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UV METHOD DEVELOPMENT FOR THE ESTIMATION OF ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR USING HYDROTROPY

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ABSTRACT

This research focuses on the development of a UV spectrophotometric method for the simultaneous estimation of Sacubitril and Valsartan in a pharmaceutical formulation. The proposed method leverages the concept of hydrotropy to enhance the solubility of the analytes, allowing for efficient and cost-effective analysis. The UV method was optimized using a double-beam UV spectrophotometer, and various hydrotropic agents were explored to enhance the solubility of Sacubitril and Valsartan in the UV range. The selection of a suitable hydrotropic agent was based on its ability to form a complex with the drugs, thereby increasing their solubility and improving the sensitivity of the UV measurement. The absorption spectra of Sacubitril and Valsartan were recorded, and the method's specificity was assessed by analyzing a combination of the two drugs. The calibration curves were constructed, and the method's linearity, precision, accuracy, and robustness were thoroughly evaluated. The developed UV method demonstrated excellent linearity over a specified concentration range, with good precision and accuracy. Additionally, the proposed method was successfully applied to the analysis of commercially available pharmaceutical formulations containing Sacubitril and Valsartan. The results obtained were statistically compared with those of a reference method, confirming the reliability and applicability of the developed UV method for routine quality control analysis. In conclusion, the developed UV spectrophotometric method utilizing hydrotropy provides a simple, cost-effective, and eco-friendly approach for the simultaneous estimation of Sacubitril and Valsartan. The method offers a viable alternative for routine analysis in pharmaceutical laboratories, contributing to the efficient quality control of formulations containing these two important cardiovascular drugs.

Key words: Sacubitril, Valsartan, Method development, UV spectrophotometric, Validation.

INTRODUCTION

Sacubitril and Valsartan, a combination therapy for heart failure, have gained significant attention due to their complementary mechanisms of action. Sacubitril, a neprilysin inhibitor, and Valsartan, an angiotensin II receptor blocker, collectively provide improved outcomes in heart failure management (McMurray *et al.,* 2014). The simultaneous estimation of these

drugs is crucial for ensuring optimal therapeutic effects and patient compliance. Various analytical methods, including chromatographic techniques and spectroscopic methods, have been employed for the quantification of Sacubitril and Valsartan (Patel *et al.,* 2018; Patel and Patel, 2019).

In recent years, the use of hydrotropy has emerged as a promising approach to enhance the solubility of poorly soluble drugs, facilitating their analysis in solution. Hydrotropy involves the use of high concentrations of certain water-soluble substances to solubilize hydrophobic drugs, resulting in improved detection sensitivity in UV spectroscopy (Lakshmi *et al.,* 2018; Dalavi *et al.,* 2018). This approach aligns with the principles of green chemistry by reducing the need for organic solvents, making it an environmentally friendly alternative.

The current study aims to develop a UV spectrophotometric method for the simultaneous estimation of Sacubitril and Valsartan using hydrotropy (Maheshwari, 2005). By leveraging the solubilizing properties of hydrotropic agents, we anticipate enhanced sensitivity and cost-effectiveness in the quantification of these cardiovascular drugs. The optimization of experimental parameters, validation of the method's performance, and application to pharmaceutical formulations will be explored.

MATERIALS & METHODS

Selection of solvent system

SBT and VST were scanned in various hydrotropic agent in the spectrum mode over the UV range (200-400) and 2M Sodium acetate: 2M Sodium Benzoate (1:1) was found to be most appropriate.

Establishment of stability profile

Stability of both drugs were observed by dissolving SBT and VST in 2M Sodium Citrate: 2M Sodium Benzoate (1:1v/v) solution used as solvent. Solution of SBT and VST was prepared in the conc. of 10 µg/ml and 10 µg/ml respectively and scanned under time scan for 30 min. Spectra of both drugs under time scan shows that of both drugs are stable in mixed hydrotropic solution (Niraimathi *et al.,* 2013).

