Acta Pharm. Sci. Vol 63:(1), 2025
Original article
DOI: 10.23893/1307-2080.APS6309

# Stability indicating RP-HPLC method development for ondansetron hydrochloride estimation in bulk

Prathamesh SHIROLE[1], Dhanashree P. SANAP[2*], Kisan JADHAV[2]

1 University of Mumbai, School of Pharmacy, Department of Quality Assurance, Navi Mumbai, India
2 University of Mumbai, School of Pharmacy, Department of Pharmaceutics, Navi Mumbai, India

## ABSTRACT

To determine ondansetron hydrochloride in bulk drug, an easy, fast, sensitive, and discerning stability-indicating (RP-HPLC) approach is proposed. Ondansetron hydrochloride was eluted from C18 column (4.6 × 250 mm, 5 µm) and mobile phase containing methanol, acetonitrile and water (50: 30: 20 v/v/v). According to ICH Q2 (R1) guidelines, the entire analytical technique validation was completed. The results of the retrieval study, which was conducted at working concentration levels between 80 to 120%, ranged from 99% to 101%. With a linear regression curve ($R^2$=0.9941), the linearity was assessed in the working concentration range of 5-35 µg $mL^{-1}$, with a limit of quantitation (LOQ) and detection (LOD) of 0.2559 µg $mL^{-1}$ and 0.7755 µg $mL^{-1}$, respectively. Ondansetron hydrochloride showed a retention time of 4.997 min. The approach exhibited good recovery with relative standard deviations under 2% for intra and inter-day precision.

**Keywords:** ondansetron hydrochloride, RP-HPLC, ICH guidelines, validation, stability studies

*Corresponding author: Dhanashree P. SANAP
E-mail: dhanashree.sanap@bvcop.in
ORCIDs:
Prathamesh SHIROLE: 0009-0007-1474-1175
Dhanashree P. SANAP: 0000-0002-4794-7598
Kisan JADHAV: 0000-0001-7563-3935
(Received 26 Jul 2023, Accepted 22 Mar 2024)

## INTRODUCTION

1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4one(ondansetron), the antiemetic drug is a selective inhibitor of type 3 serotonin (5-HT) receptors[1,2]. It has the chemical formula $C_{18}H_{19}N_3O$ (Figure 1) and a molecular weight of 293.4 g $mol^{-1}$, respectively[3,4]. From the literature survey, various methods UV[1,5], HPLC[6,7], HPTLC[8], LC-ESI-MS/MS[9], Spectrofluorimetry[10], were reported for the analysis of ondansetron hydrochloride.

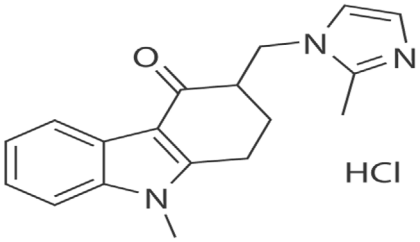



**Figure 1.** Structure of ondansetron hydrochloride

Pharmaceutical parameter analysis is an essential step in the entire process of developing drugs. Therefore, easy and fast methods are required for checking the quality of commercial formulations. To improve knowledge of the stability of the active pharmaceutical ingredient (API) and drug product stability, and to assist the development of analytical methodology and to achieve details on the degradation products, forced degradation studies are utilised. The purpose of this work was to create a stability-indicating reversed-phase high-performance liquid chromatography (RP-HPLC) method for analysing ondansetron (OND) in pharmaceutical formulations.

## METHODOLOGY

### Instruments

UV experimentation was performed using a Shimadzu UV- 1800 double beam UV/vis spectrophotometer with a 1 nm spectral bandwidth and a thickness of 1 cm quartz cells, and the calibrated analytical balance (Mettler Toledo) was used.

Shimadzu UFLC (LC 2030) system was used to carry out the chromatographic analysis, AutoSampler, SPD-20 prominence UV/VIS detector. Lab Solutions software was used to check and process the output signals. The analytical column was Hemochrom Intsil C18 – 5U (4.6 mm × 250 mm).

## Materials

M/s ZIM Laboratories, B-21/22, MIDC Area, Kalmeshwar, Nagpur, Maharashtra, provided the bulk drug Ondansetron hydrochloride as a gift sample. HPLC-grade chemicals were used (Finar Ltd., Ahmedabad, Avantor Performance Materials India Private Ltd., Thane) and distilled water was used for mobile phase preparation. Before use, solutions and solvents were filtered via a membrane filter (0.45 μm pore size) and then degassed by sonication.

