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ASSAY OF CEFTAZIDIME IN BULK AND ITS PHARMACEUTICAL FORMULATIONS BY VISIBLE SPECTROPHOTOMETRY

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ABSTRACT

Three simple and sensitive visible spectrophotometric methods (M_1, M_2, and M_3) have been described for the estimation of Ceftazidime (CTZ). The methods that are based on the formation of radical anion with the involvement of basic nitrogen in CTZ (donor) and quinones [2,3-dichloro-5,6-dicyano-p-benzoquinone(DDQ), chloranilic acid (DHQ), 2,3,5,6-tetrachloro-p-benzoquinone (TQ)] (acceptor). The variable parameters in all these methods have been optimized and the chemical reactions involved are presented. The results obtained in the three methods are statistically validated and recoveries range from 99.7 to 101.3%. Common excipients used in additives in pharmaceutical preparations do not interfere in the proposed methods.

Key Words: ceftazidime, DDQ, DHQ, TQ, spectrophotometric, pharmaceutical formulations**.**

INTRODUCTION

Ceftazidime (CTZ) is a thrid-generation cephalosporin antibiotic. Like other thire-generation cephalosporins, it has broad spectrum activity against Gram-positive and Garm-negative bacteria. Unlike most third-generation agents, it is active against pseudomonas aeruginosa, however it has weaker activity against Gram-positive microorganisms and it is not used for such infections. It is also used in the empirical therapy of febrile neutropenia, in combination with other antibiotics, chemically known as (6r,7r,a)-7-(2-aminothiazol-4-yl)- 2-(2-carboxypropan-2-yloxyimino) acetamindo)-8-oxo-3-(pyridinium-1-ylmethyl)-5thia-1-aza-bicyclo [4.2.0] oct-2-ene-2-carboxylate. A number of methods such as Spectrophotometic[1-12] and HPLC[13-31], were reported for the estimation of CTZ. Literature survey revealed that only two visible spectrophotometric method was reported for it quantitative determination in bulk drug and pharmaceutical formulations. Hence there is a need to develop to sensitive and flexible spectrophotometric methods for the assay of CTZ.

A direct chemical analysis based on the reactivity of the intact molecule with out cleavage is not frequently encountered. The methods that are based on the charge transfer complexation are usually rapid and simple to perform.π-acceptors such as 2,3-dichloro-5,6-dicyano-p-benzoquinone(DDQ), 2,3,5,6-tetrachloro-p-benzoquinone(TQ), chloranilic acid (DHQ) are known to yield charge transfer complexes with a variety of electron donors. The present work describes an improved direct simple analytical procedure that can be applied at quality control laboratories for the analysis of Ceftazidime.

EXPERIMENTAL

Instrument

A Systronics model 117 UV – Visible spectrophotometric with 1cm matched quartz cells was used for spectral and absorbance measurements in the UV and visible regions respectively.

Materials and reagents

All reagents used were of Analytical Grade and freshly prepared solutions were always used. DDQ (Fluka, 4.4×10^{-3}M) solution in acetonitrile for Method A, DHQ (Sd-Fine, 0.1%,

4.785×10^{-3}M) solution in methanol for Method B, TQ (BDH, 0.1%, 4.067×10^{-3}M) solution in 1.4-dioxane for Method C were prepared.

Table-1: Reaction time and intensity in polar solvent

Acceptor	Reaction time	Solvent	Absorptiom Maxima
TQ	10	Dimethyl formamide	620
DHQ	5	Methanol	520
DDQ	15	Acetonitrile	440

Table-2: Optical Characteristics, Precision and Accuracy of the Proposed Methods for CFT

Parameters	DDQ	DHQ	TQ
λ_{max} (nm)	440	520	620
Beer's Law limits (µg/mL)	20-80	20-100	20-60
Molar absorptivity (l $mol^{-1}cm^{-1}$)	5.258×10^3	3.597×10^3	6.417×10^3
Correlation coefficient (r)	0.9999	0.9999	0.9999
Sandell's sensitivity (µg/cm^2/ 0.001 absorbance unit)	0.121	0.177	0.099
Regression Equation (y = a + bc) (i)Slope (b)	0.0084	0.0056	0.0101
(iii) Intercept (a)	-0.0066	-0.0031	0.0028
Relative Standard Deviation *	0.3605	0.3544	0.3313
% Range of error (confidence limits) (i) 0.05 level	0.301	0.296	0.277
(ii) 0.01 level	0.446	0.438	0.410

*Average of six determinations considered. **Average of three determinations.

