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Original Article

Degradation Kinetic Study of Antipsychotic drug and it's Chemical Analysis

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ABSTRACT

A simple, precise, accurate Spectrophotometric method was developed & validated for the determination of Lurasidone HCl in bulk & pharmaceutical formulation & its degradation kinetic study & its chemical analysis was done successfully. Beer's law followed the concentration range of 2 to 55 µg/ml at 315 nm with good co-relation coefficient (r^2=1). The % estimation was found to be 98.1% with % RSD 1.75%. The % recovery studies was performed & found to be 99.04% with % RSD 0.6%. Hydrolytic degradation of Lurasidone HCl was carried out by using 1N NaOH, 1N HCl & water was found to be 46.49%, 68.48% & 87.5% respectively. The degradation kinetic was found to be 82% in acidic medium at 80^0c & 50% in alkaline medium at 80°C.

Key words: Lurasidone HCl, Spectrophotometric methods, Degradation studies, Kinetic studies.

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INTRODUCTION

The **atypical antipsychotics** (**AAP**; also known as **second generation antipsychotics** (**SGAs**)) are a group of antipsychotic drugs (antipsychotic drugs in general are also known as major tranquilizers and neuroleptics, although the latter is usually reserved for the *typical antipsychotics*) used to treat psychiatric conditions. Some atypical antipsychotics have received regulatory approval (e.g. by the FDA of the US, the TGA of Australia, the MHRA of the UK) for schizophrenia, bipolar disorder, autism, and as an adjunct in major depressive disorder.

Both generations of medication tend to block receptors in the brain's dopamine pathways. Atypical are less likely – than the most widely used typical antipsychotic haloperidol – to cause extrapyramidal motor control disabilities in patients such as unsteady Parkinson's disease-type movements, body rigidity, and involuntary tremors. However, only a few of the atypical have been demonstrated to be superior to lesser-used, low-potency first-generation antipsychotics in this regard.

As experience with these agents has grown, several studies have questioned the utility of broadly characterizing antipsychotic drugs as "atypical/second generation" as opposed to "first generation," noting that each agent has its own efficacy and side-effect profile. It has been argued that a more nuanced view in which the needs of individual patients are matched to the properties of individual drugs is more appropriate. Although atypical antipsychotics are thought to be safer than typical antipsychotics, they still have severe side effects, including tardive dyskinesia (a serious movement disorder), neuroleptic malignant syndrome, and increased risk of stroke, sudden cardiac death, blood clots, and diabetes. Significant weight gain may also occur. Critics have argued that "the time has come to abandon the terms first-generation and second-generation antipsychotics, as they do not merit this distinction."

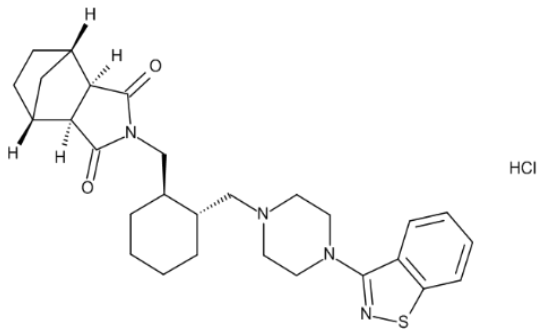

Figure 1: Chemical structure of Lurasidone HCl

MATERIALS, EQUIPMENTS AND METHODS

Table 1: List of Equipments

Equipment	Make/ Model
Electronic balance	Citizen 1
UV spectrophotometer	Japan Shimadzu UV 1601.
Ultrasonicator	FAST CLEAN Ultrasonic Cleaner
Precision Balance	Mettler Tolledo

Table 2: List of chemicals & reagents

Chemicals/ reagents	Grade	Manufactured by
Methanol	AR Grade	Merck
Water	HPLC Grade Water	In house.

Table 3: Working standard details

Working standard	Gifted by
Lurasidone HCl	Alkem.Pvt.Ltd Mumbai

DRUG IDENTIFICATION

Melting Point: Melting point determination of the obtained drug sample was done as it is of first indication purity of the sample. It was determining by thiel's tube method and it is reported in results**. (Table 4**.)

