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Research Article

METHOD DEVELOPMENT AND VALIDATION OF SIMULTANEOUS ESTIMATION OF OLANZAPINE AND SAMIDORPHAN BY USING RP –HPLC METHOD

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ABSTRACT

The estimate of Samidorphan and Olanzapine in tablet form is simple, accurate, and precise. Chromatograms were examined using ZORBAX Eclipse Plus C18, 4.6mm x 100mm, 5 µm. A 0.01N Ammonium Formate: Acetonitrile 80:20 mobile phase was pumped through the column at 1 ml/min. Temperature was 30°C. The optimal wavelength was 268 nm. Retention time of Samidorphan and Olanzapine was 2.232min and 2.706, respectively. %RSD was 0.4 and 0.2. Samidorphan recovered 99.80% and Olanzapine 99.77%. LOD, LOQ values from regression equations of Samidorphan and Olanzapine were 0.06, 0.17, 0.09, 0.28. Samidorphan and Olanzapine regression equations are y = 31939x + 4951.1. The method was simple and economical, reducing retention and run times for regular quality control tests in industries. Regression equations for Samidorphan and Olanzapine are 31939x + 4951.1 and 37650x + 4959.1, respectively. Retention times and run time were reduced, making the method simple and cost-effective for industrial quality control tests.

Keywords: Bilastine, Samidorphan, RP-HPLC

INTRODUCTION

Schizophrenia, derived from the Greek ‘schizo’ and ‘phren’ meaning ‘splitting mind,’ is a debilitating psychotic disorder characterized by positive symptoms such as delusions, hallucinations, and disorganized thoughts, and negative symptoms like lack of effect or motivation.[1,2] The disease has a multifactorial etiology with many associated risk factors, including maternal malnutrition, influenza during gestation, cannabis use, urbanization, and birthing complications.[1,3] The diagnosis of schizophrenia is clinical and requires the exclusion of any other potential causes of psychosis. Suicide has been found to be a leading cause of decreased life expectancy in schizophrenia [4].

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The Estimates are that schizophrenia affects approximately 1% of adults, whereas prevalence in the United States is 0.6 to 1.9% [5]. Men are slightly more likely to be diagnosed and have an earlier onset than women, while African-Caribbean migrants and their descendants also have a higher incidence.[6]

Olanzapine is a thienobenzodiazepine classified as an atypical or second-generation antipsychotic agent.[2] The second-generation antipsychotics were introduced in the 90s and quickly gained traction due to their impressive efficacy, reduced risk for extrapyramidal side effects and reduced susceptibility to drug-drug interactions.[5] Olanzapine very closely resembles clozapine and only differs by two additional methyl groups and the absence of a chloride moiety.[10] It was discovered by scientists at Eli Lilly and approved to be marketed in the US in 1996.[8]

Samidorphan is a novel opioid antagonist structurally related to naltrexone, with a higher affinity for opioid receptors, more potent μ-opioid receptor antagonism, higher oral bioavailability, and a longer half-life, making it an attractive candidate for oral dosing.,[11] Although antipsychotic-induced weight gain is incompletely understood, it is thought that the opioid system plays a key role in feeding and metabolism, such that opioid antagonism may be expected to ameliorate these negative effects.

Selection of antipsychotic medications for individual patients is based on efficacy and their safety and tolerability profiles, which commonly include extrapyramidal symptoms and/or metabolic effects,6 including the risk of significant weight gain.7, Olanzapine is a highly effective treatment with established antipsychotic efficacy and a low incidence of extrapyramidal symptoms.[9–13] placing patients at significant risk of relapse, hospitalization, and disease progression [12].Weight gain also profoundly affects quality of life, psychosocial adaptation, body image, and self-esteem[13,14], an impact superimposed on the challenges accompanying a psychiatric diagnosis, including stigma and social isolation[15].

Olanzapine remains one of the most efficacious antipsychotic medications for the treatment of schizophrenia, there are significant tolerability concerns related to its weight and metabolic profile. Olanzapine-samidorphan combination tablets (OLZ/SAM), branded as Lybalvi, is a newly FDA approved formulation aimed at attenuating antipsychotic induced weight gain via modulation of the endogenous opioid system with samidorphan, while retaining the robust antipsychotic efficacy of olanzapine.

