



Stability Indicating Methodology Development to Quantify Odevixibat Content: Application of LC-MS Methodology to Characterize Five Degradants of Odevixibat

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This investigation is concerned with development of HPLC technique that made use of a PDA sensor technology for the speedy assessment of odevixibat (OVBT) for the quality control of both their commercially marketed formulations as well as bulk form. The ODS inertsil column (4.6 mm, 5 μ m, 250 mm), mobile phase set up by mixing 0.1% formic acid and acetonitrile in a 60:40 volumes, rate of flow of 1.0 mL/min and with detection using PDA at 223.7 nm was adopted for present procedure. Applying ICH specifications, the HPLC-based OVBT assay strategy was validated successfully for linearity (5.00 to 30.00 μ g/mL), sensitivity (LOD-0.60 μ g/mL; LOQ-2.00 μ g/mL), precision (0.207-0.600% RSD), accuracy (98.9-100.8% assay) and robustness (0.53-1.16% RSD). Numerous stress degradations [acid, alkaline, reduction, oxidation, thermal, hydrolysis and photolytic] have been applied to odevixibat. The odevixibat is reported to be prone to instability in oxidative stress and more persistent during photo stress. The HPLC-based odevixibat assay approach could be implemented in quality assurance labs for the quantitative measurement of odevixibat in routine and stability sample analysis of odevixibat bulk and odevixibat capsule doses. Five degradants [OVBT-DP1 (acid stress), OVBT-DP2 (alkali stress), OVBT-DP3 (oxidative stress), OVBT-DP4 (reduction stress) and OVBT-DP5 (heat stress)] were formed. By evaluating mass spectral data of five degradants obtained through LC-MS approach, chemical structures of OVBT-DP1, OVBT-DP2, OVBT-DP3, OVBT-DP4 and OVBT-DP5 were elucidated. The degradation possible mechanisms for all the five degradants formation are also suggested.

Keywords: Odevixibat, Quality control, HPLC, Stress degradation, LC-MS, Degradants, Characterization.

INTRODUCTION

Odevixibat (OVBT) is a reversible suppressor of sodium/bile acid co-transporter [1] and used is an oral medical therapy which redirects bile acids from the liver. In July 2021, the European Union approved odevixibat for the medical management of progressive familial intrahepatic cholestasis in children who were 6-months aged and in August 2021, the USA approved odevixibat for the therapy of pruritus in progressive familial intrahepatic cholestasis children who were 3-months aged [2,3]. Odevixibat successfully decreased pruritus and also serum bile acids in kids with progressive familial intrahepatic cholestasis and odevixibat seemed generally tolerated satisfactorily in them [4].

Pharmaceutical preparations and bulk pharmaceuticals both benefit greatly from pharmaceutical analysis, which makes

it necessary for assurance of quality and quality management [5,6]. Pharmaceutical analysis encompasses separating, identifying and estimating the relative quantities of the sample's components. Human health underwent a revolution as a consequence of the discovery and development of several novel drugs. These medications are only going to fulfill their purpose if they were provided in the right quantity and were free of contaminants [6]. Different chemical together with instrumental techniques that are used in drug assessment have all been developed over time in order to make medications function as intended [7,8]. These medications need to be identified and quantitated since impurities can form in them at different points during production, transit and storage, making treatment dangerous [9,10]. Analytical tools and methodologies are crucial in this regard. In order to more efficiently understand how different molecules function within intricate combinations of

molecules found in chemical and biological systems, HPLC is utilized [11,12]. To ensure that every one of the components are determined in liquid chromatography, choosing the right kind of detection method is crucial. When a PDA is employed, a wavelength range may be programmed, allowing for the identification of every substance that absorb around this range in a single assessment [13,14].

Ahmed *et al.* [15] devised an HPLC method that utilized a UV sensor for determining odevixibat in pharmaceutical formulations and pure form. The approach developed by Ahmed *et al.* [15], however, fails to include reporting on peak purity while stability investigations and on the characterization of degradants.

The development of an HPLC technique that made use of a PDA sensor technology for the speedy assessment of odevixibat for the quality control of both their commercially marketed formulations as well as bulk form was one of the key focuses of the research. Numerous stress circumstances (acid, alkaline, reduction, oxidation, thermal, hydrolysis and photolytic) have been applied to investigate the forced degradation of HPLC-based odevixibat assay. Utilizing LC-MS, the degradation products generated pursuant to stress circumstances were characterized and a possible mechanism for their development was also put forward.

EXPERIMENTAL

Reference sample drugs and formulations: Odevixibat was supplied by Cadila Healthcare Ltd. (Ahmedabad, India). In this study, Bylvay capsules with 400 µg per capsule label from Alberto AB (Sweden) were utilized. The solvent, acetonitrile (chromatography grade), while the other analytical grade chemicals *viz.* disodium hydrogen phosphate, hydrochloric acid, sodium hydroxide, hydrogen peroxide were procured from Sd chemicals Ltd., India). The distilled water (chromatography, Milli Q, India) was used in this study analysis.

Configuration of chromatography for odevixibat assay: The HPLC type e-2695 series (Water Alliance) with PDA based detector (Water Alliance) was used to accomplish the odevixibat assay determination. The ODS inertsil column (4.6 mm, 5 µm, 250 mm,) was adopted to implement the current procedure. The mobile phase was set up by mixing 0.1% formic acid and acetonitrile in a 60:40 volumes ratio exactly with a average rate of flow of 1.0 mL/min, with detection using PDA at 223.7 nm at room condition temperature and injecting volume equal to 10 µL. After being degassed, the mobile phase prepared underwent filtering making use of 0.45 µ membrane filter paper.

Configuration of mass spectrometer: Xevo TQ-XS (Waters Alliance) triple quadrupole mass spectrometer was used to accomplish the degradants characterization. The positive ion ionization electrospray interfacing approach was put to use to regulate the mass spectrometer. The investigation of odevixibat degradation has been accomplished adopting the multiple reactions monitoring technique. Following are the operational parameters: 14 V and 5500 V of collision voltage energy and ion spray voltage, respectively; 550 and 120-250 °C of source and drying gas temperatures, respectively; nitrogen as collision gas with 5 mL/min flow stream; 40 V, 10 V and 7 V of potential

at decluster, entrance and exit, respectively; and dwell period of 1.0 s.

Odevixibat solutions: An amount of odevixibat standard equal to 20 mg/100 mL of acetonitrile was dissolved to obtain stock odevixibat solution. The stock odevixibat solution was serially gradient diluted using acetonitrile to produce the standard odevixibat solution, which contained the subsequent concentrations: 5.00, 10.00, 15.00, 20.00, 25.00 and 30.00 µg/mL, in order to make up the calibration odevixibat curve.

Calibration odevixibat curve: By evaluating standard odevixibat solutions with six different odevixibat concentrations, calibration graphs for odevixibat were established. Peak area of odevixibat was sketched on the Y-axis while odevixibat theoretical concentration was plotted over the X-axis to get a calibration odevixibat curve. The slope, intercept, correlation and regression model equation for odevixibat was derived.

