INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

DOI: https://dx.doi.org/10.33289/IJRPC.12.4.2022.12(42)

ISOLATION AND STRUCTURAL CHARACTERIZATION OF MAJOR DEGRADATION PRODUCT OF VENLAFAXINE HYDROCHLORIDE

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ABSTRACT

Venlafaxine, an antidepressant drug was subjected to hydrolytic stress condition in acidic medium. The drug was found to be degraded under acid hydrolytic condition and produce one major degradation product. The Rf of the degradation product was well resolved from that of the pure drug. Isolation of degraded product was carried out by performing preparative TLC using mobile phase n-Hexane: Ethyl acetate (7:3). Identification and structural characterization of degradation product was done by IR, ^{1}H NMR and Mass spectrometric studies. Its fragmentation pathway was proposed. Current study presents isolation and characterization of unidentified impurity in a drug product with the purpose of identification of the degradation products that could form during manufacturing, storage, shipping, and in therapeutic use of a drug or its formulations for properly defining the quality specification of product.

Keywords: Venlafaxine Hydrochloride, Acid Hydrolysis and Degradation product.

INTRODUCTION

Forced degradation studies of a drug are an important part of the drug development process. Stress testing studies of any drug substances and drug products help in identification of the degradation products of the drugs that could form during manufacturing, storage, shipping and in therapeutic use of a drug or its formulations[1]. Stress Testing also furnishes the information about the stability of the drug and its chemical behaviour which can also be useful in examining the Degradation mechanism of drug molecule[2].Venlafaxine hydrochloride, 1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl]-cyclohexan-1-ol hydrochloride, an antidepressant belonging to class of drugs called as Serotonin norepinephrine reuptake inhibitor (SNRI)[3]. Serotonin is a neurotransmitter which plays a key role in mood, digestion, emotions and norepinephrine, chemically Catechol amine derivative is a neurotransmitter responsible for memory, alertness, stress reaction[4].Serotonin and norepinephrine are the two major neurotransmitters known to play a role in pathophysiology of depression. These neurotransmitters are thought to affect mood and responsible for good mood. SNRI works by preventing the reuptake of These chemical messengers from synaptic cleft to presynaptic neurons[5]. Venlafaxine Hydrochloride is marketed as a racemates of equimolar mixture of R (+) and S (−)[6].

Various analytical techniques such as UV spectroscopic[7], HPTLC[8] and RP-HPLC[9] methods have been reported in the literature for the estimation of venlafaxine in bulk as well as from its pharmaceutical dosage form.

S.D. Sheorey et al[10] has reported stability indicating method for venlafaxine hydrochloride and showed degradation in acid stressor but structural characterization was not performed. R. Bokka et al[11] has reported stability indicating HPTLC method for analysis of venlafaxine hydrochloride but no information exists in literature on degradation product. C. Rambabu et al[12] performed stability indicating RP-HPLC method for the assay of venlafaxine

in pharmaceutical dosage form, degradation product was formed but structural characterization was not carried out. R. Vijayaraghavan et al[13] has reported Stability Indicating HPLC Method for Venlafaxine Hydrochloride Capsules. No degradation product was found in any stressor as milder conditions were used. Literature survey on Venlafaxine revealed that there are numbers of impurities reported, which are identified and synthesized. There is no literature reported for synthesis of this new impurity.

The purpose of this work was to perform the stress degradation study of API followed by separation, identification and structural characterisation of degradant using various spectroscopic and chromatographic techniques like TLC, IR, 1H NMR, MS.

EXPERIMENTAL

MATERIALS AND METHODS

Venlafaxine hydrochloride API (Active Pharmaceutical Ingredient) was obtained from Torrent Pharmaceutical Ltd., Gandhinagar, Gujarat as a gift sample.

All solvents used were of Analytical grade and were obtained from Merk.

Degradation of Venlafaxine Hydrochloride

Hydrolytic degradation of venlafaxine Hydrochloride was performed using parallel synthesizer (Carousel 6 Plus Reaction Station, Radleys, United Kingdom). Accurately weighed 5 g of venlafaxine hydrochloride was transferred into a 200 ml RB flask and 35ml of freshly prepared 5 N HCl was added. the resultant solution was refluxed at 80°C and allowed to rotate at 120 rpm. Samples were collected at regular intervals to check the formation of degradation product of venlafaxine hydrochloride. After completion of degradation the resultant solution was cooled and neutralised with 5N NaOH. The mixture was then separated by using preparative TLC. Similarly, degradation was performed with 1N and 0.1N strengths of HCl.

