Original Article

Development and Validation of Stability-Indicating RP-HPLC method for the simultaneous estimation of Olanzapine and Samidorphan in pure API and tablet dosage form in accordance with ICH guidelines

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DOI: 10.47750/pnr.2022.13.S06.114

Abstract

The objective of this study is to evaluate Olanzapine and Samidorphan in bulk and tablet dose forms simultaneously.

Materials and procedures: On an Xterra (4.6 x 150mm, 5 m) analytical column, the separation was conducted using a mobile phase of 40% buffer (Ortho phosphoric Acid): 60% methanol. The eluents were discovered using a UV detector at 220.0 nm.

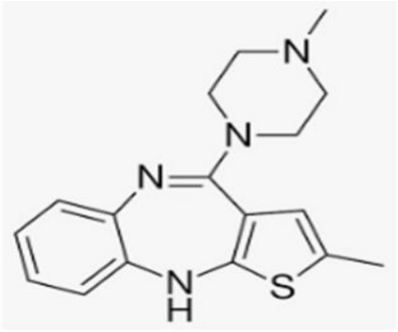
Results: Olanzapine and Samidorphan were separated at 3.124 and 4.270 minutes, respectively, under ideal conditions. Samidorphan had a detection limit of 0.21 g/mL while Olanzapine had a detection limit of 0.20 g/mL. Olanzapine had a recovery rate of 100.34 percent compared to Samidorphan's percentage mean recovery of 100.01 percent.

Conclusion: In each stressful scenario, the proportion of degradation was found to be incredibly low. It was discovered that under optimum conditions, all of them could be determined simultaneously in bulk and marketing dose form.

Keywords: Olanzapine, Samidorphan, method development, validation, and RP-HPLC..

INTRODUCTION

Olanzapine and Samidorphan are combined to treat the signs and symptoms of schizophrenia in adults. It is also used to treat manic episodes in individuals with bipolar illness, either on its alone or in combination with other drugs. Olanzapine belongs to the group of drugs known as atypical antipsychotics. It functions by altering the activity of certain natural substances in the brain. An antagonist of opioids is samidorphan. It serves to lessen potential Olanzapine side effects, such as weight gain. (1) Olanzapine and Samidorphan are chemically described as 17-(Cyclopropylmethyl)-4, 14-dihydroxy-6-oxomorphinan-3-carboxamide and 2-Methyl-4-(4-methyl-1-piperazinyl)-10H-thieno [2, 3-b][1,5]benzodiazepine. Olanzapine and Samidorphan's structural diagrams are shown in Figures 1 and 2, respectively. (2-3)The current study seeks to develop a rapid, stability-indicating RP-HPLC method for the simultaneous quantification of Olanzapine and Samidorphan in bulk pharmaceuticals and commercial dosage forms. This is accomplished by improving sensitivity and reducing elution times. The validation study was also finished in compliance with ICH Guidelines Q2 (International Conference on Harmonization) (R1). (4-5)



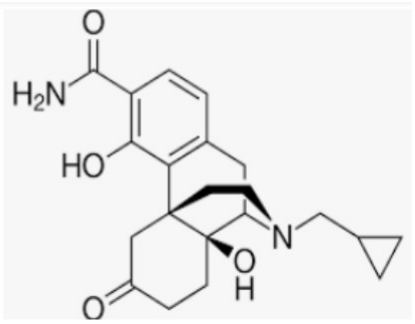


Fig1: Chemical Structure of Olanzapine Fig 2: Chemical Structure of Samidorphan

MATERIALS AND METHODS:

Chemicals:

Laurus Labsgenerously contributed pharmaceutical-grade Olanzapine and Samidorphan FINER Chemical LTD, LICHROSOLV (MERCK), and Sigma Aldrich (Mumbai) provided analytical reagent grade solvents and chemicals for this study.

Instruments:

Afcoset ER-100A analytical balance, WATERS, software: Empower, 2695 separation module, UV detector, LABINDIA UV 12.500, Adwa – AD 10100 pH meter, Borosil Pipettes, Burettes and Beakers.

HPLC method development:

Mobile phase preparation:

Accurately measured 400 ml (40%) of above buffer and 600 ml of Acetonitrile HPLC (60%) were mixed and degassed in an ultrasonic water bath for 10 minutes and then filtered through 0.45 µ filter under vacuum filtration.

