Composition and stability of complexes of Ephedrine hydrochloride with Ni$^{2+}$, Zn$^{2+}$ and Cd$^{2+}$ as toxic ions.

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Abstract
The complexes of Ephedrine with Nickel, Zinc and Cadmium ions have been investigated spectrophotometricaly using the method of corresponding solutions [1-3] and pH-metrically using Irving and Rossoti technique[4] Two compositions were observed spectrophotometrically 1:1 and 2:1 (L: M) for concentration of metal ions (0.5 x 10$^{-3}$M and 1 x 10$^{-3}$M) while the first composition only predominate at concentration of metal ions (1.5 x 10$^{-3}$ M and 2 x 10$^{-3}$ M ). The stability of complexes show that complexes of Ni$^{2+}$ are more stable than that of Zn$^{2+}$ and Cd$^{2+}$, Moreover, the composition and stabilities of complexes were studied pH-metrically in aqueous medium at 0.1 M NaCl and two different temperatures 30°C and 40°C; hence the value of the free energy change ($\Delta G^\circ$), the enthalpy ($\Delta H^\circ$) and the entropy ($\Delta S^\circ$) were calculated at 30°C. Beside the role of Ephedrine as chelating agent to toxic elements, the complexometric method was used for the determination of Ephedrine in its pure form and in tablets.

Keywords
Ephedrine determination, Metal ions, Spectrophotometry, Corresponding solutions method, Potentiometry.

Introduction
Ephedrine hydrochloride may be obtained from the plant Ephedra which is a kind of alkaloids or prepared synthetically. It is one of the most important drugs used primarily for asthma and other respiratory conditions [5] and for treating circulatory collapse during surgery and as bronchodilator [6]. The aim of the study of Ephedrine chelation with the three metal ions cited (Ni$^{2+}$, Zn$^{2+}$ and Cd$^{2+}$) taken as toxic elements; is to remove most of the unwanted metal ions in biological fluids; since it is known that the excess of any element, whether essential or not is harmful
The degree of harm being dependent on the element. The classification of the degree of toxicity [7] shows that the heavier elements are generally more toxic [8-10]. We could take care that we obtain trace elements from drinking water, unwashed vegetables and fruits, cooking pots, dental fillings and many other sources. Then for removing unwanted metal ions, the ideal reagent will be a multidentate chelate containing both oxygen and nitrogen as donor atoms, that coordinatively saturates the metal ion and gives a water soluble, easily excreted complexes [11].

Several methods have been reported for the determination of Ephedrine hydrochloride spectrophotometrically [12-15], by capillary electrophoresis [16,17] potentiometry [18,19] and by chromatographic methods [20-22]. None of these methods utilize the above metal ions for the determination of Ephedrine and studying the composition and stabilities of its complexes. The present work describes a spectrophotometric method [1-3] for the first time for determination of the composition and stability of the complexes of Ephedrine with toxic ions (Ni^{2+}, Zn^{2+} and Cd^{2+}) and for determination of Ephedrine in its pure form and in tablets. The work also discuss a potentiometric method for determination of composition and stabilities of the above complexes at one and the same ionic strength (0.1 M NaCl) and at two different temperatures 30°C and 40°C. Thereby ΔG°, ΔH° and ΔS° were calculated.

**Experimental**

**i) Apparatus**

Spectrophotometric measurements were made using super scan (3) varian spectrophotometer. The applied part was measured on an Schima Dzu (1601) UV-visible spectrophotometer. The pH measurements were carried out using a digital (I C H 163 S.w.Frameen) pH meter. The electrode system was calibrated before and after each series of measurements using standard buffer of pH (4 and 10). All values reported are an average of two separate determinations. The precision of the pH measurements was ± 0.02-pH unit. All calculations are based on a constant volume of 50 ml and furthermore adjusting the ionic strength.
ii) Materials
Ephedrine (Merk) was obtained as the hydrochloride and used without purification as fresh solution. All other chemicals were of analytical grade. Sodium chloride was used to maintain the ionic strength constant at 0.1 M. Stock solutions were prepared, 2.5 x 10^{-2} M Ephedrine hydrochloride; 1 x 10^{-2} M metal ions, 0.2 M sodium hydroxide free carbonate; standardized 0.1 M hydrochloric acid and 1 M sodium chloride. The prepared metal ion solutions were standardized against EDTA solution [23]. For determining the ionization constant of Ephedrine as well as its stability constants with metal ions, pH-metrically, the technique of Sarin and Munshi [24] was applied where their mixtures were as follows:

A- 5 ml standard 10^{-1} M + 5 ml 1 M NaCl
B- A + 20 ml from 10^{-3} M Ephedrine hydrochloride
C- B + 5 ml from 10^{-3} M metal ion.