Analysis of odevixibat in Bylvay capsules: Ten Bylvay (200 µg) capsules were emptied for odevixibat analysis. The capsule material, equivalent to 10 mg of odevixibat, was dissolved in 50 mL volumetric flask containing acetonitrile. After placing them in the sonicator for 15 min, the contents went through filtering *via* 0.45 µ membrane filter paper into dry flasks and filled up with acetonitrile to an exact amount of 50 mL. Aliquots of the above-mentioned Bylvay capsule solution were diluted with acetonitrile for generating Test Bylvay capsule solutions, resulting in odevixibat concentrations of 20 µg/mL and subsequently 10 µL test Bylvay capsule solution injected and analyzed HPLC-based odevixibat assay.

Stability studies: Numerous stress degradations (acid, alkaline, reduction, oxidation, thermal, hydrolysis and photolytic) have been applied to investigate the stability of odevixibat [16].

Acid degradation: Bylvay capsule content was precisely weighed at 67 mg (equal to 200 µg of odevixibat) into a 10 mL volumetric glass flask, to which 5 mL of acetonitrile was added and the mixture was subsequently sonicated for 20 min. The 1 mL of 1 N HCl was added and then left for 15 min. After 15 min, neutralized the solution through 1 mL of 1 N NaOH addition before diluting the solution to volume (10 mL) with acetonitrile and then mixed. In order to analyze the quantities of odevixibat in this solution while its acid degradation products were present, the solution was assessed through the HPLC-based odevixibat assay.

Alkaline degradation: In this assay, Bylvay capsule content (67 mg, equivalent to 200 µg of odevixibat) with 5 mL of acetonitrile and sonicated for 20 min in a 10 mL volumetric glass flask. The 1 mL of 1 N NaOH was added and then left for 15 min. After 15 min, the solution was neutralized using 1 mL of 1 N HCl addition before diluting the solution with acetonitrile. The components in volumetric glass flask were thoroughly shaken before being evaluated for odevixibat remove.

Peroxide degradation: For this analysis, the Bylvay capsule content (67 mg, equivalent to 200 µg of odevixibat) was freshly dissolved employing 5 mL of acetonitrile and sonicated for 20 min. This solution was oxidized with 1 mL of 10% H₂O₂ before being set aside for 15 min and then the mixture was adequately diluted with acetonitrile.

Reduction degradation: Bylvay capsule content was accurately weighed at 67 mg (200 µg of odevixibat) into a 10 mL volumetric glass flask, to which 5 mL of acetonitrile was added and then the mixture was sonicated for 20 min. Now, 1 mL of 10% sodium bisulphite was added and left aside for 15 min and then diluted the solution with acetonitrile and shaken the solution well.

Hydrolytic degradation: By mixing Bylvay capsule content (67 mg, equivalent to 200 µg of odevixibat) with 5 mL of acetonitrile, the solution was sonicated for 20 min and then 1 mL of HPLC water was added and waited for 15 min. After 15 min, the solution was diluted with acetonitrile.

Thermal degradation-procedure: The Bylvay capsule's contents (67 mg) were exposed for a duration of 6 h in oven at 105 °C and then mixed with 5 mL of acetonitrile and finally sonicated for 20 min. After that make up with acetonitrile to the mark (10 mL).

Photolytic degradation: The Bylvay capsule's contents (67 mg or 200 g of odevixibat) were exposed for a duration of 6 h in sun light and then mixed with acetonitrile and sonicated for 20 min. After that make up with acetonitrile to the mark (10 mL).

RESULTS AND DISCUSSION

HPLC-based odevixibat assay optimization: The 200–400 nm range of wavelength was investigated to establish the odevixibat UV spectral characteristics. Two peaks (one at 223.7 nm and another at 292.4 nm) were observed after a quick scan at this spectrum (Fig. 1). The sensitivity and peak area of odevixibat were optimal at 223.7 nm, as a result, the same method was chosen for the odevixibat analysis.

The trail experimentations to optimize mobile phase for HPLC-based odevixibat assay were conducted using the ODS inertsil column (4.6 mm, 5 µm, 250 mm) with an average rate of flow of 1.0 mL/min, with detection using PDA at 223.7 nm at room condition temperature and injecting volume equal to 10 µL. When mobile phase was set up by mixing 0.1% phosphoric acid and acetonitrile in a 20:80 volumes ratio, good peak for odevixibat was obtained, but column efficiency was least (159 plate counts). Same combination (0.1% phosphoric acid + acetonitrile) in 40:60 volumes ratio produced unacceptable odevixibat peak shape. Same combination (0.1% phosphoric acid + acetonitrile) in equal volumes ratio also produced unacceptable odevixibat peak shape with broadening effect. Now, 0.1% formic acid was implemented as buffer instead of 0.1% phosphoric acid. The base line disturbance became apparent when the mobile phase was made up by combining 0.1% formic acid and acetonitrile in 50:50 volume ratios and 70:30 volume ratios, respectively. The 0.1% formic acid and acetonitrile in a 60:40 volume ratio combination were obtained in a well-mannered peak shape (tailing factor – 1.01), better sensitivity (peak area – 2518100), acceptable column efficiency (plate count – 6671) and with reasonable elution time (3.580 min) was obtained (Fig. 2).

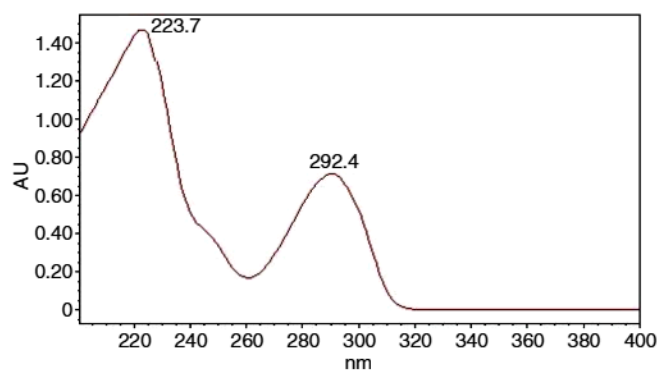


Fig. 1. UV spectrum of odevixibat

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Validation: Applying ICH specifications, the HPLC based odevixibat assay strategy was validated [17].

System suitability: Six evaluations of the working odevixibat solution (20 µg/mL) were performed utilizing the HPLC-based odevixibat assay strategy. To demonstrate that the system as a whole worked well, the peak symmetry, the plate counts and the elution times were determined as system suitability

