International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 1153-1161, Oct-Dec 2009

SPECTROPHOTOMETRIC DETERMINATION OF AN ATYPICAL ANTIPSYCHOTIC COMPOUND IN PHARMACEUTICAL FORMULATION

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Abstract: Quetiapine (bis [2-(2-[4-(dibenzo [b, f][1,4]thiazepin-11-yl]ethoxy)ethanol]fumarate) is the most recent agent introduced on the drug market for the treatment of psychotic disorders. Two different spectrophotometric analytical methods for the quality control of Quetiapine Fumarate in commercial marketed formulation have been developed. One is the zero order derivative spectroscopic method (Method-I) and other is area under curve method (Method-II), for the first method, wavelength selected i.e. 290.0nm and that of for other 295.0nm to 281.0nm respectively. The absorbance data was obtained by the measurements at selected wavelengths by using Milli-Q water as solvent. Beers Lambert's law obeyed at concentration range 12-60 mg ml^{-1} concentration range of Quetiapine for both spectrophotometric methods at selected wavelengths. Proposed methods gave satisfactory results in terms of repeatability and precision i.e. % RSD 0.60% and 0.73% resp. Also accuracy values were very good for both methods i.e. % RSD 0.60 and 0.75% resp. which is drawn out by recovery studies, were found satisfactory. Both spectroscopic methods have excellent linearity and range (r^2 = 0.999). Ruggedness of both methods checks in terms of intraday and interday studies having % RSD 0.55 %, 0.15% and 0.33%, 0.46% respectively. The procedures do not require any separation step. These methods were successfully applied to any solid dosage form containing same drug and was found to be utter, swift and efficient for their estimation from pharmaceuticals.
Keywords: Quetiapine Fumarate, UV spectrophotometry, Area under curve method, Zero order derivative spectroscopy, Tablet analysis.

Introduction

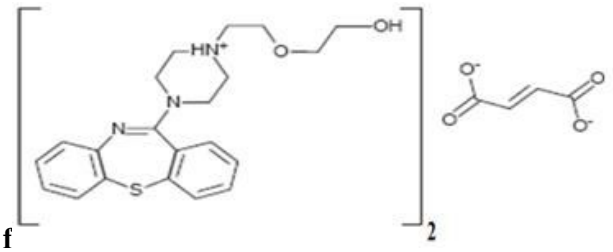
An atypical antipsychotic, Quetiapine fumarate (2-[2-(4-dibenzo[*b*,*f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol fumarate (2:1 salt)) which has a unique receptor-binding profile belonging to a new chemical class, the dibenzothiazepine derivatives [1–4]. Quetiapine is an antagonist at a broad range of neurotransmitter receptors. Quetiapine is used in the treatment of schizophrenia or manic episodes associated with bipolar disorder. These antipsychotics have a low incidence of extrapyramidal side effects and tardive-dyskinesias compared to older antipsychotics. The advantages of the therapeutic profile of quetiapine have led to increasing use in the clinical practice, which encourages the development of new pharmaceutical preparations. As a consequence, there is an increasing demand for new analytical methods for determination of same drug in most economical way.

Several HPLC methods for the determination of QUET have been reported, most of these require ultraviolet detection [5-8] as QUET is not electro active, some stability indicating [9-10], impurity characterizing [11]. A HPTLC method has been developed [12]. However none of these methods is sensitive enough for determination of the expected drug levels and some of them are time-consuming and require complex sample pretreatment or long run times [13]. Some gas chromatography–mass spectrometry (GC–MS) methods have also been employed, however here QUET needs to be derivatized

before analysis [14-15]. Some HPLC–MS-MS methods has been published for determination of QUET [16-17].

The goal of our work was to develop an UV spectrophotometric method for determination of QUET in solid dosage form and to use the results for analysis of drug in pharmaceuticals in most economic way, as rapid and effective ways for determination of drugs in sample matrix by spectroscopy is desirable as such no analytical paper is available for the quality control of pharmaceutical formulations containing quetiapine fumarate by spectroscopy.