They might be side effects with Olanzapine + Samidorphan like Rhinitis, Headache, Eczema, Urticaria, Abdominal pain/Upper abdominal pain14

According to a literature review, there are some techniques for the simultaneous estimate of these medicines as well as others for assessment of the drugs alone or in combination with other drugs. Utilizing UV-Spectrophotometry RP-HPLC. There is no established technique for the stability-indicating simultaneous measurement of Olanzapine and Samidorphan by RP-HPLC in pharmaceutical dosage form, according to a survey of the literature

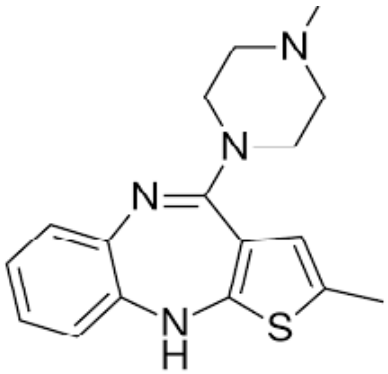

Figure 1: Structure of Olanzapine

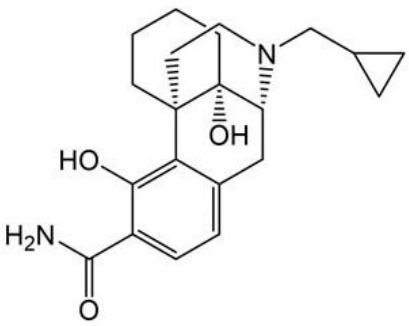

Figure 2: Structure of Samidorphan

The primary goal of this work is to provide an efficient, quick, and accurate RP-HPLC approach for estimating of Olanzapine and Samidorphan in medicinal dose and tablet form. According to ICH recommendations, a proven approach was also used to estimate the amounts of Olanzapine and Samidorphan .[17-20]

MATERIALS AND REAGENTS

Olanzapine and Samidorphan pure drugs were received from Spectrum Pharma research solutions, Hyderabad. The combination tablet Olanzapine and Samidorphan (Lybalvi,) was purchased from a local pharmacy store. Rankem in India provided all of the chemicals and buffers utilised in this method like Acetonitrile, Phosphate buffer, Methanol, Potassium dihydrogen Ortho phosphate buffer, Ortho-phosphoric acid, Distilled water.

Instrumentation and Chromatographic Conditions

For the development and validation method, an automated sample injector was employed with a WATERS HPLC, model: 2695 SYSTEM with Photo diode array detector. For the separation, a Discovery 150 (C18 250 mm x 4.6 mm, 5µm) column was employed. Acetonitrile is employed as mobile phase B, while 0.1% ortho phosphoric acid is used as mobile phase A. (35:65 Ratio). The analysis was done in isocratic mode with an injection volume of 10 mL and a flow rate of 1 mL/min. The duration was six minutes. The measurements were made at 254 nm.

PREPARATION OF SOLUTIONS

Diluent: Based up on the solubility of the drugs, diluent was selected, Acetonitrile and Water taken in the ratio of 50:50

Preparation of buffer:

Buffer: (0.1% OPA)

Accurately 1ml of OPA in a 1000ml of Volumetric flask add about 900ml of milli-Q water added and degas to sonicate and finally make up the volume with water.

Buffer:

0.01N Potassium dihyrogenortho phosphate

Accurately weighed 1.36gm of Potassium dihyrogen Ortho phosphate in a 1000ml of Volumetric flask add about 900ml of milli-Q water added and degas to sonicate and finally make up the volume with water.

Buffer: 0.01N Sodium dihydrogen phosphate

Accurately weighed 1.42gm of Potassium dihyrogen Ortho phosphate in a 1000ml of Volumetric flask add about 900ml of milli-Q water added and degas to sonicate and finally make up the volume with water then PH adjusted to 3.5 with dil. Orthophosphoric acid solution.

Preparation of Standard stock solutions: Accurately weighed 15mg of Olanzapine, 10mg of Samidorphan and transferred to 50ml volumetric flask. 3/4th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (300µg/ml of Olanzapine, and 200µg/ml Samidorphan)

Preparation of Standard working solutions (100% solution): 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (30µg/ml of Olanzapine, and 20µg/ml of Samidorphan).

Preparation of Sample stock solutions: weighed 15mg of Olanzapine, 10mg of Samidorphan and transferred to 50ml volumetric flask. 3/4th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (300µg/ml of Olanzapine, and 200µg/ml Samidorphan)

Preparation of Sample working solutions (100% solution): 1ml from each stock solution was pipetted out and taken into a 10ml volumetric flask and made up with diluent. (30µg/ml of Olanzapine,a nd 20µg/ml of Samidorphan).

