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Stability Indicating RP-HPLC Method Development & Validation for Lumateperone Tosylate Drug in Bulk & It's Capsule Dosage Form

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Abstract
A stability-indicating reverse phase high performance liquid chromatography method was developed and validated for Lumateperone tosylate. The wavelength selected for quantitation was 227 nm. The method has been validated for linearity, accuracy, precision, robustness, limit of detection and limit of quantitation. Linearity was observed in the concentration range of 2-10 µg/ml. For RP-HPLC, the separation was achieved by column Phenomenex C18 (250 mm X 4.6mm ID, particle size 5 µm). At a flow rate 1.00 ml/min using the mobile phase Methanol:0.1% OPA in water (45:55%V/V) at a wavelength 227nm with a chromatographic run time 10 min, The retention time Lumateperone tosylate were found to be 9.28 min. respectively. During force degradation, drug product was exposed to hydrolysis (acid and base hydrolysis), H_2O_2, thermal degradation and photo degradation. The % degradation was found to be 10 to 20% for dug in the given condition. The method specifically estimates the drug in presence of all the degradants generated during forced degradation study. The developed methods were simple, specific and economic which can be used for estimation of Lumateperone tosylate in bulk & its pharmaceutical dosage form.

Keywords: *Lumateperone tosylate, RP-HPLC method, forced degradation and validation*

INTRODUCTION

Lumateperone (ITI-007, proposed tradename: Caplyta) is a new molecular entity atypical antipsychotic that has been developed for the treatment of schizophrenia. Lumateperone is also being developed for the treatment of sleep disorders, depression and other neuropsychiatric and neurological disorders. Lumateperone appears to function to as a serotonin 5HT2A and postsynaptic Dopamine D2 receptor antagonist. In addition, lumateperone displays relatively high binding affinity for the serotonin transporter (SERT).

Schizophrenia is a mental disorder characterized by distruptions in thought processes, perceptions, emotional responsiveness and social interactions. Although the course of Schizophrenia is typically persistent and can be both severe and disabling.

Lumateperone is a newly approved 2nd generation antipsychotic currently indicated for the treatment of schizophrenia. It has a unique receptor binding profile and differs from other antipsychotics in that it modulates glutamate, serotonin and dopamine, which are all neurotransmitters that contribute to the pathophysiology of schizophrenia.

Lumateperone, sold under the brand name Caplyta, is an atypical antipsychotic medication of the butyrophenone class. It has approved for the treatment of schizophrenia as well as bipolar depression, as either monotherapy or adjunctive therapy (with lithium or Valproate). Lumateperone was approved for medical use in the United States in December 2019 with an initial indication for Schizophrenia.

Lumateperone, also known as ITI-007, is an atypical antipsychotic that has proven to be effective in the treatment of schizophrenia. Lumateperone's receptor binding profile is unique, allowing it to target schizophrenia related symptoms while minimizing adverse effects. In contrast to other second generation antipsychotics such as lurasidone and bexpiprazole, lumateperone behaves as a partial agonist and as an antagonist at pre and post synaptic dopamine (D2) receptors respectively.

Patients with moderate or severe hepatic impairment (Child-Pugh class B or C) tend to have higher plasma concentrations of lumateperone than those with normal hepatic function. For this reason, patients with moderate or severe hepatic impairment should receive half the recommended daily dosage.

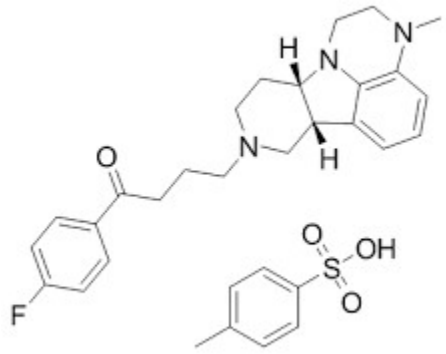
There is much to learn about the pathophysiology of schizophrenia; however, dopamine abnormalities, specifically in the prefrontal and mesolimbic brain regions, are consistent in people with schizophrenia. In addition to dopamine, other neurotransmitters such as serotonin, glutamate, GABA and acetylcholine are thought to play a role.

Lumateperone is unique among second generation antipsychotics based on its target profile and dopamine D2 receptor occupancy. Unlike other antipsychotics, lumateperone has partial agonist activity at presynaptic dopamine (D2) receptors, resulting in reduced presynaptic release of dopamine, and antagonistic activity at postsynaptic dopamine (D2) receptors. These characteristics allow lumateperone to efficiently reduce dopamine signalling.

Lumateperone also targets dopamine (D1) receptors, and a useful secondary result of D1 activation is increased glutamatergic N-methyl-D-aspartate (NMDA) GluN2B receptor phosphorylation. This is significant since NMDA mediated glutamate signaling appears to be impaired in patients who have schizophrenia.

Finally, lumateperone is capable of modulating serotonin by inhibiting serotonin transporters (SERT), and by behaving as a 5-HT2A receptor antagonist.

General drug profile: Lumateperone tosylate



Category	atypical antipsychotic
Chemical Name	1-(4-fluorophenyl)-4-[(10R,15S)-4-methyl-1,4,12-triazatetracyclo[7.6.1.0^{5,16}.0^{10,15}]hexadeca-5,7,9(16)-trien-12-yl]butan-1-one; 4-methylbenzene-1-sulfonic acid
Molecular Formula	$C_{31}H_{36}FN_3O_4S$
Molecular Weight	565.7 g/mole
Other Name	ITI-007, ITI-722
Odour	Odourless

Description such	White to off white powder. Solubility soluble in organic solvents such as ethanol, DMSO and dimethyl formamide (DMF), it is sparingly soluble in aqueous buffers
pKa	8.47 (Strongest Basic)
Melting point	182-183°C
Protein binding	Lumateperone is approximately 97.4% plasma protein bound
Uses	Lumateperone is a newly FDA-approved, first in class drug used for the treatment of schizophrenia. It is available in 42mg capsule for a once a daily.

MATERIALS AND METHODS: Lumateperone tosylate was a gift sample from Swapnroop research Pvt. Ltd. Lumateperone tosylate capsule used were 42mg from Lupin pharmaceuticals. HPLC grade Methanol, Water ,OPA used.

