Non-extractive spectrophotometric determination of valsartan in pure form and in pharmaceutical products by ion-pair complex formation with bromophenol blue and methyl red

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Abstract

Two simple, rapid, green non extractive spectrophotometric methods are described for the estimation of valsartan in tablet dosage form. The determination is based on the ion-pair formation using the dyes, bromophenol blue (BPB) and methyl red (MR). Valsartan forms ion-pair complex selectively with the dyes, as indicated by the formation of a coloured complex with BPB at pH 5.5 with λmax at 424 nm and MR at pH 4.3 with λmax at 494 nm. For both methods, optimal spectrophotometric conditions were established. The linear relationship was found between absorbance at λmax and concentration of drug in the range 8–24 µg/mL for BPB and 4–20 µg/mL for MR. Regression analysis of Beer’s law plot at 424 nm yielded the regression equation, y = 0.0102x + 0.1636 (BPB) and at 494 nm y = 0.0222x – 0.0063 (MR). High values of correlations coefficient (R² = 0.9988 (BPB) and R² = 0.9991 (MR)) and small values of intercept validated the linearity of calibration curve and obedience to Beer’s law. The LOD and LOQ values were calculated to be 1.03 µg/mL and 3.43 µg/mL respectively (BPB) and 0.68 µg/mL and 2.26 µg/mL respectively (MR). Intra-day and inter-day accuracy and precision, robustness were in acceptable limits. The proposed methods were applied for the quantification of valsartan in tablets pertaining to three commercial formulations. Analytical eco-scale for greenness assessment of the proposed spectrophotometric methods showed that both methods corresponds to excellent green analysis with a score of 89.

Keywords

Analytical Eco-Scale, Bromophenol blue, Methyl red, Spectrophotometry, Valsartan

Introduction

Valsartan is an antihypertensive drug, a specific angiotensin II receptor antagonist. Valsartan acts selectively on AT1 subtype receptors. It is prescribed for hypertension, post-infarction, for the treatment of symptomatic heart failure, when it is impossible to use ACE inhibitors or as adjunctive therapy with ACE inhibitors, when it is impossible to use β-blockers. Chemically, valsartan is (2S)-3-methyl-2-[pentanoyl[[2`- (1H-tetrazol-5-yl) biphenyl-4-yl] methyl] amino] butanoic acid (Figure 1) (Ph. Eur 2020).
Ph. Eur 2020 has a monograph on the substance valsartan. Identification of valsartan is regulated by absorption spectrophotometry in the infrared region, determination of enantiomeric purity and optical rotation, quantitative determination - titrimetry (solvent - 2-propanol, titrant - 0.1 M tetrabutylammonium hydroxide).

The chemical structure of valsartan is shown below.

![Chemical structure of valsartan](image)

Figure 1. Chemical structure of valsartan.

The scientific literature describes methods for quantitative determination of valsartan by spectrophotometry – by intrinsic light absorption (Tatar and Saghkh 2002; Kumar et al. 2011; Gupta et al. 2010; Tajane 2018; Jadhav et al. 2014; Lotfyia et al. 2015; Kamal et al. 2020; Peleshok et al. 2021; Drapak et al. 2019a, 2019b) and by reaction products with different reagents (Ramachandran et al. 2011; Omar et al. 2011). Indian scientists have been developed spectrophotometric methods for the determination of valsartan and ezetimibe in drugs using sulfophthalein dyes such as bromophenol blue and bromocresol green (Ramachandran et al. 2011). The method was based on the formation of an ionic associate – a product of the interaction of valsartan with sulfophthalein dyes. The formed yellow ion-pair product gave a batochromic shift in the spectrum with absorption maxima of 425 nm (bromophenol blue) and 428 nm (bromocresol green). The authors found that the stoichiometric ratios of the reacting components were 1:1 for both reaction products. Egyptian scientists from the University of Minia have been proposed spectrophotometric and spectrofluorimetric methods for determining of some angiotensin II receptor antagonists such as losartan, irbesartan, telmisartan and valsartan in substances and tablets (Omar et al. 2011). Spectrophotometric methods were based on the interaction of losartan, irbesartan, telmisartan with sulfophthalein dyes to form a stable yellow complex with a maximum absorption at 413–419 nm. The spectrofluorimetric method was based on the formation between them of a non-extractive binary complex of eosin and losartan, irbesartan, telmisartan and valsartan.

However, many of these methods are limited in their applications or rather much tedious and time consuming. There is, therefore, a need for a rapid simple green spectrophotometric methods for the assay of valsartan in tablet dosage form. The determination is based on the ion-pair formation using the dyes, namely bromophenol blue (BPB) and methyl red (MR).

**Aim of work**

We aimed to develop and validate rapid, simple and green non extractive spectrophotometric methods for the determination of valsartan in tablet dosage form.