METHOD VALIDATION

To prove that the technique is suggested for routine analysis, the HPLC method's validation was done for the simultaneous estimation of Olanzapine, and Samidorphan drug material in accordance with the ICH criteria.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific.

Linearity: stock solutions of Olanzapine, and Samidorphan is taken in to 6 different volumetric flasks and diluted to 10ml with diluents. Linearity solutions are prepared such that 0.25, 0.5, 0.75, 1, 1.25, 1.5ml.

Accuracy:

Preparation of Standard stock solutions: Accurately weighed 15mg of Olanzapine, 10mg of Samidorphan and transferred to 50ml volumetric flask. 3/4 th of diluents was added to the flask and sonicated for 10 minutes. Flask was made up with diluents and labeled as Standard stock solution. (300µg/ml of Olanzapine and 200µg/ml Samidorphan)

Preparation of 50% Spiked Solution: 0.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 100% Spiked Solution: 1.0ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Preparation of 150% Spiked Solution: 1.5ml of sample stock solution was taken into a 10ml volumetric flask, to that 1.0ml from each standard stock solution was pipetted out, and made up to the mark with diluent.

Acceptance Criteria:

The % Recovery for each level should be in between 98.0 to 102.

Robustness: Small deliberate changes in method like Flow rate, mobile phase ratio, and temperature are made but there were no recognized change in the result and are within range as per ICH Guide lines.

Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus, mobile phase plus, temperature minus (25°C) and temperature plus(35°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

LOD sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10ml volumetric flasks and made up with diluents. From the above solutions 0.1ml each of Olanzapine and Samidorphan, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluents

LOQ sample Preparation: 0.25ml each from two standard stock solutions was pipetted out and transferred to two separate 10ml volumetric flask and made up with diluent. From the above solutions 0.3ml each ofOlanzapine and Samidorphan, solutions respectively were transferred to 10ml volumetric flasks and made up with the same diluent.

System suitability parameters: The system suitability parameters were determined by preparing standard solutions of Olanzapine (30ppm) and Samidorphan (20ppm) and the solutions were injected six times and the parameters like peak tailing, resolution and USP plate count were determined.

Degradation studies:

Oxidation:

To 1 ml of stock solution of Olanzapine and Samidorphan, 1 ml of 20% hydrogen peroxide (H2O2) was added separately. The solutions were kept for 30 min at 600c. For HPLC study, the resultant solution was diluted to obtain 30 µg/ml &20 µg/ml solutionand10µlwereinjectedintothe system and the chromatograms were recorded to assess the stability of sample.

Acid Degradation Studies:

To 1 ml of stock solution Olanzapine and Samidorphan, 1ml of 2N Hydrochloric acid was added and refluxed for 30mins at 60 0C. The resultant solution was diluted to obtain 30µg/ml & 20µg/ml solution and10µl solutions were injected into the system and the chromatograms were recorded to assess the stability of sample.

Alkali Degradation Studies:

To 1 ml of stock solution Olanzapine and Samidorphan, 1 ml of 2N sodium hydroxide was added and refluxed for 30mins at 600c. The resultant solution was diluted to obtain 30µg/ml & 20µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Dry Heat Degradation Studies:

The standard drug solution was placed in oven at105°C for 6h to study dry heat degradation. For HPLC study, the resultant solution was diluted to 30µg/ml & 20µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

Photo Stability studies:

The photochemical stability of the drug was also studied by exposing the 200µg/ml&&100µg/ml solution to UV Light by keeping the beaker in UV Chamber for 7days or 200 Watt hours/m2 in photo stability chamber. For HPLC study, the resultant solution was diluted to obtain 30µg/ml &20µg/ml solutions and 10µl were injected into the system and the chromatograms were recorded to assess the stability of sample.

Neutral Degradation Studies:

Stress testing under neutral conditions was studied by refluxingthedruginwaterfor6hrs at a temperature of 60º. For HPLC study, the resultant solution was diluted to 30µg/ml&20µg/ml solution and 10µl were injected into the system and the chromatograms were recorded to assess the stability of the sample.