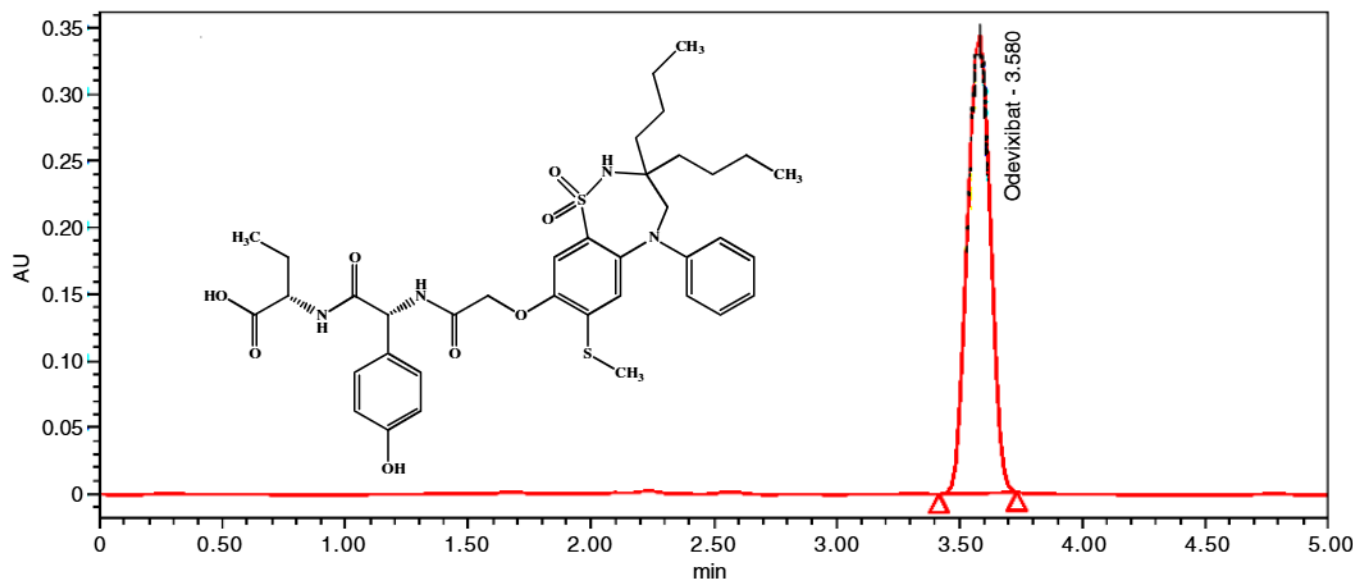


Fig. 2. HPLC chromatogram of odevixibat

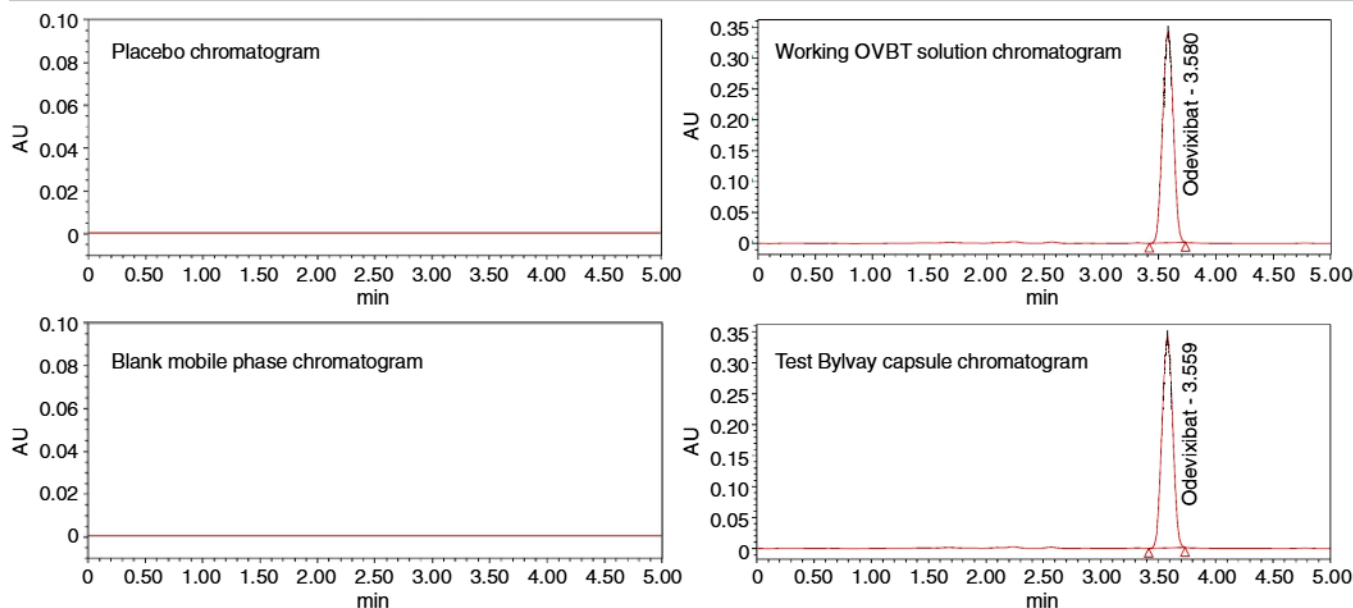


Fig. 3. Chromatograms for HPLC-based odevixibat assay for selectivity

metrics. According to Table-1, the collected data remained within the allowed constraints.

Sample	Plate count	Tailing factor	Elution time
OVBT 1	6675.0	1.01	3.580
OVBT 2	6684.0	1.02	3.584
OVBT 3	6657.0	1.04	3.582
OVBT 4	6672.0	1.02	3.588
OVBT 5	6663.0	1.05	3.587
OVBT 6	6624.0	1.04	3.581
Mean	6662.5	1.03	3.584
SD/RSD	21.0784/0.3164	0.0155/1.5041	0.0033/0.0911

Selectivity: By analyzing the working odevixibat solution (20 µg/mL), the placebo, the test Bylvay capsule solution (20 µg/mL) and the blank mobile phase and selectivity of the HPLC-based odevixibat assay was attained. The positive results (Fig. 3) obtained from employing the HPLC assay approach on the analyzed solutions indicate that the presence of additives in capsules and components in the mobile phase does not have any impact on the odevixibat evaluation.

Linearity: The linearity of the HPLC assay was assessed by measuring the peak area of different concentrations (5.00, 10.00, 15.00, 20.00, 25.00 and 30.00 µg/mL) of odevixibat under optimal conditions. Calibration curves were then developed to establish the relationship between the peak area and the corresponding quantities of odevixibat. The calibration curve (Fig. 4) demonstrated an acceptable connection over the concentration range of 5.00 to 30.00 µg/mL for odevixibat.

Sensitivity: The detection limit and quantification limit for odevixibat were calculated by applying ICH specifications (SD of odevixibat response/slope of odevixibat linearity curve $\times 3.3$ formula for detection limit and SD of odevixibat response/slope of odevixibat $\times 10$ formula for quantification limit). The detection limit and quantification limit were 0.60 µg/mL and

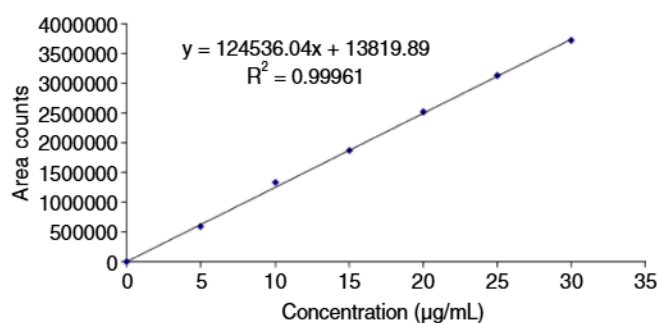


Fig. 4. Linearity curve of odevixibat

2.00 µg/mL, respectively for odevixibat, which illustrated the satisfactory sensitivity for HPLC assay.

