Development of Green Spectrophotometric Method for Determination of Metoclopramide Hydrochloride

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Abstract

A simple, sensitive and green spectrophotometric method for the determination of metoclopramide hydrochloride (MTC) was developed. The method was based on the reaction of MTC with \( p \)-dimethylaminobenzaldehyde (DAB) in acidic aqueous medium (pH 2) in the presence of anionic surfactant sodium dodecyl sulfate (SDS) to give a yellow colored Schiff’s base with a maximum absorbance at 452 nm. Obedience to Beer’s law is achieved in the concentration range 0.2–18.0 \( \mu g \) mL\(^{-1}\) (5.6\( \times \)10\(^{-7}\) – 5.1\( \times \)10\(^{-5}\) mol L\(^{-1}\)), with relative error about 1%, relative standard deviation of less than 0.8% and molar absorptivity 3.02\( \times \)10\(^{4}\) L mol\(^{-1}\) cm\(^{-1}\). The effect of the presence of some common pharmaceutical additives was investigated. The developed procedure was successfully applied to the determination of the drug in pharmaceutical formulations.

Keywords: Metoclopramide hydrochloride, \( p \)-Dimethylaminobenzaldehyde, Spectrophotometric determination, Sodium dodecyl sulfate, Schiff’s base.

1. Introduction

Metoclopramide hydrochloride (MTC) (Fig. 1) chemically named: 4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride [1] is a dopamine receptor antagonist drug [2], it is used as an antiemetic in pharmaceutical preparations [3]. According to its pharmacological importance, several studies were reported for determination in bulk and pharmaceutical forms by using various techniques including spectrophotometric [4-8], chromatographic [9-11] and electrochemical methods [12-13] were reported.

![Figure 1: Structure of Metoclopramide hydrochloride](image)

M. W. = 354.3

Recently, reactions in the presence of surface active agents (surfactants) were attracted considerable attention. The di-phlic behavior of surfactant molecules and formation of micelles in aqueous solution created a new concept of organic reactions in aqueous medium [14]. The micellar phase behaves as organic medium for reaction process [15]. In other words; excluding organic solvents by environmentally friendly surfactants which could be called “green solvents” [16]. Such solvents have several benefits. These involve enhancement of sensitivity by increasing molar absorptivity, decreasing reaction time (colored product formation) and improving stability of the product [17]. One more advantage of using surfactants is the facility of glassware cleaning after use. According to literature, Patel et al were reported spectrophotometric method for estimation of MTC through its reaction with DAB in strong acidic methanolic medium [18]. The produced Schiff’s base gave maximum absorbance at 438 nm. The remarkable advantages of using surfactants medium encourage us to develop this method. The developed procedure excludes toxic methanol solvent [19] by using anionic surfactant sodium dodecyl sulfate (SDS). The developed method gave stable colored Schiff’s base with red shift in maximum absorbance at 452 nm and enhanced the molar absorptivity.
2. Experimental

2.1. Apparatus

All spectrophotometric measurements were carried out on a Shimadzu (UV-160A) UV-Visible Spectrophotometer with 1 cm path-length quartz cells. For controlled measurements in various temperatures, a water circular thermostat Thermo Haake K20 was used. For pH measurements a pH meter HANNA pH211 was used. A Sartorius 2004 MP6 electronic balance was used for weighing.

2.2. Chemicals and Reagents

All Chemicals used were of analytical reagent grade. Distilled water was used to prepare all the solutions. MTC was obtained in highly pure form from the State Drug Industries (SDI), Samarra-Iraq. MTC pharmaceutical preparations were obtained from local market.

Stock solutions equivalent to 100 µg mL\(^{-1}\) of pure MTC was prepared by dissolving 0.0100 g of its powder in distilled water then completed to 100 mL with distilled water. Working solutions equivalent to 10, 20 and 40 µg mL\(^{-1}\) were prepared by appropriate dilution of stock solution.