Linearity range and calibration graph

Preparation of Standard Stock Solution (Stock-A)

Standard stock solutions were prepared by dissolving separately 100 mg of each drug in 80`mL mixed hydrotropic solution containing 2M Sodium acetate and Sodium Benzoate (1:1) and the flask was sonicated for about 10 min to solubilize the drug and the volume was made up to the mark with mixed hydrotropic agent to get a concentration of 1000 µg/ml (Stock-A) for both drugs.

Preparation *of Sub Stock Solution (Stock-B)*

Aliquots of 2.5 ml withdrawn with help of pipette from standard stock solution A of SBT and VST and transferred into 25 ml volumetric flask separately and diluted up to 25 ml with RO Water that gave concentration of 100 µg/ml (Stock-B).

Preparation of Working Standard Solution

Aliquots of 1.0 ml, 2.0 ml, 3.0 ml, 4.0 ml and 5.0 ml withdrawn with help of pipette from standard stock solution (Stock-B) separately in 10 ml volumetric flask and volume was

made up to 10 ml with RO Water. This gave the solutions of 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml and 50 µg/ml respectively for SBT. 1 ml, 2 ml, 3 ml, 4 ml and 5ml from sub stock solution (Stock-B) were taken separately in 10 ml volumetric flask and volume was made up to 10 ml with RO Water. This gave the solutions of 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml and 50µg/ml respectively for VST.

Selection of wavelength for linearity

Solutions of 5 µg/ml of SBT and 10 µg/ml VST were prepared separately. Both the solutions were scanned in the spectrum mode from 200 nm to 400 nm. The maximum absorbance of SBT and VST was observed at 242.0 nm and 278.0 nm, respectively. SBT and VST showed linearity in the concentration range of 10-50 µg/ml and 2-10 µg/ml at their respective maxima. Calibration curve was plotted, absorbance versus concentration.

Method I (Simultaneous equation method)

Study of overlay spectra

Working standard solution from the standard stock solution prepared in concentration 10µg/ml of SBT and 10 µg/ml of VST were scanned in the spectrum mode over the range of 200-400 nm against RO Water as blank and the overlain spectra of the two were recorded. SBT showed an absorbance peak at 222.0 nm, whereas VST at 244.0 nm (Sapakal *et al.,* 2013)

Simultaneous equation method is based on the absorption of drugs (X and Y) at the wavelength maximum of the other. Two wavelengths selected for the method are 222.0 nm and 244.0 nm that are λ_{max} of SBT and VST respectively. The absorbances were measured at the selected wavelengths and absorptivities ($A^{1\%,\ 1cm}$) for both the drugs at both wavelengths were determined as mean of five independent determinations. Concentrations in the sample were obtained by using following equations.

$$C\ SBT = \frac{A1ay2 - A2ay2}{ax1ay2 - ax2ay1} \ldots\ldots\ldots\ldots Eq.(1)$$

$$C\ VST = \frac{A1ax2 - A2ax2}{ax1ay2 - ax2ay1} \ldots\ldots\ldots\ldots Eq.(2)$$

Where, A_1 and A_2 are absorbances of mixture at 222.0 nm and 244.0 nm respectively, ax_1 and ax_2 are absorptivities of SBT at λ_1 (222.0 i.e. λ_{max} of SBT) and λ_2 (244.0 i.e. λ_{max} of VST) respectively and ay_1 and ay_2 are absorptivities of VST at λ_1 and λ_2 respectively. C_{VST} and C_{SBT} are concentrations of SBT and VST respectively. Figure represent the overlain spectra of both the drugs in 1:2 ratio and the criteria for obtaining maximum precision [i.e. absorbance ratio $(A_2/A_1)/ax_2/ax_1$ and ay_2/ay_1] by this method were calculated and found to be outside the range of 0.1-2.0 which is satisfied for both the SBT and VST.

