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# A novel LC-MS method development and validation for the determination of phenyl vinyl sulfone in eletriptan hydrobromide

Indhu Priya Mabbu[1*], G. Sumathi[2] and N. Devanna[1]

## Abstract

**Background:** The aim of the present method is to develop and validate a specific, sensitive, precise, and accurate liquid chromatography-mass spectrometry (LC-MS) method for the estimation of the phenyl vinyl sulfone in the eletriptan hydrobromide. The effective separation of the phenyl vinyl sulfone was achieved by the Symmetry C18 (50 × 4.6 mm, 3.5 µm) column and a mobile phase composition of 0.1%v/v ammonia buffer to methanol (5:95 v/v), using 0.45 ml/min flow rate and 20 µl of injection volume, with methanol used as diluent. The phenyl vinyl sulfone was monitored on atomic pressure chemical ionization mode mass spectrometer with positive polarity mode.

**Results:** The retention time of phenyl vinyl sulfone was found at 2.13 min. The limit of detection (LOD) and limit of quantification (LOQ) were observed at 1.43 ppm and 4.77 ppm concentration respectively; the linear range was found in the concentration ranges from 4.77 to 27.00 ppm with regression coefficient of 0.9990 and accuracy in the range of 97.50–102.10%. The percentage relative standard deviation (% RSD) for six replicates said to be injections were less than 10%.

**Conclusion:** The proposed method was validated successfully as per ICH guidelines. Hence, this is employed for the determination of phenyl vinyl sulfone in the eletriptan hydrobromide.

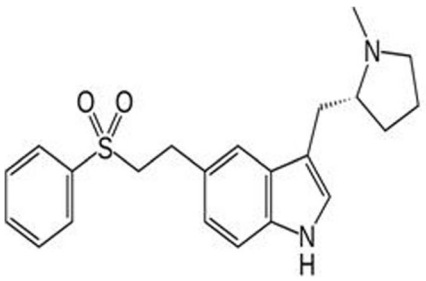
**Keywords:** Phenyl vinyl sulfone, Eletriptan, Atomic pressure chemical ionization, Limit of detection

## Background

Eletriptan is a selective serotonin receptor agonist, which especially blocks the 5-$HT_{1B/1D}$ receptors [1–3]. It was used as the first line drug of choice for the severe headache and migraine. Chemically, eletriptan is 5-[2-(benzenesulfonyl)ethyl]-3-{[(2R)-1-methylpyrrolidin-2-yl]methyl}-1H-indole [4]. Phenyl vinyl sulfone is used as building blocks in the synthesis of a number of organic substances, involved in polymerization reactions. Chemically, it is ethenyl sulfonyl benzene [5]. Chemical structures of eletriptan and phenyl vinyl sulfone were shown in Fig. 1.

The phenyl vinyl sulfone is used in the synthesis of eletriptan; hence, phenyl vinyl sulfone can be considered as process impurity [6]. As per ICH Q3 guidelines, the acceptance limit for the presence of unknown and known impurities in the drug substance is 0.10 to 0.15% [7]. In general, various analytical methods like high-performance liquid chromatography (HPLC), Fourier-transform infrared spectroscopy, and liquid chromatography-mass spectrometry (LC-MS) are used for identification, characterization, and quantification of impurities present in the drug substance and drug product. Based on literature review, few analytical methods like high-performance liquid chromatography methods and LC-MS methods were available for separation of forced degradation impurities of eletriptan [8–11]. But as of now, no LC-MS method has been reported for the determination of phenyl

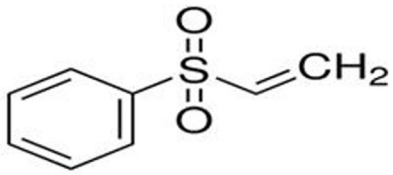
* Correspondence: priyamabbu245@gmail.com
[1]Department of Chemistry, Jawaharlal Nehru Technological University Anantapur, Anantapur, Andhra Pradesh 515002, India
Full list of author information is available at the end of the article



Eletriptan

Molecular weight: 382.52 g/mol

Molecular formula: $C_{22}H_{26}N_2O_2S$



Phenyl vinyl sulfone

Molecular Weight: 168.21 g/mol

Molecular Formula: C8H8O2S

**Fig. 1** Chemical structures of eletriptan and phenyl vinyl sulfone

vinyl sulfone in eletriptan hydrobromide. Hence, we aimed to develop a LC-MS method for the determination of phenyl vinyl sulfone in eletriptan hydrobromide.