INSTRUMENTS: Waters corp HPLC, column Phenomenex C18 , UV – visible detector, manual inject port, breeze software, precision balance, digital pH meter, Digital ultra sonicator.

Preparation of Mobile Phase:

Methanol: 0.1% Ortho Phosphoric Acid (45:55v/v)

Preparation of Standard Stock Solution:
25mg Lumateperone tosylae was accurately weighed and transferred into 25 ml volumetric flask make up the volume up to the mark with the diluent to obtained concentration 1000µg/ml. through this solution prepare further dilution.

Test solution preparation:
Take twenty capsule, each containing 42 mg of Lumateperone tosylate . The capsule were extinguished to small powder and quantity of powder parallel to 25 mg of Lumateperone tosylate were measured and added in 25 ml volumetric flask make up with methanol and shaked to make transparent solution. The solution was flow by using membrane filter and degassed.

VALIDATION PARAMETERS

A) Linearity:
Unknown conc. reports that are parallel to the concentration of analyte in samples within a given limit known as linearity.

Determination
Take 6 different concentration and each take 3 replicate. Prepare graph conc. Vs. Area andcalculate correlation coefficient and %RSD

B) Accuracy (%Recovery):
The belonging of unknown conc. solutions reports obtained by that method to the observed value is known as accuracy. The % recovery checked by add known conc. of STD solution against test solution .

C) Precision:
The number of test solutions of a same sample giving same results known as precision. Through this calculated SD and RSD

Method for precision:

Determination:
Take either 3 different conc. and each take 3 replicate or take 6 replication of same concentration and calculate precision

D) Robustness:
It is the quantitate of capacity of the method to unchanged by little but intentional difference in method

framework and provides an signal of its constant under normal usage.

Determination:
Quantitated by changing different variable which effect on method performance in within limit. The unknown conc. solution and known conc. solution was injected under variable chromatographic state as shown below.

E) Limit of Detection (LOD):
The lower conc.of the analyte in the sample that the method can found but not necessarily measured under the given experimental state simply shows that the sample is below or above certain range. Limit test prescribed as percentage or as parts per million. The limit of detection will not only depend on the procedure of analysis but also on type of instrument.

Limit of Quantitation (LOQ):
The lowest conc. of test sample can be measured under the given experimental conditions. The S/N ratio should not less than 10 and RSD ≤ 2%.

RESULT AND DISCUSSION:

UV spectra of Lumateperone Tosylate (20 PPM):

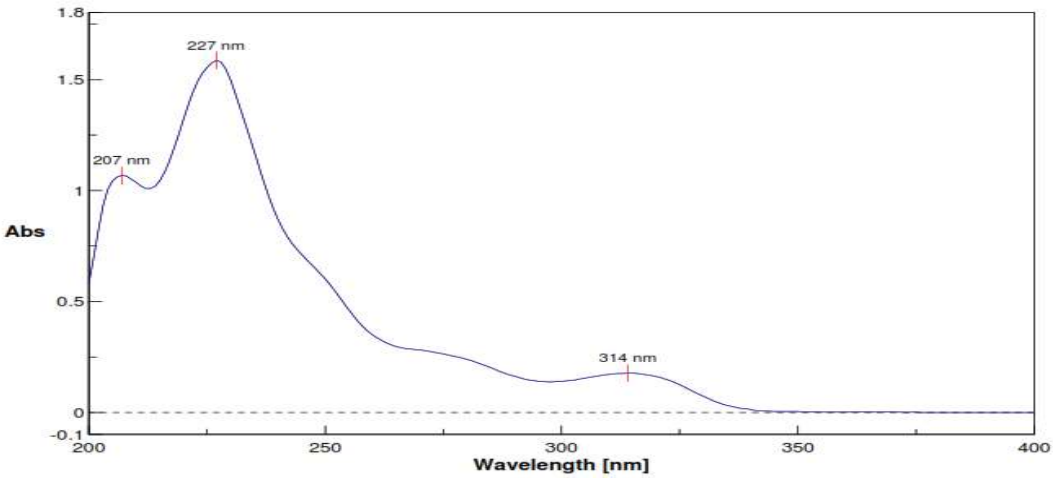
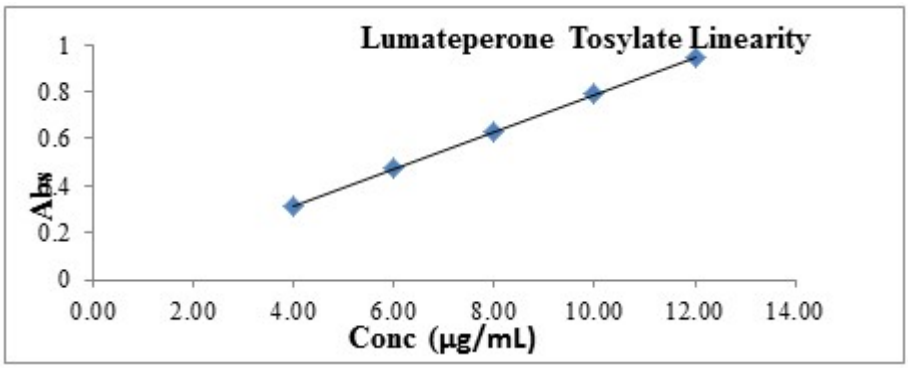


Fig 1: UV spectra of Lumateperone Tosylate

Observation: The standard solution was scanned from 400 nm to 200 nm. Wavelength of maximum absorption was determined for drug. Lumateperone Tosylate showed absorbance at 314, 227 and 207 nm. 227 nm considered as an analytical wavelength for further determination.