Table-3: Assay of CFT in pharmaceutical formulations

Sample	Labelled amount (mg)	Amount found by Proposed Methods*			Amount found by reference method	%Recovery by Proposed methods**		
		A	B	C		A	B	C
Inj. 1	250 mg	249.7± 0.49 F=2.82 t=0.61	249.59 ±0.62 F=2.38 t=0.47	250.09± 0.34 F=1.46 t=0.86	250.45± 1.24	99.96	99.88	99.83
Inj. II	250 mg	249.51 ±1.69 F=1.45 t=0.71	249.28 ±1.10 F=1.20 t=1.58	249.00 ±0.83 F=1.43 t=1.71	250.09± 0.69	99.80	99.71	99.59
Inj. III	250 mg	250.74 ±0.74 F=2.25 t=0.96	249.59± 0.65 F=1.58 t=0.49	251.86 ±1.82 F=1.30 t=1.43	249.26± 1.59	100.29	99.82	100.74
Inj. IV	250 mg	250.06±0.42 F=2.13 t=0.64	250.92± 0.34 F=1.03 t=1.66	250.64 ±0.67 F=1.88 t=0.27	250.45± 1.24	100.02	100.37	100.25

*Average ± standard deviation of six determinations.
**After adding 3 different amounts of the pure labelled to the pharmaceutical formulation, each value is an average of 3 determinations.

Standard Drug Solution

The stock solution (1mg/ml) of Ceftazidime (CTZ) was prepared by dissolving 100 mg of it initially in 10 ml of DMF, followed by dilution to 100 ml with dioxane. This stock solution was further diluted stepwise with dioxane to obtain the working standard solution of concentration of of 200 µg/ml (Method A and C), 400 µg/ml (Method B).

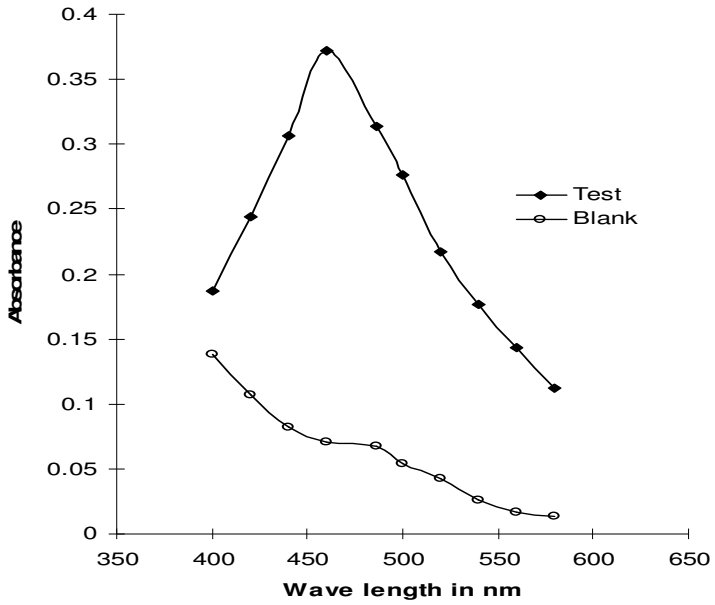

Fig.-1: Absorption spectra of the CFT-DDQ system (♦ ♦) and reagent blank vs. chloroform (o-o) (concentration of DDQ: 3.52 x 10^{-4} M)

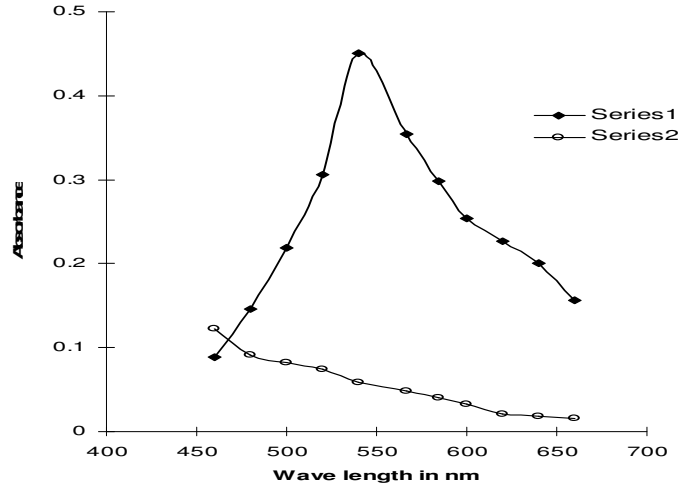

Fig.-2: Absorption spectra of the CFT-DHQ system (♦ ♦) and reagent blank vs. chloroform (o-o). (concentration of DHQ: 4.78 x 10^{-4} M)

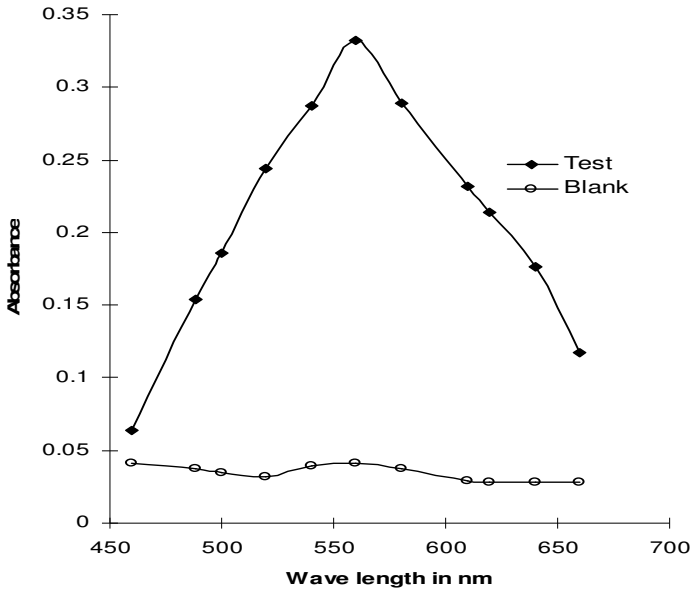

Fig.-3: Absorption spectra of the CFT-TQ system (♦ ♦) and reagent blank vs. chloroform (o-o). (concentration of TQ: 8.18 x 10^{-4} M)

