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RESEARCH

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A validated RP-UPLC method for estimation of Samidorphan and Olanzapine in mixed powder and combined tablets

Krishnaphanisri Ponnekanti[1,3*] and Ramreddy Godela[2]

Abstract

Back ground The key objective of the research study is to develop a new stability-indicating RP-UPLC approach to determine the presence of Samidorphan and Olanzapine simultaneously in bulk and their combination. A successful separation of Samidorphan and Olanzapine was achieved by using HSS column C18 (100 × 2.1 mm), a mobile phase of 0.1% orthophospharic acid: Acetonitrile (70:30 v/v), flow rate of 0.3 mL/min, and detection wavelength of 230 nm. The stability of the analytes in bulk and dosage forms was evaluated using extreme forced conditions, such as hydrolysis with acid and base, peroxide oxidation, and heat degradation, following ICH guidelines.

Results Olanzapine and Samidorphan had retention times of 0.46 and 0.93 min, respectively. Olanzapine and Samidorphan have linear responses from the proposed method in the concentration ranges of 5–30 µg/mL and 2.5–15 µg/mL, respectively. The computed detection and quantification limits for Olanzapine were 0.22 µg/mL and 0.471 µg/mL, and for Samidorphan were 0.12 µg/mL and 0.36 µg/mL. All method validation parameters have complied with the ICH guidelines' Q2 acceptance limits. The stability representing the feature of the approach has been seen with the excellent resolution among the Olanzapine and Samidorphan and degradation products.

Conclusion The suggested RP-UPLC method was extremely sensitive, precise, and stable-indicating. The technique can potentially be used in the production of Olanzapine and Samidorphan for routine analysis in the quality control department.

Keywords Olanzapine, Samidorphan, Stability representing, Simultaneous analysis, HSS C18

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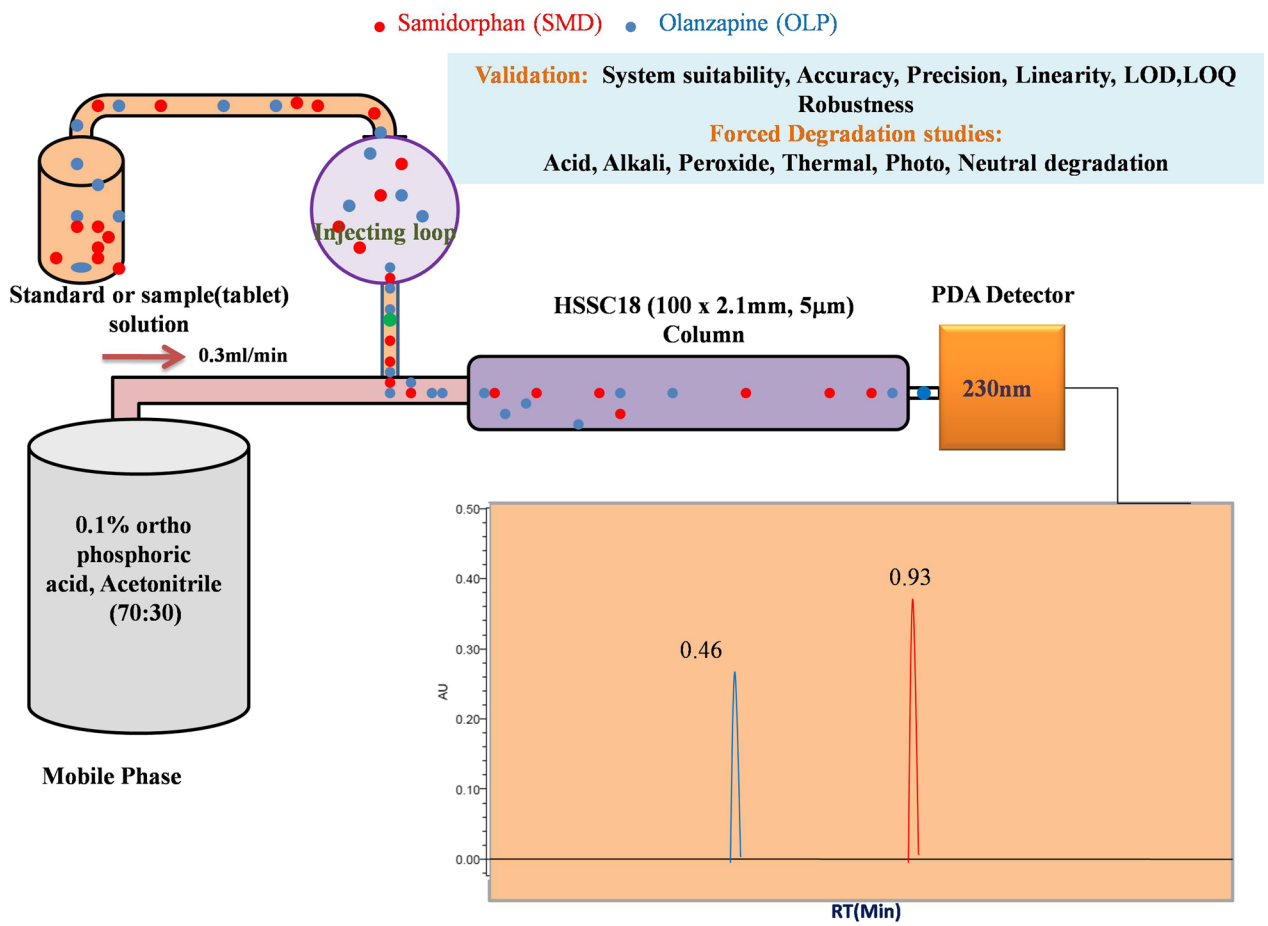
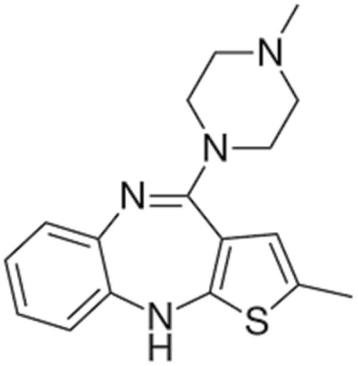
Graphical abstract