Table 4: Result for observed M.P.

Reported Melting point	Observed Melting point
178^{o} C	176 to 178^{o} C

UV-Visible spectrophotometer study: In order to ascertain the wave length of maximum absorbance (λ max) of the drug. Solution of the drug 10µg/ml in methanol was analysed using spectrophotometer within wave length region of 400-200nm using methanol as a blank, the absorption spectra shows peaks at 315nm.**(Figure 2 & table 6)**

Method Development

Selection of Solvent: A number of trials were made to find out the ideal solvent system for dissolving the drug. The solvents such as water, methanol, ethyl acetoacetate and acetonitrile were tried based on the solubility of the drug. Better absorption maximum was found to be 315 nm with methanol. So methanol was selected as optimized solvent in this spectrophotometric method.

Determination of maximum absorption wave length: In order to obtained the wavelength of maximum absorption (λ max) of the drug, 10µg/mL Lurasidone HCl aqueous solution was scanned using spectrophotometer within the wavelength region of 200-400 nm against methanol as blank.

The resulting absorption spectra showed characteristic absorption maxima at 315 nm. This wavelength of maximum absorption (315 nm) was selected and the absorption spectrum is represented in Figure 2.

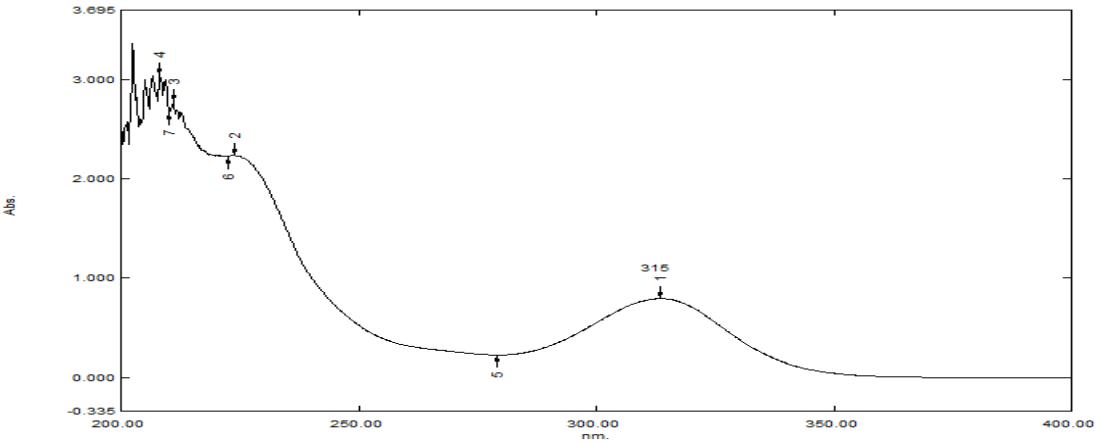

Figure 2: UV spectrum of Lurasidone HCl

Determination of Concentration Range: Appropriate aliquots were pipetted out from the primary stock solution in to a series of 10mL volumetric flask. The volume was made up to the mark with methanol to get solutions having the concentration range of 2-55µg/mL. Absorbances of the above solutions were measured at 315nm and a calibration curve of absorbance against concentration was plotted. The drug obeys Beer's Law in the concentration range of 2-55µg/mL.(fig. no. 3).

