World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.org/
Original Article

A new approach to forced degradation studies using zolmitriptan tablets by a sensitive liquid chromatographic method

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Received: 24-11-2015 / Revised: 02-03-2016 / Accepted: 09-04-2016 / Published: 28-04-2016

ABSTRACT

Forced degradation is a process that involves degradation of drug products and drug substances at conditions more severe than accelerated conditions and thus generates degradation products that can be studied to determine the stability of the molecule. Chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. Zolmitriptan is a drug used for medication in the treatment of migraines and cluster headaches. This paper focuses on developing forced degradation methods for Zolmitriptan and validated the stability of the Zolmitriptan under different testing conditions. The results obtained from the stress testing show that zolmitriptan drug substance is particularly unstable under acidic, hydrolytic, alkaline, oxidative, photolytic conditions and also thermal degradation process. The results also indicate that the described method is suitable for quantitative determination and the stability study of zolmitriptan.

Key Words: Zolmitriptan, HPLC, Stress testing, Stability- indicating, acidic, neutral, alkaline, oxidation, photolysis, tablets, degradation study.

INTRODUCTION

Zolmitriptan is a selective agonist of 5-HT1B/D receptors[1]. The therapeutic activity of zolmitriptan for the treatment of migraine[2] headache can most likely be attributed to the agonist effects at the 5-$HT_{1B/D}$ receptors on intracranial blood vessels and sensory nerves of the trigeminal system, which result in cranial vessel constriction, and inhibition of pro- inflammatory neuropeptide release. Due to presence of the indole moiety, it is susceptible to undergo degradation. Its chemical structure is shown in Fig. 1.

The IUPAC name is (S)-4-[[3-[2-(dimethyl amino) ethyl]-1H-indole-5-yl] methyl]-2-oxazolidinone. The empirical formula is $C_{16}H_{21}N_3O_2$, representing a molecular weight of 287.36. The ICH guideline states that stress testing is intended to identify the likely degradation products which further helps in determination of the intrinsic stability of the molecule and establishing degradation pathways and to validate the stability indicating procedures used. In the majority of cases, these guidelines only apply to the marketing applications for new products, i.e they do not apply during clinical development. In the literature, few methods have been reported for the estimation of zolmitriptan by spectrophotometric methods, HPLC[3-7]. The main objective of the present work is to develop stress degradation studies of zolmitriptan under different ICH recommended stress conditions[8-10], and to establish a validated stability – indicating RP-HPLC method for pharmaceutical dosage form.

MATERIALS AND METHODS

Zolmitriptan was obtained as a gift sample from Natco Pharma Ltd, Hyderabad, India. The branded formulation of zolmitriptan was procured from the local market. Analytical reagent (AR) NaOH and H_2O_2 were purchased from S.D. Fine-chem. HCl, acetonitrile, methanol, and orthophosphoric acid was from Merk India (Mumbai). All other chemicals were of analytical grade.

Instrumentation and chromatographic conditions: Chromatography was performed by using a shimadzu VP series HPLC model chromatograph equipped with a reverse phase

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inters phenomenex Chromosil ODS C_{18} column (250mm×4.6mm, 5µ), equipped with a manual injector, a 7725 Rhedyne injecting value using a 20µl Hamilton syringe performed sample injection. Shimadzu electronic balance (AX -200) is used for weighing.

All analyses were performed at room temperature (25 $\pm 2^0$ C) under isocratic conditions. The mobile phase consisted of acetonitrile, methanol, and 0.1% orthophosphoric acid (69:29:2, v/v/v). The p^H of the mobile phase was adjusted to 5.1 by adding 0.1% orthophosphoric acid drop by drop. The UV detection was made at 210 nm and the flow rate was1.0 ml/mts.

Preparation of standard solution: A stock solution of zolmitriptan was prepared at about 1 mg/ml in methanol. Standard solutions were prepared from the stock solution after adequate dilution.

Preparation of sample: Ten tablets of zolmitriptan 2.5 mg were weighed and powdered. A portion equivalent to 10 mg of zolmitriptan was accurately weighed and transferred to a 100ml volumetric flask, then 20 ml of acetonitrile, methanol, and 0.1% orthophosphoric acid (69:29:2, v/v/v) was added. The solution was sonicated for 10 mts and the volume was made up with acetonitrile, methanol, and 0.1% orthophosphoric acid (69:29:2, v/v/v) (final concentration of 100 µg/ml), the mixture was vortexed for 15 sec, filtered, and centrifuged for 5 mts, and supernatant was chromatographed. Further dilutions were prepared from the stock solution with a concentration ranging from 0.1959 – 50 µg /ml of the drug in 10 ml volumetric flasks for the concentration of calibration curve.