Background

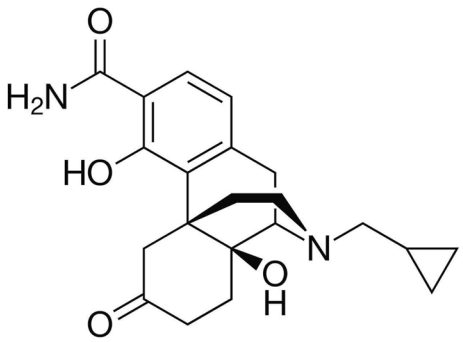
Schizophrenia is a devastating psychological disorder indicated by symptoms including confusion, hallucinations, delusions, unorganized thoughts, and lack of interest or motivation [1]. Bipolar disorder (BD) is a chronic mood disorder and mental health condition that produces abrupt changes in mood, energy levels, thought processes, and behavior. These shifts interfere with your ability to complete daily duties and can persist for a few minutes or several days, weeks, or even months [1–3]. Effective medication, treatment, and behavioral therapies are necessary to reduce the symptoms of both schizophrenia and BD, enhance social functioning and quality of life, increase the likelihood of recovery, and provide more favorable long-term results [3–5]. Recently, FDA approved a combination of Samidorphan and Olanzapine (SMD/OLP) for the treatment of both schizophrenia and BD [6]. OLP is a second-generation atypical anti-psychotic agent that antagonizes the dopamine D2 receptors and 5HT2A receptors to regulate the dopamine and serotonin levels in postsynaptic receptors and the frontal cortex, respectively [7]. SMD is a new opioid moiety acting as an µ-opioid receptor antagonist [8]. OLP is a chemical derivative of thienobenzodiazepine with molecular formula of $C_{17}H_{20}N_4S$ (Fig. 1) [9]. SMD is an opioid antagonist chemical structure similar to Naltrexone with the molecular formula of $C_{21}H_{26}N_2O_4$ (Fig. 1) [10].