Calibration curve:



Graph 1: Calibration curve of Lumateperone Tosylate

Correlation coefficient (R^2): 0.9999

Slope: 0.07886

METHOD DEVELOPMENT BY RP – HPLC

Table no.1 Chromatographic Conditions

Mode	:	Isocratic mode
Standard solution	:	Lumateperone Tosylate 100 PPM
Detector	:	U.V. Detector
Wavelength	:	227 nm
Column Make	:	Phenomenex
Column Chemistry	:	C18
Column Dimension	:	250 mm X 4.6 mm i.d., 5µm
Column Oven temperature	:	40º C
Injection Volume	:	20µl
Mobile phase	:	**Methanol: 0.1% OPA in water (45:55 % v/v)**
Flow Rate	:	1.0 ml/min

Chromatogram:

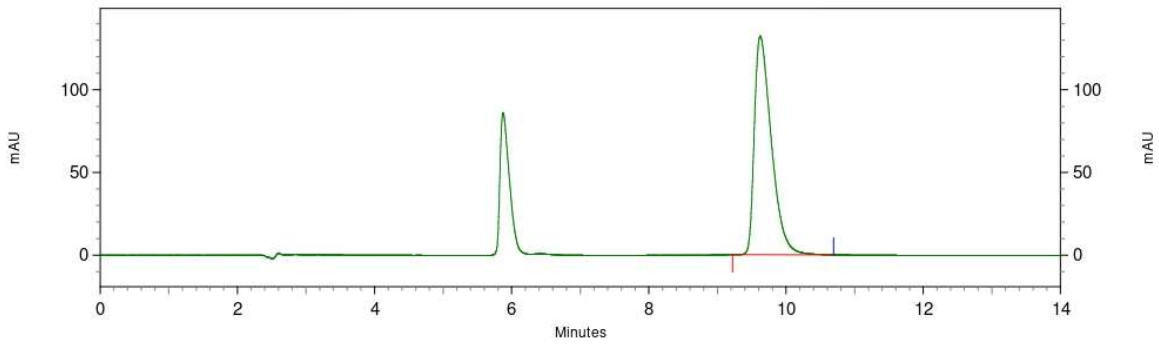


Fig 2: Typical chromatogram of Trial 4

Observation: Lumateperone Tosylate eluted at 9.28 minutes with acceptable chromatography. R.T. of Lumateperone is suitable for force degradation study.

Conclusion: Method can be accepted and use to apply for further FD study.

In above chromatogram we got two peaks. One of which may be of tosylate. In order to confirm these peaks, sample analyzed on mass analyzer to determine the name of peak.

RESULTS:

