Validated Spectrophotometric Determination of Rizatriptan Benzoate in Pharmaceutical Formulations using Alizarin Derivatives

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ABSTRACT
Two simple, sensitive, accurate, precise and economical spectrophotometric methods have been developed and validated for the determination of rizatriptan benzoate (RZT) in pure form and pharmaceutical formulations. These methods were based on the formation of charge transfer complex between RZT as n-electron donor and alizarin red S (ARS) or quinalizarin (Quinz) as π-acceptor in methanol to form highly colored chromogens which showed an absorption maximum at 532 and 574 nm using ARS and Quinz, respectively. The optimization of the reaction conditions such as the type of solvent, reagent concentration and reaction time were investigated. Under the optimum conditions, Beer’s law is obeyed in the concentration ranges 1.0-16 and 2.0-20 μg mL−1 using ARS and Quinz, respectively with good correlation coefficient (r2 ≥ 0.9996) and with a relative standard deviation (RSD% ≤ 1.16). The molar absorptivity, Sandell sensitivity, detection and quantification limits were also calculated. The methods were successfully applied to the determination of RZT in its pharmaceutical formulations and the validity assesses by applying the standard addition technique. Results obtained by the proposed methods for the pure RZT and commercial tablets agreed well with those obtained by the reported method.

Keywords: Rizatriptan benzoate, Spectrophotometry, Alizarin red S, Quinalizarin, Charge transfer reaction, Pharmaceutical formulations.

INTRODUCTION
Rizatriptan is benzoate (RZT) is a new selective 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonist which is chemically described as N, N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate. RZT has a weak affinity for other 5-HT receptor subtypes and is used for the acute treatment of migraine in adults. Rizatriptan (RZT) is official in United States pharmacopoeia (USP)1,2. The literature survey revealed several reported analytical approaches for the determination of RZT in dosage forms and biological materials including liquid chromatography-electrospray tandem mass spectrometry, LC-MS/MS3 for human plasma and high-performance liquid chromatography with fluorescence detection4,5 and in human serum by LC-MS/MS6, high-performance liquid chromatography (HPLC)7,8, electrochemical method9 and spectrofluorimetry11,12. These methods are complex, require long and tedious pre-treatment of the samples and laborious clean up procedures prior to analysis.

A thorough literature search has revealed that only a few spectrophotometric methods have been developed for the determination of RZT in pure and dosage forms13-30. However, many of the above methods suffered from one or other disadvantage like poor sensitivity, require high cost solvents in addition to elaborate treatment, need tedious extraction procedures, rigid pH control, measurements done at shorter wavelengths, heating or cooling step, use of expensive chemical and/or complicated experimental set up as can be seen from Table 1. In contrast, visible spectrophotometry is considered as the most convenient analytical technique in most quality control and clinical laboratories. Spectrophotometric technique, because of simplicity and low cost, sensitivity and good analytical selectivity, significant accuracy and precision and broad availability and applicability for pharmaceutical analysis. In the present work, we developed simple, sensitive, rapid, accurate and validated spectrophotometric method for the determination of RZT in pure and pharmaceutical formulations. The proposed method involves the formation of charge transfer complex between DXL and two alizarin derivatives; quinalizarin (Quinz) and alizarin red S (ARS) as chromogenic reagents. The proposed methods have been validated statistically for their accuracy, precision, sensitivity, selectivity, robustness, and ruggedness as per ICH guidelines.

EXPERIMENTAL

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All absorption spectra were made using Varian UV–Vis spectrophotometer (Cary 100 Conc., Australia) equipped with a 10 mm quartz cell was used for absorbance measurements. This spectrophotometer has a wavelength accuracy of ±0.2 nm with a scanning speed of 200 nm/min and a bandwidth of 2.0 nm in the wavelength range of 200–900 nm.

**Materials and Reagents**

All employed chemicals and solvents (dimethyl sulfoxide, methanol, acetonitrile, acetone and ethanol) were of analytical-reagent grade and high-purified water was used throughout the study.

**Pure RZT drug and pharmaceutical formulations**

Pharmaceutical grade RZT was kindly supplied by Delta Pharmaceutical Industries, Cairo, Egypt. The commercial pharmaceutical formulations (Rizatriptane tablets (Sandoz Pharmaceutical Company, Cairo, Egypt), labeled to contain 10 mg RZT per tablet) were purchased from local market were subjected to the analytical procedure.