Precision: Six assay assessments were executed on working odevixibat solution (20 µg/mL, for system precision) and odevixibat spiked Bylvay capsule solution (20 µg/mL, for method precision) on the exact same day with one operator and also on an alternate day (for intermediate precision) by another operator on distinct apparatus employing the HPLC assay. Table-2 displays the outcomes for precision that have been generated. The RSD values of precision for the system, method and intermediate were 0.207%, 0.600% and 0.440%, respectively. The relative standard deviation (RSD) values for all precisions were found to be below the pre-determined limit ($> 2\%$), which demonstrates the exceptional precision of the HPLC analysis.

Accuracy: The standard odevixibat was added to a Bylvay capsule solution in triplicate at concentration spiking extents of 50%, 100% as well as 150%. An evaluation of the average recovery of three levels is presented in Table-3. The average recovery for odevixibat was 99.8%, which falls within the generally acceptable accuracy limit.

Robustness: Three samples of Bylvay capsule solutions containing odevixibat (20 µg/mL) were injected while the flow rate and acetonitrile proportion were changed. The odevixibat percent assay was observed for evaluating the robustness of

TABLE-2
PRECISION STUDIES FOR EVALUATION OF ODEVIXIBAT

Precision →	System	Method	Intermediate
Sample ↓	Odevixibat area	Odevixibat assay (%)	Odevixibat assay (%)
OVB1 1	2518100	99.5	100.8
OVB1 2	2512025	100.2	99.5
OVB1 3	2512025	99.9	100.2
OVB1 4	2516525	99.6	100.1
OVB1 5	2518100	100.2	100.4
OVB1 6	2526125	98.6	99.9
Mean	2517150	99.7	100.2
SD/RSD	5201.49/0.207	0.599/0.600	0.442/0.440

TABLE-3
ACCURACY STUDIES FOR EVALUATION OF ODEVIXIBAT

Accuracy level	Odevixibat added (mg)	Odevixibat area counts	Odevixibat quantity (mg)	Odevixibat recovered (%)
50% accuracy	0.10	1257441	0.0999	99.9
	0.10	1263234	0.1004	100.4
	0.10	1249126	0.0992	99.2
100% accuracy	0.20	2535921	0.2015	100.8
	0.20	2526023	0.2007	100.4
	0.20	2507308	0.1992	99.6
150% accuracy	0.30	3772308	0.2997	99.9
	0.30	3761124	0.2988	99.6
	0.30	3733564	0.2967	98.9
			Mean	99.8
			SD/RSD	0.351/0.35

the HPLC-based OVB1 assay in terms of % RSD. According to Table-4, the observed findings varied within the intended limits ($RSD < 2\%$), demonstrating that purposefully changing the acetonitrile portion and flow rate parameters had no effect on the odevixibat HPLC assay.

Application: The proposed HPLC method was utilized to determine the odevixibat quantitatively and qualitatively in Bylvay capsules. The precision, as evaluated by the relative standard deviation (RSD%), was found to be 0.685%, whereas the accuracy, determined by the recovery rate, was 100.6%. The results indicated that the HPLC assay may be utilized to correctly and precisely evaluate the odevixibat concentration in Bylvay capsules.

Stability studies: The stability and degradation behavior of odevixibat were investigated under various conditions including acid, alkaline, reduction, oxidation, thermal, hydrolysis, and photolytic stress. These stress conditions were used to assess the stability-indicating and specificity traits of the approach. The extent of odevixibat degradation in all stress degradation experiments was determined based on the amount of odevixibat remaining in the directed stress degradations (Table-5). According to Table-5, odevixibat demonstrated stability in the specified order when subjected to various stress degradations. The order of stress levels, from highest to lowest, is as follows: photo stress > hydrolytic stress > heat stress > reduction stress > acid stress > alkali stress > oxidation stress. Odevixibat is susceptible to instability when exposed to oxidative stress and has enhanced persistence when exposed to photo stress.

TABLE-4
ROBUSTNESS STUDIES FOR EVALUATION OF ODEVIXIBAT

Flow plus (mL/min)	Odevixibat quantity (µg/mL)	Odevixibat area	Odevixibat assay (%)	Flow minus (mL/min)	Odevixibat quantity (µg/mL)	Odevixibat area	Odevixibat assay (%)
1.1	20	2632709	99.4	0.9	20	2441736	100.6
1.1	20	2608951	98.5	0.9	20	2438961	100.5
1.1	20	2670654	100.8	0.9	20	2410764	99.3
		Mean	99.6			Mean	100.1
		SD/RSD	1.159/1.16			SD/RSD	0.723/0.72
Acetonitrile proportion plus	Odevixibat quantity (µg/mL)	Odevixibat area	Odevixibat assay (%)	Acetonitrile proportion minus	Odevixibat quantity (µg/mL)	Odevixibat area	Odevixibat assay (%)
45	20	2771340	99.8	35	20	2222811	99.1
45	20	2766851	99.6	35	20	2248629	100.3
45	20	2795160	100.6	35	20	2239482	99.9
		Mean	100.00			Mean	99.8
		SD/RSD	0.529/0.53			SD/RSD	0.611/0.61

TABLE-5
STABILITY STUDIES FOR ODEVIXIBAT

Stress applied	Odevixibat quantity (µg/mL)	Odevixibat peak area	Odevixibat stability (%)	Odevixibat degradation (%)	Angle of purity for odevixibat peak	Threshold of purity for odevixibat peak
Control	20	2515530	100.00	0.0	0.293	4.061
Acid stress	20	2224763	88.4	11.6	0.407	4.035
Alkali stress	20	2202274	87.6	12.4	0.401	4.055
Peroxide stress	20	2170715	86.3	13.7	0.473	4.054
Reduction stress	20	2245289	89.3	10.7	0.422	4.065
Thermal stress	20	2292177	91.1	8.9	0.485	4.062
Photo stress	20	2451436	97.5	2.5	0.454	4.071
Hydrolytic stress	20	2406401	95.7	4.3	0.425	4.057

Stability indicating trait and method's specificity trait:

The designed HPLC method can separate odevixibat from every single degradation products, as illustrated in Fig. 5. To determine the purity of odevixibat peak, a diode-array analyzer and Empower edition two software were utilized. The Empower edition two software reported the peak purity for each spectrum to be within an automatically determined threshold limit as shown in Table-5. The results showed that the peak signal of odevixibat at 3.57 min remained consistent under various stress conditions (Fig. 6). The HPLC method yielded specific results and can be utilized as a stability indicating approach to evaluate odevixibat content in various materials, including stability samples.

MS characterization: Odevixibat's positive ESI-MS reveals a significant $[M+H]^+$ ion with m/z 188.997 (Fig. 7).

MS characterization of OVBT-DP1: Under acidic conditions, the degradation product OVBT-DP1 has m/z at 296.958 $[M+H]^+$ (Fig. 7); molecular formula of $C_9H_9ClO_5S_2$ was eluted

at 0.864 min. The OVBT-DP1 can be elucidated as 2-(5-hydrosulfonyl-2-(methylthio)phenoxy)acetic hypochlorous anhydride derived from the odevixibat structure. The potential degradation of odevixibat to OVBT-DP1 was suggested based on the observed MS data (Fig. 8).