Hydrochloric acid solution (1.37 mol L\(^{-1}\)) was prepared by diluting 11.7 mL of concentrated acid (Scharlu-Spain, density 1.19 g cm\(^{-3}\)) to 100 mL with distilled water. Working solutions equivalent to 10, 20 and 40 µg mL\(^{-1}\) were prepared by appropriate dilution of stock solution.

A solution of 2×10\(^{-2}\) mol L\(^{-1}\) DAB in 4×10\(^{-2}\) mol L\(^{-1}\) SDS (both Sigma-Aldrich) was prepared by dissolving 0.7460 g of DAB and 2.8837 g of SDS together in distilled water with stirring on hotplate, then diluted after cooling to 250 mL by distilled water.

2.3. Procedure for calibration graph

A 1 mL of 0.137 mol L\(^{-1}\) HCl was added to obtain the desired pH (pH 2) in final dilution and 1 mL of 2×10\(^{-2}\) mol L\(^{-1}\)/4×10\(^{-2}\) mol L\(^{-1}\) of DAB/SDS reagent were added to a series of 10 mL volumetric flask. A known volume of sample or stock MTC was pipetted into the flasks then diluted to 10 mL by distilled water. The reaction mixture immediately became yellow and left to stand at room temperature for 5 min. The absorbance of the colored solution was measured at 452 nm against the blank solution.

2.4. Procedure for tablets

Ten tablets of product (certified value 5 mg MTC) were weighed and ground into delicate powder. An appropriate amount of powder equivalent to one tablet was weighed and dissolved in distilled water and completed to 100 mL in volumetric flask. The solution was filtrated through Whatman No. 42 filter paper, the filtrate solutions were suitably diluted to obtain 10, 20 and 40 µg mL\(^{-1}\) for the analysis.

3. Results and Discussion

3.1. Preliminary study

According to literature MTC was determined spectrophotometrically by its reaction with DAB in methanolic acidic medium at the wavelength of 438 nm [18]. The molar ratio of MTC to DAB is 1:1 according to kinetic study of the reaction [20]. It seemed to be interesting to develop the facilities of this method by using an aqueous medium consisted of anionic surfactant (SDS) instead of organic solvents which have toxic effects, especially with a good solubility of MTC in water. This improved procedure shifted wavelength to 452 nm (Fig. 2) with more enhanced features of microdetermination of the drug.

3.2. Effect of SDS concentration

Preliminary experiments were performed by studying the effect of SDS concentration upon the color development of 3.5 µg mL\(^{-1}\) MTC with 8×10\(^{4}\) mol L\(^{-1}\) DAB at pH 2 medium (Fig. 3). The latter indicates that the optimal concentration of SDS for this purpose was 4×10\(^{-3}\) mol L\(^{-1}\). The absorbance decreases with decreasing SDS because of the lack in micelles which could contain all reactants molecules, in other case the increasing in SDS could also decrease the absorbance due to dilution of reactants molecules in the micellar phase [21].

3.3. Effect of DAB concentration

The effect of DAB concentration upon the absorbance was also explored and shown in Fig. 4 which revealed that the suitable concentration of DAB is 2×10\(^{-3}\) mol L\(^{-1}\) to give maximum absorbance. We couldn't achieve more than 2×10\(^{-3}\) mol L\(^{-1}\) of DAB because of its limited solubility in SDS [22].

3.4. Effect of pH

The effect of pH on the intensity of color was explored and illustrated in Fig. 5. It should be noticed...
that the presence of SDS salt prevented ionic strength and also buffers the composition of the solution [21]. However, the optimum pH for determination was equal to 2. This pH guaranteed the protonation of imine group which is responsible of the visible coloring of produced Schiff’s base [20].