## Methods

The phenyl vinyl sulfone reference standard (claim 99.32%) was procured from Fortune Pharma, Hyderabad, as a gift sample. All HPLC grade solvents were obtained from the Merck India Limited, Mumbai, India. All the solvents and solutions used were filtered through millipore (0.25 μm) filters.

### Optimized LC-MS method conditions

The Waters LC-MS with auto sampling system was used to perform the method. Separation of the phenyl vinyl sulfone was successfully achieved by the Symmetry C18 (50 × 4.6 mm, 3.5 μm) column and a mobile phase composition of 0.1%v/v ammonia buffer to methanol (5:95 v/v), using 0.45 ml/min flow rate and 20 μl of injection volume, with methanol used as diluent. The temperature maintained in the auto sampler and column was 5 °C and ambient respectively. MS parameters were mentioned in the Table 1.

### Preparation of phenyl vinyl sulfone standard stock solution (1000 ppm)

Two hundred fifty milligrams of phenyl vinyl sulfone standard substance was weighed accurately and transferred into 10 ml volumetric flask and diluted with diluent. The 0.4 ml of above solution was further diluted to 10 ml to get a concentration of 1000 ppm.

### Preparation of standard solution (18.0 ppm)

0.36 ml of the standard stock solution was diluted to 20 ml to obtain a standard concentration of 18 ppm.

### Preparation of test solution

The test solution accurately weighed about 100.00 mg of the eletriptan test sample and was diluted to 10 ml with diluent.

### Method validation

#### *System suitability test*

The system suitability of the method was performed by injecting blank solution once and 100% level standard solution of phenyl vinyl sulfone for six times into LC-MS system. The system suitability was confirmed by assessing the % RSD.

#### *Linearity*

The linearity of a method represents the direct proportional relationship between concentration and test result. It was conducted for the phenyl vinyl sulfone in the range of LOQ level (4.767 ppm) to about 150% of limit (27.00 ppm) by injecting each level of concentration two times and plotted a curve between

**Table 1** MS parameters

| | |
|---|---|
| Ionization mode | APCI |
| Acquisition mode | SIM |
| Polarity mode | Positive |
| Ch1 | 169.14 $[M + H]^+$ |
| Light source temperature | 120 °C |
| Heat block | 350 °C |
| Cone gas flow | 50 L/Hr. |
| Desolvation gas flow | 950 L/Hr |
| Capillary [KV] | 3.50 [KV] |
| Cone [V] | 25.00 V |
| Extractor [V] | 3.0 V |