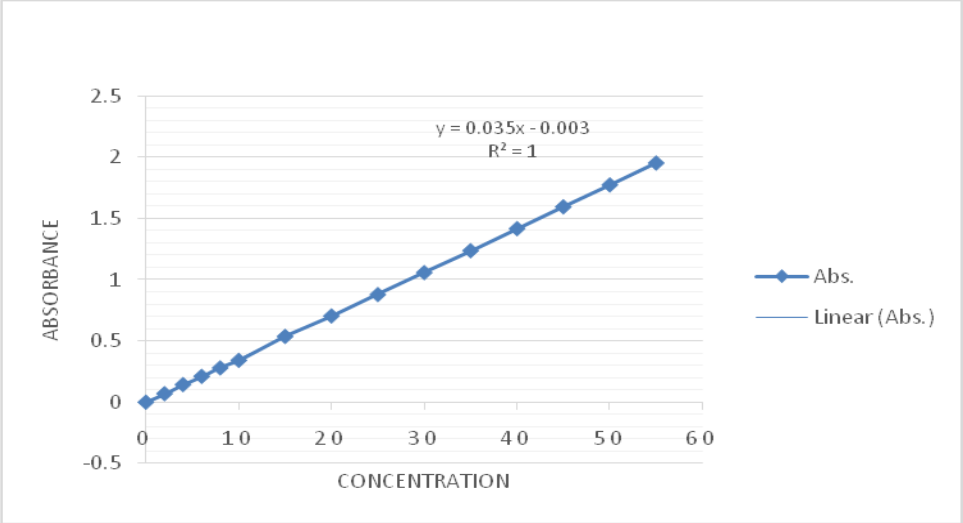

Figure 3: Calibration curve of Lurasidone HCl by UV method

Validation of developed analytical method:

Accuracy: The percent recovery of the triplicate solutions was determined and average of the percent recovery was calculated. (Table No.5)

Precision: The percent relative standard deviation (% RSD) was calculated which is within the acceptable criteria of not more than 2.0. The results for intra-day and inter-day precision are presented in (**Table 6 and Table 7).**

Linearity and Range: According to USP tablet powder equivalent to 20, 40, 60, 80 and 100% of label claim was takenand dissolved in solvent, diluted appropriately to obtain a concentration in the range of 20% - 100% of test concentration. The absorbances of the resulting solutions were recorded at 315 nm. **(Table no.8 & figure no.9).**

Table 5: Observation and results for % Recovery study

Spiked level	Amount of drug from formulation added (µg/ml)	Amount of standard solution added (µg/ml)	Amount recovered (µg/ml)	% Recovery	% R.S.D
80%	2	10	12.08	99.84	0.70
			12.07	99.00	
			12.08	98.30	
100%	2	12	14.05	99.66	0.57
			14.09	99.26	
			14.08	98.53	
120%	2	14	16.07	99.82	0.53
			16.08	99,29	
			16.09	98.76	

Table 6: Results and Statistical data for inter-day of Lurasidone HCl.

Concentration (µg/ml)	Absorbance		
	DAY 1	**DAY 2**	**DAY 3**
10	0.342	0.340	0.349
10	0.344	0.347	0.345
10	0.349	0.335	0.338
10	0.344	0.338	0.334
10	0.345	0.334	0.337
10	0.349	0.338	0.334
MEAN	**0.3455**	**0.3386**	**0.3395**
SD	**0.0028**	**0.0046**	**0.0061**
%RSD	**0.8104**	**1.3585**	**1.7967**

Table 7: Results and statistical data for intra-day of Lurasidone HCl

Concentration (µg/ml)	Absorbance			
	0 hour	**2 hour**	**4 hour**	**6 hour**
10	0.331	0.347	0.341	0.340
10	0.336	0.349	0.345	0.349
10	0.337	0.343	0.347	0.345
10	0.336	0.345	0.348	0.341
10	0.336	0.343	0.345	0.339
10	0.337	0.345	0.344	0.336
Mean	**0.3355**	**0.3453**	**0.345**	**0.3416**
SD	**0.0022**	**0.0023**	**0.0024**	**0.0046**
% RSD	**0.6557**	**0.6660**	**0.6956**	**1.3466**

Table 8 : Observation table of linearity and range

Sr. No	% Test Concentration	Absorbance
1	20	1.058
2	40	1.237
3	60	1.417
4	80	1.595
5	100	1.774