## Analytical method development

### Wavelength detection

Accurately weighed 10 mg of ondansetron, was transferred to a 100 mL volumetric flask, and distilled water was used to make up the final concentration. About 20 μg $mL^{-1}$ standard solution of OND was prepared using distilled water and scanned in a range of 200-400 nm to determine the maximum wavelength (Figure 2).

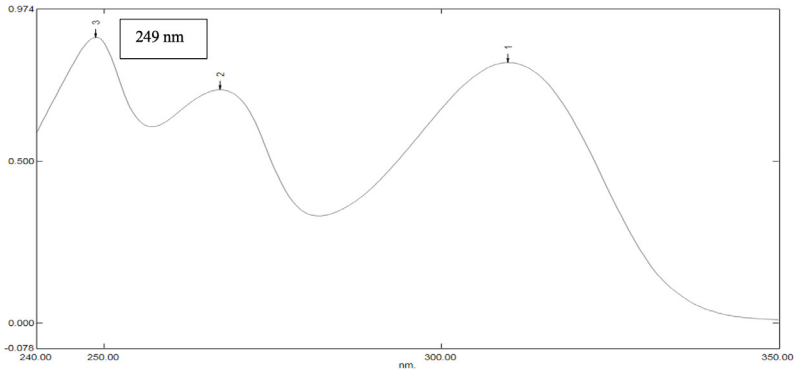



**Figure 2.** UV Spectrum of pure ondansetron

### Chromatographic parameters

To achieve a sharp peak and adequate resolution of OND, various ratios of mobile phase consisting of water and methanol, acetonitrile and water were tried. When methanol: distilled water (80:20 % v/v) was tried, $R_t$ was obtained at 7.296 min with tailing. Further changes were done by taking methanol: acetonitrile: distilled water (60: 20: 20 v/v/v) which showed $R_t$ at 5.21 min along with peak tailing. By adjusting the mobile phase composition, column packing, flow rate, temperature, and detection wavelength, the method was improved, and the impact on retention time and peak form was observed (Figure 3).

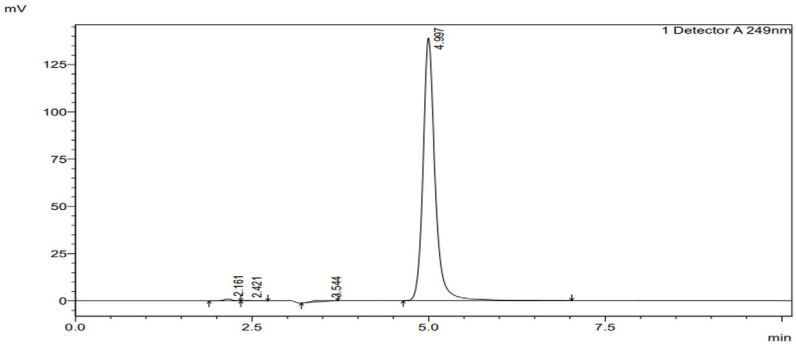



**Figure 3.** HPLC chromatogram of ondansetron hydrochloride

### Sample and standard stock solution preparation

100 mg of OND were dissolved in 100 mL of distilled water (1000 μg $mL^{-1}$) to create a standard stock solution. 1.0 mL was pipetted out from the above solution and diluted with distilled water in a 10 mL volumetric flask to get a solution of 100 μg $mL^{-1}$.

### Validation of an analytical method

### Linearity determination

Aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, and 3.5 mL from the aforementioned stock solution were taken in volumetric flasks of 10 mL and diluted with distilled water to get a final concentration in the range of 5-35 μg $mL^{-1}$ [11]. To produce the calibration curve, a graph of the peak area vs drug concentration was created (Figure 4).

