

# Metal Ion Effect on the Absorbance Response of Chlorpheniramine Maleate in Pharmaceutical Dosage Form: A Study on Correlation between Spectroscopic and Potentiometric Measurements

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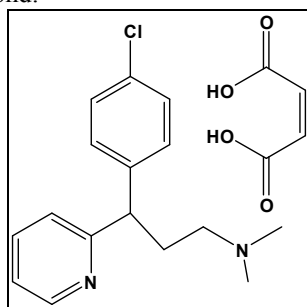
## Abstract

The interference between metal ions in human body and drug molecules is highly serious. A widely used drug by children and adults to treat throat pain and tonsillitis has been studied. The absorbance intensity of Chlorpheniramine Maleate drug in the presence of  $\text{Fe}^{3+}$ ,  $\text{Co}^{+2}$ ,  $\text{Ca}^{+2}$  and  $\text{Mg}^{+2}$  metal ions has been studied. The addition of  $\text{Fe}^{3+}$ ,  $\text{Co}^{+2}$ ,  $\text{Ca}^{+2}$  and  $\text{Mg}^{+2}$  metal ions to an aqueous solution of chlorpheniramine maleate increases the absorbance signal significantly and rapidly. These metals are chosen because they have high concentration in human body. Increasing the pH value of the aqueous solution of chlorpheniramine maleate has a contrary effect on the absorbance signal. Potentiometric measurements have been performed to correlate the spectrophotometric results and found to be consistent. Potentiometric and spectrophotometric measurements prove that there is a change in drug concentration at different pH value and to think carefully when using such drugs.

**Keywords:** Chlorpheniramine Maleate, spectrophotometric and Potentiometric measurements.

## 1. Introduction

Chlorpheniramine maleate is an antihistamine used to relieve symptoms of allergy, hay fever, and the common cold (<http://www.healthcentral.com> 2015). These symptoms include rash, watery eyes, itchy eyes/nose/throat/skin, cough, runny nose, and sneezing (Hood & Cheung 2003, Al-Rimawi 2010). survey regarding quantitative analysis of this drug revealed that attempts have been made to develop analytical methods for the estimation of chlorpheniramine maleate alone and in combination with other drugs by liquid chromatographic (HPLC) (Maithani *et al.* 2010, Geetha & Rama 2012, Wanjari *et al.* 2004, Senyuva & Özden 2002, Rajurkar 2011) and HPTLC (Subramanyan & Das 2004, Hunan & Multal 1986). By introducing a metal ion to drug molecules, there are biochemical processes in which  $\text{Fe}^{3+}$ ,  $\text{Co}^{+2}$ ,  $\text{Ca}^{+2}$  and  $\text{Mg}^{+2}$  are important participants. Iron for example, is incorporated as the central metal ion in heme in red blood cells. When coordinated to drug molecules, iron is inhibited from taking its place as the central metal ion. As a result, there will be a deficiency of iron during the heme formation processes (Valenzuela *et al.* 2014, Hod & Spitalnik 2012). Calcium (II) is very essential in bones, teeth and saliva. Continuous removal of calcium from the biological system through coordination to drug molecules, calcium is inhibited from taking its place as the central metal ion in building up bones and teeth as well as important component of saliva (Bansal *et al.* 2013, Sajewicz 2009). The same hypothesis when considering cobalt (II), the metal center in vitamin B12 (Panzeca 2009). A similar consideration is taken for *magnesium* ion which regulates over 300 biochemical reactions in the *body* through their role as enzyme co-factors (Rogolino *et al.* 2012, Evangelopoulos *et al.* 2008). This idea encouraged us to study the effect of combination of the mentioned metal ions with molecules (drugs) that can form coordination bonds. A coordination complex has a central metal ion bonded to surrounding atoms known as ligands. When cations of  $\text{Fe}^{3+}$ ,  $\text{Co}^{+2}$ ,  $\text{Ca}^{+2}$  and  $\text{Mg}^{+2}$  react with chlorpheniramine maleate, they accept pairs of electrons from nitrogen atoms. This way, the nitrogen atoms act as ligands. The bond between the central metal ion and the nitrogen atoms is a strong coordination bond.



