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Determination of Olanzapine with DDQ by charge transfer complexaction using UV spectrophotometric method

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Abstract: *The simple and sensitive spectrophotometric method for the determination of Olanzapine reacts with 1ml of DDQ (2, 3 –dichloro -5, 6-dicylano-1, 4-benzoquinone) by charge –transfer complex method. In this method the drug Olanzapine as n-electron donors with acceptor 2, 3 dichloro-5, 6- dicyano 1,4- benzoquinone (DDQ) to form reddish pink color charge-transfer complexes. This reaction is instantaneous and quantitative. The drug maximum absorbance at 450 nm and Beer's law limit was obeyed at 30-150 µg/ml. The optical characteristics of the proposed method such as molar absorptivity, sandell's sensitivity, slope and intercept were 5.16x10^3 L.mole^{-1} cm^{-1} , 0.00161 µg.cm^{-2} ,0.0050 and -0.005 the correlation coefficient is 0.9999 for Olanzapine respectively. The developed method was found to be simple, specific, robust, accurate and precise for the determination of Olanzapine.*

Key words: *Olanzpine, chloroform, methanol, DDQ and UV-Spectrophotometric method.*

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I. Introduction

Olanzapine is an atypical antipsychotic, approved by the U.S. Food and Drug Administration (FDA) for the treatment of schizophrenia and bipolar disorder [1]. Chemically olanzapine is 2-methyl- 4-(4-methyl1-1-piperaziny1) – 10H- thin (2, 3-b) (1, 5) benzodiazepine. Its trade names are lazed, zypadhera, zappers and molecular formal is C_{17} H_{20} N_4 S and molecular weight is 312.439 olanzapine melting point is 195^0C(383 F) Olanzapine is used for schizophrenia and bipolar disorder [2].

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Olanzapine tastes ranging from 2.5 to 20 milligrams. Zyprexa (and generic olanzapine) is available as an orally dis integrating water which rapidly dissolves in salive. It is also available in 10 milligram vials for intramuscular injection.

The principal side effect of olanzapine is weight gain which may be profound in some cases and for associated with dearrangements in the blood lipid sugar profiles. Extrapyramidal side effects may include tremors and muscle rigidity

Various methods have been reported in literature for the estimation of olanzapine and other combination drugs which includes UV spectrophotometric method [3-5], HPLC [6-9], GC [10] and FIA [11]. A few visible spectrophotometric methods [12, 13] have been reported.

The spectrophotometric method is based on the reaction of olanzapine 2, 3 –dichloro5, 6- dicyano-1, 4-benzoquinone (DDQ) to form a red colured charge – transfer complex. The red coloured solution is used to determine the olanzpine spectrophotometrically. The reaction sequence can be shown in scheme 1.

II. Experimental

2.1 Instrumentation

A Shimadzu UV-visible double beam spectrophotometer (model 2450) with 1 cm matched quartz cells was used for the spectral measurements.

2.2 Chemicals and reagents

All the chemicals used were of analytical grade. Double distilled water was used for all the experimental studies.

2.3 DDQ solution (1% w/v)

DDQ (2, 3-dichloro5, 6-dicyano-p-benzoqunone) (Loba Chem., India) solution is prepared by dissolving 100 mg in 100 ml of distilled water.

