Spectrophotometric determination of trifluoperazine via oxidative coupling reaction with sulfanilic acid

Theia'a N. Al-Sabha                                      Omar A. Al-Taee
Department of Chemistry / College of Education
Mosul University

Maha T. Al-Obidi
Department of Chemistry / College of Science
Mosul University

Received 18 / 01 / 2009  Accepted 25 / 02 / 2009

Abstract

A simple spectrophotometric method has been developed for the determination of trifluoperazine hydrochloride in pure and in dosage forms. The method is based on the oxidative coupling reaction with sulfanilic acid in the presence of sodium hypochlorite in acetic acid medium to give a red coloured product with absorption maximum at 510 nm. The product is stable for more than 6 h. Beer's law is obeyed over the concentration range of 0.2–7.0 µg ml⁻¹ with molar absorptivity of
5.15×10³ l.mol⁻¹cm⁻¹. Different experimental parameters affecting the development and stability of the formed coloured product were carefully studied and optimized and a proposal of the reaction pathway was presented. The proposed method was applied successfully to the determination of trifluoperazine hydrochloride in tablets and compared favorably with the official method. Common excipients used as additives in pharmaceutical preparations do not interfere in the proposed method.

**Keywords:** Trifluoperazine hydrochloride, oxidative coupling, sulfanilic acid, spectrophotometry.

**Introduction**

Trifluoperazine hydrochloride (10-[3-(4-methyl-1-piperazinyl) propyl]-2-trifluoro-methylphenothizine dihydrochloride) (I) is a typical antipsychotic drug of the phenothiazine group. It has a central antiadrenergic, antidopaminergic, minimal anticholinergic effects and commonly used antipsychotic drug [1]. It has been known to induce QT prolongation and ventricular tachycardia, which can cause sudden death [2] and hence is used in the treatment of various mental illnesses such as schizophrenia.

![Chemical Structure of Trifluoperazine](image)

The importance of trifluoperazine has prompted many investigators to look for methods for its rapid determination. The official method is based on non-aqueous titration of the pure drug or its dosage forms [3]. Many titrimetric methods based on oxidation by oxidizing agents such as hexacyanoferrate [4], ammonium metavanadate [5], N-bromosuccinimide and other brominating agents [6] and l-chlorobenzotriazole [7] have been proposed. Most other methods are based on oxidation prior to analytical measurement. Typical oxidants used are potassium iodate [8], ammonium molybdate [9], ammonium metavanadate [10], hexacyanoferrate(III) [11], nitroprusside [12], N-bromoprophalimide [13] iron (III) chloride [14] and iodic acid [15] and the final products are determined spectrophotometrically. Spectrofluorimetry has been used after oxidation by N-bromosuccinimide [16] and cerium(IV) [17]. Also potentiometry [18] with an oxidative column in a flow injection system has been applied. High-performance liquid chromatography (HPLC) [19] with electrochemical
detection has been proposed for the determination of phenothiazines in pharmaceuticals and human serum. Other methods proposed for the assay of phenothiazines include potentiometry\cite{20,21}, voltammetry\cite{22,23}, deferential spectrophotometry\cite{24} and chemiluminescene spectroscopy \cite{25,26}.

In this work, a spectrophotometric method for the determination of trifluoperazine hydrochloride is proposed and based on its oxidation by sodium hypochlorite followed by coupling with sulfanilic acid in the presence of acetic acid, The proposed method was applied to determine trifluoperazine hydrochloride in tablets as drug formulations. A satisfactory results were obtained in comparison with official method.

**Experimental**

**Apparatus**

All absorption measurements were carried out on a Shimadzu UV-210A double - beam spectrophotometer supplied with a digital printer DP80Z and matched 1-cm optical silica cells.

**Reagents**

All chemicals used were of analytical reagent grade, the pure trifluoperazine hydrochloride was provided from State Company for Drug Industries and Medical Appliance-(SDI) Sammara-Iraq.

**Trifluoperazine hydrochloride (1000 µg/ml)**

A stock solution of 1000 µg/ml of trifluoperazine hydrochloride was prepared by dissolving of 0.1g in distilled water and then made up to 100 ml in volumetric flask with the same solvent. The working solution of 100 µg/ml was prepared by simple dilution of stock solution and kept protected from sun light in ambient bottle.

