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Trace-level analysis of genotoxic sulfonate ester impurities in teneligliptin by GC-MS

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ABSTRACT

The formation of various sulfonate esters is unavoidable during the synthesis of teneligliptin (TEN), an important drug of type 2 diabetes mellitus. They are essentially to be eliminated from the drug due to their potential genotoxic nature, but there are no effective methods in practice. Hence, we developed an efficient method to get rid of those genotoxic impurities from the drug. The successfully developed method was validated for the trace-level analysis of methyl 1-octanesulfonate (MOS), ethyl 1-octanesulfonate (EOS), and butyl 1-octanesulfonate (BOS) in TEN by gas chromatography-mass spectrometry, in terms of detection limit (LOD), quantification limit (LOQ), precision, accuracy, linearity, robustness, and specificity. The LOD and LOQ values are 0.74, 0.68, and 0.61 ppm and 2.48, 2.25, and 2.03 ppm, respectively, for MOS, EOS, and BOS. The approach was linear in the LOQ of 56 ppm with the correlation coefficient of 0.9979 and above. The average %recovery of residual sulfonate esters from the drug was 94.5 (MOS), 97.5 (EOS), and 97.2 (BOS). The developed method is suitable for even trace-level quantification of MOS, EOS, and BOS content in TEN.

INTRODUCTION

Teneligliptin (TEN) is a dipeptidyl peptidase (DPP)-4 inhibitor, the consumption of TEN with healthy food and regular physical practice as a comprehensive treatment of type 2 diabetes is successful to control high blood sugar. The intake of TEN increases the level of incretin hormones, which control the blood sugar level by balancing insulin release, particularly after meals.

In practice, multiple steps are involved in drug synthesis; hence, it is essential to take into account the unreacted raw materials, intermediates, impurities from the process, and degradation products while providing the rationale for impurities. Also, the residual solvents and catalysts may exist in the pharmaceuticals through the manufacturing process of drugs (Goda and Kadowaki, 2013; Kishimoto, 2013; Kutoh *et al*., 2014; Sharma *et al*., 2016). Hence, it is very important to analyze, identify, and possibly control or remove all substances other than the drug, as long as they do not provide any therapeutic benefits (United States Pharmacopoeia, 2016).

In the synthesis of TEN, *tert*-butyl(2*S*,4*S*)-4-(4-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)piperazin-1-yl)-2-(thiazolidine-3-carbonyl)pyrrolidine-1-carboxylate is an intermediate with the Boc group (Fig. 1). The deprotection of Boc using 1-octanesulfonic acid (Kumar et al., 2017) afforded teneligliptinoctanesulfonic acid salt, which upon further workup provided TEN with octanesulfonic acid (carcinogen), and methyl 1-octanesulfonate (MOS), ethyl 1-octanesulfonate (EOS), and butyl 1-octanesulfonate (BOS) (known as potential genotoxic impurities (PGIs)) by reacting with the process solvents. In fact, the impurities are neither completely controlled nor removed simply by practical manufacturing techniques (European Council of Health and Consumers, 2012; International Conference on Harmonization ICH, 2011). However, it is very crucial to control all the impurities by process optimization (to prove the effective control strategy of the

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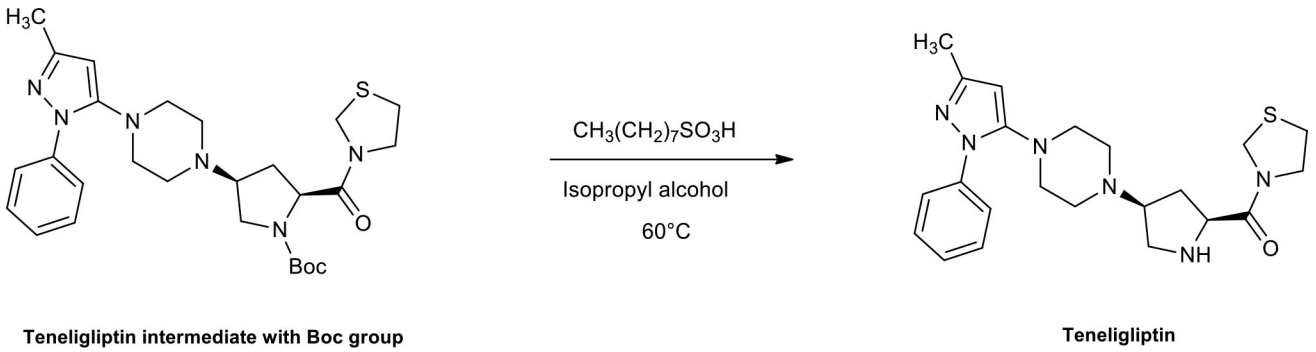

Figure 1. Deprotection of Boc using octane sulphonic acid to obtain Teneligliptin.

drug process) to meet the requirements of the European Medicines Agency (EMA), International Council for Harmonization (ICH), and United States Food and Drug Administration (USFDA).