**Stock standard Solutions**

A standard stock solution of RZT containing 100 μg mL⁻¹ was prepared by dissolving 10 mg of pure drug in 20 mL DMSO and was further diluted to 100 mL with the same solvent to obtain the working concentration. The standard solution was kept in the refrigerator and was found to be stable for at least one week if they had been stored in a cool (< 25 °C) and dark place.

**Reagents**

Alizarin red S, 3,4-dihydroxy-9, 10-dioxo-2-anthracene sulfonic acid (ARS) and quinalizarin 1,2,5,8-tetrahydroxy-anthraquinone (Quinz) were Sigma-Aldrich products and used without further purification. A stock
solution $1.0 \times 10^{-3}$ mol L$^{-1}$ was prepared by dissolving the appropriate weight of the reagent in approximately 25 mL of DMSO, then completed to the mark with methanol in 100 mL volumetric flask. This solution was stable for one week.

**General procedures**

Aliquots of the standard working solution of RZT in the concentration ranges (1.0-16 μg mL$^{-1}$) and (2.0-1206 μg mL$^{-1}$) using ARS and Quinz, respectively were transferred into a set of 10 mL volumetric flasks. To each flask 2.0 mL of ($1.0 \times 10^{-3}$ mol L$^{-1}$) ARS or Quinz solution was added. Then the mixture was shaken to promote the reaction and the volume was completed to the mark with methanol. The absorbance of the resulting solutions was measured at 532 and 574 nm using ARS and Quinz, respectively against a reagent blanks prepared simultaneously. The calibration graph was constructed by plotting the absorbance versus the final concentration of RZT. The corresponding regression equation was derived.

**Assay procedure for pharmaceutical formulations**

The content of twenty tablets each containing 10 mg RZT was finely powdered using an agate mortar and weighed accurately. An accurately weighed quantity of the powder equivalent to 10 mg RZT were transferred into 100 mL calibrated flask and dissolved in 25 mL methanol. The content of the flask was shaken and sonicated for about 10 min, mixed well and then filtered using Whatman No.42 filter paper. The first portion of the filtrate was
Figure 5: Application of Job’s method to the reaction between reagents and RZT at optimum wavelength.

Scheme 1: Possible mechanism of radical anion formation from RZT and Quinz reaction.
Method bands - the addition of resolution in methanol exhibits an absorption following the volume in a employed, a absorbance.

Coober attributable to complexes formed between The stoichiometric ratios of the charge transfer Stoichiometric relationship graphs.

The nominal content of the tablets was determined using the corresponding regression equations or the calibration graphs.

Stoichiometric relationship

The stoichiometric ratios of the charge transfer complexes formed between RZT and reagents were determined by applying the continuous variation method attributable to Job\(^*\) and modified by Vosburgh and Coober\(^*\) at the optimum wavelengths of maximum absorbance. Job’s method of continuous variation was employed, a \(1.0 \times 10^{-3}\) mol L\(^{-1}\) standard solution of RZT and \(1.0 \times 10^{-3}\) mol L\(^{-1}\) solution of reagent were used. A series of solution were prepared in which the total volume of drug and reagent was kept at 2.0 mL. The reagents were mixed in various proportions with drug and diluted to volume in a 10-mL calibrated flask with methanol following the above-mentioned procedures

RESULTS AND DISCUSSION

Table 1: Comparison between the reported methods for spectrophotometric determination of RZT.