**Sulfanilic acid (4x10^{-3} M)**

This solution was prepared by dissolving 0.11g of sulfanilic acid reagent in distilled water and diluted to the mark in 1L volumetric flask with the same solvent.

**Sodium hypochlorite (0.1% v/v)**

This solution was prepared by dilution of 1.25 ml of 8% sodium hypochlorite to 100 ml with distilled water in a volumetric flask.

**Acetic acid (3.5% w/v)**

This solution was prepared by dilution of 3.5 g of glacial acetic acid to 100 ml with distilled water in a volumetric flask.
Spectrophotometric determination of trifluoperazine via oxidative coupling …

Recommended procedure

Aliquots of standard solution of trifluoperazine hydrochloride covering the range (1.25-175µg) were transferred to a 25-ml calibrated flasks containing 5ml of 4x10^-3 M sulfanilic acid solution, 3ml of 0.1% sodium hypochlorite and 1.0 ml of 3.5% acetic acid, then the solutions were made up to the mark with distilled water and left for 10 min. The absorbance was measured at 510 nm against reagent blank.

Analysis of Tablets

Twenty five tablets (each tablet containing 1mg) or five tablets (each tablet containing 5mg) were weighed and finely powdered. An amount of the powder equivalent to 5mg of pure drug of trifluoperazine hydrochloride was extracted with 5ml acetone, filtered and the filtrate evaporated to dryness. The residue was dissolved in a portion of distilled water and the volume was made up to 100ml in volumetric flask. The solution was kept in amber-coloured bottle and stored in a refrigerator. The solution was further diluted as needed.

Results and discussion

Absorption spectra

An orange-coloured oxidizing coupling product with an absorption maximum at 510 nm is formed when trifluoperazine hydrochloride was allowed to react with sulfanilic acid in the presence of sodium hypochlorite in acetic acid medium. Figure (1) shows the spectra of orange product formed and of the reagent blank, so; the maximum absorption at 510 nm is used in all subsequent experiments.

Fig.1 Absorption spectra of (a) 75µg trifluoperazine hydrochloride with sulfanilic acid against reagent blank, and (b) reagent blank versus distilled water.
Study of the optimum reaction conditions

The effect of various parameters on the absorption intensity of the dye formed was studied and the reaction conditions are optimized.

Effect of acid

It was found that the presence of acid led to an increase the intensity of the produced product, therefore some acids such as HCl, H₂SO₄ and CH₃COOH are examined and was found that all these acids gave almost equal intensity, so; CH₃COOH was selected which was found that 1ml of this acid gave higher sensitivity and this amount was selected in subsequent experiments.

Effect of sulfanilic acid

When various concentrations of sulfanilic acid reagent solution were added to fixed amount of the drug solution, a 5 ml of 4x10⁻³M solution was found enough to develop the colour in its full intensity and gave a minimum blank value, therefore it was considered to be an optimum amount.

Effect of oxidant concentration

The product formation was reached its maximum intensity when 4-6 ml of 0.1M of sodium hypochlorite solution were added to a mixture of trifluoperazine hydrochloride, sulfanilic acid and acetic acid, therefore 5 ml was selected in the procedure since it gives high sensitivity, minimum blank value and ensure a quantitative determination at the upper limit of the calibration graph.

Effect of temperature and reaction time

The reaction time was determined by following the colour development at room temperature and at different temperatures in thermostatically controlled water-bath. The absorbance was measured at 5min intervals against reagent blank treated similarly. It was observed that formation of coloured complex for trifluoperazine Hydrochloride was achieved its maximum intensity after 10min at room temperature and remain stable for at least 6 hours.

Effect of order of addition

To obtain optimum results the order of addition of reagents should be followed as given under the general procedure, otherwise a loss in colour intensity was observed.

Calibration graph

Employing the optimum conditions described in the recommended procedure, a linear calibration graph for trifluoperazine hydrochloride is obtained (Fig.2), which shows that Beer’s law is obeyed over the
concentration range of 0.2–7.0µg/ml with correlation coefficient of 0.9998 and an intercept of 0.0451. The conditional molar absorptivity of the red product formed was found to be $5.15 \times 10^3$ L.mol$^{-1}$.cm$^{-1}$.