Figure 3. Effect of SDS concentration on the absorbance of 3.5 µg mL\(^{-1}\) MTC

![Graph](image)

Figure 4. The effect of DAB concentration on the absorbance of 3.5 µg mL\(^{-1}\) MTC

![Graph](image)

Figure 5. The effect of pH on the absorbance of 3.5 µg mL\(^{-1}\) MTC

![Graph](image)

3.5. Effect of order of addition and suggested mechanism

The order of addition was studied as shown in Table 1. No significant difference in absorbance was noticed as expected in such three reaction components. However, the order of addition that gives maximum absorbance (HCl + DAB + MTC) was adopted. This is pretty consistent with the described reaction’s theoretical bases. In other words, the reaction occurred mainly via the attack of the protonated carbonyl group of DAB and that of the amino group of MTC to give the product (Scheme 1) [21].

**Table 1. The effect of order of addition upon the absorbance**

<table>
<thead>
<tr>
<th>Order of Addition</th>
<th>Abs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCl + DAB + MTC</td>
<td>0.339</td>
</tr>
<tr>
<td>HCl + MTC + DAB</td>
<td>0.334</td>
</tr>
<tr>
<td>DAB + HCl + MTC</td>
<td>0.333</td>
</tr>
<tr>
<td>DAB + MTC + HCl</td>
<td>0.335</td>
</tr>
<tr>
<td>MTC + DAB + HCl</td>
<td>0.335</td>
</tr>
<tr>
<td>MTC + HCl + DAB</td>
<td>0.332</td>
</tr>
</tbody>
</table>

**Scheme 1: Suggested reaction mechanism**

3.6. Effect of different types of surfactants

The effect of the presence of other types of surfactants (instead of SDS) on the absorbance was investigated. Two types were used, cationic; cetyl tetra ammonium bromide (CTAB) and nonionic; triton X-100. No color development was observed, due to the negative charged surface of anionic surfactants (SDS), this could be increasing the stability of the positively charged intermediate. Such an intermediate belongs to the formed group of hemiaminal through the MTC amino group (Scheme 1) attack of positively charged carbon atoms of protonated aldehyde (presence of HCl) unable to materialize this in the presence of cationic or nonionic surfactants

3.7. Effect of time and temperature

The stability of colored product in different temperatures was explored. Table 2 showed that in room temperature or higher, the color developed immediately and remained stable for more than one hour, and more than 24 hours. While in lower than room temperature the color needed more than 15 minutes to complete developing.
4. Method validation

The typical calibration data for MTC obtained from linear regression analysis of absorbance against concentration (Fig. 6) of the presented procedure gave Beer’s law limit in the range of 0.2 - 18.0 µg mL⁻¹. The slope, intercept, molar absorptivity and related data are listed in Table 3.

5. Accuracy and precision

The accuracy and precision of the suggested method were explored by performing five duplicates analysis on pure drug solutions at three different concentrations. The relative standard deviation (RSD) and average recovery (%) indicated that the method is quite accurate and precise (Table 4).

Table 4: Precision and accuracy of developed method

<table>
<thead>
<tr>
<th>Amount taken (µg mL⁻¹)</th>
<th>Recovery* (%)</th>
<th>Average recovery (%)</th>
<th>RSD %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>101.64</td>
<td></td>
<td>0.744</td>
</tr>
<tr>
<td>10</td>
<td>101.36</td>
<td>100.82</td>
<td>0.749</td>
</tr>
<tr>
<td>16</td>
<td>99.46</td>
<td></td>
<td>0.347</td>
</tr>
</tbody>
</table>

*Average of five determinations.

5.1. Interference study

The effect of the presence of some common pharmaceutical additives on the efficiency of the presented method was examined and listed in Table 5. The results indicate that there are no significant interferences produced by these foreign substances on the presented procedure.