Preparation of the Diluent: The Mobile phase served as the diluent.

Olanzapine and Samidorphan standard and sample solution preparation:

Preparation of standard Solution:

In a 10 ml clean, dry volumetric flask, accurately weigh and transfer 10 mg of samidorphan and 5 mg of olanzapine as the working standard. Add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to put the volume up to the mark using the same solvent. (Stock solution)

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

Preparation of sample Solution:

In a 10 ml clean, dry volumetric flask, accurately weigh and transfer 10 mg of samidorphan and 5 mg of olanzapine as the working standard. Add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to put the volume up to the mark using the same solvent. (Stock solution) (avg weight 76 mg)

Pipette 0.3 ml of the aforementioned stock solutions into a volumetric flask with a 10 ml capacity, then diluting it to the appropriate concentration.

Procedure:

It is necessary to inject 10 L of the standard, place the sample into the chromatographic system, measure the areas of the samidorphan and olanzapine peaks, and then use the formulas to compute the assay's percentage.

Mobile Phase Optimization:

The first mobile phases tested were methanol: ammonium acetate buffer and methanol: phosphate buffer with different pH and molar ratio combinations. Finally, orthophosphoric acid with buffer (pH 3) and methanol in proportions of 60: 40 v/v were chosen as the mobile phase's optimal components.

Wave length selection:

The UV spectra of samidorphan and olanzapine at 10 g/ml in diluents (the composition of the mobile phase) was captured by scanning in the 200–400 nm range. 220nm was chosen as the wavelength from the UV spectrum. At this wavelength, both medicines exhibit strong absorption.

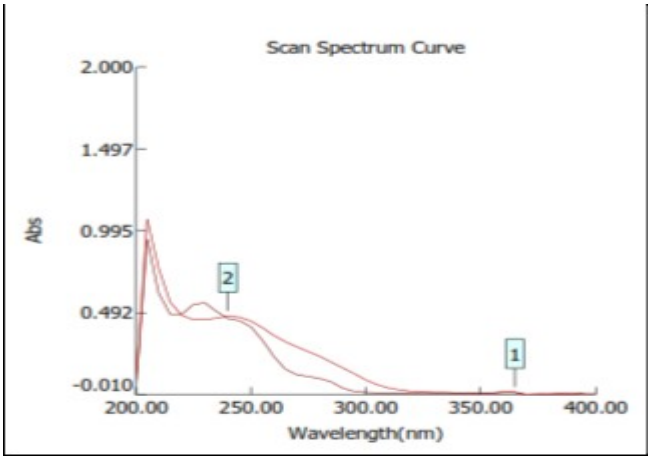


Figure 3: Represents Isobestic point of Olanzapine and Samidorphan.

Optimization of Colum:

The best column discovered to be Xterra RP18 (4.6 x 150mm, 5µm), which provided good peak shape and resolution at 1.0 ml/min.

Optimized chromatographic conditions:

Instrument used : Waters HPLC with auto sampler and 2487 UV detector.

Temperature : Ambient

Column : Xterrra 4.6*150mm

Buffer : 1ml of orthophosphoric acid in 1000ml water, pH adjusted with

NaOH.