Structure of quetiapine fumarate



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Materials & methods

A SHIMADZU Model PHARAMASPEC-1700 UV–Vis spectrophotometer with 1.0 cm matched cells was used for the electronic spectral measurements. Quetiapine Fumarate and all other chemicals used were analytical reagent grade (AR grade). Milli-Q water was used as a solvent in all experimental purpose. SOCALM tablet from RANBAXY was taken for analysis.

I. Solutions

An accurately weighed quantity of 30 mg QUET was transferred in 100 mL volumetric flask, sonicate for sufficient quantity of Milli-Q water. The volume was made up to the mark with freshly prepared Milli-Q water (Concentration: 300µg/ml). Aliquots of this standard stock solution (SSS) of QUET was diluted with Milli-Que water and scanned over the UV range of 200-400 nm. Spectral measurements were made with Spectral band width 1 nm. The UV spectra of quetiapine fumarate in distilled water shows quite satisfactory spectrum. A spectrum of drug was Drawn out and studied as for derivative spectroscopic method and for area under curve method. In case of derivative spectroscopy, zero order selected at wavelength 290.0 nm for the analysis at which drug show maximum absorbance (**Fig. No.1-A**). As concerns to Area under curve method wavelength selected are 295.0 nm - 281.0 nm at which QUET had equal absorbance (**Fig. No.1-B**). Hence these two wavelengths have been selected for measurement of absorbance for determination of quetiapine fumarate.

II. Procedure

1. For calibration curve: (study of Beer-Lambert's Law)

Five mixed standards of QUET having concentrations 12.0, 24.0, 36.0, 48.0 and 60.0 µg/mL prepared from SSS. The absorption spectra were processed to obtain zero order derivative spectra for derivative spectrometry at 290.0nm (**Fig. No.2-A and 3-A**) and at 295.0-281.0nm for area under curve method (**Fig. No.2-B and 3-B**). Absorbance at five different standards plotted against concentration and calibration graph forms.

2. For absorptivity study:

From the SSS, 5.0mL pipette out and dilute it to 100mL getting final concentration 15.0 µg/ml. Absorbance of such five of QUET standard solution measured and results of absorptivity study drawn out by $A^{1\%}_{1cm.}$ (**Table No.1**)

3. Estimation of QUET in commercial marketed samples:

Twenty tablets were weighed accurately and powdered. Powder equivalent to 1 tablet (Label claim-300 mg) was taken and transferred to 100 ml volumetric flask and dissolved in Milli-Q water, sonicate for 10 min., filtered and further 5.0 mL of the filtrate was further diluted in a 100.0 mL volumetric flask with Milli-Q water to get concentration of 15 µg/mL of QUET (on labeled claim basis). The solution is then scanned in the range of 200-400 nm against blank and a zero order derivative graph was then plotted followed by absorbance measured at the selected wavelengths range i.e. 295.0nm-281.0nm for Area under curve method of the drugs. (**Table No.2**)

III. Result and discussion

a) General

The developed methods i.e. zero order derivative and area under curve method of spectrophotometric determination of QUET in tablet formulation was found to be absolute and persuading for the routine analysis of drug. Practically no interference from tablet excipient was observed in these methods. The method is used to eliminate the spectral interference observed from tablet excipient at the selected wavelength. The methods are accurate, simple, rapid, precise, reliable, sensitive, reproducible and economical. In our study, QUET was analyzed using ^{0}D-UV-spectrophotometric methods (N-0) (Method-I). Derivative-UV-spectrophotometry offers greater selectivity than UV-spectrophotometry because of better resolution. The zero order UV-spectra of QUET alone were recorded over the range 200–400 nm in Milli-Q water. However, when ^{0}D-UV spectra (N-0) was recorded, sharp bands with high amplitudes were obtained, which might permit more selective identification and determination of QUET in the standard. Apart from that in case of area under curve method (AUC, Method-II) absorbance measured at selected wavelengths i.e.295.0nm & 281.0nm. AUC involves the calculation of integrated value of absorbance with respect to the wavelengths λ1 and λ2. Area calculation processing item calculates the area bound by the curve and the horizontal axis. The horizontal axis was selected by entering the wavelength range over which the area has to be calculated. The wavelength range from 295.0 nm - 281.0 nm was selected which showed good linearity between area under curve and concentration.