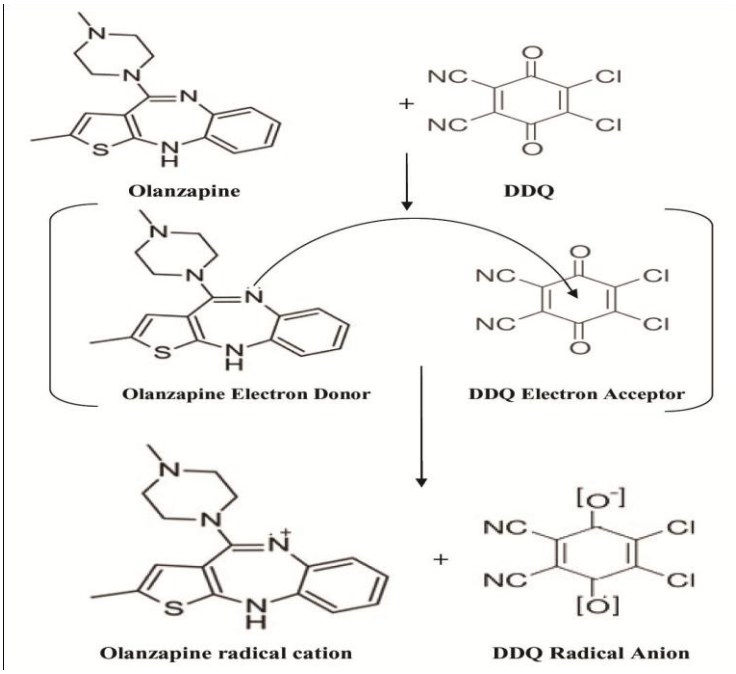
2.4 Olanzapine solution

An accurately weighed 50 mg of olanzpine is dissolved in methanol and the volume was adjusted to 50 ml with methanol. Further dilution is made to obtain the working concentration of 100 µg /ml. 2.5 Spectrum of

olanzpine treated with DDQ 1.0ml of olanzpine standard solutions was taken into a standard flask. To this solution 1ml of DDQ

2.5 Spectrum of olanzpine treated with DDQ

Aliquots of standard drug solution of olanzapine 1ml (100µg/ml) are transferred into a standard flask. To this solution, 1.0 ml of DDQ reagent is added to form a red colored solution. The final volume was brought to 10 ml with methanol. The resultant solution is well mixed and allowed to stand for 5 min for completion of the reaction. The reaction sequence is shown in scheme 1. The absorbance of the red colored solution is measured in the wavelength range of 400 to 700 nm against the reagent blank. The spectrum is given in figure 1.



Scheme 1: The reaction sequence of charge transfer complex

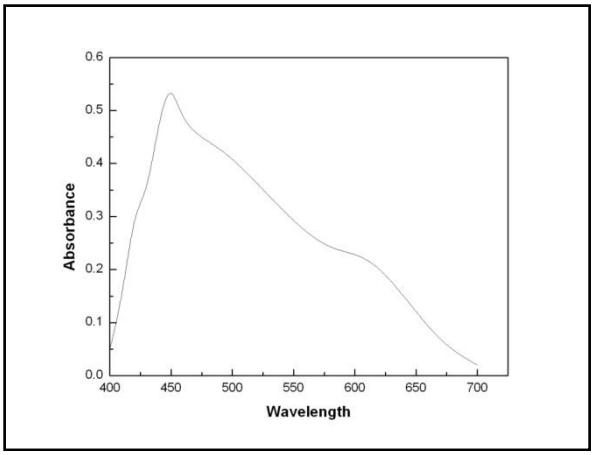


Figure 1 Spectrum of olanzapine treated with DDQ solution

It is evident from Figure 1. That the olanzapine drug treated with DDQ solution has maximum absorbance at 450 nm. Hence, all the further studies are made at 450 nm.

2.6 Effect of concentration of DDQ solution on the absorbance of charge transfer complex is studied by the following procedure.

Varying amounts of DDQ solution are added to a series of standard flasks containing 1.0 ml of olanzapine. The contents are made up to the mark with methanol. Reaction mixture was shaken gently for 5 minutes and allowed to stand for 5 minutes to complete the reaction. The absorbance of the resultant solutions is measured at 450 nm and the data are presented in table 1.

Table 1: Effect of concentration of DDQ solution

Volume of DDQ solution(ml)	Absorbance at 450 nm
0.5	0.245
1.0	0.375
1.5	0.389
2.0	0.450
2.5	0.369

The data is presented in table 1 Indicate that 2.0 ml of DDQ is necessary for achieving maximum absorbance and hence maintained throughout the experimental studies.

2.7 Assay procedures

2.0-1.6 µg/ml of aliquots of standard drug solution (100µg/ml) were transferred into 125ml separating flasks and added 2.0 ml of DDQ solution, heated on water both for 25 min, cooled at room temperature and then followed by addition of dilute Hcl. The mixture was extracted twice with 10ml chloroform by shaking for 2.0 min, and then allowed to stand for clear separation of the two phases and the chloroform layer was dried with anhydrous sodium sulphate. The absorbance of the red colored solution is measured at 450nm against the reagent blank prepared in similar manner omitting drug solution. Calibration graph is obtained by plotting absorbance values against the concentration of olanzapine solution. The calibration curve is found to be linear over a concentration range of 30 to 150 µg / ml of the amount of olanzpine present in the sample is read from the calibration graph. The results are presented in figure 2.