pH : 3

Mobile phase : 40% buffer 60% methanol

Flow rate : 1 ml per min

Wavelength : 220 nm

Injection volume : 10 □l

Run time : 10 min

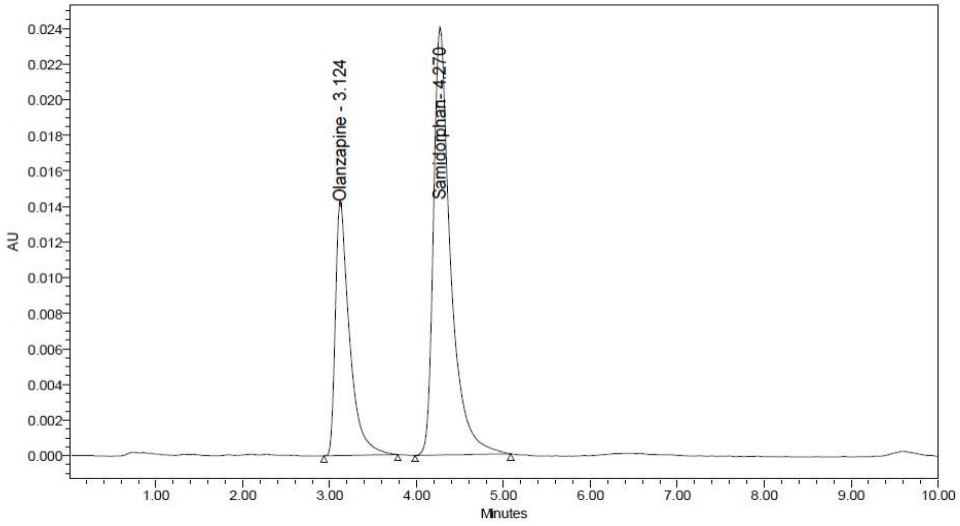


Fig 4: Represents standard Optimized Chromatogram

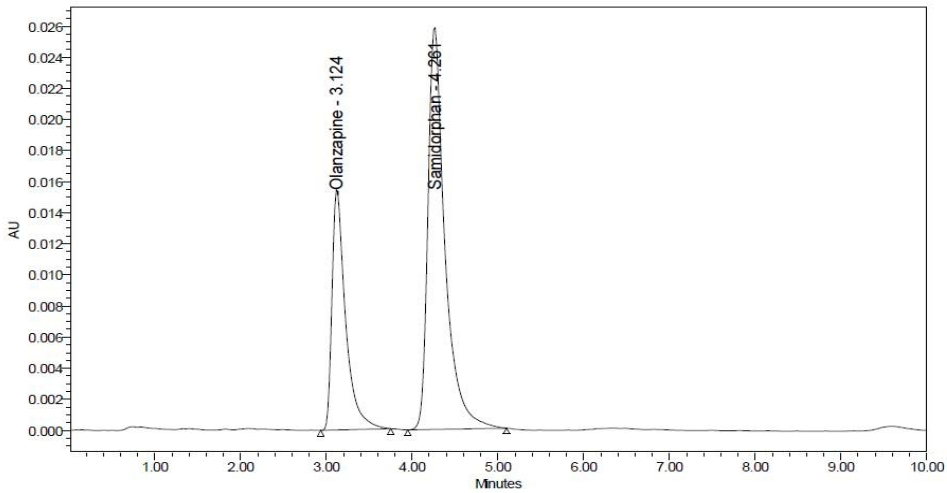
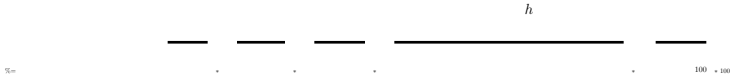


Fig 5: Represents Sample Optimized Chromatogram

Assay Calculations:

Calculation: (For Samidorphan)



AT = average area counts of sample preparation.

AS = average area counts of standard preparation.

WS = Weight of working standard taken in mg.

P = Percentage purity of working standard

LC = Label Claim mg/ml.

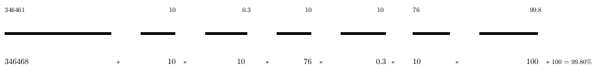
RESULTS:

System Suitability Results:

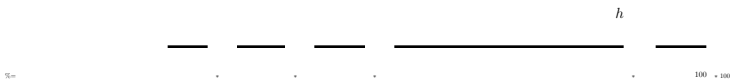
1. Tailing factor Obtained from the standard injection is 1.87

2. Theoretical Plates Obtained from the standard injection is 2940.49

Assay Results: (Samidorphan)



Calculation: (For Olanzapine)



Where:

AT = average area counts of sample preparation.

AS = average area counts of standard preparation.

WS = Weight of working standard taken in mg.

P = Percentage purity of working standard

LC = Label Claim mg/ml.

Results:

System Suitability Results:

1. Tailing factor Obtained from the standard injection is 1.84

2. Theoretical Plates Obtained from the standard injection is 3415.94

3. Resolution Obtained from the standard injection is 6.06

Assay Results: (For Olanzapine)

$$\frac{171004}{171146} * \frac{10}{10} * \frac{76}{76} * \frac{0.3}{0.3} * \frac{5}{5} * \frac{100}{100} * 100 = 99.72\%$$

Method validation:

System suitability study:

It was carried out to guarantee that an analytical system was operating correctly. Olanzapine (30 g/ml) and Samidorphan (15 g/ml) were injected into the chromatographic system six times each to test it. The theoretical plate, retention time, and asymmetry factor were all taken into account while calculating the percentage relative standard.