1) **Mass spectra of first peak eluted at 4.15 minutes:**

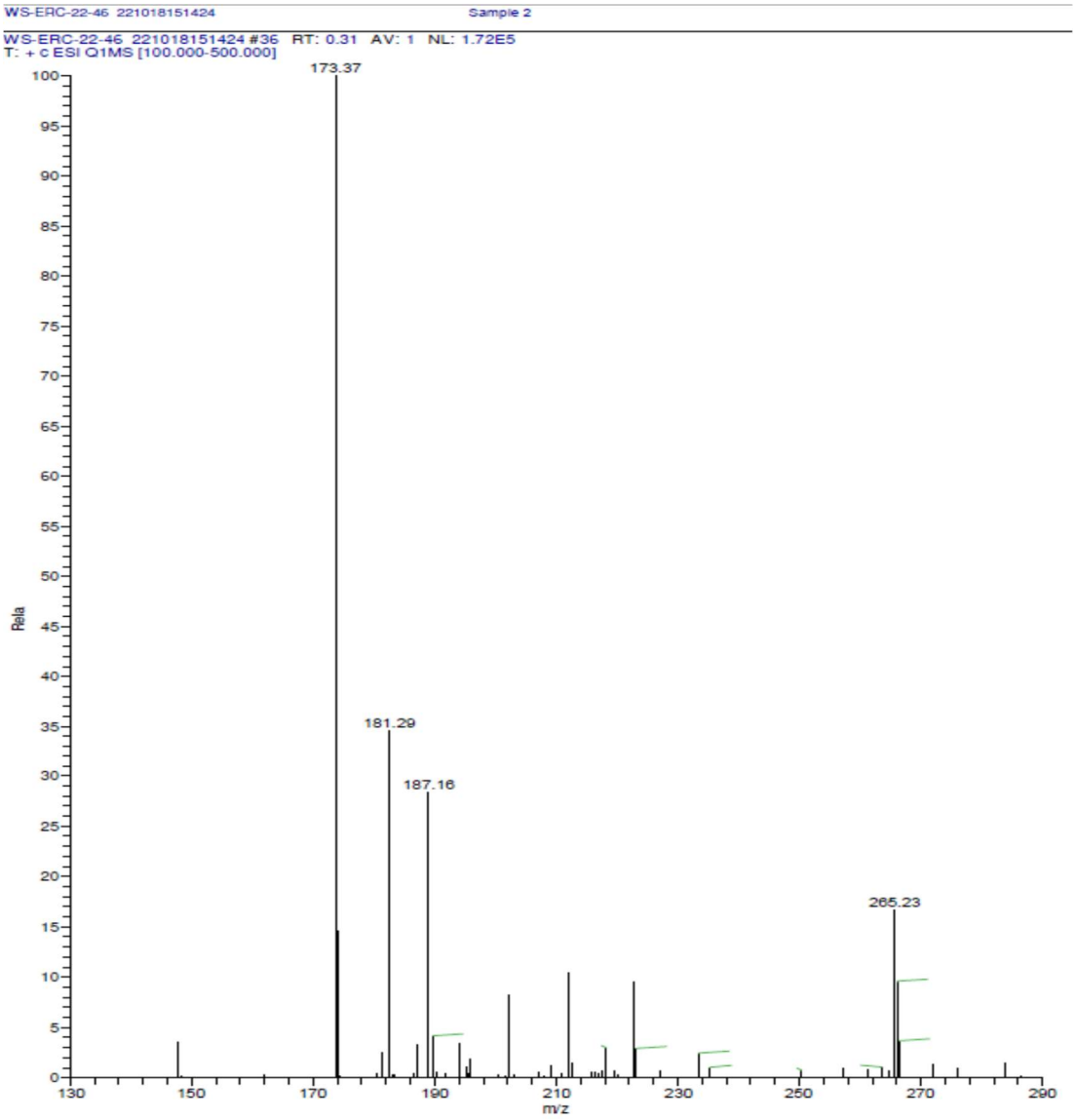


Fig 3: Mass spectra of first peak

1) **Mass spectra of Second peak eluted at 8.85 minutes:**

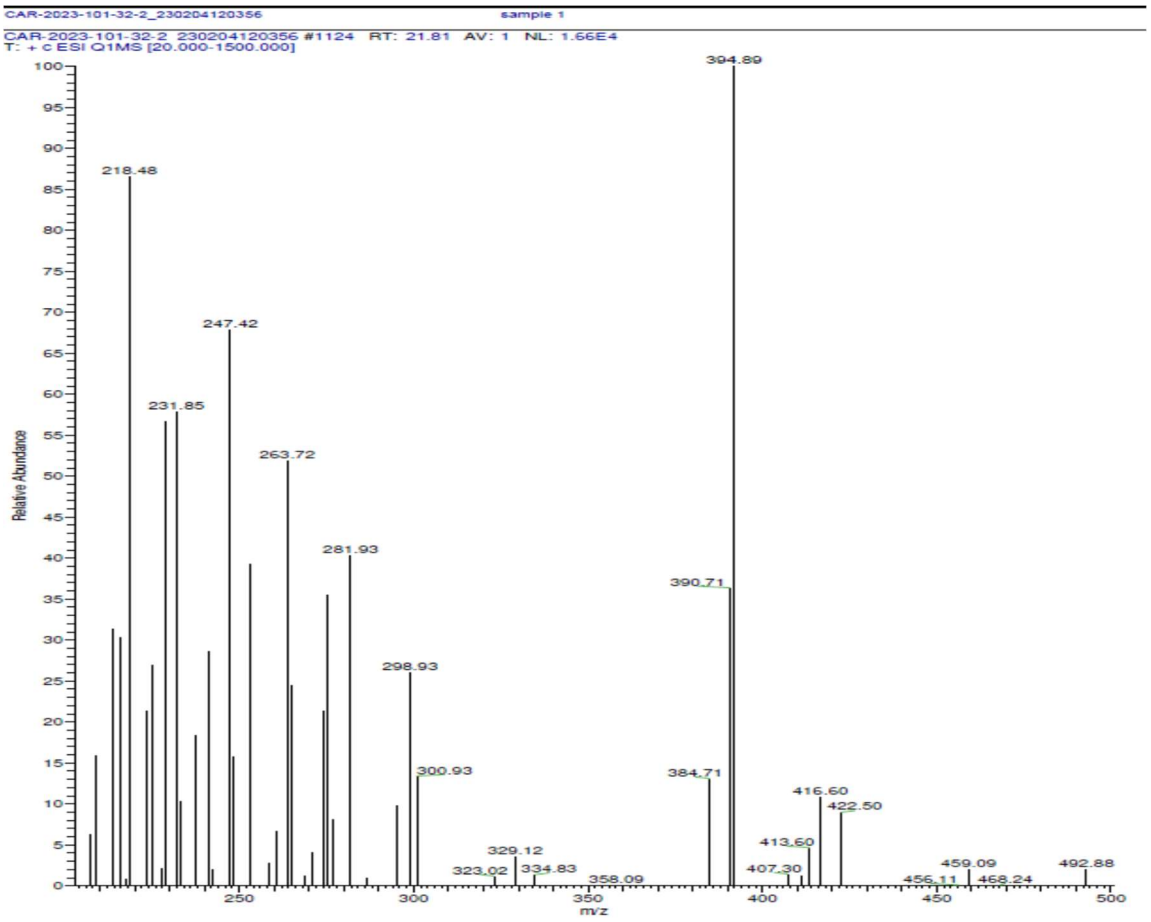


Fig 4: Mass spectra of second peak

OBSERVATION:

Mass spectra of first peak: m/z is 173.37. Tosylate molecular weight is 172.20 g/mol . **Mass spectra of Second peak**: m/z is 394.89. Lumateperone molecular weight is 393.51 g/mol . Mass spectra observed on basis of principle of M+1 rule on mass.

CONCLUSION: First peaks is of tosylate and second peak is of Lumateperone.

Validation:

System Suitability test: (100PPM Std. solution)

Observation Summary:

Sr No.	Standard solution	Area	Asymmetry	Theoretical plates
1	Standard-1	40635284	1.72	7186
2	Standard-2	40638951	1.72	7149
3	Standard-3	40629765	1.72	7162
4	Standard-4	40627583	1.71	7203
5	Standard-5	40610586	1.72	7139
Mean		**40628434**	**1.72**	**7168**
STD Dev		**40628434**		
% RSD		**40628434**		

Acceptance Criteria:

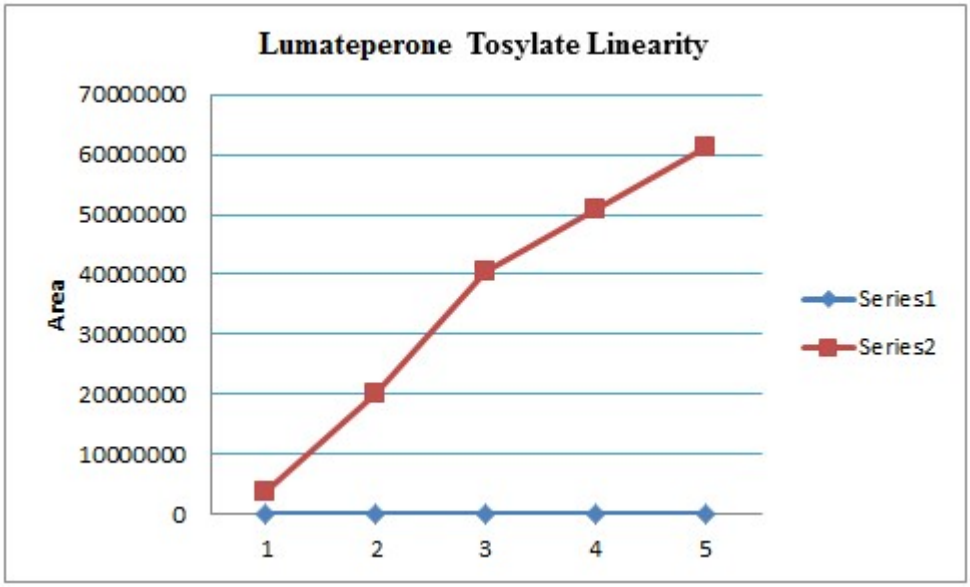
1. RSD should NMT 2.0 % for six duplicate injections of known conc. solution
2. USP Tailing Factor NMT 2.0.
3. The Plate Count more than 2000.

