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A validated UPLC method for the determination of process-related impurities in Antimigraine bulk drug

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Abstract: *An UPLC method has been developed and subsequently validated for the determination of antimigraine drug and its process-related impurities. Separation was achieved with Halo C18, 50x 4.6 mm, 2.7µm column and 1.36 g ofmonobasic potassium phosphate in 1000 mL of water with 2 mL of triethylamine at pH 6.8 using H_3PO_4, acetonitrile and methanol in the ratio of 55 : 38 : 7 as eluent in isocratic mode. Flow rate was set as 1 mL.min^{-1}UV detection was performed at 225 nm. The method was validated with respect to specificity, accuracy, precision, linearity, robustness, limit of quantification and limit of detection. The accuracy of the method demonstrated at three levels in the range of 50-150% of the specification limit and the recovery of impurities were found to be in range of 98 to 102%. The detection limits of the process related impurities ranged between 0.16 and 0.24 µgmL^{-1}. The described method is simple, rapid, linear, precise, accurate, robust and stability indicating. The method is useful during process development and quality of bulk manufacturing.*

Keywords: *Ultra performance liquid chromatography (UPLC), Antimigrainedrugs, Validationand Process related impurities.*

I. Introduction

Eletriptan hydrobromide is a novel, orally active, selective serotonin 5-HT1B/1D receptor agonist and is second generation anti-migraine drug. Eletriptan hydrobromide is chemically designated as (R)-3-[(1-methyl-2-pyrrolidinyl) methyl]-5-[2-(phenylsulfonyl) ethyl]-1H-indoleMonohydrobromide. Eletriptan hydrobromide used for the treatment of acute migraine headaches. Its pharmacological effects include the constriction of cerebral blood vessels and neuropeptides secretion blockade which eventually relieves the pain. The pharmacokinetics and metabolism of Eletriptan hydrobromide have been investigated in the rat, dog and human. In all three species, Eletriptan hydrobromide was rapidly absorbed and extensively cleared by metabolism. The pathways of Eletriptan metabolism are similar in the rat, dog and human and principal routes include pyrrolidine N-demethylationto N-desmethyl Eletriptan, together with N-oxidation, oxidation of the pyrrolidine ring and formation of tetra cyclic quaternary ammonium metabolites.

A few methods are reported in the literature for the analysis of drugs by HPLC [1-7], LC-MS [8-10], MS-MS [11], spectrometric [12-16] and TLC [17]. UPLC is a new category of separation science which builds upon well-established principlesof liquid chromatography, using sub-2µm porous particles. These particles operate at elevated mobilephase linear velocities to produce rapid separation with increased sensitivity and increased resolution.

In this study, Eletriptan hydrobromide is selected from antimigraine category of drugs. The objective of this work was to develop and validate a stability indicating UPLC method forthe determination of process related impurities in Eletriptan hydrobromide.

II. Experimental Data

2.1. Chemicals

Jiangsu Pharma limited (China) kindly supplied samples of Eletriptan hydrobromide and its process-related impurities (Table 1). HPLC grade acetonitrile, HPLC grade methanol, monobasic potassium phosphate, orthophosphoric acid and triethylamine were purchased from Merck (India). Sodium hydroxide (NaOH), Hydrochloric acid (HCl) and Hydrogen peroxide (H_2O_2) were obtained from Fisher Scientific (Mumbai, India).High purity water was obtained by Siemens Ultra clear water purification system. Solvents, mobile phase components and all required solutions were filtered through 0.22 µ syringe filter purchased from Millipore, India.

2.2. Equipment

A Waters Acquity UPLC system equipped with binary solvent delivery pump, an auto sampler, a column oven and diode array detector was utilized for method development and validation. The output signal was monitored and processed using Empower software.

Cintex digital water bath was used for acid and base hydrolysis studies. Photostability studies were carried out in a Sanyo Photostability chamber (Leicestershire, UK). Thermal stability studies were performed in a dry air oven from Thermo (Mumbai, India).

2.3. Sample preparation

2.3.1. Test solution

The test solution of 1.0 mg mL^{-1} was prepared in diluent (methanol) and injected inthe system for the test of determination of related impurities in Eletriptan hydrobromide bulk drug.

2.3.2. Solution for determination of relative response factor

The blend solution containing 5 µg mL^{-1} concentration of Eletriptan hydrobromide and each impurity was prepared in methanol. Thissolution was used for the determination of relative response factor of all the impurities.