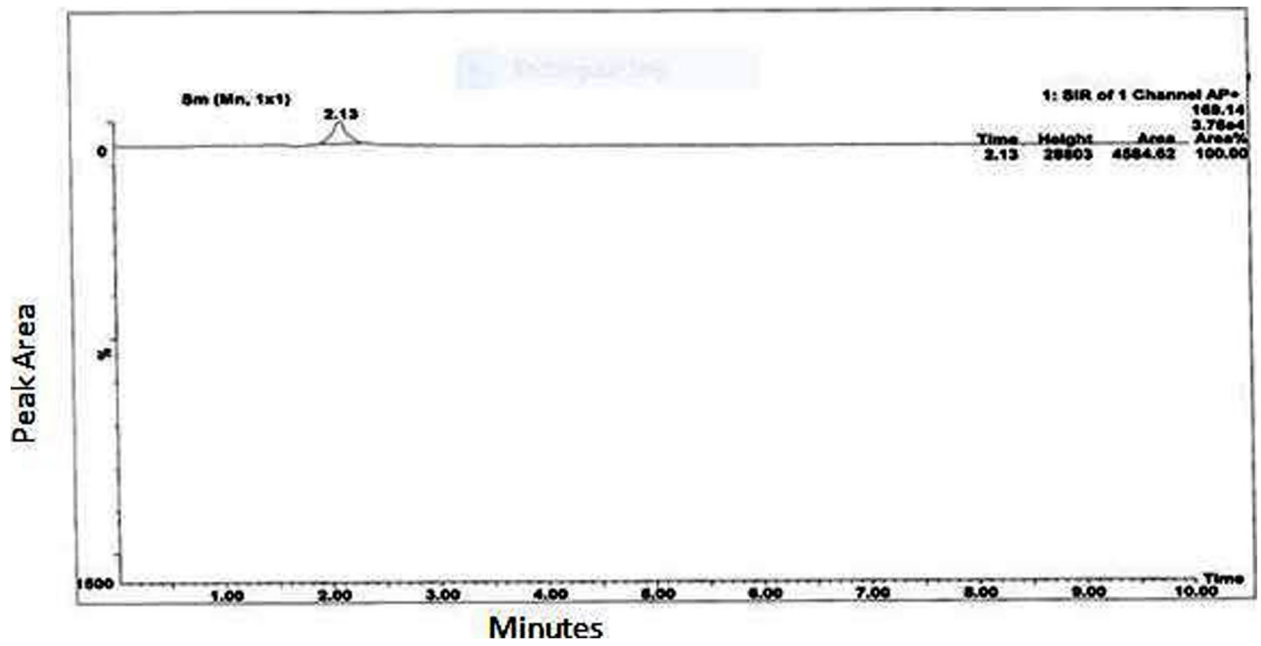



**Fig. 2** Chromatogram of phenyl vinyl sulfone

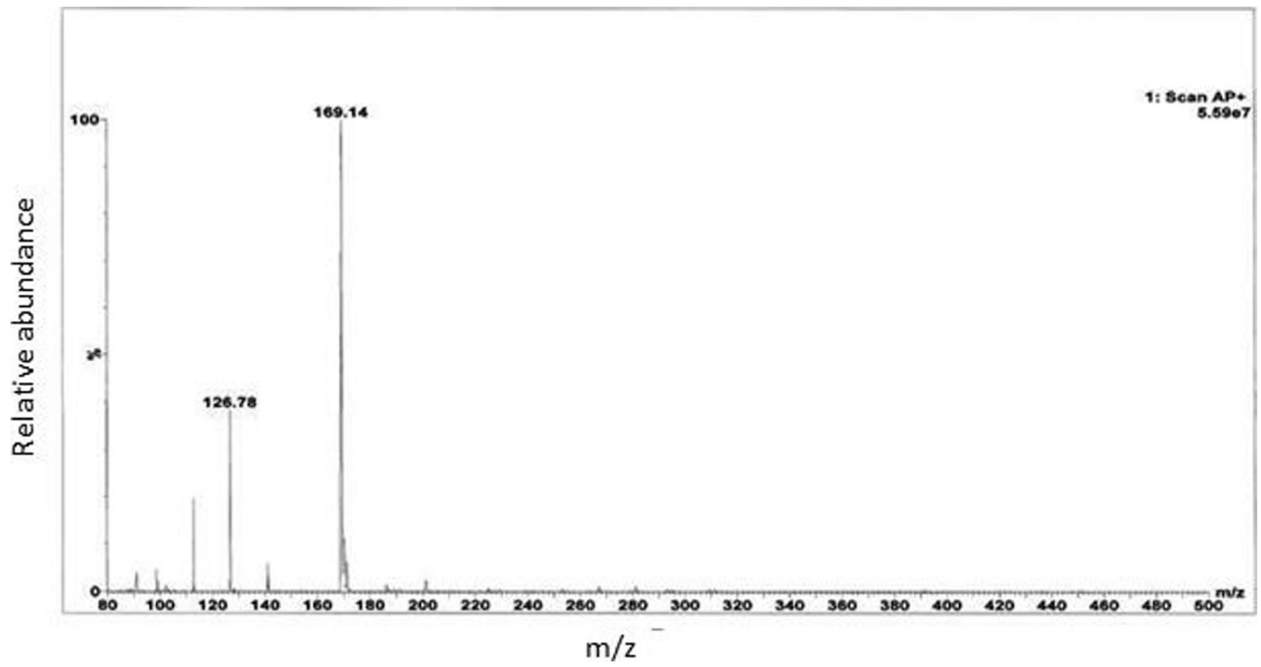



**Fig. 3** Mass spectrum of phenyl vinyl sulfone

average peak area versus concentration in ppm to find out the regression coefficient value.

### *Accuracy*

The accuracy of the method has been done by performing the recovery studies, at LOQ level, 50%, 100%, and 150% level. A known amount of phenyl vinyl sulfone spiked separately to pre-analyzed samples of the mentioned levels. Each spiked level was injected for three times into the LC-MS system and calculated the percent recovery of each level.

### *Method precision*

The method precision was performed by spiking the sample with phenyl vinyl sulfone at 100% of the specified limit with respect to the sample concentration. Six homogenous replicates were injected and calculated the content of phenyl vinyl sulfone to determine the % RSD.

### *Intermediate precision*

The intermediate precision was performed by spiking the sample with phenyl vinyl sulfone at 100% of the specified limit with respect to the sample concentration in six preparations. The intermediate precision study was carried out on different days with different analysts. We calculated the content of phenyl vinyl sulfone in spiked preparations and determined the % RSD.