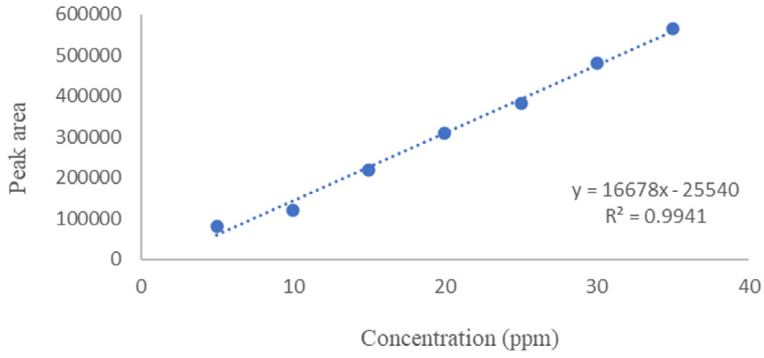



**Figure 4.** Standard plot of ondansetron hydrochloride

### Precision

Repeatability and intermediate precision are two alternative levels of accuracy that can be used. Repeatability is the term used to describe the application of the analytical technique within the laboratory across a shorter period that was assessed by analysing the samples on the same day. Six replicates of the sample injection were used to test repeatability. The three distinct OND concentrations, 5, 20, and 35 μg $mL^{-1}$ were examined three times on the same day to evaluate the intra-day precision. The three concentrations described above were examined for inter-day precision over three consecutive days to determine day-to-day variability[12,13].

### Accuracy

Recovery studies were used to determine accuracy at levels of 80 %, 100 % and 120 % using the standard addition method, the sample was then supplemented with a known concentration of OND and it was then exposed to the suggested HPLC procedure[12,14]. Three accuracy studies were carried out, with the results of each research being used to calculate the % recovery and RSD %.

### Robustness

By making minor, deliberate changes to a few parameters, the robustness of the technique was investigated. The rate of flow, detection wavelength and mobile phase composition were changed by ± 0.2 mL/min, ± 2nm and ± 10 mL, respectively. At a concentration of 20 μg $mL^{-1}$, robustness tests were conducted[15,16].

### Limit of Detection (LOD) and Quantitation (LOQ)

According to the ICH, a process limit of quantitation is the smallest amount of analyte that can be quantitatively recognised in a sample, whereas a process limit of detection is the lowest concentration of analyte that can occasionally be detected but not exactly defined as a value[17,18,19]. LOD and LOQ were determined using the formula below:

$$LOD = 3.3 \times \sigma / S \text{ and } LOQ = 10 \times \sigma / S$$

σ=regression line's y-intercept standard deviation

S=calibration curve's slope

### Marketed formulation analysis

The marketed tablet dosage formulation of OND (Vomikind MD 4, Mankind Pharma Limited) was used for the determination of tablet drug content by the proposed method. A precise 10 mg dose of ondansetron hydrochloride from

the formulation was taken in a 100 mL volumetric flask and then distilled water was added up to 50 mL and sonicated for 10 min, final volume was made up to 100 mL with the distilled water. For analysis, the resultant solution was further diluted to a concentration of 25 µg $mL^{-1}$ and filtered using a 0.45 µm filter (Figure 5).

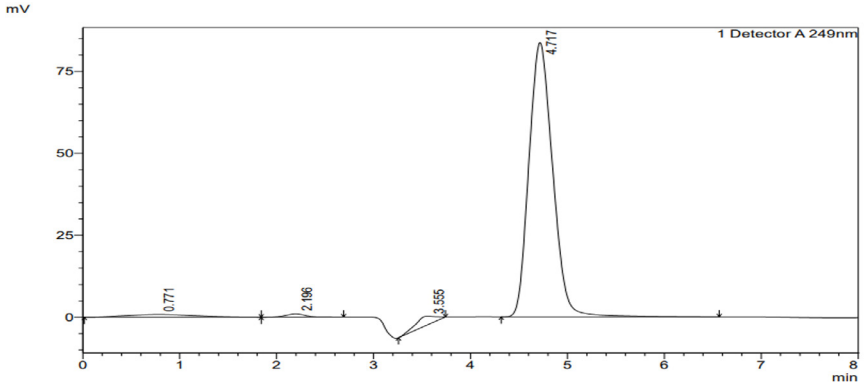
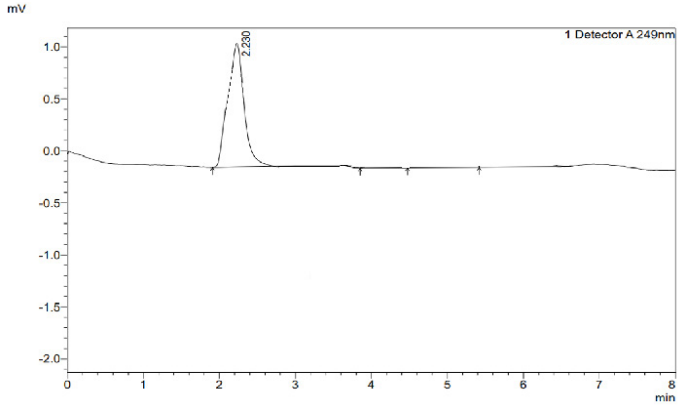