The genotoxic/carcinogenic impurity limit has been defined by the USFDA and EMA guidelines as the "threshold of toxicological concern" (TTC). TTC exposure of 1.5 g/day of mutagenic impurities is considered an insignificant risk. A predicted daily dose of a patient can be used to calculate the ppm limit of genotoxic impurities in the TTC-derived drug. The recommended maximum dose of TEN is 40 mg/day.

$$\text{Concentration limit of PGIs (ppm)} = \frac{\text{TTC (µg / day)}}{\text{Dose (g / day)}} = \frac{1.5}{0.040} = 37.5 \text{ ppm}$$

The average of MOS, EOS, and BOS should not exceed 37.5 ppm of TEN per day. Therefore, it is important to have a suitable analytical technique with good sensitivity, preciseness, and accuracy for the estimation of MOS, EOS, and BOS impurities in drug substances. But the available gas chromatography-mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC-MS) methods (designed based on the different volatility of sulfonate esters) are useful to eliminate certain impurities only. Specifically, to detect the methyl methanesulfonate (MMS), ethyl methanesulfonate (EMS), and methyl isopropylsulfonates in Active pharmaceutical ingredient (API) and/or formulated products, the GC-MS methods are effective (Ramakrishna *et al*., 2008; Wollein and Schramek, 2012; Zhang *et al*., 2016), whereas using either a simple LC-MS or tandem mass spectrometry (LC-MS/MS) mesylates in benzenesulfonate and/or in *p*-toluenesulfonates were detected (Kakadiya *et al*., 2011; Taylor *et al*., 2006). In addition, a headspace GC-MS *in-situ* derivatization method for the concurrent measurement of methyl, ethyl, and isopropyl esters of methane/benzene/p-toluenesulfonates, and other sulfates in drug substances was successful (Ahirrao *et al*., 2020; Alzaga *et al*., 2007), but already a nonderivatization method was reported for the abovementioned sulfonates by LC- Atmospheric pressure chemical ionization (APCI)-MS/MS (Jin *et al*., 2019).

On the other hand, alkyl sulfonates and dialkylsulfonates in drug substances were detected by electrospray ionization mass spectrometry detection and hydrophilic interaction chromatography separation technique (An *et al*., 2008). The HPLC–UV method was employed to detect the methyl and ethyl mesylates and tosylates by derivatization (Li *et al*., 2019; Nageswari *et al*., 2011; Wang *et al*., 2022), and at an LOQ of 0.60 ppm was effective in the detection of EMS and MMS (Zhou *et al*., 2017).

Based on the literature strategy, we understand that there is neither a specific nor generalized method to determine the genotoxic MOS, EOS, and BOS. Thus, we were motivated to develop a suitable, selective and sensitive method for the estimation of the abovementioned genotoxic sulfonate ester impurities. Consequently, the following attempts were made to estimate even a trace level of those PGIs in TEN by GC-MS.

MATERIALS AND METHODS

Materials

MOS, EOS, BOS, dichloromethane (DCM), acetonitrile (MeCN), and methanol (MeOH) solvent were purchased from Sigma-Aldrich, India.

Optimized GC-MS conditions

The following chromatographic parameters were optimized during the method development to obtain an acceptable peak shape and recoveries to meet the GC system aptness: (a) flow rate (0.8–1.5 mL at constant flow), (b) initial column oven temperature (60–150°C), (c) temperature ramp, (d) injector temperature, (e) detector temperature, (f) split ratio (2:1–10:1), (g) injection volume, (h) diluent (DCM, MeCN, and MeOH), and (i) columns.

During the method optimization, a variety of capillary GC columns, like HP-5, DB-1, DB-1701, and DB-624, with varied film thickness were tested. Among them, DB-624 (60 m length, 0.25 mm, 1.4 µm film thickness) and DB-1701 (30 m length, 0.25 mm, 1 µm film thickness) have had acceptable retention periods. However, a sensible level of retention, sensitivity, resolution, and chromatographic selectivity with a stable baseline was attained with DB-1701 (than the other) through the helium carrier gas.

The MOS (*m/z* 97), EOS (*m/z* 111), and BOS (*m/z* 112) were studied through scan mode from 29 to 150 Da to fix the selective ion monitoring (SIM) process.

As an outcome of various trials, the following method was identified as the best one (optimized) with a single quadrupole mass spectrometer (Agilent 5977B GC/MSD, USA) using the DB-1701 capillary column with the injection volume of 1 µl through a 5:1 split inlet.

The GC oven ramping temperature was initially maintained at 80°C for 2 minutes, then raised to 220°C at the rate of 20°C/minute and held for 11 minutes. Afterward, it was raised to 240°C at the rate of 20°C/minute and held for 9 minutes.

Summary of the optimized parameters are as follows: injector temperature: 240°C; GC-MS interface: 250°C; quad temperature: 150°C, ion source temperature: 230°C; flow rate: 1.0 ml/minute; carrier gas: helium; ionizing energy: 70 eV; solvent delay: 11 minutes; gain factor: 5.0; detector off: 19.0 minutes; SIM

mode mass spectra (Fig. 2): MOS (*m/z* 97), EOS (*m/z* 111), and BOS (*m/z* 112). The GC-MS mass hunter software was employed to the analysis and identification of the chemicals was achieved by National Institute of Standards and Technology mass spectral data.