All the above three mixtures were made up to a total volume of 50 ml each with bidistilled water. Each mixture apart was titrated against (0.2 M) sodium hydroxide at 30°C and 40°C... The solutions were adjusted at the desired temperature throughout the course of the experiment.

iii) Calculation of stability constants
The stability constants of the complexes have been determined in the following way [25]:

\[
K_1 = \frac{n}{(1-n)} \cdot \frac{1}{[L]}
\]

\[
K_2 = \frac{(n-1)}{(2-n)} \cdot \frac{1}{[L]}
\]

iv) Method for tablets
Three samples containing Ephedrine hydrochloride were chosen from three Egyptian sources; all the drugs contain Ephedrine with other pharmaceutical constituents as: diprophylline, chlorphenamine maleate, phenobarbitone, caffeine and papaverine hydrochloride in different ratios.

The content of 10 tablets from each sample under investigation was weighed and ground into a fine powder. A mass of powder containing approximately 100 mg of Ephedrine was weighed accurately; dissolved in bidistilled water and filtered. An
 aliquot of 5 ml was diluted to 25 ml after adding nickel ion as reagent, adjusting to the convenient pH, adding 2.5 ml NaCl and then measuring at 274 nm.

Results and Discussion

![Chemical structure of Ephedrine hydrochloride](image)

**Fig. 1. Ephedrine hydrochloride**

For aqueous solution of Ephedrine hydrochloride \([1 \times 10^{-3} \text{ M}]\) one absorption maximum appears at 257 nm, whereas in the presence of metal ions \([0.5 \times 10^{-3} \text{ M}]\) bathochromic shifts occur, since for nickel ion the absorption maximum appears at 274 nm, while for Ephedrine containing zinc ion the maximum absorption was shown at 270 nm whereas for Cd\(^{2+}\) at 280 nm, without the appearance of new absorption band. The effect of pH was studied on the complexes formed with the same above ligand and metal ion concentration. As the shape of the absorption

![Absorbance vs pH graph](image)

**Fig. 2. Abs- pH relationship for metal-Ephedrine complexes**
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Curves and position of the absorption maxima do not vary with pH we assumed that there is only one type of complexes formed. By using the method of corresponding solutions [1-3], it was found that the $n$ (The metal ligand formation number) does not exceed one indicating the presence of 1:1 L: M composition except in the case of nickel where the composition showed was 1:1 and 2:1 (L: M). From the cited method, Fig. 3, the free ligand concentration was also determined in each case. Fig. 4 a, b, c. at these concentrations. In other word it was found that the optimal pH for zinc ion complexes was 6 for nickel ion complexes 5 and for cadmium ion complexes pH=4. Fig. 2. From these figures it was shown that the lowest free ligand concentration was that for nickel ion complexes indicating that this metal ion had more ability to form complexes with Ephedrine than zinc and cadmium ions. Moreover the ligand to metal ratio in the complexes was studied by molar ratio method [26]. The method was applied to a series of metal solutions with a fixed concentration at 0.5x10^{-3}M, 1x10^{-3}M, 1.5x10^{-3}M and 2x10^{-3}M and variable concentration of the ligand under investigation; taking into consideration the fixed ionic strength 0.1M sodium chloride and the suitable pH for each metal ion complex. A plot of absorbance versus the mole ratio of [Ephedrine: Metal ion] showed breaks at 1:1 and 2:1 (L:M) for the two first concentrations of metal ions (0.5x10^{-3}M &
1x10^{-3}M) but with higher metal ion concentrations (1.5x10^{-3}M & 2x10^{-3}M) only the 1:1 ratio predominates, Tab. 1.

In addition the dissociation constant of the drug was calculated pH-metrically by the method of Irving and Rossotti [5] and it was found as shown from Fig. 5. that it was
Composition and stability of complexes of Ephedrine hydrochloride with \( \text{Ni}^{2+}, \text{Zn}^{2+} \) ...