MS characterization of OVBT-DP2: Under alkaline conditions, the degradation product OVBT-DP2 has m/z at 188.997 $[M+H]^+$ (Fig. 7) having molecular formula of $C_7H_8O_2S_2$ and was eluted at 1.219 min. The OVBT-DP2 structure was assigned as 4-hydrosulfonyl phenyl(methyl)sulfane derived from the odevixibat structure. The structure of OVBT-DP2 as shown in (Fig. 9) is suggested on the basis of degradation mass data of odevixibat.

MS characterization of OVBT-DP3: Under oxidative stress conditions, the degradation product OVBT-DP3 has m/z at 77.016 $[M+H]^+$ (Fig. 7) having molecular formula of $C_4H_4O_3$ and was eluted at 1.911 min. The OVBT-DP3 is assigned as 2-hydroxy acetic hypochlorous anhydride which was derived

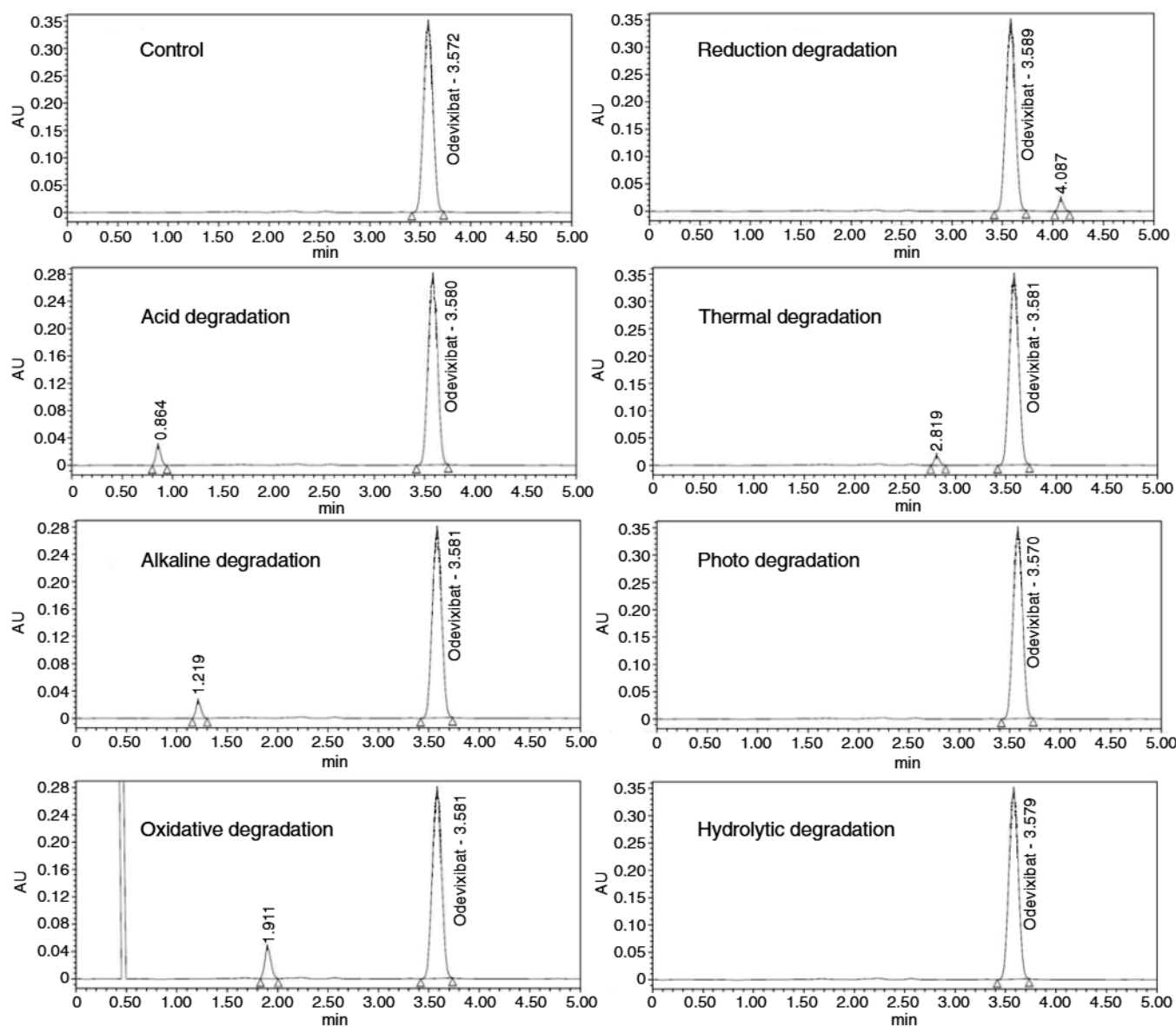


Fig. 5. Chromatograms for odevixibat under different degradation conditions

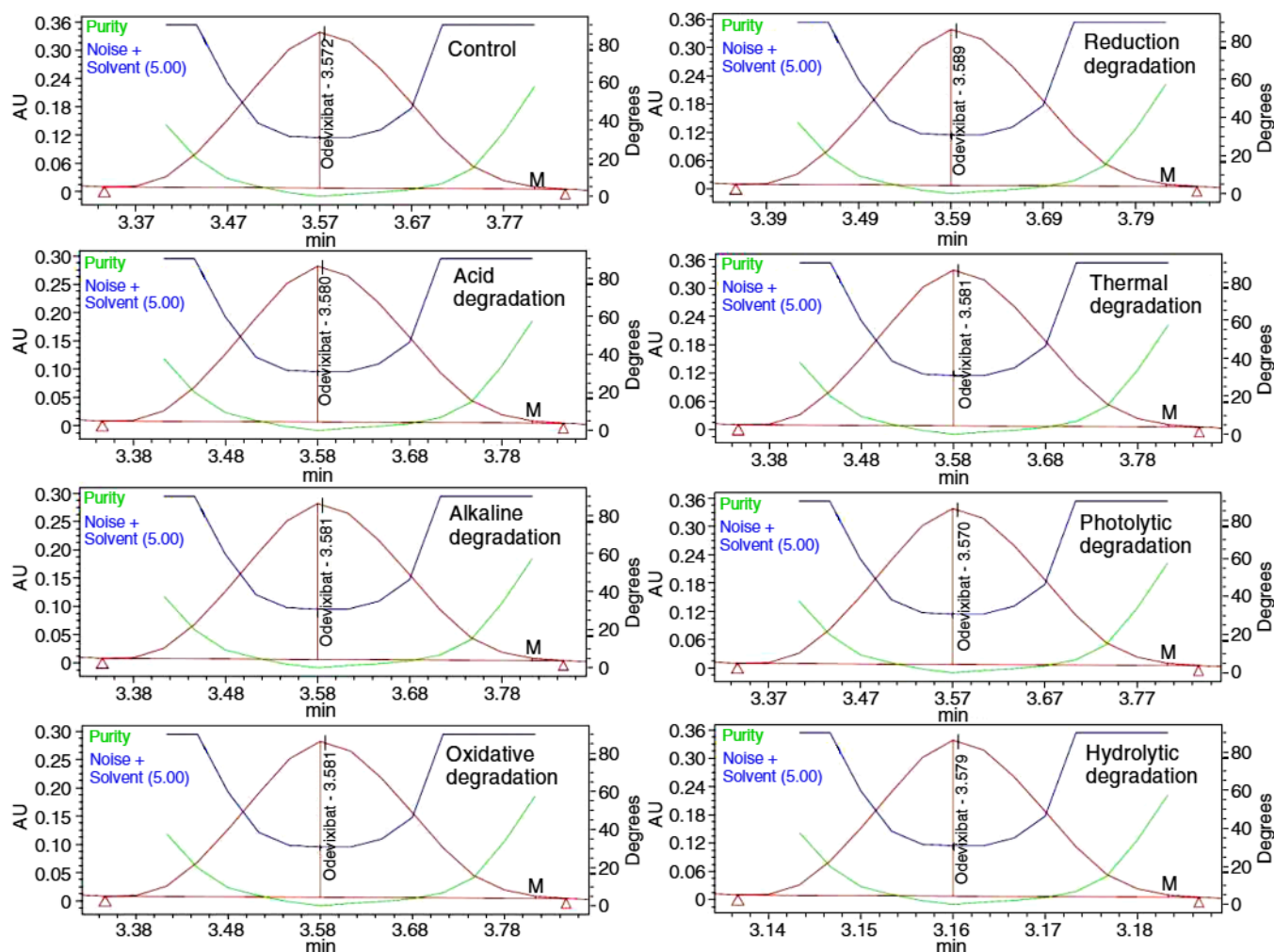


Fig. 6. Plots for peak purity of odevixibat in stress degradations

from the mass degradation spectral data of odevixibat (Fig. 10).

MS characterization of OVBT-DP4: The degraded product OVBT-DP4 m/z at 571.1535 $[M+H]^+$ (Fig. 7) having molecular formula of $C_{25}H_{34}N_2O_7S_3$ was eluted at 4.067 min. The structure of OVBT-DP4 is assigned as 2-((3,3-dibutyl-7-(methylthio)-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,2,5]thiadiazepin-8-yl)oxyl)-1-oxoethane-1-sulfonic acid] derived from the odevixibat structure (Fig. 11).