Identifying and quantifying the intended analyte and other impurities in both drug substance and drug product is essential before commercialization [11]. A competent liquid chromatographic method should be required to analyze the drug moieties [12]. Many analytical procedures were available in the literature for the analysis of SMD and OLP as a single moiety or in a mixture with other pharmaceutical moieties [13–16]. Few HPLC and LC–MS methods were reported for concurrent analysis



Olanzapine

2-methyl-4-(4-methylpiperazin-1-yl)-10*H*-thieno[2,3-b][1,5]benzodiazepine



Samidorphan

17-(Cyclopropylmethyl)-4,14-dihydroxy-6-oxomorphinan-3-carboxamide

Fig. 1 Molecular structures of OLP and SMD

of SMD and OLP in blended powder and combined dosage form [17–20]. HPLC and UPLC are the prominent methods for the analysis of drug moiety during the synthesis of drugs and manufacturing of drug products in the quality control section of Pharmaceutical industries [12]. The reported HPLC possessed drawbacks, including longer retention time, lesser sensitivity, and uneconomical solvent systems [18–20]. All these drawbacks need to be ensuring the competence of the methods. Moreover, forced degradation studies are an integral aspect of ensuring the stability-indicating property of the LC method. UPLC method has more advanced features than HPLC in improved resolution, shorter elution time, and higher sensitivity. Hence, the present research work was focused on developing a new RP-UPLC method for the determination of SMD and OLP in bulk and formulation.

Methods

The API powders of SMD and OLP were obtained as gift samples from Rainbow labs, Hyderabad. The required solvents and chemicals used for the present research study were procured from SD fine chemicals, India.

Chromatographic conditions

In the development of the suggested procedure, a Waters UPLC system equipped with a PDA detector was used. SMD and OLP were separated with excellent resolution by using an HSS C18 column in combination with a mobile phase consisting of 0.1% v/v orthophosphoric acid in water and Acetonitrile (70:30 v/v). A flow rate of 0.3 mL/min of the mobile phase was injected into the column, and a wavelength of 230 nm was employed to identify the SMD and OLP that were eluted from the column. In the process of preparing the standard and sample solutions, water and acetonitrile were mixed at a ratio of 50:50 was used as diluent. Table 1 contains an explanation of the chromatographic conditions that led to the best results.

Stock solution preparation

The stock solution was prepared by transferring API powders of OLP (20 mg) and SMD (10 mg) into a volumetric flask, measuring 100 mL to produce 200 µg/mL and 100 µg/mL of OLP and SMD, respectively.

Standard solution preparation

Transfer 1 mL of the mentioned stock solution to a volumetric flask of 10 mL capacity. Make up the volume with diluent to produce a solution of 20 µg/mL and 10 µg/mL of OLP and SMD, which was referred to be 100% level solution. The prepared standard solution was used in method development and validation of system suitability and precision of the developed method.

Table 1 Optimized chromatographic conditions of current method

Mobile Phase	0.1% OPA in water: Acetonitrile (70:30 v/v)
Column	HSS C18 (100 × 2.1 mm, 5 µm)
Flow Rate	0.3 mL/min
Temperature	Ambient
Volume	2µL
Wavelength	230 nm
Diluent	Water: Acetonitrile (50:50)
Retention time	Olanzapine – 0.46 min
	Samidorphan – 0.93 min

Preparation of sample solution

Tablet (LYBALVI) powder equivalent to 20 mg of 10 mg OLP and SMD was transferred into a volumetric flask of 100 mL. The remaining volume was made up with diluent in order to get solutions of 200 µg/mL and 100 µg/mL for OLP and SMD, respectively. 1 mL of the resultant solution was placed in a 10 mL volumetric flask, and the remaining volume was made up with a diluent to get 20 µg/ml for OLP and 10 µg/mL for OLP. The undissolved particulate matter was excluded by the use of 0.25 µm Nylon filters. The prepared sample solution was used to validate the specificity of the developed method and to determine the % assay of the commercially available combined dosage forms.

Method validation

The current method validation was ensured as per Q2 provisions of the ICH.

System suitability test

Six replicates of the standard solution of 20 µg/mL and 10 µg/mL of OLP and SMD were injected consecutively into the UPLC. The various system suitability parameters like percentage relative standard deviation (%RSD), USP plates (N), and USP tailing (T) were evaluated.

Linearity

The linearity represents direct proportionality between the method's peak areas and input concentrations. In the current method, linear graphs were generated for both OLP and SMD between concentrations and peak areas using concentrations ranging from 5 µg/mL to 30 µg/mL of OLP and 2.5 µg/mL to 15 µg/mL. The regression coefficient (r^2) values were assessed.

Precision

Usually, it will be measured in terms of system and method precision. The system precision was assessed in the same way as system suitability by analyzing six replicates of the standard solution of 20 µg/mL and 10 µg/mL of OLP and SMD. The method precision was confirmed by determining the %RSD value of assay of six replicate injections of sample solution.

