Research Article

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Development of trace analysis for alkyl methanesulfonates in the delgocitinib drug substance using GC-FID and liquid–liquid extraction with ionic liquid<https://doi.org/10.1515/chem-2020-0093>

received April 26, 2020; accepted June 18, 2020

Abstract: Alkyl methanesulfonates are genotoxic impurities that should be limited to an intake of not more than 1.5 µg/day, as regulated by the International Council for Harmonization guideline M7. We herein report a trace analysis of methyl methanesulfonate (MMS), ethyl methanesulfonate (EMS), and isopropyl methanesulfonate (IPMS) in the delgocitinib drug substance using liquid–liquid extraction, with an ionic liquid as the sample-solving medium, and direct injection gas chromatography detected with a flame-ionization detector. The proposed method takes advantage of the fine solubility of ionic liquids toward the drug substance, the good extraction efficiency of alkyl methanesulfonates in liquid–liquid extraction using the Chem Elut cartridge with low-polar organic solvents, and the ability of alkyl methanesulfonates to concentrate in minimum amounts of organic solvent, resulting in excellent sensitivity and selectivity. Specifically, for the preparation of the sample solution, a mixture of 1-butyl-3-methylimidazolium chloride, water, and acetonitrile was used as the sample-solving media, extracted with diethyl ether, and the eluent was concentrated to 1 mL. The method showed good linearity, accuracy, and precision from 1 to 5 ppm, and the limits of detection of MMS, EMS, and IPMS were 0.1, 0.05, and 0.05 ppm, respectively.

Keywords: alkyl methanesulfonates, ionic liquid, extraction, GC-FID, validation

1 Introduction

Sulfonic acids are often used as salts of drug substances, and sulfonyl halides are frequently employed to introduce the sulfonyl leaving group during the synthesis of drug substances [1,2]. Alcohols such as methanol, ethanol, or isopropanol are also commonly employed as solvents in the synthesis of drug substances. The reactions between the sulfonates and alcohols may result in the formation of alkyl sulfonates, which are considered as potential genotoxic impurities (PGIs) [3–5]. Regarding PGIs, in the pharmaceutical industry, the International Council for Harmonization (ICH) in their ICH M7 guideline has established a threshold of toxicological concern of 1.5 µg/day for durations of more than 10 years [6]. It is not reasonable to consider that the drug product is contaminated by these PGIs if the above chemicals were employed at the primary step of the drug synthesis. However, from a risk-assessment point of view, the development of an analytical method for measuring the residual alkyl sulfonates, and ensuring that their amount in the drug substances and products is less than the recommended maximum value, is still required, according to this guideline [7].

Several analytical approaches have reported on the trace analysis of alkyl sulfonates in drug substances. In the case of alkyl methanesulfonates, which have no UV absorbance, gas chromatography coupled with mass spectrometry (GC-MS) is the most commonly used [8,9]. Due to the high selectivity and sensitivity of MS, liquid chromatography coupled with MS (LC-MS) is also frequently utilized [10,11]. Another approach reported is the derivatization pretreatment prior to GC analysis [12] and solid phase microextraction (SPME) for sample preconcentration [13,14]. However, GC-MS, LC-MS, or SPME techniques are not globally available at pharmaceutical manufacturing sites, and also these techniques require advanced skills for their operation. In this context, there is a need to develop convenient and highly sensitive methods for the analysis of alkyl methanesulfonates using conventionally acquired materials at the general manufacturing sites [15].

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In this article, we present a procedure for trace analysis of methyl methanesulfonate, ethyl methanesulfonate, and isopropyl methanesulfonate (MMS, EMS and IPMS, respectively) in a drug substance, using ionic liquid as the sample-solving medium for extraction, followed by identification with a conventional direct injection GC detected with a flame-ionization detector (GC-FID). This method was successfully applied to delgocitinib, a Janus kinase inhibitor, currently in New Drug Application in Japan for the topical treatment of inflammatory skin conditions [16–20]. The method was also validated with respect to specificity, accuracy, precision, linearity, range, limits of detection (LOD), limits of quantitation (LOQ), and system suitability, according to the ICH Q2 guidelines [21].