Diluent

The diluent used was DCM.

Blank solution

DCM was the diluent; its chromatogram is shown in Figure 3.

Standard stock preparation

Each 75 mg of MOS, EOS and BOS was transferred into separate 50 ml standard flasks and diluted. Then, 2.5 ml of each solution was diluted to 10 ml.

Standard solution preparation

1.0 ml of standard stock was diluted to 50 ml. The chromatogram of the standard solution is shown in Figure 4.

Sample preparation

200 mg of the sample was diluted to 5 ml; the chromatogram of the sample is shown in Figure 5.

RESULTS AND DISCUSSION

Method validation

The current analytical procedure is validated by the International Conference for Harmonization (ICH, 2005) recommendations (United States Food and Drug Administration USFDA, 2015).

System suitability

The standard solutions (37.5 ppm) of MOS, EOS, and BOS were injected as a part of the system suitability and the data are presented in Table 1. The percentage of relative standard deviation (%RSD) area of MOS, EOS, and BOS peaks was obtained from six preparations of standard solution. The observed %RSD values of MOS (6.25), EOS (4.84), and BOS (5.71) are in the acceptance limit (i.e., %RSD < 15), and hence the system is suitable for the estimation of the abovementioned sulfonate esters in TEN.

Specificity

Specificity study was carried out by injecting the solvents used during the manufacturing process of TEN. As an outcome of the study, no interference was observed at the retention time of the analyte components.

Limit of detection and limit of quantification

As stated in the ICH guidelines for analytical method validation, the calibration curve method was used for the determination of LOD and LOQ values (Table 2). The LOD values of MOS, EOS, and BOS are 0.74, 0.68, and 0.61 ppm (Fig. 6) and LOQ values are 2.48, 2.25, and 2.03 ppm, respectively (Fig. 7). The %RSD peak areas of MOS, EOS, and BOS obtained from six LOQ preparations are 5.3, 2.6, and 2.7, respectively.

Linearity

Linearity was carried out in the range of LOQ to 150% and the correlation coefficients were 0.9980, 0.9981, and 0.9979 for MOS, EOS, and BOS, respectively. In addition, the slope and regression coefficient data of the abovementioned sulfonates are given in Table 3.

Table 3 indicates the system suitability (which passes the acceptance criteria) as follows: (i) the correlation coefficient of MOS, EOS, and BOS are more than 0.99; and (ii) the %RSD areas of each solvent peak obtained from the six preparations of linearity levels 1 and 6 are not more than 15.

Precision and accuracy

Precision of this method was verified by injecting six replicate preparations of the standard solution (37.5 ppm) of MOS, EOS, and BOS, and as a consequence, the %RSD of the six replicates were 5.8, 4.2, and 8.1, respectively. The complete data is shown in Table 4; the low %RSD is within the acceptance criteria and thus precision of this method is witnessed.

Recovery was carried out by spiking the samples of MOS, EOS, and BOS at the QL level: 50%, 100% (Fig. 8), and 150 % (Table 5). Based on the limits, the recovery should be between 80% and 120% for all precision levels of MOS, EOS, and BOS. From the obtained accuracy values, it is observed that the average recoveries are within the acceptable limit, and hence the method is accurate.

Robustness

Method robustness was assessed by studying the impact of small variations in the temperature of oven, injector, and detector to evaluate the impact on the peak area of MOS, EOS, and BOS at 37.5 ppm. The %RSD of the octane sulfonates peak area is summarized in Table 6. The %RSD of the standard solution of the modified and optimized GC conditions were all within ±10.0%. The data in Table 6 demonstrate the robustness of this method.

Acceptance criteria: The %RSD of peak areas should be ≤15% for all the six injections.

Method recommendation

There are a considerable number of reports on the other sulfonates, such as MMS, EMS, IMS or analogous besylates and tosylates, which are comparatively lower boiling chemicals than the octane sulfonates, such as MOS, EOS, and BOS. To the best of our knowledge, there is no report on the estimation of octane sulfonates; hence, we made this attempt on the higher boiling octane sulfonates. As a result, the chromatographic conditions and validation parameters are effective in the estimation of them in TEN.