Isolation of degradation product

Pure degradation product of venlafaxine Hydrochloride was isolated by using preparative TLC. The sample solution was dissolved in methanol and it was applied on TLC pre-coated with silica gel G as a spot. Plate was developed in mobile phase (n-Hexane: Ethyl acetate= 7:3). The plate was dried at room temperature and the spot was detected under UV light. The spot of degradation product was scrapped off using spatula and dissolved in methanol and stirred manually. The extracted material was filtered and methanol was evaporated to yield the pure degradation product.

Spectral analysis

The degradation product was analysed on GC-MS instrument. The mass spectrometer was run to get mass/charge (m/z) ratio. Further, structure elucidation of impurity was done by 1H NMR and IR studies.

a) NMR spectroscopy

The 1H NMR spectra was recorded in DMSO-d6 on a Bruker 400-MHz Fourier transform (FT)– NMR spectrometer. Chemical shift values of 1 H were measured on δ scale in ppm comparative to tetra methyl silane (TMS) as internal standard. The spectra were referenced to δ 0.00 ppm in 1 H NMR (TMS).

b) IR spectroscopy

The IR spectrum was recorded in the solid state as KBr disc using a PerkinElmer FTIR spectrophotometer.

c) Mass Spectrometry

For further characterization of major acid degradation product as well as to elucidate degradation pathway of venlafaxine, GC-MS study of acid degradation stress sample was carried out. The mass spectra were recorded on a Perkin ElmerGC-MS instrument.

RESULTS AND DISCUSSION

Venlafaxine hydrochloride was forcefully degraded under acid hydrolytic stress condition. The drug was found to be liable to acid hydrolysis at higher strengths of acid 5N HCl. No degradation was observed with lower strengths of 0.1N, 1N HCl. Since, the degradation was observed with 5N HCl, the study was stopped at this stage. The degradation product generated under stress condition was separated by using preparative TLC. Degradation of the drug was confirmed by TLC showing Rf value different from that of venlafaxine. Chromatogram of degraded product of Venlafaxine Hydrochloride is depicted in fig. 1 and labelled as DP.

In this study, IR, 1H NMR and MS were used to characterize a previously unknown hydrolytic product of venlafaxine, which was formed during a forced degradation study. Table 1 summarizes 1H NMR, IR and Mass spectrometric data of Degraded product. The proposed fragmentation pattern of degradation product of Venlafaxine Hydrochloride with 5M HCl is presented in (fig. II) and Table -II shows structural comparison of Venlafaxine Hydrochloride and it's degradation product.

CONCLUSION

The structure of degradation product formed during forced degradation study of venlafaxine hydrochloride at specific condition was elucidated as1-[(1- hydroxy-cyclohexyl)methyl]-4-methoxybenzene. The degradation product was characterized its structure using various spectroscopic techniques (IR, ^{1}H NMR and MS). The degradation product formation by degradation of venlafaxine HCl was confirmed by performing correlation study at different time interval after performing work out procedure of crude sample solution by TLC analysis.

It is believed that the discussion included herein would be beneficial for process development by avoiding formation of impurities before introduction into manufacturing setting with high quality of API and useful to optimise process for drug molecule who contains this impurity.

ACKNOLEDGEMENT

The authors are thankful to Torrent Pharmaceutical Ltd. (Gandhinagar) for providing the gift sample of Venlafaxine hydrochloride and also to SICART-Vallabh Vidyanagar for providing us with the spectral analysis results.

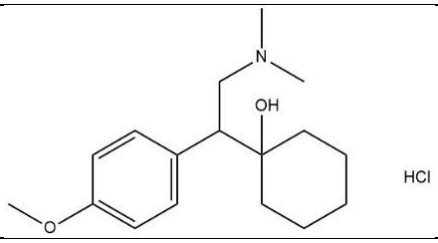
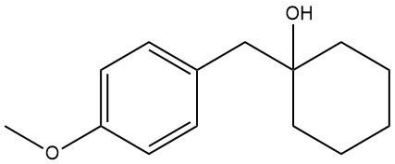
CONFLICTS OF INTEREST

The authors stated that “There are no conflicts of interest to declare”.