**Figure 5.** HPLC chromatogram of ondansetron hydrochloride marketed tablet

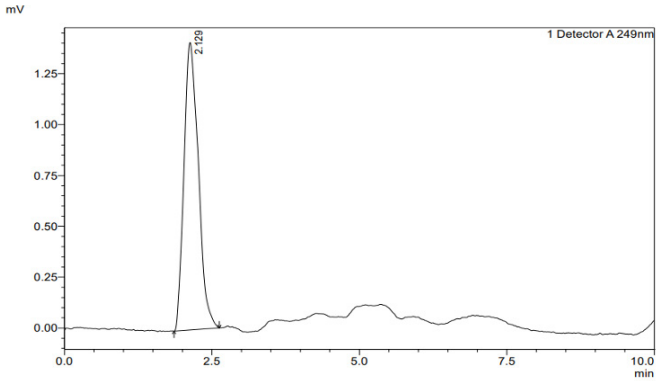
## Forced degradation studies

According to ICH stability criteria, various stress factors, including acidic, alkaline, thermal, peroxide, and photolytic conditions, were used[11,15,20-27] and their blank chromatograph was taken as exhibited in Figure 6 ([a] to [e]).

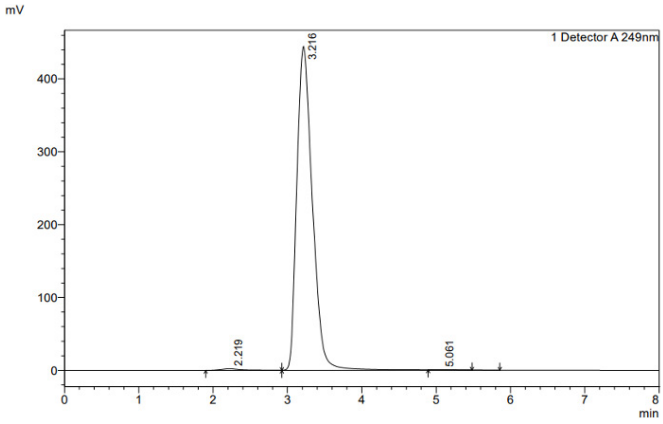
(a)



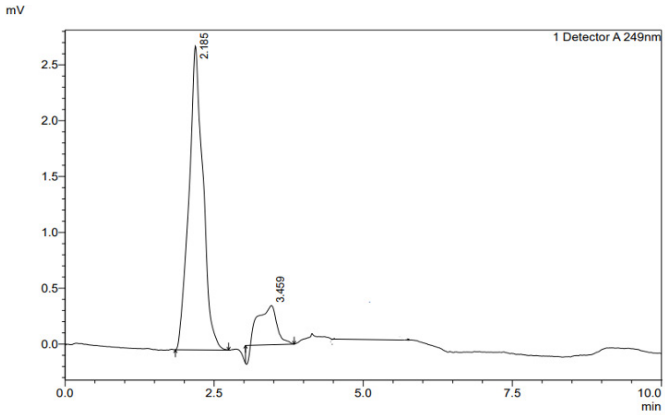
(b)


mV
1 Detector A 249nm
2.129
1.25
1.00
0.75
0.50
0.25
0.00
0.0
2.5
5.0
7.5
10.0
min

(c)


mV
1 Detector A 249nm
3.216
400
300
200
100
0
2.219
5.061
0
1
2
3
4
5
6
7
8
min

(d)


mV
1 Detector A 249nm
2.185
2.5
2.0
1.5
1.0
0.5
0.0
3.459
0.0
2.5
5.0
7.5
10.0
min

(e)