Accuracy

The standard addition technique was employed to confirm the accuracy of the stated method. In this procedure, different level of standard solution (50,100 and 150%) was added to a known amount of sample solution (20 µg/mL and 10 µg/mL of OLP and SMD) individually. The amount of standard solution recovered from spiked solutions was computed in terms of mean % recovery. Each spiked solution was analyzed in triplicate.

Specificity

The specificity of the analytical technique is defined as the capacity of the method to identify the analyte under investigation in the presence of other compounds, such as degradants, impurities, and placebo, with no interference. The specificity of the current approach was ensured by injecting blank, placebo, standard, sample, and forced degradation solutions of OLP and SMD in a successive manner. Any interference among the RT of analytes(OLP and SMD), degradants, and placebo was observed.

Sensitivity

The sensitivity of the current procedure is assessed in terms of limit of detection (LOD) and limit of quantification (LOQ). The standard deviation procedure was adopted to assess the LOD and LOQ.

$LOD = 3\sigma/S$

$LOQ = 10\ \sigma/S$

Where σ is the standard deviation of the intercept ($n = 3$).

S is the average slope value of the linearity curve ($n = 3$).

Robustness

The robustness of the method was examined by slightly varying the optimal method parameters such as mobile phase ratio (± 1 mL), temperature (± 5°C), and flow rate (± 0.1 mL/min). The % RSD value of obtained peak areas by the altered method conditions was computed to confirm the robustness of the stated approach.

Forced degradation studies

In the forced degradation approach, drug material is purposefully subjected to more intense stress conditions than those for accelerated stability. These investigations were helpful in determining the drug substance's stability, which is a fundamental factor in creating a stable dosage form. The forced deterioration studies were carried out in accordance with ICH Q1A, QIB, and Q2B guidelines [21].

Acid and base hydrolysis

Equal portions of stock solution (200 µg/mL of OLP and 100 µg/mL of SMD) and 2N HCl were mixed uniformly and refluxed at 60° C for 30 min, further cooled to room temperature neutralized with 2N NaOH. The resultant solution was further diluted to obtain a concentration of 20 µg/mL and 10 µg/mL of OLP and SMD, correspondingly. The above solution was considered as acid degradation solution. Similarly, alkali or base degradation solution was prepared by replacing 2N HCl with 2N NaOH in the acid hydrolysis procedure. After 24 h, the prepared solutions were introduced into the UPLC system.

Oxidative degradation

Equal portions of stock solution (200 µg/mL of OLP and 100 µg/mL of SMD) and 10% H_2O_2 were mixed uniformly and refluxed at 60 °C for 30 min and further cooled to room temperature. The resultant solution was further diluted to obtain a concentration of 20 µg/mL and 10 µg/mL of OLP and SMD, correspondingly. After 24 h, the prepared solutions were introduced into UPLC system.

Thermal degradation

The standard stock solution (200 µg/mL of OLP and 100 µg/mL of SMD) was kept at 80 °C/75% RH for 24 h in the heating chamber. Further dilution of the resultant solution was done to make a solution consisting of 20 µg/mL of OLP and 10 µg/mL of SMD.

Photodegradation

The standard stock solution (200 µg/mL of OLP and 100 µg/mL of SMD) was placed in a UV chamber at 254 nm wavelength with dark control for 24 h. Further dilution of the resultant solution was done to make a solution consisting of 20 µg/mL of OLP and10µg/mL of SMD.

Neutral degradation

The standard stock solution (200 µg/mL of OLP and 100 µg/mL of SMD) was mixed with water (pH-7) and refluxed for 15 min at 60°C. Further dilution of the resultant solution was done to make a solution consisting of 20 µg/mL of OLP and10µg/mL of SMD. After 24 h, the prepared solution was used for analysis.

Assay of marketed tablets by the current method

The assay of the commercial tablets (LYBALVI) was performed by injecting both standard and sample solutions consecutively. The %purity of OLP and SMD was determined by computing the peak areas OLP and SMD of the standard and sample solution chromatograms [16].

