Spectrophotometric Determination of Promethazine Hydrochloride in Pure and Pharmaceutical Dosage Forms

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ABSTRACT

A rapid and simple spectrophotometric procedure for the estimation of promethazine HCl in pure and pharmaceutical dosage forms is reported with the aid of the oxidation of the drug. The promethazine HCl is oxidized with chromium trioxide in acidic medium, which leads to form a product, existing maximum absorption at 515 nm. Many parameters of the reaction conditions have been studied and optimized to enhance the sensitivity of the proposed method. After plotting the calibration graph, it was found that Beer’s law is obeyed over the concentration range of 5.0 – 100.0 µg/mL, with 3.0 µg/mL and 5.2×10³ l/mol. cm. of detection limit and molar absorptivity, respectively. The accuracy and precision of the method were tested and obtained values were acceptable. The influence of common interferences on the proposed method was studied and the method was applied for the estimation of promethazine HCl in different pharmaceutical formulations available in market with good recoveries.

1. INTRODUCTION

Promethazine hydrochloride (PH) [N,N-dimethyl-1-(10H-phenothiazine-10-yl)propan-2-amine] hydrochloride, is a derivative of the family of phenothiazine compounds that considered as the first-generation antihistamine drugs (Badawy and El Said, 2013), (Fig. 1). Although promethazine in the 1950’s as antipsychotic drugs is introduced for the first time but still widely used in the treatment of several mental disorders from moderate to severe illnesses such as schizophrenia (Basavaiah and Swamy, 2001). The drug also is widely used as antihistaminic, antiemetic, antipruritic, analgesic and anticholinergic, sedative and anti-motion sickness. In addition to its effect for treatment of insomnia (Badawy and El Said, 2013), (Basavaiah and Swamy, 2001), (Balammal et al., 2012).

The therapeutic significance of promethazine has induced many researchers to establish and report different methods for determination of promethazine in
pharmaceutical formulations and body fluids (Basavaiah and Swamy, 2001).

In literature survey, many methods have been described for quantification of PH in pure and/or in pharmaceutical dosage forms. They include HPLC (Thumma et al., 2008, Borkar et al., 2009, Kakadiay et al., 2014), capillary zone electrophoresis (Lara et al., 2005), potentiometric (Badawy and El Said, 2013, Ganjali et al., 2009, Hassan et al., 2011), voltammetric (Xiao et al., 2007), chemometric (Shamsipur et al., 2002, Ni and Qi, 2006), chemiluminescence (Sultan et al., 2003, Jabbar and Faizullah, 2015), derivative spectrophotometric (Shamsipur et al., 2002, Al-Saidi and Hammza, 2014), and UV/Visible spectrophotometric methods (Nagaraja et al., 2000, Ramesh et al., 2003, Basavaiah, 2004, Saif and Anwar, 2005, Al-Ward, 2005, Abdulrahman et al., 2005, Mohamad et al., 2006, Al-Sabha et al., 2006, AL-Ayash et al., 2008, Al-Talib and Al-Sabha, 2009, Mezal, 2009, Balamimal et al., 2012, Nurahmanto, 2013, Shakir and Turkey, 2013, Al-khadimy, 2016, Zare and Mohammadlo, 2016).

Spectrophotometric technique because of its simplicity, acceptable sensitivity and economic factors nowadays is the preferred methodology for most routine analysis (Ramesh et al., 2003). Hence numerous direct spectrophotometric methods have been suggested for estimation of PH, most of these developed methods are based on the oxidation of the drug by using oxidizing agents such as iodate, bromate, molybdate, iron (III), vanadate, cerium (IV), N-bromosuccinimide, p-benzoquinone and 2-iodobenzoate to the radical cations and subsequent measurement of absorbance of coloured product (Basavaiah and Swamy, 2001).

In the current work here a rapid and cost-effective spectrophotometric method proposed for quantitative analysis of PH in pure and pharmaceutical dosage forms based on the oxidation of PH with chromium trioxide in acidic medium to produce a coloured free radical cation.

![Figure (1): Chemical structure of PH](image)

2. MATERIALS AND METHODS

2.1. Apparatus

The spectral and absorbance records were carried out on a UV/Visible digital single-beam spectrophotometer of BIO-TEK Instruments (BIO-TEK Instruments manufactured in the UK for Bio-Tek instruments, model: KP-99-90283, Milan, ITALY) with using 10-mm path length quartz cell.

2.2. Reagents and chemicals

All of the used chemicals were of analytical reagent grade.

