

Mixed Hydrotropy Solubilization Approach for Quantitative Estimation of Eprosartan Mesylate and Hydrochlorothiazide by UV Spectrophotometer

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Abstract

Two simple, accurate, novel, safe and precise methods were developed for the simultaneous estimation of poorly water-soluble drugs Eprosartan Mesylate and Hydrochlorothiazide in tablet dosage form using 2M Sodium acetate and 8M Urea solution (50:50% W/V) as a mixed hydrotropic solution. Eprosartan Mesylate and Hydrochlorothiazide show maximum absorbances at 267.5 and 271.5 nm respectively. Sodium acetate and Urea solution did not show any absorbance above 240 nm and thus no interference in the estimation of drugs was seen. Eprosartan Mesylate and Hydrochlorothiazide follows the Beer's law in the concentration range of 15-75 and 5-25 µg/ml ($r^2= 0.9994$ and 0.9996). Method-A employs a simultaneous equation method using 267.5 and 271.5 nm as two analytical wavelengths, Method-B, an absorption ratio method, uses 271.5 and 277 nm as two analytical wavelengths for estimation of Eprosartan Mesylate and Hydrochlorothiazide. The optimized methods showed good reproducibility and recovery with ranging from 95.08 ± 0.086 to 99.82 ± 0.097 EPS and HCZ respectively. The developed methods were validated according to ICH guidelines and values of accuracy, precision and other statistical analysis were found to be in good accordance with the prescribed values therefore the both methods can be used for routine monitoring of EPS and HCZ in industry in the assay of bulk drug and tablets.

Keywords: Eprosartan mesylate; Hydrochlorothiazide; Simultaneous equation method; Absorption ratio method; Mixed hydrotropic solubilizing agents

Introduction

Chemically Eprosartan Mesylate (EPS) is (*E*)-2-butyl-1-(*p* carboxy benzyl)- α -2 thienylmethylimidazole-5- acrylic acid. It is an angiotensin II receptor antagonist used for the treatment of high blood pressure. Hydrochlorothiazide (HCZ) is a thiazide diuretic. It reduces the reabsorption of electrolytes from the renal tubules. It has been used in the treatment of several disorders including edema, hypertension, diabetes insipidus, and hypoparathyroidism. Chemically it is 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7- Sulphonamide 1, 1-dioxide.

Literature survey reveals few analytical methods for the determination of EPS in pharmaceutical preparations and biological fluids, viz. spectrophotometry [1,2], and HPLC [3]. UV Spectroscopy [4-7], HPLC [8-12] methods are reported for simultaneous estimation of HCZ in combined dosage form.

Hydrotropic solubilization is the phenomenon by which aqueous solubility of poorly water soluble drugs and insoluble drugs increases. Various techniques have been employed to enhance the aqueous solubility and hydrotropy is one of them. Sodium salicylate, sodium benzoate, urea, nicotinamide, sodium citrate and sodium acetate are the most common examples of hydrotropic agents utilized to increase the water solubility of drug [13-18]. Maheshwari and Jain et al has analyzed various poorly water-soluble drugs using hydrotropic solubilization phenomenon viz. ketoprofen, salicylic acid, frusemide, torsemide, hydrochlorothiazide, pramipexole, amlodipine besylate. Various organic solvents such as methanol, chloroform, dimethyl formamide and acetonitrile have been employed for solubilization of poorly water-soluble drugs to carry out spectrophotometric analysis. Drawbacks of organic solvents include their higher cost, toxicity and pollution. Hydrotropic solution may be a proper choice to preclude the use of organic solvents.

Therefore, it was thought worthwhile to employ this mixed hydrotropic solution to extract out the drug from fine powder of tablets to carry out spectrophotometric estimation. There are no reports yet for determination of this combination by proposed methods. Present work emphasizes on the quantitative estimation of EPS and HCZ in their combined dosage form by UV Spectroscopic methods.

Material and Methods

Chemicals

Pure sample of EPS and HCZ was obtained as gift sample from Dishman Pharmaceutical & Chemicals Ltd., Navrangpura, Ahmedabad (India) and Hetero Drugs Ltd., Baddi, Himachal Pradesh (India) respectively. Sodium acetate and urea obtained from Merck Chemical Division, Mumbai. Reverse Osmosis Water was used throughout the study.