2.3.3. Validation solution

The solution of 10 µg mL^{-1}concentration for each impurity separately as well as blend solution was prepared. These two solutions were used as stock solution to prepare validation solutions.

2.4. Chromatographic conditions

A Halo C18 analytical column (50 mm x 4.6 mm, 2.7 µm) was used for analysis at 30°C. The bufferwas prepared asdissolved 1.36 g of monobasic potassium phosphate in 1000 mL of water, added 2.0 mL of triethylamine and adjusted the pH to 6.8 with orthophosphoric acid. The mobile phase consisted of buffer, acetonitrileand methanol in the ratio of 55 : 38 : 7 in isocratic mode and was pumped through the column at a flowrate of 1.0 mL min^{-1}. The sample injection volume was 1 µL. The wavelength was set at 225 nm for the detection.

2.5. Method validation

2.5.1. Resolution and Selectivity

The resolution (Rs) was calculated as $Rs = 2(t_2 - t_1)/ (w_1 + w_2)$ where, t_1, t_2 refer to the retention time of the first and second analytes; w_1 and w_2 are the peak widths for the first and second eluting analytes, respectively. The selectivity (α) is the relative retention measured for two adjacent peaks. It was calculated as, $\alpha = (t_2 - t_0)/ (t_1 - t_0)$ where, t_0 refers to the retention time of the unretained peak.

2.5.2. Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components, which may beexpected to be present. The specificity of the method was demonstrated by injecting each process-related impurity (Table 1) as well as spiked with Eletriptan sample. The retention time of each impurity was specified.

2.5.3. Precision (repeatability and reproducibility)

The precision of an analytical procedure expresses the closeness of agreementbetween a series of measurements from multiple sampling of the same homogeneous sample under prescribed conditions. Precision maybe considered as a repeatability and reproducibility. Repeatability expresses the precision under the same operatingconditions over a short interval of time. Repeatability of the method was studied by spiking impurities with Eletriptanwhich contains 10 µg mL^{-1}concentration for each impurity separately. The precision was examined by analyzing six replicates and the percentage relative standard deviation was calculated for the area and retention time of all the impurities and Eletriptanto demonstrate repeatability. Reproducibility reveals the precision between laboratories. Reproducibility is normally expressed as the lack of the influence on the test results of operational and environmental variables of the analytical method. In order to demonstrate reproducibility of the method the precision experiment was repeated by using different laboratory, different instrument, and different column on another day. The percentage bias of result was calculated between original condition and changed condition.

2.5.4. Linearity

The linearity of an analytical procedure is its ability to obtain test results, which are directly proportional tothe concentration of the analyte in the sample. Standard solutions at six different concentration levels ranging from 0.3 µg$mL^{-1}$to 3 µg mL^{-1}were prepared and analyzed in order to demonstrate the linearity for all theimpurities. The regression curve was obtained by plotting peak area versus concentration, using the least squares method andregression equation was obtained for all the impurities.

2.5.5. Limit of detection and limit of quantification

The limit of detection (LOD) of a compound is defined as the lowestconcentration that can be detected. The limit of quantification (LOQ) is the lowest concentration of a compound that can bequantified with acceptable precision and accuracy. The LOD and LOQ for impurities were calculated from the linearity data using formula 3σ/S and 10σ/S respectively. The six points linearity curve obtained in linearity study in the range of 0.3 µg mL^{-1} to 3 µg mL^{-1} for each impurity was used to determined residual standard deviation (σ) and slope (S).

2.5.6. Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value, which isaccepted either as a conventional true value or an accepted reference value and the value found. The standard addition andrecovery experiments were conducted to demonstrate accuracy of the method. The study was carried out in triplicate for the determination of recovery at 50, 100 and 150% concentration of specification level for all the impurities. The peak area for eachimpurity was determined and recovery was calculated from the peak area of impurity standard solution at the same concentrationlevel.

2.5.7. Robustness

The robustness of an analytical procedure is the measure of its capacity to remain unaffected by small, butdeliberate, variations in method parameters and provides an indication of its reliability during normal usage. The robustnessof a method was demonstrated by altering experimental conditions and chromatographic resolution between Eletriptan hydrobromide(ETN) and its closest eluting impurity i.e. Impurity-B was used to evaluate robustness. The deliberate changes were made in thechromatographic conditions, viz. change in flow rate by$\pm$0.2 mL $min^{-1}$and change in the column temperature $\pm$5°C.