<table>
<thead>
<tr>
<th>Method</th>
<th>(\lambda_{\text{max}}) (nm)</th>
<th>Linear range ((\mu)g mL(^{-1}))</th>
<th>(\varepsilon (\text{l mol}^{-1}\text{cm}^{-1})) x 10(^4)</th>
<th>LOD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPP</td>
<td>425</td>
<td>0.8-16</td>
<td>1.76</td>
<td>0.13</td>
<td>[13]</td>
</tr>
<tr>
<td>BCP</td>
<td>425</td>
<td>1-20</td>
<td>1.96</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>BTB</td>
<td>420</td>
<td>1.2-24</td>
<td>1.63</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>NBS/janus green (JG)</td>
<td>620</td>
<td>0.5-8.0</td>
<td>3.03</td>
<td>0.28</td>
<td>[14]</td>
</tr>
<tr>
<td>NBS/calgamite (CMG)</td>
<td>540</td>
<td>1.5-30</td>
<td>1.15</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>(a) p-CA</td>
<td>530</td>
<td>14-245</td>
<td>0.13</td>
<td>1.36</td>
<td>[15]</td>
</tr>
<tr>
<td>(a) DDQ</td>
<td>590</td>
<td>4-70</td>
<td>0.522</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>(a) MO</td>
<td>420</td>
<td>10-50</td>
<td>1.02</td>
<td></td>
<td>[16]</td>
</tr>
<tr>
<td>(b) FeCl(_2)/2,2’- bipyridyl</td>
<td>490</td>
<td>4.0-20</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) FeCl(_3)/1,10-phenanthroline</td>
<td>2.0-10</td>
<td></td>
<td>3.85</td>
<td></td>
<td>[17]</td>
</tr>
<tr>
<td>(b) Folin–Ciocalteu reagent/</td>
<td>510</td>
<td></td>
<td>2.0-10</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>NaOH</td>
<td>610</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) ARS</td>
<td>425</td>
<td>4.0-20</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) DCQC</td>
<td>610</td>
<td>5-25</td>
<td>1.34</td>
<td>0.134</td>
<td>[18]</td>
</tr>
<tr>
<td>(b) NQS</td>
<td>480</td>
<td>15-75</td>
<td>0.43</td>
<td>0.412</td>
<td></td>
</tr>
<tr>
<td>(c) Brucine/ sodium</td>
<td>530</td>
<td>8-40</td>
<td>0.81</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>metaperiodate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCNQ</td>
<td>744</td>
<td>10-100</td>
<td></td>
<td></td>
<td>[12]</td>
</tr>
<tr>
<td>UV</td>
<td>226</td>
<td>1.0-8.0</td>
<td>0.00368</td>
<td></td>
<td>[19]</td>
</tr>
<tr>
<td>UV</td>
<td>280</td>
<td>0.5-80</td>
<td>0.703</td>
<td></td>
<td>[20]</td>
</tr>
<tr>
<td>Vanillin</td>
<td>590</td>
<td>50-250</td>
<td>1.33</td>
<td>0.156</td>
<td>[21]</td>
</tr>
<tr>
<td>BCG</td>
<td>416</td>
<td>0.5-50</td>
<td>0.5</td>
<td>0.5</td>
<td>[22]</td>
</tr>
<tr>
<td>Sodium Nitro prusside-Acetaldehyde</td>
<td>560</td>
<td>2.0-10</td>
<td>1.09</td>
<td>0.145</td>
<td>[23]</td>
</tr>
<tr>
<td>Chloramine-B in HCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial rate</td>
<td>490</td>
<td>0.01-0.1</td>
<td>0.244</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fixed rate</td>
<td>0.01-0.1</td>
<td></td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>variable time</td>
<td>0.01-0.1</td>
<td></td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ammonium molybdate / H(_2)SO(_4)</td>
<td>590</td>
<td>2.0-10</td>
<td>24.2</td>
<td>0.073</td>
<td>[25]</td>
</tr>
<tr>
<td>p-dimethylaminobenzaldehyde</td>
<td>545</td>
<td>5.0-25</td>
<td>18.3</td>
<td>0.120</td>
<td></td>
</tr>
<tr>
<td>ARS</td>
<td>532</td>
<td>1.0-16</td>
<td>1.957</td>
<td>0.27</td>
<td>The proposed methods</td>
</tr>
<tr>
<td>Quinze</td>
<td>574</td>
<td>2.0-20</td>
<td>1.644</td>
<td>0.60</td>
<td></td>
</tr>
</tbody>
</table>

Rejected, and the solution was then completed to volume with methanol to prepare a stock solution of 100 \(\mu\)g mL\(^{-1}\). Aliquots covering the working concentration ranges for each method were transferred into a series of 10 mL volumetric flasks and the proposed methods were applied. The nominal content of the tablets was determined using the corresponding regression equations or the calibration graphs.

**Stoichiometric relationship**

The stoichiometric ratios of the charge transfer reaction was tested in DMSO, methanol, acetonitrile, acetone and ethanol solvents. Although the highest dielectric constant of DMSO and acetonitrile, best sensitivity was achieved with methanol, probably because of the capacity of this solvent to form stable hydrogen bonds with the addition of methanol to the solution. The high difference between maximum wavelength of the absorbing species in methanol caused an immediate change in the absorption spectrum with the appearance of a new characteristic band for the radical anion (absorbing species) with maximum absorption at 432 and 491 nm for ARS and Quinz, respectively, while RZT solution in methanol showed no absorption in the 400-700 nm range. At optimum conditions, the addition of RZT to reagent solution in methanol caused an immediate change in the absorption spectrum with the appearance of a new characteristic band for the radical anion (absorbing species) with maximum absorption at 432 and 491 nm for ARS and Quinz, respectively (Figure 2). The high difference between maximum wavelength of the reagent and the charge transfer product absorption bands ~ 111 and 83 nm using ARS and Quinz, respectively, allowed the measurement of the charge transfer products with only a small contribution of the reagents that was added in excess in the medium.