RESULTS AND DISCUSSIONS:

Table 1: System suitability table

S.No	Samidorphan			Olanzapine			
Injection	RT (min)	USP Plate Count	Tailing	RT(min)	USP Plate Count	Tailing	RS
1	2.220	6650	1.08	2.784	13479	1.20	5.4
2	2.220	6939	1.11	2.785	13522	1.19	5.5
3	2.221	6644	1.07	2.787	13391	1.19	5.4
4	2.223	6465	0.99	2.793	13528	1.11	5.5
5	2.224	6551	1.04	2.793	13418	1.11	5.5
6	2.224	6784	1.07	2.794	13699	1.11	5.6

Table 2: Specificity data

Sample name	Retention time (Mins)	Area
Samidorphan	2.232	627527
Olanzapine	2.706	1202828

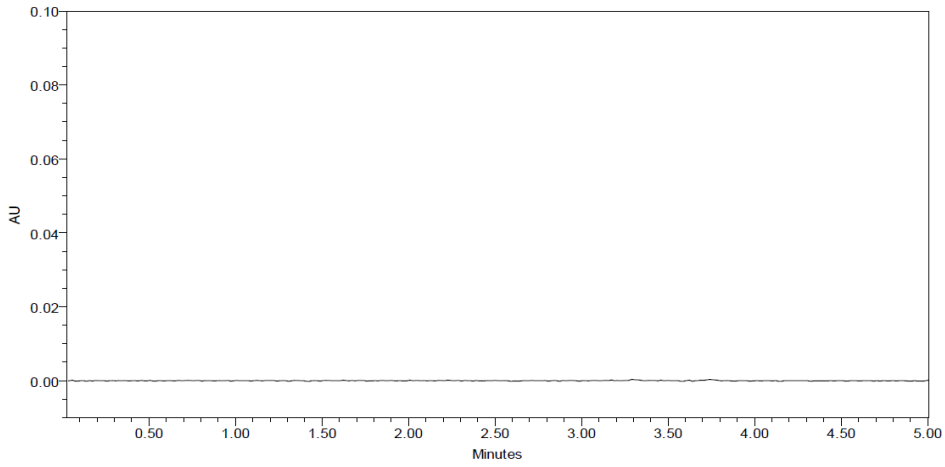

Figure 3. Blank Chromatogram

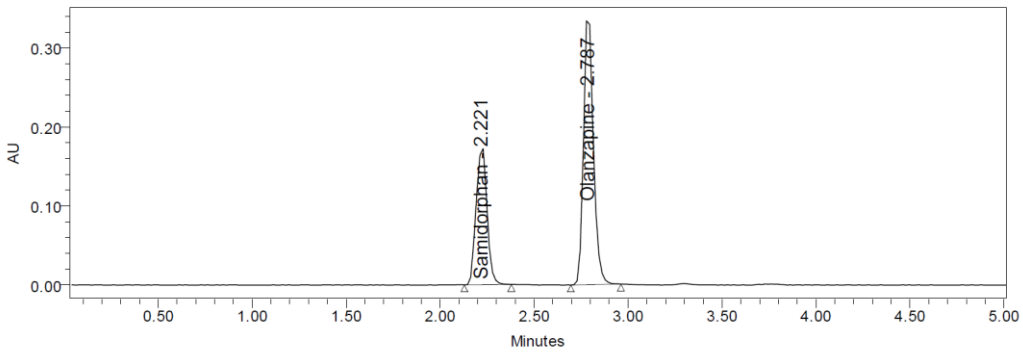

Figure 4. Specificity Chromatograms of Samidorphan and Olanzapine.

Linearity

Table 3. Linearity table for Samidorphan and Olanzapine

Samidorphan		Olanzapine	
Conc (µg/mL)	**Peak area**	**Conc(µg/mL)**	**Peak area**
0	0	**0**	0
5	167363	**7.5**	283267
10	326755	**15**	580378
15	484942	**22.5**	853314
20	643968	**30**	1142675
25	806689	**37.5**	1404034
30	958527	**45**	1700863