**Figure 1:** The chemical structure of chlorpheniramine maleate.

The goal of this work was to study the effect of addition of metal ions and pH on the absorbance signal of chlorpheniramine maleate. To perform this, an investigation with three experimental method was carried out in which Chlorpheniramine Maleate is tested alone as a first experiment followed by addition of ( $\text{Fe}^{3+}$ ,  $\text{Co}^{+2}$ ,  $\text{Ca}^{+2}$  and  $\text{Mg}^{+2}$ ) central metal ions as the second experiment. Finally, the pH value is increased gradually with monitoring the absorbance value.

## 2. Experimental Part

### 2.1 Reagents and Materials

Aldrich Analytically pure Chlorpheniramine Maleate was obtained as gift samples from a pharmaceutical company in Amman. All measurements were performed in water. Water was distilled and deionised by using a distillator type GLF-2012. Suspension formulation containing labeled amount of 2.5 mg/5 mL of chlorpheniramine maleate suspension was purchased from a local pharmacy and used in the study. Metal ions: iron chloride hexahydrate  $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$ , cobalt nitrate hexahydrate  $\text{CoNO}_3 \cdot 6 \text{H}_2\text{O}$ , magnesium chloride hexahydrate  $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$  and calcium chloride hexahydrate  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$  were purchased from Aldrich and used without further purification.

### 2.2 Apparatus

All absorbance measurements were performed by a spectrophotometer type Shimadzu UV-1800. All titrations were made in triplicate and completed with the same volume of titrant (10 mL) to facilitate a comparison of the metals. Potentiometric measurements and pH manipulation were carried out using a Mettler pH meter with Ag/AgCl as the reference electrode and a glass electrode as the indicator electrode. Precision of the instrument was ( $\pm 0.001$ ) pH unit. The pH meter was calibrated using pH 4.01, 7.00, and 9.00 buffers from Merck. A 0.1 mol  $\text{L}^{-1}$  KOH solution was used as the titrant in all titrations with 0.10 mol  $\text{L}^{-1}$   $\text{KNO}_3$  as the inert electrolyte. A thermostatic water bath and a polystyrene cover with two holes were used to achieve these conditions. All measurements were made in inert atmosphere (nitrogen), at the ionic strength of the 0.10 ( $\text{KNO}_3$ ), at  $T = (25 \pm 1)^\circ\text{C}$ . A  $\text{CO}_2$  free KOH solution was used as a titrant. The pH meter glass electrode was always inserted in the solution, about 1.5 cm below the surface of the solution. A burette containing 0.1 mol  $\text{L}^{-1}$  potassium hydroxide was prepared and the addition of potassium hydroxide was done by recording the pH values as well as the volume reading at every point. The computer program HYPERQUAD was used for the calibration of the glass electrode, in term of  $\text{pH} = -\log[\text{H}^+]$ , by titrating  $\text{HNO}_3$  against KOH standard solution (at the same temperature and ionic strength). The resulting titration data were used to calculate the standard electrode potential  $E^\circ$  and Kw for water before each experiment.

### 2.3 Preparation of chlorpheniramine maleate stock solutions

A stock solution of a concentration of 500  $\mu\text{g}/\text{mL}$  was prepared by weighing  $50.0 \pm 0.1$  mg of chlorpheniramine maleate powder and transfer to 100 ml volumetric flask. The powder is dissolved in a rough amount of water, and sonicate for 15 minutes until clear solution is obtained then dilute to volume with water.

### 2.4 Preparation of chlorpheniramine maleate standard solutions

Aliquots of 0.2, 0.4, 0.8, 1.6 and 2.4 mL of the stock solution (500  $\mu\text{g}/\text{mL}$ ) were transferred to a separate five volumetric flasks (10 mL each). The corresponding concentrations of the prepared solutions were 10, 20, 40, 80 and 120  $\mu\text{g}/\text{mL}$ , respectively.