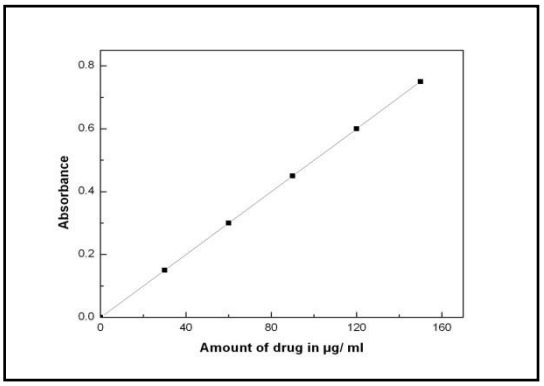


Figure 2 Calibration curve of Olanzpine

2.8 Assay of olanzapine in pharmaceutical formulations

Ten tablets were weighed and grinded to a fine powder using a pestle and mortar. The average weight of a tablet was calculated. As accurately weighed portion of the powder, equivalent to 100 mg of olanzapine was transferred into a 100ml volumetric flask. The volume was made up to the mark with water, shakein well and filtered through a whattman filter paper no 41. The concentration of the resulting solution was found to be 1mg/ml. This solution was considered as the stock. This solution was to taken for the determination of olanzapine and results are shown in table 3. The amount of drug present in the sample is estimated from calibration graph.

III. Method Validation

3.1 Linearity

Under the above experimental conditions linear calibration graphs were obtained by plotting the absorbance of the studied drug concentration versus absorbance within the specified range.

The optical characteristics such as Beer's law limit, molar absorptivity, and sandell's sensitivity are presented in table 2. The regression analysis was made for the slope as, intercept (b) and correlation coefficient (r) and the results are summarized in table 2.

3.2 Robustness and Ruggedness

Robustness of the method was studied by changing pH, reagent concentration, wave length range and shaking time. The capacity remains unaffected by small deliberate and shaking time. Method ruggedness was expressed as RSD% of the same procedure applied by two analyses and in two different instruments on different days. The result is analysis and instruments suggesting that the developed methods were robust and rugged.

3.3 Accuracy

Accuracy results show that the recovery values in bulk drug, serum and urine were 99.46-99.75% for olanzpine table 6. All the results are good within the acceptable boundary. The percentage recovery was calculated as

Percentage Recovery = [(a-b)/c] x 100.

Where 'a' is the total amount of the drug estimated.

'b' is the amount of the drug found on pre-analyzed basis (standard drug solution).

'c' is the amount of the pure drug added to the formulation.

3.4 Precision

Precision is evaluated using three separate determinations for repeatability; intermediate precision and reproducibility. The inter and intraday variations were analyzed by coefficient of variation (% CV) through the linear range of concentrations are listed in table 3.

The precision calculated as inter and intraday % RSD less than 2, which indicates that there was no significant difference for the assay which was tested within day and between days in active pharmaceutical ingredients and results are shown in table 3.

3.5 Limit of Detection (LOD) and Limit of Quantification (LOQ)

The analytical sensitivity of the method was anticipated from the signal to noise ratios 3:1 and 10:1. The minimum limits at which analyze can be readily detected (LOD) and quantified (LOQ) for olanzpine.

LOD and LOQ were determined by using the formula based on the standard deviation of the response and slope.

LOD and LOQ were calculated by using the equations.

LOD= 3x s/S and LOQ = 10xs/S.

Where's' is the standard deviation of the intercept.

S is the slope.

3.6 Recovery

Recovery studies were carried out by following procedure. The drug samples of different concentrations were linear, accurate, precise and selective by running three replicates of each concentration measured for three days. The average recoveries were recorded in table 6.

3.7 Effect of interferences

To study the importance of the proposed analytical method, the effect of the excipients, viz. Glucose, Sucrose, Lactose, Dextrose, Talc and Starch which frequently come with the drug olanzapine in its dosage forms was studied. The results showed that there is no interference from the degradation which indicates a high selectivity in determining olanzapine in its dosage form. These results are recorded in table 5.