The method is simple, efficient, and sensitive, and particularly does not require any derivatization process, which can be directly employed to estimate the octane sulfonates in a short time with high sensitivity. The standard test procedure of MOS, EOS, and BOS content in TEN by GC-MS is provided in Table 7. The LODs and LOQs of MOS, EOS, and BOS are 0.74, 0.68, and 0.61 and 2.48, 2.25, and 2.03 ppm, respectively. The sensitivity of this method is comparable to the analogous lower boiling methyl, ethyl, and isopropyl methane sulfonates, where the LODs and LOQs are reported in ng/g to ppm (Ahirrao *et al*., 2020; Kakadiya

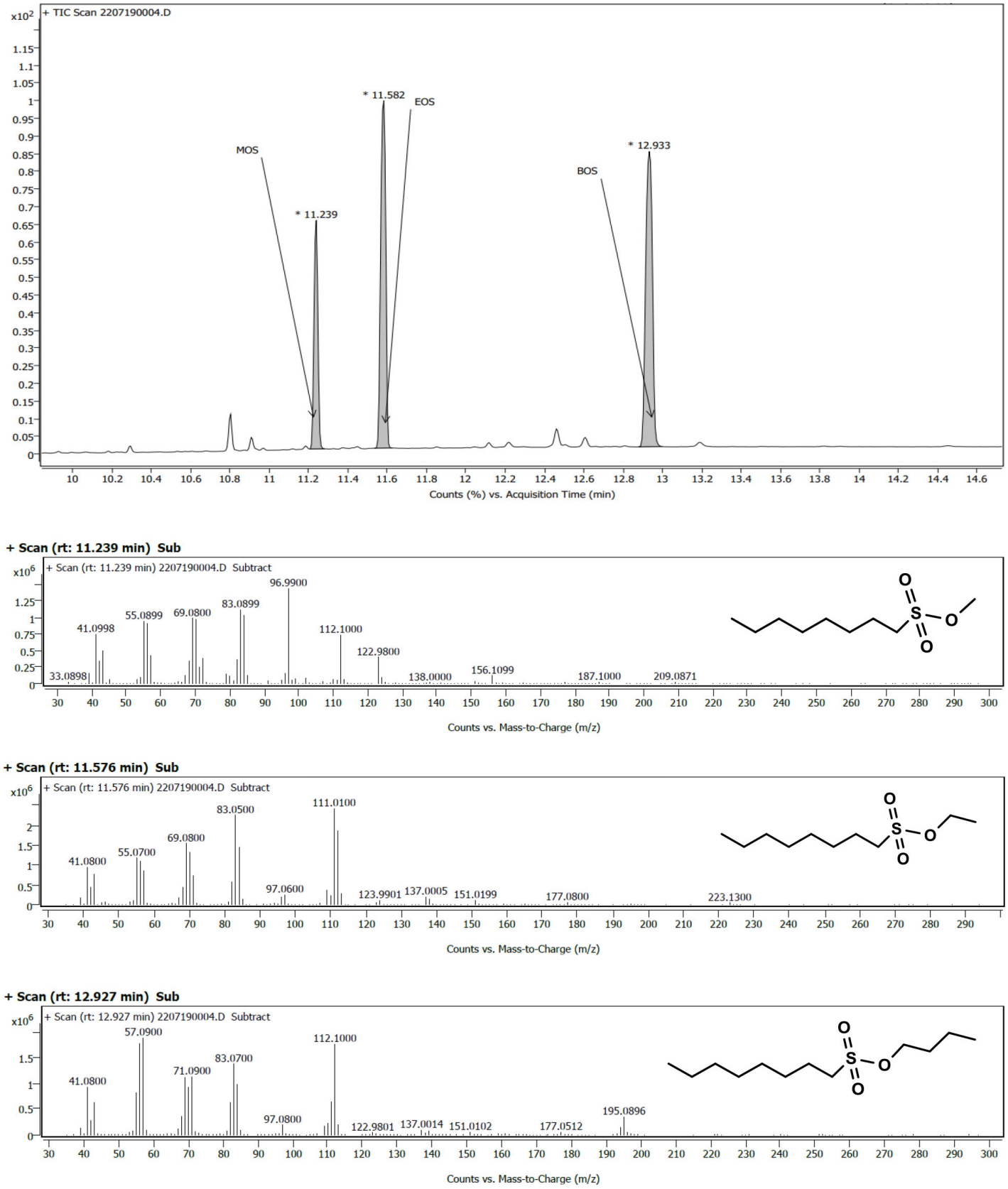

Figure 2. GC-MS mass pattern of MOS, EOS and BOS standards.

et al., 2011; Liu *et al*., 2019; Wollein and Schramek 2012). The linearity, %RSD, and mean recoveries are comparable and even better than a few of the abovementioned reports. In fact, it is not a straightforward comparison of the validation parameters of these higher boiling octane sulfonates with the lower boiling methane sulfonates. However, the present study excels its importance by a simple GC-MS technique even without derivatization, unlike the abovementioned reports.