### 2.5 Preparation of chlorpheniramine maleate sample solutions

Suspension formulation containing labeled amount of 2.5 mg/5 mL of chlorpheniramine maleate suspension was purchased from a local pharmacy and used in the study. Aliquots of 0.2, 0.4, 0.8, 1.6 and 2.4 mL of the solution were transferred to a separate five volumetric flasks (10 mL each). The corresponding hypothetical concentrations of the prepared solutions were 10, 20, 40, 80 and 120  $\mu\text{g}/\text{mL}$ , respectively.

### 2.6 Preparation of $\text{Fe}^{3+}$ , $\text{Co}^{+2}$ , $\text{Ca}^{+2}$ and $\text{Mg}^{+2}$ metal ions standards

Accurately weigh (0.27, 0.23, 0.22, and 0.20 g  $\pm 0.01$  g) of  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{CoNO}_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$ ,  $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$  and transfer to 100 mL volumetric flask. Add distilled water and shake gently to obtain a clear solution with concentrations of 0.01 M solutions.

### 2.7 pH variation of chlorpheniramine maleate standard solutions

Twenty five solutions of 40  $\mu\text{g}/\text{mL}$  standard solution of chlorpheniramine maleate were prepared by different diluent solutions as follows: five solutions were diluted with water, five solutions were diluted with 0.01 M solution of  $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$ , five solutions were diluted with 0.01 M solution of  $\text{CoNO}_3 \cdot 6\text{H}_2\text{O}$ , five solutions were diluted with 0.01 M solution of  $\text{CaCl}_2 \cdot 6\text{H}_2\text{O}$  and five solutions were diluted with 0.01 M solution of

MgCl<sub>2</sub>.6H<sub>2</sub>O. The pH value of one solution of each series was modified to 4.00 using saturated solution of NaOH; another one solution from each series was changed to 5.5. The modification of the rest solution was continues to pH 9.5 and 11. The last series was kept without modification and used for potentiometric measurements (pH vs. volume of the titrant, 0.01 M NaOH)

### 2.8 Measurements general procedure

The absorption spectrum (wavelength ( $\lambda$ ) vs Absorbance) of chlorpheniramine maleate was performed. The maximum absorbance was found to be at  $\lambda_{\text{max}}$  equal to 265 nm. The absorbance of all solutions of standards prepared as described up were measured and reported. The measurements included pure chlorpheniramine maleate, chlorpheniramine maleate diluted by metal ion solutions, pH manipulation solutions, and measurement of the marketed formulation.

### 3. Results and discussion

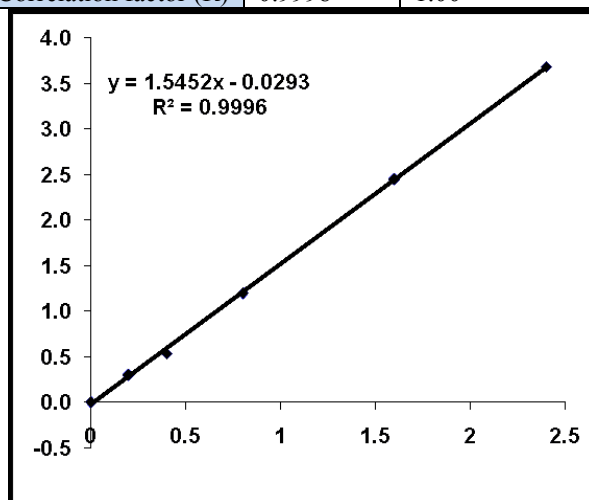
The research question for this extended assay is as follows: What is the effect of combination of metal ions and change of PH value on the absorption of Chlorpheniramine Maleate. To answer this question, an investigation with three experimental method was carried out in which Chlorpheniramine Maleate is tested alone as a first experiment followed by addition of Fe<sup>3+</sup>, Co<sup>+2</sup>, Ca<sup>+2</sup> and Mg<sup>+2</sup> central metal ions as the second experiment. A third experiment was performed simultaneously by mixing of Chlorpheniramine Maleate with Fe<sup>3+</sup>, Co<sup>+2</sup>, Ca<sup>+2</sup> and Mg<sup>+2</sup> metal ions with pH variation.