Conclusion: System suitability pass the test.

A) Linearity:

Table no.2 - Dilution table for linearity of Lumateperone Tosylate

Level	Conc (µg/mL)	Area	Mean	STD DEV	% RSD
10%	10	3767049	3767153	1318.599	0.035
		3768521			
		3765890			
50%	50	19997337	19999008	43337.178	0.217
		19956531			
		20043157			
100%	100	40627767	40630455	3878.099	0.010
		40628698			
		40634901			
125%	125	50978522	50958864	18602.295	0.037
		50956534			
		50941537			
150%	150	61343762	61348885	5273.443	0.009



Graph 2: Linearity curve Lumateperone tosylate

Results:

Correlation coefficient: 0.9999

Intercept: -455968.8459

Slope: 411457.9523

Acceptance criteria:

Correlation coefficient ≥ 0.98

Conclusion: Regression coefficient was found well within acceptance limit for proposed range.

Accuracy (%Recovery):

Table no.3: Observation table of Accuracy

Level (50 %)	Area	Recovered conc	Added conc	% Recovery	Mean Recovery	% RSD	Overall Recovery	% RSD for over all recvoery
50	20522469	50.513	51.000	99.05	**99.81**	**0.846**	**99.43**	**0.627**
	20665497	50.865	50.500	100.72				
	20450064	50.334	50.500	99.67				
100	40625604	99.993	100.000	99.99	**99.49**	**0.513**		
	40609977	99.955	101.000	98.97				
	40635626	100.018	100.500	99.52				
150	60553284	149.042	150.500	99.03	**98.97**	**0.213**		
	60578536	149.104	151.000	98.74				
	60625132	149.218	150.500	99.15				

Acceptance criteria: % Recovery- 98.0 % to 102.0 %

Conclusion: % Recovery was found well within acceptance range at all three levels.

C) Precision:

Table no.4: Observation table of Precision

Sample	Area	% Assay
Sample 1	40716482	98.25
Sample 2	40751846	99.80
Sample 3	40652164	98.58
Sample 4	40702569	98.70
Sample 5	40785149	99.89
Sample 6	40726517	99.25
Mean		**99.08**
STD DEV		**0.676267**
% RSD		**0.683**

Acceptance criteria: % Assay (Individual & mean value): 98.0 to 102.0%

% RSD for 6 samples: NMT 2.0 %

Precision pass the criteria, no variation found by preparing six different samples. Results are good reproducible.

Intermediate precision:

Table no.5: Observation Summary and Results

Sample	Area	% Assay
Sample 1	40759846	99.82
Sample 2	40796584	98.93
Sample 3	40814527	100.46
Sample 4	40792016	99.41

Sample 5	40658744	99.58
Sample 6	40559745	98.84
Mean		**99.51**
STD DEV		**0.5998**
% RSD		**0.603**
Precision plus Intermediate precision	**Mean**	**99.293**
	STD DEV	**0.6492**
	% RSD	**0.654**

Acceptance Criteria:

% Assay (Individual & mean value): 98 to 102%

% RSD for 6 samples: NMT 2%

% RSD for 12 samples: (Precision and Intermediate precision): NMT 2%

D) Robustness:

Determination:
Quantitated by changing different variable which affect on method performance in within limit.

The unknown conc. solution and known conc. solution was injected under variable chromatographic state as shown below.

- Changes in flow rate. (±10%)
- Change in wavelength. (±3nm)
- Change in column oven temperature (± 2°C)

Change in Wavelength ±3nm:

Table no.6: Observation Table of Change in Wavelength

Sr.No.	System Suitability parameter	Observations			Limits
		As such (227nm)	360nm	254nm	
1	Peak area response	3767153	40927574	37230216	
2	Theoretical plates	7148	7241	7265	NLT 2000
3	Asymmetry	1.72	1.73	1.71	NMT 2
4	Retention time (min)	9.62	10.07	10.01	

Changes in flow rate. (±10%)

Table no.7: Observation Table for Change in flow rate

Sr.No.	System Suitability parameter	Observations			Limits
		As such	+10%	-10%	
1	Peak area response	3767153	37067580	45505718	
2	Theoretical plates	7148	7032	7586	NLT 2000
3	Asymmetry	1.72	1.68	1.76	NMT 2
4	Retention time (min)	9.62	9.05	10.98	

Change in column oven temperature +2°C:

Table no.8: Observation Table for Change in Column Oven temperature

Sr. No.	System Suitability parameter	Observations			Limits
		As such	+2°C	-2°C	
1	Peak area response	3767153	40758465	40248579	
2	Theoretical plates	7148	7364	40248579	NLT 2000
3	Asymmetry	1.72	1.69	1.75	NMT 2
4	Retention time (min)	9.62	10.19	10.23	

E) DETECTION:

(1) Limit of Detection & Quantitation:

Table no 9: Result and statistical data of LOD & LOQ of Lumateperone tosylate

Lumateperone tosylate					
Sr.no	**Concentration(µg/ml)**	**RT (min)**	**Area**	**Plate Count**	**Tailing**
1	10	10.96	3767153	7216	1.34
2	50	10.65	19999008	7214	1.59
3	100	10.21	40630455	7219	1.71
4	125	10.39	50958864	6822	1.76
5	150	10.24	61348885	6249	1.78
Correlation Coefficient			0.99999		
Slope			411457.95		
SD			96096.96		
LOD			0.771ppm		
LOQ			2.336ppm		

Forced Degradation Study:
Forced degradation also known as stress testing is a process that involves degradation of drug product and drug substance by applying various stress condition which leads to generation of degradation of drug and helps us to determine various possible degradation pathways & determine the stability of drug molecule.