For trace analysis of MMS, EMS, and IPMS by the conventional analytical device, we anticipated that organic – aqueous bilayer extraction procedures would overcome the matrix effect of MMS, EMS, and IPMS due to the presence of drug substances, by effectively concentrating them in the organic phase, while keeping the drug substances themselves in the aqueous phase. In the organic – aqueous bilayer extraction procedures, we adopted the Chem Elut cartridge, which economically and effectively supported liquid–liquid extraction. Regarding the selection of the sample-solving medium, we previously reported the trace analysis of residual benzene in the delgocitinib drug substance using liquid–liquid extraction and conventional high-performance liquid chromatography (HPLC); and hence, we recommended potassium hydroxide and a hydrochloric acid solution as the sample-solving medium, as most marketed drug substances are soluble in them [22]. However, because MMS, EMS, and IPMS are hydrolyzed under the acidic or basic condition, we focused on ionic liquids that can solubilize complex polar molecules [23,24]. Ionic liquids are typically composed of organic cations and a variety of anions and are commonly defined as salts that melt below 100°C. They are often referred to as “designer solvents” due to the variability of cation and anion selection, which exhibit unique physicochemical properties such as high thermal stability, negligible vapor pressure, no flammability, and tunable water miscibility. Therefore, ionic liquids find application in various research fields, including electronics [25], biorefinery [26], metals [27], synthesis [28], separation [29], and so on; and studies using ionic liquids in analytical chemistry have continued to increase in the last two decades. It is essential for the approach we adopted in this article to solve the drug substance in high concentration and to design the

polarity of sample solution, so ionic liquids are considered the most suitable sample-solving medium. We adopted a mixture of high-polar ionic liquids, water, and acetonitrile as the sample-solving medium, and diethyl ether as the organic solvent to meet the pretreatment of liquid–liquid extraction and increase the sensitivity and selectivity of MMS, EMS, and IPMS, thus allowing the application of conventional direct injection GC-FID.

2 Experimental

2.1 Materials and reagents

MMS (research purpose, >96%, expiry date: May 2020), EMS (research purpose, >97%, expiry date: May 2020), special-grade *n*-hexane (>96.0%, expiry date: May 2020), special-grade diethyl ether (>99.5%, expiry date: May 2020), and HPLC-grade acetonitrile (>99.8%, expiry date: June 2019) were obtained from FUJIFILM Wako Pure Chemical Industries. 1-Butyl-3-methylimidazolium chloride ([BMIM]Cl); research purpose, >98.0%, expiry date: January 2020), 1-butyl-3-methylimidazolium bromide ([BMIM]Br); research purpose, >97.0%, expiry date: January 2020), 1-hexyl-3-methylimidazolium chloride ([HMIM]Cl); research purpose, >97.0%, expiry date: January 2020), 1-methyl-3-octylimidazolium chloride ([OMIM]Cl); research purpose, >97.0%, expiry date: January 2020), 1-butyl-1-methylpyrrolidinium chloride (research purpose, >99.0%, expiry date: January 2020), special-grade sodium sulfate (>99.0%, expiry date: February 2022), and special-grade ethyl acetate (>99.5%, expiry date: May 2020) were obtained from Sigma Aldrich. 1-Butyl-4-methylpyridinium chloride (research purpose, >99.0%, expiry date: January 2020) and 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl); research purpose, >98.0%, expiry date: January 2020) were obtained from the Tokyo Chemical Industry. IPMS (research purpose, >99%, expiry date: January 2020) and HPLC-grade water (expiry date: June 2019) were obtained from ACROS ORGANICS and Nacalai Tesque, respectively. The delgocitinib drug substance used was manufactured by Shiono Finesse, Ltd, Japan, for clinical trials (>99.0%, expiry date: March 2022). As methanesulfonyl chloride was employed during the previous manufacturing process of delgocitinib, the drug substance for clinical use potentially contained methanesulfonates as impurities.