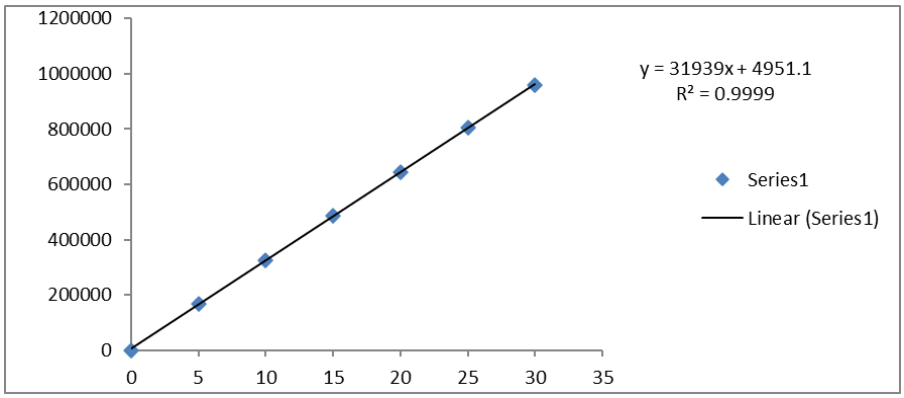

Figure 5. Calibration curve of Samidorphan

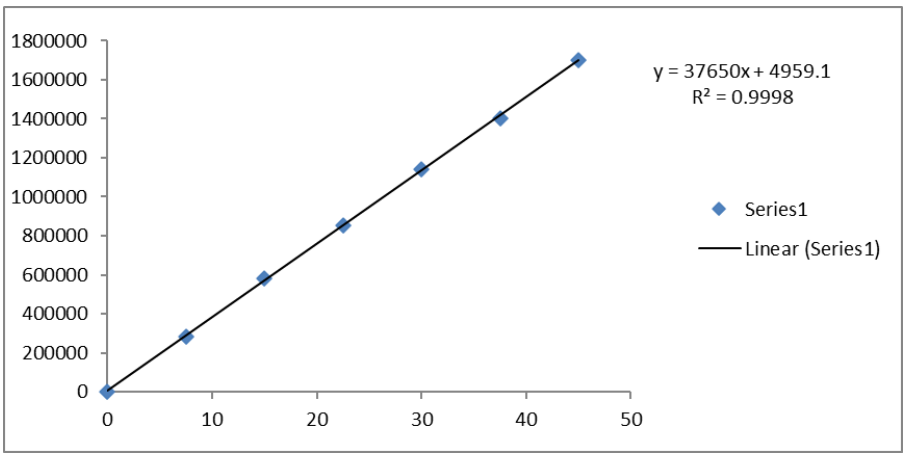

Figure 6. Calibration curve of Olanzapine

Accuracy:

Table 4. Accuracy table of Samidorphan

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	5	4.97	99.32	99.78%
	5	5.00	100.03	
	5	5.00	99.98	
100%	10	10.04	100.44	
	10	9.96	99.61	
	10	10.00	100.01	
150%	15	14.93	99.52	
	15	14.93	99.56	
	15	14.96	99.75	

Table 5. Accuracy table of Olanzapine

% Level	Amount Spiked (µg/mL)	Amount recovered (µg/mL)	% Recovery	Mean %Recovery
50%	10	9.89	98.87	99.78%
	10	10.08	100.82	
	10	10.04	100.37	
100%	20	19.95	99.76	
	20	19.94	99.68	
	20	19.97	99.83	
150%	30	29.87	99.56	
	30	29.85	99.51	
	30	29.88	99.60	

System Precision: With regard to the working strength of Olanzapine and Samidorphan, six duplicate injections of the standard solution at 100% of the prescribed limit were analysed to determine the system accuracy. In Table 5, the results of the peak area are compiled.

Table 6. System precision

S. No	Area of Samidorphan	Area of Olanzapine
1.	669950	1228135
2.	670156	1227803
3.	670117	1229668
4.	676337	1221670
5.	669699	1226402
6.	670142	1226556
Mean	**671067**	**1226706**
S.D	**2587.7**	**2738.4**
%RSD	**0.4**	**0.2**

The % RSD for the peak areas of Olanzapine and Samidorphan obtained from six replicate injections of standard solution was within the limit of (<2%).

Method precision: Analyzing a sample of Olanzapine and Samidorphan allowed researchers to gauge the method's accuracy (Six individual sample preparations). Table 6 provides a summary of the data.