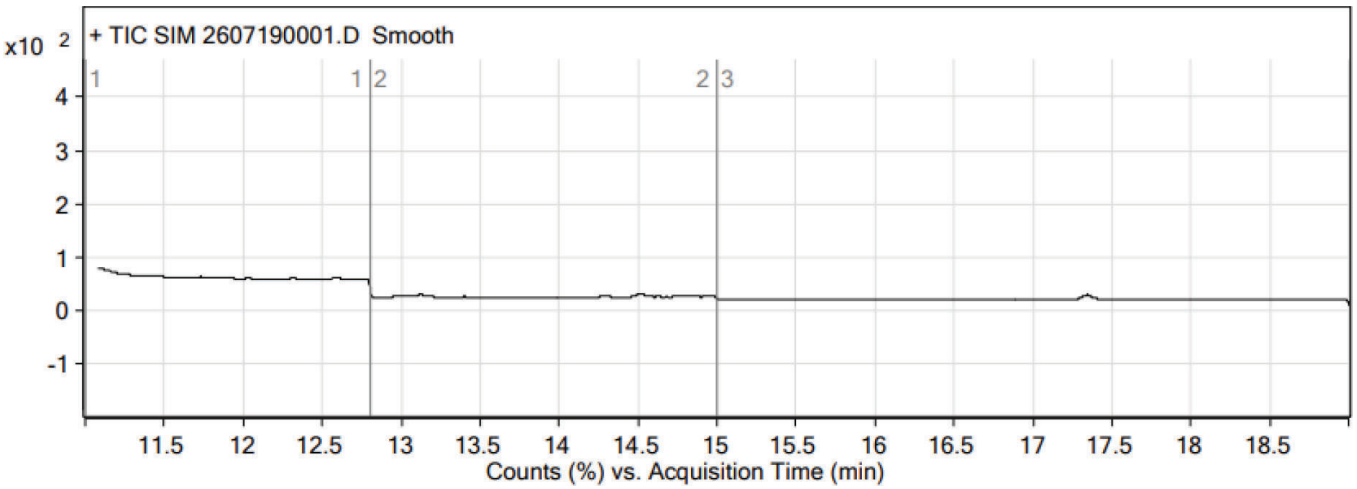

Figure 3. Typical blank chromatogram.

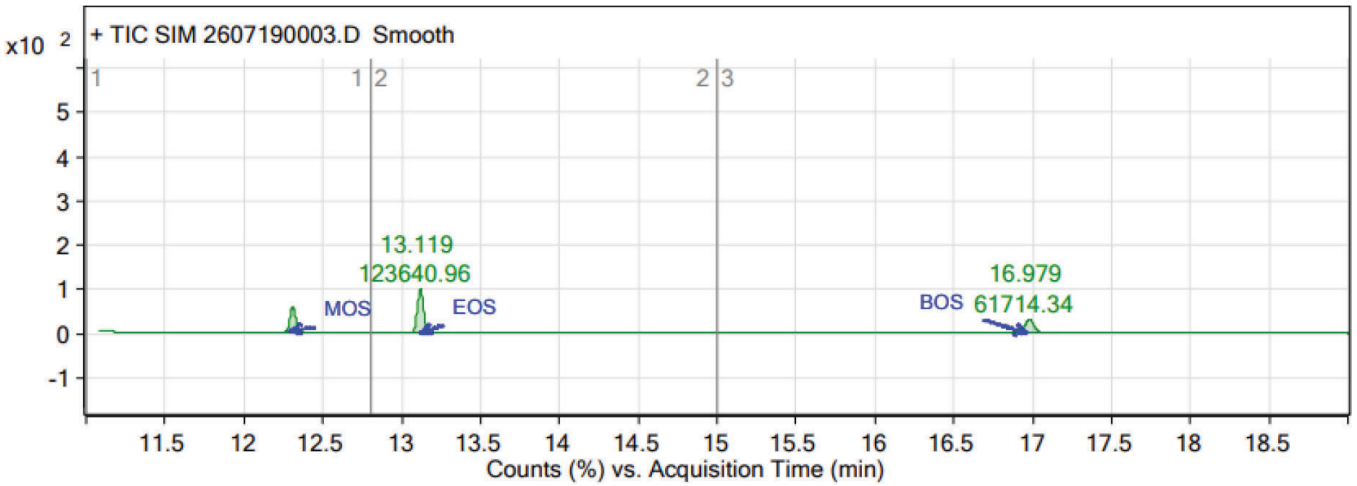

Figure 4. Typical standard chromatogram.