b) validation of analytical data

The study of Beer's-Lambert's law was checked by preparing standard solutions at 5 different concentrations and the linearity of the calibration graphs and conformity of the ^{0}D-UV measurements of the proposed methods to Beer's law were proven by the high values of the correlation coefficient (r) of the absorptivity study. The linear range of concentrations for the analysis of QUET was found to be 12.0-60.0 µg mL^{-1} for both AUC and ^{0}D-UV spectrophotometric method, which found to be linear. (**Figure No.2-A & Figure No.2-B)**

The utility of these methods was verified by means of a recovery assay in the marketed tablet samples. Tablet sample (Label claim-300mg) QUET was prepared and processed according to the proposed methods. Recoveries were determined by standard addition method (SAM). The mean percentage recoveries of QUET by ^{0}D-UV method were found to be 99.52% and that of AUC was found to be 99.37%. Results represent accuracy by study of recovery. (**Table No.3**)

The reproducibility of these developed method established by study of precision for QUET was determined by five replicates analyses on a synthetic tablet sample. The mean relative standard deviations were found to be 0.60% and 0.73% for AUC and ^{0}D-UV spectrophotometric methods respectively. (**Table No.2**)

The linearity and range established by preparing five different concentration of solution based on labeled claim (Label claim-300mg) of QUET. Absorbance of 90% - 120 % solution measured and linearity graph plots between absorbance and % label claim. Correlation coefficient for AUC and ^{0}D-UV spectrophotometric method was found to be 0.9999 & 0.9996 of QUET resp. found to be linear. (**Figure No.4-A & Figure No.4-B)** (**Table No.4**)

Specificity studies were carried out by treating sample with 0.5N NaOH for 3 hrs., 0.5N HCL for 3 hrs., 3% H_2O_2 for 24 hrs., 75% humidity and 40^o temp. for 24 hrs., UV exposure for 24 hrs. and finally photochemical degradation i.e. direct sunlight exposure for 6 hrs. Results of specificity studies quoted at **Table No.5 and Figure No.5**

The Ruggedness of the proposed method checked by means of two parameters i.e. Intraday & Interday. Ruggedness is nothing but intermediate precision which was established by the different circumstances under which the procedure is intended to be used. For intra-day study, mean % label claim & mean % relative standard deviations were found to be 100.10%, 100.19% and 0.55, 0.14 (**Table No.6**) and for inter-day study 99.75 %, 99.98 % and 0.32, 0.45 (**Table No.7**) respectively for AUC and ^{0}D-UV spectrophotometric methods respectively.

IV. Conclusion

Validation parameters consents, the applied spectrophotometric methods of analysis are simple, sensitive, accurate, precise and satisfactorily capable for determination of QUET in tablet formulation with reproducible specific results. The linear concentration range of preordain elaborated methods were observed wider. In addition, the analyses by proposed methods are cheaper and economic too. Thus, proposed AUC and ^{0}D-UV spectrophotometric methods are applicable for the quality control and routine analysis and may also be proposed for determination from biological fluids or other solid dosage form containing same drugs.