**Materials and methods**

**Apparatus**

A double–beam Shimadzu UV-Visible spectrophotometer, with spectral bandwidth of 1 nm wavelength accuracy ±0.5 nm, Model –UV 1800 (Japan), Software UV-Probe 2.62, and a pair of 1 cm matched quartz cells, was used to measure absorbance of the resulting solution. Designed in accordance with the governing Japanese and European Pharmacopoeia, the new UV-1800 UV-VIS spectrophotometer achieves a resolution of 1 nm, the highest in its class, in a compact design.

**Reagents and standards**

All the chemicals used were of analytical reagent grade. The valsartan was provided by Sigma-Aldrich (≥ 98%, HPLC). Bromophenol blue (Honeywell Fluka) was prepared as 1.3 × 10⁻³ M methanol solution. Methyl red (Honeywell Fluka) was prepared as 3.7 × 10⁻³ M ethanol solution.

**Spectrophotometric method for the determination of valsartan with BPB**

**Proposed procedure for the determination of valsartan with BPB**

24.54 mg of CRS valsartan was transferred into a 25 mL volumetric flask with 15 mL methanol. The mixture was shaken and diluted to volume with methanol. Aliquot 0.4 mL was added to 1.0 mL of 1.3 × 10⁻³ M methanol solution of BPB. The volume 25.0 mL was made up to the mark by adding methanol. The absorbance was measured at 424 nm against the reagent blank, which was similarly prepared by omitting the drug. The calibration curve was performed by plotting the measured absorbance values versus concentration.

**Procedure for pharmaceutical formulation for the determination of valsartan with BPB**

Twenty tablets were accurately weighed and powdered. A quantity of powder containing 24.54 mg of valsartan was transferred into a 25 mL volumetric flask with 15 mL methanol. The mixture was shaken for 15 min, diluted to volume with methanol and then filtered using 0.2 µm Nylon filter membrane. Aliquot 0.4 mL was added to 1.0 mL of 1.3 × 10⁻³ M methanol solution of BPB. The volume 25.0 mL was made up to the mark by adding methanol. The absorbance was measured at 424 nm against the reagent blank, which was similarly prepared by omitting the drug. The calibration curve was performed by plotting the measured absorbance values versus concentration.
Spectrophotometric method for the determination of valsartan with MR

Proposed procedure for the determination of valsartan with MR

11.73 mg of CRS valsartan was transferred into a 25 mL volumetric flask with 15 mL ethanol. The mixture was shaken and diluted to volume with ethanol. Aliquot 0.3 mL was added to 0.5 mL of 3.7 × 10⁻³ M ethanol solution of MR. The volume 25.0 mL was made up to the mark by adding ethanol. The absorbance was measured at 494 nm against the reagent blank, which was similarly prepared by omitting the drug. The calibration curve was performed by plotting the measured absorbance values versus concentration.

Procedure for pharmaceutical formulation for the determination of valsartan with MR

Twenty tablets were accurately weighed and powdered. A quantity of powder containing 11.73 mg of valsartan was transferred into a 25 mL volumetric flask with 15 mL ethanol. The mixture was shaken for 15 min, diluted to volume with ethanol and then filtered using 0.2 µm Nylon filter membrane. Aliquot 0.3 mL was added to 0.5 mL of 3.7 × 10⁻³ M ethanol solution of MR. The volume 25.0 mL was made up to the mark by adding ethanol. The absorbance was measured at 494 nm against the reagent blank, which was similarly prepared by omitting the drug. The calibration curve was performed by plotting the measured absorbance values versus concentration.

Validation of analytical methods

The developed analytical methods were validated in accordance with the requirements of ICH Q2 (ICH 2005) on the following parameters: selectivity, linearity, limits of detection and quantification, range of application, accuracy, precision and robustness.

Results and discussion

Method development

A non extractive binary complexes between valsartan and bromophenol blue (BPB) and methyl red (MR) were formed based on ion-pair associates. This might be due to the electron-donating groups (tetrazole and amino butanoic acid) present in the valsartan structure. Valsartan forms ion-pair complex selectively with the dyes, as indicated by the formation of a coloured complex with BPB at pH 5.5 with λmax at 424 nm and MR at pH 4.3 with λmax at 494 nm. These ion pair associates of valsartan with the anion of dye were slightly soluble in water, but under the optimized experimental conditions, they become freely soluble and neither needed an extraction into organic solvents nor addition of non-ionic surfactants. Absorption spectra of valsartan with BPB and MR are presented in Figures 2, 3.