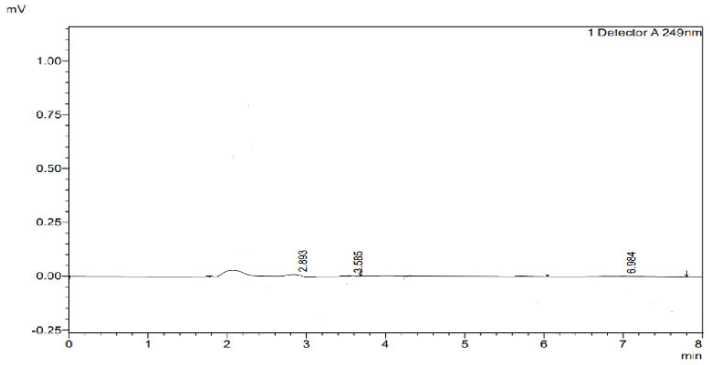



**Figure 6.** Blank degradation chromatogram of ondansetron (a) acidic degradation; (b) alkaline degradation; (c) peroxide degradation; (d) photolytic degradation; (e) thermal degradation

### Thermal degradation

A 25 mL volumetric flask was filled with 5 mL of the standard stock solution, diluent was added, and the combination was heated at 105°C for 6 h. The solution was filtered using a 0.45 µm nylon syringe filter, with some of the filtrate being discarded. Without using the sample, prepare the thermal degradation blank in the same way.

### Peroxide degradation

5 mL of the standard stock solution was transferred to a 25 mL volumetric flask, to which 2 mL of 30% $H_2O_2$ were added. A small amount of diluent was also added, and the mixture was heated at 60°C for 30 min. After cooling, diluent was added to increase volume. A small portion of the solution was discarded after the solution was filtered using a 0.45 µm nylon syringe filter. In the same way, prepare the peroxide degradation blank without utilising the sample.

### Acid degradation

A small amount of diluent was added, 5 mL of the standard stock solution and 2 mL of 0.05M HCl were added to a 25 mL volumetric flask, and the mixture was heated at 60°C for 30 min. By adding 2 mL of 0.05M NaOH, the capacity was filled with diluent to neutralise the solution once it has cooled. A small portion of the fluid was eliminated after filtering it with a 0.45 µm nylon syringe filter. Without utilising the sample, prepare the acid degradation blank according to the same procedure[28].

### Alkaline degradation

5 mL of the standard stock solution and 2 mL of 0.05M NaOH were added to a 25 mL volumetric flask, some diluent, and heated for 30 min at 60°C. By adding 2 mL of 0.05M HCl and cooling the solution, the solution is neutralised. The volume is then made up with diluent. With a 0.45 µm nylon syringe filter, the solution was filtered, with a small quantity of solution being discarded. Without using the sample, prepare the alkaline degradation blank in the same way.

### Photolytic degradation

5 mL of the sample was obtained and placed in a 25 ml volumetric flask using the standard solutions. Diluent was then added to produce the volume, and the sample was then exposed to sunlight for 12 h. The solution was filtered using a 0.45 µm nylon syringe filter, with some of the filtrate being discarded. Without utilising the sample, prepare the photolytic degradation blank in the same way[29].

## RESULTS and DISCUSSION

### Analytical method development

The choice of an appropriate mobile phase is a crucial step in the development of the HPLC method. The existing literature on OND was used to guide the trial-and-error process of choosing and optimising the mobile phase. Various combinations of mobile phases were tried based on the polarity and solubility of ondansetron after a thorough literature survey. At first methanol: distilled water was used in the ratio of 70:30 and 80:20 %v/v, but no proper peak was observed. Then, acetonitrile: distilled water in a ratio of 80:20 and 70:30 %v/v was tried, and peak tailing of ondansetron was observed. After that, acetonitrile: distilled water (85:15 %v/v) showed a good peak, but the results were not reproducible. A further modification was done, and the mobile phase was changed methanol: acetonitrile: distilled water in the ratio 40:40:20 %v/v/v was optimized in that a broad peak was obtained. Furtherly, methanol: acetonitrile: distilled water in a ratio of 50:30:20 %v/v/v was used which gave well resolved peak without tailing.

After the selection of the appropriate mobile phase, further optimization was carried out to set chromatographic parameters like flow rate, column temperature and injection volume to get a well-resolved peak. Different flow rates range from 0.5-1.5 mL/min, column temperature in the range of 25°C-40°C and injection volume in the range of 5-20 µL. The column temperature was maintained at 30°C for better results. To minimize the carryover of a drug, the

injection volume was set at 5 µL, which shows good sensitivity and to decrease the backpressure of the column, the flow rate was kept at 1.0 mL/min.

