to 313 K was measured by keeping the other experimental conditions constant. The temperature effect was studied for three concentration of PHE. It was observed that the rate constant of the reaction increases with increase in temperature for given concentration of PHE. Further the rate constant increases with increasing the concentration of PHE for a given temperature. The results are given in [Table.9.4 and Fig. 9.4].

Also, the Arrhenius plot of log $k'$ vs.1/T, which is linear as in [Fig. 9.5], was used to calculate the activation parameters.

**Table. 9.4** Effect of varying Phenylephrine hydrochloride [PHE] concentrations on the reaction rate at different temperatures.

<table>
<thead>
<tr>
<th>$10^3$[PHE]/M</th>
<th>k'($\times 10^4$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>293K</td>
</tr>
<tr>
<td>05</td>
<td>0.741</td>
</tr>
<tr>
<td>10</td>
<td>1.6</td>
</tr>
<tr>
<td>20</td>
<td>3.35</td>
</tr>
</tbody>
</table>

[CAT] = $10 \times 10^{-4}$ mol dm$^{-3}$; [HCl] = $5 \times 10^{-3}$ mol dm$^{-3}$; T = 303 K
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Phenylephrine hydrochloride

Fig. 9.4 Effect of variation of [PHE] at different of temperature on the oxidation of PHE by CAT in HCl.

(Conditions as in Table 9.4)

Table 9.5 Effect of varying temperature and the values of activation parameters for the composite reaction between CAT and PHE

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>k'($\times 10^4$ s$^{-1}$)</th>
<th>Activation parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>293</td>
<td>1.60</td>
<td>$E_a = 45.01$ kJmol$^{-1}$</td>
</tr>
<tr>
<td>303</td>
<td>2.80</td>
<td>$\Delta H^e = 42.48$ kJmol$^{-1}$</td>
</tr>
<tr>
<td>313</td>
<td>5.34</td>
<td>$\Delta G^e = 95.12$ kJmol$^{-1}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\Delta S^e = -173.72$ JK$^{-1}$mol$^{-1}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\log A = 4.1963$</td>
</tr>
</tbody>
</table>

$[\text{CAT}] = 10 \times 10^{-4}$ mol dm$^{-3}$; $[\text{PHE}] = 10 \times 10^{-3}$ mol dm$^{-3}$; $[\text{HCl}] = 5 \times 10^{-3}$ mol dm$^{-3}$
Fig. 9.5 Effect of Temperature on the oxidation of PHE by CAT in HCl.
(Conditions as in Table. 9.5)
Fig. 9.6 GC- Mass spectrum of 2-hydroxy-(3-hydroxy phenyl)acetaldehyde with its molecular ion peak at 151 amu.
9.2.7. Test for free radicals

The addition of small amount of the oxidation reaction mixture to the aqueous acryl amide solution did not initiate polymerization, showing the absence of free radicals species (non ionic species) during the reaction sequences.

9.3 Discussion

Chloramine-T (TsNCINa) behave as a strong electrolyte in aqueous solution [12-22] and depends on the pH of the medium and gives the following species in solution eq (2) to (8)

\[
\text{TsNCINa} \leftrightarrow \text{TsNCl}^- + \text{Na}^+ \quad \ldots (2)
\]

\[
\text{TsNCl}^- + \text{H}^+ \leftrightarrow \text{TsNHCl} \quad \ldots (3)
\]

\[
2 \text{TsNHCl}^- \leftrightarrow \text{TsNH}_2 + \text{TsNCl}_2 \quad \ldots (4)
\]

\[
\text{TsNCl}_2 + \text{H}_2\text{O} \leftrightarrow \text{TsNHCL} + \text{HOCl} \quad \ldots (5)
\]

\[
\text{HOCl} + \text{H}_2\text{O} \leftrightarrow \text{H}_3\text{O}^+ + \text{ClO}^- \quad \ldots (7)
\]

\[
\text{HOCl} + \text{H}^+ \leftrightarrow \text{H}_2\text{OCl}^+ \quad \ldots (8)
\]

[Here Ts = p-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}SO\textsubscript{2}⁻]

In acidic medium, the possible oxidizing species are free acid ,TsNHCl , TsNCl\textsubscript{2}, HOCl ,H\textsubscript{2}OCl\textsuperscript{+} .The involvement of TsNCl\textsubscript{2} as the oxidizing is ruled out, since the first order dependence on CAT. Added p-toluene sulfonamide does not retard the reaction indicating that the HOCl is not involved in the rate limiting step. Further [HOCl] is very small and is independent of [CAT]\textsubscript{0}. The predominant species of CAT is TsNHCl under acidic conditions. It is also reported that TsNHCl can further protonated as
TsNHCl + H^+ ⇌ TsNH2Cl^+ and the protonation constant for the reaction is found to be $1.02 \times 10^2$ at 298 K.

In the present case the first order dependence on [H^+] suggests that protonation of TsNCr results in the formation of TsNHCl which is likely to be the active oxidizing species involved in the oxidation of phenylephirine in acid medium.

$$\begin{align*}
\text{TsNCr} + \text{H}^+ & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{TsNHCl} \\
\text{TsNHCl} + \text{PHE} & \rightarrow \text{X} \\
\text{X} & \rightarrow \text{Products}
\end{align*}$$

\textbf{Scheme 1}

Applying steady state conditions for TsNHCl and with the assumption that $k_{-1} > > k_2$ [PHE],

$$\text{Rate} = \frac{k_1 k_2 [\text{CAT}] [\text{H}^+] [\text{PHE}]}{k_{-1}} \quad \text{(9)}$$

Rate law (9) is in agreement with the experimental results.

The effect of [PHE] on the rate at different temperatures (293-313K) was studied. Addition of halide ions had no effect on the rate indicating that no inter halogen compound or free bromine was formed. The reduction product PTS had no influence on the rate showing that it was not involved in pre-equilibrium. The change in the ionic strength of the medium did not alter the rate indicating that non-ionic species were involved in the rate determining step. Amis [23] has shown that a plot of log $k'$ versus $1/D$ is linear. It gives a negative slope for a reaction between the cations and dipole. The
negative dielectric effect, in the present studies, supports the interaction of dipolar species in the rate limiting step.

The proposed mechanism is also supported by the moderate value of energy of activation. The fairly high positive value of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the negative entropy of activation suggests the formation of the compact activated complex.
Scheme-2
9.4 Conclusion

The kinetics of oxidation of (PHE) by CAT in HCl medium has been studied, the stoichiometry of oxidation of Phenylephrine by CAT is found to be 1:1. The oxidation product identified was 2-hydroxy-2-(3-hydroxyphenyl) acetaldehyde. The active oxidizing species involved in HCl medium is TsNHCl. Activation parameters are calculated and the observed results supported the proposed mechanism and derived rate law.

References


[2]. Drug Properties

[3]. Pharmacogenetics and Pharmacogenomics Knowledge Base entry on phenylephrine


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