Specificity:

For the purpose of determining specificity, a blank and a standard are introduced into the chromatographic system. There is no interference from any peak in the blank with reference to the retention times of the analytical peaks.

Precision & Intermediate Precision:

Six injections of the standard solution were made into the HPLC, and the area of each was measured. It was discovered that the%RSD for the region of six replicate injections was within the predetermined range. The outcomes for Samidorphan and Olanzapine are summarised..

Table 1: Represents Precision study results

Injection	**Area for Samidorphan**	**Area for Olanzapine**
Injection-1	341368	178876
Injection-2	340717	177224
Injection-3	342655	179055
Injection-4	343939	178739
Injection-5	343013	176699
Injection-6	342282	179220
Average	342329.0	178302.2
Standard Deviation	1156.8	1064.1
%RSD	0.3	0.6

Table 2: Represents Intermediate precision study results

Injection	Area for Samidorphan	Area for Olanzapine
Injection-1	349453	172535
Injection-2	347162	171224
Injection-3	349458	172915
Injection-4	348377	173391
Injection-5	348482	173108
Injection-6	349771	172959
Average	348783.8	172688.7
Standard Deviation	976.1	769.7
%RSD	0.3	0.4

Accuracy:

Preparation of Standard stock solution:

In a 10 ml clean, dry volumetric flask, accurately weigh and transfer 10 mg of samidorphan and 5 mg of olanzapine as the working standard. Add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to put the volume up to the mark using the same solvent. (Stock solution).

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

Preparation Sample solutions:

For preparation of 50% solution (With respect to target Assay concentration):

In a 10 ml clean, dry volumetric flask, accurately weigh and transfer 5 mg of samidorphan and 2.5 mg of olanzapine as the working standard. Add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to put the volume up to the mark using the same solvent. (Stock solution)

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

For preparation of 100% solution (With respect to target Assay concentration):

In a 10 ml clean, dry volumetric flask, accurately weigh and transfer 10 mg of samidorphan and 5 mg of olanzapine as the working standard. Add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to put the volume up to the mark using the same solvent. (Stock solution)

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

For preparation of 150% solution (With respect to target Assay concentration):

In a 10 ml clean, dry volumetric flask, accurately weigh and transfer 15 mg of samidorphan and 7.5 mg of olanzapine as the working standard. Add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to put the volume up to the mark using the same solvent. (Stock solution)

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

Procedure:

Inject the accuracy -50%, accuracy -100%, and accuracy -150% solutions along with the standard solution. Calculate the individual recovery and mean recovery values as well as the amounts that were found and added for the drugs samidorphan and olanzapine. Results for Samidorphan's accuracy.

Table 3: Represents Accuracy results of Samidorphan

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	172505.0	5	5.97	99.38	100.01
100%	346412	10	9.97	99.78	
150%	525309.0	15	15.62	100.88	

Table 4: Represents Accuracy results of Olanzapine

%Concentration (at specification Level)	Area	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	85620	2.5	2.50	100	100.34
100%	171845	5	5.01	100.21	
150%	259676.0	7.5	7.57	100.95	

Acceptance Criteria: The % Recovery for each level should be between 98.0 to 102.0%.

Linearity:

Preparation of stock solution:

In a 10 ml clean, dry volumetric flask, accurately weigh and transfer 10 mg of samidorphan and 5 mg of olanzapine as the working standard. Add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough liquid to put the volume up to the mark using the same solvent. (Stock solution)

Preparation of Level – I:

0.1 ml of above stock solutions has taken in different 10ml of volumetric flasks, dilute up to the mark with diluent.

Preparation of Level – II:

0.2ml of above stock solutions has taken in different 10ml of volumetric flasks, dilute up to the mark with diluent.

Preparation of Level – III:

0.3 ml of above stock solutions has taken in different 10ml of volumetric flasks, dilute up to the mark with diluent.