Optimisation of conditions is necessary for rapid and quantitative formation of colored ion-pair complexes with maximum stability and sensitivity. Maximal absorbance was observed in methanol solution with BPB and ethanol solution with MR and while chloroform, propanol, acetonitrile and ethylacetate were not suitable. Absorption spectra of valsartan with BPB and MR in different solvents are presented in Figures 4, 6. The absolute values Δ A of the difference in the absorption of valsartan with dyes in different solvents with the absorption of dyes in different solvents are presented in Figures 5, 7.

To establish the analytical sensitivity of valsartan with BPB and MR, the sensitivity of the reactions were calculated. The molar absorption index (ε) was 4.43 × 10⁴ for BPB and 2.36 × 10⁴ for MR, the specific absorption (α) was 1.07 × 10⁻¹ for BPB and 5.4 × 10⁻¹ for MR, and the Sendel coefficient (Ws) was 9.83 × 10⁻² for BPB and 1.84 × 10⁻² for MR. As a result of calculations of analytical indicators of sensitivity of reactions it was established that reaction of valsartan with MR has higher sensitivity, than reaction of valsartan with BPB that was testified by high value of molar coefficient of absorption and low value of an opening minimum.

The stoichiometry of the reactions was determined using Job’s method of continuous variation (Job P. 1936). Master equimolar solutions of 1.3 × 10⁻³ M BPB and 3.7 × 10⁻³ M MR with valsartan were prepared. The method revealed 1:1 ratio for both dyes (dye:drug). The results obtained from molar ratio studies were in agreement with the suggested reaction mechanism (scheme 1, 2) (Figures 8, 9).
Optimisation of conditions is necessary for rapid and quantitative formation of colored ion-pair complexes with maximum stability and sensitivity. Maximal absorbance was observed in methanol solution with BPB and ethanol solution with MR and while chloroform, propanol, acetonitrile and ethylacetate were not suitable. Absorption spectra of valsartan with BPB and MR in different solvents are presented in Figures 4, 6. The absolute values $\Delta A$ of the difference in the absorption of valsartan with dyes in different solvents with the absorption of dyes in different solvents are presented in Figures 5, 7.

\[ y = 0.0102x + 0.1636 \] (BPB) and at 494 nm $y$

Linearity
Beer’s law limit, molar absorptivity, detection limit, regression equation and correlation coefficient were obtained by least square treatment of results (ICH 2005). The linear relationship was found between absorbance at $\lambda_{max}$ and concentration of drug in the range 8–24 $\mu$g/mL for BPB and 4–20 $\mu$g/mL for MR. Regression analysis of Beer’s law plot at 424 nm yielded the regression equation, $y = 0.0102x + 0.1636$ (BPB) and at 494 nm $y$

Limits of detection and quantification
The ICH guidelines were followed in order to determine the LOD and LOQ. Accordingly, the method based on the standard deviation of the response and the slope has been
coefficient (R²=0.9988 (BPB) and R²=0.9991 (MR)) and small values of intercept validated the linearity of calibration curve and obedience to Beer’s law. Calibration curves are presented in Figures 10, 11.

The ICH guidelines were followed in order to determine the LOD and LOQ. Accordingly, the Limits of detection and quantification were obtained by least square treatment of results (ICH 2005). The linear relationship was found between absorbance at λmax and concentration of drug in the range 8-24 µg/mL for BPB and 4-15 (MR).

The proposed method applied, so that 3.3 and 10 times the standard deviation values of y-intercept of regression line and the regression equation were used to calculate the LOD and LOQ. The LOD and LOQ values were calculated to be 1.03 µg/mL and 3.43 µg/mL respectively (BPB) and 0.68 µg/mL and 2.26 µg/mL respectively (MR).

Selectivity

The proposed methods were tested in order to assess its selectivity using the artificial mixture for analysis. It has been confirmed that the measured absorbance was only produced by the analyte. A synthetic mixture was prepared, containing valsartan (160 mg), lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide. The extract was yielded according to the procedure that was described for tablets and subsequently analyzed using the procedure previously described. The replicate analysis (n = 5) for a concentration level of 16 µg/mL valsartan has yielded the % valsartan recovery at 100.14 ± 1.03 (BPB) and for a concentration level of 12 µg/mL has yielded the % valsartan recovery at 100.27 ± 1.15 (MR), and thus revealed that the inactive ingredients did not interfere with valsartan determination.

Precision and accuracy

Intra-day and inter-day precision values have been calculated by replicate analysis (n = 5) of calibration standard, at three different concentration levels, during the same day, and then during 5 consecutive days. The RSD (%) values of intra-day and inter-day measurements have indicated a good precision. (Table 1). Accuracy, defined as the closeness between the reference and the found values, has been evaluated, on the other hand, as percentage relative error between the measured and theoretical concentration of valsartan. The results are presented in Table 1, and show good accuracy for developed methods.