Table No.1. Absorptivity(1%, 1cm) values of QUET at 290.0 nm

Sr. No.	Conc. g/100mL	Absorbance	A (1%, 1cm)*
1	0.0015003	0.179	119.30
2	0.0015034	0.180	119.72
3	0.0015093	0.178	118.31
4	0.0015126	0.181	119.67
5	0.0015072	0.179	118.76
Mean			**119.15**
± S.D.			**0.654**
% RSD			**0.6**

Table No. 2: Estimation of QUET in marketed formulation

Sr. No.	Wt. of tablet powder taken mg	Observations		Observations	
		Method I, Abs. At 290.0 nm	Method II, Area Under Curve 295.0 to 281.0	Method I, Abs. At 290.0 nm	Method II, Area Under Curve 295.0 to 281.0
1	99.92	0.179	2.4706	99.91	100.31
2	99.95	0.180	2.4795	99.36	99.56
3	99.98	0.176	2.4193	98.37	98.36
4	99.87	0.181	2.4892	99.8	99.46
5	99.89	0.179	2.4739	99.42	99.95
MEAN				**99.37**	**99.52**
± SD				**0.608**	**0.734**
% RSD				**0.6**	**0.7**
Variance				**0.369**	**0.539**

Table No.3: Results of estimation of QUET under recovery Study

Sr. No.	Method-I (^{0}D-UV)			Method-II (AUC)		
	Total drug estimated (mg)	Amount of pure drug recovered (mg)	% Recovery*	Total drug estimated (mg)	Amount of pure drug recovered (mg)	% Recovery*
1	31.62	1.03	101.43	31.60	1.01	101.0
2	33.92	1.94	100.02	34.03	1.99	99.50
3	37.93	3.01	100.34	39.34	3.02	100.34
MEAN			100.596			100.34
±SD			0.603			0.751
%RSD			0.6			0.7
Variance			0.546			0.565

Table No.4: Study of Linearity and Range

Sr. No.	Weight of Tablet powder taken equivalent to % Label Claim	Method I	Method II
1	80	0.521	7.3789
2	90	0.581	8.1878
3	100	0.637	8.8973
4	110	0.694	9.5903
5	120	0.751	10.354
Coefficient of Correlation		**0.9999**	**0.9996**

Table No.5: Results of specificity studies

Sr. No.	Sample ID	% Label Claim	
		Method I	Method II
1	Alkali (0.5N NaOH)	99.03	99.15
2	Acid (0.5N HCL)	89.33	93.39
3	Oxide (3% H2O2)	99.76	100.10
4	Humidity 75% & Temp.40°C	99.21	98.13
5	UV Exposure	102.64	102.54
6	Photochemical (Direct sunlight)	97.19	97.30

Table No.6: Results of Estimation in Intra-day studies

Sr. No.	Hour	Wt. of tablet powder taken (mg)	% of Labeled Claim	
			Method I	Method II
1	0 hr	99.92	99.49	100.22
2	3 hr		100.25	100.03
3	6 hr		100.57	100.32
Mean			100.10	100.19
± SD			0.554	0.147
%RSD			0.6	0.9
Variance			0.307	0.021

Table No.7: Results of Estimation in Inter-day studies

Sr. No.	DAY	Wt. of tablet powder taken (mg)	% Label Claim	
			Method I	Method II
1	DAY-1	99.92	100.06	100.54
2	DAY-4		99.48	99.50
3	DAY-7		99.46	100.15
4	DAY-15		100.02	99.74
Mean			99.755	99.982
± SD			0.329	0.458
%RSD			0.3	0.4
Variance			0.1086	0.2101

Caption:

1. **UV - Ultraviolet**
2. **QUET –Quetiapine Fumarate**
3. **AR- Analytical Grade**
4. **^{0}D UV - zero order derivative ultraviolet spectrophotometry.**
5. **SSS –Standard stock solution**
6. **nm- nanometer**
7. **µg/ml – microgram per milliliter**
8. **S.D. – standard deviation**
9. **R.S.D. – Relative standard deviation**
10. **Wt. –Weight**
11. **Hrs.-Hours**

Figure No. 1(A): Zero order derivative spectra of QUET (290.0nm)