Drug sample was exposed to following stress conditions:

- Acidic hydrolysis
- Basic hydrolysis
- Oxidative degradation
- Thermal degradation

Acidic hydrolysis: Weigh 20.4mg of Lumateperone tosylate API & transferred to 20ml volumetric flask. Added 15ml of methanol and sonicated to dissolve the API completely. Added 2mL of 5N, 1N, 0.1N HCl. Kept the sample on bench for 24hrs. After 24hrs, reaction was neutralized by adding 2mL of 5N NaOH solution. Volume made up to the mark with methanol. (About 1000ppm of Stock).

Further diluted 1mL of stock solution to 10mL with mobile phase (About 100ppm of Lumateperone tosylate).

Basic degradation: Weigh 20.2mg of Lumateperone tosylate API & transferred to 20ml volumetric flask. Added 15ml of methanol and sonicated to dissolve the API completely. Added 2mL of 5N, 1N, 0.1N NaOH. Kept the sample on bench for 24hrs. After 24hrs, reaction was neutralized by adding 2mL of 5N HCl solution. Volume made up to the mark with methanol. (About 1000ppm of Stock).

Further diluted 1mL of stock solution to 10mL with mobile phase (About 100ppm of Lumateperone tosylate).

Oxidative degradation: Weigh 20.4mg of Lumateperone tosylate API & transferred to 20ml volumetric

flask. Added 15ml of methanol and sonicated to dissolve the API completely. Added 2mL of 30% hydrogen peroxide. Kept the sample on bench for 24, 6 hours, volume made up the mark with methanol. (About 1000 ppm of stock).

Further diluted 1mL of stock solution to 10mL with mobile phase (About 100ppm of Lumateperone tosylate).

Thermal degradation: Placed sufficient amount of API in petri dish and covered with aluminium foil and made holes on aluminium foil with pointed object. Kept in hot air oven at 60°C for 72 hours sample was taken out and kept in desiccator. to reach at R.T. Subjected API prepared as per sample preparation method.

Weigh 20.7mg of Lumateperone tosylate thermal treated API & transferred to 20ml volumetric flask. Added 15ml of methanol and sonicated to dissolve the API completely. Volume made up to the mark with methanol (About 1000 ppm of stock).

Further diluted 1mL of stock solution to 10mL with mobile phase (About 100 ppm of Lumateperone tosylate).

Photolytic Degradation: Placed sufficient amount of API in petri dish and covered with aluminium foil and made holes on aluminium foil with pointed object. Kept in Sun light for 7 days. After 7 days sample was taken out and kept on bench top to reach at R.T. Subjected API prepared as per sample preparation method.

Weigh 20.3mg of Lumateperone tosylate thermal treated API & transferred to 20ml volumetric flask. Added 15ml of methanol and sonicated to dissolve the API completely. Volume made up to the mark with methanol (About 1000 ppm of stock).

Further diluted 1mL of stock solution to 10mL with mobile phase (About 100 ppm of Lumateperone tosylate).

Preparation of solutions used for stress testing:

1. Hydrochloric acid: 0.1, 0.5, 1N solutions of HCl were prepared according IP 2007 by diluting 8.5×0.1, 0.5, 1ml of hydrochloric acid to 100 ml with water.

2. Sodium Hydroxide: 0.1 N solution of NaOH was prepared according to IP 2007, by dissolving 0.4 g of sodium hydroxide in sufficient water to produce 100 ml.

Acceptance criteria:

1. Degradation should not be more than 10%

2. Degradation product should be resolved from drugs peak.

Table no.10: Forced Degradation Summary

Sample Name	Treatment	Exposure condition	% Assay	% Degradation
API	Sample as such	NA	100.00	NA
	Thermal	60°C for 72 Hours	100.82	Nil
	Photolytic	Sunlight for 7 days	100.21	Nil
	Acid	2 mL of 5 N HCl for 24 Hours at R.T.	99.95	Nil
		2 mL of 5 N HCl for 48 Hours at R.T.	99.2	Nil
		2 mL of 5 N HCl heated at 80°C for 24 Hours	100.06	Nil
		2 mL of 5 N NaOH for 24 Hour at R.T.	0	100
		2 mL of 1 N NaOH for 30 minutes at R.T.	30.12	69.88
		1 mL of 0.1 N NaOH for 30 minutes at R.T.	61.66	38.34
		0.5 mL of 0.1 N NaOH for 10 minutes at R.T.	84.68	15.32
	Peroxide	2 mL of 30% H2O2 for 24 Hour at R.T.	59.42	40.58
		2 mL of 30% H2O2 for 6 Hour at R.T.	91.83	8.17

Chromatogram of Forced degradation Studies:

Sample as such:

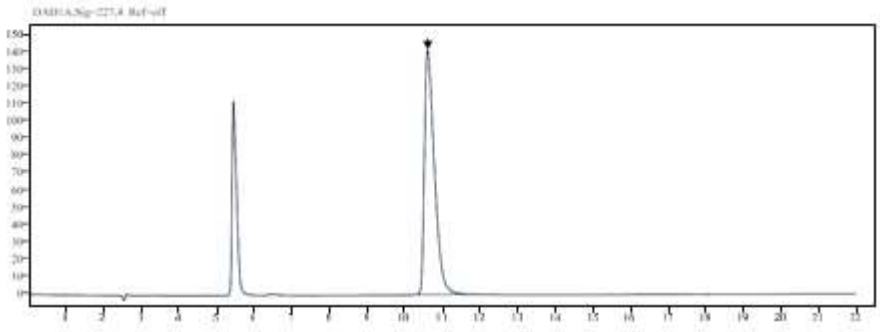


Fig. no. 3: Chromatogram of Sample as such

Condition	Amount of drug	Amount of degradation	R.T.	Area
Sample as such	100	NA	10.62	2620
			Total= 2620	