Method Validation[11]: The method was validated according to the ICH guidelines for validation of analytical procedures.

Stress Testing

Stress testing was carried out according to the ICH stability testing guidance. Zolmitriptan was stressed under various conditions until to facilitate approximate 27% degradation[12]. For each condition, a blank solution was prepared and was subjected to stress in the same manner as the drug; also a control solution of zolmitriptan was prepared, which was stored without the stress condition.

a) Hydrolysis acidic, neutral, and alkaline: A solution of zolmitriptan 10 mg/ml was prepared in methanol, and then an aliquot of 2 ml was transferred to a 10 ml volumetric flask and diluted with 0.1 N HCl, water and 0.1 N NaOH to volume. Samples of 3 ml were kept on a hot place at 80^0 C for acid and neutral hydrolysis for 30 h, 60^0 C for basic hydrolysis for 5 mts, after which they have been cooled to room temperature, then the samples were transferred to a 25 ml volumetric flask, neutralized, and they were diluted to volume.

b) Oxidation: A solution of zolmitriptan 10 mg/ml was prepared in methanol, and then an aliquot of 2 ml was transferred to a 10 ml volumetric flask and diluted with 3% H_2O_2. Samples of 3 ml were kept on a hot place at 80^0C for 6 h and at room temperature (25 $\pm$ 2^0 C) for 7 days in the dark, then they were transferred to a 25 ml volumetric flask, and they were diluted to volume.

c) Thermal degradation: About 50 mg of zolmitriptan was exposed to dry heat at 70^0C in an oven for 21 days. Then a solution of zolmitriptan 100 mg/ml was prepared

d) Photostability: An aqueous/ methanolic solution of zolmitriptan 2mg/ml and solid drug in 1 mm layer in a petri-plate were exposed to UV (210) and VIS radiation (60,000-70,000 lux) for8 days. Then solutions of zolmitriptan 100 mg/ml were prepared. Dark controls were run simultaneously.

RESULTS AND DISCUSSION

Degradation Conditions of Zolmitriptan: In designing forced degradation studies, it must be remembered that more strenuous conditions than those used for accelerated studies should be used. A control solution of zolmitriptan was prepared, which was stored without the stress conditions and it is used with various degradations and the results are presented in Table 1. The following stress conditions should be investigated.

a) Hydrolysis: In all the stress conditions studies the degradation of zolmitriptan was higher under acid hydrolysis stress. After one hr of hydrolysis in 0.1N HCl, the percentage of zolmitriptan degradation was 27.6 %. And after one hour of hydrolysis in water and 0.1N NaOH, it was 4.43 % and 17.5 % respectively. Results are shown in Fig. 2-4.

b) Oxidation: Zolmitriptan was degraded under oxidative stress at room temperature and at 60^o C. After one hrof oxidation at 60^0 C the percentage of zolmitriptan degradation was 0.6%. It was observed that formation of the degradation product was less when compared to that appeared during the same retention time of the hydrolysis. Results are shown in Fig. 5.

c) Thermal degradation: Stress by heat produces a 1.6% of zolmitriptan degradation with the formation of zolmitriptan impurities as the principal degradation product. Results are shown in Fig. 6.

d) Photolytic degradation (VIS light & UV): An aqueous/methanolic solution of zolmitriptan 2

mg/ml and solid drug in 1 mm layer in a Petri-plate, were exposed to UV (210 nm) and VIS radiation (60,000-70,000 lux) for 2 days and was found to be stable. Results are shown in Fig. 7-8.

CONCLUSIONS

A simple stability-indicating LC method for determination of zolmitriptan in the presence of its degradation products has been developed and validated. The method developed can be used for quality control and for stability studies. The results obtained from the stress testing show that zolmitriptan drug substance is particularly unstable under acidic conditions and also in alkaline and thermal degradation process. In order to avoid degradation, care should be taken in the manufacturing process and storage of the product otherwise drug will be degraded and could result in diminution of the therapeutic activity and safety.

Table 1 - Forced degradation summary

Stress conditions	Degradation studies (Hrs.)	ZMT	
		% Assay	% Degradation
Control	-----	99.80	-----
Acid hydrolysis	1	72.11	-27.60
Base hydrolysis	1	82.50	-17.50
Hydrolytic	1	104.43	+4.43
Oxidative	1	99.40	-0.60
Thermal	48	98.40	-1.60
Photolytic degradation (VIS Light)	48	107.73	+7.73
Photolytic degradation (UV Light)	48	100.50	+0.50