**Optimization of the experimental conditions**

**The effect of the solvent nature**

Charge transfer reaction was tested in DMSO, methanol, acetonitrile, acetone and ethanol solvents. Although the highest dielectric constant of DMSO and acetonitrile, best sensitivity was achieved with methanol, probably because of the capacity of this solvent to form stable hydrogen bonds with the addition of methanol to the solution of reagent. The high difference between maximum wavelength of the reagent and the charge transfer product absorption bands ~ 111 and 83 nm using ARS and Quinz, respectively (Figure 2). The high difference between maximum wavelength of the reagent and the charge transfer product absorption bands ~ 111 and 83 nm using ARS and Quinz, respectively, allowed the measurement of the charge transfer products with only a small contribution of the reagents that was added in excess in the medium.

**Absorption spectra**

Reagent solution in methanol exhibits an absorption bands with a well-defined maximum at 421 and 491 nm for ARS and Quinz, respectively, while RZT solution in methanol showed no absorption in the 400-700 nm range. At optimum conditions, the addition of RZT to reagent solution in methanol caused an immediate change in the absorption spectrum with the appearance of a new characteristic band for the radical anion (absorbing species) with maximum absorption at 432 and 491 nm for ARS and Quinz, respectively (Figure 2). The high difference between maximum wavelength of the reagent and the charge transfer product absorption bands ~ 111 and 83 nm using ARS and Quinz, respectively, allowed the measurement of the charge transfer products with only a small contribution of the reagents that was added in excess in the medium.

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The results are also shown that there was a linear dependence of the absorbance to the concentration of RZT in the range 1.0-16 and 2.0-20 using ARS and Quinz, respectively. Linear regression analysis of the data gave the following equations. For ARS, A = 0.0039 + 0.0493C, r² = 0.9996 and A = -0.0079 + 0.0426C, r² = 0.9996 using Quinz, where A is the absorbance, C is the concentration of RZT (μg mL⁻¹), and r² is the correlation coefficient.

The limits of detection (LOD) were determined by establishing the lowest concentration that can be measured with acceptable accuracy and precision according to ICH guidelines. The limits of detection (LOD) were determined by establishing the minimum level at which the analyte can be reliably detected, and the limit of quantification (LOQ) was determined by establishing the lowest concentration under the same conditions as for the sample analysis in the absence of the analyte. The results are also summarized in Table 2. LOQ and LOD were calculated according to the following equations:

LOD = 3.3s /k
LOQ = 10s /k

Where s is the standard deviation of replicate determination values under the same conditions as for the sample analysis in the absence of the analyte. k is the slope of the calibration graph. In accordance with the formula, the LOD were found to be 0.27 and 0.60 μg mL⁻¹ and LOQ were found to be 0.9 and 2.0 using ARS and Quinz, respectively.

Accuracy and precision
To evaluate the accuracy and precision of the proposed methods, intraday and inter-day determination of RZT at three different concentrations for each method were performed using ARS and Quinz. The results are summarized in Table 2, which shows that the methods have acceptable accuracy and precision.

Effect of the reagent concentration
To achieve this objective, an experiment was performed when various volumes of reagents solutions (1.0 x 10⁻³ mol L⁻¹) in the range of 0.5-5.0 mL were added to a fixed RZT concentration (15 μg mL⁻¹) (Figure 4). The results are shown that 2.0 mL of (1.0 x 10⁻³ mol L⁻¹) ARS or Quinz reagent solution was enough to develop the color to its full intensity and gave the highest and constant absorbance values.

Effect of the reaction time and temperature
The optimum reaction time was determined by following the color development at laboratory ambient temperature (25±2°C). Complete color development was attained after 5.0 min for mixing RZT with both reagents. On raising the temperature, the absorbance of the charge transfer complex was decrease with a hypochromic shift, until decayed at 50 °C.

Sequence of additions
The most favorable sequence of addition is "RZT-reagent-solvent" for complete colour development, highest absorbance and stability at the recommended wavelength. Other sequences needed longer time in addition to lower stability. The complexes with this sequence remain stable for at least 3.0 h.

Stoichiometric ratio
The molar ratio of RZT to reagent (ARS or Quinz) in the charge transfer complex was determined by Job’s method of continuous variations, keeping the sum of the molar concentrations of the investigated RZT and reagent fixed. As shown in Figure 5, the molar ratio which gave maximum absorbance was found to be (1:1) (RZT: reagent).