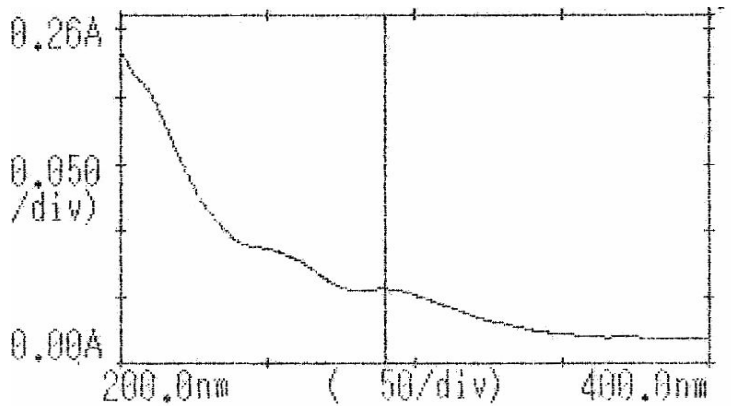

Figure No. 1(B): Area under curve method (295.0nm and 281.0nm)

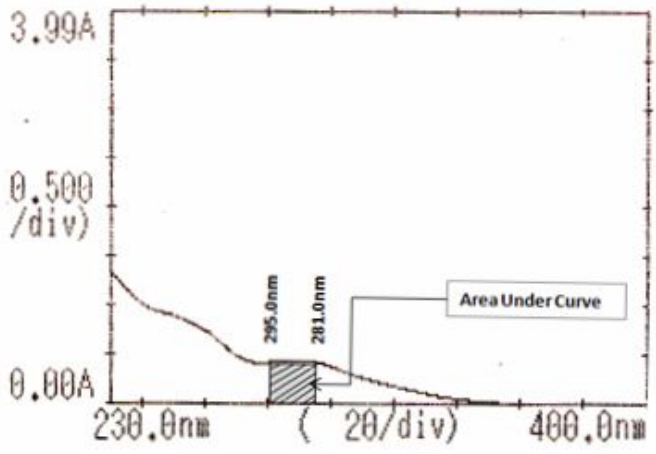

Figure No. 2(A): Overlain Spectra of five different standards by Method-

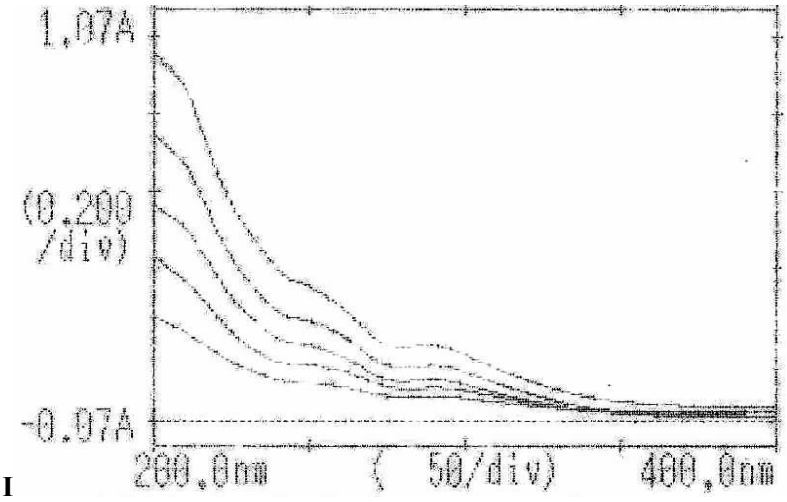

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Figure No.2(B): Overlain Spectra of five different standards by Method-II