3.8 Assay in serum and urine samples

Blood and urine samples were collected from donors, and centrifuged at 3000 rpm for nearly 10 min. The resulted solutions were filtered and preserved in the absence of light at a temperature of 4^{o} C. From these solutions, various concentrations of the drug olanzapine were analyzed with the help of proposed analytical method and these results were recorded in table 6. Hence, the proposed method can be successfully applied to recover olanzapine in biological samples, viz. urine and serum due to its high accuracy and good recoveries.

IV. Results and Discussion

In this method the drug reacts with DDQ solution to form an orange red charge complex. The red coloured charge complex solution formed is measured at 450 nm against reagent blank. The amount of drug read from calibration curve. The calibration curve is linear over the range of 30-150 μg/ml of olanzapine the optical characteristics of the proposed method such as absorption maxima, Beer's law limits, molar absorptivity and Sandell's senstitivity are presented in table 2. The molar absorptivity and Sandell's sensitivity values show that method is sensitive. The regression analysis using method of least squares was made for the slope (b), intercept (a) and correlation (r) obtained from different concentrations and results are summarized in the table 2. The value of correlation coefficient (r) was 0.999 which indicated the good linearity of calibration lines. The percent relative standard deviation calculated from the five measurements of olanzapine shown in table 2. The % RSD is less than 2, which indicates that the method has good reproducibility. The values of standard deviation values are low and indicate high accuracy and reproducibility of the method. The't' calculated values are compares well with the theoretical value of 2.78 there by indicating that the precision of the method. There is no effect of additives and excipients such starch, calcium lactose and glucose in the concentrations those present in general pharmaceutical preparations.

The proposed method is found to be simple, precise, accurate and time saving, reproducible and can be conveniently adopted for routine analysis of estimation of olanzapine in bulk drugs samples and pharmaceutical formulations

Table 2: Optical characteristics of the proposed methods

Parameters	Proposed method
λ max(nm)	450
Beer's law limit(μg/ml)	30-150
Molar absorptivity (L.mole^{-1} cm^{-1})	5.16x10^{3}
Sandal's sensitivity (μg.cm^{-2}/0.001 A.U)	0.00161
Slope(b)	0.0050
Intercept(a)	-0.005
Correlation coefficient(r^2)	0.9999
Relative standard deviation(RSD)%	0.1612
LOD(μg/ml)	0.5909
LOQ(μg/ml)	1.9680
Color	Brick Red color

Table3: Evaluation of inter and intraday accuracy

Taken μg/ml	Inter day				Intra day			
	Found	Recovery %	±SD	%RSD	Found	Recovery %	±SD	%RSD
8	7.985	99.81	0.042	0.045	7.968	99.61	0.0427	0.536
9	8.977	99.81	0.007	0.077	8.989	99.87	0.0070	0.077
10	9.989	99.74	0.998	0.053	9.987	99.87	0.9987	0.083
11	10.975	99.89	0.009	0.090	10.987	99.88	0.0099	0.090

*** Average of five determinations**

Table 4: Optical characteristics of the proposed methods

Tablets	Labelled amount mg/ml	Amount found mg/ml	%Recovery	±SD	% RSD
Olexar	100	99.83	99.83	0.057	0.0578
olanzotic	200	199.8	99.9	0.125	0.0526
Zyprexa	300	299.5	99.83	0.520	0.0017

***Average of five determinations based on label claim**

Table 5: Determination of olanzapine in presence of excipients

Excipients	Amount taken mg/ml	*Found mg/ml	Recovery %	±SD	RSD %
Glucose	15	14.98	99.86	0.010	0.0667
Sucrose	25	24.96	99.86	0.015	0.0611
Lactose	35	34.97	99.93	0.005	0.0165
Dextrose	45	44.97	99.94	0.005	0.1283
Talc	55	54.98	99.60	0.010	0.1818
Starch	65	64.97	99.96	0.015	0.2350

*** Average of five determinations**

Table 6: Method accuracy from recovery assay

Sample	Added mg/ml	*Found mg/ml	Recovery %	±SD	RSD%
Serum samples	0.5	0.49	99.46	0.0020	0.4185
	0.6	0.59	99.55	0.0020	0.3484
	0.7	0.69	99.75	0.0011	0.1577
	0.8	0.79	99.25	0.0055	0.7012
Urine samples	0.8	0.79	99.66	0.0076	0.9688
	1	0.99	99.71	0.0057	0.5851
	1.2	0.19	99.66	0.0045	0.3774
	1.4	1.39	99.75	0.0045	0.3233

*** Average of five determinations**

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