Table 1: Spectral report of DP

Molecular formula	$C_{14}H_{20}O_2$
Molecular weight (gm/mole)	220 gm/mole
Rf (n-hexane: ethyl acetate) (7:3)	0.27
IR spectral data (KBr disc) (cm-1)	3427.40 (-OH) 2854.64 (Aliphatic C-H) 1512 (Aromatic C-C) 1249.53 (-C-O)
1H NMR	δ 4.36 (s, 1H, C<u>H</u>) δ 8.51 (s, 1H, O<u>H</u>) δ 3.72 (s, 3H, OC<u>H</u>$_3$) δ 1.37-2.5 (m,10H, C<u>H</u>$_2$) δ 6.79-7.18 (m, 4H, Ar-<u>H</u>)
Mass spectra	219(M+), 202, 134, 119, 91, 58

Table 2: Structural comparison of Venlafaxine hydrochloride and it’s degradation product

Name of the compound	Venlafaxine Hydrochloride	Degradation Product (DP)
Molecular Formula	C17H28ClNO2	C14H20O2
Structure		
Molecular weight	313	220
IUPAC name	1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexan-1-ol;hydrochloride	1-(4-Methoxyphenyl methyl)cyclohexan-1-ol

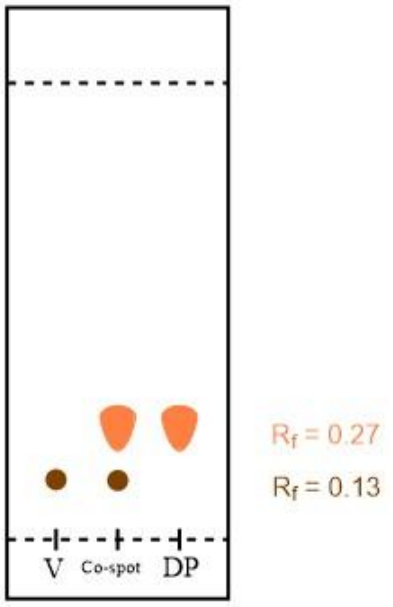


Fig. 1: TLC of Venlafaxine hydrochloride and it's degradation product (DP)

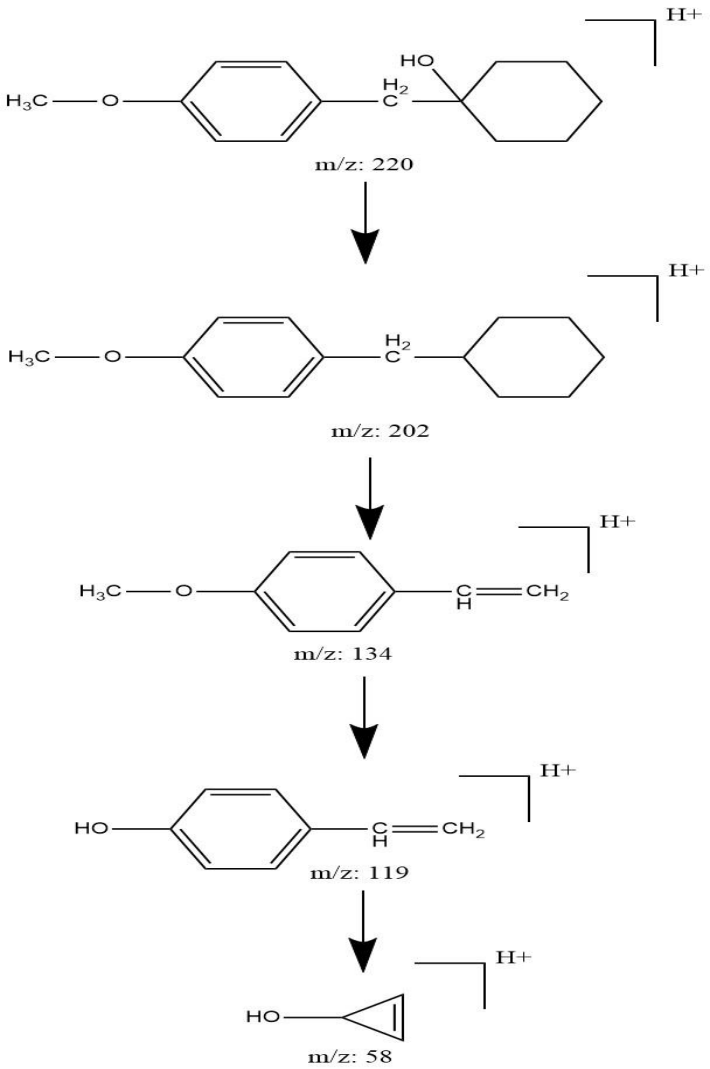


Fig. 2: Fragmentation pattern of DP

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