#### 3.1 Study of Chlorpheniramine Maleate

The absorption spectrum was obtained and  $\lambda_{\text{max}}$  was selected to be 265 nm. A linear Graph was plotted between the theoretical concentrations and absorbance of the standard solutions. Slope, y-intercept, and correlation coefficient (R) were calculated. Results are shown in table 1. The obtained equation for the standard curve was  $Y = 0.0309X - 0.0293$  with a correlation coefficient R of 0.9998, Figure 2. Test results observed are in conformity to acceptance criteria. Therefore, the method is linear for Chlorpheniramine Maleate between 10 and 120  $\mu\text{g/mL}$  concentration range.

**Table 1:** Standard curve for Chlorpheniramine Maleate between 10 and 120  $\mu\text{g/mL}$  concentration range.

Concentration $\mu\text{g/mL}$	Absorbance	Concentration Back calculation
0	0	0.94822
10	0.299	10.6246
20	0.535	18.26214
40	1.199	39.75081
80	2.452	80.30097
120	3.683	120.1392
Slope	0.0309	0.0309
Intercept	-0.0293	-0.0293
Correlation factor (R)	0.9998	1.00



**Figure 2:** Standard curve (concentration vs absorbance) for Chlorpheniramine Maleate in the range 10 and 120  $\mu\text{g/mL}$ .

### 3.2 Study of the absorbance of Chlorpheniramine Maleate combined with ( $Fe^{3+}$ , $Co^{+2}$ , $Ca^{+2}$ and $Mg^{+2}$ ) metal ions

The absorption spectra for the prepared metal ions were obtained and compared to that of Chlorpheniramine Maleate. No bands are observed at 265 nm to eliminate interference. Excess amounts of  $Fe^{3+}$ ,  $Co^{+2}$ ,  $Ca^{+2}$  and  $Mg^{+2}$  metal ions were added to separate solutions of Chlorpheniramine Maleate in the range 10 and 120  $\mu\text{g/mL}$  to form complexes of the mentioned metal ions based on chlorpheniramine Maleate. Finally, the absorbance of solutions is measure and compared to that of pure Chlorpheniramine Maleate. The results showed that the metal ions have a hyperchromic effect on the Chlorpheniramine Maleate band at 265 nm. Graphs were plotted between the theoretical concentrations and the new absorbance values of standard solutions combined with metal ions. Slope, y-intercept, and correlation coefficient (R) were calculated. From the graphs, it was observed that the slope values are increased significantly which indicates an increase in absorbance. The results are shown in table 2.

**Table 2:** Absorbance values of Chlorpheniramine Maleate after combination of excess amounts of  $Fe^{3+}$ ,  $Co^{+2}$ ,  $Ca^{+2}$  and  $Mg^{+2}$  metal ions

Concentration Chlorpheniramine Maleate $\mu\text{g/mL}$	Absorbance of pure Chlorpheniramine Maleate	Absorbance of Chlorpheniramine Maleate combined with $Fe^{+3}$	Absorbance of Chlorpheniramine Maleate combined with $Ca^{+2}$	Absorbance of Chlorpheniramine Maleate combined with $Co^{+2}$
0	0	0	0	0
10	0.299	0.352	0.313	0.322
20	0.535	0.606	0.675	0.639
40	1.199	1.248	1.263	1.361
80	2.452	2.518	3.329	2.704
120	3.683	NA <sup>a</sup>	NA <sup>a</sup>	3.85
Slope	1.5452	0.033	0.0415	0.0325
Intercept	0.0293	0.0296	0.1295	0.0170
Correlation coefecient (R)	0.9998	0.9992	0.9922	0.9993

a. Not aplicable

However, the investigation of spectroscopic and molecular theory in relation to Chlorpheniramine Maleate lead to the conclusion that mixing with  $Fe^{3+}$ ,  $Co^{+2}$ ,  $Ca^{+2}$  and  $Mg^{+2}$  metal ions has a hyperchromic effect on the absorption of Chlorpheniramine Maleate. By addition of metal ions at low pH values, maleic acid is coordinated. As a result, the chlorpheniramine part of the drug is free. The nitrogen atoms remain with low basicity and unavailable for coordination bond with  $Fe^{3+}$ ,  $Co^{+2}$ ,  $Ca^{+2}$  and  $Mg^{+2}$  metal ions. This will lead to increase absorptivity of the chlorpheniramine and hence the absorbance.