![Calibration graph for determination of trifluoperazine hydrochloride](image)

**Fig.2 Calibration graph for determination of trifluoperazine hydrochloride**

**Interference**

In order to assess the possible analytical applications of the proposed method, the effect of some foreign ions which often accompany with this drug in pharmaceutical products were studied by adding different amounts of foreign ions to 5µg/ml of trifluoperazine hydrochloride. The colour was developed following the recommended procedure described earlier. Substance was considered to interfere with determination if the obtained absorbance values differed by more than ±2% from that of the drug alone. It was observed that the talc, glucose, starch, sulfate, acetate, phosphate and magnesium stearate did not interfere with the determination at levels found in dosage form.

**Precision and accuracy**

Trifluoperazine hydrochloride was determined at three different concentrations. The results shown in Table (1), a satisfactory precision and accuracy has been obtained with the proposed method.

<table>
<thead>
<tr>
<th>Amount of trifluoperazine hydrochloride taken (µg/ml)</th>
<th>Recovery* %</th>
<th>Average recovery %</th>
<th>Relative standard deviation* %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>91.9</td>
<td>99,59</td>
<td>0.81</td>
</tr>
<tr>
<td>4</td>
<td>99.6</td>
<td></td>
<td>1.63</td>
</tr>
<tr>
<td>6</td>
<td>100.2</td>
<td></td>
<td>1.08</td>
</tr>
</tbody>
</table>

* Average of five determinations
Analytical application

Tablets containing trifluoperazine hydrochloride have been analyzed and they showed good accuracy and precision, the results obtained were compared successfully with the official method (Table 2).

Table (2): Determination comparison of trifluoperazine Hydrochloride in tablets by the proposed method and British pharmacopoeia method

<table>
<thead>
<tr>
<th>Procedure applied</th>
<th>Pharmaceutical formulation</th>
<th>Drug amount present (µg/ml)</th>
<th>Recovery* (%)</th>
<th>Drug content found (mg)</th>
<th>Average Drug content found (mg)</th>
<th>Certified value (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed method</td>
<td>Tablet* (Iralzin 1)</td>
<td>0.5 3 6</td>
<td>100.75 101.37 99.12</td>
<td>1.007 1.013 0.991</td>
<td>1.003</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Tablet* (Iralzin 5)</td>
<td>0.5 3 6</td>
<td>99.14 100.18 97.83</td>
<td>4.957 5.009 4.891</td>
<td>4.952</td>
<td>5.0</td>
</tr>
<tr>
<td>British Pharmaco poeia method [6]</td>
<td>Tablet</td>
<td>1mg 5mg</td>
<td>99.61 101.66</td>
<td>0.980 5.083</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

* Mean of three determinations.

** Marketed by S.D.I, Iraq.

Statistical analysis of the results by Student's t-test (1.63) and F-test (3.47) at 95% confidence level showed no significant deference in accuracy and precision between the proposed and official method.

Structure of the dye

The stoichiometry of the reaction between trifluoperazine hydrochloride and sulfanilic acid was investigated applying the Job’s method[27] and mole ratio method[28] using equimolar solutions ($1 \times 10^{-4}$ M) of drug and sulfanilic reagent. The results obtained, as shown in figure 3, indicated that the ratio of 1:2 drug to reagent complex was formed at 510nm.

![Fig.3: Job's plot method (a) and molar ratio method (b) of trifluoperazine hydrochloride - sulfanilic acid in the presence of NaOCl.](image_url)
Therefore the formation of the product probably occurs as follows:

\[
\text{The product formed was water soluble, the stability constant was calculated by comparing the absorbance of a solution containing stoichiometric amount of trifluoperazine hydrochloride and sulfanilic acid with that of solution containing the optimum amount of sulfanilic acid (5 ml of 4x10^{-3}M). The average conditional stability constant of the dye in water under the described experimental conditions was 1.2 \times 10^8 \text{ M}^{-1}\text{.mol}^{-2}.}
\]

**Conclusions**

A simple, rapid, precise and sensitive spectrophotometric method has been developed for the determination of trace amounts of trifluoperazine hydrochloride in aqueous solution based on its oxidative coupling reaction with sulfanilic acid and sodium hypochlorite in the presence of acetic acid. The proposed method does not require temperature control or the solvent extraction step; the method was applied successfully on pharmaceutical tablets.

**References**

1) http://en.wikipedia.org/wiki/Trifluoperazine#Uses