Figure 1: Preparation scheme of the sample solution.

2.2 Instruments

GC analysis was conducted using an Agilent 6890N GC/FID series equipped with an autoinjector of Agilent 7683 series. A DB-624 UI column (0.25 mm $\times$ 30 m, 1.4 μ m; J&W Scientific) and glass insert (Part number 5183-4711; Agilent Technologies) were used for analysis. Supported by the liquid-liquid extraction cartridge, Chem Elut 3 mL cartridge was obtained from Agilent Technologies. A Mettler Toledo AT261 Semi-Micro Balance was also used for sample preparation.

2.3 Operating conditions for GC

For direct injection GC analysis, the FID and split-less injection were adopted, with an injection volume of 5 μ L, injection port temperature of 220°C; detector temperature of 300°C; temperature program set at 50°C for 2 min, raised to 250°C at a rate of 15°C per minute and then maintained at 250°C for 10 min with flow rate of 5.0 mL/min (constant flow); and helium was used as the carrier gas.

2.4 Preparation of sample and standard solutions

For sample preparation, 0.5 g of delgocitinib drug substance was accurately weighed and to this about 50 mg of

[BMIM]Cl, 2 mL of water, and 1 mL of acetonitrile were added. After dissolving the analyte, the entire solution was applied to the Chem Elut 3 mL cartridge, followed by a waiting period of 5 min. Next, 12 mL of diethyl ether is eluted to the cartridge and 0.2 g of sodium sulfate was added to the elute (diethyl ether) and vigorously stirred. After removing the precipitate, the elute is evaporated with nitrogen gas to achieve a volume of exactly 1 mL, and this solution is used in the GC analysis (Figure 1). In a separate flask, about 0.1 g of MMS, EMS, and IPMS are accurately weighed, and acetonitrile is added to make up the volume to exactly 10 mL. Next, 0.1 mL of this solution was pipetted and acetonitrile was added to make up the volume to exactly 10 mL. Finally, 0.5 mL of this solution was pipetted, and diethyl ether was added to make up the volume to exactly 20 mL and this was used as the standard solution.

2.5 Preparation of solutions for method validation

A mixture of MMS, EMS, and IPMS in diethyl ether was prepared at a concentration of 2.5 μ g/mL (equivalent to 5 ppm in the delgocitinib drug substance) to measure the specificity. The samples of MMS, EMS, and IPMS in diethyl ether for linearity were also prepared at 0.25, 0.5, 1, 2.5 and 5 μ g/mL (equivalent to 0.5, 1, 2, 5 and 10 ppm in the delgocitinib drug substance), respectively. For accuracy and precision, the sample solutions spiked with MMS, EMS, and IPMS at 0.5, 1 and 2.5 μ g/mL were additionally prepared in

Table 1: Summary for the screening ionic liquids and organic solvents focused on the carbon chain length of ionic liquids

Recovery (%) of spiked MMS, EMS, and IPMS at 0.5 µg/mL into the sample solution (equivalent to 1 ppm in the delgocitinib drug substance)			
Ionic liquids		Organic solvents ^a	
		Diethyl ether	Ethyl acetate
1-Ethyl-3-methylimidazolium chloride ([EMIM]Cl)	MMS: 96.5% EMS: 127.0% IPMS: 93.7%	MMS: 14.3% EMS: 37.6% IPMS: 22.7%
	1-Butyl-3-methylimidazolium chloride ([BMIM]Cl)	MMS: 115.6% EMS: 103.9% IPMS: 104.6%	MMS: not detected EMS: 53.8% IPMS: 78.2%
	1-Hexyl-3-methylimidazolium chloride ([HMIM]Cl)	MMS: not detected EMS: 45.7% IPMS: 44.0%	MMS: not detected EMS: not detected IPMS: not detected
	1-Methyl-3-octylimidazolium chloride ([OMIM]Cl)	MMS: not detected EMS: not detected IPMS: not detected	MMS: not detected EMS: not detected IPMS: not detected