The thermodynamic parameters as free energy change (\( \Delta G^\circ \)), enthalpy (\( \Delta H^\circ \)) and entropy (\( \Delta S^\circ \)) were calculated since these parameters were obtained from the dependence of equilibrium constant on temperature. In this case one determines the stability constants of complex formation at two temperatures (30°C and 40°C). The relation between the Gibb's free energy and the equilibrium constant was given by:

\[
\Delta G^\circ = -RT \ln k \ldots \ldots \ldots (1)
\]

In addition, we have the relationship

\[
\Delta G^\circ = \Delta H^\circ - T \Delta S^\circ \ldots \ldots (2)
\]

And \( \Delta H^\circ \) was determined from Van't Hoff's equation (3) which could be used when utilizing two different temperatures. Tab.1.

\[
\ln \frac{K_2}{K_1} = \frac{\Delta H^\circ (T_2 - T_1)}{R \left( \frac{T_1 T_2}{T_2 - T_1} \right)} \ldots \ldots (3)
\]

Where \( K_1 \) and \( K_2 \) are the stabilities at the two absolute temperatures \( T_1 \) and \( T_2 \).

From Tab.1, it was shown that all methods used confirm each other. Moreover, large negative values of the free energy change indicate the spontaneity of the exothermic reactions forming complexes. These reactions are all entropy unfavored due to the fact that the internal entropy of the ligand is related to its chain length; since the greater the chain length the greater the internal entropy of the ligand. On coordination much of the internal entropy will be lost, which will disfavor complex formation [27].
9.6. Also the stability constants of its complexes with Ni$^{2+}$, Zn$^{2+}$ and Cd$^{2+}$ at temperatures 30°C and 40°C and 0.1M ionic strength were calculated by the same method. Tab.1. From the results shown the stability decreases in the order Ni$^{2+}$ > Zn$^{2+}$ > Cd$^{2+}$ and decreases with increasing temperature.

![Graph showing pH vs. ml of NaOH added](image1)

**Fig. 5a.** pH-metric titration of metal-ephebrine complexes.
<table>
<thead>
<tr>
<th>Methods</th>
<th>Reagents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Corresponding Solutions</td>
<td>Ni(^{2+})</td>
</tr>
<tr>
<td>1:1 (L: M)</td>
<td>1:1</td>
</tr>
<tr>
<td>2:1</td>
<td>1:1</td>
</tr>
<tr>
<td>2) Mole ratio method</td>
<td>Ni(^{2+})</td>
</tr>
<tr>
<td>1:1 (L: M)</td>
<td>1:1</td>
</tr>
<tr>
<td>2:1</td>
<td>1:1</td>
</tr>
<tr>
<td>3) pH-metric method</td>
<td>Ni(^{2+})</td>
</tr>
<tr>
<td>1:1 (L: M)</td>
<td>1:1</td>
</tr>
<tr>
<td>2:1</td>
<td>1:1</td>
</tr>
<tr>
<td>4) Stabilities by Corresponding Solutions</td>
<td>Ni(^{2+})</td>
</tr>
<tr>
<td>log(k_1) = 5.88 + 0.01</td>
<td>log(k_1) = 4.2 + 0.3</td>
</tr>
<tr>
<td>Log(k_2) = 3.8 + 0.1</td>
<td></td>
</tr>
<tr>
<td>5) Stabilities by pH method (30(^{\circ})C)</td>
<td>Ni(^{2+})</td>
</tr>
<tr>
<td>log(k_1) = 7.3 + 0.05</td>
<td>log(k_1) = 4.8 + 0.2</td>
</tr>
<tr>
<td>log(k_2) = 3.5 + 0.1</td>
<td></td>
</tr>
<tr>
<td>6) (at 40(^{\circ})C)</td>
<td>Ni(^{2+})</td>
</tr>
<tr>
<td>log(k_1) = 6.6 + 0.03</td>
<td>log(k_1) = 4.3 + 0.05</td>
</tr>
<tr>
<td>log(k_2) = 3 + 0.02</td>
<td></td>
</tr>
<tr>
<td>7) ((\Delta G^\circ))</td>
<td>-42.280 KJ/mol</td>
</tr>
<tr>
<td>8) ((\Delta H^\circ))</td>
<td>-126.91 KJ/mol</td>
</tr>
<tr>
<td>9) ((\Delta S^\circ))</td>
<td>-277.59 J.deg(^{-1})mol(^{-1})</td>
</tr>
</tbody>
</table>

Tab. 1. Calculated parameters for Ephedrine-metal ion complexes
About the site of chelation, Ephedrine has two coordination centers; namely the hydroxyl group and the nitrogen. Fig. 1. However, through these two centers different arrangements are possible. It is possible that the metal ion substituted the hydrogen atom of the hydroxyl group and coordinate to the nitrogen forming a five member chelate which may be the case when the ligand acts as bidentate forming 1:1 and 1:2 (M:L) complexes. Another possibility is the coordination via nitrogen alone or oxygen alone acting as monodentate ligand and also 1:1 and 1:2 (M:L) complexes may be formed. Although the metal ions used were derived from metals having filled $\text{t}_{2g}$ with no acceptable $\pi$ orbital on the ligand. The complexes were stable to a great extent, only by $\sigma$- bonding, as shown by the results, i.e. the ligand in this case acts as $\sigma$- donor only.