Recommended Procedures

For Bulk Samples

Method A: Aliquots of standard drug CTZ solution (1.0-3.0 mL, 200 µg/mL) were delivered into 10 mL graduated tubes. Then 2mL of (4.4 ×10^{-3}M) DDQ in acetonitrile was added and kept aside for 15 min. The volume was made upto 10 mL with acetonitrile and read at 440 nm against reagent blank during the stability period (15-60min). The amount of drug present was computed from the appropriate calibration curve

Method B: Aliquots of standard drug CTZ solution (0.5 – 2.5 mL, 400 µg/mL), was transferred into 10mL-graduated tubes. 2.0 mL of (4.785 x 10^{-3}M) DHQ was added and kept aside for 5 min. Then the volumes of the contents were made upto 10 mL with methanol and read at 520 nm for CTZ against a reagent blank within 30 min. The amount of drug was computed from the appropriate calibration curve.

Method C: Aliquots of standard drug CTZ solution (1.0 – 3.0 mL, 200 µg/mL) in dioxan were delivered into 10 ml graduated tubes. Two mL of (4.067 × 10^{-3}M) TQ in 1, 4-dioxan, followed by dioxan was added for bringing the volume to 7 mL. The final volume was brought to 10 mL with dimethyl formamide and the absorbance was measured against a reagent blank at 620 nm for CTZ within the stability period (15-60min). The amount of the drug present was computed from the appropriate calibration graph.

For Pharmaceutical Formulations

An accurately weighed amount of injection powder equivalent to 100 mg of CTZ was dissolved in 10 ml of DMF, followed by dilution to 100 ml with dioxane. The working standard solution of CTZ of required strength prepared by further dilution of the stock solution of CTZ with required solvent in the respective method and analyzed under procedure described for bulk samples.

RESULTS AND DISCUSSION

The optimum conditions for the colour development of method were established by varying the parameters one at a time in each method, keeping the others fixed and observing the effect produced on the absorbance of the coloured species.

The optical characteristics such as Beer's law limits, molar absorptivity for each method are given in Table 2. The precision of each method was found by measuring absorbances of six replicate samples containing known amounts of drug and the results obtained are incorporated in Table 2. Regression analysis using the method of least squares was made to evaluate the slope (b), intercept (a) and correlation coefficient (r) for each method and are presented in Table 2. The accuracy of each method was ascertained by comparing the results by proposed and reference methods (UV) statistically (Table 3). This comparison shows that there is no significant difference between the results of proposed methods and those of the reference ones. The similarity of the results is obvious evidence that during the application of these methods, the additives and excipients that are usually present in tablets do not interfere in the assay of proposed methods. As an additional check of accuracy of the proposed methods, recovery experiments were performed by adding a fixed amount of the drug to the preanalysed formulations. The amount of drug found, the % recovery was calculated in the usual way.

Chemistry

The interaction of any of the investigated compounds with poly halo and polycyanoquinone π-acceptors in nonpolar solvents was found to produce colored charge-transfer complexes with low molecular absorptivity values. In polar solvents such acetonitrile or methanol, complete electron transfer from donor to the acceptor moiety takes place with formations of intensely colored radical ions with higher molar absporptivity values according to the following scheme.

$$D^{\cdot\cdot} + A \rightarrow \underset{\text{Complex}}{(D\text{–}A)} \xrightarrow{\text{Polar solvent}} A^{-\cdot} + D^{+\cdot}$$

The dissociation of the D-A Complex is promoted by the high ionizing power of the acetonitrile and the resulting bands of the named drugs with acceptors are similar to the maxima of radical anions of the acceptors obtained by the iodide reduction method.

Acetonitrile was considered an ideal solvent as it afforded maximum sensitivity yield of radical anions in addition to its high solvating power of the reagents. Methanol gave maximum sensitivity in case of DDQ and DMF gave maximum sensitivity in case of TQ. The interaction of CTZ with TQ, DHQ, DDQ, gave a colored chromogens with a strong absorption maxima in different solvents given in Table-1

CONCLUSIONS

The proposed methods are applicable for the assay of drug (CTZ) and have the advantage of wider range under Beer's law limits. The decreasing order of sensitivity and λ_{max} among the proposed methods are C>B>A respectively. The proposed methods are simple, selective and can be used in the routine determination of CTZ in bulk samples and formulations with reasonable precision and accuracy.

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