Journal of Pharmaceutical and Biomedical Analysis 55 (2011) 1237–1238

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Letter to the Editor

What is the degradation product of ezetimibe?

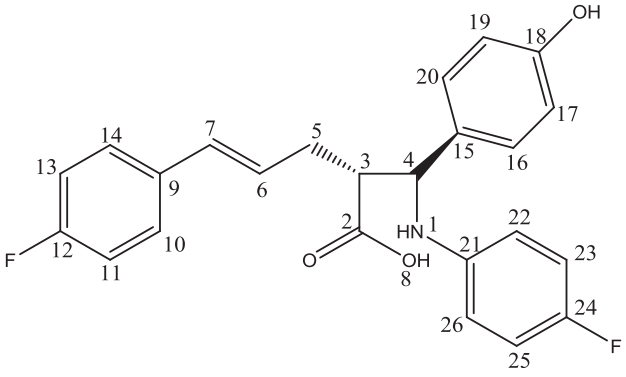
Keywords:
Degradation product
Ezetimibe
^{1}H NMR
^{13}C NMR

Dear Sir,

Gajjar and Shah [1] described the isolation and structure elucidation of the major alkaline degradant of ezetimibe. The authors isolated the degradation product using preparative HPLC, and elucidated its structure as 5-(4-fluorophenyl)-2-[(4-fluorophenylamino)-(4-hydroxyphenyl)methyl]-pent-4-enoic acid using ^{1}H NMR, ^{13}C NMR and mass spectrometry. However, the interpretation of the spectral data is wrong.

In ^{1}H NMR spectrum of the degradation product, protons on C-6 and C-7 (Table 1) showed δ values of 1.48–1.59 ppm (m, 1H) and 2.087–2.116 ppm (d, 1H), respectively, which is an inappropriate assignment, since protons on double bond show δ values between 4.5 and 7.5 ppm [2] and mostly between 5 and 6.5 ppm. Authors claimed the presence of a carboxylic acid proton showing δ value at 4.64 ppm. Ideally the carboxylic protons show a signal at δ values between 10 and 13 ppm [2]. Similarly, in ^{13}C NMR, the authors comment, "Signal at 71.25 ppm of EZE was shifted upfield to 52.99 ppm in the spectrum of degradant confirming loss of –OH on C7 and theformation of double bond between C6 and C7" is incorrect. The

Table 1
^{13}C and ^{1}H NMR spectral assignments of alkaline degradant of EZE reported by Gajjar and Shah [1] and ideal values.



^{13}C NMR				^{1}H NMR			
Assignments	Chemical shift (ppm) for degradant		Remarks	Assignments	Chemical shift (ppm) for degradant		Remarks
	Reported	Approximate ideal values			Reported	Approximate ideal values	
C-7	71.25	127.9	C6 and C7 are alkenic carbons and will show signals at δ values grater than 100 and not less than 100 as reported	H-4 (1H)	4.60 (m)	4.13 (d)	Only a doublet will be seen since it will couple with proton on C3
C-6	36.48	114.8		OH (1H)-on C_2 COOH (H-8)	4.64 (s)	10–13 (s)	Carboxylic acid proton's signal is observed at δ values between 10 and 13
				H-7 (1H)	2.087–2.116 (d)	6.44 (d)	H-6 and H-7 are alkenic protons and will come at δ values at 5–6.5 and not at 1.48–2.1 ppm
				H-6 (1H)	1.48–1.59 (m)	6.06 (d of t)	

doi:10.1016/j.jpba.2011.03.004

formation of double bond will cause a downfield shift in the δ values of carbons and not an upfield shift. The double bond carbons are at δ values between 100 and 140 ppm [2].

The authors found that the molecular ion peak in the mass spectrum of the degradant at m/z value 410 amu $[M+H]^+$ was similar to molecular ion peak of ezetimibe [3]. Further fragmentation of the isolated degradant gives two ions at 392 amu and 299 amu, which are also observed in the fragmentation of ezetimibe. The opening of β-lactam ring in presence of alkali is well known. Ezetimibe degrades rapidly at higher pH values even at room temperature [4,5]. From certain chemical shift values in NMR studies provided by the authors, it is possible that only hydrolysis has taken place and no further dehydration has occurred. But the mass spectrum of the proposed degradant shows molecular ion of m/z value of 410 amu, which can not be accounted for by the hydrolyzed product. Hence the data provided seems to be ambiguous and does not provide any solid information about the structure of degradation product. Mass spectroscopy with different ionization process or a LC–MS/MS method which can further fragment the ions is essential to confirm the structure.

It is also necessary to isolate and characterize the intermediate proposed by the authors in fragmentation pathway determination. Hence an in-depth study on degradation pattern of ezetimibe with conclusive proof by spectral means is very essential before any conclusions are made.

References

[1] A.K. Gajjar, V.D. Shah, Isolation and structure elucidation of major alkaline degradant of ezetimibe, J. Pharm. Biomed. Anal. 55 (2011) 225–229.
[2] R.M. Silverstein, F.X. Webster, D.J. Kiemle, Spectrometric Identification of Organic Compounds, seventh ed., John Wiley & Sons, Inc., NJ, USA, 2005.
[3] B. Raman, B.A. Sharma, R. Butala, P.D. Ghugare, A. Kumar, Structural elucidation of a process-related impurity in ezetimibe by LC/MS/MS and NMR, J. Pharm. Biomed. Anal. 52 (2010) 73–78.
[4] R.P. Dixit, C.R. Barhate, M.S. Nagarsenker, Stability-indicating HPTLC method for simultaneous determination of ezetimibe and simvastatin, Chromatographia 67 (2008) 101–107.
[5] S. Singh, B. Singh, R. Bahuguna, L. Wadhwa, R. Saxena, Stress degradation studies on ezetimibe and development of a validated stability-indicating HPLC assay, J. Pharm. Biomed. Anal. 41 (2006) 1037–1040.

Chandrashekhar R. Barhate*
Krishnapriya Mohanraj
Department of Pharmaceutical Chemistry, Bombay College of Pharmacy, Kalina, Santacruz (E), Mumbai 400 098, Maharashtra, India

* Corresponding author.
E-mail address: cstbar@gmail.com (C.R. Barhate)

25 January 2011
Available online 8 March 2011