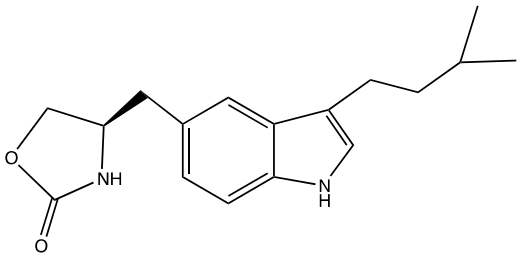

Fig. 1 Structure of Zolmitriptan

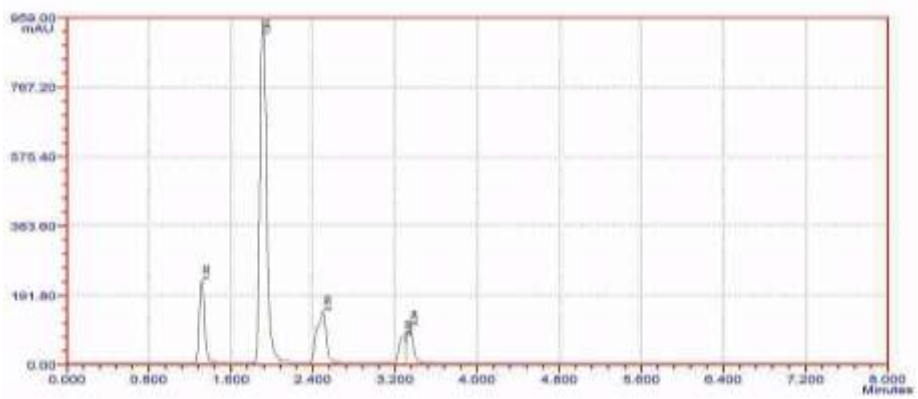

Fig. 2 Chromatogram of acid degradation showing ZMT

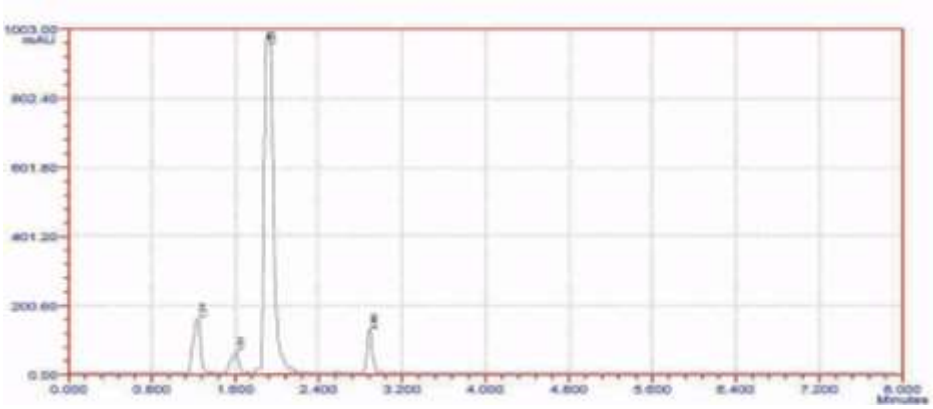

Fig. 3 Chromatogram of base degradation showing ZMT

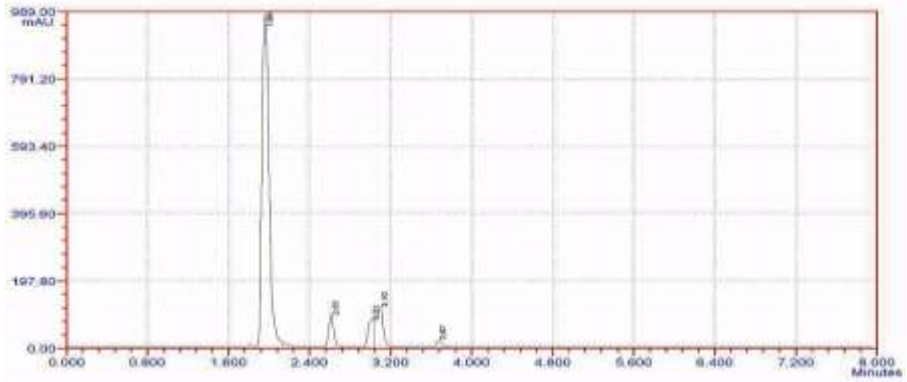

Fig. 4 Chromatogram of hydrolytic degradation showing ZMT

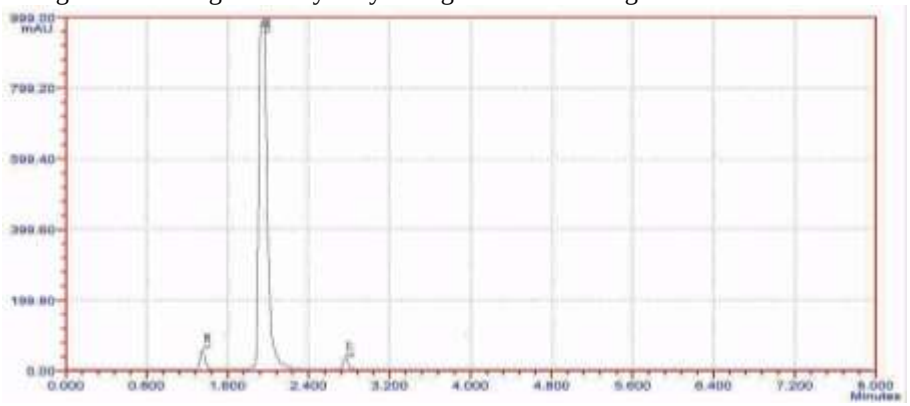