MS characterization of OVBT-DP5: Upon thermal degradation, the degraded product OVBT-DP5 exhibit m/z at 303.145 $[M+H]^+$ (Fig. 7) having molecular formula of $C_{17}H_{22}N_2OS$ was eluted at 2.819 min. Based on the mass spectral data, the structure of OVBT-DP5 is assigned as sodium 2-(5-hydro-sulfonyl-4-(methyl(phenyl)amino)-2-(methylthio)phenoxy)acetate (Fig. 12) derived from the odevixibat structure.

Conclusion

An efficient and rapid high-performance liquid chromatography (HPLC) method was developed to quantify odevixibat in capsule formulations. The proposed HPLC assay was validated in terms of selectivity, linearity, quantification limit, precision, accuracy, robustness, specificity and detection limit.

The selectivity and stability of the HPLC method were proved by its capacity to resolve the various degradation components, including acid, alkaline, reduction, oxidation, thermal, hydrolysis and photolytic components. The validated HPLC method has successfully been analyzed odevixibat in capsule dosages. The degradation products resulting from the acid stress (OVBT-DP1), alkali stress (OVBT-DP2), oxidative stress (OVBT-DP3), reduction stress (OVBT-DP4) and thermal stress (OVBT-DP5) has been identified and their chemical composition and possible formation pathways were determined using LC-MS evaluations.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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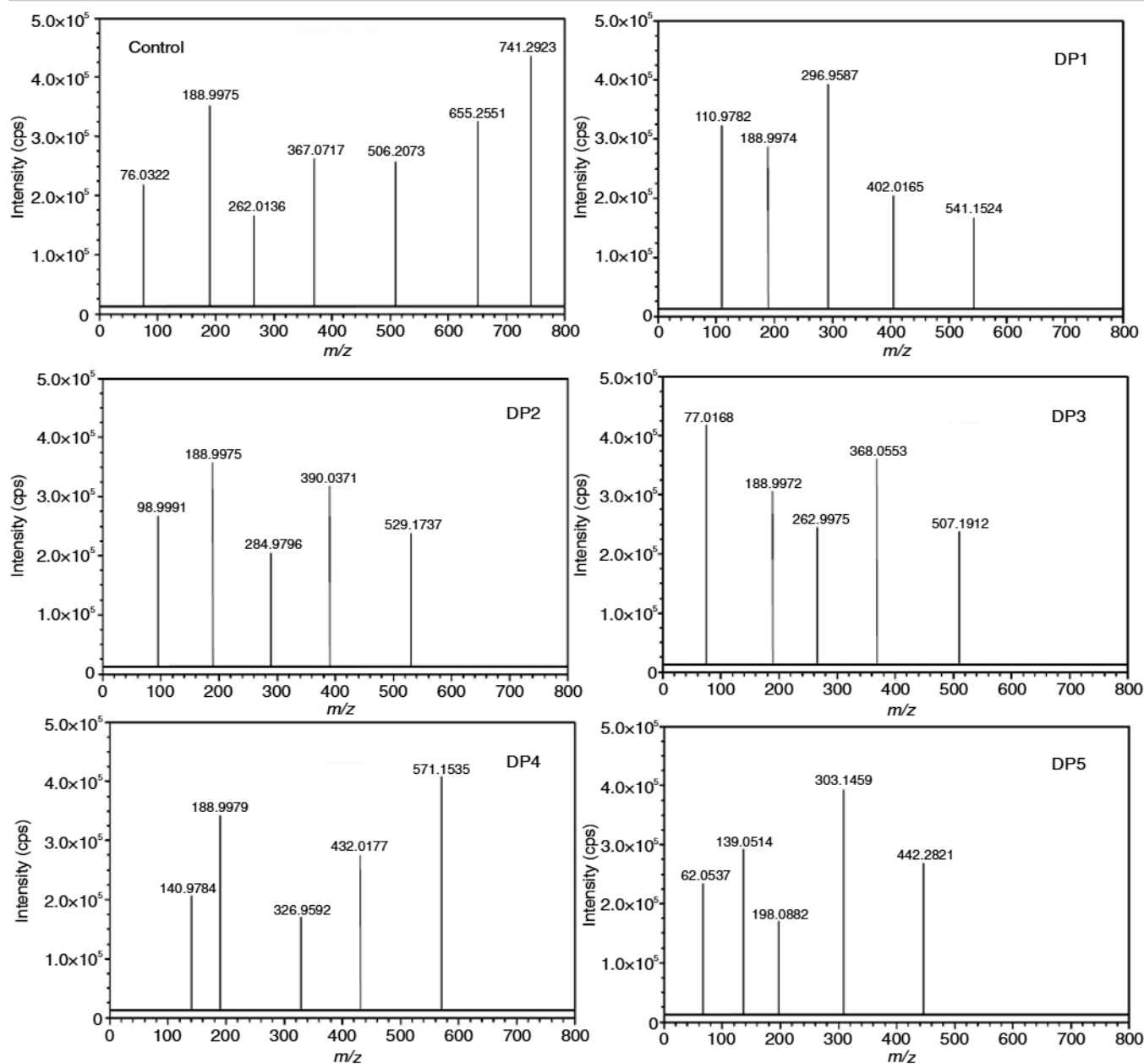


Fig. 7. MS spectrum of odevixibat, OVBT-DP1, OVBT-DP2, OVBT-DP3, OVBT-DP4 and OVBT-DP5