Results

Method optimization

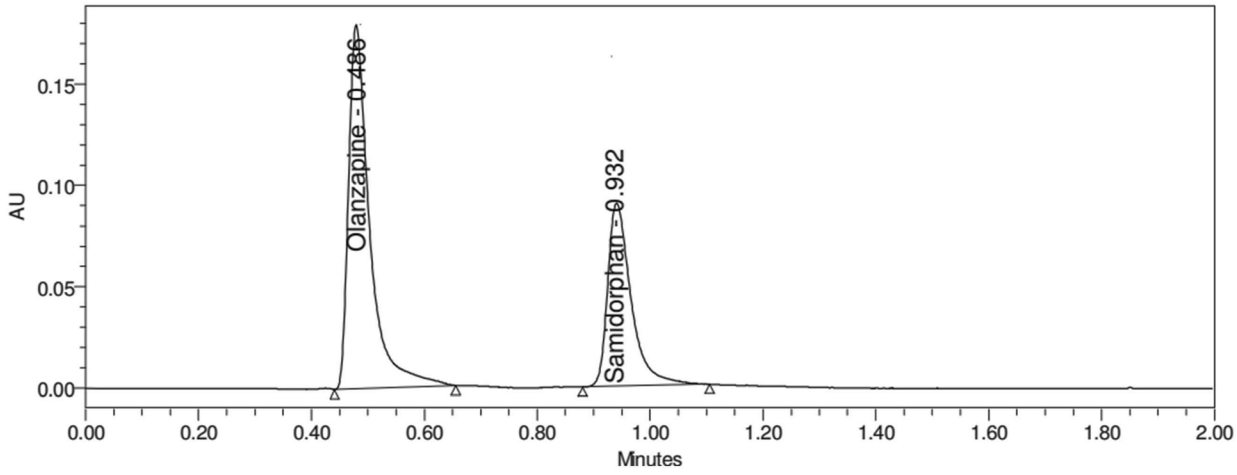
To achieve peaks in the chromatogram with appropriate tailing, resolution, and USP plates, the process was repeatedly tested using various solvent systems, ratios of solvent systems, and flow rates. At last, HSS C18 column and a mobile phase of 0.1% v/v OPA and Acetonitrile (70:30 v/v) were used to separate SMD and OLP with remarkable resolution. The earlier discussed optimum parameters were employed to validate the approach. Upon using above stated chromatographic conditions, OLP and SMD eluted at shorter retention times (RT) of 0.46 min and 0.93 min, correspondingly with proper resolution (Fig. 2).

Method validation

The indicators for system acceptability, such as % RSD, USP plates, and USP tailing values, were in line with ICH (Q2) acceptance window (Table 2). For the stated concentration ranges, the r^2 values for the OLP and SMD were determined to be 0.999 and 0.999, correspondingly (Fig. 3). Hence, the approach has a significant linear relation for the specified range of concentrations. The average % recovery of OLP and SMD in spike solutions of different levels was found in the range of 98.5 to 100.8% for both OLP and SMD, representing the accuracy of the approach (Table 3). In system and method precisions, the % RSD was assessed to be less than 2 (Table 4). The calculated results clearly demonstrate the method's accuracy. The robustness of the technique was strongly supported by the significantly created %RSD values in the ICH consideration limits (Table 5), which were achieved even when modest and intentional modifications in the control factors did not impair the method's performance. Results from other system suitability parameters, such as tailing and plate count, along with the %RSD, clearly supported the method's robustness.

Interference at RT of OLP and SMD could not be seen with the RT of blank, degradants, and placebo, unveiling the specificity of the method only toward OLP and SMD. The LOD and LOQ of OLP and SMD were observed to be 0.22 µg/mL, 0.47 µg/mL, and 0.12 µg/mL, 0.36 µg/mL in that order.

On comparing the peak regions obtained from the newly prepared standard solution with the FD solution, the % degradation of OLP and SMD was quantified. Table 6 shows OLP and SMD's peak purity and % degradation. The stability of analytes in neutral pH environments was proven by the minimal degradation of both analytes under these conditions. Due to a significant % of degradation as compared to other stress conditions, both OLP and SMD were susceptible to an acidic environment. OLP and SMD both showed very low percentages of degradation under the specified thermal and photodegradation conditions, highlighting that both OLP and SMD were highly stable. Therefore, it is claimed that the new approach is stability-indicating to evaluate the stability of API and dosage forms. The generated chromatograms of stressed samples are published in Fig. 4. The purity threshold value of each peak was more than the purity angle of the peak, which represents the peak purity of OLP, SMD, and degradants. The observed results of FD studies significantly show the stability-indicating character of the method.