2.2.1 PH solution (250 µg/mL) (Fluka): 0.025 g of PH compound was dissolved and diluted to the mark with distilled water in 100 mL volumetric flask. Each working standard solutions were freshly prepared by further dilution of the stock solution with distilled water.

2.2.2 Chromium trioxide solution, CrO₃ (0.05% w/v) (Fluka): 0.050 g of this compound was dissolved and diluted to 100 mL with distilled water.

2.2.3 Sulfuric acid solution, H₂SO₄ (3.0 M) (S.d. Chemi Limited, Mumbai)

2.3. Recommended procedure

In a series of 25 mL volumetric flasks, each one containing 0.5 mL CrO₃ (0.05%), 2.0 mL
H₂SO₄ (3.0 M), and (125.0 – 2500.0) μg of PH, then the contents in each flask were diluted to the mark with distilled water, and the coloured product is monitored spectrophotometrically against a reagent blank at 515 nm. The reagent blank is prepared in the same manner but without PH.

3. RESULTS AND DISCUSSION

3.1. Absorption Spectra

After treating PH according to the recommended procedure, the absorption spectra of the coloured compound showed that maximum absorption can be obtained at 515 nm. While, the reagent blank has no significant absorbance in this region, as it is shown in the Fig.2.

![Figure (2): Absorption spectra of reagent blank against distilled water (1) and coloured product against reagent blank (2) treated according to the recommended procedure.](image)

3.1.1. Optimization of reaction conditions

Basing upon the idea which recommended by some described methods (Al-Talib and Al-Sabha, 2009, Shakir and Turkey, 2013, Al-khadimy, 2016), formation of coloured free radical cation of promethazinium upon the oxidation of the drug by an oxidizing agent in acidic medium, a reaction mechanism has been proposed for the current work as illustrated in Scheme 1. Then optimization of the reaction condition has been studied as follows:

![Scheme (1): Proposed reaction mechanism for the formation of coloured compound.](image)

The effect of the type and concentration of acids were studied. The results showed that use of 2.0 mL H₂SO₄ (3.0 M) was found to give better results as shown in Figs. 3, 4 and 5. The effect of volume of 0.05% CrO₃ solutions as oxidizing agent was examined, 0.5 mL of this solution gave the maximum intensity (Fig. 6). The order of addition of the reactants should be followed, as mentioned in the recommended procedure.

![Figure (3): Effect of type of acids on colour intensity or reaction product.](image)

![Figure (4): Effect of the concentration of H₂SO₄ on colour intensity of reaction mixture.](image)
Figure (5): Effect the volume of 3.0 M of H₂SO₄ on colour intensity of the product.

Figure (6): Effect the volume of 0.05% of CrO₃ on absorbance of the coloured product.

The effect of temperature on the absorbance of the product was examined, the results showed that there was no significant difference in the absorbance measurements of the compound under study; therefore, the experiments have been carried out at room temperature.

Under the optimized conditions, stability of the coloured product was studied, the results indicated that the colour developed instantaneously and remains stable just for about 5.0 minutes and after that time the colour begins to diminish.

3.2. Calibration curve and its statistical data

Under the chosen optimum conditions, a calibration curve was constructed (Fig. 7). The graph showed that the colour system seems to obey Beer’s law within the concentration range of 125.0 – 2500.0 μg of PH in a 25 mL of final volume (i.e. 3.0 – 100.0 μg/mL of PH). Table 1 summarized the statistical data of the calibration curve of proposed spectrophotometric method for determination of PH.

![Calibration curve constructed under optimum conditions.](image)

Table 1 - Statistical data of the calibration curve for the determination of PH spectrophotometrically.

| Parameters       | Values |
|------------------|--------|
| λ<sub>max</sub> (nm) | 515    |
| Colour           | Red    |
| Linear range     | 5.0 – 100.0 |
| Regression       | A = 0.0052x |
| Slope            | 0.0052 |
| Intercept        | 0.0344 |
| Molar            | 5.2 × 10<sup>3</sup> |
| Correlation      | 0.9995 |
| Detection        | 3.0    |

3.3. Accuracy and precision

Depending upon the values of the relative error percentage (Error %) and percentage of the relative standard deviation (RSD %), accuracy and precision of the proposed method for determination of PH were studied by estimation of five replicate standard PH solution at three concentration levels, respectively. Table 2 summarizes the results.