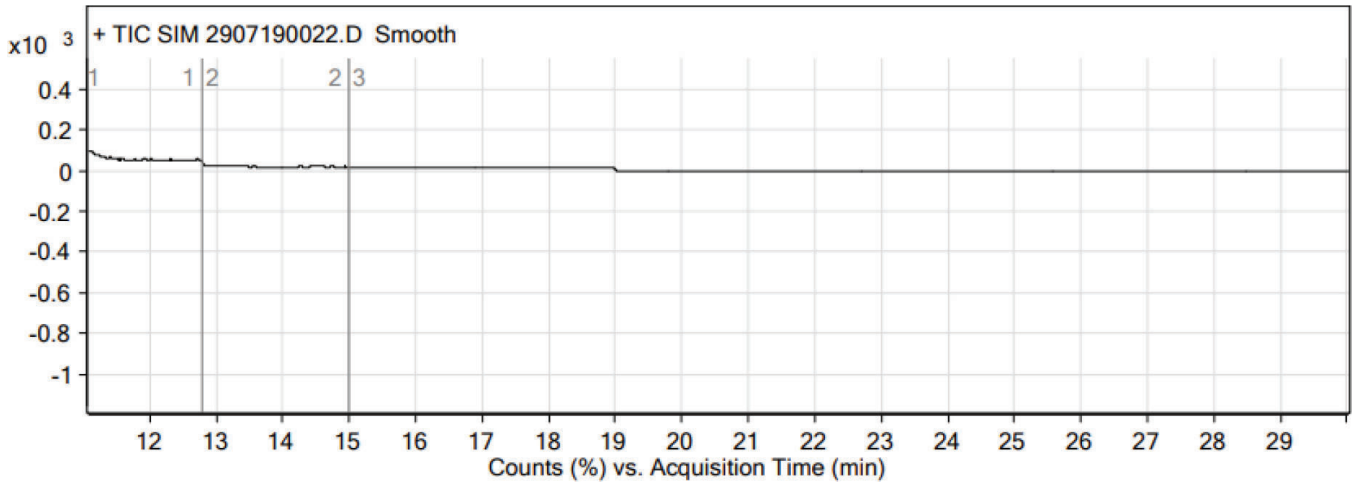

Figure 5. Typical sample chromatogram.

Table 1. System suitability data for standard samples.

Preparation	Response of MOS	Response of EOS	Response of BOS
STD-1	63,850.84	123,640.96	61,714.34
STD-2	55,189.65	109,972.79	54,251.25
STD-3	54,195.45	107,993.86	52,687.33
STD-4	60,065.09	116,160.05	56,547.65
STD-5	60,437.69	116,446.86	56,063.86
STD-6	61,032.03	113,606.01	54,018.87
Average	**59,128.46**	**114.636.76**	**55,880.55**
SD	**3,697.692**	**5,542.845**	**3,188.381**
% RSD	**6.25**	**4.84**	**5.71**

Table 2. Precision at LOQ level.

Preparation	Response of MOS	Response of EOS	Response of BOS
Concentration	**2.48 pm**	**2.25 ppm**	**2.03 ppm**
STD-1	3,712.35	7,244.04	3,148.89
STD-2	3,817.94	7,218.70	3,133.73
STD-3	3,875.38	7,212.53	3,187.44
STD-4	3,662.38	7,030.84	3,085.11
STD-5	4,191.07	7,557.42	3,320.85
STD-6	4,063.77	7,461.59	3,257.73
Average	**3,887.15**	**7,287.52**	**3,188.96**
S.D.	**204.728**	**190.411**	**86.680**
% RSD	**5.27**	**2.61**	**2.72**

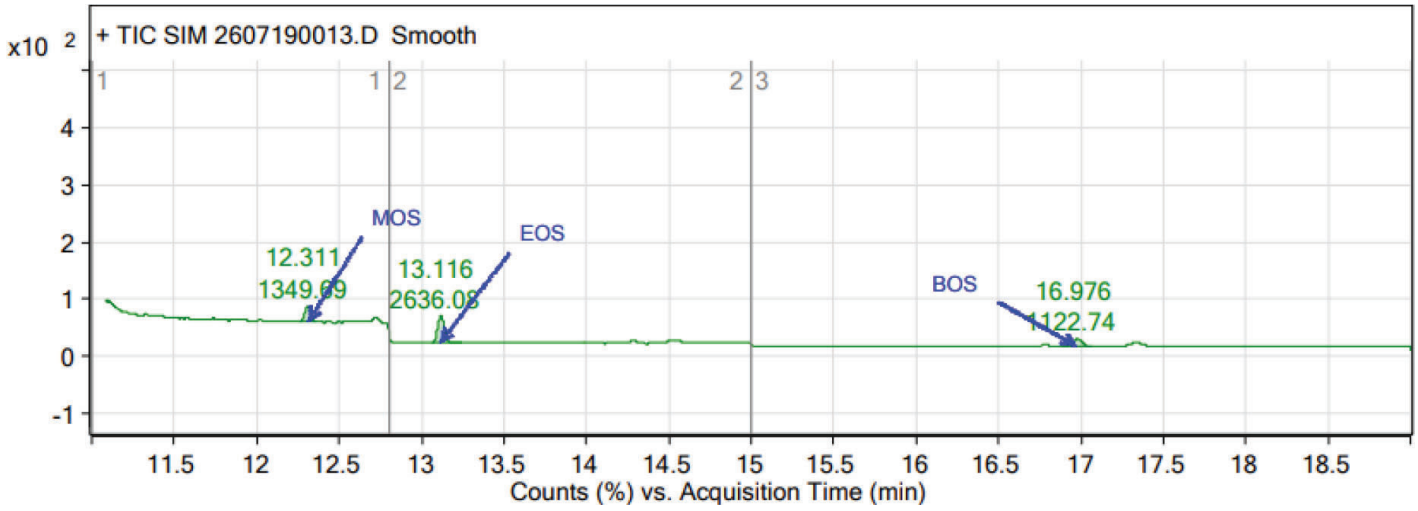

Figure 6. Typical LOD chromatogram.