### 3.3 Effect of pH on the absorbance of Chlorpheniramine Maleate combined with ( $Fe^{3+}$ , $Co^{+2}$ , $Ca^{+2}$ and $Mg^{+2}$ ) metal ions

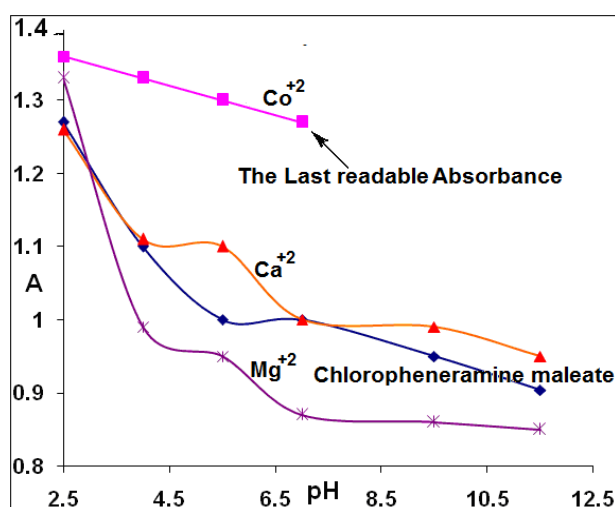
Excess amounts of  $Fe^{3+}$ ,  $Co^{+2}$ ,  $Ca^{+2}$  and  $Mg^{+2}$  metal ions were added to separate solutions of Chlorpheniramine Maleate with a concentration of 40  $\mu\text{g/mL}$ . This concentration was selected as it is the mid-point in the calibration curve. The pH values were changed to the values listed in table 3. The color of  $Fe^{+3}$  solution turned from light yellow to dark yellow and the absorbance values became nonreadable (out of range) except that at pH 2.5. The gradual increase of pH for  $Co^{+2}$  solutions resulting in decrease of absorbance reading until pH 9.5 at which a pink precipitate appeared (Figure 3) and the absorbance started to be nonreadable. Combination of chlorpheniramine Maleate with  $Ca^{+2}$  and  $Mg^{+2}$  metal ions exhibit a gradual decrease of the absorbance, Figure 3. In all cases the decrease of absorbance values may be due to the increase of complexation possibility between the corresponding metal ions with chlorpheniramine Maleate resulting from the increase of basisity of the nitrogen atoms.

Potentiometric measurements have been performed to correlate the spectrophotometric results. Figure 4 shows the speciation curves for the combination reaction of  $Ca^{+2}$  and  $Co^{+2}$  with Chlorpheniramine Maleate. The combination of  $Mg^{+2}$  produced curves similar to that of  $Ca^{+2}$ . The curves illustrate the concentration growth of Calcium-maleic acid with the decline of the concentration of  $Ca^{+2}$  metal ion. At high pH values, maleic acid is coordinated to metal ions, the nitrogen atom is nonprotonated and relatively stronger as a base. As a result the chlorpheniramine part of the drug is free for coordination with  $Fe^{3+}$ ,  $Co^{+2}$ ,  $Ca^{+2}$  and  $Mg^{+2}$  metal ions. That leads to decrease of the concentration of chlorpheniramine and hence the absorbance.