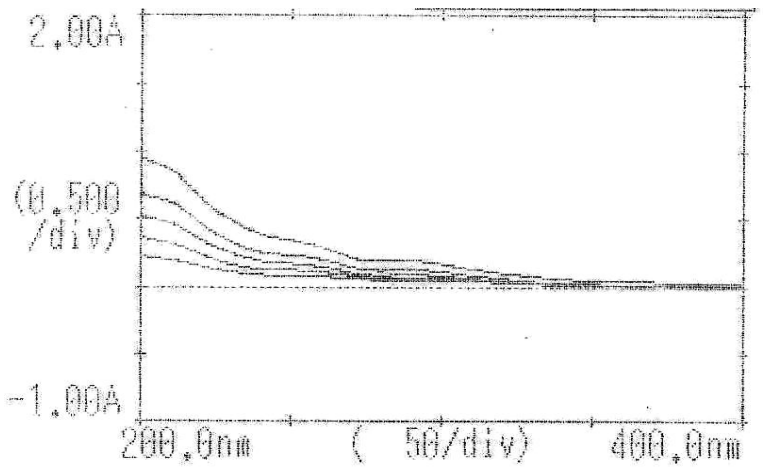


Figure No. 3(A): Plot of Beers- Lambert's law for QUET at 290.0 nm (^{0}D-UV)

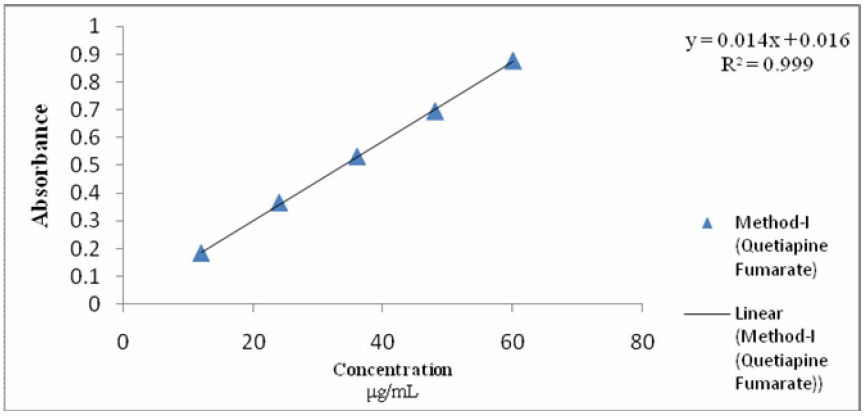


Figure No. 3(B): Plot of Beers- Lambert's law for QUET at 295.0 nm-281.0nm (Area Under Curve Method)

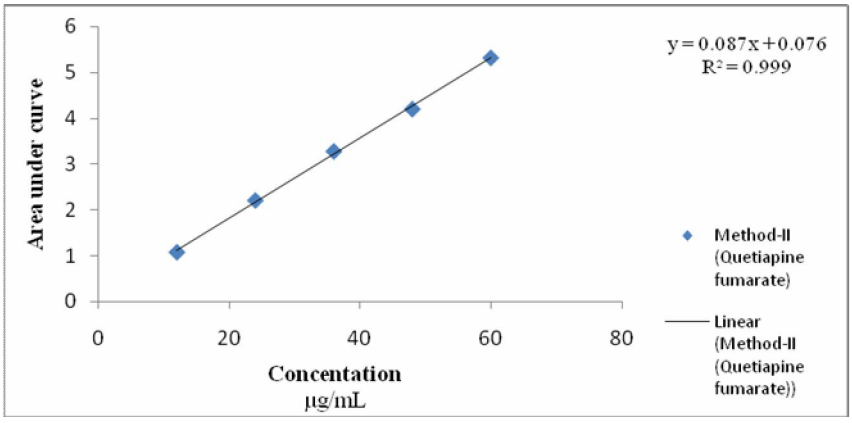


Figure No.4-A: 10.A: Study of Linearity and Range of QUET (Method-I)

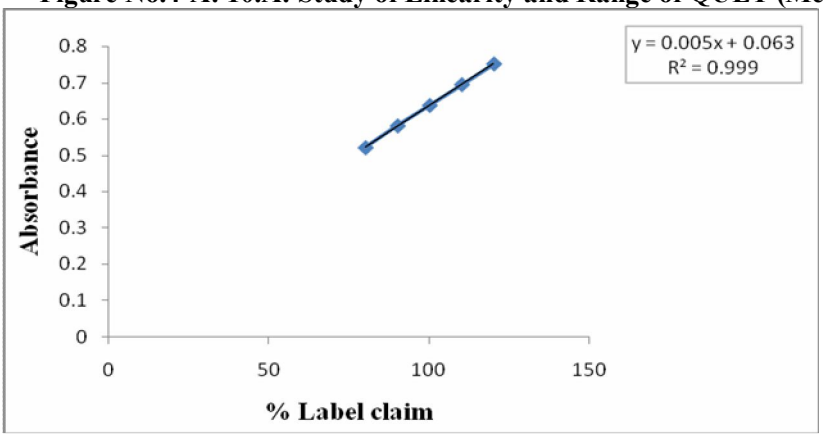


Figure No.4-B: Study of Linearity and Range of QUET (Method-II)