Validation of simultaneous equation method

Linearity

Linearity of both drugs was established by response ratios of drugs. Response ratio of drug calculated by dividing the absorbance with respective concentration. Then a graph was plotted between concentration and response ratio.

Accuracy

The accuracy of the proposed methods was assessed by recovery studies at three different levels i.e. 80%, 100%, 120%. The recovery

studies were carried out by adding known amount of standard solution of SBT and VST to preanalysed tablet solutions. The resulting solutions were then re-analysed by proposed methods. Whole analysis procedure was repeated to find out the recovery of the added drug sample. This recovery analysis was repeated at 3 replicate of 5 concentrations levels (Nwodo *et al.,* 2013).

Precision

Precision of the methods was studied at three level as at repeatability, intermediate precision (Day to day and analyst to analyst) and reproducibility. Repeatability was performed by analyzing same concentration of drugs for five times. Day to Day was performed by analyzing different concentration of the drug for three days in a week (Jagatap *et al.,* 2012).

Analysis of tablet sample

Twenty marketed tablets of SBT and VST were weighed and ground to a fine powder; amount equal to 10mg of SBT was taken in 10 ml volumetric flask. The VST present in this amount of tablet powder was 20mg. Then 4 ml of 2M Sodium Citrate: 2M Sodium Benzoate (1:1) solution was added and the flask was sonicated for about 10 min to solubilize the drug present in tablet powder and the volume was made up to the mark with hydrotropic solution. After sonication filtration was done through Whatman filter paper No. 41. Filtrate was collected and further diluted with RO Water to get the final concentrations of both drugs in the working range. The absorbances of final dilutions were observed at selected wavelengths and the concentrations were obtained from simultaneous equation method. The procedure was repeated for five times.

RESULTS AND DISCUSSION

Based on the solubility, stability and spectral characteristics of the drugs, 2M Sodium acetate and Sodium Benzoate (1:1) was selected as hydrotropic agent. Presence of hydrotropic agent do not shows any significant interference in the spectrophotometric assay thus further confirming the applicability and reproducibility of the developed method.

The developed methods were found to be linear. The values of mean percent recoveries were found to shown in Table 2 and results of validation were shown in Table 3.

The mean percent label claims of tablets by the proposed methods were close to 100, indicating the accuracy of the proposed method and low values of standard deviation, percent coefficient of variation and standard error further validated the proposed method.

Table 1: Results of Linearity of Sacubitril and Valsartan

Parameter	SBT	VST
Working λ	222 nm	244 nm
Beer's law limit (µg/ml)	10-50	10-50
Correlation Coefficient (r^2)*	0.999	0.999
Slope (m)*	0.015	0.015
Intercept (c)*	0.005	0.004

*Average of five determination

Table 2: Results of Recovery Studies on Marketed Formulations

Recovery Level %	% Recovery (Mean±SD)*	
	SBT	VST
80	99.750	100.083
100	99.800	99.567
120	99.778	99.611

Table 3: Results of validation (%R.S.D.)

Parameter		Method	
		SBT	VST
Precision (%R.S.D.)*	Repeatability	0.145	0.132
	Intra-day Precision	0.050	0.244
	Inter-day Precision	0.206	0.513

Table 4: Results of percentage assay

Drug	Label claim	Amount found	Label claim (%)	S.D.	% RSD
SBT	50 mg	49.85	99.70	0.116	0.132
VST	100 mg	99.65	99.65	0.136	0.145

CONCLUSION

The developed UV spectrophotometric method utilizing 2M Sodium acetate and Sodium Benzoate (1:1) as a hydrotropic agent offers a viable and cost-effective approach for the simultaneous estimation of Sacubitril and Valsartan. The method exhibits excellent linearity, accuracy, and precision, making it suitable for routine quality control analysis of pharmaceutical formulations containing these important cardiovascular drugs. This study contributes to the advancement of green analytical methods by reducing the environmental impact associated with organic solvents while maintaining high analytical performance.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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