2. Thermal Degradation:

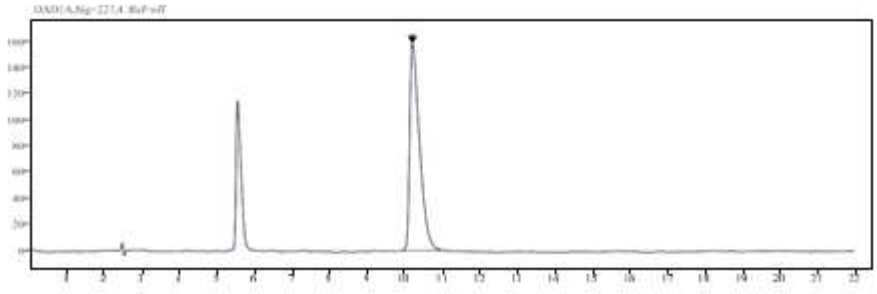


Fig.no.4: Chromatogram of Thermal Degradation

Condition	Amount of drug	Amount of degradation	R.T.	Area
60°C for 72 Hours	100.82	Nil	10.22	2734
			Total= 2734	

3. Photolytic Degradation:

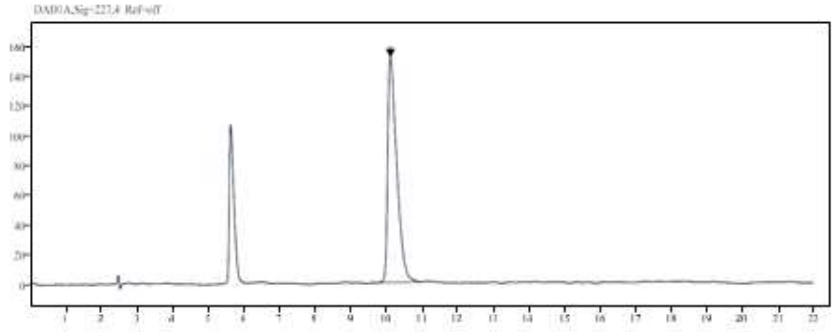


Fig no. 5: Photolytic degradation

Condition	Amount of drug	Amount of degradation	R.T.	Area
Sunlight for 7 days	100.12	Nil	10.13	2665

			Total= 2665

Acid Trial no. 1:

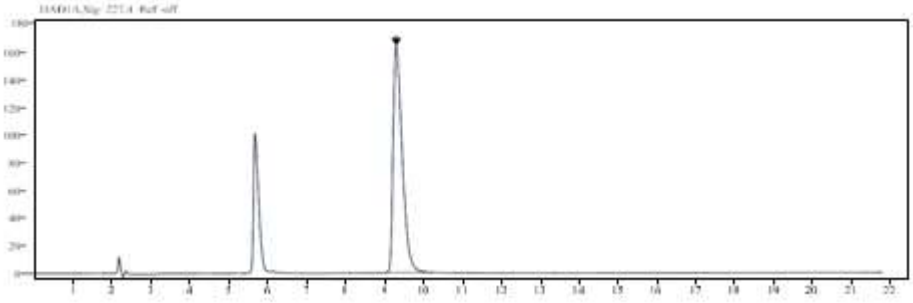


Fig. no. 6: Chromatogram of Acid trial 1 Degradation

Condition	Amount of drug	Amount of degradation	R.T.	Area
2 mL of 5 N HCl for 24 Hours at R.T.	99.95	Nil	9.51	2671
			Total= 2671	

12. Acid Trial 2:

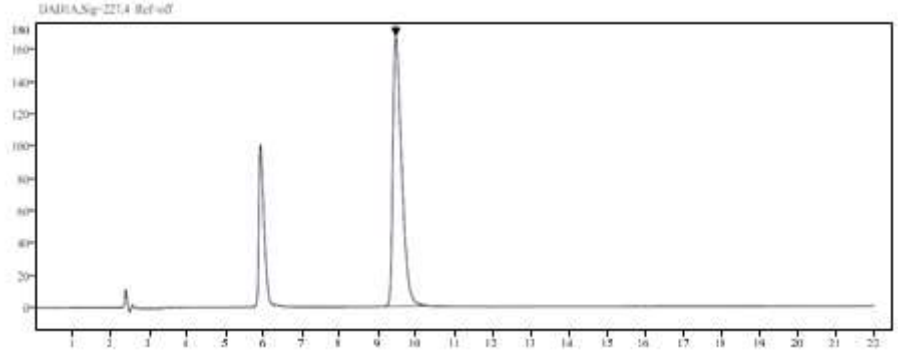


Fig. no.7: Chromatogram of Acid trial 2 degradation

Condition	Amount of drug	Amount of degradation	R.T.	Area
2 mL of 5 N HCl for 48 Hours at R.T.	99.2	Nil	9.47	2677
			Total = 2677	

6. Acid Trial 3:

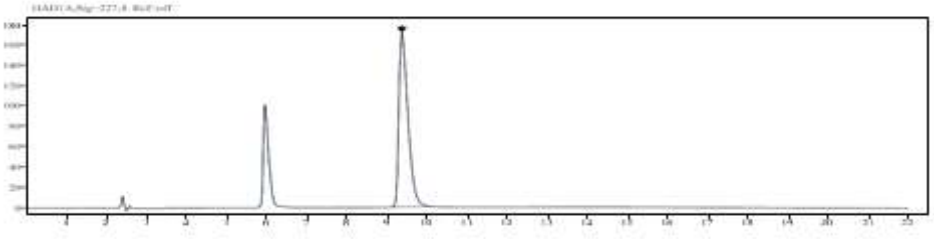


Fig. no. 8: Chromatogram of Acid Trial 3 Degradation

Condition	Amount of drug	Amount of degradation	R.T.	Area
2 mL of 5 N HCl heated	100.06	Nil	9.37	2661

at 80°C for 24 Hours				
			Total = 2661	

7. Base Trial no. 1:

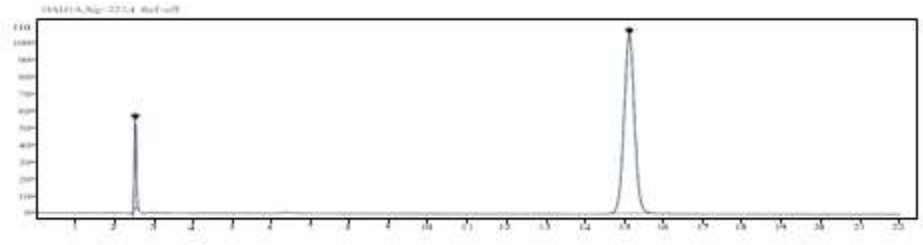


Fig.no. 9: Chromatogram of Base Trial 1 Degradation

Condition	DP	Amount of drug	Amount of degradation	R.T.	Area
2 mL of 5 N NaOH for 24 Hour at R.T.	DP 1	0	100	10.13	2665
				Total = 2665	