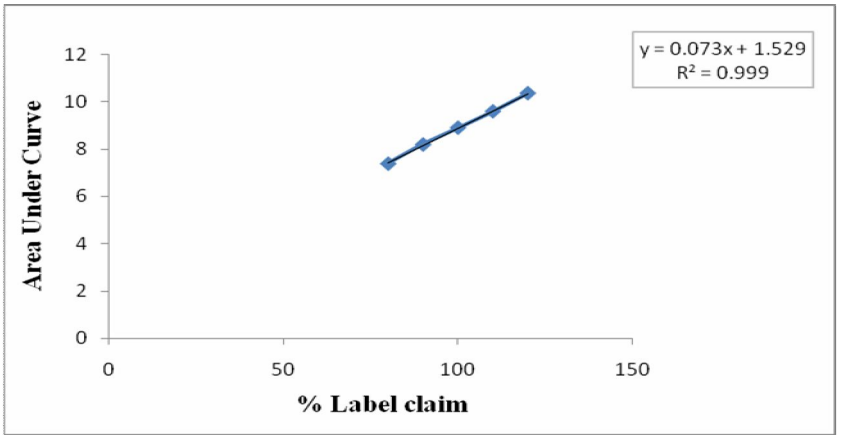
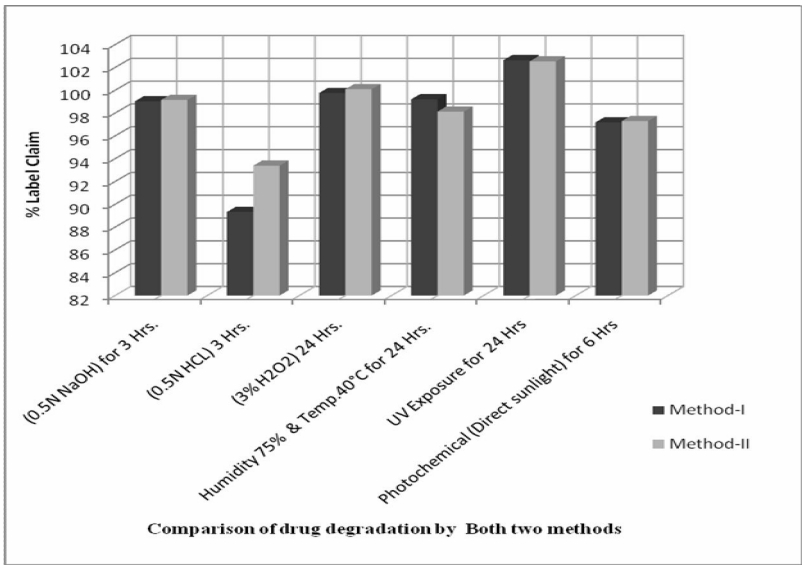


Figure No.5: Results of specificity Studies



Acknowledgements

Author would like to give thanks to, Mr. Satish Vyahare, chairman of Vama Pharmaceuticals Pvt. Ltd. (Nagpur, Maharashtra, India) for providing an opportunity to work in quality control department of an industry and providing a drug for analysis, necessary facilities and equipments for proposed research. I would like to give special thanks to Dr. M. J. Umekar Principal of S.K.B. College of pharmacy, Kamptee, Nagpur, Maharashtra and finally to Mr. R.T. Lohiya, Asst. professor in pharmaceutical chemistry for their valuable guidance to perform this work.

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