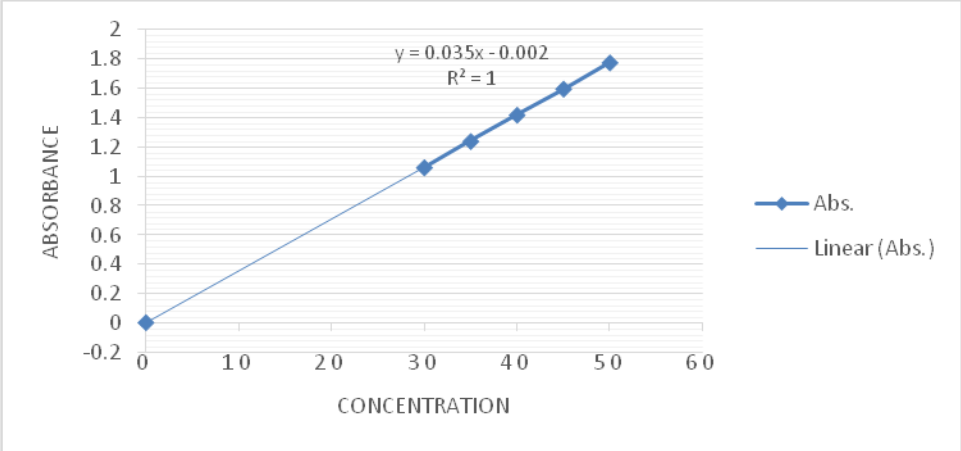

Figure 4: Graph for linearity and range

Table 9: Optical characteristics for the proposed method.

Parameter	Result
Quantitation λ	315nm
Beer's law limits (µg / mL)	2-55
Molar absorptivity (L. mole $^{-1}$ cm^{-1})	315.66
Regression equation (Y = a+ bc): Slope (b)	0.0355
Correlation coefficient (R^2)	1

Application of method to hydrolytic stress condition sample: Degradation study were carried out as per ICH guideline Q1A where drug was subjected to various stress condition like *hydrolysis* and the parameter were optimised hydrolytic stress condition were followed for producing stress degradant sample. **(Table 10).**

Evaluation of degradation kinetics for Lurasidone HCl under hydrolytic stress condition sample using UV- spectroscopic approach.

Degradation Kinetic study: It is defined as how drug changes with time i.e, study of rate change. Many drugs are not chemically stable and the principles of chemical kinetics are used to predict the time span for which a drug (pure or formulation) will maintain its therapeutic effectiveness or efficiency are a specified temperature.

Degradation kinetics aim to predict the intrinsic stability of a drug in order to anticipate problems that may arise during development, Among the various factors that influence drug stability, change in temperature is crucial parameter and hence for study, temperature parameter is varied while other factor were kept constant.

Table 10: Optimum stress conditions.

Sr.No	Stress Condition	Optimum stress condition	Time
1	Acidic Hydrolysis	1N HCL at RT (Acidic medium).	1hr
2	Basic Hydrolysis	1N NaOH at RT (Alkaline medium).	1hr
3	Neutral Solution	Neutral solution at room temperature	1hr

Table 11: Observation and Results for hydrolytic stress degradation sample

Stress Sampling	Abs.	Conc.	% assay	%Degradation
i) Acid 1N HCL for 1hr	0.54	5.35µg/mL	53.51%	46.49%
ii) Base 1N NaOH for 1hr	0.32	3.15µg/mL	31.52 %	68.48%
iii) Neutral (In H2O)	0.13	1.25µg/mL	12.5 %	87.5%