![Fig. 6. Proposed structure for (1:1) metal-ephedrine complex](image)

Since nickel ion was the more stable reagent forming complexes than the other two ions (zinc & cadmium), standard calibration curve for Ni$^{2+}$-Ephedrine complex was constructed by plotting absorbance versus concentration at metal ion concentration (100.85µg/ml) and $\lambda$=274nm. The Beer's law range was from 25.21µg/ml up to 302.55µg/ml, with a limit of detection (L.O.D) equal to 24.85µg/ml. The regression coefficient was 0.001046 and the intercept was -0.0123. The molar absorptivity was 180 l mol$^{-1}$ cm$^{-1}$ and finally the correlation coefficient was 0.9927.

Four replicate determinations at different concentration levels were carried out to test the precision of the method, Tab.2. The relative standard deviations were found to be less than 1.5% indicating reasonable repeatability of the selected method.
From the above constituent of the drugs used, the only possible soluble species are the salts (maleate and papaverine hydrochloride). It was found that there is no significant interference observed, since our band showed its $\lambda_{\text{max}}$ at 274 nm.

<table>
<thead>
<tr>
<th>Taken $\mu g / ml$</th>
<th>Found + SD $\mu g / ml$</th>
<th>Recovery %</th>
<th>RSD %</th>
<th>Standard error</th>
<th>Confidence Limit (P=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40.34</td>
<td>40.08+ 0.46</td>
<td>99.36</td>
<td>1.15</td>
<td>0.075</td>
<td>40.08+ 0.73</td>
</tr>
<tr>
<td>80.68</td>
<td>80.17+ 0.26</td>
<td>99.79</td>
<td>0.32</td>
<td>0.13</td>
<td>80.17+ 0.57</td>
</tr>
<tr>
<td>121.02</td>
<td>120.56+ 0.43</td>
<td>99.62</td>
<td>0.36</td>
<td>0.22</td>
<td>120.56+ 0.68</td>
</tr>
<tr>
<td>242.04</td>
<td>242.10+ 0.39</td>
<td>100.02</td>
<td>0.16</td>
<td>0.195</td>
<td>242.10+ 0.62</td>
</tr>
<tr>
<td>322.72</td>
<td>322.12+ 0.27</td>
<td>99.81</td>
<td>0.08</td>
<td>0.135</td>
<td>322.12+ 0.43</td>
</tr>
<tr>
<td>352.98</td>
<td>351.96+ 99.71</td>
<td>99.71</td>
<td>0.09</td>
<td>0.155</td>
<td>351.96+ 0.49</td>
</tr>
</tbody>
</table>

*n = 4

Tab.2. Analytical data for the determination of Ephedrine in its pure form using nickel ion.

To compare the proposed method to a reference method, Ephedrine hydrochloride in tablets was assayed by the BP method [28]. For this reason statistical comparison for the results of the proposed and BP method was performed with regard to accuracy and precision using the student's t and F-ratio tests. Tab.3. At 95% calculated t and F values did not exceed the critical values, indicating that there is no significant difference between the proposed method and BP method with regard to accuracy.
Tab. 3. Determination of Ephedrine in tablets

<table>
<thead>
<tr>
<th>Sample</th>
<th>Proposed procedure Recovery + SD% (a)</th>
<th>BP method (28)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Asmoline (b) | 98.25 + 1.01  
t= 2.061  
F = 2.746 | 98.92 + 0.95  
(2.447) C  
(9.28) C |
| Asmacid (b) | 98.25 + 0.55  
t= 1.034  
F = 1.271 | 99.10 + 0.62 |
| Efanol (b)  | 98.99 + 0.36  
t= 1.034  
F = 1.271 | 98.54 + 0.45 |

(a) Recovery ± Standard deviation of four determinations.
(b) All ephedrine tablets containing 20 mg ephedrine hydrochloride per tablet: Asmoline (Epico); Asmacid (Cid); Efanol (Memphesis).
(c) Values in parentheses are the critical values at P=0.05
References:


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