Hence, based on the validation parameters, we strongly recommend this method even for trace-level estimation of octane sulfonates not only in gliptins, also for a wide range of pharmaceuticals as it does not require derivatization and is easy to adapt in any industrial laboratories.

Mass spectral analysis

In the GC-MS, the observed retention time of 12.3, 13.1, and 17.0 minutes authenticated the presence of MOS, EOS, and BOS, respectively. In the mass spectrum of MOS ($C_9H_{20}O_3S$, 208.11), the major fragments reflect the *m/z* of 123, 112, 97, 83, and 69. As shown in the mass spectrum of EOS ($C_{10}H_{22}O_3S$, 222.13) peaks associated with major fragments reflect the *m/z* of 111, 83, and 69. In the BOS mass spectrum ($C_{12}H_{26}O_3S$, 250.16), m/z 123, 112, 83, and 71 are the major fragments. The analysis of fragmentation pattern of the mass spectra (Fig. 2) clearly supports the presence of MOS, EOS, and BOS impurities in TEN.

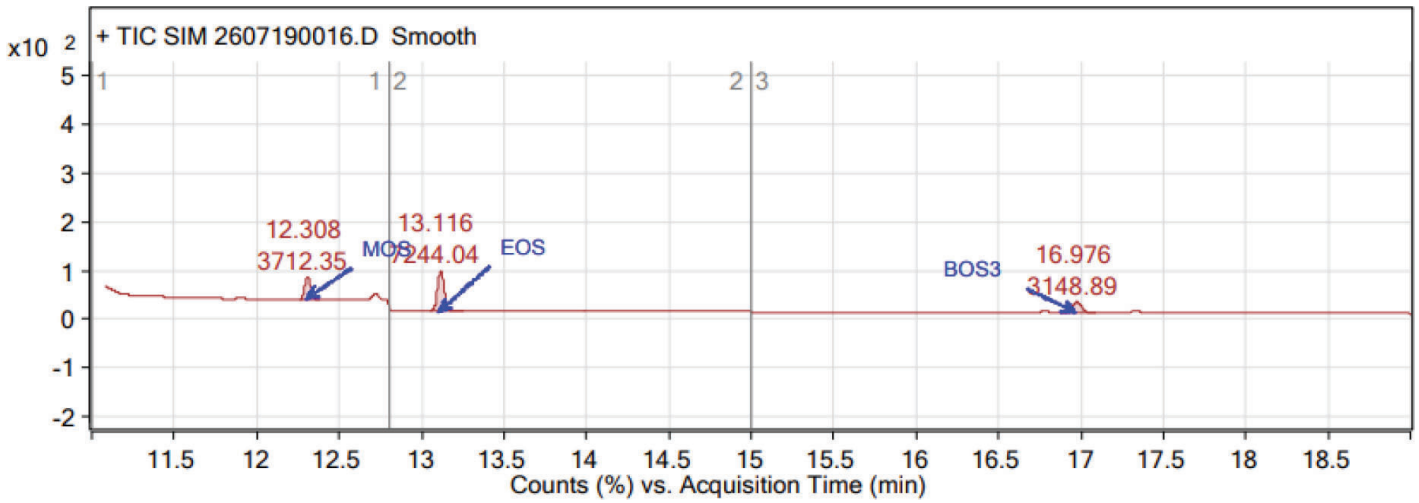

Figure 7. Typical LOQ chromatogram.

Table 3. Linearity of MOS, EOS, and BOS.

	Linearity of MOS		Linearity of EOS		Linearity of BOS	
Linearity	**Conc. (ppm)**	**Mean area**	**Conc. (ppm)**	**Mean Area**	**Conc. (ppm)**	**Mean area**
Linearity-1 (QL)	2.48	3,822.47	2.25	1,912.36	2.03	2,911.17
Linearity-2 (50%)	18.75	22,059.08	18.75	11,038.92	18.75	18,055.82
Linearity-3 (75%)	28.13	35,386.61	28.13	17,707.37	28.13	28,705.71
Linearity-4 (100%)	37.50	45,079.00	37.50	22,558.25	37.50	36,482.20
Linearity-5 (125%)	46.88	53,224.21	46.88	26,635.55	46.88	43,316.88
Linearity-6 (150%)	56.25	63,723.35	56.25	31,889.80	56.25	50,999.78
Correlation co-efficient	**0.9980**		**0.9981**		**0.9979**	
Regression co-efficient	**0.9960**		**0.9962**		**0.9958**	
Slope	**1,114.104**		**555.639**		**891.519**	

Table 4. Precision of MOS, EOS, and BOS.