Preparation of Level – IV:

0.4 ml of above stock solutions has taken in different 10ml of volumetric flasks, dilute up to the mark with diluent

Preparation of Level – V:

0.5 ml of above stock solutions has taken in different 10ml of volumetric flasks, dilute up to the mark with diluent

Procedure:

Inject each level into the chromatographic system and measure the peak area.

Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

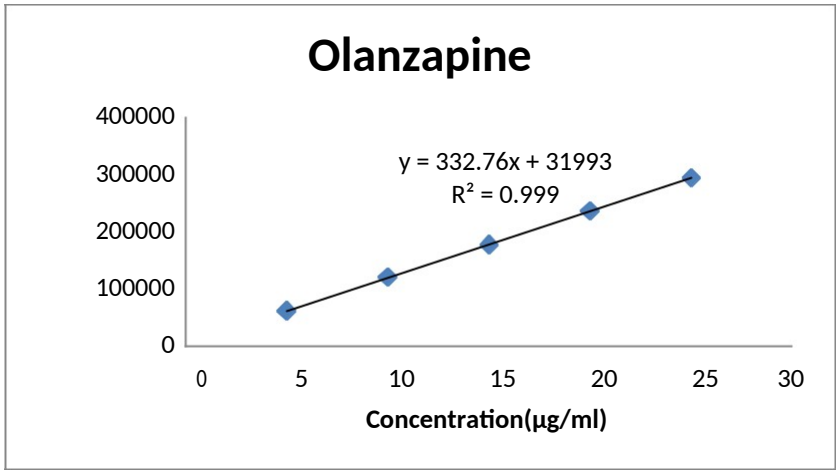


Figure 6: Represents Olanzapine Linearity

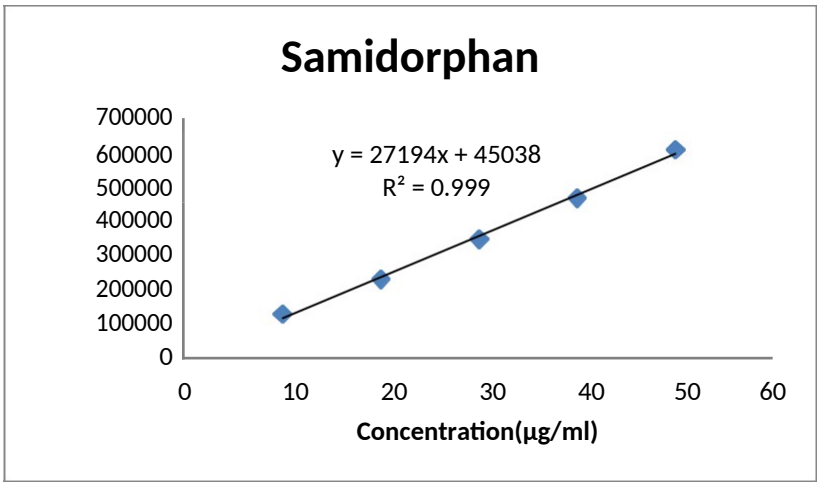


Figure 7: Represents Samidorphan Linearity

Table 5: Represents Linearity results of Samidorphan

S. No	Linearity Level	Concentration	Area
1	I	10	127774
2	II	20	228918
3	III	30	345340
4	IV	40	465502
5	V	50	607979
Correlation Coefficient			0.999

Table 6: Represents Linearity results of Olanzapine

S. No	Linearity Level	Concentration	Area
1	I	5	61241
2	II	10	119943
3	III	15	176636
4	IV	20	235363
5	V	25	293580
Correlation Coefficient			0.999

Acceptance Criteria: Correlation coefficient should be not less than 0.9

Limit of detection study (LOD): (forSamidorphan)

Preparation of 0.21 µg/ml solution:

Once the 10 mg of samidorphan working standard has been accurately weighed and transferred into a 10 ml clean, dry volumetric flask, add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to make the volume up to the target with the same solvent. (Stock solution)

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

Pipette 1.5 ml of the aforementioned stock solution into a 10 ml volumetric flask, and then add diluent to the mark.

Pipette 0.51 ml of the aforementioned stock solution into a 10 ml volumetric flask and add diluent to get the desired concentration.