^a *n*-Hexane was not listed in the table because MMS, EMS, and IPMS were not recovered in every condition.

triplicates. For the LOQ and LOD, sample solutions at concentrations of 0.15 and 0.05 µg/mL of MMS (equivalent to 0.3 and 0.1 ppm in the delgocitinib drug substance), 0.05 and 0.025 µg/mL of EMS (equivalent to 0.1 and 0.05 ppm in the delgocitinib drug substance), and 0.05 and 0.025 µg/mL of IPMS (equivalent to 0.1 and 0.05 ppm in the delgocitinib drug substance) were also prepared.

Ethical approval: The conducted research is not related to either human or animal use.

3 Results and discussion

3.1 Optimization of solvent extraction and GC method

The selection of an ionic liquid that can completely dissolve the delgocitinib drug substance and show high polarity are

keys to analyzing MMS, EMS, and IPMS with the method proposed here. As ionic liquids, we tested [EMIM]Cl, [BMIM]Cl, [BMIM]Br, [HMIM]Cl, [OMIM]Cl, 1-butyl-1-methylpyrrolidinium chloride, and 1-butyl-4-methylpyridinium chloride. Due to high electronegativity, the anion candidates adopted in the ionic liquids were chloride and bromide. In the various marketed ionic liquids, candidates were focused on the cation's chemical structure and the length of carbon chain; imidazolium salt (1-ethyl-3-methylimidazolium, 1-butyl-3-methylimidazolium, 1-hexyl-3-methylimidazolium, and 1-methyl-3-octylimidazolium), pyridinium salt (1-butyl-4-methylpyridinium), and pyrrolidinium salt (1-butyl-1-methylpyrrolidinium). However, because these ionic liquids are solid at room temperature, small amounts of water and acetonitrile were added to improve the experimental operation. As the organic layer for MMS, EMS, and IPMS extraction, we tested *n*-hexane, ethyl acetate, and diethyl ether. Although the use of low-polar ionic liquid was considered, the headspace of the GC is not applied to the measurement of MMS, EMS, and IPMS

Table 2: Summary for the screening ionic liquids and organic solvents focused on the cation's structure and the anion's electronegativity

Recovery (%) of spiked MMS, EMS, and IPMS at 0.5 µg/mL into the sample solution (equivalent to 1 ppm in the delgocitinib drug substance)			
Ionic liquids		Organic solvents ^a	
		Diethyl ether	Ethyl acetate
1-Butyl-3-methylimidazolium chloride ([BMIM]Cl)	MMS: 115.6% EMS: 103.9% IPMS: 104.6%	MMS: not detected EMS: 53.8% IPMS: 78.2%
	1-Butyl-3-methylimidazolium bromide ([BMIM]Br)	MMS: 33.7% EMS: 30.3% IPMS: 28.8%	MMS: not detected EMS: 49.8% IPMS: 45.7%
	1-Butyl-4-methylpyridinium chloride	MMS: 24.8% EMS: 32.8% IPMS: 24.1%	MMS: not detected EMS: 28.1% IPMS: 36.7%
	1-Butyl-1-methylpyrrolidinium chloride	MMS: 85.0% EMS: 82.1% IPMS: 81.2%	MMS: not detected EMS: 44.4% IPMS: 50.8%

^a *n*-Hexane was not listed in the table because MMS, EMS, and IPMS were not recovered in every condition.

due to the high boiling point, and ionic liquid is not suitable for direct injection GC due to its negligible vapor pressure. Therefore, in this article, we adopted organic solvent for liquid–liquid extraction. In order to find the best combination of ionic liquid and organic solvent, the recovery of spiked MMS, EMS, and IPMS at 0.5 µg/mL (which corresponds to 1 ppm in the delgocitinib drug substance) was compared using the abovementioned media and solvent candidates, according to the preparation method for each sample solution and GC conditions.