Preparation	**Response of MOS**	**Response of EOS**	**Response of BOS**
Concentration	**37.5 ppm**	**3.75 ppm**	**3.75 ppm**
Preparation-1	38.40	37.16	35.04
Preparation-2	37.95	38.92	34.67
Preparation-3	36.63	37.50	33.10
Preparation-4	37.21	37.44	32.97
Preparation-5	33.36	34.84	39.13
Preparation-6	33.98	35.25	39.54
Average	**36.26**	**36.85**	**35.74**
S.D.	**2.102**	**1.533**	**2.905**
% RSD	**5.80**	**4.16**	**8.13**

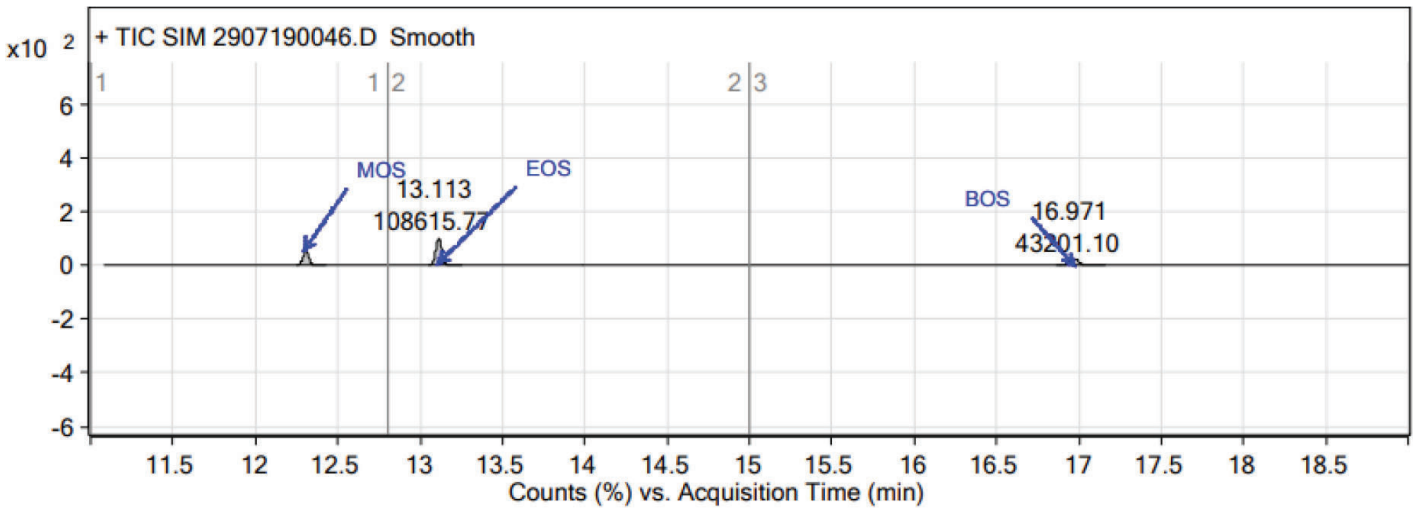

Figure 8. Typical chromatogram of Teneligliptin sample spiked with MOS, EOS and BOS standards.

Table 5. Accuracy of MOS, EOS, and BOS.

Level	% Recovery of MOS	% Recovery of EOS	% Recovery of BOS
QL level	98.99	103.11	103.87
0.50	94.58	94.61	96.55
1.00	96.68	98.27	95.31
1.50	87.63	93.90	94.81
Mean	**94.47**	**97.47**	**97.64**

Table 6. Robustness of MOS, EOS, and BOS.

Robustness of MOS							
Injection	Idle condition	Oven temperature (80°C)		Injector temperature (240°)		Flow rate (1.0 ml/minute)	
		72	88	216	264	0.90	1.10
RSD	6.25	5.91	4.98	7.77	6.24	4.62	3.99
Robustness of EOS							
Injection	As per method ideal condition	Oven temperature (80°C)		Injector temperature (240°)		Flow rate (1.0 ml/minute)	
		72	88	216	264	0.90	1.10
RSD	4.84	3.88	3.67	5.21	5.44	2.22	2.32
Robustness of BOS							
Injection	As per method ideal condition	Oven temperature (80°C)		Injector temperature (240°)		Flow rate (1.0 ml/minute)	
		72	88	216	264	0.90	1.10
RSD	5.71	5.10	5.21	6.45	6.78	1.89	1.46

Table 7. Method recommendations for MOS, EOS, and BOS.

Substance name	Limit of detection (ppm)	Limit of quantitation (ppm)	Retention time (minutes)
MOS	0.74	2.48	12.3
EOS	0.68	2.25	13.0
BOS	0.61	2.03	17.0

CONCLUSION

A new GC-MS method has been developed for the estimation of octane sulfonates and then validated as per the ICH guidelines. Based on the results of various validation parameters, the proposed GC-MS method is simple, specific, robust, linear, precise, and accurate for the intended purpose. In addition, the method is very simple to adapt in any industrial analytical lab as it does not require derivatization. Accordingly, the validated method can detect the MOS, EOS, and BOS at 0.74, 0.68, and 0.61 ppm as LOD and 2.48, 2.25, and 2.03 ppm as LOQ, respectively. This is

an appreciable level detection of PGIs in drug substances. Hence, we recommend this method for even the trace-level quantification of octane sulfonates in gliptins. In the future, this method can be expanded to other classes of drug substances to quantify a range of sulfonates and may be employed as a generalized method as well.

AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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