Peak Name	RT	Area	USP Plate Count	USP Tailing	USP Resolution
Olanzapine	0.49	408799	2789	1.72	-
Samidorphan	0.93	249048	3335	1.57	6.7

Fig. 2 Optimized method chromatogram

Table 2 System suitability data of OLP and SMD in standard solution

Drug name (n = 6)	RT (Min)	Area		Tailing (T)	Plate Count (N)	Resolution ®
		*Mean ± SD	%RSD			
OLP	0.46	406,896 ± 5146.8	1.3	1.71	2770	-
SMD	0.93	243,259 ± 1474.5	0.6	0.15	3281	5.9

*mean of six replicates of standard solution

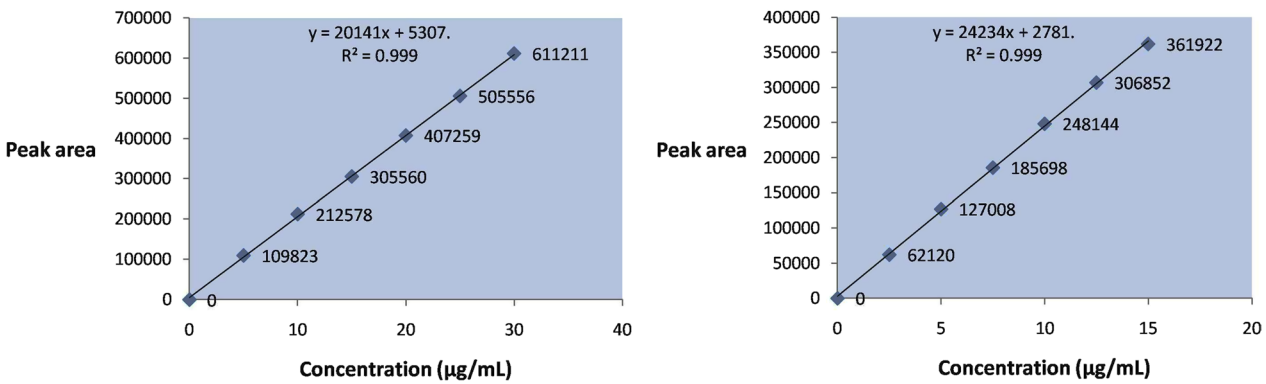


Fig. 3 Linearity results of OLP and SMD

Table 3 Percentage recovery results of OLP and SMP

Name of the drug	% Level of standard	*Amount spiked (µg/ml)	*Amount recovered (µg/ml)	% Recovery *(Mean ± SD)
OLP	50	10	9.9	99.0 ± 0.98
	100	20	19.7	98.5 ± 0.50
	150	30	29.83	99.43 ± 0.49
SMP	50	5	5.04	100.8 ± 0.74
	100	10	9.87	98.7 ± 0.16
	150	15	14.99	99.93 ± 0.63

* Mean of three replicates

Table 4 Precision of OLP and SMD

Name	Precision type	*Mean ± SD (n = 6)	% RSD	Acceptance limit
OLP	System precision	393,534 ± 2201.1	0.6	% RSD ≤ 2
	Method Precision	99.1 ± 0.74	0.75	
SMD	System precision	241,627 ± 646.1	0.26	
	Method Precision	98.6 ± 0.32	0.32	

*Mean of six replicates

Assay

The %purity of the OLP and SMD in commercial tablets (LYBALVI) was assessed to be 99.2 ± 0.28 and 98.24 ± 0.34, respectively (Table 7).

Discussion

In general, the stability indicating LC technique is crucial for both qualitative and quantitative drug confirmation. Only two HPLC techniques are now available, and they are only for the combination tablet form with a set dose of OLP and SMD. In the past approaches, one has the problem of a longer runtime and RT for SMD (7.7 min) [21]. In another method, the drawback in sensitivity (LOD and LOQ) was noticed for OLP (45 and 83 µg/mL) and SMD (27 and 42 µg/mL) [21]. The reported method assessed no degradant peaks by forced degradation studies [2]. To overcome such drawbacks and imperfections in the past approaches, research study was carried out to develop an RP-UPLC method with less RT, high sensitivity, and simple solvent composition. In the suggested approach, OLP and SMD were shown RT at 0.46 min and 0.93 min correspondingly, which reminds the shorter elution time with minimal runtime. A solvent phase of 0.1% OPA mixed with Acetonitrile in 70:30 v/v ratios with high sensitivity and shorter RT indicates the economic feature of the system. The current method can hasten the sample analysis time. The approach provides significant specificity for the analysis of OLP and SMD, according to the statistical data of the validation parameters. The LOD and LOQ of OLP (0.22 µg/mL and 0.47 µg/mL) and SMD (0.12 µg/mL, 0.36 µg/mL) outcomes were far better than the previously described method (18–20). Stability studies are the most crucial criterion for evaluating the quality of drug ingredients and drug products. The method's feasibility to judge the stability of OLP and SMD is demonstrated