In order to improve the efficiency of extraction, the Chem Elut cartridge, which economically and effectively supported liquid–liquid extraction, was adopted, and smaller amounts of organic solvent were used to achieve higher sensitivity to MMS, EMS, and IPMS; therefore, the amount of sample-solving medium and the cartridge size of Chem Elut adopted were small, and elution is concentrated to 1 mL and injected to GC-FID. The recovery rates of MMS, EMS, and IPMS in sample solutions were considered successful between 70.0 and

130.0% and were calculated by using spiked MMS, EMS, and IPMS at 0.5 µg/mL in the sample solution. The results of screening for ionic liquids and organic solvents are summarized in Tables 1 and 2. The typical chromatogram of spiked MMS, EMS, and IPMS in the sample solution is shown in Figure 2.

With respect to the selection of organic solvents, the results showed that diethyl ether was a better organic solvent in terms of the recovery rate, compared to the other solvents. In the case of ethyl acetate, it was speculated to result in lower recovery rates due to the matrix effect resulting in the precipitation of delgocitinib drug substance during elution concentration. Also, it was indicated that *n*-hexane being a non-polar solvent was not suitable for the extraction of alkyl methanesulfonate.

With respect to the selection of ionic liquids, the results showed that [BMIM]Cl, [EMIM]Cl, and 1-butyl-1-methylpyrrolidinium chloride were better ionic liquids in terms of recovery rate, compared to the other ionic liquids. In the selection of an anion, chloride showed a

Figure 2: GC chromatograms for MMS, EMS, and IPMS spiked sample solutions and standard solution equivalent to 1 ppm in the delgocitinib drug substance.

better recovery rate than bromide; and in terms of cation selection, the cations with shorter carbon chains demonstrated better recovery rates. Chloride has higher electronegativity compared to bromide, and shorter carbon chains have lower affinity for organic solvents. Therefore, it was speculated that the extracting efficiency are correlated with difference in the polarity between ionic liquids and selected organic solvent. Although some ionic liquids showed good recovery rates, considering the commercial availability and the price, [BMIM]Cl was adopted as the ionic liquid of choice.

Following the design of the alkyl methanesulfonate extraction method, a simple conventional GC-FID condition is found in Section 2. The split-less injection and ultra-inert column were adopted in order to raise sensitivity. These conditions were successful in detecting 0.10 ppm of MMS, and 0.05 ppm of EMS, and 0.05 ppm of IPMS in the delgocitinib drug substance at a sample intake of 0.5 g with adequate sensitivity.

3.2 Method validation

3.2.1 Specificity

The GC conditions used in this study resulted in a clear separation of MMS, EMS, and IPMS peaks from those of the blank, respectively. The GC chromatograms of a blank (diethyl ether) solution and a standard solution containing

0.5 µg/mL of MMS, EMS, and IPMS (which corresponds to 1 ppm in the delgocitinib drug substance) are shown in Figure 2. No peaks were observed at the retention time of MMS, EMS, and IPMS in the blank solution chromatogram, whereas the chromatogram of the mixed solution showed clear peak separation for MMS, EMS, and IPMS.

3.2.2 Accuracy

The accuracy of the method proposed in this article was determined by the recovery rate of MMS, EMS, and IPMS using sample solutions spiked with MMS, EMS, and IPMS at concentrations of 0.5, 1, and 2.5 µg/mL (equivalent to 1, 2, and 5 ppm in the delgocitinib drug substance). Recovery rates were evaluated in triplicate and obtained by comparing the calculated values with the theoretical value. The average recovery for MMS, EMS, and IPMS at concentrations ranging from 1 to 5 ppm was between 78.9 and 116.2% for MMS, 74.7 and 109.9% for EMS and 82.7 and 123.8% for IPMS (acceptance criteria: 70.0–130.0%; Table 3).