Table 7. Method precision

S. No	Area of Samidorphan	Area of Olanzapine
1.	668610	1219900
2.	672192	1226720
3.	670118	1218428
4.	670535	1216699
5.	674226	1217616
6.	671722	1228069
Mean	**671234**	**1221239**
S.D	**1935.3**	**4901.5**
%RSD	**0.3**	**0.4**

Results shows, the % RSD of Repeatability study was within the range for Olanzapine and Samidorphan is (<2%)

Table 8: Robustness

S.No.	Condition	%RSD of Samidorphan	%RSD of Olanzapine
1	**Flow rate (-) 0.9ml/min**	0.2	0.2
2	**Flow rate (+) 1.1ml/min**	0.3	0.2
3	**Mobile phase (-) 60B:40A**	1.2	1.1
4	**Mobile phase (+) 70B:30A**	1.2	1.1
5	**Temperature (-) 25°C**	0.7	0.8
6	**Temperature (+) 35°C**	1.2	1.0

Table 9. Forced degradation for Olanzapine and Samidorphan

Stress condition	Solvent	Temp (^{0}C)	Exposed time
Acid	2N HCL	60^0c	30 mins
Base	2N NAOH	60^0c	30 mins
Oxidation	20% H_2O_2	60^0c	30 mins
Thermal	Diluent	105^0c	6 hours
Photolytic	Diluent	-	-
Hydrolytic	Water	60^0c	

DEGRADATION

Degradation Studies: Degradation studies were performed with the formulation and the degraded samples were injected. Assay of the injected samples was calculated and all the samples passed the limits of degradation

Table 10. Degradation results of Olanzapine and Samidorphan

Type of degradation	Samidorphan		Olanzapine	
	%Recovered	% Degraded	%Recovered	% Degraded
Acid	93.55	6.45	90.45	9.55
Base	93.05	6.95	96.78	3.22
Peroxide	94.48	5.52	95.19	4.81
Thermal	96.20	3.80	95.54	4.46
Uv	97.42	2.58	97.99	2.01
Water	99.71	0.29	99.23	0.77