Instrument

UV-Visible double beam double detector spectrophotometer, Shimadzu model-1700 having spectral bandwidth 3 nm and of wavelength accuracy ± 1 nm, with 1cm quartz cells was used.

Preliminary solubility studies of drugs

Solubility of both drugs was determined at $25 \pm 1^\circ\text{C}$. An excess

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Received June 08, 2011; Accepted September 12, 2011; Published September 14, 2011

Citation: Jain R, Sahu V, Jain N, Jain S (2011) Mixed Hydrotropy Solubilization Approach for Quantitative Estimation of Eprosartan Mesylate and Hydrochlorothiazide by UV Spectrophotometer. Pharm Anal Acta 2:135. doi:10.4172/2153-2435.1000135

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amount of drug was added to two screw capped 25 ml of volumetric flask containing different aqueous systems viz distilled water, buffer of pH 6.4, buffer of pH 8.2, and 2M sodium acetate and 8M urea solution. The volumetric flasks were shaken mechanically for 12 h at 25±1°C in a mechanical shaker. These solutions were allowed to equilibrate for next 24 h and then centrifuged for 5 min at 2000 rpm. The supernatant liquid was taken for appropriate dilution after filtered through whatmann filter paper #41 and analyzed spectrophotometrically against corresponding solvent blank. After analysis, it was found that the enhancement in the solubility of EPS and HCZ was found to be more than and 56 and 74 folds respectively in 2M sodium acetate and 8M urea solution as compared to solubility studies in other solvents.

Preparation of standard stock solution and selection of method

Standard stock solutions were prepared by dissolving separately 100 mg of each drug in mixed hydrotropic solution and the flask was sonicated for about 10 min to solubilize the drug. Different dilutions were prepared ranging from 15-75 µg/ml for EPS and 5-25 µg/ml for HCZ. A concentration of 30 µg/ml of EPS and 10 µg/ml of HCZ were scanned over the range of 200-400 nm in the spectrum mode to get the overlain spectra of both drugs. The spectra exhibit major absorbance maxima at 267.5 nm and 271.5 nm for EPS and HCZ respectively and isobestic point at 277 nm (Figure 1).

Method

Vierordt's simultaneous equation method (Method A)

The wavelength 267.5 nm (λ_{max} of EPS) and 271.5 nm (λ_{max} of HCZ) was selected (Figure 1 to 3). The absorbencies of EPS and HCZ were measured at 267.5 nm and 271.5 nm. This method of analysis is based on the absorption of drugs X and Y at the wavelength maxima of the other. The quantification analysis of EPS and HCZ in a binary mixture was performed by using Eqn-1 and Eqn-2. Where C_x and C_y are the concentrations of EPS and HCZ respectively in the diluted sample, ax_1 and ax_2 are absorptivities of EPS at λ_1 and λ_2 , ay_1 and ay_2 are absorptivities of HCZ at λ_1 and λ_2 respectively. A_1 and A_2 are the absorbances of samples at the 267.5 and 271.5 nm respectively.

$$C_x = A_2ay_1 - A_1ay_2 / ax_2ay_1 - ax_1ay_2 \dots\dots Eqn.1$$

$$C_y = A_1ax_2 - A_2ax_1 / ax_2ay_1 - ax_1ay_2 \dots\dots Eqn.2$$

Q-analysis method (Method B)

In this method absorbances of both the drugs were calculated at two

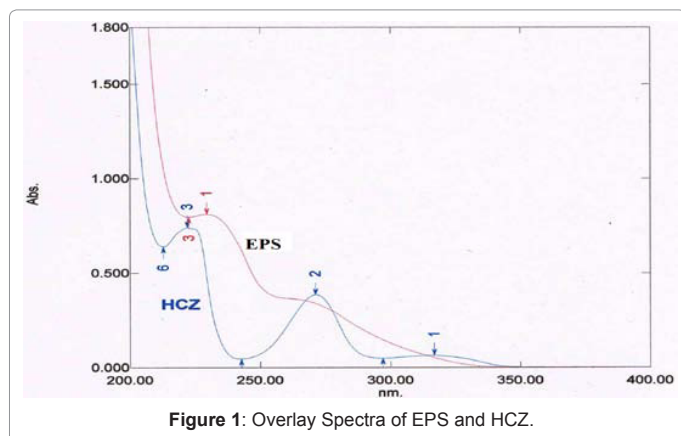


Figure 1: Overlay Spectra of EPS and HCZ.