3.2.3 Precision

The precision of the method proposed in this article was determined by the relative standard deviation (RSD) of the recovery test described in Section 3.2.2, in which MMS, EMS, and IPMS were evaluated in triplicate at

Table 3: Recovery of MMS, EMS, and IPMS at 0.5, 1, and 2.5 µg/mL (equivalent to 1, 2, and 5 ppm in the delgocitinib drug substance) obtained in triplicate

Replicate	Recovery (%)								
	0.5 µg/mL			1 µg/mL			2.5 µg/mL		
	MMS	EMS	IPMS	MMS	EMS	IPMS	MMS	EMS	IPMS
1	99.6	75.0	112.1	98.6	90.4	111.0	99.0	89.5	82.7
2	82.8	74.7	90.2	86.2	82.8	114.3	116.2	100.1	116.5
3	78.9	78.8	123.8	95.6	109.9	120.4	103.6	91.2	100.7
Average (%)	87.1	76.2	108.7	93.5	94.4	115.2	106.3	93.6	100.0
RSD (%)	12.6	3.0	15.7	6.9	14.8	4.1	8.4	6.1	16.9
95% lower limit	59.8	70.5	66.3	77.4	59.7	103.4	84.2	79.5	58.0
95% upper limit	114.4	81.9	151.1	109.6	129.1	127.0	128.4	107.7	142.0
Acceptance criteria	Recovery (%): 70.0–130.0 RSD (%): Not more than 20								

concentrations of 0.5, 1, and 2.5 µg/mL (equivalent to 1, 2, and 5 ppm in the delgocitinib drug substance). As shown in Table 3, the RSD of MMS, EMS, and IPMS recovery was found to be between 6.9 and 12.6% for MMS, 3.0 and 14.8% for EMS, and 4.1 and 16.9% for IPMS (acceptance criteria: not more than 20%).

3.2.4 LOD and LOQ

The LOD and LOQ were assessed using a signal to noise ratio. Solutions containing 0.05 and 0.15 µg/mL of MMS (which correspond to 0.1 and 0.3 ppm in the delgocitinib drug substance, respectively), 0.025 and 0.05 µg/mL of EMS and IPMS (which correspond to 0.05 and 0.1 ppm in the delgocitinib drug substance, respectively) were assessed. The signal to noise ratio of the 0.05 and 0.15 µg/mL concentrations for MMS was 4.7 and 13.3, the 0.025 and 0.05 µg/mL concentrations for EMS were 4.7 and 10.6, and the 0.025 and 0.05 µg/mL concentrations for IPMS were 7.5 and 16.4, respectively. The data indicated that the LOD (acceptance criteria: signal to noise ratio > 2) for MMS, EMS, and IPMS was approximately 0.05 µg/mL (0.1 ppm), 0.025 µg/mL (0.05 ppm), and 0.025 µg/mL (0.05 ppm), respectively; and the LOQ (acceptance criteria: signal to noise ratio > 10) for MMS, EMS, and IPMS was approximately 0.15 µg/mL (0.3 ppm), 0.05 µg/mL (0.1 ppm), and 0.05 µg/mL (0.1 ppm), respectively.

3.2.5 Linearity and range

Linearity testing (data summarized in Table 4) was conducted over a range from 0.25 to 5 µg/mL (equivalent

of 0.5–10 ppm in the delgocitinib drug substance) of MMS, EMS, and IPMS. Figure 3 shows the linear plot of the peak response versus the concentration of MMS, EMS, and IPMS. For MMS, EMS, and IPMS, the coefficient of correlation (r) was 1.00 (acceptance criteria: no less than 0.99), the Y -intercept was close to zero, and no biased trends were observed in the residual plots. Analyzing the results for accuracy, precision, and linearity, the method proposed in this article shows sensitiveness to MMS, EMS, and IPMS concentrations ranging between 0.5 and 2.5 µg/mL (equivalent of 1–5 ppm in the delgocitinib drug substance).