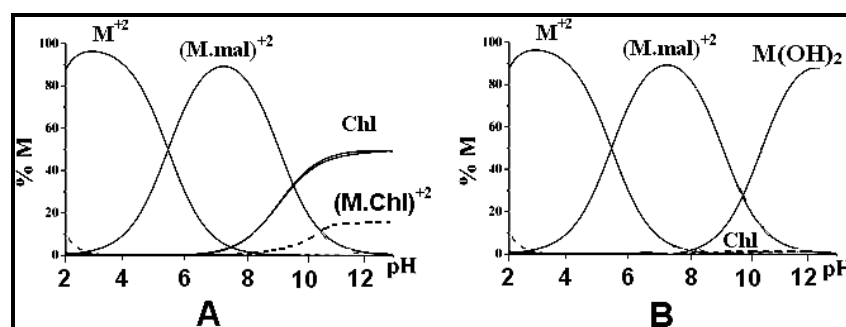
**Table 3:** Absorbance versus pH values of Chlorpheniramine Maleate (conc. 40 µg/mL) after combination of excess amounts of Fe<sup>3+</sup>, Co<sup>+2</sup>, Ca<sup>+2</sup> and Mg<sup>+2</sup> metal ions

pH value	Absorbance of Pure Chlorpheniramine Maleate	Combination with Co <sup>+2</sup>	Combination with Ca <sup>+2</sup>	Combination with Fe <sup>3+</sup>	Combination with Mg <sup>+2</sup>
2.5	1.27	1.36	1.26	1.248	1.33
4	1.1	1.33	1.11	NA <sup>a</sup>	0.99
5.5	1	1.3	1.1	NA <sup>a</sup>	0.95
7	1	1.27	1	NA <sup>a</sup>	0.87
9.5	0.95	NA <sup>a</sup>	0.99	NA <sup>a</sup>	0.86
11.5	0.904	NA <sup>a</sup>	0.95	NA <sup>a</sup>	0.85

a. Not applicable



**Figure 3:** pH versus absorbance of Chlorpheniramine Maleate (conc. 40 µg/mL) after combination of excess amounts of Co<sup>+2</sup>, Ca<sup>+2</sup> and Mg<sup>+2</sup> metal ions. The decline of Co<sup>+2</sup> curves is stopped at pH 9.5 because precipitate was observed. All absorbance values in case of Fe<sup>+3</sup> are nonreadable.



**Figure 4:** A) Speciation curves after combination of Ca<sup>+2</sup> with Chlorpheniramine Maleate. The combination of Mg<sup>+2</sup> produced similar curves to Ca<sup>+2</sup>. B) Speciation curves after combination of Co<sup>+2</sup> with Chlorpheniramine Maleate. (mal=Maleate group, Chl= chlorpheniramine)

The order of decreasing the absorbance values is as follows: Mg<sup>+2</sup>, Ca<sup>+2</sup>, and Co<sup>+2</sup>. All absorbance values in case of Fe<sup>+3</sup> are nonreadable. This is a logical result since magnesium ion has the smallest size between the four metal ions, that facilitate its crossing through the dimethyl groups and bonding to the nitrogen atom.

#### 4. Conclusions

The absorbance intensity of Chlorpheniramine Maleate drug in the presence of Fe<sup>3+</sup>, Co<sup>+2</sup>, Ca<sup>+2</sup> and Mg<sup>+2</sup> metal ions have been studied. The investigation of spectroscopic and molecular theory in relation to Chlorpheniramine Maleate lead to the conclusion that forming complex ions from Chlorpheniramine Maleate with Fe<sup>3+</sup>, Co<sup>+2</sup>, Ca<sup>+2</sup> and Mg<sup>+2</sup> metal ions has a hyperchromic effect on the absorption of Chlorpheniramine Maleate. A reverse

behavior was observed when a gradual increase in pH value was performed on the combinations. The absorbance measurements were correlated by potentiometric measurement which facilitates the determination of the free metal ion, free ligand or metal-ligand complex concentrations. The spectroscopic and potentiometric results are found to be consistent. This work can be applied to other drugs with different functional groups such as thiols and alcohols which may show interesting results. This can lead to crucial decisions before introducing functional drugs to human body.

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