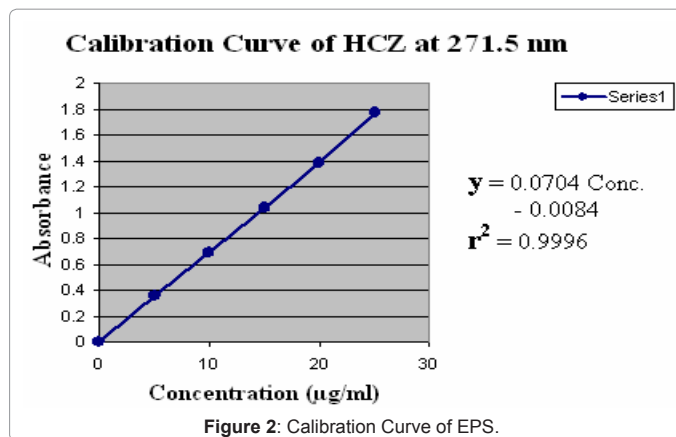


Figure 2: Calibration Curve of EPS.

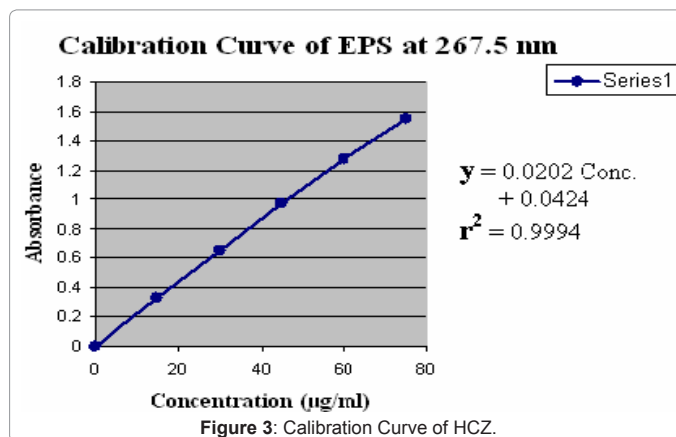


Figure 3: Calibration Curve of HCZ.

selected wavelengths; among which λ_1 is the wavelength of isoabsorptive point of both drugs and λ_2 is the λ_{max} of either drug among both drugs. From the overlain spectra wavelength 277 nm (isoabsorption point) and 271.5 (λ_{max} of HCZ) were selected for study. The absorbencies at 277 nm and 271.5 nm for EPS were obtained and similarly for HCZ absorbencies are measured at 277 nm and 271.5 nm. The concentration of the individual components were calculated by using the following equations; $C_x = Qm - Qy / Qx - Qy \times A_1 / ax_1$ (Eqn.3), $C_y = Qm - Qy / Qy - Qx \times A_1 / ax_1$ (Eqn.4) where $Qm = A_2 / A_1$, A_1 is absorbance of sample at isoabsorptive point, A_2 is absorbance of sample at λ_{max} of one of the two components. ax_1 and ax_2 represent absorptivities of EPS at λ_1 and λ_2 and ay_1 and ay_2 denote absorptivities of HCZ at λ_1 and λ_2 respectively; C_x and C_y be the concentration of EPS and HCZ respectively [19,20].

Analysis of tablet formulation

Twenty marketed tablets of EPS and HCZ (TEVETEN® HCT) were weighed and ground to a fine powder; amount equal to 60 mg of EPS was taken in 10 ml volumetric flask. The HCZ present in this amount of tablet powder was 2.5 mg. Then 8 ml of sodium acetate and urea 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 and absorbance ratio method.

Validation of the developed methods

The developed methods for simultaneous estimation of EPS and HCZ were validated as per ICH guidelines (Linearity, Accuracy, Precision and Robustness) [21].

Linearity

The EPS shows the linearity in the range of 15-75 µg/ml and HCZ 5-25 µg/ml. An excellent correlation was observed in the absorbance and the concentration of EPS and HCZ.

Accuracy

To check the accuracy of the developed methods and to study the interference of formulation additives, analytical recovery experiments was carried out by standard addition method. The accuracy of the proposed methods was assessed by recovery studies at three different levels i.e. 80%, 100% and 120%. The recovery studies were carried out by adding known amount of standard solution of EPS and HCZ to preanalysed tablet solutions. The resulting solutions were then re-analysed by proposed methods. Total amount of drug found and percentage recovery was calculated.