2.5.8. Solution stability

Chromatographic analyses typically are performed by using auto samplers and overnight runs. As such,it is important to verify that the sample is stable in the solution prescribed by the method for periods encompassing the expectedanalysis duration period. Stability of test solution at analyte concentration was studied by keeping the solution in tightly cappedvolumetric flask at room temperature on a laboratory bench for 24 h. The purity of the test solution was checked for 6 h interval.

2.6. Quantification of process related impurities

The relative response factors for process related impurities were determined from the solution containing Eletriptan and allthe process related impurities in known amounts i.e. 5 µg mL^{-1}. The accurate weight percentage of the impurity present in Eletriptan sample was calculated using its RRF value and peak response. The percentage area obtained from the areanormalized method was divided by corresponding RRF value to determine accurate amount of each impurity.

III. Results and discussion

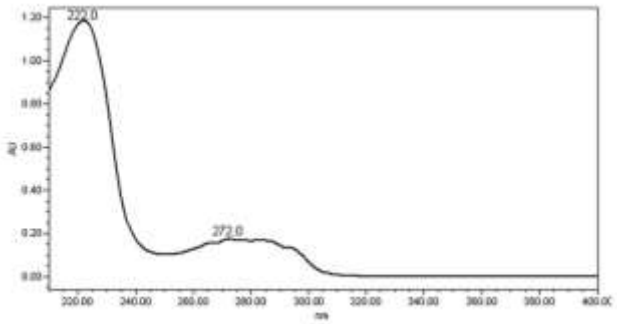
3.1. Method development

The present study is aimed at developing anUPLCsystem capable of eluting and resolving Eletriptan and its synthesis relatedimpurities. Structure of impurities and Eletriptanare shown in Table 1. The selection of wavelength becomes a challenging task to detect all the compounds at single wavelength since the UV profile of all the compounds is different. UV spectra of all thecompounds were studied by scanning them between 190 nm to 400 nm (Fig. 1). It can be seen that it is difficult to detect all thecompounds at single wavelength with equal response. However, 220 or 225 nm wavelength can be selected as common wavelength for detection. During the experiments, it has been observed that baseline stability, mobile phase interference and noise level weremore desirable at 225 nm than 220 nm. Moreover, theadequate detection and quantification limit were found for all theimpurities at 225 nm therefore, 225 nm was finalized as commonwavelength for detection. Additionally, relative response factor ofall the impurities was evaluated for accurate determination.The method development was initiated with water :acetonitrile or methanol (90 : 10 v/v) as a mobile phase in isocraticmode using Acuity UPLC BEH C18 (100 x 2.1 mm,1.7 µm) column at 30°C. Under this condition results were notsatisfactory. Water was replaced by 0.01Mmonobasic potassium phosphate inwater, whichwas slightly improved peak shape but not the resolution. After the addition of triethylamine in buffer with pH 6.8 using H_3PO_4, which enhanced the peak shape and all the impurities were well separated. This much difference in the retention time isindicative of differences in the polarity of the each compound.Several, permutationsand combination of buffer, acetonitrile and methanol have been scanned to finalize thecomponents of mobile phase. It has been observed that 55 : 38 :7 (Buffer, acetonitrile and methanol) gave better result than any other tested combinations. Finally, isocratic program of 55 : 38 :7 (Buffer, acetonitrile and methanol), with flow rate of 1.0 mL min^{-1} was found to be optimal. The representative chromatogram isshown in Fig. 2 and resolution and selectivity data are summarized

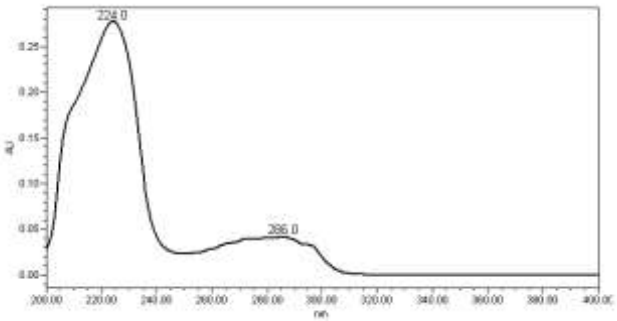
in Table 2. UPLC column HSS T3 C18 (100 x 2.1 mm,1.8 µm) and different buffers were also tried but the results were not encouraging.