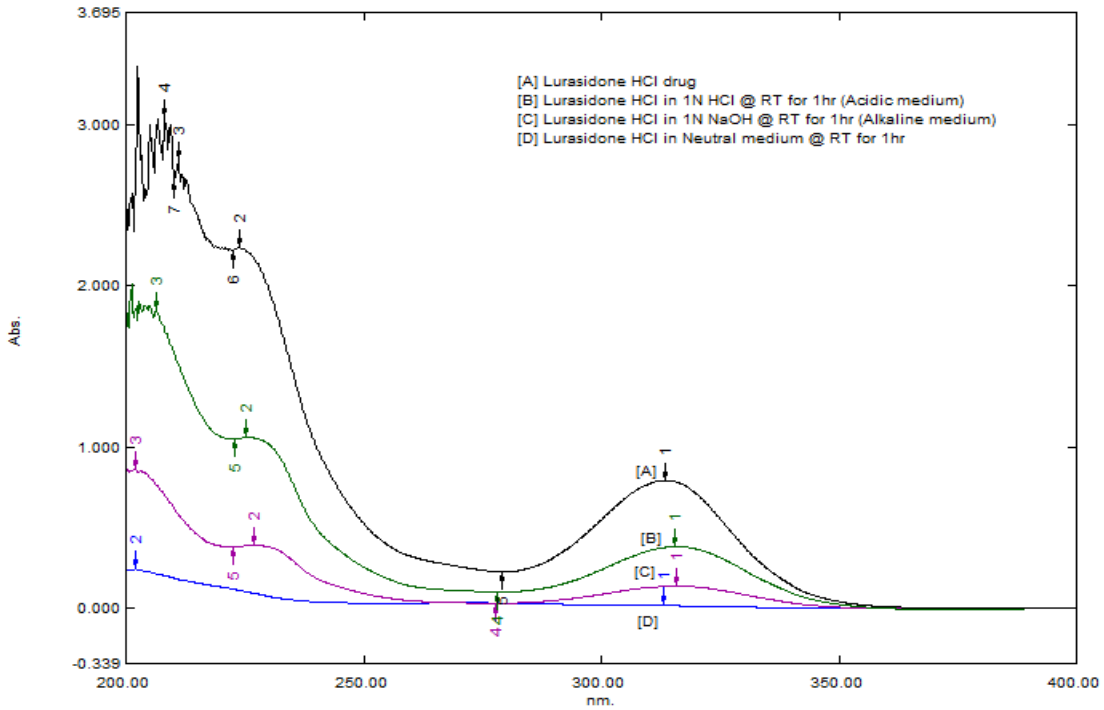

Figure 5: Overlain spectra of Lurasidone HCl over its all stress conditions

Kinetics of degradation in acidic medium

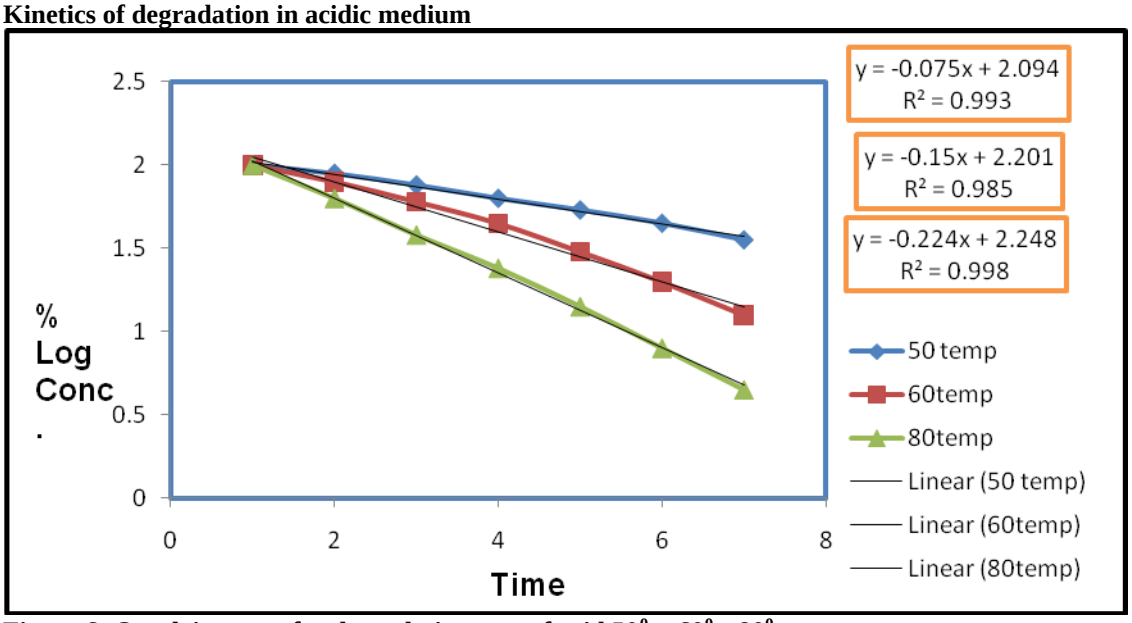

Figure 6: Overlain curve for degradation rate of acid 50^0 c, 60^0c, 80^0c

Table 12: Observation in Acid medium (1N HCl at 50^0c, 60^0c. 80^0c.)