Precision

Precision of the methods was studied at three level as at repeatability, intermediate precision (Day to Day and analyst to analyst) and reproducibility.

Robustness

Robustness of the analytical method was performed by changing the concentration and ratio of hydrotropic solution for check the analytical methods capacity to remain unchanged. For the robustness of the analytical method we changed the ratio of hydrotropic solution. Instead the 50:50 ratio of sodium acetate and urea 60:40 sodium acetate and urea was used as solvent.

Results and Discussions

Linearity range for EPS and HCZ were found to be 15-75 µg/ml and 5-25 µg/ml at respective selected wavelengths (Table 1). To check the accuracy of the developed methods and to study the interference of formulation additives, analytical recovery experiments was carried out by standard addition method and the values of mean percent recoveries for EPS and HCZ were ranging from 95.08±0.086 to 99.82±0.097 respectively (Table 2), moreover satisfactorily low values of statistical parameters (Table 3), further validated the method. By performing

	PARAMETER	METHOD-A		METHOD-B	
		EPS	HCZ	EPS	HCZ
1	Working λ	267.5 nm	271.5 nm	277 nm	271.5 nm
2	Beer's law limit (µg/ml)	15-75	5-25	15-75	5-25
3	Correlation Coefficient (r ²)*	0.9994	0.9996	0.9994	0.9996
4	Slope (m)*	0.0202	0.0704	0.0202	0.0704
5	Intercept (c)*	0.0424	-0.0084	0.0424	-0.0084

*Average of five determination

Table 1: Optical Characteristics and Linearity Data of EPS and HCZ.

Recovery Level %	% Recovery (Mean±SD)*			
	Method A		Method B	
	EPS	HCZ	EPS	HCZ
80	99.78±0.105	95.20±0.101	99.82±0.188	95.32±0.102
100	99.80±0.100	96.62±0.093	99.80±0.083	98.15±0.050
120	99.80±0.105	95.08±0.086	99.82±0.097	96.23±0.070

*Average of five determination

Table 2: Results of Recovery Studies on Marketed Formulations.

	PARAMETER	Method - A		Method - B	
		EPS	HCZ	EPS	HCZ
Precision (Mean±SD)*	Repeatability	99.39±0.33	99.66±0.10	99.64±0.08	98.95±0.25
	Day to Day	99.72±0.05	99.50±0.11	99.38±0.13	99.15±0.11
	Analyst to Analyst	99.75±0.04	99.94±0.16	99.46±0.14	98.56±0.20
	Reproducibility	99.69±0.05	99.66±0.09	99.60±0.09	99.35±0.19
	Robustness*	99.79±0.04	100.03±0.18	99.32±0.12	98.47±0.20

*Average of five determination

Table 3: Results of Validation (Mean±SD).

S. No	DRUG	Label Claim	Amount Found	MEAN*	S.D.*	%COV*	STD. ERROR*
Method A	EPS	600	598.2	99.7	0.091	0.051	0.025
	HCZ	25	24.3	97.2	0.053	0.960	0.011
Method B	EPS	600	598.98	99.83	0.055	0.055	0.015
	HCZ	25	24.5	98.00	0.038	0.517	0.012

*Average of five determination

Table 4: Results and Statistical Parameters for Tablet Analysis.

these methods it was found that both drugs show good regression value at their respective wavelengths and percentage of estimation of both drugs in tablet dosage form were 99.7 ± 0.091 and 97.2 ± 0.053 in method A, 99.83 ± 0.055 and 98.00 ± 0.038 in method B for EPS and HCZ respectively (Table 4). The standard deviation, coefficient of variance and standard error were obtained for EPS and HCZ as per required specification.

Conclusion

There was no interference of 2M sodium acetate and 8M urea solution (50:50% W/V) in the estimation and hence the two UV spectrophotometric methods were found to be simple, accurate, economic and rapid for simultaneous estimation of EPS and HCZ in bulk and tablet dosage form. The proposed method can be successfully employed for the routine analysis of EPS and HCZ containing dosage forms.

Acknowledgement

Authors are grateful to Dr. Surendra Jain, Director SIRT Bhopal for providing facility for this work.

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