8. Base Trial no 2:

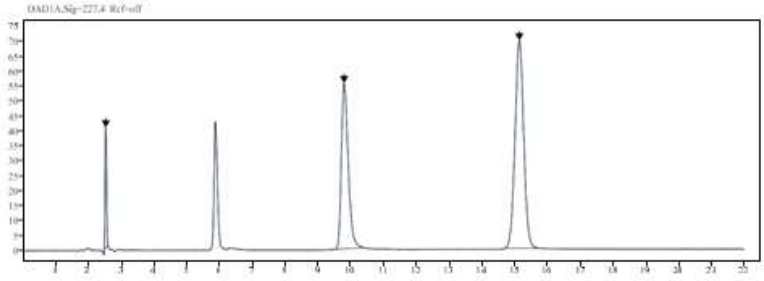


Fig.no.10: Chromatogram of Base trial 2 Degradation

Condition	DP	Amount of drug	Amount of degradation	R.T.	Area
2 mL of 1 N NaOH for 30 minutes at R.T	DP1	30.12	69.88	2.53	122
	LT			9.80	801
	DP2			15.14	1285
				Total = 2208	

9. Base Trial no. 3:

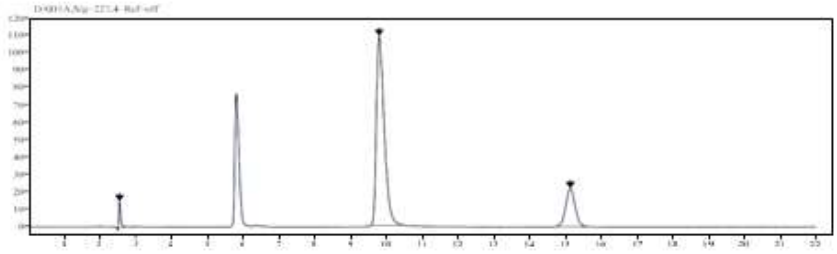


Fig.no.11: Chromatogram of Base trial 3 Degradation

Condition	DP	Amount of	Amount of	R.T.	Area

		drug	degradation		
1 mL of 0.1 N NaOH for 30 minutes at R.T.	DP1	61.66	38.34	2.53	52
	LT			9.78	1656
	DP2			15.12	399
				Total= 2665	

10. Base Trial no. 4:

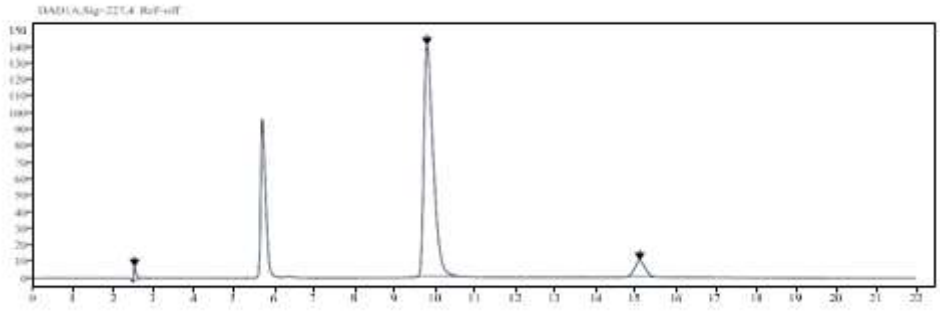


Fig.no.12: Chromatogram of Base trial 4 Degradation

Condition	DP	Amount of drug	Amount of degradation	R.T.	Area
0.5 mL of 0.1 N NaOH for 10 minutes at R.T.	DP1	84.68	15.32	2.54	33
	LT			9.83	2252
	DP2			15.13	63
				Total = 2448	

11. Peroxide Trial no. 1:

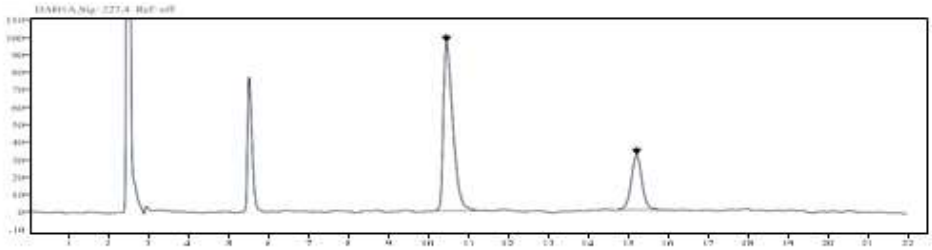


Fig.no.13: Chromatogram of Peroxide trial 1 Degradation

Condition	DP	Amount of drug	Amount of degradation	R.T.	Area
2 mL of 30% H2O2 for 24 Hour at R.T.	LT	59.42	40.58	10.46	1588
	DP1			15.23	581
				Total = 2169	

CONCLUSION

In this project, as per my objective Stability indicating RP-HPLC method for Lumateperone Tosylate was developed by using mobile phase methanol: 0.1% OPA (45:55v/v). The flow rate was used at 1.00 ml/min and UV detection was carried out at 227 nm. The retention time for Lumateperone tosylate was found to be 9.28 min. The 9.28 retention time of drug are useful for forced degrdation studies. At that retention time all degradants with drug moiety was easily get separated out and studied.

The RP-HPLC method was developed for estimation of Lumateperone tosylate was validated as per ICH

Q2(R1) guidelines using various parameters.

Moreover, the lower solvent consumption along with the short analytical run time of 10 min leads to a cost effective and environmentally friendly chromatographic procedure. Thus, the proposed methodology is rapid, selective, requires a simple sample preparation procedure, and represents a good procedure for Lumateperone tosylate.

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