3.2.6 System suitability

When the procedure was carried out using the standard solution under the GC operating conditions, the symmetry factor of the MMS, EMS, and IPMS peaks was 1.5, 1.2, and 1.1, respectively, and peak resolution among the MMS, EMS, and IPMS peaks was 20.2 (MMS-EMS) and 7.5 (EMS-IPMS). After

Figure 3: Linear plot for MMS, EMS, and IPMS from 0.25 to 5 µg/mL (corresponding to 0.5–10 ppm in the delgocitinib drug substance).

Table 4: Linear regression data of MMS, EMS, and IPMS from 0.25 to 5 µg/mL (corresponding to 0.5–10 ppm in the delgocitinib drug substance)

Concentration (µg/mL)		Peak response	<i>r</i>	Slope	Y-intercept	95% lower limit	95% upper limit
MMS	0.25	0.920951	0.999	3.58	−0.00965	−0.647	0.628
	0.5	1.86033					
	1	3.73529					
	2.5	8.48502					
	5	18.09925					
EMS	0.25	2.09934	0.999	8.55	0.0750	−1.51	1.66
	0.5	4.42802					
	1	9.33186					
	2.5	20.41108					
	5	43.22175					
IPMS	0.25	3.03998	0.999	12.3	0.177	−2.32	2.68
	0.5	6.38903					
	1	13.6064					
	2.5	29.20741					
	5	62.07457					

repeating the test six times, the RSD of the peak areas of MMS, EMS, and IPMS was 1.3%, 1.2%, and 1.3%, respectively.

this approach could also be applicable for the trace analysis of other PGIs.

4 Conclusions

A trace analysis method for MMS, EMS, and IPMS in pharmaceutical drug substances, using GC-FID and liquid–liquid extraction with ionic liquid, was successfully developed. The method was proven to be applicable to the trace analysis of MMS, EMS, and IPMS in the delgocitinib drug substance, in line with the requirements of ICH M7 guideline, and reported that in every lot of delgocitinib manufactured for clinical use so far, MMS, EMS and IPMS were not detected.

The method presented here showed the almost equivalent relative sensitivity of MMS, EMS, and IPMS compared to the other analytical method presented in Section 1 [8–14] and possess the uniqueness to be able to conduct the quantitative analysis of them using the conventional direct injection GC-FID. This method is expected to be particularly useful for the analysis of MMS, EMS, and IPMS in drug substances, since many drug substances are soluble in ionic liquids. Although [BMIM]Cl and diethyl ether were selected as the ionic liquid and the organic solvent, respectively, we also demonstrated that other combinations of ionic liquids and organic solvents could be used for this method, thus making this approach applicable to other analytes. Since the pharmaceutical industry is currently required by ICH M7 guideline to evaluate various PGIs, we speculate that

Abbreviations

ICH	International Council for Harmonization
MMS	methyl methanesulfonate
EMS	ethyl methanesulfonate
IPMS	isopropyl methanesulfonate
PGIs	potential genotoxic impurities
[EMIM]Cl	1-ethyl-3-methylimidazolium chloride
[BMIM]Cl	1-butyl-3-methylimidazolium chloride
[BMIM]Br	1-butyl-3-methylimidazolium bromide
[HMIM]Cl	1-hexyl-3-methylimidazolium chloride
[OMIM]Cl	1-methyl-3-octylimidazolium chloride

Acknowledgments: Our greatest appreciation to Hideto Uehara and Shoji Onogi who provided considerable feedback and valuable comments. We would also like to thank our colleagues who encouraged us with invaluable comments.

Conflict of interest: The authors declare that there is no conflict of interest with respect to this article.

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