Table 5: Effect of interferences on recovery of 3.5 µg mL⁻¹ of MTC

<table>
<thead>
<tr>
<th>Foreign compound</th>
<th>Recovery (%) of 3.5 µg MTC per µg of foreign compound added</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starch</td>
<td>99.05, 101.99, 103.29</td>
</tr>
<tr>
<td>Acacia</td>
<td>102.97, 102.53, 99.92</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>101.44, 103.07, 100.14</td>
</tr>
<tr>
<td>Glucose</td>
<td>103.94, 102.42, 101.77</td>
</tr>
<tr>
<td>Sucrose</td>
<td>102.97, 104.05, 102.2</td>
</tr>
<tr>
<td>Lactose</td>
<td>102.97, 103.62, 102.86</td>
</tr>
<tr>
<td>Glycerin</td>
<td>103.62, 102.75, 101.33</td>
</tr>
</tbody>
</table>

5.2. Real samples

Application of the presented method for determination of MTC in some pharmaceutical preparations as tablets in three different concentrations was carried out (Table 6). Good results were obtained for the applicability of the suggested method for such preparations which promote the possibility of using the developed method for routine determination procedure of these preparations in quality control laboratories.
Table 6. Determination of pharmaceutical preparations of MTC by suggested method

<table>
<thead>
<tr>
<th>Pharmaceutical preparation</th>
<th>Certified value (mg)</th>
<th>Amount taken (µg/mL)</th>
<th>Drug content found (mg or g)</th>
<th>Recovery %**</th>
<th>Average recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet (1)</td>
<td>5</td>
<td>3</td>
<td>10</td>
<td>5.18</td>
<td>103.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.01</td>
<td>100.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.91</td>
<td>98.26</td>
</tr>
<tr>
<td>Tablet (2)</td>
<td>5</td>
<td>3</td>
<td>10</td>
<td>4.97</td>
<td>99.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.89</td>
<td>97.87</td>
</tr>
</tbody>
</table>

* Table 1 was obtained from State Drug Industry (SDI), Samarra, Iraq. Tablet 2 from Ajanta Pharma, India, batch no. AN002XL.
** Mean of five determinations.

However, it seems interesting to make a comparison between the presented procedure with this of Patel [18] (in methanolic medium and in the absence of SDS). The comparison included some analytical parameters for the determination of MTC in bulk form. It is apparent from the summarized results of Table 7; that the presented procedure is more sensitive and applicable than the other. Furthermore, the exclusion of organic solvents by using surfactant medium (SDS) which is quite green. Furthermore, the exclusion of organic solvents by using surfactant medium (SDS) which is quite green.

Table 7. A comparison between presented and Patel’s method for determination of MTC in bulk form.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Presented method</th>
<th>Patel’s method</th>
</tr>
</thead>
<tbody>
<tr>
<td>λ_max (nm)</td>
<td>452</td>
<td>438</td>
</tr>
<tr>
<td>Beer’s Law limits (µg/mL)</td>
<td>0.2 - 18.0</td>
<td>10-100</td>
</tr>
<tr>
<td>Molar absorptivity (L·mol⁻¹·cm⁻¹)</td>
<td>3.02×10⁴</td>
<td>2.19×10³</td>
</tr>
<tr>
<td>Coefficient of determination (r²)</td>
<td>0.9988</td>
<td>0.9927</td>
</tr>
<tr>
<td>Solvent</td>
<td>Water</td>
<td>Methanol</td>
</tr>
</tbody>
</table>

6. Conclusions

It can be concluded that the presented procedure has the advantages of simplicity, accuracy and high sensitivity over the reported method. The suggested method obeys Beer’s law in the range of 0.2 - 18.0 µg mL⁻¹ with relative error about 1%, relative standard deviation of less than 0.8% and molar absorptivity 3.02×10⁴ L·mol⁻¹·cm⁻¹. In addition, this investigation promotes studies of replacing organic solvents by aqueous surfactants as green solvent for organic reagents such as DAB in aqueous medium. It should also be noted the interesting advantages especially with trending of the researchers towards using green materials. However, the using of surfactant solution in analytical applications; noting that the suitable type of surfactant can be selected experimentally in such a way that it produces a red shift in the wavelength of absorbance maximum. The obtained results from the above investigation strongly suggest to use the presented method in pharmaceutical applications as routine procedure with good benefits.

7. References

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