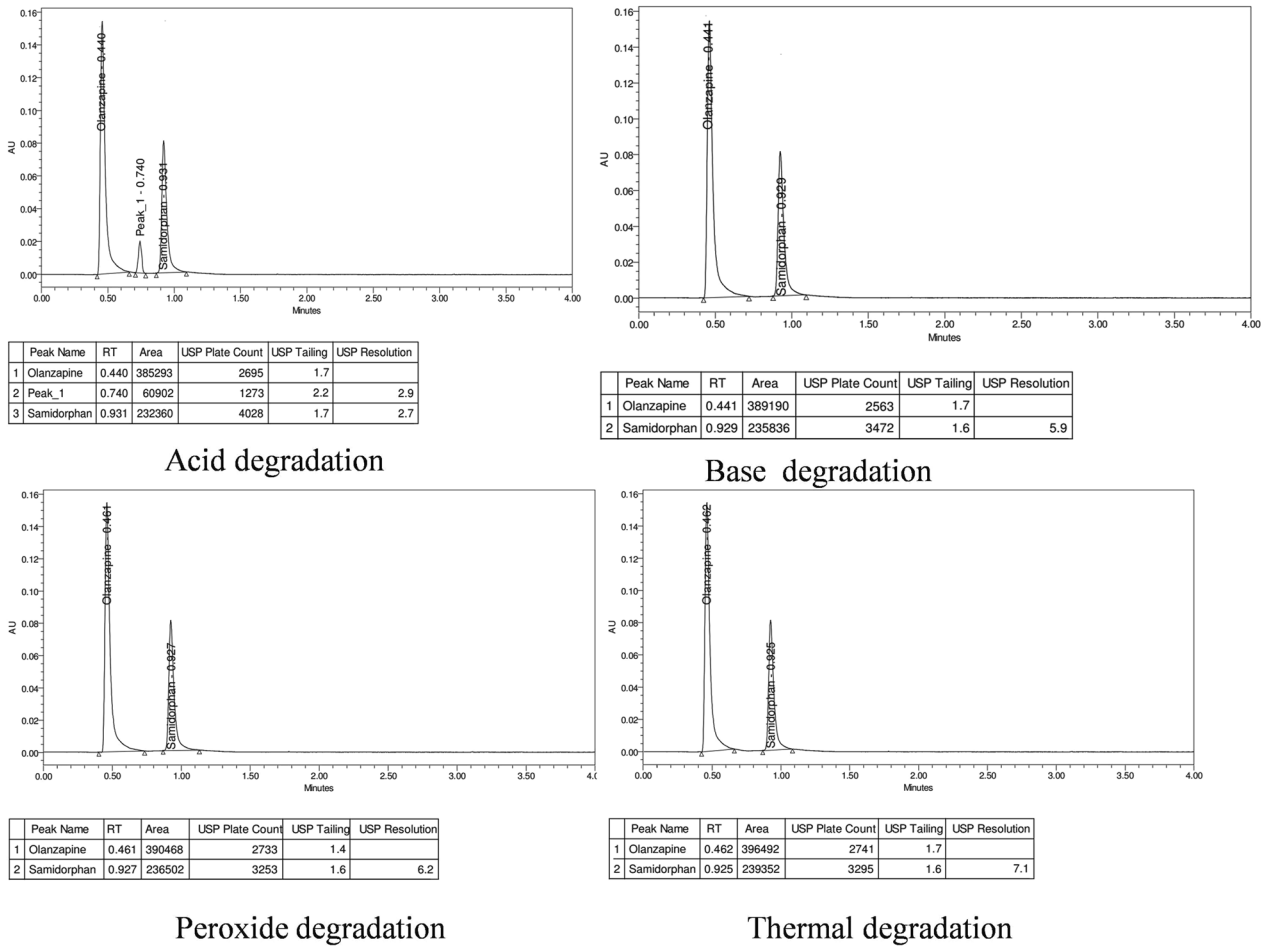
Table 5 P Results of robustness of OLP and SMD