Sr no.	Sampling time	Temperature					
		50^0c		60^0c		80^0c	
		Abs.	%estimation of drug	Abs.	%estimation of drug	Abs.	%estimation of drug
1	0hr	0.330	96	0.342	100	0.342	100
2	Half hr	0.304	89	0.123	36	0.086	25
3	1hr	0.215	63	0.064	19	0.062	18
4	3hr	0.096	28	0.035	10	0.035	10

Kinetics of degradation in basic medium

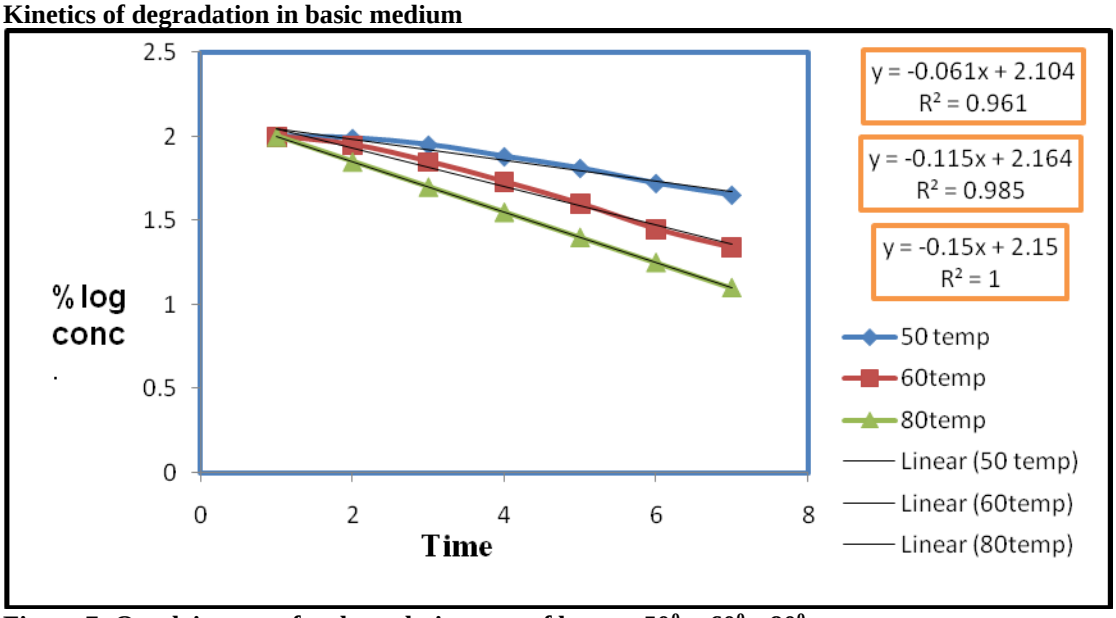

Figure 7: Overlain curve for degradation rate of base at 50^0 c, 60^{0}c, 80^{0}c

Table 13: Observation in Alkaline medium (1N NaOH at 50^{0}c, 60^{0}c, 80^{0}c.)

Sr no.	Sampling time	Temperature					
		50^{0}c		60^{0}c		80^{0}c	
		Abs.	%estimation of drug	Abs.	%estimation of drug	Abs.	%estimation of drug
1	0hr	0.330	96	0.325	95	0.318	93
2	Half hr	0.291	85	0.253	74	0.233	68
3	1hr	0.198	58	0.188	55	0.171	50
4	3hr	0.106	31	0.086	25	0.150	43.99