Robustness

The evaluation of robustness was carried out at the stage of development of spectrophotometric methods for the determination of valsartan during the establishment of optimal conditions for the course of reactions and determination of factors that may affect the optical density (volume of BPB and MR and stability of solutions over time). It was found that fluctuations in the volume of BPB and MR within ± 10% did not affect the results of the study (Figures 12, 13, Tables 2, 3) and the studied solutions were stable for at least 45 minutes (Figures 14, 15).
Table 1. Intra-day and inter-day accuracy and precision.

| Method | Valsartan taken, µg/mL | Intra-day accuracy and precision | Inter-day accuracy and precision |
|--------|------------------------|---------------------------------|--------------------------------|
|        |                        | Valsartan found, µg/mL | RE, % | RSD, % | Valsartan found, µg/mL | RE, % | RSD, % |
| BPB    | 8                      | 8.03                        | 0.59  | 1.03  | 7.91                    | 0.53  | 1.08  |
|        | 15                     | 15.05                       | 0.64  | 1.13  | 15.09                    | 0.67  | 1.17  |
|        | 24                     | 23.87                       | 1.14  | 1.17  | 24.13                    | 0.86  | 1.23  |
| MR     | 4                      | 4.05                        | 0.63  | 1.12  | 4.05                    | 0.56  | 1.05  |
|        | 12                     | 11.94                       | 0.56  | 1.06  | 12.11                    | 0.64  | 1.09  |
|        | 20                     | 20.11                       | 0.69  | 1.09  | 19.92                    | 0.65  | 1.11  |

RE: Relative error; RSD: Relative standard deviation

Figure 12. Absorption spectra of BPB and valsartan with BPB under conditions of studying the amount of added BPB.

Figure 13. Absorption spectra of MR and valsartan with MR under conditions of studying the amount of added MR.

Figure 14. Graph of the dependence of the adsorption of the reaction product of valsartan with BPB on time.

Figure 15. Graph of the dependence of the adsorption of the reaction product of valsartan with MR on time.

Table 2. The results of the change in optical density from the amount of added BPB.

| Amount of added BPB, mL | ∆ A |
|-------------------------|-----|
| 0.9                     | 0.164|
| 1.0                     | 0.165|
| 1.1                     | 0.166|

Table 3. The results of the change in optical density from the amount of added MR.

| Amount of added MR, mL | ∆ A |
|------------------------|-----|
| 0.4                    | 0.370|
| 0.5                    | 0.374|
| 0.6                    | 0.373|

Table 4. Determination of valsartan formulation by the proposed methods.

| Tablet brand name | Label claim, mg/tablet | Found (label claim ± SD), % | BPB | MR |
|-------------------|-------------------------|-----------------------------|-----|----|
| Valsartan KIPA    | 160                     | 100.045 ± 0.538             | 100.035 ± 0.324 | t=2.11 | t=2.48 | F=4.27 | F=3.04 |
| Valsartan Sandox  | 160                     | 100.028 ± 0.345             | 100.039 ± 0.482 | t=2.29 | t=2.12 | F=3.35 | F=3.51 |
| Valsartan-Teva    | 160                     | 100.045 ± 0.485             | 101.004 ± 0.567 | t=2.31 | t=2.04 | F=3.86 | F=3.29 |

Tabulated t-value at 95 % confidence level is 2.57
Tabulated F-value at 95 % confidence level is 6.39.
Application to pharmaceutical formulation

The proposed methods were applied for the quantification of valsartan in tablets pertaining to three commercial formulations. The results as presented in Table 4 reveal no significant differences between the proposed methods. The Student’s t- and the F-values at 95% confidence level are less than the theoretical one, but nevertheless confirming a good agreement between the results obtained by the proposed methods.

Analytical eco-scale for greenness assessment

An important aspect of modern pharmaceutical analysis is compliance with the principles of green chemistry, which must be taken into account when developing analytical methods for the determination of valsartan in substances and drugs (Van Aken K. et al. 2006; Peleshok K. et al. 2021a, 2021b; Galuszka A. et al. 2012; Shulyak N. et al. 2021; Yuryeva O. et al. 2018; Polyauk O. and Logoyda L. 2017; Mykhalkiv M. et al. 2018; Logoyda L. et al. 2018). Table 5 summarizes the results of developed methods found to be an excellent green analysis with a score of 89 for both.

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Conclusion

Two simple, rapid and green non extractive spectrophotometric methods were developed for the determination of valsartan in tablet dosage form. The determination was based on the ion-pair formation using the dyes, bromophenol blue (BPB) and methyl red (MR). Optimal spectrophotometric conditions were established. Proposed methods are very simple, requiring only one reagent and non expensive instrumentation. The lower quantification limits of the proposed methods are much lower (3.43 µg/mL and 2.26 µg/mL) comparing to existing ones. These advantages encourage the application of the proposed methods in routine quality control evaluation.

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