3.4. Interferences study

The selectivity of the proposed method was examined by studying the effects of different additives and excipients that generally present in dosage forms of PH such as; starch, talk, lactose, dextrose, mannitol, fructose, glucose,
sucrose and Mg-stearate on the determination of 50 μg/mL of PH. The interferent is a species that caused a relative error percentage in the sample absorbance greater than ±5.0%. The results indicated that the studied excipients did not interfere in the examined method, even when they are present at more than 100-folds of cited drug except Mg-stearate which starts to effect on the method when its concentration exceed 10-folds that of the analyte due to the formation of colloidal solution.

Table 2 -Accuracy and precision of the proposed spectrophotometric method.

| PH Concentration (μg/mL) | Error %  | RSD %  |
|--------------------------|----------|--------|
| 5.0                      | -3.41    | +2.21  |
| 50.0                     | -1.15    | +0.88  |
| 100.0                    | -3.60    | +1.89  |

4. Application of the method

The proposed method was applied successfully to the determination of PH in different pharmaceutical formulations (tablet, syrup and injection) which commercially available in Erbil market.

The preparation of tablet and syrup samples were carried out according to the procedure reported by Al-Ward (Al-Ward, 2005), while injection sample was treated according to the procedure that used by Al-Kahdimy (Al-Khadimy, 2016), and the measurement was made by applying the recommended procedure.

In addition, study of the recovery was carried out by adding known quantities from the standard PH to the pre-determined dosage forms. Then total amount of PH was determined with the proposed method and the added drug amount was calculated by the difference. Table 3 summarized the compositions, companies, trade names, determination of PH contained in pharmaceutical formulations with the proposed method and the recovery of the proposed method.

5. Conclusions

The proposed method was applied successfully for the estimation of PH in the bulk and different pharmaceutical formulation samples. The proposed method offers some advantages such as; simplicity, rapidity, reproducibility, more sensitivity than some of the reported methods (Ramesh et al., 2003, Basavaiah, 2004, Al-Ayash et al., 2008, Mezal, 2009), and wide applicable range compare with other published methods (Balammal et al., 2012, Nagaraja et al., 2000, Ramesh et al., 2003, Basavaiah, 2004, Al-Ward, 2005, Abdulrahman et al., 2005, Mohamad et al., 2006, Al-Sabha et al., 2006, Al-Talib and Al-Sabha, 2009, Mezal, 2009, Al-Khadimy, 2016, Zare and Mohammadloo, 2016). In addition, the procedure requires neither heating nor extraction process. Table 4 summarizes the comparison of present proposed work with the some reported methods.

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Table 3- Determination of PH in commercial pharmaceutical formulations with the recovery results of the proposed method.

| Item Type                  | Company                        | Trade Name | Found Amount (mg) | Recovery % |
|----------------------------|--------------------------------|------------|-------------------|------------|
| Tablet, 25 mg              | United Pharmaceuticals, Jordan | HISTAZIN   | 24.680            | 98.75      |
| Promethazine HCl, Syrup    | Sina Darou, Iran               | Promethazine | 5.238           | 102.10     |
| Promethazine HCl Solution for Injection, 25 mg/mL | Sanofi Aventis, Ireland | Phenergan © | 24.854          | 99.10      |

Table 4- Comparison of the present method for the spectrophotometric determination of PH with some published methods.

| Reagents                                      | $\lambda_{\text{max}}$ nm | Determination Limit (μg/mL) | Molar Absorptivity (L/mol.cm) | Ref.                     |
|-----------------------------------------------|-----------------------------|-----------------------------|-------------------------------|--------------------------|
| Fe (III) + K$_3$[Fe(CN)$_6$]                  | 700                         | 0.1 – 7.0                   | $3.66 \times 10^4$            | (Nagaraja et al., 2000)  |
| $o$-Toludine + N-Bromosuccinimide             | 516                         | 2.0 – 15                    | $4.64 \times 10^3$            | (Ramesh et al., 2003)   |
| K$_2$Cr$_2$O$_7$ + Fe (II) + 1,10-phenanthroline | 510                      | 2.5 – 25                    | $3.46 \times 10^3$            | (Basavaiah, 2004)       |
| Sulphanilamide + FeCl$_3$                     | 600                         | 1.0 – 36.0                  | $1.74 \times 10^4$            | (Al-Ward, 2005)         |
| $p$-Aminobenzoic acid + N-Bromosuccinimide    | 600                         | 2.0 – 30.0                  | $1.0 \times 10^4$             | (Abdulrahman et al., 2005) |
| Sodium hypochloride + sulphanilic acid        | 513                         | 4.0 – 28.0                  | $8.28 \times 10^3$            | (Al-Sabha et al., 2006) |
| Rhodium (II)                                 | 472                         | 30.0 – 150.0                | $3.8 \times 10^3$             | (AL-Ayash et al., 2008) |
| N-Bromosuccinimide                           | 516                         | 2.0 – 20.0                  | $6.16 \times 10^3$            | (Al-Talib and Al-Sabha, 2009) |
| In (III)                                      | 304                         | 2.0 – 20.0                  | $1.92 \times 10^3$            | (Mezal, 2009)           |
| Bromothymol blue                             | 416                         | 4.0 – 20.0                  | $3.283 \times 10^5$           | (Balammal et al., 2012) |
| Bromocrysol green                            | 414                         | 2.0 – 20.0                  | $1.341 \times 10^5$           |                          |
| CrO$_3$                                       | 515                         | 5.0 – 100.0                 | $5.2 \times 10^3$             | p.w.*                   |