According to literature review in molecular charge-transfer complexes are formed in non-polar solvents while radical anion species are predominant in polar solvents. It is believed that the addition of basic compounds that contains a lone pair of electrons, such as RZT, results in the formation of charge-transfer complexes of n-n type. This kind of complexes can be considered an intermediate molecular-association compound that forms a corresponding radical anion in polar solvents. In this case, radical anions result from the total transfer of charge (Scheme 1).

Validation of the proposed methods
The validity of the methods was tested regarding linearity, specificity, accuracy, repeatability and precision according to International Conference on Harmonization (ICH) guidelines.

Linearity, detection, and quantification limits
Following the proposed experimental conditions, linear regression equations were obtained. The regression plots showed that there was a linear dependence of the absorbance to the concentration of RZT in the range 1.0-16 and 2.0-20 using ARS and Quinz, respectively. Linear regression analysis of the data gave the following equations. For ARS, A = 0.0039 + 0.0493C, r² = 0.9996 and A = -0.0079 + 0.0426C, r² = 0.9996 using Quinz, where A is the absorbance, C is the concentration of RZT (μg mL⁻¹), and r² is the correlation coefficient.

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prepared and analyzed. The intraday studies were performed in one day and inter-day studies in five days (for each level n=6). The accuracy and precisions expressed as percent relative error (RE%) and relative standard deviation (RSD%) values, respectively, found to be within -1.0-0.40% and 0.55-1.75%, respectively for intraday analysis and within -1.1-0.60% and 0.40-1.60%, respectively for inter-day analysis (Table 3). The data proved good accuracy and precision for the developed methods.

**Ruggedness and robustness**

Robustness of the proposed method was assessed by evaluating the influence of small variation of experimental variables, including concentration of analytical reagents and reaction time, on the analytical performance of the proposed method. In these experiments, one experimental parameter was changed while the other parameters were kept unchanged, and the recovery percentage was calculated each time. The analysis was performed with altered conditions by taking three different concentrations of RZT and it was found that the small variations in any of the variables did not significantly affect the results. The RSD% values were in the ranges 0.60 – 2.50% and 0.6-2.1 for ARS and Quinz, respectively (Table 4). This indicated the reliability of the proposed method during its routine application for the analysis of RZT. The ruggedness of the proposed method was assessed by applying the procedures using two different instruments in three different laboratories (instruments) at different times and three different analysts. The inter-analysts RSD% were in the ranges 1.20-2.60% and 0.70-2.20% using ARS and Quinz, respectively, whereas the inter-instruments RSD% ranged from 0.70-2.20% and 0.80-2.30% using ARS and Quinz, respectively, these results were found to be reproducible because the RSD did not exceed 3.0% (Table 4).

**Specificity and effect of excipients**

The specificity of the proposed method was investigated by observing any interference encountered from the common capsule’s excipients. The standard addition method was applied by adding known amounts of pure RZT to a previously analyzed tablet solution. This study was performed by spiking three different levels of pure RZT (50, 100 and 150% of the level present in the tablet) to a fixed amount of drugs in tablet powder (pre-analysed) and the total concentration was found by the proposed methods. The determination with each level was repeated three times and the percent recovery of the added standard was calculated from:

\[
\text{Recovery} \% = \frac{C_F - C_I}{C_P} \times 100
\]
Where $C_F$ is the total concentration of the analyte found, $C_R$ is a concentration of analyte present in the tablet preparation; $C_F$ is a concentration of analyte (pure RZT) added to tablets preparations. The results were recorded in Table 5. The high recovery values of the proposed methods indicated that the excipients did not interfere with the proposed methods indicating the high selectivity of the proposed methods.

Analysis of the pharmaceutical preparations

The proposed methods were applied to the determination of RZT in pharmaceutical formulations (Rizatriptan tablets, 10 mg RZT per tablet). The results of Recovery ± SD values of the proposed methods agree well with the label claim and also were in agreement with the results obtained by the reported method$^{[13]}$ and were statistically compared with those obtained using the reference methods$^{[13]}$. Statistical analysis of the results, using Student’s t-test and the variance ratio F-test at 95% confidence level revealed no significant difference between the performance of the proposed and reference methods regarding the accuracy and precision, respectively (Table 6)$^{[26]}$. It is evident from these results that the proposed methods are applicable to the analysis of RZT in its dosage forms with comparable analytical performance.

CONCLUSIONS

The developed two methods are simple and rapid, sensitive, accurate, robust, and economic. It does not require extraction, heating, or pH adjustment. The chromophore formed is quite stable. These characteristics make the proposed methods very suitable for routine analysis of RZT in quality control laboratories.

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