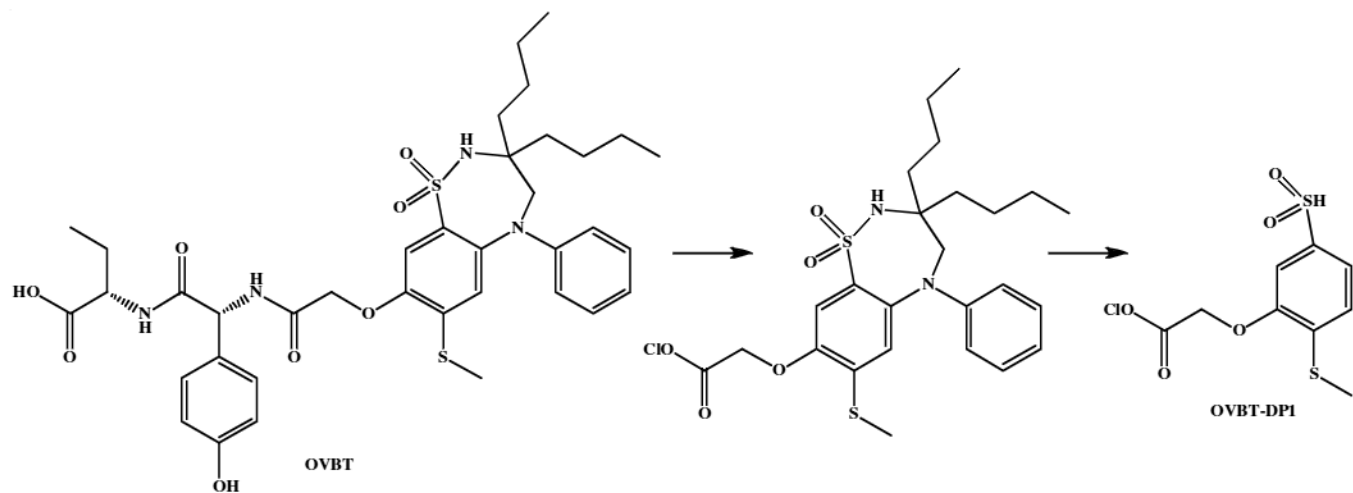


Fig. 8. Degradation of odevixibat to OVBT-DP1 under acidic condition

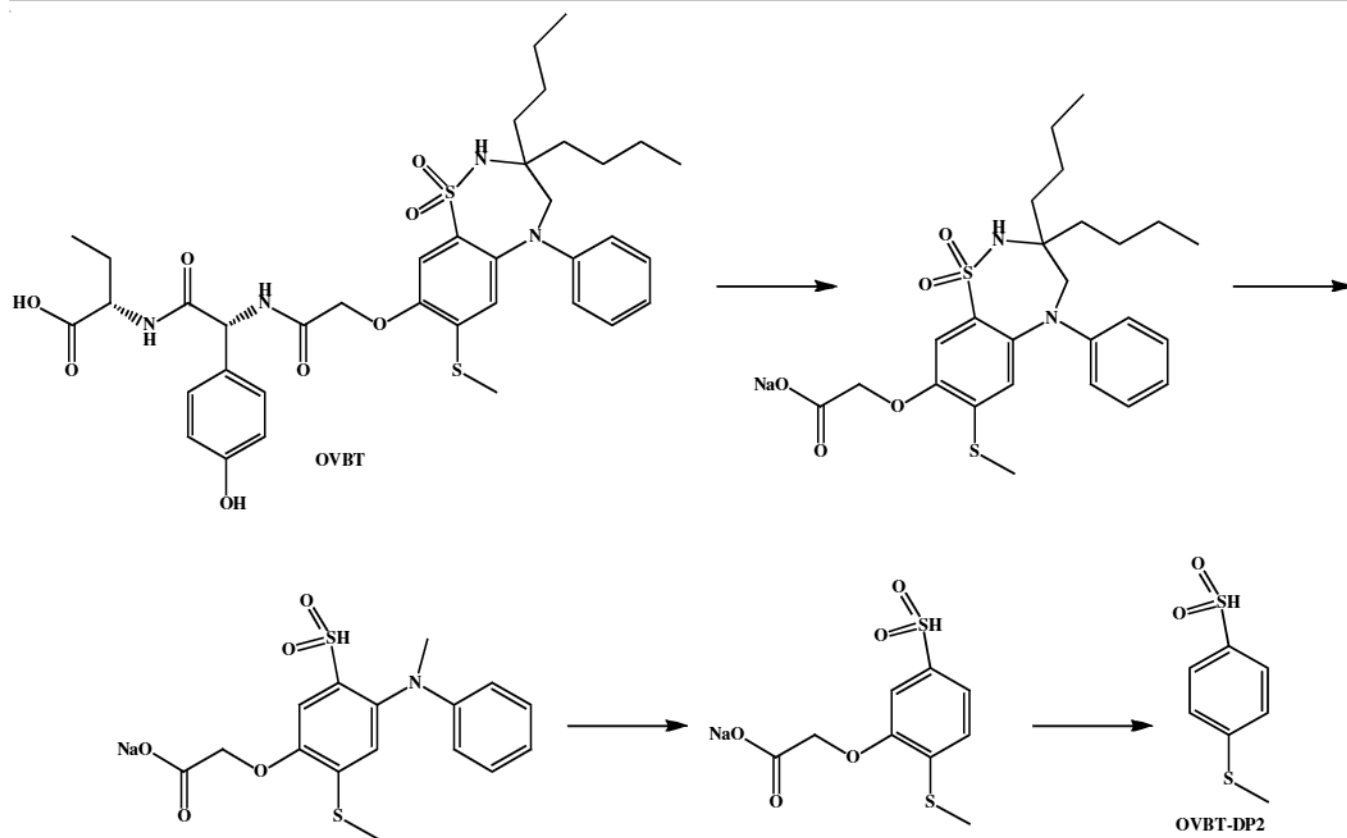


Fig. 9. Degradation of odevixibat to OVBT-DP2 under alkaline condition

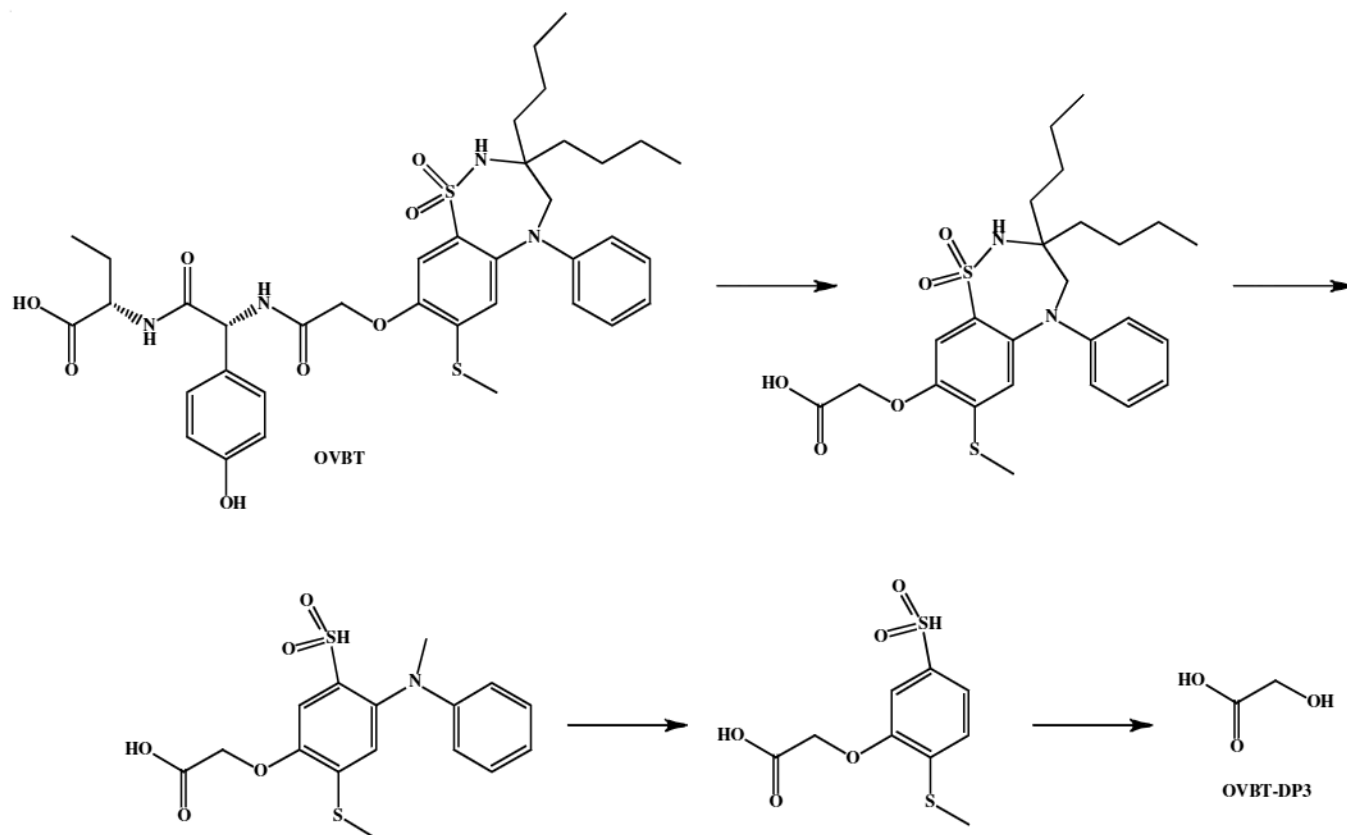


Fig. 10. Degradation of odevixibat to OVBT-DP3 under peroxide condition