Limit of detection: (for Olanzapine)

Preparation of 0.20 µg/ml solution:

Accurately weigh and transfer 5 mg of Olanzapine working standard into a 10 ml clean dry volumetric flask add about 7 mL of Diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 0.3 ml of the above stock solutions into a 10ml volumetric flask and dilute up to the mark with diluent.

Further pipette 3ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with diluent

Further pipette 0.46ml of the above stock solution into a 10ml volumetric flask and dilute up to the mark with diluent.

Limit of quantification:(for Samidorphan)

Preparation of 0.68µg/ml solution:

Once the 10 mg of samidorphan working standard has been accurately weighed and transferred into a 10 ml clean, dry volumetric flask, add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to make the volume up to the target with the same solvent. (Stock solution)

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

Pipette 3 ml of the aforementioned stock solution into a 10 ml volumetric flask and add diluent to reach the desired concentration.

Pipette 0.85 ml of the aforementioned stock solution into a 10 ml volumetric flask and add diluent to reach the desired concentration.

Limit of quantification: (for Olanzapine)

Preparation of 0.66µg/ml solution:

Once the 5 mg of olanzapine working standard has been accurately weighed and transferred into a 10 ml clean, dry volumetric flask, add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to make the volume up to the target with the same solvent. (Stock solution)

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

Pipette 4 ml of the aforementioned stock solution into a 10 ml volumetric flask and add diluent to get the desired concentration.

Pipette 1.22ml of the aforementioned stock solution into a volumetric flask with a 10ml capacity, then add diluent to the mark.

Procedure for LOD and LOQ:

The LOD and LOQ solutions was prepared injected, for three times and measured the area for all three injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Table 7: LOD Results of Olanzapine and Samidorphan

S.NO.	Peak name	RT	Area	Height	% Area	USP Resolution	USP Tailing	USP Plate Count
1	**Olanzapine**	3.106	2639.3	14208	32.40		1.18	2090.31
2	**Samidorphan**	4.248	2361.5	23642	67.60	3.77	1.13	2589.80

Table 8: LOQ Results of Olanzapine and Samidorphan

S.NO.	Peak name	RT	Area	Height	% Area	USP Resolution	USP Tailing	USP Plate Count
1	**Olanzapine**	3.106	154749	14208	32.40		1.78	2090.31
2	**Samidorphan**	4.248	322905	23642	67.60	3.77	1.63	2589.80

Robustness

In the robustness investigation of the currently proposed approach, a number of optimized parameters, including the mobile phase flow rate, the organic composition of the mobile phase, and the optimum conditions' detection wavelength, were purposely changed at a low level. The flow rate was modified by a factor of 0.1, and the organic component was changed to 10%. The tailing factor and theoretical plate were considered in order to observe the resilience. The % relative standard deviation of the parameters was calculated, and it shouldn't be greater than 2.

Table 9: Robustness results for Samidorphan(Changes in flow rate)

S. No	Flow Rate (ml/min)	System Suitability Results	
		USP Plate Count	USP Tailing
1	0.9	2452	1.12
2	1.0	2718.66	1.64
3	1.1	22	1.22

Table 10: Robustness results for Olanzapine(Changes in flow rate)

S. No	Flow Rate (ml/min)	System Suitability Results	
		USP Plate Count	USP Tailing
1	0.9	2025.5	1.18
2	1.0	3961.26	1.15
3	1.1	2644.17	1.13

* Results for actual flow (1.0ml/min) have been considered from Assay standard.

Table 11: Robustness results for Olanzapine (Change in composition of mobile phase)

S. No	Change in Organic Composition in the Mobile Phase	System Suitability Results	
		USP Plate Count	USP Tailing
1	10% less	2025	1.18
2	*Actual	3961.26	1.15
3	10% more	3644	1.10

Table 12: Robustness results for Samidorphan(Change in composition of mobile phase)

S. No	Change in Organic Composition in the Mobile Phase	System Suitability Results	
		USP Plate Count	USP Tailing
1	10% less	2452	1.10
2	*Actual	2718.66	1.64
3	10% more	2055.73	1.13

*Results for actual Mobile phase composition (60:40 met: Buffer (ph-3) has been considered from Accuracy standard.

Forced degradation study

The ICH-recommended stress conditions of acidic, alkaline, oxidative, thermal, and photolytic stress were used in a force degradation experiment on the current sample solution.