### *Sensitivity (LOD and LOQ)*

Limit of detection (LOD) and limit of quantification (LOQ) of the analytical method were determined by using signal to noise ratio. The LOD solution was prepared in such a way to obtain the S/N ratio is about 3:1 to 5:1. Based on the concentration of LOD, the LOQ solution was prepared (3 times to LOD concentration) to obtain the signal to noise ratio of about 10:1 to 15:1.

**Table 2** System suitability results of phenyl vinyl sulfone

| Injection no. | Peak area of phenyl vinyl sulfone |
|---|---|
| 1 | 4665.99 |
| 2 | 4663.07 |
| 3 | 4560.94 |
| 4 | 4740.70 |
| 5 | 4584.62 |
| 6 | 4624.78 |
| **Average** | **4640.02** |
| ***% RSD** | **1.39** |

**% RSD* percentage relative standard deviation

## Results

Initially, the solubility of the phenyl vinyl sulfone was checked in various solvents. It was found that phenyl vinyl sulfone was slightly soluble in methanol and water.

### Method optimization

The optimized LC-MS method was achieved by using trial and error methods. After several trails, an efficient method was obtained by the Symmetry C18 (50 × 4.6 mm, 3.5 µm) column and a mobile phase composition of 0.1%v/v ammonia buffer to methanol (5:95 v/v), using 0.45 ml/min flow rate and 20 µl of injection volume, with methanol used as diluent. The temperature maintained in the auto sampler and column was 5 °C and ambient respectively. The phenyl vinyl sulfone in the optimized chromatogram was eluted at 2.13 min (Fig. 2) and molecular ion and base peak at 169.14 in mass spectrum (Fig. 3).

### Method validation

The developed method was validated as per Q2 specifications of the ICH guidelines.

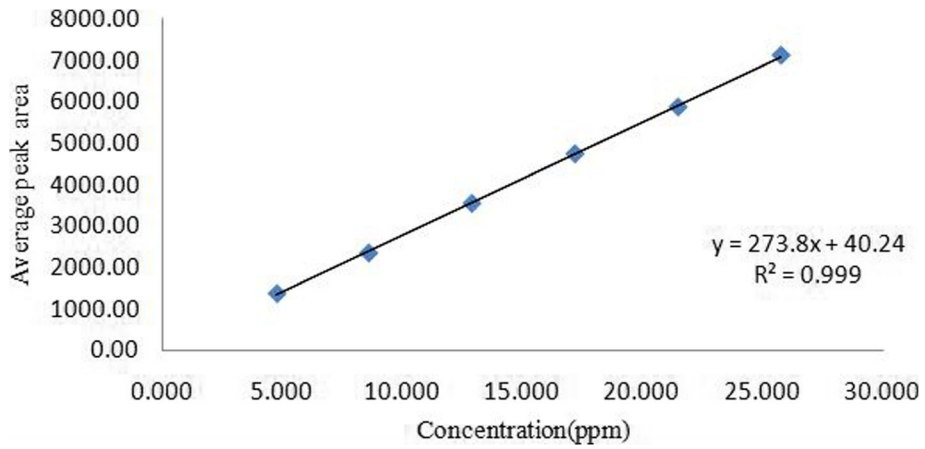



**Fig. 4** Linearity curve of phenyl vinyl sulfone

**Table 3** Linearity for phenyl vinyl sulfone

| Level | Concentration (ppm) | Area of phenyl vinyl sulfone |
|---|---|---|
| LOQ | 4.767 | 1380.85 |
| 50 | 9.00 | 2358.16 |
| 75 | 13.50 | 3555.80 |
| 100 | 18.00 | 4747.76 |
| 125 | 22.50 | 5878.87 |
| 150 | 27.00 | 7121.44 |
| **Regression coefficient ($R^2$)** | | **0.9990** |

$R^2$ value within the acceptance limit that is not less than 0.9, not more than 1

### System suitability

The system suitability of the developed method was confirmed by evaluating the typical system suitability parameters of the 100% level concentration including % RSD. The results (Table 2) satisfied the acceptance criteria.

### Linearity

The linearity of the present method was done for phenyl vinyl sulfone in the range of LOQ level to about 150% of limit. The regression coefficient ($R^2$) value was calculated from the calibration curve, which was constructed by plotting between obtained peak area and concentrations.

$R^2$ value of the calibration curve was 0.9990. The results are shown in Fig. 4 and Table 3 respectively.

### Accuracy

The percentage recovery of phenyl vinyl sulfone from the different levels of spiked sample solutions was in the range of 97.50–102.10% (Table 4) which indicates that accuracy of the proposed method was very accurate and the results were lied within the acceptance limits (± 25%) of the ICH guidelines.