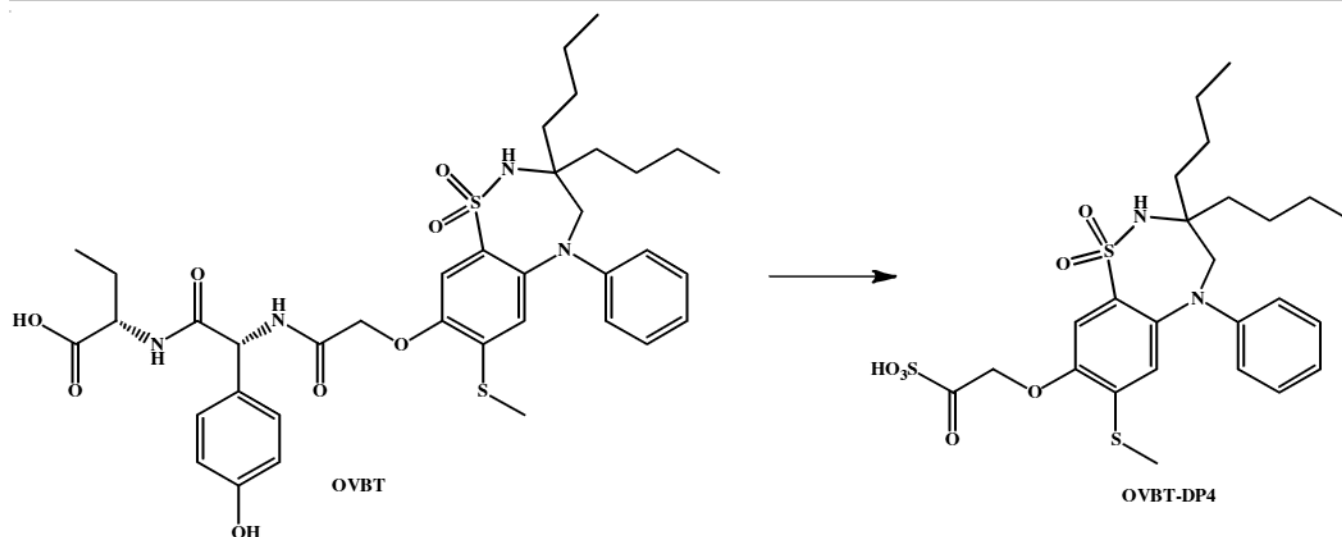


Fig. 11. Degradation of odevixibat to OVBT-DP4 under reducing condition

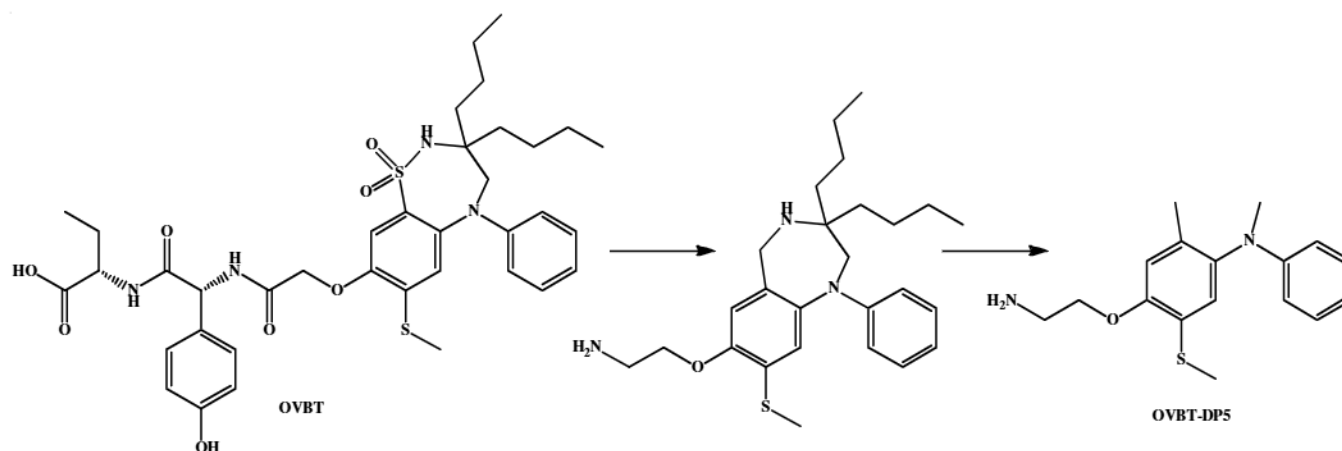


Fig. 12. Degradation of odevixibat to OVBT-DP5 under thermal condition

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