Fig. 1 UV Spectra of Eletriptan and its impurities

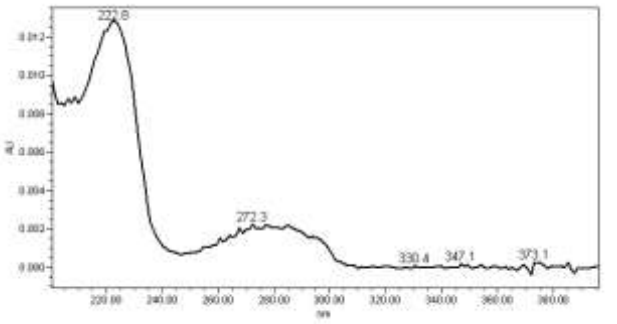
ETN



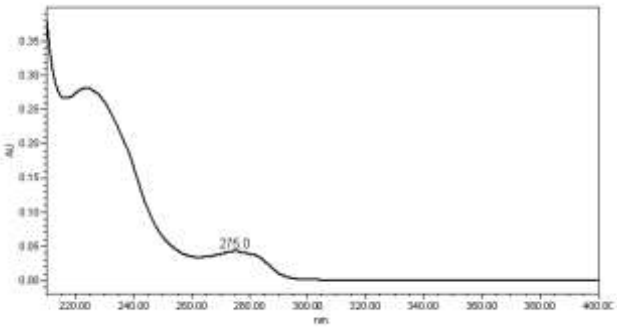
Imp-A



Imp-B



Imp-C



Imp-D

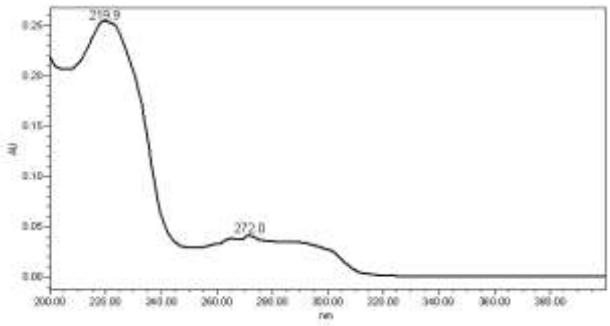


Fig. 2 UPLC finalized condition chromatogram

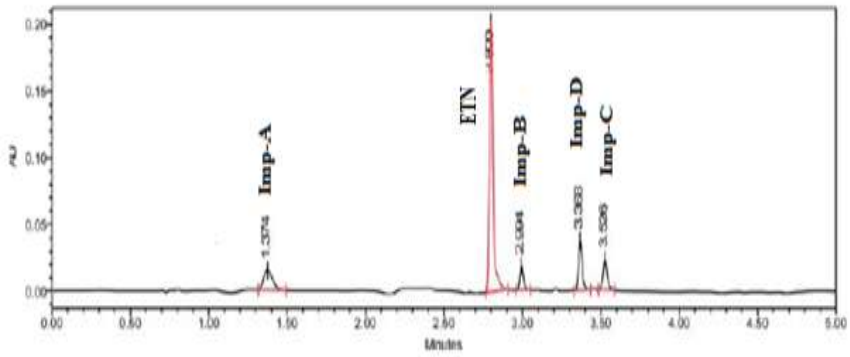


Table 1. Structure of Eletriptan and its process related impurities

Name	Structure	Details
Imp-A		(R,E)-3-((1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)vinyl)-1H-indole hydrobromide Chemical Formula: $C_{22}H_{25}BrN_2O_2S$ Molecular Weight: 461.42
Imp-B		(R)-5-ethyl-3-((1-methylpyrrolidin-2-yl)methyl)-1H-indole Chemical Formula: $C_{16}H_{22}N_2$ Molecular Weight: 242.36
Imp-C		(R,E)-3-((1-methylpyrrolidin-2-yl)methyl)-1-(2-(phenylsulfonyl)ethyl)-5-(2-(phenylsulfonyl)vinyl)-1H-indole Chemical Formula: $C_{30}H_{32}N_2O_4S_2$ Molecular Weight: 548.72
Imp-D		(R)-3-((1-methylpyrrolidin-2-yl)methyl)-1,5-bis(2-(phenylsulfonyl)ethyl)-1H-indole Chemical Formula: $C_{30}H_{34}N_2O_4S_2$ Molecular Weight: 550.73

ETN		(R)-3-((1-methylpyrrolidin-2-yl)methyl)-5-(2-(phenylsulfonyl)ethyl)-1H-indole hydrobromide Chemical Formula: $C_{22}H_{27}BrN_2O_2S$ Molecular Weight: 463.43

Table 2. Results of selectivity and resolution

Name	Retention time	Selectivity	Resolution
Impurity A	1.374	---	---
ETN	2.800	2.63	19.6
Impurity B	2.994	1.08	4.88
Impurity D	3.368	1.15	8.93
Impurity C	3.526	1.06	3.45

3.2. Result of relative response factor

The relative response factor (RRF) of Impurity-A, Impurity-B, Impurity-C, and Impurity-D with respect to Eletriptan werefound to be 0.94, 0.96, 0.92 and 0.90 respectively.