Fig.5 Chromatogram of oxidative degradation showing ZMT

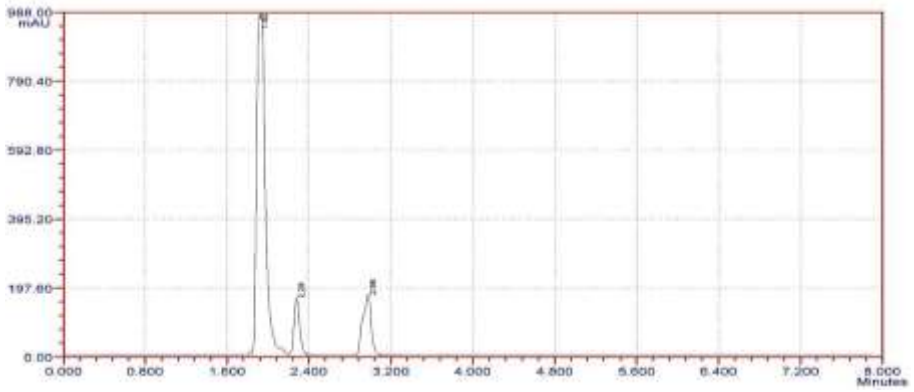

Fig. 6 Chromatogram of thermal degradation showing ZMT

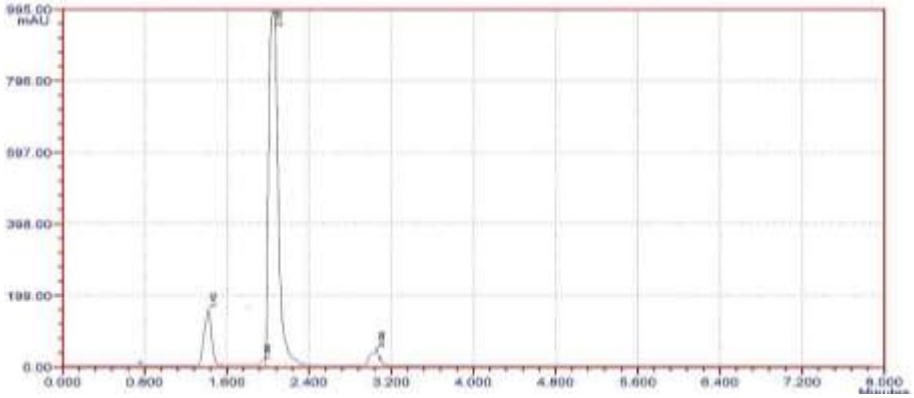

Fig.7 Chromatogram of Photo stability (VIS Light) degradation showing ZMT

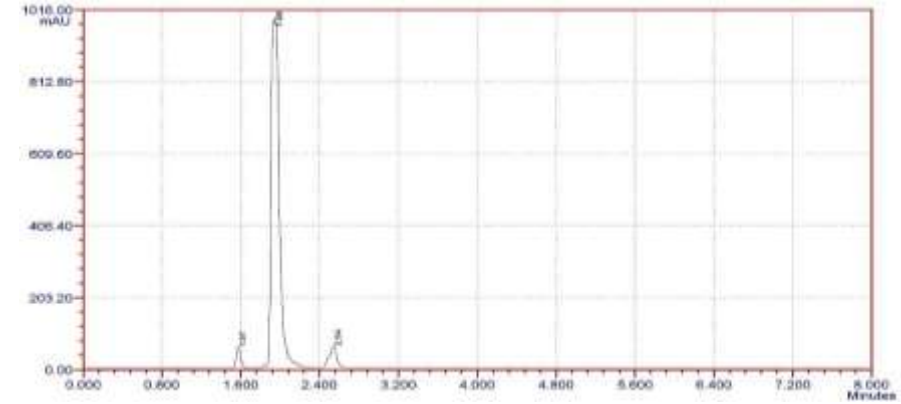

Fig. 8 Chromatogram of Photo stability (UV Light) degradation showing ZMT

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