* p.w.= present work

REFERENCES

ABDULRAHMAN, L. K., AL-ABACHI, A. M. & AL-QAISSEY, M. H. 2005. Spectrophotometric micro determination of promethazine hydrochloride in pharmaceutical dosage forms via oxidative coupling reaction with p-aminobenzoic acid and N-bromosuccinimide. Um-Salama Science Journal, 2, 471-476.

AL-AYASH, A. S., JASIM, F. & ZAIR, T. 2008. Spectrophotometric micro determination of drug promethazine hydrochloride in some pharmaceutical by chelating with Rhodium. Um-Salama Science Journal, 5, 638-645.
AL-KHADIMY, A. S. H. 2016. Flame emission and molecular absorption spectrophotometric determination of promethazine hydrochloride via potassium dichromate as oxidant reagent. *World Journal of Pharmaceutical Sciences*, 4, 323-329.

AL-SABHA, T. N., AHMAD, N. R. & IBRAHIM, M. I. 2006. Spectrophotometric determination of promethazine hydrochloride via oxidative coupling reaction with sulphanilic acid. *University of Sharjah Journal of Pure & Applied Sciences*, 3, 1-12.

AL-SAIDI, K. H. & HAMMZA, R. A. 2014. Spectrophotometric Determination of Promethazine Hydrochloride and Paracetamol in Pharmaceutical Tablets. *Journal of Al-Nahrain University*, 17, 14-23.

AL-TALIB, S. M. & AL-SABHA, T. A. N. 2009. Spectrophotometric determination of some phenothiazines using N-chlorosuccinimide. *Jou. Raf. Sci.*, 20, 27-37.

AL-WARD, H. S. 2005. Spectrophotometric micro determination of promethazine hydrochloride in pharmaceutical preparations via oxidative coupling reaction with sulphanilamide and in the presence of ferric chloride. *Journal of Um-Al-Qura for Science*, 2, 110-117.

BADAWY, S. S. & EL SAID, S. A. E. S. 2013. Promethazine-Tetraphenyl Boron (III) Modified Carbon Paste Electrode for the Determination of Promethazine Hydrochloride. *American Journal of Analytical Chemistry*, 4, 258.

BALAMMAL, G., MIDHUNA SAGARI, N., MANOJ KUMAR, B. & REDDY, P. J. 2012. Spectrophotometric Estimation of Promethazine Hydrochloride In Bulk and Pharmaceutical Formulations. *International Journal of Pharmaceutical Research and Analysis*, 2, 6-8.

BASAVAIAH, K. 2004. Indirect spectrophotometric determination of some biologically important phenothiazines using potassium dichromate, iron (II) and 1, 10-phenanthroline.

BASAVAIAH, K. & SWAMY, J. M. 2001. A highly sensitive spectrophotometric method for the determination of some phenothiazine antipsychotics using Chloramine-T and indigocarmine. *Analytical sciences*, 17, 963-967.

BORKAR, D., GODSE, V., BAFANA, Y., BHOSELA, A. & TAL-PURANDAR, D.-P. 2009. Simultaneous estimation of paracetamol and promethazine hydrochloride in pharmaceutical formulations by a RP-HPLC method. *Int. J. ChemTech Res. CODEN (USA)*, 2, 667-670.

GANJALI, M. R., VESIMOHAMMADI, B., RIAHI, S. & NOROUZI, P. 2009. Promethazine potentiometric membrane sensor for promethazine hydrochloride pharmaceutical analysis; computational study. *Int. J. Electrochem. Sci.*, 4, 740-754.