3.3. Validation results of the method

Eletriptanand its related impurities were well resolved with no interference from the blank and mobile phase. In the precisionstudy, the percentage relative standard deviation (RSD) of six replicates was found less than 0.1% for retention time and 2.0%for peak area of all the impurities and Eletriptan, indicating good repeatability of the method (Table 3). The results of the reproducibility study under a different set of conditions are also in the same order of magnitude. The percentage bias between two different sets of conditions for retention time and peak area was within $\pm$0.36 and $\pm$0.64 respectively for all the impurities (Table 3), indicates that method is rugged for its intended use. The described method was linear in the range of 0.3 $\mu g mL^{-1}$ to3 $\mu g\ mL^{-1}$ of each impurity, which was demonstrated acceptability of the method for the quantitative determination in that range. The value of slope, intercept and correlation coefficient for each impurity are shown in Table 4.The LOD and LOQ concentration were estimated for all the impurities and are in the range of 0.16 to 0.24 $\mu g\ mL^{-1}$ and 0.49to 0.74 $\mu g mL^{-1}$ respectively (Table 4). The method showed excellent recovery at three different studied concentrations, 50, 100 and 150% of specification level for all the impurities (Table 5). The mean recoveries of all the impurities were found to be in the range of 98 to 102%. The chromatographic resolution between closest eluting impurity i.e. Impurity-B and Eletriptanwas used to evaluate the method robustness under modified conditions. There was no significant change in resolution under all separation conditions tested (Table 6), demonstrating sufficient robustness. No significant change in the purity of Eletriptanwas observed during solution stability experiments. Thus, Eletriptantest solution was found to be stable for at least 24 h.

Table 3. Results of repeatability and reproducibility study

Compound	Original condition		Different condition		%Bias	Original condition		Different condition		%Bias
	Average retention time	%RSD (n=6)	Average retention time	%RSD (n=6)		Average Peak area	%RSD (n=6)	Average Peak area	%RSD (n=6)	
Impurity A	1.36	0.13	1.36	0.10	0.0	11985	0.89	12025	0.65	0.34
Impurity B	3.01	0.02	3.02	0.18	0.33	3966	0.20	3967	0.97	0.03
Impurity C	3.53	0.02	3.53	0.03	0.0	4954	0.95	4962	0.24	0.16
Impurity D	3.38	0.02	3.39	0.09	0.30	11773	1.76	11806	0.79	0.28
ETN	2.81	0.04	2.82	0.10	0.36	5744324	0.90	5707314	0.19	-0.64

Table 4. Results of linearity and LOD, LOQ study of impurities

Parameter	Result			
	Impurity A	Impurity B	Impurity C	Impurity D
Correlation coefficient	0.999	0.998	0.999	0.999
Y-Intercept	302.04	-374.09	-165.57	-78.68
Slope	6667.2	3318	4803.6	5809.1
Residual standard deviation	327.24	245.87	251.30	297.88
LOD / $\mu g\ mL^{-1}$	0.16	0.24	0.17	0.17
LOQ / $\mu g\ mL^{-1}$	0.49	0.74	0.52	0.51

Table 5. Results of accuracy study of impurities

Level (%)	Added / ng mL^{-1}	Recovered / ng mL^{-1}	% Recovery
Impurity A (n=3)			
50	1000	999.5	99.95
100	2000	1997	99.85
150	3000	3008.7	100.29
Impurity B (n=3)			
50	1000	984.4	98.44
100	2000	1976.8	98.84
150	3000	2973.6	99.12
Impurity C (n=3)			
50	1000	1001.9	100.19
100	2000	2000.2	100.01
150	3000	2985.9	99.53
Impurity D (n=3)			
50	1000	1002.1	100.21
100	2000	1997	99.85
150	3000	3007.2	100.24

Table 6. Results of robustness study

Parameter	Resolution between ETN and Impurity B (n=3)
Flow rate mL min^{-1}	
0.8	5.08
1.0	4.85
1.2	4.65
Column Temperature °C	
25	4.94
30	4.85
35	4.76
Concentration of triethylmine (%)	
0.01	4.83
0.02	4.85
0.03	4.84