About 20 µg $mL^{-1}$ standard solution of OND was prepared using distilled water and scanned in a range of 200 - 400 nm. The maximum absorbance was found at 249 nm (Figure 2).

The final mobile phase included methanol, acetonitrile, and distilled water in the ratio 50: 30: 20 v/v/v to get a resolved sharp peak. The injection volume was 5 µL with a flow rate of 1.0 mL $min^{-1}$ and the eluent was obtained at 249 nm and a 30°C column temperature. According to these specifications, the retention time of the OND peak was 4.997 min (Figure 3).

Using distilled water, acetonitrile, and methanol as the mobile phase, with a flow rate of 1 mL/min, a good peak symmetry and a decent resolution for ondansetron hydrochloride were obtained.

**Analytical method validation**

With a linear correlation coefficient of 0.9941, it was discovered that the linearity of OND was in the range of 5-35 µg $mL^{-1}$ (Figure 5) and all the quantitative parameters were estimated as listed in Table 1.

For intraday and interday precision, the RSD % was discovered to be in the range of 0.65% - 1.84% and 0.27% - 2.24%, respectively. (Table 2[a] and 2[b]). The % recovery for Ondansetron was found in the range of 98.61% - 102.50% which shows there is no interference from the excipient. Table 3 shows the results of the accuracy studies. Robustness revealed that no changes were observed in the chromatogram of OND, hence, we may claim that the suggested method is reliable (Table 4).

**Table 1.** Quantitative and validation parameters

| Parameter | Ondansetron hydrochloride |
|---|---|
| $\lambda_{max}$ (nm) | 249 |
| Beer' law limits (µg $mL^{-1}$) | 5 - 35 |
| Regression equation | 16678x - 25540 |
| Correlation coefficient ($R^2$) | 0.9941 |
| Accuracy | 98.61% - 102.50% |
| Precision (intraday) | 0.65 - 1.84 RSD % |
| Precision (interday) | 0.27 - 2.24 RSD % |
| Robustness | 0.06 - 2.00 RSD % |
| LOD and LOQ | 0.2559 µg $mL^{-1}$ and 0.7755 µg $mL^{-1}$ |

**Table 2.** Result of intra-day and inter-day precision

| | Concentration (µg mL$^{-1}$) | Peak Area | | | RSD % | | |
|---|---|---|---|---|---|---|---|
| | | Morning* | Afternoon* | Evening* | Morning | Afternoon | Evening |
| Intra-day precision | 2 | 0.0883 | 0.0893 | 0.0916 | 0.65% | 1.70% | 1.66% |
| | 12 | 0.5043 | 0.5026 | 0.5067 | 1.09% | 1.84% | 1.34% |
| | 22 | 0.9400 | 0.9380 | 0.9416 | 1.33% | 1.46% | 1.44% |
| | Concentration (µg mL$^{-1}$) | Peak Area | | | RSD % | | |
| | | Day I* | Day II* | Day III* | Day I | Day II | Day III |
| Inter-day precision | 2 | 78844.7 | 88469 | 88042.7 | 1.64% | 0.53% | 0.27% |
| | 12 | 312396 | 317032 | 326994 | 2.02% | 1.90% | 0.80% |
| | 22 | 576312 | 525265 | 669645 | 2.24% | 1.42% | 1.81% |

* Mean of three replicates n=3

**Table 3.** Result of accuracy studies

| Concentration of the sample (µg ml$^{-1}$) | Concentration of drug added (µg ml$^{-1}$) | Percent of spiked | Recovered amount* (µg ml$^{-1}$) | Percent recovery |
|---|---|---|---|---|
| 10 | 8 | 80% | 17.75 | 98.61% |
| 10 | 10 | 100% | 20.41 | 102.05% |
| 10 | 12 | 120% | 22.55 | 102.50% |