HASSAN, A. K., SAAD, B., GHANI, S. A., ADNAN, R., RAHIM, A. A., AHMAD, N., MOKHTAR, M., AMEEN, S. T. & AL-ARAIJ, S. M. 2011. Ionophore-based potentiometric sensors for the flow-injection determination of promethazine hydrochloride in pharmaceutical formulations and human urine. *Sensors*, 11, 1028-1042.

JABBAR, H. S. & FAIZULLAH, A. T. 2015. Flow Injection Analysis with Chemiluminescence detection for Determination of Two Phenothiazines. *International Journal of Pharma Sciences and Research (IJPSR)*, 6, 474-481.

KAKADIAY, J., PARMAR, N. & SHAH, N. 2014. DEVELOPMENT AND VALIDATION OF RP HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF PROMETHAZINE HYDROCHLORIDE AND PARACETAMOL IN COMBINED LIQUID FORMULATION. *Asian Journal of Research in Biological and Pharmaceutical Sciences*, 2, 11-26.

LARA, F. J., GARCÍA-CAMPAÑA, A. M., ALÉS-BARRERO, F. & BOSQUE-SENDRA, J. M. 2005. Determination of thiaziniamum, promazine and promethazine in pharmaceutical formulations using a CZE method. *Analytica chimica acta*, 535, 101-108.

MEZAL, A. N. 2009. Spectrophotometric determination of promethazine hydrochloride by In (III). *Wasit Journal for Science & Medicine*, 2, 49-59.

MOHAMAD, S. H., AL-NAJAFI, S. I. & AL-ABACHI, A. M. 2006. Spectrophotometric determination of promethazine in pharmaceutical preparations. *J. Edu. Sci.*, 18, 33-41.

NAGARAJA, P., DINESH, N. D., GOWDA, N. M. M. & RANGAPPA, K. S. 2000. A simple spectrophotometric determination of some phenothiazine drugs in pharmaceutical samples. *Analytical sciences*, 16, 1127-1131.

NI, Y. & QI, Z. 2006. Differential kinetic spectrophotometric determination of chlorpromazine hydrochloride and promethazine hydrochloride by chemometric method. *Guang pu xue yu guang pu fen xi= Guang pu*, 26, 1364-1367.

NURAHMANTO, D. 2013. Development and validation of UV spectrophotometric method for quantitative estimation of Promethazine HCl in phosphate buffer saline pH 7.4.

RAMESH, K., GOWDA, B. & KESHAVAVYA, J. 2003. Spectrophotometric determination of promethazine hydrochloride in pharmaceutical formulations. *Indian journal of pharmaceutical sciences*, 65, 432.

SAIF, M. J. & ANWAR, J. 2005. A new spectrophotometric method for the determination of promethazine–HCl from pure and pharmaceutical preparations. *Talanta*, 67, 869-872.
SHAKIR, I. M. & TURKEY, N. S. 2013. Flow injection analysis for the photometric determination of promethazine-HCl in pure and pharmaceutical preparation via oxidation by persulphate using Ayah 3SX3-3D solar micro photometer. *J. Baghdad for Sci.*, 10, 1190-1202.

SHAMSIPUR, M., HEMMATEENEJAD, B. & AKHOND, M. 2002. Simultaneous determination of promethazine, chlorpromazine, and perphenazine by multivariate calibration methods and derivative spectrophotometry. *Journal of AOAC International*, 85, 555-562.

SULTAN, S. M., HASSAN, Y. A. & ABULKIBASH, A. M. 2003. Chemiluminescence assay of promethazine hydrochloride using acidic permanganate employing flow injection mode operated with syringe and peristaltic pumps. *Talanta*, 59, 1073-1080.

THUMMA, S., ZHANG, S.-Q. & REPKA, M. 2008. Development and validation of a HPLC method for the analysis of promethazine hydrochloride in hot-melt extruded dosage forms. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*, 63, 562-567.

XIAO, P., WU, W., YU, J. & ZHAO, F. 2007. Voltammetric sensing of promethazine on a multi-walled carbon nanotubes coated gold electrode. *Int. J. Electrochem. Sci.*, 2, 149-157.

ZARE, F. & MOHAMMADLOO, Z. B. 2016. Survey Spectrophotometric Method for Determination of Phenothiazine Drug. *Nature and Science*, 14, 1-5.