3.4. Degradation study

Degradation studies were performed to demonstrate selectivity and stability-indicating capability of the proposed method. The sample was exposed to acid (0.1N HCl, 80°C for 48 hours), base (0.1N NaOH, 80°C for 48 hours), oxidation (3% H_2O_2, Room temperature for 24 hours), thermal solid state (60°C for 7 days), thermal liquid state (80°C for 6 Hours), humidity (75% RH, 40°C, 7 Days) and photolytic (1.2 million lux hours, 200 w.hr/m^2, 18 days) degradation conditions. Samples were withdrawn at appropriate times and subjected to UPLC analysis after suitable dilutionto evaluate the ability of the proposed method to separate Eletriptan from its degradation products. Photodiode array detector was employed to check and ensure the homogeneity and purity of Eletriptan peak in all the stressed sample solutions.

The degradation study revealed that Eletriptanwas sensitive to peroxide and light compared to other degradation conditions. Eletriptan hydrobromide (ETN) was degraded during oxidation (3% H_2O_2, Room temperature for 24 hours) at around 6% level and it was degraded during light exposure (1.2 million lux hours, 200 w.hr/m^2, 18 days) at around 9% level. The API and its impurities were treated with different degradation conditions including acid, base, peroxide, photolytic, humidity and thermal degradations. The degradation results were shown in Table 7.

Table 7.Forced degradation results of ETN

Degradation conditions	% Imp-A	% Imp-B	% Imp-C	% Imp-D	% Major degradation product
Acid treatment (0.1N HCl, 80°C for 48 hours)	0.04	0.08	---	0.04	0.30
Base treatment (0.1N NaOH, 80°C for 48 hours)	---	0.18	---	0.04	0.17
H_2O_2 treatment (3% H_2O_2, Room temperature for 24 hours)	---	0.14	---	0.01	6.40
Thermal (liquid state) - 80°C for 6 Hours	---	0.13	---	0.01	0.08
Thermal (solid state) - 60°C for 7 days	0.01	0.14	0.01	0.03	0.14
Humidity-75% RH, 40 °C, 7 days	---	0.16	---	0.03	0.09
Photolytic-1.2 million lux hours, 200 Wh/m^2, 18 days	---	0.09	0.07	0.04	8.77

The degradation of API in acid, base, thermal and humidity conditions was observed to be lower. Spectral purity of API and its impurities in the chromatogram of all the exposed samples are obtained from PDA and found to be spectrally pure, indicating that there was no co-elution of peak at the retention time of the respective known and unknown impurities. The max plot chromatogram of degradation sample was also checked to ensure that no degradation peak is missed due to use of wavelength of 225 nm.

3.4. Analysis of bulk drug

To demonstrate applicability of the developed method several different lots of Eletriptanbulk drug have been tested. Sampleof Eletriptanwas prepared at test concentration i. e. 1.0 mg mL^{-1} in diluent (methanol) and injected inequilibrated UPLC system after two run of diluent. Area percentage of impurities was obtained by area normalized method and the actual percentage of each known impurity was calculated by dividing area percentage with its corresponding RRF value. The results of five representative lots of Eletriptanbulk drug are presented in Table 8.

Table 8. Results of analysis of different lots of Eletriptan bulk drug

Name	Content of impurities in different lots (%)				
	ETN 001	ETN 002	ETN 003	ETN 004	ETN 005
Impurity A	0.12	0.17	0.11	0.09	0.19
Impurity B	BQL	0.05	BQL	BQL	BQL
Impurity C	0.04	0.07	BQL	BQL	0.04
Impurity D	0.05	0.11	0.06	BQL	0.07
Unknown impurity	---	0.04	---	---	0.05
Eletriptan	99.79	99.56	99.83	99.91	99.65
BQL: Below Quantification Level					

IV. Conclusion

A simple, rapid, suitable, precise, accurate and stability indicating UPLC method has been developed for the determination of the process relatedimpurities in Eletriptanbulk drug. All the impurities were well resolved within 5 min and resolution of the closest eluting peaks was more than 4.8. The developed method was completely validated with respect to specificity, system suitability, linearity, limit of detection and quantitation, accuracy, precision, robustness and solution stability. The result of validation showed satisfactory data for all the parameters tested. The developed method can be used for the determination ofprocess related impurities (Impurity-A, Impurity-B, Impurity-C and Impurity-D) in Eletriptanin the bulk drug substance.

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