Parameter	Variation	OLP				SMD			
		Peak Area *(Mean ± SD)	% RSD	Plate Count	Tailing	Peak Area *(Mean ± SD)	% RSD	Plate Count	Tailing
Mobile phase (± 1 mL)	71:29	626,632 ± 4266.0	0.7	2787	1.73	260,172 ± 1968.9	0.8	3435	1.57
	69:31	401,774 ± 1345.3	0.3	2612	1.74	242,845 ± 760.9	0.3	3302	1.66
Temperature (± 5ºC)	25 °C	315,006 ± 346.3	0.1	2691	1.71	195,916 ± 534.7	0.3	3283	1.63
	35 °C	343,675 ± 2069.0	0.6	2659	1.75	211,199 ± 1182.7	0.6	3039	1.59
Flow rate (± 0.1 mL/min)	0.2	323,962 ± 1868.4	0.6	2710	1.68	204,923 ± 843.0	0.4	3372	1.65
	0.4	285,488 ± 661.6	0.2	2602	1.75	181,521 ± 359.1	0.2	3231	1.53

*Average of six replicates of standard solution

Table 6 % Degradation of OLP and SMD at different forced degradation conditions

Stress Degradation	% Degradation	
	OLP	SMD
Acidic degradation	5.11	5.48
Alkali degradation	4.55	4.07
Oxidative degradation	3.84	3.80
Thermal degradation	2.35	2.64
Photo degradation	1.62	1.83
Neutral degradation	0.01	0.09



	Peak Name	RT	Area	USP Plate Count	USP Tailing	USP Resolution
1	Olanzapine	0.440	385293	2695	1.7	
2	Peak_1	0.740	60902	1273	2.2	2.9
3	Samidorphan	0.931	232360	4028	1.7	2.7

	Peak Name	RT	Area	USP Plate Count	USP Tailing	USP Resolution
1	Olanzapine	0.441	389190	2563	1.7	
2	Samidorphan	0.929	235836	3472	1.6	5.9

	Peak Name	RT	Area	USP Plate Count	USP Tailing	USP Resolution
1	Olanzapine	0.461	390468	2733	1.4	
2	Samidorphan	0.927	236502	3253	1.6	6.2

	Peak Name	RT	Area	USP Plate Count	USP Tailing	USP Resolution
1	Olanzapine	0.462	396492	2741	1.7	
2	Samidorphan	0.925	239352	3295	1.6	7.1

Fig. 4 Various degradation studies chromatograms of OLP and SMD

Table 7 % Assay of marketed tablets

Drug	Chromatogram name	RT	Area	*% Assay ± SD	%RSD
OLP	Standard	0.464	408,647	99.2 ± 0.28	0.28
	Test	0.487	406,214		
SMD	Standard	0.926	242,900	98.24 ± 0.24	0.24
	Test	0.936	246,981		

Average weight of tablet −40.1 mg, Label claim: OLP—20 mg, SMD—10 mg

* Mean of six measurements

by the measurement of OLP and SMD deterioration after subjecting them to different stress situations. The two analytes were highly susceptible to acid and alkali environments, highly stable in neutral environments. The stated results representing the stability indicating nature of the method. It is an improvement over earlier methods that have been developed.

Conclusion

A cost-effective, precise, and competent RP-UPLC approach with better sensitivity with short run time was developed for the analysis of OLP and SMD in mixed powder form and their fixed dose combined tablets. The study of OLP and SMD under various forced conditions ensures the stability representing the quality of the approach. The stated technique competently separated OLP and SMD and possible degradants produced by OLP and SMD with superior resolution. Hence, the developed UPLC approach can be feasible in the pharmaceutical quality control department.

Abbreviations

BD	Bipolar disorder
SMD	Samidorphan
OLP	Olanzapine
RT	Retention time
LOD	Limit of detection
LOQ	Limit of quantification
ICH	International conference on harmonisation of technical requirements

for registration of pharmaceuticals for human use
SD Standard deviation
RSD Relative standard deviation

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Author contributions
KP and RG contributed equally in design of the work, acquisition and interpretation of data, and manuscript preparation. All authors have read and approved the manuscript.

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Availability of data and materials
All data and material should be available upon request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that there is no conflict of interest.

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