**Table 4** Accuracy results of phenyl vinyl sulfone

| Accuracy levels | No. of preparations | Peak area of phenyl vinyl sulfone | % recovery of phenyl vinyl sulfone |
|---|---|---|---|
| QL | 1 | 1380.02 | 101.00 |
| | 2 | 1346.10 | 99.00 |
| | 3 | 1383.94 | 102.10 |
| 50% | 1 | 2388.88 | 103.00 |
| | 2 | 2267.30 | 97.50 |
| | 3 | 2304.20 | 98.70 |
| 100% | 1 | 4220.62 | 91.00 |
| | 2 | 4218.18 | 91.50 |
| | 3 | 4350.34 | 93.90 |
| 150% | 1 | 6354.86 | 90.90 |
| | 2 | 6499.08 | 92.80 |
| | 3 | 6114.37 | 87.50 |

*QL* quantitative limit

### Precision

The % RSD values for method precision and intermediate precision of the phenyl vinyl sulfone were found to 1.88 and 1.91 for the 100% level concentration (17.161 ppm) precision respectively (Table 5). The lower values (≤ 10) of both precisions represents that the method has good precision.

### Sensitivity

The LOD and LOQ of the phenyl vinyl sulfone were found to be 1.43 ppm and 4.77 ppm, respectively, which indicates that the method has good sensitivity. Table 6 shows the LOD and LOQ results of the phenyl vinyl sulfone.

## Discussion

As per extensive literature review, as of now, no analytical method has been reported for the estimation of phenyl vinyl sulfone in eletriptan hydrobromide. Among the various analytical techniques, the LC-MS method is a proficient and insightful technique to separate, identify, and quantify the impurities of the drug substance and drug product [8]. Few analytical methods were reported for the estimation of related substances and degradants of eletriptan hydrobromide [8–11]. During the synthesis of the eletriptan hydrobromide, polyvinyl sulfone has the possibility to exist as process impurity. The developed LC-MS method was highly effective to separate, identify, and quantify the polyvinyl sulfone. The current method has good sensitivity with a detection level of 1.43 ppm of polyvinyl sulfone with high specificity. A simple solvent system of 0.1%v/v ammonia buffer to methanol (5:95 v/

**Table 5** Summary of results for method precision and intermediate precision

| No. of preparations | Peak area of phenyl vinyl sulfone (100%level ) | |
|---|---|---|
| | Method precision | Intermediate precision |
| 1 | 4220.62 | 4210.62 |
| 2 | 4218.18 | 4218.18 |
| 3 | 4350.34 | 4340.34 |
| 4 | 4157.12 | 4137.12 |
| 5 | 4183.75 | 4283.75 |
| 6 | 4134.87 | 4134.87 |
| Average | 4210.81 | 4220.81 |
| Standard deviation | 76.15 | 80.93 |
| *% RSD | 1.88 | 1.91 |

**% RSD* percentage relative standard deviation

**Table 6** LOD and LOQ results of the phenyl vinyl sulfone

| Parameter | Signal to noise ratio (S/N) | Concentration (ppm) |
|---|---|---|
| **LOD** | 3.71 | 1.43 |
| **LOQ** | 14.19 | 4.77 |

v) represents the cost effectiveness of the method. Rapid analysis of eletriptan hydrobromide samples can be done for estimation of phenyl vinyl sulfone.

## Conclusion

A specific and sensitive LC-MS method was developed for the determination of the content of the phenyl vinyl sulfone in eletriptan hydrobromide pure and pharmaceutical dosage form. The proposed method has very good sensitivity, accuracy, and specificity. Hence, this method has intended use in the process chemistry department and quality control department to identify and quantify the phenyl vinyl sulfone impurity in eletriptan hydrobromide.

### Abbreviations

ICH: International Council for Harmonization; HPLC: High-performance liquid chromatography; RT: Retention time

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### Authors' contributions

IM, SG, and DN contributed equally in the design of the work, acquisition and interpretation of data, and manuscript preparation. All authors have read and approved the manuscript.

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### Availability of data and materials

All data and material should be available upon request.

### Ethics approval and consent to participate

No animal and human subjects were used in this study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that there is no conflict of interest.

### Author details

[1]Department of Chemistry, Jawaharlal Nehru Technological University Anantapur, Anantapur, Andhra Pradesh 515002, India. [2]Department of Chemistry, Anantha Lakshmi Institute of Technology and Sciences, Anantapur, Andhra Pradesh 515002, India.

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