* Mean of three replicates n=3

**Table 4.** Result of robustness

| Parameters | Variation | $R_t$ | Peak Area | Mean | RSD % |
|---|---|---|---|---|---|
| Flow rate | 0.8ml/min | 5.971 | 272335 | 273890 | 2.00 |
| | | 5.902 | 269348 | | |
| | | 5.953 | 279987 | | |
| | 1.2ml/min | 5.971 | 175493 | 178334.3 | 1.39 |
| | | 5.902 | 179423 | | |
| | | 5.953 | 180087 | | |
| Wavelength | 247 nm | 4.757 | 207645 | 207773.3 | 0.06 |
| | | 4.765 | 207772 | | |
| | | 4.773 | 207903 | | |
| | 251 nm | 4.765 | 195290 | 196412.3 | 0.54 |
| | | 4.773 | 196539 | | |
| | | 4.781 | 197408 | | |
| Mobile phase ratio | Methanol: ACN: Water (40: 40: 20) | 4.781 | 198412 | 199872 | 0.67 |
| | | 4.492 | 200152 | | |
| | | 4.608 | 201052 | | |
| | Methanol: ACN: Water (60: 30: 10) | 3.999 | 235275 | 233223 | 1.22 |
| | | 4.052 | 234436 | | |
| | | 4.115 | 229958 | | |

The sensitivity of the technique was assessed by calculating the LOD and LOQ, which were found to be 0.2559 μg $mL^{-1}$ and 0.7755 μg $mL^{-1}$, respectively.

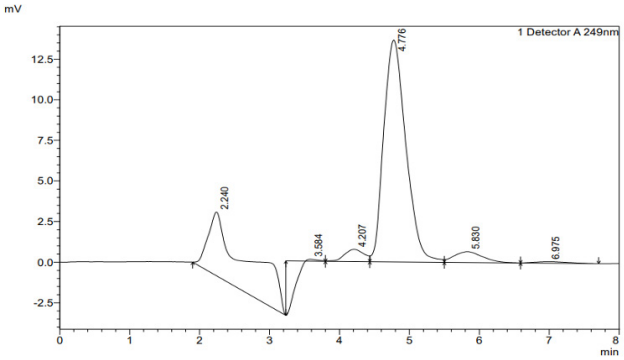
Studies on the stability of Ondansetron under various stresses revealed the following degradation behaviour.

The percent degradation of ondansetron is calculated by using the following formula:

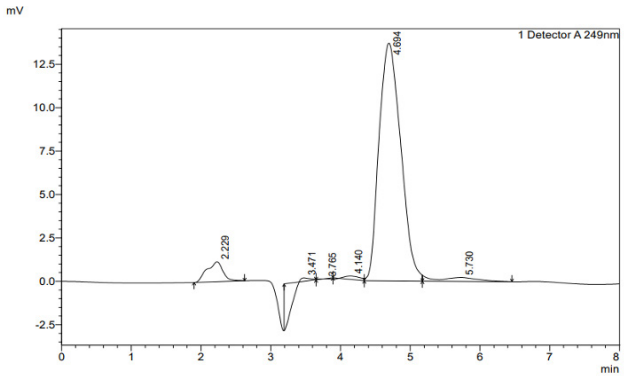
Percentage Degradation (%) = Peak area of degraded compound/Peak area of pure compound x 100

Acidic degradation occurred at retention times of 4.2 and 5.8 min (Figure 7[a], and the % degradation is 18.01%. The degradation product in alkali degradation was observed at retention times of 4.1 and 5.7 min (Figure 7[b]) and the % degradation is 19.16%. In peroxide, photolytic and thermal degradation, the % degradation was found to be 34.49%, 3.98%, and 12.55%, respectively (Table 5) (Figure 7[c], [d], and [e]).

(a)




(b)