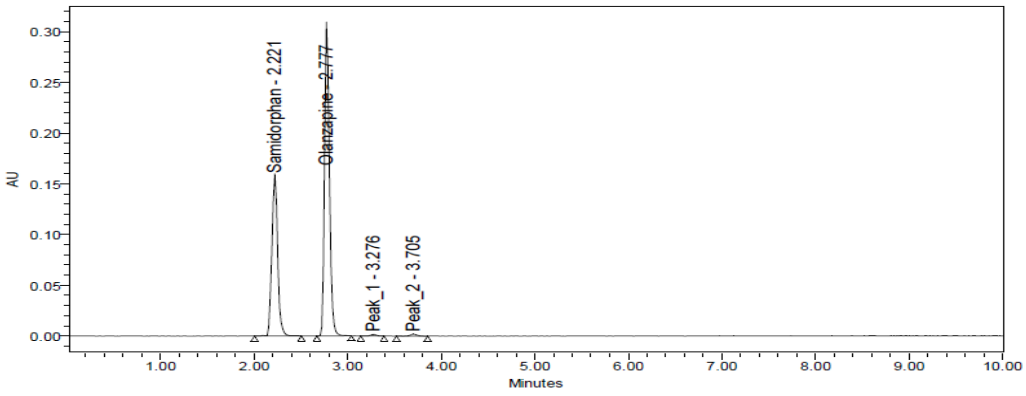

Figure 7. Acid chromatogram of Olanzapine and Samidorphan

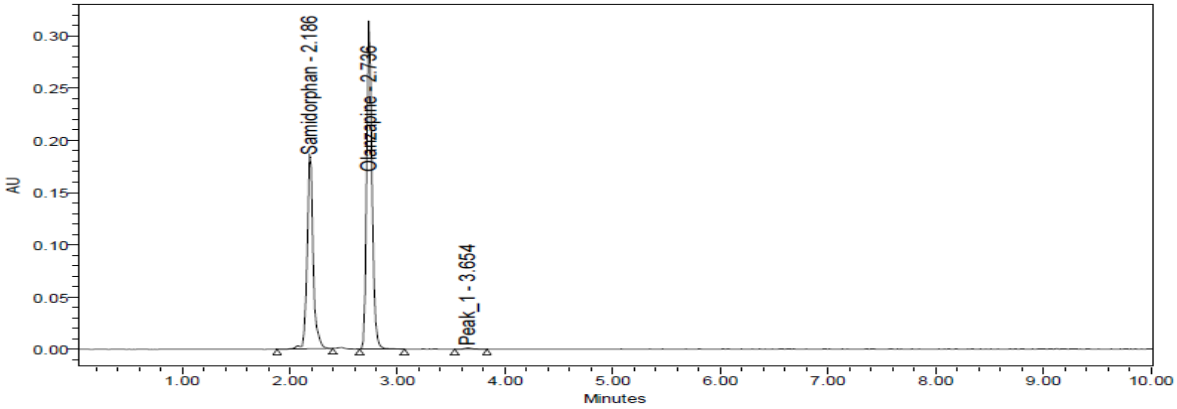

Figure 8. Base chromatogram of Olanzapine and Samidorphan

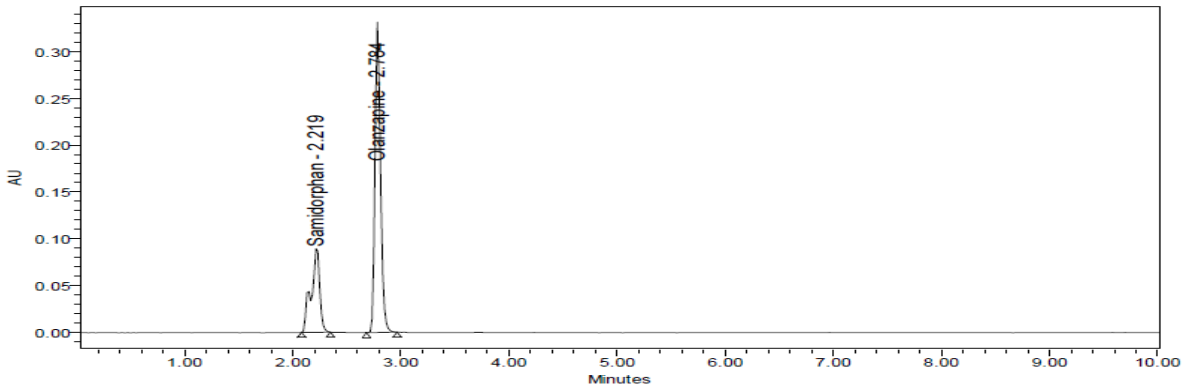

Figure 9. Peroxide chromatogram of Olanzapine and Samidorphan

According to the results, samples were degraded when they were subjected to an acid, base, and oxidation interaction. Hydrolysis reaction, heat reaction, and light reaction all showed no deterioration. According to the stress research, none of the degradants co-eluted with the maxima of the active medication.

Assay: (Lybalvi) bearing label claim, Samidorphan 10mg, Olanzapine 20mg, assay was carried out by injecting sample into HPLC System.

Table 11. Assay Data of Samidorphan

S.no	Standard Area	Sample area	% Assay
1	669950	668610	99.24
2	670156	672192	99.77
3	670117	670118	99.46
4	676337	670535	99.52
5	669699	674226	100.07
6	670142	671722	99.70
Avg	**671067**	**671234**	**99.62**
Stdev	**2587.7**	**1935.3**	**0.29**
%RSD	**0.4**	**0.3**	**0.3**

Table 12. Assay Data of Olanzapine

S.no	Standard Area	Sample area	% Assay
1	1228135	1219900	99.25
2	1227803	1226720	99.80
3	1229668	1218428	99.13
4	1221670	1216699	98.99
5	1226402	1217616	99.06
6	1226556	1228069	99.91
Avg	**1223722**	**1221239**	**99.36**
Stdev	**2738.4**	**4901.5**	**0.4**
%RSD	**0.2**	**0.4**	**0.4**

Table 13. Assay outcome for Olanzapine and Samidorphan

Drug Name	Label claim dose	%Assay	Brand Name
Olanzapine	**20mg**	**99.36**	**Lybalvi**
Samidorphan	**10mg**	**99.62**	

CONCLUSION

The proposed HPLC method was validated as per ICH guidelines and applied for the determination of Olanzapineand Samidorphan in tablet dosage form. The concurrent estimate of Samidorphan and Olanzapine in tablet form is simple, accurate, and precise. Olanzapine and Samidorphan had 2.232min and 2.706min retention times. %RSD of Samidorphan and Olanzapine were 0.4 and 0.2. %Olanzapine recovered 99.78% and Samidorphan 99.80%. LOD, LOQ values from regression equations of Samidorphan and Olanzapine were 0.06, 0.17, 0.09, 0.028. Regression equations for Samidorphan and Olanzapine are 31939x + 4951.1 and 37650x + 4959.1, respectively. Retention times and run time were reduced, making the method simple and cost-effective for industrial quality control tests.

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