Three repetitions for each type of degradation study were done, and the mean peak area was taken into account for computing the results.

Preparation of stock:

In a 10 ml clean, dry volumetric flask, accurately weigh and transfer 10 mg of samidorphan and 5 mg of olanzapine as the working standard. Add around 7 mL of diluent, sonicate to completely dissolve it, and then add enough diluent to put the volume up to the mark using the same solvent. (Stock solution)

Pipette 0.3 ml of the aforementioned stock solutions into a 10 ml volumetric flask and diluent until the desired concentration is reached.

Hydrolytic degradation under acidic condition

Pipette 3 ml of 0.1N HCl and 0.3 ml of the aforementioned solution into a 10 ml volumetric flask. The volumetric flask was then maintained at 60 °C for 6 hours, neutralized with 0.1 N NaOH, and diluted to 10 ml. Place the filtered solution in vials using 0.22 micron syringe filters.

Hydrolytic degradation under acidic condition

Pipette 3ml of 0.1N NaOH into a 10ml volumetric flask after adding 0.3ml of the aforementioned solution. The volumetric flask was then maintained at 60°C for 6 hours, neutralized with 0.1N HCl, and diluted to a final volume of 10ml. Place the filtered solution in vials using 0.22 micron syringe filters.

Thermal induced degradation

A sample of samidorphan and olanzapine was collected in a petridish and heated to 1100 C for 24 hours. Following sample collection and dilution with diluents, the HPLC was used to analyse the material.

Oxidative degradation

Pipette 0.3 ml of the stock solution into a 10 ml volumetric flask. Then, add 1 ml of hydrogen peroxide, 3% w/v, to the flask . The volume was then brought up to the required level with diluent. After that, for 15 minutes, the volumetric flask was left at room temperature. Place the filtered solution in vials using 0.45 micron syringe filters.

Photo degradation:

Pipette 0.3 ml of the stock solution into a 10 ml volumetric flask, expose it to sunlight for 24 hours, and then add diluent to the volume until it reaches the desired level. Place the filtered solution in vials using 0.45 micron syringe filters.

Table 12: Stability study results

Sample Name	Samidorphan		Olanzapine	
	Area	Area	% Degraded	% Degraded
Standard	346468.0	171146.0		
Acid	325453	155289	9.27	6.07
Base	327849	157420	8.02	5.37
Peroxide	325131	163076	4.72	6.16
Thermal	328347	163704	4.35	5.23
Photo	329359	156820	8.37	4.94

DISCUSSION:

Olanzapine and Samidorphan standard solutions in mobile phase (10µg/ml) were each individually scanned at a range of wavelengths from 200 nm to 400 nm. Olanzapine and Samidorphan were discovered to have a maximum absorption at 220 nm. As a result, the present investigation used 220nm as the maximum absorbance of samidorphan and olanzapine. Olanzapine and Samidorphan's calibration curves were discovered to be linear in the 5–25 µg/mland 10–50 µg/mlranges at 220 nm. It was evident that Olanzapine and Samidorphan might be identified in single component pharmaceutical items without the intervention of any extraneous element. The employed method was initially tested on synthetic samples of bulk pharmaceuticals, and concentrations were estimated.

Three levels of Olanzapine and Samidorphan standard concentrations—50%, 100%, and 150%—were used to determine the percentage recovery. For each recovery level, three samples were created. Following an analysis of the solutions, it was discovered that the percentage recoveries were adequate and within the permitted ranges as stated in the label claim for the commercially available tablet dosage form. According to the ICH recommendations and the method validation criteria, the recently designed technique was validated.

A number of technique validation factors, including specificity, accuracy, precision, linearity, range, limit of detection and limit of quantification, robustness, and ruggedness, were applied to the developed method.

CONCLUSION:

Based on empirical evidence, it was discovered that Olanzapine and Samidorphan could be detected simultaneously using RP-HPLC. The unique method was found to be in every way superior to the previously mentioned methods. All of the examined APIs were found to be relevant and resolute under ideal conditions for simultaneous examination in bulk form and approved dosage form.

Compliance and Ethical Standards

Ethical Approval: NA

Funding details: NA

Conflict of interest: No

Informed consent: NA

Author’s Contribution:

Each author contributed to the conception, design and execution of the study and also agreed to submit to the current journal.

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