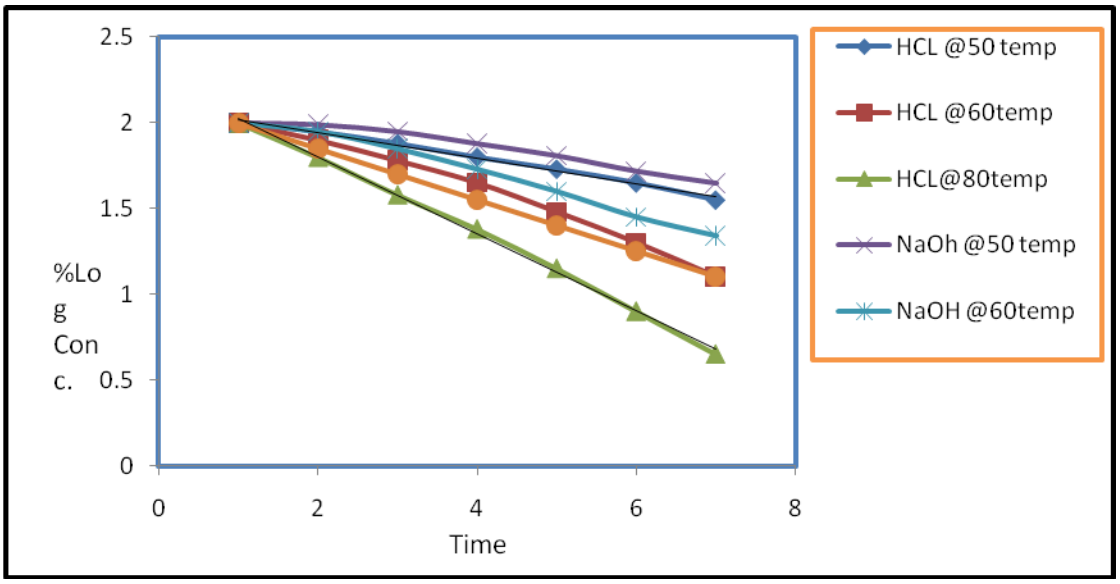

Figure 8 First order plots for the degradation of Lurasidone HCl under acidic and alkaline conditions.

Table 14: Summary of Lurasidone HCl Degradation kinetics.

Stress condition	*K* (1/hr)[a]	$t_{1/2\ (hr)}$[b]	t_{90}(hr)[c]	% degradation
1N HCL at 50^0c	0.366	0.1925	0.0291	37
1N HCL at 60^0c	0.693	1.1063	0.1676	81
1N HCL at 80^0c	0.60	1.255	0.175	82
1 N NaOH at 50^0c	2.87	0.2475	0.0375	42
1 N NaOH at 60^0c	0.3316	2.089	0.3166	45
1 N NaOH at 80^0c	0.22	3.15	0.4772	50

RESULT AND DISCUSSION

Simple, accurate and sensitive method has been developed for estimation of Lurasidone HCl. When scanned over the range of 400-200nm, 315nm was selected as working analytical wavelength for quantitation of active, as at other two wavelengths solvent interference may occur. The drug followed beer's law at 315nm in the conc. range of 2-55µg/mL, with r^2 =1.

The proposed method for quantitative analysis of Lurasidone HCl drug was first applied to laboratory sample. The percent estimation was found to be 98.1% with RSD= 1.75. The results were found to be reproducible for marketed preparation.

Hydrolytic degradation of Lurasidone HCl was carried out by using 1N NaOH, 1N HCL & water to mimic acidic, alkaline & neutral environment pH for hydrolytic degradation mechanism, as per ICH Q1A guideline. Lurasidone HCl on exposure to varying pH, shows considerable changes in its absorbance, showing hypochromic effect. This hypochromic effect can be correlated to change in auxochromic or chromophoric group of Lurasidone HCl thus leading to degradation of structure. Hence it can be concluded that Lurasidone HCl is unstable under varying pH condition on long exposure.

CONCLUSION

The proposed kinetic method of UV-Spectroscopy was proved to be simple, accurate, precise, specific and selective for quantitative analysis of Lurasidone HCl in the presence of its acidic and alkaline degradants and the degradation of Lurasidone HCl was found to follow a first-order reaction. For the degradation kinetics in acid and base media, it could be observed that, in the acid medium, the best obtained for first order kinetics, whereas for the basic medium, the best fit corresponded to also firstorder kinetics. The highest percent degradation was found to be 82 % in acidic medium at 80^0c and 50% in alkaline medium at 80^0c.

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