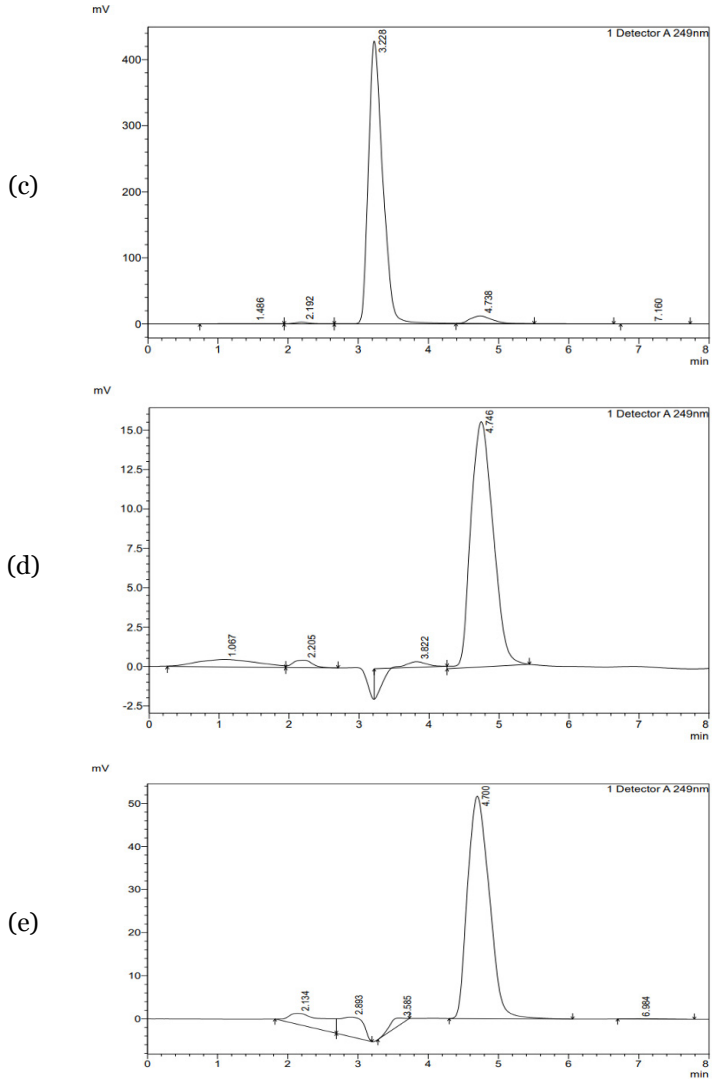



**Figure 7.** Degradation chromatogram of ondansetron (a) Acidic degradation; (b) Alkaline degradation; (c) Peroxide degradation; (d) Photolytic degradation; (e) Thermal degradation

**Table 5.** Result of forced-degradation studies

| Condition of Stress | Exposure Period | Temperature (ºC) | New Degradation peaks | | | Degradation Rate (%) |
|---|---|---|---|---|---|---|
| | | | No of degradation peak observed | $R_t$ (min) | RRT | |
| Acidic | 30 min | 60ºC | 2 | Peak 1: 4.207 | Peak 1: 0.881 | 18.01 |
| | | | | Peak 2: 5.830 | Peak 2: 1.220 | |
| Alkaline | 30 min | 60ºC | 2 | Peak 1: 4.140 | Peak 1: 0.882 | 19.16 |
| | | | | Peak 2: 5.730 | Peak 2: 1.221 | |
| Peroxide | 30 min | 60ºC | 0 | - | - | 34.49 |
| Photolytic | 12 h | Sunlight | 1 | Peak 1: 3.822 | Peak 1: 0.805 | 3.98 |
| Thermal | 6 h | 105ºC | 0 | - | - | 12.55 |

The method that was devised is simple, quick, linear, accurate, exact, and specific. The method's reliability and accuracy are demonstrated by the results of the validation studies. The investigation findings demonstrated that the method is appropriate for identifying ondansetron in bulk and tablet dosage forms without interference from degradation products, and it is advised for regular quality control analysis of the drug ondansetron in pharmaceutical formulation.

## STATEMENT OF ETHICS

This study does not require ethical permission to be carried out.

## CONFLICT OF INTEREST STATEMENT

No conflicts of interest exist, according to the authors, with the publishing of this paper.

## AUTHOR CONTRIBUTIONS

Concept – K.J., P.S., D.S.; Design – K.J., D.S., P.S.; Supervision – D.S.; Resources – D.S., P.S.; Materials – K.J.; Data Collection and/or Processing – D.S., P.S.; Analysis – K.J., D.Ş., P.S.; Literature Search – P.S, D.Ş.; Writing – D.S.; Critical Reviews – D.S., K.J.

## FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**ACKNOWLEDGMENT**

The instruments and facilities were provided by Bharati Vidyapeeth's College of Pharmacy in CBD Belapur, Navi Mumbai, which the authors gratefully acknowledge. The authors are appreciative of Zim Laboratories, Kalmeshwar, Dist. Nagpur (M.S.), India for providing a gift sample of ondansetron hydrochloride.

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